THE UNIVERSITY
of EDINBURGH

Systematic review and meta-analysis of experimental multiple sclerosis studies

Hanna Mikaela Vesterinen

BSc (Hons)

THE UNIVERSITY *of* EDINBURGH

PhD by Research

2013

Abstract

Background: Multiple sclerosis (MS) is the most common cause of disability in young people and yet there are no interventions available which reliably alter disease progression. This is despite several decades of research using the most common animal model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE). There is now emerging evidence across the neurosciences to suggest that limited internal validity (measures to reduce bias) and external validity (e.g. using a clinically relevant animal model) may influence the translational success.

Aim and objectives: To provide an unbiased summary of the scope of the literature on candidate drugs for MS tested in EAE to identify potential reasons for the failures to translate efficacy to clinical trials. My objectives were, across all of the identified publications, to: (1) describe the reporting of measures to reduce bias and to assess their impact on measures of drug efficacy; (2) assess the relationship between treatment related effects measured using different outcome measures; (3) assess the prevalence and impact of any publication bias; (4) compare findings from the above with another disease with limited translational success (Parkinson's disease; PD).

Methods: I used systematic searches of three online databases to identify relevant publications. Estimates of efficacy were extracted for neurobehavioural scores, inflammation, demyelination and axon loss. For PD experiments, we searched for dopamine agonists tested in animal models of PD with outcome assessed as change in neurobehavioural scores. I calculated normalised mean difference or standardised mean difference effect sizes and combined these in a meta-analysis using a random effects model. I used stratified meta-analysis or meta-regression to assess the extent to which different study design characteristics explained differences in reported efficacies. These characteristics included: measures to reduce bias (random allocation to group and blinded assessment of outcome), the animal species, sex, time of drug administration, route of drug administration and the number of animals per group. Publication bias was assessed using funnel plotting, Egger regression and "trim and fill".

Results: I identified 1464 publications reporting drugs tested in EAE. Reported study quality was poor: 11% reported random allocation to group, 17% reported blinded

assessment of neurobehavioural outcomes, 28% reported blinded assessment of histological outcomes, and <1% reported a sample size calculation. Estimates of efficacy measured as the reduction in inflammation were substantially higher in un-blinded studies (47.1% reduction (95% CI 41.8-52.4)) versus blinded studies (33.1% (25.8-40.4). Moreover, the same finding was identified for 121 publications on dopamine agonists tested in experimental PD models where efficacy was measured as change in neurobehavioural outcomes. For EAE studies we were unable to include data from 631 publications describing original research. Usually this was because the publication did not include basic details such as the number of animals in each group (115 publications), the observed variance (592) or suitable control data (49). For each category of outcome I found evidence of a substantial publication bias. Interventions were most commonly administered on or before the induction of EAE with shorter times to treatment associated with higher estimates of efficacy for the reduction in mean severity scores (a neurobehavioural outcome). Treatment related effects were found to vary across different outcome measures with the largest effect being for the reduction in axon loss. Where neurobehavioural scores and axon loss were measured in the same cohort of animals, the concordance between efficacies in these increased with later times to treatment.

Conclusions: In this, the largest systematic review and meta-analysis of animal studies in any domain, I have found that a large number of publications present incomplete data. In addition, measures to reduce bias are seldom reported, the lack of which is associated with overstatements of efficacy for both a measure of drug efficacy in EAE and experimental PD studies. Translational success may have also been affected by the majority of studies administering drugs on or before EAE induction which is of limited relevance in the clinical setting where patients do not present at that stage of disease. Moreover, my analysis of the relationship between outcome measures provides empirical evidence from systematically identified studies to suggest that targeting axon loss as later time points is most strongly associated with improvements in neurobehavioural scores. Therefore drugs which are successfully able to target axon loss at these time points may offer substantial hope for clinical success. Overall, improvements in the conduct and reporting of preclinical studies are likely to improve their utility, and the prospects for translational success. While my findings relate predominately to the animal modelling of MS and PD it is likely that they also hold for other animal research.

Declaration

I hereby declare that all of the material presented in this thesis is my own work. Contributions made by others are stated in the relevant sections of this thesis.

This thesis has not been submitted for any other degree or qualification.

Signed..... Date……..

Publications arising from the work presented in this thesis

ROOKE, E.D.M., VESTERINEN, H.M., SENA, E.S., EGAN, K. J. & MACLEOD, M.R. 2011. Dopamine agonists in animal models of Parkinson's disease: A systematic review and meta-analysis. Parkinsonism & Related Disorders, 17, 313-320.

VESTERINEN, H.M., SENA, E.S., FFRENCH-CONSTANT, C., WILLIAMS, A., CHANDRAN, S. & MACLEOD, M.R. 2010. Improving the translational hit of experimental treatments in multiple sclerosis. Multiple Sclerosis Journal, 16, 1044-1055.

VESTERINEN, H.M., EGAN, K., DEISTER, A., SCHLATTMANN, P., MACLEOD, M.R. & DIRNAGL, U. 2011. Systematic survey of the design, statistical analysis, and reporting of studies published in the 2008 volume of the Journal of Cerebral Blood Flow and Metabolism. Journal of Cerebral Blood Flow and Metabolism, 31, 1064-1072.

VESTERINEN, H.M., SENA, E.S., EGAN, K.J., HIRST, T., CURRIE, G., ANTONIC, A., HOWELLS, D.W. & MACLEOD, M.R. Meta-analysis of data from animal studies: a practical guide. *Under review.*

VESTERINEN, H.M., SENA, E.S. & MACLEOD M.R. The prevalence and impact of study quality, publication bias and incomplete reporting in experimental autoimmune encephalomyelitis. *Under review.*

VESTERINEN, H.M., SENA, E.S. & MACLEOD M.R. The relationship between treatment related effects on neurobehavioural and histological outcomes in EAE: a systematic approach to regression and path analyses. *Manuscript in preparation.*

Acknowledgements

I am extremely grateful to Malcolm Macleod for giving me this opportunity which has been so rewarding, for excellent supervision, for always having an answer for my most difficult questions, and for continually reminding me that data *are* plural.

Emily Sena, I am grateful for all of the following and more: word of the day, semi-colons, correcting my split infinitives, and for hosting such good parties. Thank you especially for reading and re-reading my manuscripts, proof reading this thesis and for all of the many hours spent teaching me how to use the database, run analyses, etc... I couldn't have got through this PhD without this support. The benchmark of publishing 18 manuscripts during a PhD was too much to match, but was inspirational nonetheless.

This PhD was funded by the Centre for Clinical Brain Sciences PhD scholarship, and part of the research was funded by the Multiple Sclerosis Society of Great Britain. The financial support is much appreciated. In addition I am grateful to the following: my second supervisor, Anna Williams for sharing her expertise on EAE and MS; Kieren Egan for sharing the highs and lows of doing a PhD and for the fun we had at two conferences in Barcelona; Siddharthan Chandran and Charles ffrench-Constant for helpful discussions; Aidan Hutchison for teaching me to use Microsoft Access and for fixing it every time I broke it; Deirdre Beecher and Filippino Graziella from MS Cochrane; Professor Martino for kindly letting me observe the EAE experiments in his lab and to all the people that made my stay in Milan so enjoyable; Helen Cullion, Rachel Burrow, Judi Clarke, the interlibrary loan staff and Chris Mathews.

Finally I would also like to thank: my family for continual support; Gareth Williams, Alex Urquhart-Taylor and Samantha "boftastic" Capewell for sharing sport, fun and general merriment over the last few years; Rebecca Pottinger for continual encouragement; and Lucille Tong for her unreserved support which was especially appreciated in the final year of this PhD.

Abbreviations

ALoss	Axon loss
BBB	Blood brain barrier
CFA	Freunds complete adjuvant
CIS	Clinically isolated syndrome
CNS	Central nervous system
CSF	Cerebrospinal fluid
CSLD	Clinical score on the last day of assessment
Demy	Demyelination
DMT	Disease modifying therapy
DNA	Deoxyribonucleic acid
DV	Dependent variable
EAE	Experimental autoimmune encephalomyelitis
EBV	Epstein Barr virus
EDSS	Expanded disability status scale
ELISA	Enzyme linked immunosorbent assay
ES	Effect size
FACS	Fluorescence-activated cell sorting
GA	Glatiramer acetate
GCP	Good clinical practice
GLP	Good laboratory practice
GWAS	Genome wide association studies
HLA	Human leucocyte antigen
ICH	Intracerebral haemorrhage IFN
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
Inflm	Inflammation
IQR	Interquartile range
IV	Independent variable
JCBFM	Journal of Cerebral Blood Flow and Metabolism
L95% CI	Lower 95% confidence interval
MA	Meta-analysis
MBP	Myelin basic protein
MCCS	Mean clinical and cumulative score

MDi	Difference in means
MHC	Major histocompatibility complex
MOG	Myelin oligodendrocyte glycoprotein
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSS	Mean severity score
Neuro	Neurobehavioural scores
NMD	Normalised mean difference
NMO	Neuromyelitis optica
PD	Parkinson's disease
PLP	Proteolipid protein
PML	Progressive multifocal eukoencephalooathy
PPMS	Primary progressive multiple sclerosis
PRMS	Primary relapsing multiple sclerosis
RCT	Randomised control trial
RRMS	Relapsing remitting multiple sclerosis
SD	Standard deviation
SE	Standard error
SMD	Standardised mean difference
SNP	Single nucleotide polymorphism
SPMS	Secondary progressive multiple sclerosis
SR	Systematic review
tPA	Thrombolytic plasminogen activator
Treg	Regulatory T cells
U95% CI	Upper 95% confidence interval

Contents

List of Figures

List of Tables

1. Introduction

> "After what precedes, need I detain you long over the question of treatment? The time has not yet come when such a subject can be seriously considered. I can only tell you of some experiments which have been tried the results of which have, unfortunately, not been very encouraging" (Jean-Martin Charcot on the treatment of multiple sclerosis, 19th century).

Multiple sclerosis (MS) affects over 2.5 million individuals worldwide and is the leading cause of disability in young and middle aged adults in the developed world. Of concern is that for such a devastating and life altering disease there are just a few clinically available interventions, none of which are able to reliably alter disease progression. With this in mind it could be argued – with perhaps a little less pessimism – that Charcot's statement could well be mistaken for a description of treatments written in the 21st century.

Descriptions of MS possibly date back as far as the fourteenth century but it was only described and named in the terms we understand it today by French neurologist Jean-Martin Charcot in 1868 (Murray, 2009). Described then as "sclerose en plaques" based on Charcot's observations of post-mortem brains from patients with paraplegia, he noted disseminated scars or "plaques" (lesions) of the nerve sheaths (before the official discovery of myelin by Rudolf Virchow) in the central nervous system (CNS). From the earliest descriptions it took another three centuries to gain a more accurate perspective of the disease pathophysiology; for example an early hypothesis was that suppression of sweat was to blame (Putman, 1938) and the earliest treatments were most likely ineffective and/or potentially toxic, including for example bleeding, arsenic or chloroform (Murray, 2009).

Currently the life expectancy of an MS patient is 5-10 years less than a non-affected individual (Compston and Coles, 2008). Despite this however, 50% of patients are unable to perform household or employment tasks after 10 years, and 50% are nonambulatory after 25 years (Trapp and Nave, 2008). As many as 50% also suffer depression, have a lower quality of life, and have an increased risk of both suicidal

ideation and suicide compared to the general population (Feinstein, 2002, Feinstein, 2011, Feinstein, 1997, Wynia et al., 2008).

The list of potential symptoms suffered by MS patients is extensive. They manifest as a result of inflammation and compromised axons, predominately in the white matter of the CNS which results in partial to complete loss of signal conduction in the affected axons. The location and extent of this pathology determines the range and severity of clinical symptoms which include, but are not limited to, muscle weakness, stiffness, painful spasms, loss of vision, loss of balance and/or limb coordination, cognitive disruption (dementia, attention deficits), fatigue, chronic pain, bladder and/or bowel dysfunction, erectile dysfunction, speech disruption and temperature sensitivity, (Compston and Coles, 2002).

1.1. Problem statement

Experimental autoimmune encephalomyelitis (EAE) is the most commonly used animal model of MS. A vast number of treatments are considered to have shown promise in EAE; however, few have successfully translated from bench to bedside (Sriram and Steiner, 2005). As I will describe in this introductory chapter, there have been numerous failed clinical trials, and the long term efficacy of all clinically available interventions has been questioned.

The problem I aim to address in this PhD thesis is whether we can explain some of this limited clinical success through a robust analysis of the supporting preclinical literature using systematic review and meta-analysis.

1.2. Multiple Sclerosis

1.2.1. The clinical course and diagnosis of MS

There are four clear patterns (courses) in the presentation of clinical symptoms of MS over the lifetime of the disease (Figure 1.1) (Lublin and Reingold, 1996, Compston and Coles, 2008). *Relapsing remitting MS* (RRMS) is the most common course, affecting

approximately 80% of patients, and is characterised by periods of remission between relapses, the duration of which can vary considerably between individuals. Many years of RRMS may pass, but in time approximately 65% of patients begin to steadily decline with no further periods of remission in a disease course known as *secondary progressive MS* (SPMS). *Primary progressive MS* (PPMS) is less common, affecting approximately 10% of MS patients, and is characterised by a steady decline from onset of symptoms until death. Finally, *progressive relapsing MS* (PRMS) affects approximately 5% of patients and is characterised by a progressive disease course from the onset with periods of increased symptoms which then improve.

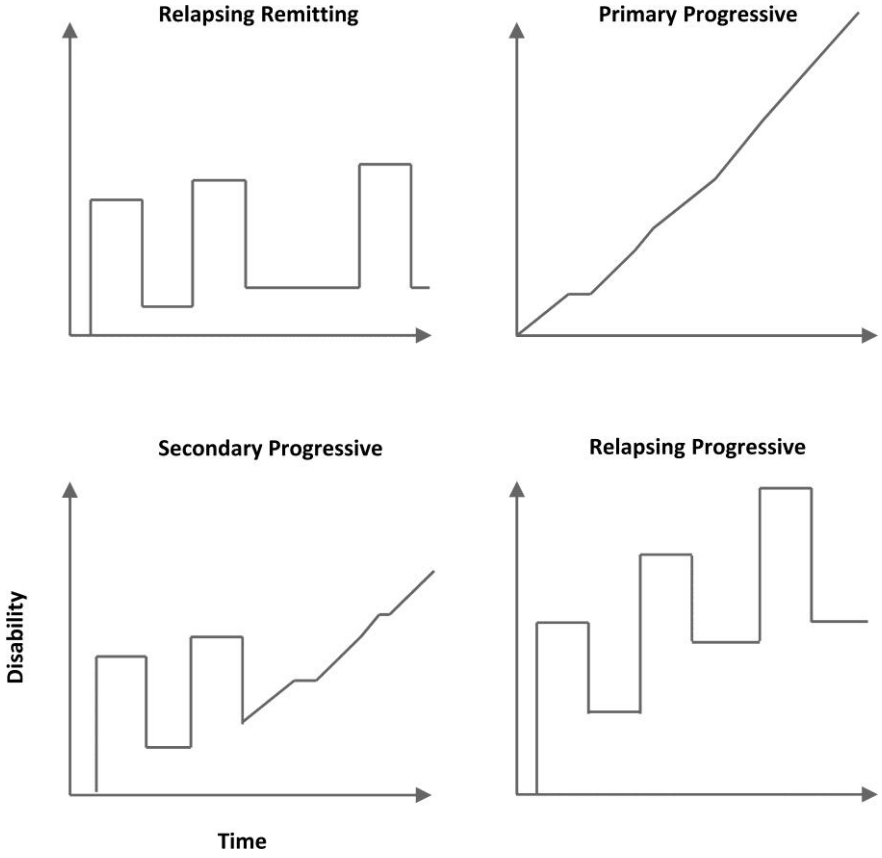


Figure 1.1. The four typical presentations of clinical disease severity in MS.

MS is a disease which typically strikes in young people. The median age of onset for RRMS patients is in the late twenties, although primary progressive MS typically begins a decade later. Different clinical courses are also associated with different sex ratios; RRMS patients are roughly twice as likely to be female as male but this ratio declines with progressive forms of the disease (Confavreux and Vukusic, 2006).

The clinical diagnosis of MS is not always straight forward. A combination of clinical and paraclinical parameters may be used to try and differentiate MS from a number of diseases which manifest with similar signs and symptoms, including for example autoimmune (e.g. Srjögen syndrome), psychiatric (e.g. somatisation disorder) or vascular diseases (e.g. spinal vascular malformation) (Rolak and Fleming, 2007). As such, diagnosis depends on the demonstration of lesion dissemination in space (i.e. within the CNS) and time (i.e. monophasic or multiphasic disease course) as well as the exclusion of other diseases. The task of a neurologist is to assess both the risk of presenting with further episodes (a diagnostic criterion for MS), and to predict the prognosis, thus determining how aggressive any treatment strategy should be (Miller et al., 2005, Thrower, 2007).

Diagnostic criteria for MS were introduced in the 1960's to aid clinicians and standardise the diagnosis (Schumacker et al., 1965). In the early 1980's the Poser criteria described four diagnostic categories: clinically definite MS; laboratory supported definite MS; clinically probably MS; and laboratory supported probable MS (Poser et al., 1983). The more recent McDonald criteria[1] were introduced to try to cut down on the number of misdiagnoses and are now the gold-standard diagnostic tool for patients who present with a typical clinically isolated syndrome (CIS), an acute or sub-acute episode of neurological disturbance which 85% of MS patients first present with (McDonald et al., 2001, Polman et al., 2011, Miller et al., 2005, Miller et al., 2012). The McDonald criteria also take into account the more recent advances in diagnostic tools (e.g. magnetic resonance imaging; MRI) and simplified the diagnosis into three categories: MS; possible MS; and not MS.

Patients can be diagnosed on clinical presentation alone, but paraclinical tests are recommended to aid diagnosis when there are strong suspicions of MS but the McDonald criteria are not completely met. MRI has become an important paraclinical diagnostic tool with 95% of patients showing some white matter abnormalities

[1]The first edition of the McDonald criteria were published in 2001 and aided in earlier diagnoses with a high degree of sensitivity and specificity. The criteria were updated in 2005 and 2011. The latter edition is a simplified version which preserves diagnostic sensitivity and specificity and helps to differentiate between MS of neuromyelitis optica (NMO) and NMO spectrum disorders. The criteria are relevant to patients who present with a typical CIS or symptoms suggestive of CNS inflammatory demyelinating disease.

(Compston and Coles, 2008). Moreover, MRI is a strong predictor for the conversion of CIS to clinically definite MS which can be crucial for early diagnosis and treatment (Barkhof et al., 1997, O'Riordan et al., 1998). There are no known specific blood biomarkers which can confirm the diagnosis of MS, but the presence of oligoclonal bands or elevated immunoglobulin G (IgG) in the cerebrospinal fluid (CSF) are strongly linked with MS (though not specific) and can thus also be used to aid diagnosis (Link and Huang, 2006, Tintore et al., 2008). A reduction in evoked potentials, suggestive of axon damage, is indicative of MS and is a feature in even the earliest stages of disease pathology (Trapp et al., 1998).

1.2.2. Aetiology: nature versus nurture

The aetiology of MS is not known. It is almost universally accepted that there is an interplay between genetic and environmental factors, although the extent of their individual roles is still a major source of debate (Hutchinson, 2011).

Whilst it might be more straightforward to try and treat a disease after we have established its cause, this is unfortunately not a luxury that has been afforded to the MS drug research community. In the following two sections I will briefly describe some of the theories on the aetiology of MS in order to further place into context the complex nature of MS.

1.2.2.1. Environment factors

A number of non-inheritable factors have been proposed to explain the aetiology of MS with some of the strongest clues coming from epidemiological studies (for review see: Ascherio and Munger, 2007a, Ascherio and Munger, 2007b, Ramagopalan et al., 2010). Geographically we know that MS is relatively rare in Asia and Africa but common in the US, Europe, New Zealand and parts of Australia (Milo and Kahana, 2010, Rosati, 2001), and it is rarer in the tropics and subtropics of all continents (Ascherio and Munger, 2007a). Up until recently MS was also found to be more prevalent with higher latitudes (Simpson et al., 2011) both above and below the equator (Compston and Coles, 2008), but this is a trend which may be disappearing due to the increased prevalence in lower latitude regions (Alonso and Hernan, 2008). The relative lack of MS in warmer climates

led to the hypothesis that the risk of MS increased with vitamin D deficiency from a lack of sunlight (Goldberg, 1974, Ascherio et al., 2010). Specifically it is thought that vitamin D may interact with, and alter the expression of a gene with known association to MS susceptibly (HLA-DRB1; see section 1.2.2.2) (Ramagopalan et al., 2009). As an intervention, vitamin D has been shown to be effective as an adjunct to another disease modifying therapy (Soilu-Hanninen et al., 2012). However, evidence of efficacy from vitamin D supplementation (as an individual therapy) in large, high quality clinical trials has yet to be established, with inconclusive results from smaller studies (Kampman et al., 2012, Mosayebi et al., 2011).

Epidemiological differences have also led to the hypothesis that MS is caused by a wide-spread pathogenic infection which confers protection against MS if the individual is infected in early childhood, but causes MS if it is contracted at a later age (Hernan et al., 2001, Alvord et al., 1987, Ascherio and Munger, 2010). This idea was termed the *hygiene hypothesis* because areas with greater hygiene are more strongly linked to a higher prevalence and incidence of MS. In support of the hygiene hypothesis there is a plethora of evidence linking MS to contraction of the Epstein Barr Virus (EBV) (Levin et al., 2010, Ascherio and Munch, 2000, Sumaya et al., 1980), which the majority of people in developing countries are infected with in the earliest years of life. In fact over 90% of the worldwide population become infected (Cohen, 2000), and it is therefore thought that later age of infection is a risk factor for EBV causing MS. Advocates for the role of infection in MS aetiology also suggest links to a rarer pathogen that is more common in regions of high MS prevalence (Kurtzke, 1993), or infection with pathogens such as the Human Herpes Virus 6 (HHV6s) or chlamydia pneumonia (Sriram and Steiner, 2006, Fainardi et al., 2008, Bagos et al., 2006, Swanborg et al., 2003).

Although it cannot explain the latitude difference in the epidemiology of MS, cigarette smoke has also been hypothesised to increase the risk of disease (Hedstrom et al., 2011, Sundstrom et al., 2008, Handel et al., 2011). Moreover, there is evidence both supporting and refuting the idea that cigarette smoke is associated with an increased risk of transition from relapsing-remitting MS to secondary progressive MS (Hernan et al., 2005, Koch et al., 2007), and it offers a novel, albeit incomplete, hypothesis for the skewed sex ratio in MS prevalence (Palacios et al., 2011).

1.2.2.2. Genetic factors

Early indications for the role of genetic susceptibility in MS came from observations of greater prevalence in relatives (Robinson, 1929). The familial risk of MS is as much as 300 times greater in monozygotic twins and 20-40 times greater in a biological first degree relative (Ebers et al., 1995). However, these observations alone are insufficient to determine the extent to which environmental sharing plays a role.

In the early 1970's the association between the human leucocyte antigen (HLA) region of the major histocompatibility complex (MHC) to diseases with a known genetic susceptibility was discovered. In fact the first associated diseases were with coeliac disease (Falchuk et al., 1972) and psoriasis (Russell et al., 1972), and since then almost all autoimmune diseases have been associated with loci of this region (Svejgaard, 2008). MS is most strongly associated with allelic variation in the HLA class II region, although the class I region has also been recently implicated (for a recent review see Gourraud et al., 2012). Carrying the HLA DRB1*1501 haplotype has been suggested to increase the risk of developing MS by an odds ratio of 3.08 (Sawcer et al., 2011) which provides the strongest genetic link to MS susceptibility identified so far.

The major breakthrough in genetic epidemiology came when it became affordable to screen thousands of single nucleotide polymorphisms (SNPs), leading to the development of genome wide association studies (GWAS). This approach was used to identify the first non-HLA region genes associated with MS. These were the interleukin 7 receptor alpha (IL7Rα) and IL2Rα (Hafler et al., 2007), and since then over 50 associated loci have been identified in this manner (Gourraud et al., 2012). However, it has also been suggested that GWAS are prone to bias such as being underpowered (Elbers et al., 2009, Pluzhnikov et al., 2010, Zhong and Prentice, 2008, Ioannidis, 2008). Attempts have been made to address these concerns in future studies but nonetheless results should be interpreted with some caution (Pearson and Manolio, 2008, Laurie et al., 2010).

1.2.2.3. Interplay between environment and genetic factors

Migration studies have afforded invaluable insights into the potential roles of genes and environment in MS aetiology. As already mentioned, there are regions of high and low MS prevalence and incidence. Interestingly, if an individual moves from a high risk area to a low risk area, the risk decreases; however, moving in the opposite direction, from low risk to high risk does not result in an increased risk of MS. Moreover this protection from MS is unfortunately not conferred to that individual's child, as their risk is equal to the overall risk for that area (Ascherio and Munger, 2007a). Both the hygiene hypothesis and genetic factors go some way to explain the lack of change in risk from low to high risk areas; however both fall short in explaining how individuals migrating from a high to low risk area have a decreased risk. If infection at a young age confers protection, moving to a "less hygienic" area should increase the risk of MS if the migration occurred after infancy; and likewise, if genetics are the sole cause of MS, migration should not affect the risk.

It is clear that MS cannot be explained in full by any individual risk factor. What is *known* is that genetics play a role in predisposing some individuals to MS and some environmental factor(s) can trigger the onset of MS. What *is not known* is which environmental factors, alone or combination, are vital, associated or merely coincidental; and how allelic variation contributes to disease aetiology.

1.2.3. Pathology and Disease Mechanisms

MS is driven by a complex relationship between inflammation and neurodegeneration in the CNS. More recent advances in imaging techniques have allowed us to probe deeper into the CNS. In turn this has led to novel insights such as the extent of atrophy in the grey matter, when before MS was widely regarded as a disease of the white matter (Dalton et al., 2004). Despite these advances however, the underpinnings of MS remain an enigma. Importantly, there are both subtle and stark differences in the pathophysiology and pathology within and between patient populations with a particular clinical course. Current research is no doubt aided by a greater – albeit not complete – knowledge of some of these differences, which include for example,

different lesion pathology (described below) and patients either being interferon-beta (IFN-β) responders or non-responders (Killestein and Polman, 2011).

1.2.3.1. Pathology

The pathological hallmark of MS is the presence of demyelinating, inflammatory lesions occurring both within the white and grey matter of the CNS. Axon loss is considered the cause of permanent disability (Trapp et al., 1999) and occurs within the setting of acute demyelinating lesions or chronic demyelination (Ferguson et al., 1997). Myelinated axons conduct fast and efficient electrical impulses via sodium channels at the nodes of Ranvier (saltatory conduction). As myelin is lost, sodium channels are redistributed, but this process is not sufficient and conduction velocity reduces. Moreover, chronic demyelination renders axons vulnerable to immune cell attack and/or neurodegeneration. Axons become transected and eventually fully degenerated, leading to complete loss of impulse conduction, and the subsequent neurological deficits. Symptomatology therefore depends on the location of lesions within the CNS.

1.2.3.2. Mechanisms of damage

In the past it was considered that the CNS was immunologically inert and separated from the immune cells of the periphery by the tightly controlled blood brain barrier (BBB) in a state called “immune privilege”. We now know that the immune cells of the periphery actively engage with the CNS and can cross the BBB but that their action within the CNS is tightly controlled by the microenvironment and resident regulatory cells of the CNS. In MS there is a breakdown of the BBB which may allow immune cells to freely enter the CNS either as, or becoming, auto-reactive cells to self-myelin antigens, and may result in dilution of the aforementioned immunosuppressive environment (Galea et al., 2007). The precise trigger and order of events is unknown, however autoimmune responses may occur through mechanisms such as molecular mimicry, bystander activation and/or epitope spreading (Fujinami et al., 2006), or as a result of neurodegenerative processes (Zipp and Aktas, 2006, Trapp and Nave, 2008). The immune cells which invade the CNS are thought to include Th17 cells which produce IL17 cytokines, and/or Th1 cells which produce IFN-gamma. Perhaps due to disruption of the regulatory processes in specific areas of the brain, which would

usually prevent autoimmune responses, these cells are able to unleash their repertoire of pro-inflammatory reactions in localised areas in the CNS (lesions).

Lesions are characterised by distinct areas of acute inflammation. Four distinct lesion patterns have been described based on macrophage and T cell involvement with or without antibody or compliment deposition, how well the lesion edge is defined and the extent of oligodendrocyte death (Lucchinetti et al., 2000).

One of the major areas of debate surrounding MS pathophysiology is the relationship between inflammatory and neurodegenerative processes in the CNS. It seems clear that inflammation plays an important role in the pathogenesis of the disease; however it remains unclear whether inflammatory processes are the primary factor in subsequent demyelination and axon loss, or whether inflammation is secondary to neurodegenerative processes (for two comprehensive reviews see Trapp and Nave, 2008, Peterson and Fujinami, 2007). To add to this complex "chicken and egg" scenario, we do not know to what extent these processes interact beyond the primary cause including the extent to which inflammatory cells play a detrimental and protective role in axon survival (Peterson and Fujinami, 2007).

1.2.3.3. Mechanisms of repair

The spatial pattern of destruction in the CNS and the physical symptoms of MS are defined by the interplay between mechanisms of damage and repair (Stadelmann and Bruck, 2008). Anti-inflammatory processes, including the removal of myelin debris and recruitment of M2 macrophages and regulatory T-cells (Treg), lead to the acute inflammatory phase fading. In terms of actual repair, one such mechanism is remyelination by the recruitment of mature oligodendrocytes in the white matter of the CNS. This generates new myelin sheaths for exposed, demyelinated axons (Franklin and ffrench-Constant, 2008, Franklin and Kotter, 2008). Remyelination efficiency appears to differ amongst individuals and is therefore difficult to quantify collectively, however estimates suggest that in 20% of patients their lesions will remyelinate extensively, and that it also occurs in progressive forms of the disease (Patrikios et al., 2006). Remyelinated lesions are called shadow plaques – so called because although the new

myelin sheaths restore sufficient conduction velocity to potentially allow the patient to function normally, they are both shorter and thinner than the lost myelin that they replace. Thus in RRMS the temporal pattern of remission corresponds to the anti-inflammatory processes initially, and then remyelination and the subsequent resolution of saltatory conduction. Over time remyelination becomes less efficient and eventually fails, ultimately leading to the prolonged exposure of axons to an inflammatory environment. Furthermore the longer axons are exposed, the greater the risk of attack by immune cells, or degeneration, which ultimately leads to the increasing permanent disability.

1.2.3.4. Pathophysiology of the clinical disease course

Complex pathophysiology translates to a heterogeneous disease course. The most obvious indication of this is the differences in clinical presentation between RRMS and progressive forms of the disease. A fundamental pathological hallmark which defines the differences between these subtypes is the accumulation of neurodegeneration, and beyond a certain threshold the patient transitions to a progressive disease course (Figure 1.2). Likewise, in PPMS, neurodegenerative processes are prominent from the start of the disease and have been likened to SPMS with an amputated relapsing remitting phase (Compston and Coles, 2008).

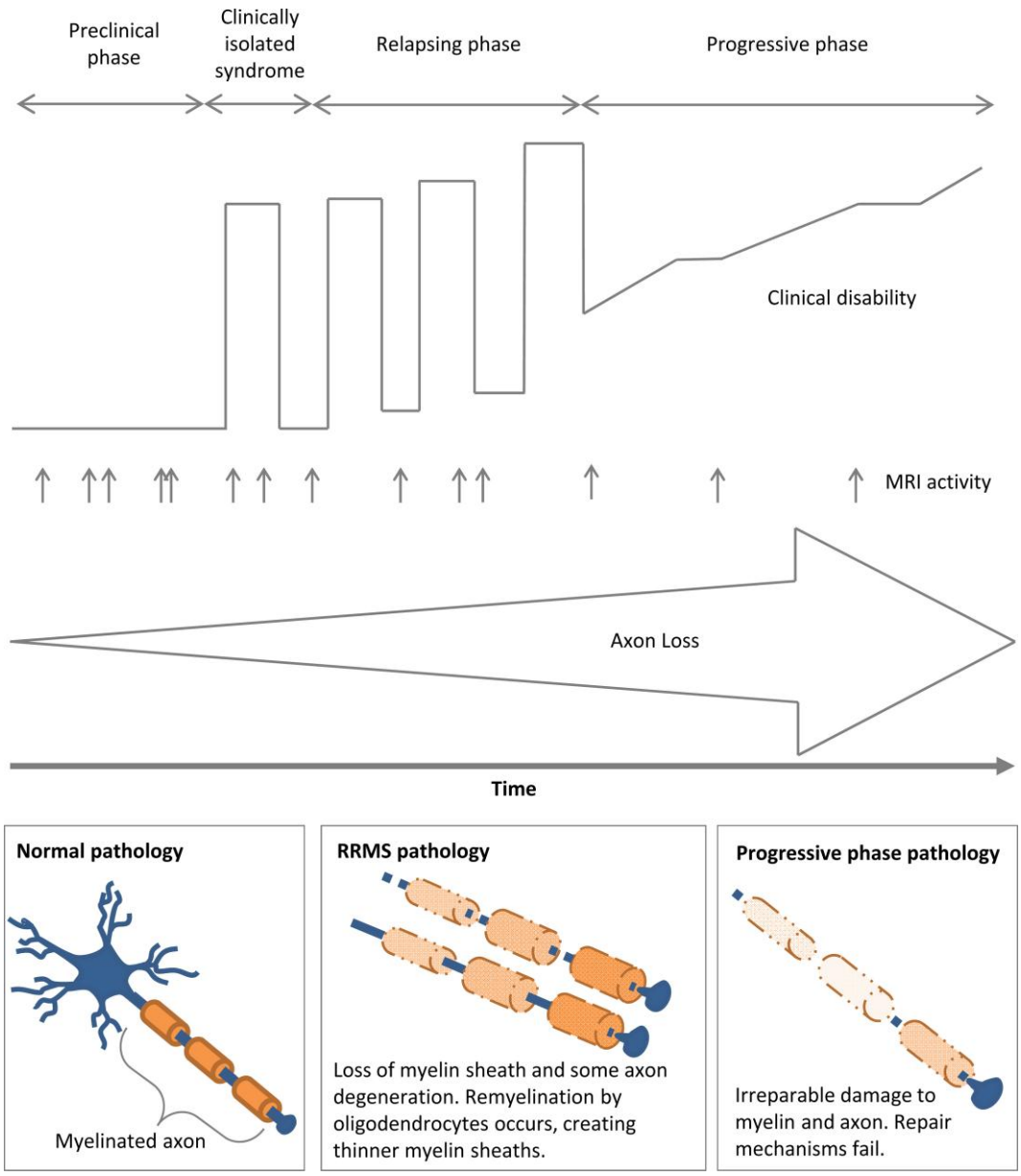


Figure 1.2. A typical clinical course of MS showing the transition from the preclinical to a progressive phase over time. From left to right the lower panels represent: the pathology of a normal axon; the degeneration of myelin and the axon during the relapsing-remitting phase of disease; and the axon loss that occurs during the progressive phases of disease including SPMS and PPMS. The arrows beneath the clinical course represent MRI positive activity, and the large arrow represents the increase in axon loss over time.

1.2.4. Treatment strategies

1.2.4.1. Current treatment strategies

Since the first descriptions of MS, the arsenal of treatment strategies has reflected the evolution of theories on its pathogenesis and pathophysiology. In the earliest era of MS therapeutics these included vomiting (to treat a suspected blood toxin), quinine or arsenic therapies and a range of equally forbidding therapies in between (Murray, 2009). All of the currently approved interventions which could reasonably fall under the category of "disease modifying therapy" (DMT), rather than symptom management, reflect the discovery of the role of inflammation and autoimmunity in MS. The first of these was IFN-β-1b (Betaseron®) which was approved in 1993. This was followed by the approval of IFN-β-1a (Avonex®) in 1996, glatiramer acetate (GA; Copaxone®) in 1997 and a second formulation of IFN-β-1b (Rebif®) in 1998. The next decade saw the approval of mitoxantrone (Novantrone®) in 2000 which was the first intervention for SPMS (this is not licensed for use in MS in the UK but is widely used). A monoclonal antibody to integrin 4, natalizumab (Tysabi®) was approved in 2004 but removed in 2005 following safety concerns and subsequently re-introduced in 2006 under strict guidance on its use. Finally, in 2010 the first oral intervention for RRMS, fingolimod (Gilenya®), was FDA approved[2].

1.2.4.2. Evidence of efficacy

The clinical success of the aforementioned DMTs has been variable. GA was introduced to the drug market amidst a great deal of expectation and hype. Chemically, GA is a random copolymer of myelin basic protein (MBP) and was therefore initially used in the laboratory to try and induce EAE by eliciting an autoimmune response (reflecting the theory of MS being autoimmune mediated). Surprisingly, treatment of animals with GA rendered them resistant to further attempts to induce disease via the typical method (fragments of, or whole MBP; see section 1.3.1); possibly by mechanisms such as immune tolerance (Racke et al., 2010). However, a systematic review of its use in randomised control trials (RCTs) suggests that it is only marginally effective in reducing relapse rate in RRMS patients, and has no discernible effect in progressive

[2]Approved for use in the European Union in 2011 although use is dependent on specific licensing within each country. Approved for use in England and Wales in 2012 but currently not available in Scotland.

forms of the disease (La Mantia et al., 2010). On the other hand, the interferons and natalizumab have shown significant benefit in reducing annualised relapse rate in RRMS patients (Nikfar et al., 2010, Oliver et al., 2011, Hutchinson et al., 2009, Rudick et al., 2006). However, natalizumab as a monotherapy has also been found to have no impact on the progression of disease as measured by a change in the expanded disability status scale (EDSS) (O'Connor et al., 2004) although it is currently being trialled in SPMS (Biogen Idec., 2012). A systematic review of mitoxantrone found evidence of moderate efficacy in reducing progression of relapsing and progressive forms of the disease (Boneschi et al., 2005). However the use of mitoxantrone has been limited to secondary progressive MS and worsening RRMS due to the potential for serious adverse side effects (see next section). The newest addition to the clinically approved interventions, and the first oral intervention, fingolimod has also shown promise in short term RRMS studies (Kappos et al., 2006, Kappos et al., 2010, Devonshire et al., 2012).

A challenge for clinicians is weighing up the benefits versus the risk of adverse events for the DMTs, which are extensive and include for example flu like symptoms and injection site reactions. However, the most serious adverse effects are linked to the three interventions which could also be considered the most powerful disease modifiers, mitoxantrone, natalizumab and fingolimod. The first evidence for the serious implications of applying a strong immunomodulator in MS came from a phase III clinical trial on combination treatment with natalizumab and IFN-β-1a (Kleinschmidt-DeMasters and Tyler, 2005). Three patients developed progressive multifocal eukoencephalopathy (PML), a rare and often fatal neurological disease (Rudick et al., 2006, Kleinschmidt-DeMasters and Tyler, 2005). PML is caused by the JC virus which is commonly harboured by humans, but while this is successfully kept in-check by the immune system in most individuals, treatment with natalizumab (most often as a monotherapy) allows this to manifest in the CNS. Approximately 1 in 500 patients on this treatment develop PML. Those with the highest risk are JC positive, have previously taken immunosuppressants and have had prolonged treatment with natalizumab (Bloomgren et al., 2012).

1.2.4.3. The therapeutic gap

All of the clinically available DMTs, bar mitoxantrone, are aimed primarily at treating RRMS, although mitoxantrone was also used for this patient group. However, even in these patients neurodegeneration may continue whilst the disease is clinically silent. It was not until the end of the last century that we learnt the importance of axon loss in disease progression and crucially it is this pathological hallmark that no intervention has been shown to reliably target in long term, high quality clinical trials. Whereas RRMS patients therefore have a handful of DMTs available to them, there is no treatment available for patients with progressive forms of the disease. If we take the estimate that 65% of patients with RRMS will transition to SPMS, and that 10% begin with PPMS, roughly 75% of all MS patients currently have, or will have very few treatment options. If in fact MS is a primary neurodegenerative disease (or has an element of this) it is perhaps no wonder that the plethora of immunomodulatory drugs have little benefit beyond the short term relief of acute inflammation in RRMS.

1.2.4.4. Is there a failure to translate efficacy?

With every relative success in the clinic, there has been a host of failures; either due to a lack of efficacy or serious adverse effects (for review see: Meuth et al., 2010, Ulzheimer et al., 2010, Ziemssen, 2008, Chan and Gold, 2007). The key question is why these failed to show efficacy after promising preclinical tests, and whether these adverse effects might have been predicted.

Clinical trials should be conducted based on reliable evidence from animal studies, or from other clinical trials which are themselves based on reliable evidence from animal studies (Figure 1.3). Reliable animal studies are those which are of low risk of bias, are pragmatically designed to reflect what is achievable in the human disease, use a sample size large enough to obtain statistical significance, and have a replicable study design. Literature on drug efficacy tested in preclinical models of focal-ischaemia, glioma, intracerebral haemorrhage and Alzheimer's disease have shown that this is not always the case (Perel et al., 2007, Egan et al. (under review), Hirst et al., 2012).

There are three broad explanations for the failure to translate efficacy from animals to humans: (1) efficacy was understated in clinical trials (falsely negative); (2) efficacy was overstated in the animals model (falsely positive); or (3) the animal model did not replicate robustly the human disease. Beyond the biological differences between animals and humans (point 3), or even between EAE and MS, a number of tools have emerged which have afforded us novel insights into the reasons for the lack of clinical trial success. Namely these are systematic review and meta-analysis which are described in detail in section 1.4.1.

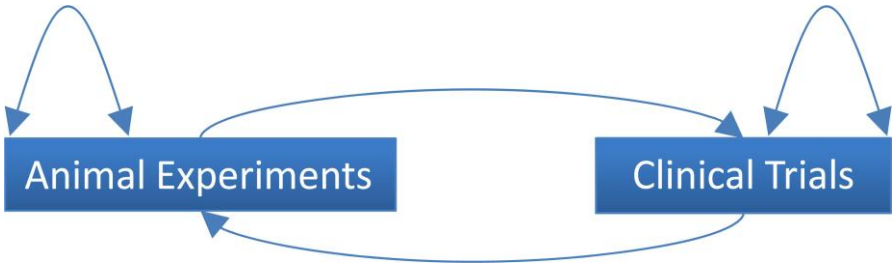


Figure 1.3. The relationship between clinical trials and animal experiments. Clinical trials should be based on reliable evidence from animal experiments; observations from clinical trials can likewise be used to inform the design of further animal studies; and clinical trials can be based on other high quality clinical trials of other diseases where they have shown sufficient evidence of safety and efficacy; and animal studies can be used to inform further animal studies.

1.3. Animal models of MS

To our knowledge, MS is a uniquely human condition. Being such a complex disease, it is of little surprise that there is a repertoire of animal models available which are designed to mimic the different hypotheses on its aetiology and pathophysiology, and which can be used to test potential therapeutics. Animal models of any human disease are important tools in translational research. Models of MS are also particularly critical for assessing the pathology and pathophysiology at various stages of the disease as we currently have no way of predicting who will develop MS (and even if we did, obvious ethical reasons preclude conducting a biopsy on them). Moreover, on the rare occasions that biopsies have been done on patients with established MS, they typically represent a chronic, burnt-out phase of the disease, although actively demyelinating lesions have also been seen (Lucchinetti et al., 2000).

There are four broad ways to model MS which are toxin, virus, transgenic or autoimmune based and each of these have advantages and disadvantages for studying different aspects of MS (Table 1.1). The latter, commonly known as experimental autoimmune encephalomyelitis (EAE), is the most commonly used model of MS and also the main focus of this thesis. However, as I will describe below it is also the most widely debated over its utility as a model to identify suitable drugs for clinical use.

Model	Description
Viral	Viral models include Theiler's murine encephalomyelitis virus (TMEV) and murine hepatitis virus (MHV). These are useful models of autoimmunity triggered by a virus which reflects the corresponding hypothesis in humans.
Toxin	Toxin models commonly include lysolecithin (an activator of phospholipase A2) or cuprizone (a copper chelator). Not a model of MS as a whole, but rather a model of focal demyelination and remyelination.
Transgenic	Spontaneous development of EAE-like pathology. Typically generated on the C57BL/6 background and so the disease course is characteristic of this strain (monophasic with poor recovery).
Autoimmune	EAE is the most common animal model of MS. See section 1.3.1 for details.

Table 1.1. Describing the broad animal models of MS. (For a comprehensive overview, see Lavi and Constantinescu, 2005)

1.3.1. Experimental autoimmune encephalomyelitis

> "The most disappointing aspect of EAE as a potential model for MS is its almost total inability to point toward a meaningful therapy or therapeutic approach for MS" (Sriram and Steiner, 2005)

Over the past decade the usefulness of EAE has been criticised, no doubt because of the frustrating lack of successful clinically available DMTs which have emerged from its use. The question therefore is whether these criticisms are valid. In this section I will provide a brief history of EAE and its pathophysiology, and summarise some of the currently held views on its utility in translational research.

EAE was born out of the accidental discovery in the 1920s that the myelin antigens in rabies vaccinations could sometime cause "paralytic accidents" in humans (Stuart and Krikorian, 1928) which was later attributed to the fact that repeated injection of brain tissue might have caused an allergic reaction. Thomas Rivers was the first to formally generate the EAE model, which was initially created in monkeys (Rivers et al., 1933). Over the next decade some fine tuning was required – mostly with the co-use of Freunds adjuvant that enabled a reduction in the number of injections of myelin antigen from up to 85 over a year to a single injection (Kabat et al., 1947, Van Epps, 2005). EAE has thus had over 8 decades worth of model-refinement and research into pathophysiology and pathology – both of the model itself and the human disease, and as a tool in translational drug research.

EAE cannot accurately be described as one model, but rather represents a spectrum of MS-like diseases because each individual species and strain reacts differently, and not always subtly, to the immunogenic agents used to induce disease (Gold et al., 2006). Typically there are two methods to induce EAE. *Active EAE* is induced by injection of whole CNS antigens or their fragments (including myelin basic protein (MBP), proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG)) mixed with adjuvant (Freunds complete adjuvant; CFA) into the periphery. In the induction phase of active EAE, peripheral antigen-specific T-cells become activated and proliferate in the lymph nodes. In the subsequent effector phase, the autoreactive T-cells migrate to the CNS where they encounter their specific myelin antigen, causing autoimmune damage and clinical signs. The second method, *passive EAE*, models the effector phase in isolation from the induction phase. Autoreactive T-cells, typically taken from the peripheral lymph nodes, of EAE donors are adoptively transferred to naive recipients. Passive EAE is useful for being largely reproducible as it bypasses the often-variable and strain specific induction phase. However, the actual rate of successful induction for

both active and passive EAE is dependent on a number of factors such as any infections in the animal house, the dosing regime, the background strain and the researchers ability to successfully administer the immunogens.

Within individual strains and the specific method used to induce disease, the course of EAE is largely predictable in animals that are successfully induced (Gold et al., 2006). The symptomatic correlate to the effector phase is called the prodromal phase, during which time the animal continues to appear normal. This is typically followed by weight loss and ascending paralysis starting at the tail tip, and EAE is commonly assessed on an ordinal scale (e.g. from 0=healthy to 5 or 6=death) which resembles the 10 point EDSS in human clinical trials. In some EAE models the animals may rapidly progress to a paralytic state (acute EAE), or they may spontaneously recover from clinical signs, or develop chronic paralysis (chronic EAE), or they may develop a relapsing remitting disease course (Wekerle, 2008).

In human MS, the role of B cells, T cells, innate and adaptive immunity and processes of neurodegeneration, amongst others, are becoming better defined (for a useful review see Mix et al., 2010). EAE is generally considered to be mediated by CD4+ Th1 cells (Damsker 2010), however roles for other immune cells, particularly Th17 have been extensively researched and debated (Koenders 2010). Adding to the complexity of EAE is the need to understand how and why different species and strains react uniquely to each induction method. Moreover, none of the models successfully recapitulate the full complexity of the human disease, but each one has similarities and differences in terms of pathophysiology, pathology and clinical course (Gold et al., 2006).

The value of EAE has been questioned. It has been used specifically in the development of four clinically available interventions: glatiramer acetate, mitoxantrone, natalizumab and more recently fingolimod. However, these relative success stories are balanced somewhat by the large volume of failed clinical trials after reported success in EAE (Chan and Gold, 2007). There is no shortage of opinion on why EAE has not always been successful in identifying clinically useful interventions. Proposed reasons for the discrepancies include: genetics (species differences, peculiarities of inbred animal strains), pathogenics (individual variability between MS patients) and kinetics

(different ontogeny and biorhythms, temporal differences of immune reactivity and response to therapy) (Mix et al., 2010); difficulties in choosing the correct dosing regimen which meets the fine balance between efficacy and safety (Steinman and Zamvil, 2006); differences in the immune system of human and murine animals and the inadequacies in modelling such a complex disease using one animal model (Wekerle, 2008). Finally it has been said that:

> "the reasons for this failure are not only, as shown here, that MS and EAE differ quite substantially, but also that even from the larger, more comprehensive picture, most of the evidence suggests that the EAE models do not reflect the pathology of a progressive disorder as MS. Moreover, the various EAE models are dissimilar in their pathology and immunology to such an extent that it is unclear why one EAE model will be better served than another" (Sriram and Steiner, 2005).

Interestingly, questions have also been asked about experimental design and interpretation including whether the choice of model for the human condition contains the answers, and whether there are inadequacies in the execution of studies or the treatment and interpretation of data (Bolton, 2007). Research on the biological underpinnings of this complex translational issue is not complete, but is nonetheless extensive (Denic et al., 2011, Mix et al., 2010). However it is interesting that the adequacy of EAE trial design has until recently received less attention.

1.4. Systematic review and meta-analysis

As we are faced with ever increasing literature on interventions for diseases in the life sciences, so too is there an increasing need to be able to critically appraise the literature and weigh competing evidence. Systematic review is a tool to identify and summarise all of the available research on a specific research question to allow the wider research community to make informed decisions from the best available evidence. Meta-analysis is often applied to data identified in a systematic review; it is the statistical aggregation of data from relevant publications identified in the systematic review.

1.4.1. Systematic reviews

Reviews are necessary to summarise the available information on any given topic. For some topics, the volume of available information can be gargantuan. To date, Pubmed holds over 21.5 million records (data accessed on May 20th 2012) dating from 1809 to 2012. Moreover, in 2012 alone, 690 of these have "multiple sclerosis" in the title. Thus keeping up to date on a field of research can be an almost impossible task without reviews of the relevant literature.

Traditionally reviews are narrative, where the author can choose which literature to include and how to summarise the information. Narrative reviews can be particularly prone to bias because the author may choose only the literature which supports his/her own views. Moreover, even authors with no vested interest in the conclusions of a review can be subject to bias (Antman et al., 1992). Consequently systematic reviews are becoming increasingly popular. The most recent published audit in 2007 suggested that there is an estimated annual publication rate of 25,000 systematic reviews (Moher et al., 2007). In a more recent study, a random sample of 1000 publications taken from Pubmed, 1% were systematic reviews (Baginskaitė, 2012).

A systematic review involves applying scientific, reproducible and transparent methodology to the selection, critical appraisal and synthesise of all the available primary research which is relevant to a specific research question (Cook et al., 1997, Greenhalgh, 1997). Systematic reviews are not immune to bias, but their purpose is to try and minimise it. The methods should be included with the review, allowing the reader to cast judgement on the efforts made to avoid bias. To aid in this task, systematic reviews have been subject to the same scrutiny as many other areas of research, namely in the form of field-specific reporting guidelines (the PRISMA statement, Moher et al., 2009; discussed in more detail in Chapter 4). Additionally systematic reviews are most often treated as pieces of original research (Meerpohl et al., 2012) and therefore should include criticisms and their limitations in the discussion (Alexandrov, 2004).

1.4.2. Meta-analysis

A systematic review without the statistical aggregation of data is often called a *qualitative* systematic review; and with the statistical aggregation of data it is called a *quantitative* systematic review or more commonly, a *meta-analysis*. Meta-analyses in the life sciences are commonly used to try and identify consistencies amongst treatment effects (source of homogeneity), as well as sources of variation between treatment effects (heterogeneity). Fundamental to the practice of conventional meta-analysis however is identifying the information which will be most beneficial to clinicians, for which meta-analysis has played a role in changing clinical practice (Lau et al., 1992).

Systematic reviews and meta-analyses of clinical data typically involve selecting the best available evidence – that is data from *all* randomised controlled trials (RCTs). The endpoints for analysis can be, for example, those which are deemed clinically relevant to the patient subpopulation for which evidence of efficacy is being sought. Pooling these data together gives a global estimate of efficacy, which in itself is only meaningful if an assessment is made to estimate whether there is substantial heterogeneity (Thompson, 1994). However, when an assessment of heterogeneity is conducted, and potential sources of it are identified, meta-analyses can give invaluable insights into, for example: whether the treatment works under any condition in the patient subpopulation of interest (e.g. SPMS rather than RRMS); whether different study design paradigms increase the chances of positive findings (e.g. intravenous injection rather than oral administration); or whether there is a dose response (e.g. is a "high" dose significantly more beneficial than a "low" dose); and whether a particular drug is beneficial at for example improving one outcome measure with no effect on another.

Meta-analysis is not considered a novel practice. The first is cited as having been conducted by Karl Pearson in 1904 (O'Rourke, 2007). However, meta-analysis has only become widely recognised within the last few decades. In part, this wider recognition must be attributed to the inspiring work of Iain Chalmers who set up and established the *Cochrane collaboration*[3] (www.cochrane.org). In 2004 alone this worldwide

[3] Named after Archie Cochrane, a British physician and epidemiologist. His influential book "*Effectiveness and Efficiency: Random Reflections on Health Services"* described the importance of evidence from RCTs and the lack of reliable evidence on which many common healthcare

collaboration published over 100 systematic reviews (Moher et al., 2007) representing nearly half of the total number published.

Secondary analyses of clinical trial datasets have allowed the identification of methodological shortcomings in clinical trials. Because similar approaches to understanding shortcomings in *in vivo* experiments were plausible, the Collaborrative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies[4] (CAMARADES; www.camarades.info) was set up to conduct systematic reviews and meta-analyses of preclinical research. This was to see if these experiments hold any of the clues to translational failures and/or the conditions under which translation is most likely to occur sucessfully. These approaches have led to a clinical trial of hypothermia in patients with focal ischaemia, based on the best available evidence of efficacy from animal models (van der Worp et al., 2007, van der Worp et al., 2010b, Macleod et al., 2010).

To date CAMARADES have conducted reviews on experimental models of stroke, glioma, Alzheimer's disease, Huntington's disease, and bone cancer induced pain. The original focus for the collaboration was the translational failures in focal ischaemia, for which there are only four available treatments for patients: rehabilitation, hemicraniotomy or pharmacologic treatment with either aspirin or thrombolytic plasminogen activator (tPA) (Khaja and Grotta, 2007). Interestingly, a systematic review of the interventions tested in animals and/or humans identified that of 1026 interventions tested in either animals and/or humans, 17 had only been tested in humans (O'Collins et al., 2006). Moreover, for 51% of the 114 drugs tested in humans, the first report of its clinical use was published before the first report of its use in a focal ischemia model of stroke. This suggests that animal data are not always used to inform the design of clinical trials.

---

interventions were based. His work and vision is seen as pioneering in the development of evidence based healthcare practices.

[4] The "S" in the acronym CAMARADES originally represented "stroke" until 2007 when work begun on Parkinson's disease and multiple sclerosis. It was subsequently changed to represent "studies" and since then the group has conducted reviews on an increasing number of disease models.

The importance of adequate internal validity of a study, that is measures to reduce bias such as random allocation to group and blinded assessment of outcome, are well documented in the clinical literature (Gluud, 2006). This has led to the development of reporting guidelines (CONSORT statement, Begg et al., 1996) which have had at least some positive impact on the quality of clinical trials (Hopewell et al., 2010). However these factors have been shown to be true of the experimental literature also. Consistently it has been found that publications which do not report these measures to reduce bias tend to over-estimate efficacy (van der Worp and Macleod, 2011). Such information has in turn led to the development of reporting guidelines for the preclinical literature (ARRIVE guidelines, Kilkenny et al., 2011), and the establishment of organisations to oversee the proper conduct of animal research including the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs; *www.nc3rs.org.uk*).

1.5. Aim and objectives

As I have described in the preceding sections, MS is a devastating disease, and perhaps understandably because of its complex nature, one which is difficult to treat. Systematic review and meta-analysis have emerged as useful tools in both the clinical and preclinical literature to understand translational failures and so I have adopted these methods to try and provide further insights into the translational failure from EAE studies to clinical trials.

The aim of this PhD was to provide an unbiased summary of the scope of the literature on candidate drugs for MS tested in EAE to identify potential reasons for the failures to translate efficacy to clinical trials. Specifically my objectives were, across all of the identified literature, to: (1) describe the reporting of measures to reduce bias and to assess their impact on measures of drug efficacy (Chapter 3); (2) assess the prevalence and impact of any publication bias (Chapter 3); (3) compare findings from the above with another disease with limited translational success (Parkinson's disease, PD; Chapter 4); (4) assess all of the literature in one volume of a leading journal to assess the study quality and reporting across a broader field of research (Chapter 5); and (5) assess the relationship between treatment related effects measured using different outcome measures in EAE (Chapter 6).

In addition I set out to describe the differences between common methodologies used in meta-analysis using data from my analyses (Chapter 7) and to describe my experience of trying to use systematic review and meta-analysis of the preclinical EAE literature alongside evidence from clinical trials to identify putative drugs to take forward to a clinical trial of SPMS (Chapter 8).

1.6. Hypotheses

My hypothesis is that systematic review and meta-analysis will identify areas for further improvement in the use of EAE as a therapeutic tool in MS research. In particular, I hypothesise that the EAE literature is prone to the same biases and limits to efficacy - associated with compromised internal and external validity - as identified in other disease models.

2. Methods

By convention I predominately use the pronoun “we” throughout this thesis. Specific contributions from others are detailed in each results chapter.

As part of this PhD I refined the methodological approach to the estimation of normalised mean difference (NMD) effect sizes (section 2.2.2i) to be more appropriate for data reported from animal experiments and so I have provided a detailed description of these calculations. For the purpose of continuity the same detail is given to the calculations for standardised mean differences (SMD) effect sizes (section 2.2.2ii). Less detail is given to other approaches where the methodology is well established and applied unchanged to animal data.

2.1. Systematic Review

The aim of a systematic review is to summarise all of the relevant literature on a particular topic of interest. Systematic reviews should therefore have transparent, reproducible methodology and every effort should be made to reduce selection bias.

2.1.1. Electronic search

A thorough search strategy was formulated to identify relevant publications for each research question, details of which are given in the relevant results chapter of this thesis. Up to three online databases were searched: Embase, ISI Web of Knowledge and Pubmed. Results were downloaded onto Reference Manager (Version 11) and duplicate entries (from multiple online databases) were deleted.

References were screened by two reviewers against pre-specified inclusion and exclusion criteria (described in each results chapter), with the exception of the updated EAE literature review which was screened by one reviewer. We reviewed titles and/or abstracts or the full PDF if further investigation was required. Electronic PDFs were obtained for publications which met the inclusion criteria. Where articles could not be obtained electronically or as hard-copies via The University of Edinburgh, they were

obtained via inter-library loan. There were no language or date restrictions on any search.

2.1.2. Data Extraction

All data were extracted onto the CAMARADES data-manager, a centralised Microsoft Access database (2003 version). The CAMARADES data-manager was originally developed to collate data on animal models of stroke. As part of this PhD, I modified and enhanced the data-manager to support the collation of data from publications describing other animal models including EAE.

Where relevant outcomes were expressed graphically, we measured data using digital ruler software (Universal Desktop Ruler).

2.1.3. Methodological Quality

Each publication reporting animal experiments was assessed against a pre-specified study quality checklist, amended from (Sena et al., 2007a). The quality checklist for animal studies included: (1) being published in a peer reviewed journal; and the reporting of: (2) random allocation to group; (3) blinded assessment of outcome; (4) a sample size calculation; (5) compliance with animal welfare regulations; and (6) a statement of a potential conflict of interest.

We separately noted whether blinded assessment of outcome was for neurobehavioural and/or histological outcome. Each checklist item was awarded one point except where publications reported either one or both of the blinded assessment of neurobehavioural and histological score where one point was awarded in total.

Details for the assessment of the quality of human clinical trials are given in Chapter 8.

2.2. Meta-Analysis

Meta-analysis involves the calculation of an *effect size* for each *comparison* which are subsequently aggregated into one *global estimate* or into two or more subgroups, hereafter referred to as *strata* (Section 2.3.2, Figure 2.1).

Throughout this thesis, the following terminology is used when referring to meta-analysis: *raw data* are the mean and variance reported in a publication; a *comparison* refers to the raw data when extracted from a control and treatment group for an outcome measure in the format suitable for, and contributing to, the meta-analysis; an *outcome measure* refers to the test used to determine effect size such as neurobehavioural score, axon loss, inflammation or demyelination; an *effect size*, for the purposes of this thesis, refers to the magnitude of the difference between the outcome in the control and treatment group; and a *global estimate* is the aggregated, weighted average calculated in a meta-analysis.

For the purposes of this thesis the term *effect size* is only used to represent the magnitude of the difference between a treatment and control group. To avoid repetition of this term, I use the term *efficacy* in the context of the global estimate and this does not have any relation to the use of this term in pharmacology.

The following steps outline the methods we used to conduct a meta-analysis and explore sources of heterogeneity (section 2.3). Table 2.1 outlines the notation used in the following equations and Figure 2.1 summarises the methods.

Notation	Corresponds to
$\bar{x}_c$	Mean in the control group
$\bar{x}_{rx}$	Mean in the treatment group
$\bar{x}_{Sham}$	Mean in the sham group
n_c	Number of animals in the control group
n_{rx}	Number of animals in the treatment group
$\mathbf{n}_c'$	True number of control animals
N	Total number of animals (Equation 2.2)
SD_c	Reported or calculated standard deviation in the control group
SD_{rx}	Reported or calculated standard deviation in the treatment group
SE_c	Reported standard error in the control group
SE_{rx}	Reported standard error in the treatment group
S_i	Pooled standard deviation for Hedge's *G*
$Direction$	A multiplication factor (see Table 2.2).

Table 2.1. The notation used in the formulae to calculate effect sizes.

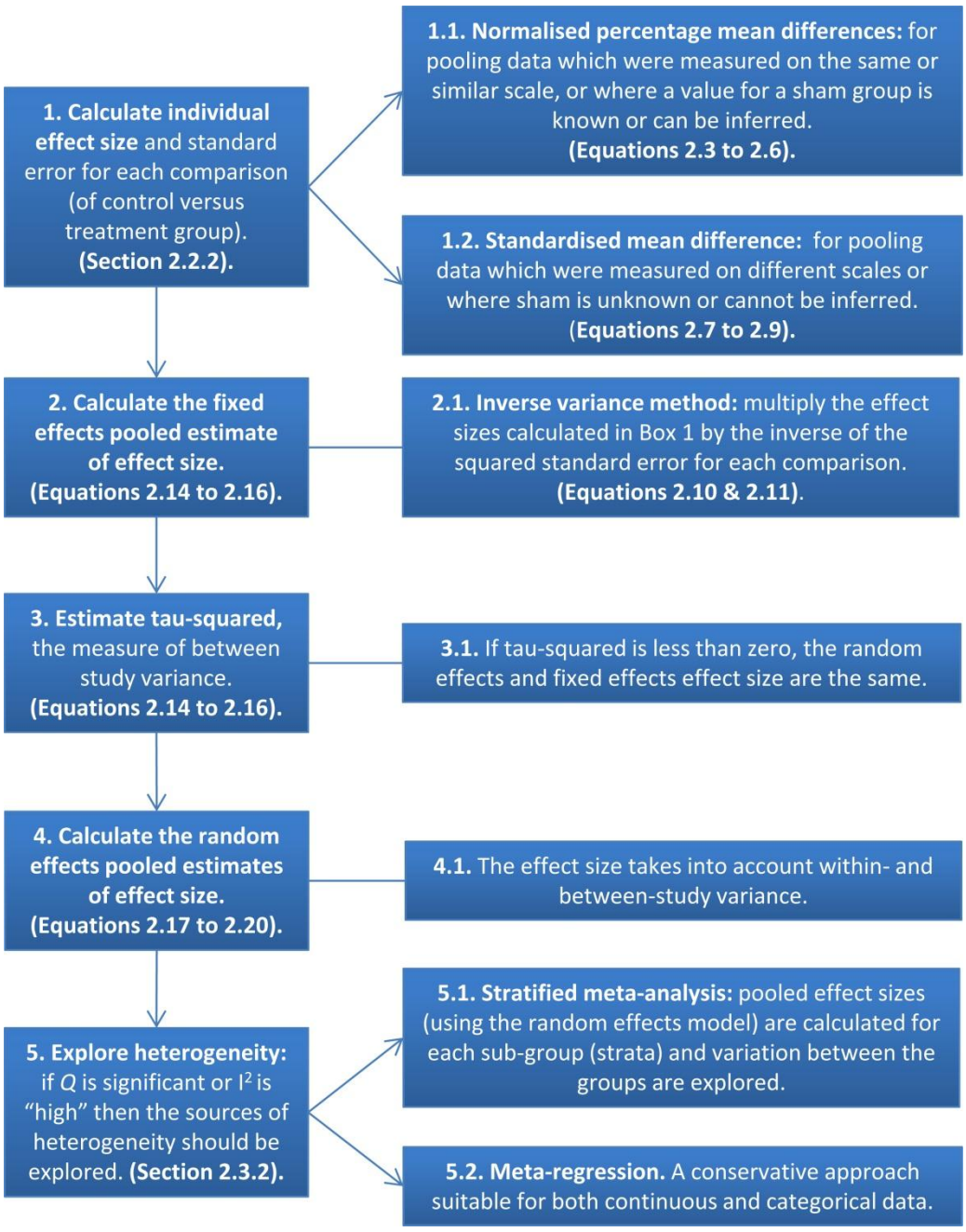


Figure 2.1. A flow diagram, starting from top left, to show the methods we used to calculate and aggregate effect sizes and explore sources of heterogeneity.

2.2.1. Calculating the total number of animals used.

The number of animals per group contributes to the measure of precision of the global estimate of efficacy in a meta-analysis. Since a control group can serve more than one treatment group, the number of animals in the control groups was adjusted to avoid giving undue weight to that study in the meta-analysis (Equation 2.1). Thus for each

outcome extracted and included in the meta-analysis, a value for the number of treatment groups served by that control group was also extracted.

Equation 2.1. $$n_c' = \frac{n_c}{\text{Treatment groups served by one control}}$$

Where n_c' refers to the true number of control animals.

The total number of animals (N) for the comparison is calculated as shown in Equation 2.2.

Equation 2.2. $$N = n_{rx} + n_c'$$

2.2.2. Effect size calculation

There are three broad methods to calculate effect sizes on continuous data: raw difference in means, normalised mean difference (NMD) and standardised mean difference (SMD). For the data described in this thesis it was only appropriate to use NMDs or SMDs (see Chapter 7). For a comprehensive overview of other calculation methods which are outside the scope of this thesis both Egger et al (2001) and Borenstein et al (2009) provide excellent resources.

i. Normalised mean difference

Where data exist on a ratio scale (that is, where the score that would be achieved by a normal, untreated, unlesioned "sham" animal is known or can be inferred), we can express the absolute difference in means as a proportion. We calculate the absolute difference between outcomes for each of the control and treatment groups and outcome in sham animals (Equation 2.3); and we express the effect size as the

difference between these two values expressed as a proportion of the larger of the two5 (Equation 2.4 to Equation 2.5).

Equation 2.3. $|\bar{x}_c - \bar{x}_{sham}|$ and $|\bar{x}_c - \bar{x}_{sham}|$

If $|\bar{x}_c - \bar{x}_{sham}| > |\bar{x}_{rx} - \bar{x}_{sham}|$, we use the formula;

Equation 2.4. $$ES_i = 100\% \times \frac{(\bar{x}_c - \bar{x}_{sham}) - (\bar{x}_{rx} - \bar{x}_{sham})}{(\bar{x}_c - \bar{x}_{sham})} \times direction$$

Or if $|\bar{x}_{rx} - \bar{x}_{sham}| > |\bar{x}_c - \bar{x}_{sham}|$, we use the formula;

Equation 2.5. $$ES_i = 100\% \times \frac{(\bar{x}_{rx} - \bar{x}_{sham}) - (\bar{x}_c - \bar{x}_{sham})}{(\bar{x}_{rx} - \bar{x}_{sham})} \times direction$$

For individual comparisons where the variance was reported as a standard error (SE), these were converted to standard deviations (SD; Equation 2.6).

Equation 2.6. $$SD = SEM \times \sqrt{n}$$

The raw standard deviations were also normalised to the same denominator used in the effect size calculation (Equation 2.4-Equation 2.5).

[5] This calculation is based on previously described methods for the meta-analysis of animal experiments (MACLEOD, M. R., BRISCOE, C. L. & SANDERCOCK, P. A. G. 2005a. Systematic review and meta-analysis of the efficacy of tPA in experimental stroke. *Journal of the Neurological Sciences,* 238**,** S73-S73. As part of this PhD I modified this calculation to account for the substantial variation in metrics used to measure the raw data. The previous method did not adequately take into account situations in which the treatment and/or control group performed "better" than the sham group. Additionally, for very precise studies, the effect size tended towards infinity. This new calculation generates effect sizes which lie between -100% to +100%, unless either one or both groups perform better than the sham group in which case the effect size can be higher or lower.

Thus if $|\bar{x}_c - \bar{x}_{sham}| > |\bar{x}_{rx} - \bar{x}_{sham}|$, we use the formulae;

Equation 2.7. $$\mathrm{SD}_{C*} = 100\% \times \frac{SD_c}{\bar{x}_c - \bar{x}_{sham}} \quad \text{and} \quad \mathrm{SD}_{rx*} = 100\% \times \frac{SD_{rx}}{\bar{x}_c - \bar{x}_{sham}}$$

Or if $|\bar{x}_{rx} - \bar{x}_{sham}| > |\bar{x}_c - \bar{x}_{sham}|$, we use the formulae;

Equation 2.8. $$\mathrm{SD}_{C*} = 100\% \times \frac{SD_c}{\bar{x}_{rc} - \bar{x}_{sham}} \quad \text{and} \quad \mathrm{SD}_{rx*} = 100\% \times \frac{SD_{rx}}{\bar{x}_{rc} - \bar{x}_{sham}}$$

Finally, the standard error for the effect size, ES_i is;

Equation 2.9. $$SE_i = \sqrt{\frac{\frac{SD_{c*}^2}{n_c'} + \frac{SD_{rx*}^2}{n_{rx}}}{N}}$$

Importantly, in the calculation of this NMD effect size, the value for sham does not provide the direction of the effect (i.e. where a higher score represents a better or worse outcome) and so the effect size needs to be adjusted according to the rules shown in Table 2.2. Specifically, the effect size was multiplied by -1 when either: the control group had a better outcome than the treatment group and where a higher score represented a better outcome; or the treatment group had a better outcome than the control group and where a higher score represented a worse outcome.

Better outcome in?	Higher mean score represents?	Multiply effect size by?
Control group	Better outcome	-1
Treatment group	Better outcome	1
Control group	Worse outcome	-1
Treatment group	Worse outcome	1

Table 2.2. The correction factor used to normalise the direction of the effect size.

Finally, for an NMD to be calculated, the value for sham either had to be reported or able to be inferred. The baseline value can sometimes be inferred using rational scientific reasoning. For example, for neurobehavioural scores measured on a 0-5 scale where 0 represents a healthy animal and 5 represents death, it can be assumed that a sham animal will be graded as 0. This approach was also applied to: any scoring system where the animal was graded on an ordinal scale with 0 representing a healthy animal; for axon loss and demyelination it was assumed that a healthy animal would have no axon loss or demyelination. For inflammatory markers, where these were not measured on an ordinal scale, they were excluded unless a value for a sham animal was reported.

ii. Standardised mean difference

If outcomes are measured on different scales without a value for sham being either reported or able to be inferred, it is not appropriate to calculate NMDs as the baseline to normalise the raw data to is unknown. Instead we can divide the difference in means by a measure of the standard deviation to convert all of the outcome measures onto a standardised scale with units measured in standard deviations. There are three primary methods to calculate a standardised mean difference (Egger et al., 2001): Cohen's *D* whereby the difference in means is divided by the pooled standard deviation of the two groups; Hedge's *G* which is based on Cohen's *D* but includes a correction factor for small sample size bias (cited as being less than ten (Hedges and Olkin, 1985)), and Glass's Delta, whereby the difference in means is divided by the standard deviation of the control group only. To account for potentially small sample sizes used in animal experiments, in this thesis I have only reported effect sizes calculated using Hedge's *G.*

The standardised effect size was calculated using the formula for Hedge's G, shown in Equation 2.10.

Equation 2.10. $$ES_i = \frac{\bar{x}_c - \bar{x}_{rx}}{S_i'} \times \left(1 - \frac{3}{4N - 9}\right) \times direction$$

Where S_i' is the pooled variance, calculated as shown in Equation 2.11, and N is the total number of animals, calculated as described in section 2.2.1. The *direction* factor is as described in Table 2.2.

Equation 2.11. $$S_i = \sqrt{\frac{(n_{c'} - 1)SD_c^2 + (n_{rx} - 1)SD_{rx}^2}{N - 2}}$$

Where the variance of both groups was reported as SEM, they were converted to SDs using the formula in Equation 2.6. The standard error of the effect size was calculated as shown in Equation 2.12.

Equation 2.12. $$SE_i = \sqrt{\frac{N}{n_{rx} \times n_{c'}} + \frac{ES_i^2}{2(N - 3.94)}}$$

2.2.3. Weighting of effect sizes

Effect sizes in a meta-analysis are weighted before aggregation. Without weighting, the global estimate would be a simple average. In this thesis the effect sizes were weighted by the inverse of the squared standard error of the effect size, as shown in Equation 2.13, to give a weighted effect size (QPE_{fixed}) as shown in Equation 2.14.

Equation 2.13. $$W_i = \frac{1}{SE_i^2}$$

Equation 2.14. $$W_i ES_i = ES_i \times \frac{1}{SE_i^2}$$

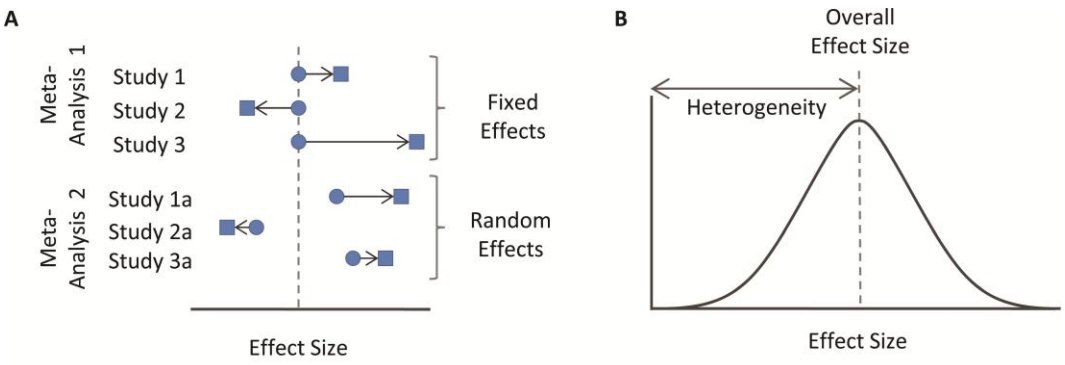
Where ES_i is calculated in Equation 2.7 (NMD) or Equation 2.10 (SMD) and SE_i is calculated as shown in Equation 2.9 (NMD) or Equation 2.12 (SMD).

2.2.4. Aggregating effect sizes (meta-analysis)

Individual effect sizes can be aggregated using either a fixed-effects or random-effects model (Borenstein, 2009). The fixed effects model is used when the underlying (true) effect size (sometimes referred to as the treatment effect in other texts) is assumed to be the same, or *fixed,* across all of the comparisons in the meta-analysis. The true effect size is what we would expect to observe if our sample size were infinitely large so that we have no random sampling error. In practice the true effect size of a study depends on the population sample and so we can expect some variation at least. However, if a meta-analysis is conducted on for example propranolol in an aged population with the same severity of hypertension (our inclusion criteria), we could reasonably assume that the true effect size is similar enough between studies to conduct a fixed effects meta-analysis. With this assumption the *observed* effect sizes vary due to random sampling error alone.

The random effects model is used when we assume that the underlying effect size is different amongst samples in the meta-analysis. A random effects meta-analysis therefore takes into account both the within-study (sampling error) and between-study (differences in the true effect size) variance. If we assume that the effect sizes lie on a normal distribution, the centre would represent the average effect, which in the case of the fixed effects model is the true treatment effect and the width would represent the differences in true effect sizes. This difference is the *heterogeneity* between studies and is represented by tau-squared (τ^2; Figure 2.2).

In this thesis I combined data from a number of different study design paradigms and thus my pre-specified criteria was to use the more conservative random effects model to account for substantial predicted heterogeneity.



C

	Use Fixed Effects Model	Use Random Effects Model
Overall Effect Size	One underlying treatment effect, fixed across all of the samples in the meta-analysis.	More than one true treatment effect.
Heterogeneity	Due to sampling error.	Due to both sampling error and differences between samples.

Figure 2.2. The distribution of effect sizes in a fixed effects and random effects model. (A) The true treatment effect (circles) is either the same amongst all of the comparisons in the meta-analysis or it is different, and the overall estimate (vertical dotted line) will be based on the observed effect sizes (squares) which differ from the true treatment effect due to sampling error within the study. (B) The effect sizes in a meta-analysis are typically assumed to be follow a normal distribution, with the centre representing the global estimate of efficacy (vertical dotted line) and the width representing the between study heterogeneity, tau-squared. The table in (C) shows the interpretation of overall effect sizes and heterogeneity.

The random effects meta-analysis was conducted as follows:

i. Nesting of similar outcomes using a fixed effects estimate

Nesting is a term used to describe the pooling of effect sizes from similar outcomes when they are measured in the same cohort of animals. For example, if the outcome of interest is inflammation, we can make the assumption that the treatment related effects will be sufficiently similar across for example the reduction in both T cells and macrophages and so we nest their effect sizes. Without this assumption, it would be necessary to choose only one of these outcomes for further analysis as animals should not be represented more than once in the same meta-analysis.

The methods to combine these estimates of effect size in the fixed effects model are outlined below, using $ES_{\theta i}$ to represent the fixed-effect effect size for each nested

comparison (Equation 2.15). For the outcomes which we grouped, ES_{θ} for each nested comparison is the sum of the individual weighted effect sizes divided by the sum of the weight which was calculated as shown in Equation 2.13.

Equation 2.15. $$ES_{\theta i} = \frac{\sum_{i=1}^{k} W_i ES_i}{\sum_{i=1}^{k} W_i}$$

Where W_i is calculated using Equation 2.13 and $W_i ES_i$ is calculated using Equation 2.14.

The standard error was calculated as shown in Equation 2.16.

Equation 2.16. $$SE_{\theta i} = \frac{1}{\sqrt{\frac{\sum_{i=1}^{k} W_i}{N_{comparisons}}}}$$

Where $N_{comparisons}$ is the number of observations from the same cohort of animals contributing to the nested estimate of effect size.

ii. Calculate a fixed effects estimate

The nested estimate of effect size, $ES_{\theta i}$ was taken forward to this stage of the analysis. In this model a fixed effects estimate is calculated for the entire population (global) or for each sub-group (strata). Equation 2.13 to Equation 2.16 are essentially repeated using $SE_{\theta i}$ in the new measure of weight (Equation 2.17) by which the nested effect size $ES_{\theta i}$ is multiplied to give a new estimate of effect size (Equation 2.18) with its standard error (Equation 2.19).

Equation 2.17. $$W^* = \frac{1}{SE_{\theta i}^2}$$

Equation 2.18.

$$ES_{fixed} = \frac{\sum_{i=1}^{k} ES_{\theta i} W^*}{\sum_{i=1}^{k} W^*}$$

Equation 2.19.

$$SE_{fixed} = \frac{1}{\sqrt{\sum_{i=1}^{k} W^*}}$$

iii. Calculate τ^2

As mentioned previously, for each outcome measure in a meta-analysis, there is a measure of between-study variation, reflecting the difference between the true treatment effect and the observed treatment effect; and the within-study variation, reflecting the difference between the observed treatment effects across different studies.

Tau-squared (τ^2) is the amount of *between-study* variation in the true effect sizes. If τ^2 is large compared to the within study variance, the global effect will tend towards a simple average. In the calculation of the fixed-effects effect size, the effect size for each outcome measure was weighted by the precision of the estimate, based on the *within-study* variance. In the random effects model, the fixed effects estimate of effect size is again weighted by the precision of the effect size estimate, but this time it takes into account both the within-study variance (SE of the fixed effects estimate) and the between-study variance (τ^2).

The true effect size for an intervention is unknown and so τ^2 cannot be calculated directly. However, it can be estimated using the method of moments (Dersimonian and Laird, 1986) as shown in Equation 2.20.

Equation 2.20. $$\tau^2 = \frac{Q - df}{C}$$

Where τ^2 is the *estimate* of between-study variance, Q is Cochrans Q (Equation 2.21; the sum of the squared differences in effect sizes between studies and the pooled effect size); df is the degrees of freedom (Equation 2.22 and C is a measure used to convert the heterogeneity value into an average rather than a sum of squared deviations, and to put the value back into its original units (Equation 2.23).

Equation 2.21. $$Q = \sum_{i=1}^{k} W^* \left(\mathrm{ES}_{\theta \mathrm{i}} - ES_{fixed}\right)^2$$

Where ES_{fixed} was calculated as shown in Equation 2.18.

Equation 2.22. $$df = k - 1$$

Where k is the number of comparisons

Equation 2.23. $$C = \sum_{i=1}^{k} W^* - \frac{\sum_{i=1}^{k} W^{*2}}{\sum_{i=1}^{k} W^*}$$

iv. Calculate a random effects estimate

To calculate the random-effects estimate of effect size, the nested effect size ($\mathrm{ES}_{\theta \mathrm{i}}$) is first weighted using the measure of within- and between-study variance, as shown in Equation 2.24 and Equation 2.25. Note that if τ^2 is less than zero, the random effects estimate will be the same as the fixed effects estimate.

Equation 2.24. $$W^*_{+\tau^2} = \frac{1}{\left(SE^2_{\theta i} + \tau^2\right)}$$

Equation 2.25. $$ES^*_{random} = ES_{\theta i} \times W^*_{+\tau^2}$$

The final estimate of effect size is calculated as shown in Equation 2.26, with its standard error shown in Equation 2.27 and 95% confidence intervals (95% CI) shown in Equation 2.28

Equation 2.26. $$ES_{random} = \frac{\sum_{i=1}^{k} ES^*_{random}}{\sum_{i=1}^{k} W^*_{+\tau^2}}$$

Equation 2.27. $$SE_{random} = \frac{1}{\sqrt{\sum_{i=1}^{k} W^*_{+\tau^2}}}$$

Equation 2.28. $$95\%\ CI = ES_{random} \pm 1.95996 \times SE_{random}$$

2.3. Heterogeneity

Heterogeneity between studies can be assessed to see if specific factors in the study design can explain variability in effect sizes. To assess the potential sources of heterogeneity, the amount of heterogeneity has to first be calculated (see next section) for which we used two methods: Cochrans Q (hereafter referred to as Q; (Cochran, 1954)) and I^2 (Higgins et al., 2003). To assess whether specific covariates could explain excess heterogeneity (where present) we used two methods: stratified meta-analysis, often referred to elsewhere as sub-group analysis (Borenstein, 2009), and meta-regression (Thompson and Higgins, 2002).

2.3.1. Estimating the amount of heterogeneity

Q is an estimate of the between study heterogeneity which is sensitive to the ratio of the observed variation to the within-study error, rather than their absolute values Equation 2.21). In other words, Q is not affected by the units of the effect size. Q is calculated from the effect sizes in the fixed effect model. If all of the true effect sizes are assumed to be the same, and that any variation is due to sampling error, the expected value of Q is simply the degrees of freedom (Equation 2.22). Assuming also that all comparisons have the same true effect size (the null hypothesis), the values of Q follow a chi-squared distribution with [k (comparisons) minus one] degrees of freedom. Therefore the difference between Q and the expected variation can be tested using the chi-squared test of significance; a significant result indicative of there being differences between the true effect sizes. Importantly, a non-significant value does not indicate that there is one true effect size. Instead, low power within studies (small sample size for the comparisons) and low power between studies (a small number of comparisons contributing to the meta-analysis) may yield a non-significant result.

Q is useful for testing the significance of the difference between true effect sizes, both in a global estimate, and in sub-group analysis (described in section 2.3.2i). However, Q is not an intuitive value and it is sensitive to the number of comparisons. I^2 is a descriptive value, developed to address this issue (Higgins et al., 2003) (Equation 2.29). It reflects the proportion of total variance between studies that is due to true differences in effect sizes as opposed to chance. I^2 lies between 0% (all variation is due to chance) and 100% (all variation reflects real differences between the true effect sizes between studies) and does not depend on the number of comparisons in the meta-analysis.

Equation 2.29. $$I^2 = \frac{Q - df}{Q} \times 100\%$$

2.3.2. Exploring sources of heterogeneity

i. Stratified Analysis

The previous equations demonstrate how to calculate an overall global estimate of efficacy. However, when comparisons from such a wide range of study design paradigms are included in the same meta-analysis, the global estimate of effect size should be interpreted with caution, and be presented along with an analysis of heterogeneity.

The rationale behind a stratified meta-analysis is to assess whether the strata can account for a significant proportion of global heterogeneity. Therefore the random-effects effect size and Q are computed as shown in equations Equation 2.20 to Equation 2.28 for each stratum. For example, if the subgroup under investigation is the route of drug delivery, an effect size and Q is calculated for each individual stratum (e.g. intravenous, intraperitoneal, oral, etc…). It follows that if effect sizes within strata follow distributions around a true estimate which are different from each other, the overall amount of heterogeneity between studies will reduce because the sum of heterogeneity within the components of the strata is reduced (Figure 2.3).

Thus for each subgroup under investigation, we calculated whether it explained a significant proportion of the between study heterogeneity using Equation 2.30 in Microsoft Excel:

Equation 2.30. $$p = CHIDIST(Q_{global} - sum(Q_{strata})), \mathrm{df})$$

Where Q_{global} is the amount of heterogeneity for the global estimate of effect size, Q_{strata} is the amount of heterogeneity within individual components of the strata, and df is the degrees of freedom (the number of components in the strata minus one).

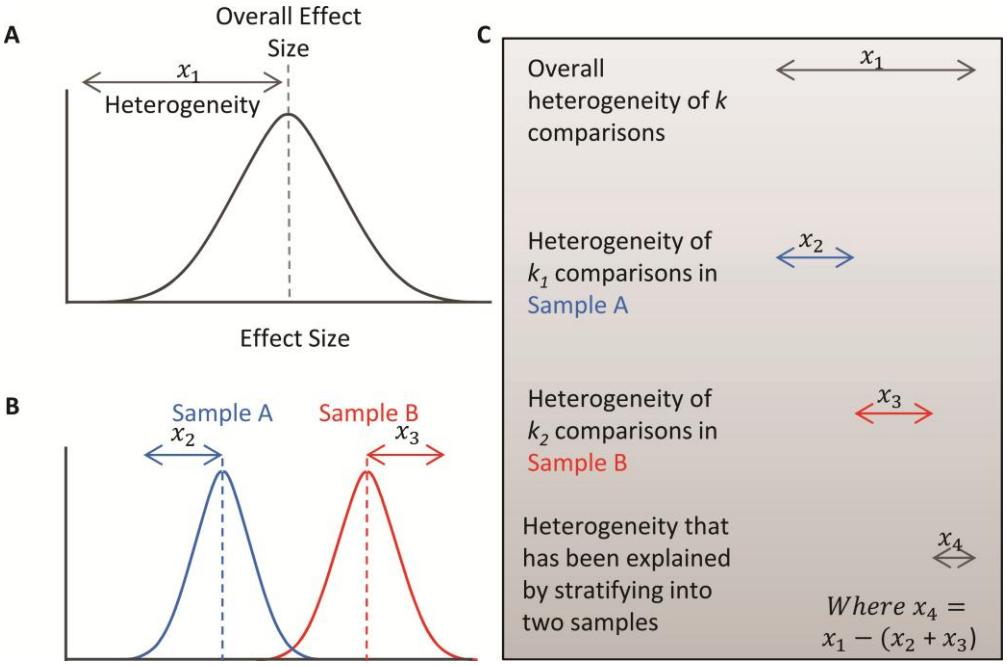


Figure 2.3. The amount of calculated heterogeneity between studies when taking all of the effect sizes together (A), or when splitting the effect sizes into two components of the stratum under investigation, whose effect size distributions centre around different global effect sizes (B); and the method used to calculate the amount of heterogeneity that has been explained by stratification (C).

ii. Meta-regression

Meta-regression takes into account both the between- and within-study variance to assess the relationship between moderator variables (independent variables; IV), such as study design characteristics and the estimates of effect size (dependent variable; DV); (Thompson and Higgins, 2002). The method used in this thesis was the least squares method which is represented by the function *metareg* in Stata (Version 10; Equation 2.31).

Equation 2.31. $$metareg\ DV\ IV, wsse(SE_{Dependentvar})$$

Where DV is the effect size, IV is the moderator variable, wsse($SE_{Dependentvar}$) is the measure of *within-study standard error* which in this case is the standard error for the dependent variable.

Where the independent variable was measured on a continuous scale (for example time to treatment), they were entered directly into the regression analysis. Where the independent variable was a binary or categorical outcome (for example blinded assessment of outcome, route of drug delivery), we converted these to dummy variables using the *tabulate* function in Stata. For *k* dummy variables within the strata, *k*-1 were entered into the regression analysis; the dropped variable being referred to as the reference variable. This avoids perfect collinearity in the model because the effect of the reference variable can be inferred, and is the variable which the others are compared to.

2.3.3. Choosing between methods

In this thesis, we preferentially chose to calculate NMDs where appropriate because the unit of the effect size is intuitive (percentage difference in means), compared to SMDs (standard deviations). Therefore NMDs were calculated if sufficient data for sham was presented; and SMDs were calculated if data for sham was not presented for the vast majority of outcomes. The decision to use either method was made after the data were extracted when it was known which category the majority of data fell into.

For the assessment of heterogeneity we preferentially choose meta-regression as it is the more conservative approach. At the time of analysis of the data from experimental PD studies (described in Chapter 4) meta-regression was not widely available and so we used stratified meta-analysis. Further exploration of the differences between these methods is described in Chapter 7.

2.4. Statistics

When we assessed heterogeneity we adjusted all p-values using Bonferonni correction to take into account multiple comparisons. Specific P values for each analysis are referred to in the methods section of the relevant results chapter.

2.5. Publication Bias

We assessed for publication bias using three methods: (1) funnel plotting (Light and Pillemer, 1984); (2) Egger regression (Egger et al., 1997); (3) and "trim and fill" (Duval and Tweedie, 2000). All three methods were conducted on pre-nested effect sizes. We conducted funnel plotting and Egger regression in Sigmaplot (version 11) using the inbuilt regression function for the latter. We conducted trim and fill analyses in Stata (version 10) and plotted the data in Sigmaplot.

2.5.1. Funnel plotting

Funnel plotting is a visual approach to the assessment of small study bias. Plotting each effect size against the inverse of its standard error (precision) should result in a symmetrical, normally distributed, funnel plot centred on the global effect size. Imprecise studies will represent the base of the "funnel" with more precise studies scattered up to the top of the funnel. If publication bias is present, a right-skewed funnel shape may be observed which is indicative of a preponderance of positive, imprecise comparisons (Figure 2.4). It should be noted that funnel plot asymmetry is not only associated with publication bias, but rather it may highlight other small-study effects. That is, where the result from a small study is inherently different of that from a larger study. These differences may be due to poorer methodological quality in smaller studies (and therefore may report overinflated estimates), citation bias, language bias or true heterogeneity (Egger et al., 1997)

2.5.2. Egger regression

Egger regression was conducted by plotting the effect size for each comparison divided by its standard error (x axis) against its precision. An abundance of imprecise, positive studies is indicated by a regression line crossing the origin above zero on the y axis.

Where effect sizes were calculated as NMDs, the precision was the inverse of the variance (Equation 2.12). Where SMDs were calculated, we noticed the unusual effect whereby there was substantial curved symmetry in the regression plot. This is due to the standardised effect size being constrained to a certain set of values by its sample

size (see Chapter 7 for details). For this reason we used a measure of pooled standard deviation (Equation 2.32) in the formula for precision:

Equation 2.32. $$Calculated\ SD = \frac{SE_{MDi}}{Si \times (1 - (\frac{3}{4N - 9})}$$

Where SE_{MDi} is the standard error of the difference in means, calculated as shown in Equation 2.33.

Equation 2.33. $$SE_{MDi} = \sqrt{\frac{SD_c^2}{n_c} + \frac{SD_{rx}^2}{n_{rx}}}$$

2.5.3. Trim and fill

Trim and fill is a non-parametric approach which makes assumptions based on asymmetry, and also uses a "trim and fill" iterative approach to impute missing studies. This analysis was conducted in Stata version 10 using the *metatrim* command Equation 2.34). The observed and "filled" (missing) values were plotted in Sigmaplot.

Equation 2.34. $$metatrim\ effectsize\ SE_i$$

Where SE_i is the standard error of the calculated nested NMD (Equation 2.9) or SMD (Equation 2.12) effect size.

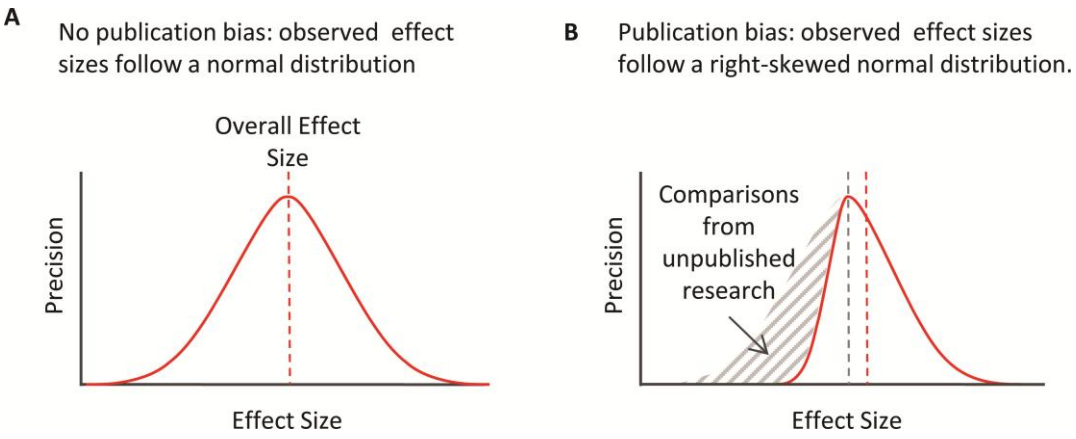


Figure 2.4. The distribution of observed effect sizes in a meta-analysis when plotted against precision (1/SE) if publication bias does not exist (A) or if it does exist (B). In (B) the dashed vertical red (right) and grey (left) lines represent the global estimates of effect size in the presence of publication bias and without publication bias respectively.

3. The prevalence and impact of study quality, publication bias and incomplete reporting in experimental autoimmune encephalomyelitis

I acknowledge the following for their contribution to this research: Malcolm Macleod and Emily Sena for help in the design of this study, Madeleine Hammar for second screening the original dataset, and Siddharthan Chandran, Anna Williams and Charles ffrench-Constant for their helpful comments on the research design and interpretation of the results.

3.1. Background

Only a few interventions tested in EAE have translated into the clinic and moreover, none have shown reliable long term efficacy. Issues relating to the internal and external validity of a preclinical study may compromise its predictive value in translational research. For example, in the preclinical stroke literature, studies of low quality, and in particular where measures to avoid bias are not reported, estimates of efficacy are substantially overinflated (Sena et al., 2007a). In addition, publication bias is prevalent; collectively across systematic reviews of 16 interventions the overall effect size reduces from 31.3% improvement in infarct volume for 1359 experiments to 23.8% with the inclusion of 214 predicted missing studies (Sena et al., 2010). For the same dataset of preclinical stroke studies, issues relating to the external validity were identified including the use of young animals, those without hypertension or those without comorbidities to model a disease which predominately affects an aged, hypertensive population which often have comorbidities (van der Worp et al., 2010a).

3.2. Aims and objectives

Previously systematic review and meta-analysis have provided empirical evidence for issues relating to the internal and external validity of a study. Our aim was therefore to determine whether these were also relevant to the preclinical literature on drugs tested in EAE. Furthermore, issues relating to external validity are considered likely to

be disease specific, and so we set out to determine which, if any, were relevant to the EAE literature. Specifically our objectives were to: (1) systematically describe all available data for any intervention tested in EAE where improvement was measured against change in neurobehavioural outcome, or reduction in inflammation, demyelination or axon loss; (2) describe the prevalence of the reporting and impact of factors relating to internal validity, including random allocation to group and blinded assessment of outcome; (3) assess the external validity of the literature including the effect of time to treatment; and (4) assess the prevalence and impact of any publication bias.

3.3. Methods

3.3.1. Electronic search

We searched Pubmed, ISI Web of Knowledge, and Ovid Embase using the terms ([multiple sclerosis] OR [EAE] OR [experimental autoimmune encephalomyelitis] OR [experimental allergic encephalomyelitis]) AND ([*myelin*] OR [wallerian degeneration] OR [inflammation] OR ([axon*] OR [nerve] AND ([degeneration] OR [loss] OR [regeneration] OR [survival] OR [damage])). We limited the search to animal studies and we imposed no language restrictions.

3.3.2. Inclusion and exclusion criteria

iii. Systematic Review

Publications were included if they reported testing an intervention (including all pharmacologic agents, dietary modifications, stem-cells, irradiation and treatments given in combination) in any *in vivo* animal model of EAE, delivered via any route (including indirectly such as via drinking water) at any stage of the lesion and where outcome was reported as a change in neurobehavioural score, axonal loss, demyelination or inflammation. Publications were excluded if they assessed the effects of environmental enrichment, exercise, stress (including a reduced weaning period) or if they used an animal model of MS other than EAE. Publications which reported the

ability of an intervention administered during pregnancy to the dam on the pups ability to withstand later EAE induction were excluded.

iv. Meta-analysis

We included data from publications where they included the number of animals, the mean score and a measure of variance (standard error (SEM) or standard deviation (SD)) for both an experimental group and control group. Any neurobehavioural outcome reported as mean severity scores, mean clinical score and mean cumulative clinical scores was valid for inclusion. Where data were presented graphically the clinical score on the last day of the treatment was also extracted.

For publications reporting histological data, we included any outcome measured as change in axon loss, demyelination or inflammation where these were measured directly (e.g. macrophage counting, MRI lesion volume); data were excluded where they described indirect measures such as a change in expression of inflammatory markers or findings from FACS or ELISA analysis.

3.3.3. Methodological quality

We assessed the quality of included studies against our six point checklist as described in Chapter 2 (section 2.1.3).

3.3.4. Data analysis

We calculated NMD effect sizes (Section 2.2.2) and pooled these using the random effects model. For neurobehavioural outcomes we combined these into three groups: (1) mean clinical score and mean cumulative score; (2) mean severity scores (mean severity score, the product of mean severity and duration, the product of mean severity plus number of exacerbations; and (3) the clinical score on the last day of assessment. For these three neurobehavioural scores and three histological outcomes we tested any impact of: (i) random allocation to group; (ii) blinded assessment of outcome; (iii) overall quality score; (iv) the number of animals used for that comparison; (v) the time

of administration; (vi) the time of outcome assessment; (vii) the route of delivery; (viii) the animal species; and (x) the sex of the animal. Additionally for histological outcome measures we assessed any impact of the CNS section analysed.

To assess for publication bias we used funnel plotting, Egger regression and trim and fill on pre-nested data. We adjusted our significance level to $p<0.005$ for 9 comparisons on neurobehavioural scores and $p<0.005$ for 10 comparisons on each histological outcome. We used the Mann Whitney U test to compare quality scores across different datasets and linear regression to assess if there was any change in quality score over time.

3.4. Results

3.4.1. Search results

We identified 1382 full publications and 82 conference abstracts (1464 in total) published between 1961 and 2009 describing interventions tested in EAE (Figure 3.1). Overall, this review includes data in the meta-analysis from 834 publications testing outcome in 4090 individual nested experiments.

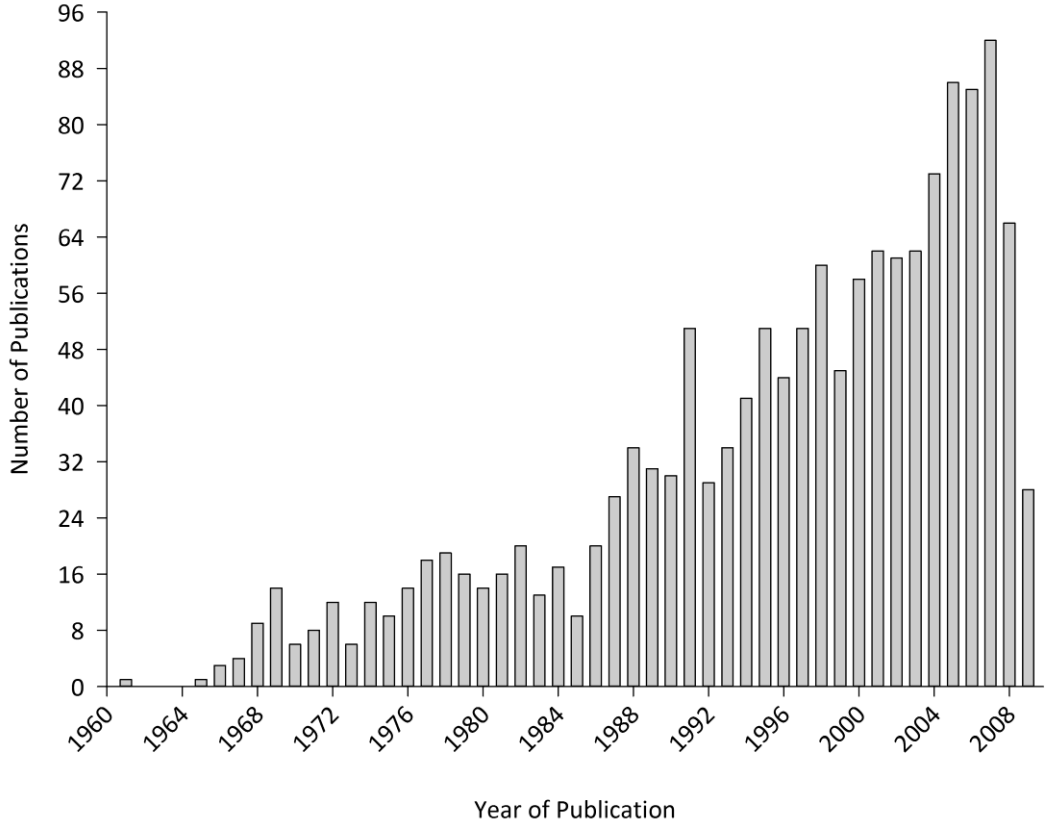


Figure 3.1. A histogram showing the number of included articles published by year.

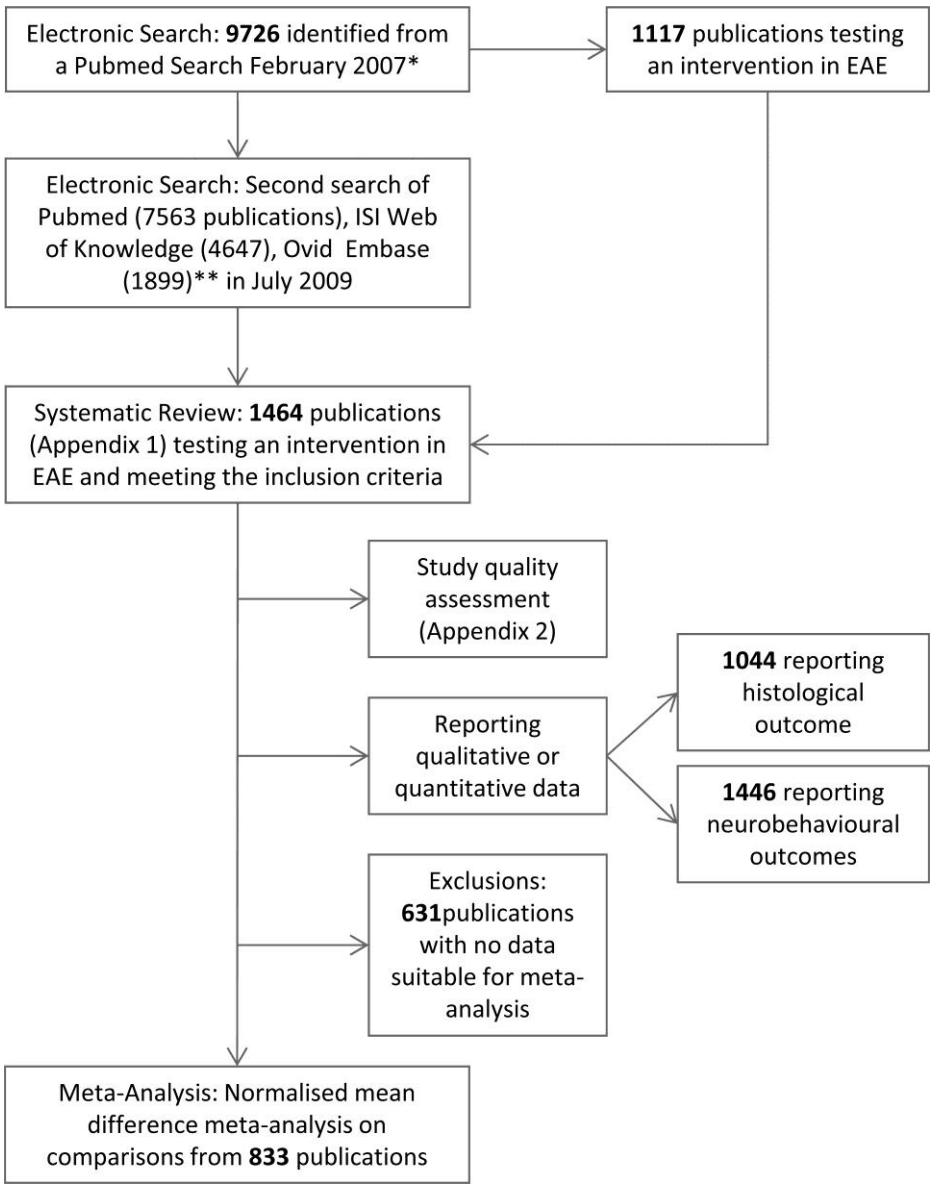


Figure 3.2. Quorum chart showing the progression from the literature search to the meta-analysis

3.4.2. Outcome Measures

Of 1646 publications in the systematic review, 1446 reported neurobehavioural outcomes and 1044 reported histological outcomes. Of these 1044 publications, 1004 reported inflammation, 388 reported demyelination and 175 reported axon loss (Figure 3.3).

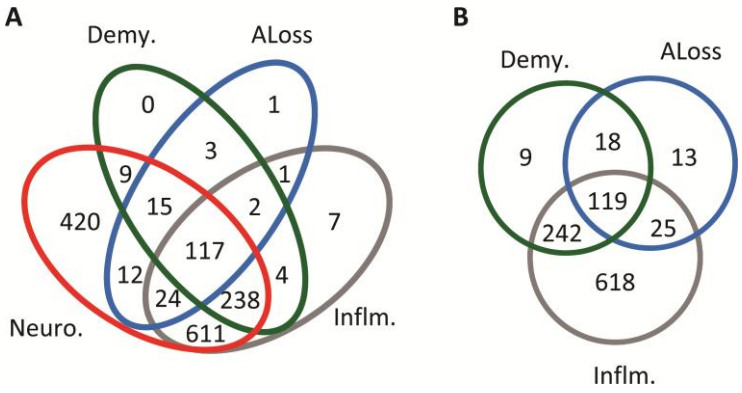


Figure 3.3. A Venn diagram of the reporting of different outcome measures in each of 1464 publications. (A) shows the publications which reported neurobehavioural scores (Neuro; red) and/or demyelination (Demy; green) and/or axon loss (ALoss; blue) and/or inflammation (Inflm; grey). In (B) only the relationships between reporting of demyelination (green), axon loss (blue) and inflammation (grey) are shown.

3.4.3. Exclusions

A large proportion of publications were excluded from the meta-analysis, usually due to insufficient reporting. Across all of the outcome measures, we were unable to include any data from 631 publications (43%). The number of exclusions and the reasons are outlined below.

v. Neurobehavioural outcomes

1446 publications reported neurobehavioural outcomes and we were able to include data from 779 publications in the meta-analysis. For 504 of these we were able to include all data, but for the remainder (275 publications) we could only include some outcomes. We were not able to include any data from the remaining 667 publications. Common reasons for exclusion included the absence of data for the variance, the

number of animals, or for a control group; the reporting of only dichotomous outcomes unsuitable for meta-analysis; and the reporting in abstracts of limited data insufficient for inclusion (See Table 1).

	All Data	Some Data
Missing variance	293	186
Dichotomous data only	150	n/a
Abstract without sufficient information	73	n/a
Calculation error	35	39
Qualitative data only	25	n/a
Missing no. of animals	20	24
Missing no. of animals; missing variance	20	8
Unsuitable/no control	19	8
Uninterpretable data	17	n/a
Neurobehavioural & histological scores combined	4	n/a
Median/range data only	3	3
Missing variance; median/range data only	3	1
Missing variance; unsuitable/no control	2	5
Duplicated data from another publication	1	n/a
Missing variance; uninterpretable data	1	n/a
Missing no. of animals; unsuitable/no control	1	n/a
Missing no. of animals; uninterpretable data	n/a	1
TOTAL	667	275

Table 3.1. Reasons for exclusion of publications with neurobehavioural outcomes from the meta-analysis.

vi. Histological outcomes

We identified 1044 publications reporting histological outcomes as changes in axon loss, demyelination or inflammation. Of these, we were able to include all relevant data from 257 publications, some relevant data from 13 publications and no data from 774 publications. Reasons for exclusion were similar to those described for neurobehavioural outcomes above, and in addition we were unable to extract data from 216 publications which presented only histological images.

	All Data	Some Data
Histological images only	216	n/a
Missing variance	114	n/a
No data for sham group	99	1
Qualitative	72	n/a
Abstract without sufficient information	60	n/a
Dichotomous data only	43	n/a
Missing no. of animals	38	n/a
Other measurement type	24	n/a
Not CNS	23	n/a
Data not shown	20	n/a
Combined histological score	17	n/a
Uninterpretable	12	n/a
Unsuitable/no control	9	n/a
Neurobehavioural & histological scores combined	5	n/a
Images only; other measurement type	5	n/a
No data for sham; missing variance	5	6
Missing no. of animals; missing variance	4	n/a
Median/range data only	3	n/a
Images only; not CNS	2	n/a
No data for sham; missing no. of animals	1	3
No data for sham; unsuitable/no control	1	1
Not CNS; other measurement type	1	n/a
No data for sham; missing variance; missing no. of animals	n/a	1
No data for sham; unsuitable/no control; calculation error	n/a	1
TOTAL	774	13

Table 3.2. Reasons for exclusion of publications with histological outcomes from the meta-analysis.

3.4.4. Estimates of effect size

The number of publications, the global estimate of efficacy and the estimates of between study heterogeneity are summarised in Table 3.3. Overall, the magnitude of efficacy was greatest for axon loss (51.8% reduction (95% CI 44.9-58.8)) and least for the improvement in mean severity scores. Across all six outcome measures there was substantial between study heterogeneity, reflecting anticipated differences between the interventions tested, animal models and study design.

		Publications (Experiments)	Global Estimate of Efficacy (95% CI)	No. of Animals	Heterogeneity I^2	Heterogeneity Tau^2
Neurobhavioural Scores	**MSS**	454 (1892)	33.1% (31.2-35.0)	28,909	92.3%	1153
	MCCS	251 (1075)	39.1% (36.6-41.6)	15,318	93.1%	1068
	CSLD	416 (1212)	41.9% (39.3-44.6)	18,988	95.8%	1518
Histological Outcomes	**Inflm.**	191 (510)	39.9 (36.1-43.6)	5641	95.9%	1251
	Demy.	117 (246)	43.9% (38.2-49.7)	2618	95.9%	1378
	ALoss	58 (113)	51.8% (44.9-58.7)	1196	92.0%	861

Table 3.3. Summaries of the improvement in six measures of drug efficacy in studies on EAE. Animals may have been used to measure efficacy for more than one outcome measure reported here. MSS, mean severity score; MCCS, mean clinical and cumulative score; CSLD, clinical score on the last day of assessment; Inflm, inflammation; Demy, demyelination; ALoss, axon loss.

3.4.5. Interventions

We identified 1560 interventions tested in EAE. For the majority (90%) of these they were reported in just one or two publications. Here we have reported summary estimates of effect size for interventions which were reported in five or more publications. These included 26 interventions with efficacy measured as improvement in neurobehavioural score, 20 for reduction in inflammation, 10 for reduction in axon loss and 18 for reduction in demyelination. Efficacy was highest for FTY720 (fingolimod) when outcome was measured as an improvement in neurobehavioural score or a reduction in inflammation. In total, all but three interventions (12%) had a significant improvement in neurobehavioural scores, 9 interventions (45%) significantly reduced inflammation, 6 (60%) significantly reduced axon loss and 10 (56%) significantly reduced demyelination. Only lovastatin had significant efficacy across all four outcome measures, followed by FTY720 which had efficacy in 3 of 3 outcome measures reported for it.

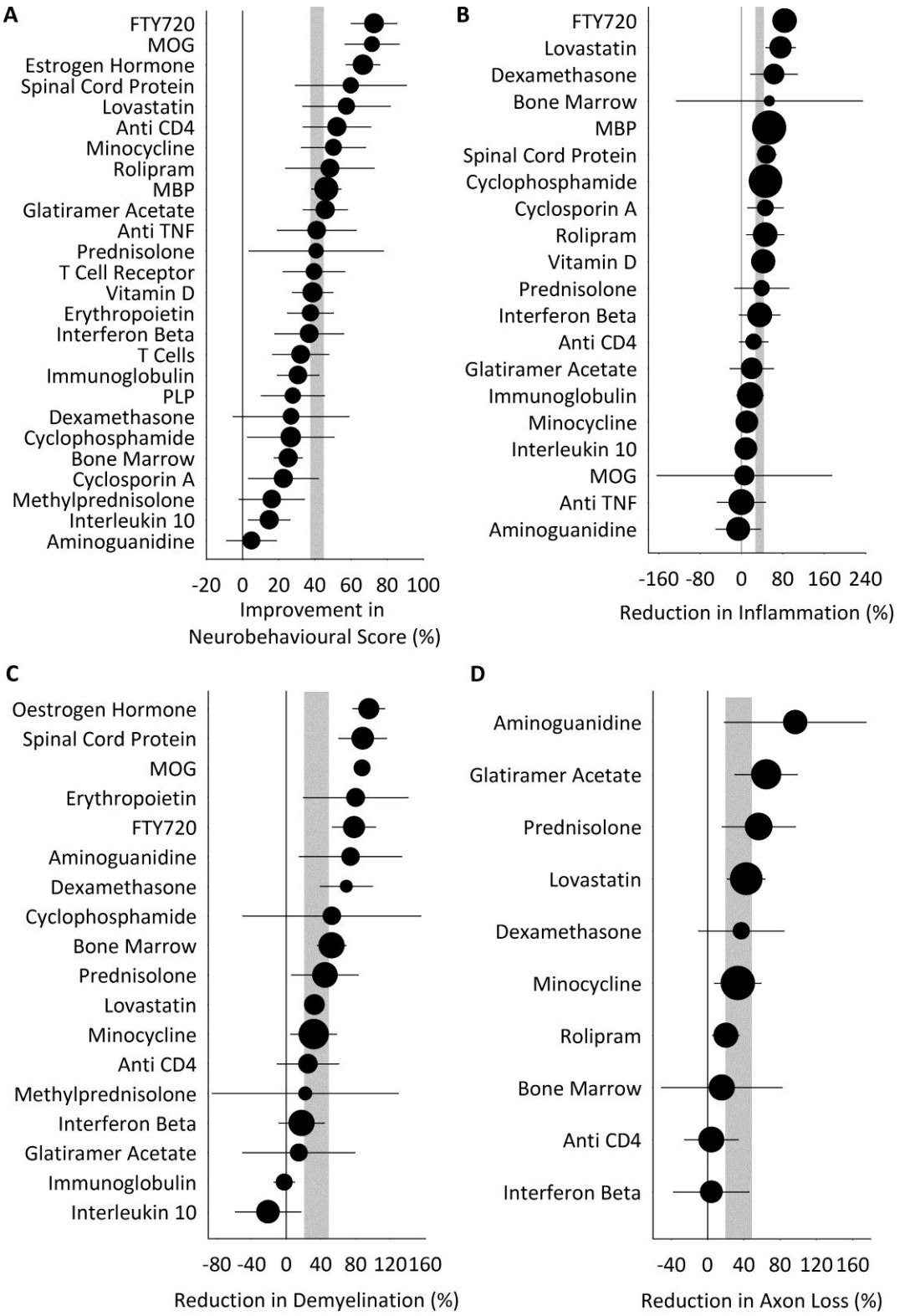


Figure 3.4. Point estimates of efficacy for the 37 most commonly tested interventions. Percentage improvement in neurobehavioural scores (A), and reduction in: inflammation (B), demyelination (C) and axon loss (D). Horizontal error bars represent 95% CI, vertical grey bar represents the global estimate and 95% CI. Symbol size represents the log of the number of animals for that comparison. Note that the symbol sizes are not relative across each outcome measure.

	Neurobehavioural Scores		Axon Loss		Demyelination		Inflammation	
	Global (95% CI)	No. Exps (animals)	Global (95% CI)	No. Exps (animals)	Global (95% CI)	No. Exps (animals)	Global (95% CI)	No. Exps (animals)
Aminoguanidine	4.9 (-9 to 18.8)	17 (290)	96.6 (18.4 to 174.8)	1 (13)	74 (14.9 to 133.1)	1 (13)	-6.2 (-49.4 to 37)	7 (55)
Anti-CD4	52.2 (33.5 to 71)	36 (464)	4.2 (-25.3 to 33.6)	1 (15)	25 (-10.3 to 60.3)	1 (15)	23.3 (-4.4 to 51.1)	1 (15)
Anti Tumor Necrosis Factor	41 (19.2 to 62.8)	21 (360)	-	-	-	-	-0.1 (-46.6 to 46.4)	5 (76)
Bone Marrow	25.2 (17.4 to 33)	19 (456)	15.6 (-50.9 to 82.2)	2 (16)	52.2 (35.7 to 68.7)	3 (39)	53.8 (-126.2 to 233.8)	1 (6)
Cyclophosphamide	26.7 (2.7 to 50.6)	24 (695)	-	-	52.5 (-50 to 155)	1 (13)	46.6 (35 to 58.2)	21 (291)
Cyclosporin A	22.6 (3.2 to 41.9)	34 (494)	-	-	-	-	46.2 (11.8 to 80.5)	1 (16)
Dexamethasone	26.8 (-5.3 to 58.9)	12 (193)	37.1 (-10.1 to 84.4)	1 (6)	69.2 (39.1 to 99.2)	1 (6)	62.8 (17.5 to 108.1)	3 (31)
Erythropoietin	37.5 (24.8 to 50.3)	22 (230)	-	-	80 (19.6 to 140.4)	1 (14)	-	-
Oestrogen Hormone	66.6 (57.3 to 75.9)	47 (688)	-	-	95.1 (76.7 to 113.5)	6 (19)	-	-
FTY720	72.7 (60.1 to 85.3)	43 (590)	-	-	78.1 (53.2 to 103)	2 (21)	83.3 (63.2 to 103.3)	6 (64)
Glatiramer Acetate	45.7 (33.5 to 58)	26 (470)	64.6 (30.3 to 98.8)	2 (24)	14.4 (-50.1 to 79)	1 (12)	19.9 (-22.3 to 62.1)	2 (37)
Immunoglobulin	30.7 (19.2 to 42.2)	16 (379)	-	-	-2.4 (-14.4 to 9.5)	1 (10)	16.5 (-9 to 42)	4 (82)

Interferon Beta	36.9 (17.8 to 55.9)	27 (442)	4.1 (-37.4 to 45.7)	1 (11)	17.6 (-8.6 to 43.7)	3 (39)	35.2 (-4 to 74.4)	4 (67)
Interleukin 10	14.7 (3.2 to 26.2)	36 (478)	-	-	-21 (-58.9 to 16.8)	9 (27)	8.6 (-8.8 to 26.1)	9 (43)
Lovastatin	57.5 (33.3 to 81.6)	15 (249)	42.6 (21.8 to 63.4)	2 (32)	32.5 (22.5 to 42.5)	1 (18)	75.6 (47.3 to 103.9)	2 (42)
MBP	46.3 (38.3 to 54.4)	162 (2248)	-	-	-	-	53.5 (40.2 to 66.9)	25 (324)
Methylprednisolone	16.1 (-1.9 to 34.2)	21 (378)	-	-	21.9 (-85.3 to 129)	1 (7)	-	-
Minocycline	50.3 (32.5 to 68)	17 (217)	33.3 (7.7 to 58.9)	3 (38)	31.6 (5 to 58.2)	6 (72)	10.3 (-7.5 to 28)	4 (45)
MOG	71.6 (56.6 to 86.5)	11 (157)	-	-	87.3 (80.4 to 94.2)	1 (10)	5.7 (-163.4 to 174.7)	2 (28)
PLP	27.8 (10.3 to 45.3)	14 (174)	-	-	-	-	-	-
Prednisolone	40.7 (3.5 to 78)	10 (129)	56.4 (16 to 96.8)	3 (18)	44.6 (6.4 to 82.8)	5 (36)	39.1 (-13.4 to 91.6)	2 (15)
Rolipram	48.3 (23.8 to 72.8)	18 (399)	20.2 (5.6 to 34.8)	1 (14)	-	-	45.9 (9.9 to 81.9)	7 (63)
Spinal Cord Protein	59.9 (29.1 to 90.6)	14 (170)	-	-	88 (60.6 to 115.4)	1 (24)	48.4 (30 to 66.8)	1 (24)
T Cells	32.2 (16.5 to 47.8)	38 (447)	-	-	-		-	-
T Cell Receptor	39.5 (22.3 to 56.7)	22 (194)	-	-	-		-	-
Vitamin D	38.8 (27.6 to 49.9)	22 (598)	-	-	-		42.1 (33 to 51.2)	3 (56)

Table 3.4. Global estimates of efficacy for the 37 most commonly tested interventions measured as change in neurobehavioural scores, axon loss, demyelination and inflammation.

3.4.6. Study quality

The number of full publications (peer reviewed) and the reporting of study quality items are summarised in Table 3.5. Across all publications, the median quality score was 2 (interquartile range (IQR) 1-2). Linear regression suggested that there was a modest increase in study quality over time (one point increment increase in quality every 26 years, R^2=16%; p<0.001).

Study Quality Checklist Item	Number of Publications (%)
Peer reviewed publication	1382 (94%)
Random allocation to group	157 (11%)
Blinded assessment of outcome*	Neurobehavioural outcomes: 242/1446 (17%) Histological Outcomes 297/1044 (28%)
Sample size calculation	4 (<1%)
Compliance with animal welfare regulations	500 (34%)
Statement of a potential conflict of interest	106 (7%)

Table 3.5. The number of publications meeting items on our study quality checklist. *1446 publications reported neurobehavioural outcome measures and 1044 reported histological outcome measures. Of 1026 publications reporting both of these outcome measures, 287 (29%) reported blinding only one of these.

We found a significantly larger estimate of efficacy for the reduction in inflammation in unblinded studies (47.1% (95% CI 41.8-52.4) for 254 comparisons versus 33.1% (25.8-40.4) for 256 blinded comparisons; R^2=4.01%, P<0.005, Figure 3). No other quality items appeared to have a significant impact on other outcome measures.

We were interested to explore differences between those publications reporting their data in sufficient detail to allow inclusion and those which did not report such detail. For neurobehavioural score, the median number of quality checklist items scored was higher for included studies (2; IQR 1-3; n=502 versus 1, IQR 1-2; n=566; Z=-9.9, p<0.0001). The median year of publication for the included studies was 11 years later (2002, IQR 1995-2006 versus 1991, IQR 1987-1999, Z=-14.0, p<0.0001). Similarly, for histological outcomes median quality score was significantly higher in included

publications (2; IQR 2-3; n=257 v 1, IQR 1-2; n=706; Z=-5.7, p<0.001) and median year of publication was 15 years later (2002, IQR 1995-2006 v 1987, IQR 1987-2004, Z=-5.8, p<0.001).

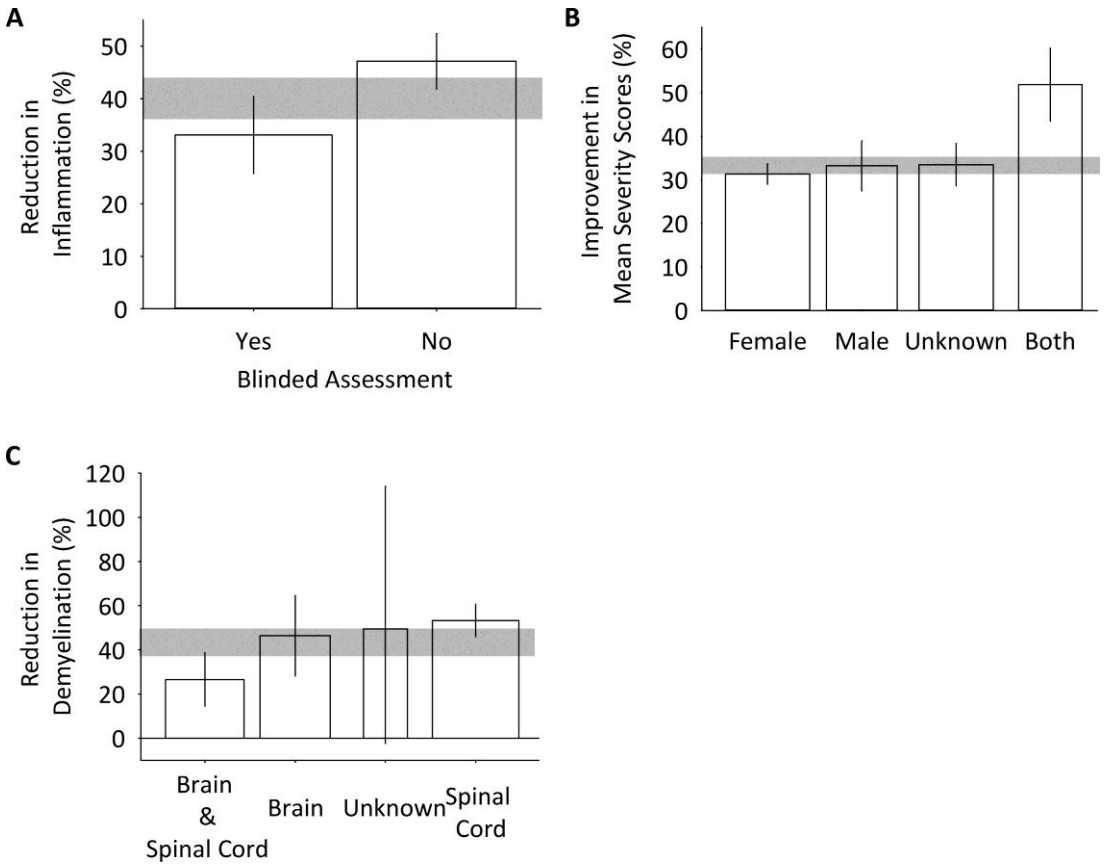


Figure 3.5. Impact of: blinded assessment of outcome on the percentage reduction in inflammation (A), the sex of the animal on the percentage improvement in mean severity scores (B) and the histological section assessed on the percentage reduction in demyelination (C). Vertical error bars represent 95% CI, the vertical grey bar represents the global estimate of efficacy for that outcome measure and its 95% CI and the bar width represents the log of the number of animals for that comparison.

3.4.7. Publication Bias

We found evidence for publication bias for all outcome measures using visual inspection of funnel plots, Egger regression and "trim and fill" (Table 3.2 and Figure 3.6). Observed outcomes on the change in mean severity scores were overstated by a relative difference of 120.7% compared to the global effect size imputed from trim and

fill. This was substantially higher than the other two neurobehavioural outcomes which had relative overstatements of efficacy of 4% for the mean clinical and cumulative scores, and 0.4% for the clinical score on the last day of observation. Outcomes measured as the reduction in demyelination or axon loss both had substantial relative overstatements of efficacy (47.9% and 31.4% respectively) whereas there was relatively little difference between the effect size for the reduction in inflammation before and after trim and fill (1.9%).

	MSS	**MCSS**	**CSLD**	**Inflm.**	**Demy.**	**ALoss**
Number of Comparisons in Meta-Analysis	1892	1075	1212	818	290	170
Reported Effect Size % (95% CI)	33.1 (31.2-35.1)	39.1 (36.4-41.9)	42.0 (39.1-44.8)	38.2 (34.7-41.7)	45.1 (39.9-50.4)	54.8 (49.4-60.2
Bias Confirmed with Egger regression	+	+	+	+	+	+
Bias confirmed with METATRIM	+	+	+	+	+	+
Additional studies considered "missing"	505	40	27	14	74	46
METATRIM adjusted effect size % (95% CI)	15.0 (12.9-17.2)	37.6 (34.8-40.3)	41.8 (39.0-44.6)	37.5 (34.0-41.1)	30.5 (25.3-35.6)	41.7 (36.3-47.2)
Absolute overstatement of effect size (%)	18.1	1.5	0.2	0.7	14.6	13.1
Relative overstatement of effect size (%)	120.7	4.0	0.4	1.9	47.9	31.4

Table 3.6. The prevalence and impact of publication bias in the EAE literature as assessed by funnel plotting, Egger regression and trim and fill. Column headers: MSS, mean severity score; MCSS, mean clinical & cumulative score; CSLD, clinical score on the last day of observation; Inflm, inflammation; Demy, demyelination; and ALoss, axon loss.

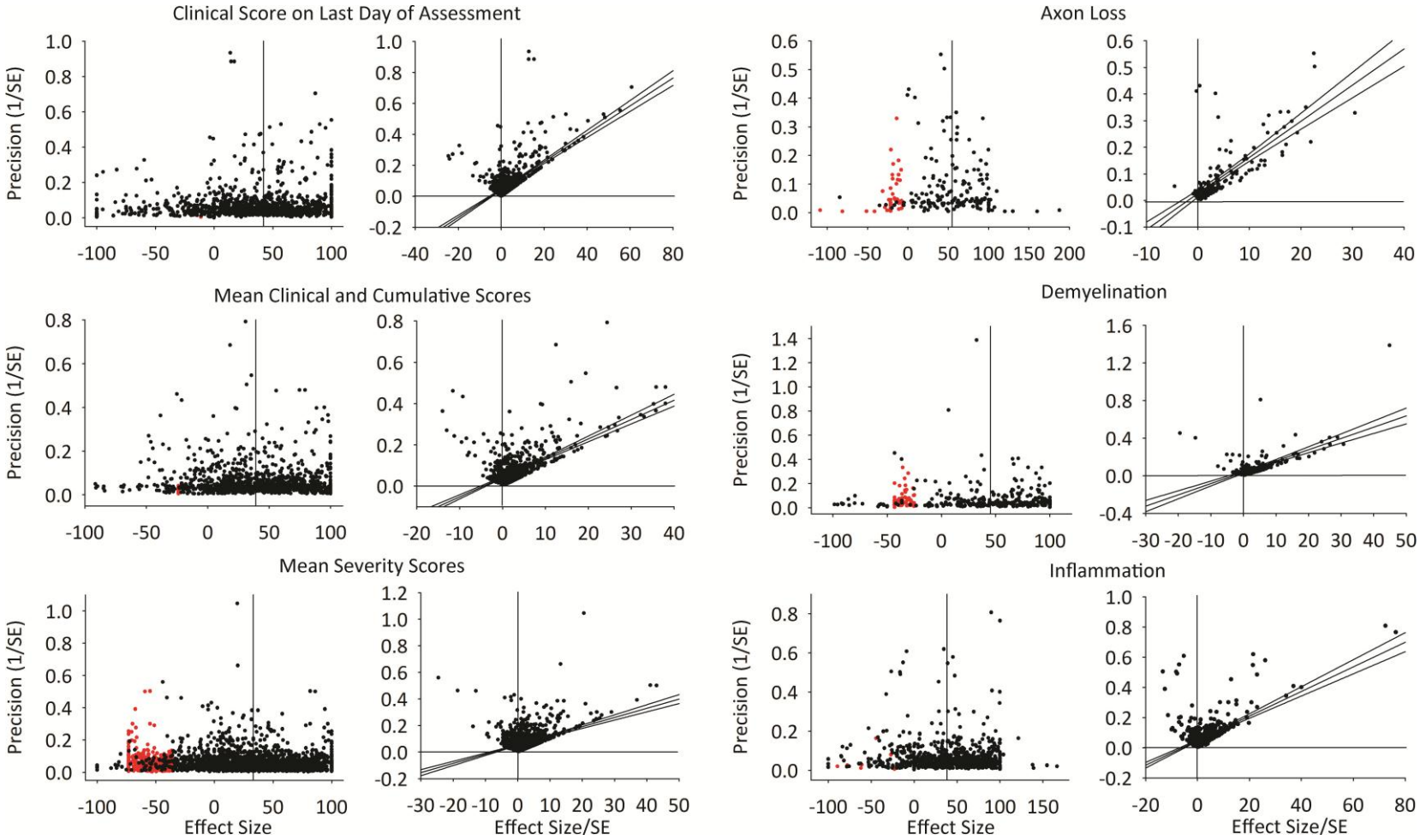


Figure 3.6. Assessing the prevalence and impact of publication bias in the EAE literature using funnel plots with observed estimates of effect size (black symbols) and filled in missing studies (red symbols; left hand panels) and Egger regression (right hand panels) for three neurobehavioural and three histological outcome measures.

3.4.8. Sample Size

Our meta-analysis included data from 47944 animals testing neurobehavioural outcomes, 5641 animals testing the change in inflammation, 2618 testing the change in demyelination and 1196 animals on the change in axon loss. It is likely that some of the animals used for neurobehavioural outcomes might have gone on to contribute to histological outcomes, but this was not always the case and it was not always possible to determine which cohorts of animals contributed to which outcomes. However, the total number of animals contributing data to this analysis lies between 47,944 and 57,326.

The median number of animals per experimental group for neurobehavioural outcomes was 12 (IQR 9-17, 3221 experiments); for axon loss 10 (8-12, 113 experiments), for inflammation 9 (6-13, 510 experiments) and for demyelination 9 (6-14, 246 experiments). The number of animals in an experiment did not account for any of the observed heterogeneity for any outcome measure.

Post hoc power calculations have limited validity, but assuming an improvement in mean maximal severity of 33% (from our global efficacy analysis), a median standard error of 21% and a median of four animals in the control group and eight animals in the treatment group, the typical EAE study included here is powered at 64%. Based on these data we have provided estimates for the number of animals required to achieve different levels of power, the power of a study for different observed effect sizes and the number of animals required to observe a specified effect size (Lenth, 2007)(Figure 3.7).

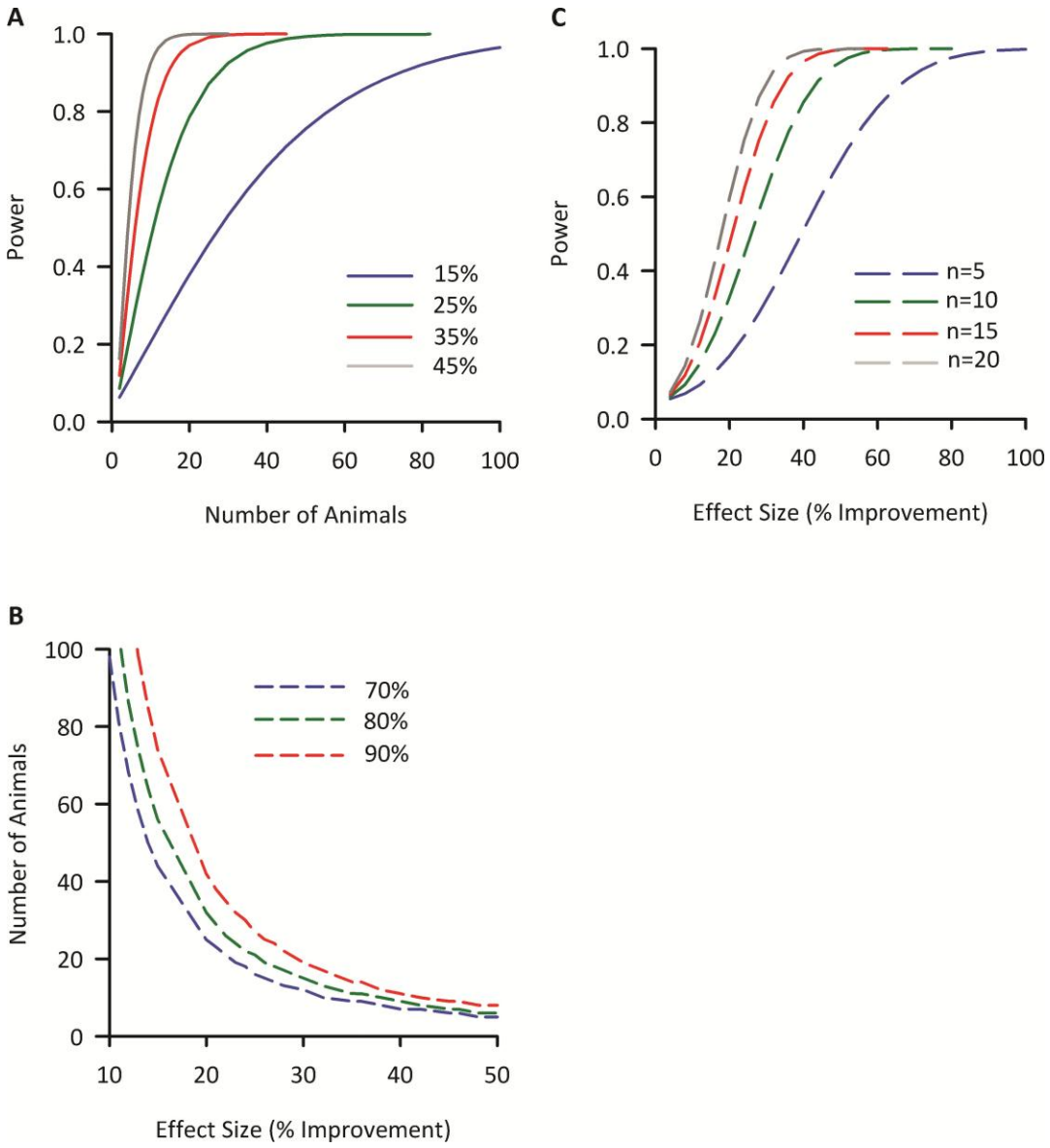


Figure 3.7. Indicative power calculations. Models of the power of a study using n number of animals per group when looking for an effect size of 15%, 25%, 35% or 45% (solid blue, green, red and grey lines, respectively, A), the power of a study when observing a specific effect size, using 5, 10, 15 or 20 animals per group (long dashed blue, green, red and grey lines, respectively, B) and the number of animals required to observe a specific effect size powered at 70%, 80% and 90% (short dashed blue, green and red lines respectively, C).

3.4.9. Time to Treatment

Taking all neurobehavioural scores together, for 3006 comparisons which reported the time quantitatively, the median time to treatment was the day of EAE induction (day 0; IQR -2 to 8). For 460 inflammation outcomes the median time to treatment was also day 0 (IQR 0 to 7), but for demyelination it was day 5 (IQR 0 to 12, 229 outcomes); and

for axon loss it was day 7 (IQR 0-10, 106 outcomes; Table 3.7). The remaining outcomes were not included in the assessment of the median time to treatment because they either did not report this information or it was administered relative to another time point such as the day of disease onset, or the time of first relapse, without further information to determine this time point.

For the mean severity scores the time to treatment accounted for a significant proportion of heterogeneity between observed effect sizes (absolute reduction in effect size of 0.23% for every additional day's delay, $p<0.005$; 1892 comparisons).

	Neurobehavioural Score		**Inflammation**		**Demyelination**		**Axon Loss**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Before Day 0	904	28	105	21	27	11	11	10
Day 0	706	22	135	26	54	22	18	16
Day 1-7	571	18	115	23	60	24	26	23
Day 8-14	614	19	73	14	51	21	36	32
Day 15+	211	7	32	6	37	15	15	13
Other	50	2	19	4	6	2	2	2
Unknown	165	5	31	6	11	4	5	4
Total Outcomes	3221 (3006)		510 (460)		246 (229)		113 (106)	

Table 3.7. The different times of administration across outcome measures which had results included in the meta-analysis. The number of outcomes which contributed to the meta-analysis for time of administration is shown in parentheses (i.e. the times of administration which were neither "other" or unknown). "Other" refers to the day of onset of the first neurological deficits or another related time period such as the day of the first relapse.

3.4.10. Time of Assessment

The time of assessment did not have any significant impact on the heterogeneity between effect sizes for any outcome measure. The median time of assessment did however vary across different outcomes, being day 28 (IQR 20-40) for the 3221

neurobehavioural outcomes with a reported a time of assessment, day 21 (IQR 15-32) for 510 outcomes on inflammation, day 32 (IQR 20-52) for 246 outcomes on demyelination and day 34 (IQR 21-50) for 113 outcomes on axon loss.

3.4.11. Species

Experiments were carried out in mice (713 publications), rats (583), guinea pigs (145), monkeys (17), rabbits (15), marmosets (8), cats (5), chickens (1) and ewes (1); a further 18 publications did not report the species used. We did not identify any experiments using chickens or ewes which had results suitable for meta-analysis. Meta-regression did not identify a significant impact of the species on the heterogeneity in effect sizes for any of the neurobehavioural or histological outcome measures.

3.4.12. Sex

Experiments were most commonly carried out using female animals (793 publications) with 230 publications reporting using males, 99 using both males and females with a further 379 not reporting the sex of the animals used. The sex of the animals accounted for a significant proportion of heterogeneity amongst effect sizes where this was measured as mean severity scores. The highest effect sizes were seen when interventions were tested in both males and females (51.9% (95% CI 43.5-60.2; 109 comparisons, $p<0.005$). Effect sizes were similar where experiments were carried out in males and females separately or where the sex was not reported (Figure 3.5).

3.4.13. Route of Delivery

Across all publications which had a result included in the meta-analysis we identified 40 different routes of delivery used. The most commonly used routes of administration were: intraperitoneal (353 publications), oral (140), intravenous (138), subcutaneous (121), subcutaneous mini-pump (25), intramuscular (24), intranasal (18), intracisternal (13), intraperitoneal & subcutaneous (8), foot pad injection (7).

The route of delivery accounted for a significant proportion of heterogeneity amongst effect sizes for the mean clinical & cumulative scores and the mean severity scores. Looking only at the routes of delivery which were used in 5 or more comparisons, for the mean cumulative and clinical scores, effect sizes were greatest when administered both orally and intraperitoneally (83.2% (95% CI 54.8-111.6); 8 comparisons), followed by using a subcutaneous mini-pump (61.2% (49.6-72.8); 50 comparisons) and intracerebroventricularly (57.9 (28.9-86.9); 9 comparisons). For the most common route of delivery, intraperitoneally, the effect size was relatively low compared to others (32.3 (28.3-36.3); 403 comparisons). For the mean severity scores, effect sizes were greatest when interventions were administered intradermally (58.6% (32.1-85.1); 9 comparisons), followed by intrathymic (56.3 (29.2-83.4); 9 comparisons), and the subcutaneous mini-pump (53.2 (42.0-64.3); 50 comparisons). Similar to the cumulative and clinical scores, the use of intraperitoneal injection was associated with a relatively low pooled effect size relative to others (28.5% (25.5-31.6); 659 comparisons; Figure 3.8).

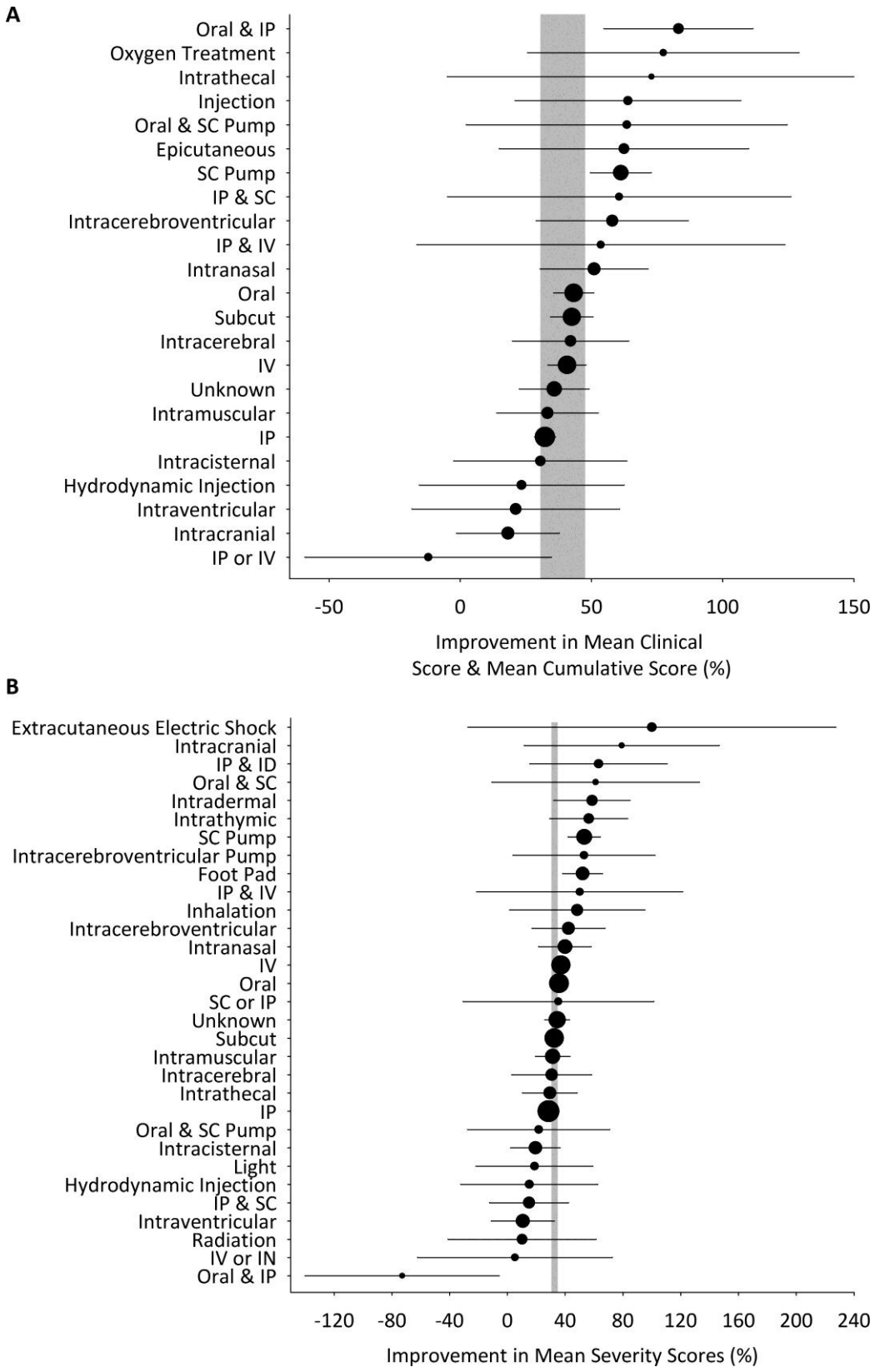


Figure 3.8. Estimates of efficacy measured as (A) improvement in mean clinical & mean cumulative scores, and (B) mean severity scores for different routes of administration. The vertical grey bar represents the global estimate of efficacy and its 95% CI. Symbol size represents the log of the number of animals for that comparison.

3.4.14. CNS Section Analysed

The majority of histological outcomes were assessed in the spinal cord (282 of 586 comparisons on inflammation; 142 of 262 outcomes on demyelination and 67 of 116 outcomes on axon loss) followed by the combination of the spinal cord and brain (163 outcomes on inflammation, 87 on demyelination and 43 on axon loss). We found a significant impact of the CNS section analysed on the heterogeneity between effect sizes for demyelination (Figure 3.5C; $p<0.005$). Specifically, effect sizes were greatest when outcome was assessed in the spinal cord (53.4% (IQR 46.0-60.7) compared to the brain (46.4% (28.2-54.7)) and both the brain and spinal cord together (26.6% (14.5-38.7)).

3.4.15. Neurobehavioural scoring method

We used publications from the year 2000 onwards to summarise the clinical scores used to measure EAE. In total this comprised 676 publications. 584 described the clinical status of the animal on an ascending scale, typically from grade 0 to 5 where 0 referred to a normal animal in all but one publication (where it represented a limp tail) and 5 typically referred to either tetraplegia, hindlimb paralysis with forelimb weakness and/or moribund or death. Ascending paralysis was typically scored (with greater or less detail) as: fully limp tail/tail paralysis (1 point), increasing hindlimb weakness and/or forelimb weakness (2), forelimb weakness (3) tetraplegia (4) and moribund or death (5 or 6 points). 30 publications described using half points for intermediate clinical findings without further description and a further 119 described details for half points; however 41 of these reported a half point as the first clinical grade (usually referring to partially or fully limp tail) without any further intermediate increments. Additionally 3 publications reported 0.25 as the first clinical score (referring to distal tail limpness). A further 18 publications didn't give sufficient information to describe the clinical scale, and 48 publications were abstracts with no details of the scale used. The maximum scale described in full went up to 11, with 4 publications reporting a ten point scale. The least descriptive scores were on a 2 (one publication) or 3 (11 publications) point scale.

3.5. Discussion

Here we have described a broad systematic review and meta-analysis of all the studies testing interventions in EAE, which to our knowledge is the largest in any field of animal research. Despite the broad nature of this review whereby we have grouped different EAE models and interventions tested, we have generated a number of potentially interesting hypotheses relating to study design, as well as a number of serious shortfalls in the reporting in this literature.

3.5.1. Reporting in the EAE literature

The reporting of information is essential to allow the reader to reach an informed view of the importance and validity of the reported findings; and indeed to allow inclusion in a meta-analysis, was very low. This information includes fundamental data such as the number of animals, the mean and a measure of variance for both a treatment and control group. Almost half of all peer reviewed publications did not report at least one of these. This problem is certainly not unique to the EAE literature however as reporting has been found to be poor across the preclinical literature in the life sciences (du Sert, 2011; see also Chapter 5). Promisingly though, more and more journals are adopting reporting guidelines (Kilkenny et al., 2010) and there is now a modified version of the ARRIVE guidelines which are considered most important to the EAE literature (Baker and Amor, 2012). We also draw some reassurance from the observation that in more recent years the proportion of studies excluded for these reasons appears to be falling.

3.5.2. Study Quality and Publication Bias

In addition to our concerns about reporting, we noted that few publications reported measures to reduce bias (random allocation to group and blinded assessment of outcome). Our analysis only identified that blinding was significant for inflammation outcomes, with higher estimates of efficacy seen in publications which did not report blinding. However, we have consistently shown across a number of domains that these measures to reduce bias are of importance and moreover, that the prevalence of these was lower in these studies than in the stroke literature (see Table 4.3).

Only four publications reported a sample size calculation, which may reflect the difficulty of performing a meaningful power calculation without a prior meta-analysis such as we have performed here. We have therefore used these data to produce some guidance as to sample sizes required to give various levels of power. Our post hoc power calculation suggests that half the experiments included in this analysis are powered at less than 64%.

3.5.3. Time to Treatment

For the best possible chance of successful translation of efficacy from bench to bedside, the design of clinical trials should reflect the conditions in which efficacy has been observed in animals. However, in turn these animal experiments should reflect plausible study design characteristics of human clinical trials. For both neurobehavioural scores and inflammation outcomes, treatments were most commonly administered on the day of EAE induction, an observation also made of the SOD1 mouse model of motor neuron disease (Benatar, 2007). Furthermore, for mean severity scores the effect size dropped with increasing time to treatment. However, interestingly the time to treatment was found to be later in experiments reporting demyelination and axon loss outcomes.

In EAE, interventions may be efficacious by blocking the induction of disease (where mechanisms such as sequestering immunogen or inhibiting the initial immune response may be most relevant) rather than through an effect on the primary pathophysiology of neuronal and glial injury or the evolution of neurological impairment over time. The relevance of such studies to the development of interventions for established relapsing–remitting disease, primary and secondary progressive disease is not clear. It could be argued that efficacy in EAE studies might only be predictive of efficacy in clinical trial if treatment were started after the onset of symptoms (some days after induction), as we presently have no way of identifying patients prior to the onset of the disease.

Finally, disease burden in MS reflects a complex interplay between inflammation, demyelination, remyelination and neurodegeneration with a temporal shift in pathological emphasis from inflammation to neurodegeneration; further work is required to describe the characteristics of different EAE models in these different domains. Thus, it may be that some of the difficulties in translating efficacy from animals to man arises because data from appropriately designed studies modelling MS pathophysiology do not provide sufficient insights to likely efficacy in human disease, where different endpoints might be considered key, and longer delays to the initiation of treatment are unavoidable.

3.5.4. Study Design

We found that the route of delivery had a significant impact on the effect size for both mean severity scores, and mean clinical and cumulative scores with subcutaneous pump showing a consistently high effect size across both outcomes and intraperitoneal injection showing a relatively low effect size for both. Additionally we found that effect sizes were greater for demyelination when the outcome was measured in the spinal cord.

The most common outcome measure reported across all publications included in the systematic review was neurobehavioural scores of which the mean severity score was most often reported. Of the histological outcome measures inflammation was most commonly reported followed by demyelination and axon loss. However it was interesting to note that demyelination was often reported without any mention of axons (251 publications). As suggested previously (Baker et al., 2011), this is not necessarily indicative of primary demyelination because axon loss may have occurred, or inflammatory infiltrates may have displaced the axons (and thus in both cases there is no myelin to lose). It is therefore possible that where we have reported demyelination as our outcome measure, this may actually be more indicative of a change in inflammation.

Across publications we found very little consistency in the grading system for neurobehavioural outcome. Different species have different clinical courses and so

whilst it is conceivable for scoring systems to reflect this, there was substantial heterogeneity in scoring even within one species. For human clinical trials the expanded disability status score (EDSS) is commonly used (Kurtzke, 1983). Like the majority of scoring systems for EAE experiments, this is a physician assessed and measures increasing disability on an ordinal scale from 0 to 9.5. Endpoints in clinical trials are discussed and reported on in some detail to ensure that they are able to capture the finer details between patient cohorts. However there appears to be very little discussion of the outcome measures used to assess disease in preclinical research.

Using behavioural scales to score EAE is subjective and may vary substantially across observers. A wide range of objective neurobehavioural outcome measures exist in, for example, the preclinical PD literature (Chapter 4), and yet very few publications report objective measures in the EAE literature. Clearly the two (broad) disease models are very different in their clinical presentation – in EAE, the rotarod for example might not be able to differentiate between mild hindlimb weakness with mild forelimb weakness, and severe hindlimb weakness with severe forelimb weakness. Perhaps more importantly however is whether the current scoring convention is able to robustly measure something that is clinically relevant. Axon loss is considered to be the main cause of permanent disability in humans, and so the question is whether neurobehavioural scores accurately reflect this pathological change.

3.5.5. Efficacy of Interventions

The value of a global estimate of efficacy for individual interventions tested in a number of unique study design paradigms without an assessment of heterogeneity is of limited value. However, we have presented data for the most commonly tested interventions in a transparent manner which allows the reader to make inferences about the robustness of the experimental data. We have shown here that for a number of these interventions there is clear heterogeneity and it demonstrates the need to carefully examine the data when there is the potential to use it to inform further clinical trials or animal experiments. In our dataset, aminoguanidine was ranked 26th (worst) out of 26 interventions for improvement in neurobehavioural scores and 18th out of 18 interventions for reduction in demyelination; conversely it was ranked 1st (best) out of 10 interventions for reduction in axon loss and 6th out of 18 interventions for reduction

in inflammation. Careful (post-hoc) inspection of the data reveals that there was substantial variability in the design of experiments testing aminoguanidine: four routes of delivery were used, five different times of administration, of which all but four experiments administered the intervention on day 2 or before, two different immunogens were used to induce disease, and mean sample sizes across the treatment and control groups ranged from 3 to 25 animals. These data should therefore just be used as a tool to recognise where further research or careful inspection of data should be undertaken.

Interestingly, our broad meta-analysis identified FTY720 as a strong candidate intervention. FTY720 was licensed for clinical use in 2010 (under the name of Gilenya) as the only current oral intervention for MS and has been shown to have substantial efficacy in reducing annualised relapse rate in RRMS patients. With time it will become clear whether FTY720 has any effect in the halting neurodegeneration in progressive MS. Lovastatin also came out favourably and was the only intervention to have significant efficacy across all four outcome measures. However there is limited evidence on lovastatin clinically, and to our knowledge no randomised control trials have been conducted. An up to date systematic review and meta-analysis of lovastatin in animal models of MS would therefore be useful to assess whether robust evidence exists to warrant a clinical trial.

3.5.6. Study Limitations

Meta-analyses can only include data from literature which have adequately reported data; as such this review includes a limited number of the total relevant publications. We have no doubt that this selection bias will have an impact on the results reported for measures of effect size; however, we were still able to include data from over 800 publications. It is difficult to judge whether the publications which were not included in the meta-analysis would be inherently different to those which were included; however we have no reason to believe that they would be any more likely to reflect more accurate underlying biological mechanisms.

Another source of selection bias in a meta-analysis is publication bias which we have found to be prevalent across all of the outcome measures in this review. With such a large number of publications being excluded due to poor reporting, it may be that the "missing" studies identified in our analysis of publication bias were within those identified but excluded. Again though we have no reason to believe that the excluded studies are any more likely to report negative results than those which had data included. In fact, had we been able to include these studies we may have identified an even stronger publication bias.

On this dataset our pre-specified approach for analysis was to use meta-regression as opposed to stratified meta-analysis. Meta-regression is a conservative approach, and in our experience (see Chapter 7), stratified meta-analysis on such a large dataset tends to identify such a large proportion of significant differences that it is difficult to judge whether this these differences reflect true underlying differences in the dataset (which may well be true), or whether it is a statistical artefact. Extensive modelling of these statistical tests on this dataset will shed light on the differences between these statistical tests but we believe it was nonetheless important to use the approach we know to be more conservative for this analysis.

Another criticism of our approach is the grouping together of EAE studies. There are a number of EAE models which follow different disease courses and show different underlying pathologies depending on a number of factors including animal species, strain, sex and the immunogens used to induce disease. In this review our focus was on the reporting in the EAE literature and to identify if there is any homogeneity within such an inherently heterogenous disease model. Additionally our approach provides an overview which will allow for more detailed reviews to be carried out on any particular drug of interest to the research community and enables comparisons to the results described here. The entire dataset on which this analysis is based is available at www.camarades.info.

Further limitations to this study and systematic review & meta-analysis in general are discussed in Chapter 9.

3.5.7. Conclusions

EAE has proven immensely valuable in modelling inflammatory aspects of MS and has led to many insights into disease mechanism as well as several licensed treatments for early disease courses. However, there remains a great need to identify the next generation of therapeutics that will particularly target the unmet need of treatment for the progressive phase of disease. However, in this, the largest systematic review of animal studies to date, we have shown that the testing in animals of candidate interventions for MS has potentially been confounded by limited internal validity (with little reported use of randomization, blinding and power calculations), limited external validity (with few treatments given at clinically appropriate time points), and inadequate reporting. Numerous efforts are now in place to address these issues, including the ARRIVE guidelines. This dataset provides evidence that these guidelines are both timely and necessary.

4. A systematic review and meta-analysis of dopamine agonists tested in preclinical models of Parkinson's disease

I acknowledge the following for their contribution to this research: Evelien Rooke (ER; conducted the initial electronic search and data extraction in 2007); Emily Sena (ES), Kieren Egan (KE) and Macleod Macleod (MM; all were involved in various aspects of the study design process, reference screening, data checking and manuscript editing). My contribution includes updating the literature search and data extraction. I conducted both the original and updated analysis of the data.

4.1. Background

Parkinson's disease (PD) is the second most common neurodegenerative disease behind Alzheimer's Disease (de Lau and Breteler, 2006b). There is a sharp increase in the prevalence of PD over the age of 60, with estimates suggesting that as much as 1% of this population may be affected (de Lau and Breteler, 2006a), with a lifetime risk of 1.5% (Lees et al., 2009). The pathological hallmark is the loss of dopamine (DA) containing neurons in the substantia nigra pars compacta (SNc), and formation of lewy bodies in the surviving cells (Schapira and Jenner, 2011). In turn, this leads to the clinical presentation of resting tremor, rigidity, postural instability and bradykinesia (Jankovic, 2008). However, these symptoms typically appear when neuronal death has exceeded a threshold, somewhere in the region of 70-80% in the SNc (Golde, 2009). As with MS, our understanding of the aetiology of PD is unclear, but similarly considered to be due to the interplay between genetic susceptibility and an environmental trigger (Schapira and Jenner, 2011, Lees et al., 2009), and these two factors define the two most common types of animal model for PD (Jackson-Lewis et al., 2012, Duty and Jenner, 2011, Bezard and Przedborski, 2011).

There are a number of symptomatic treatment options for PD and these have continued to increase with the development of new classes of drugs and new formulations of existing drugs. However there remains a need to identify interventions which reliably achieve substantial efficacy with minimal adverse effects. Although dopamine agonists

should seemingly offer the most pragmatic approach to a disease defined by a reduction in dopamine, clinical evidence has not always been convincing (Antonini et al., 2009, Stowe et al., 2008, Clarke and Guttman, 2002). Dopamine itself is unable to cross the blood brain barrier and so instead, its precursor, L-DOPA was, and still is a popular first-line agent (Rascol et al., 2011). However, L-DOPA is associated with motor-complications with longer term use (Thanvi and Lo, 2004) and may even accelerate neuronal death (Fahn et al., 2004). A number of dopamine agonists have since progressed to clinical use for the symptomatic mono-therapeutic treatment of all stages of the disease; or alternatively they are used as an adjunct to reduce L-DOPA related motor adverse effects (Antonini et al., 2009). Although they are generally considered less efficacious than L-DOPA in relieving motor symptoms, they are typically used to reduce L-DOPA associated motor complications. (Bonuccelli et al., 2009). In addition dopamine agonists are more limited by their numerous adverse effects, sometimes so severe that the only viable option is treatment cessation (Lees et al., 2009). Despite these setbacks, the clinical efficacy of dopamine agonists has kept them in the running as a potential therapeutic option.

4.2. Aims and Objectives

Our primary aim was to assess the impact of study quality and study design characteristics on efficacy reported in the literature on dopamine agonists tested in animal models of PD. Specifically our objectives were to: (1) identify publications reporting the use of a dopamine agonist in an animal model of PD; (2) report summary estimates of efficacy; (3) identify the impact of study design and study quality on the reported efficacy; (4) assess for the presence and impact of any publication bias; (5) describe the limits and potentials for clinical success; and (6) compare and contrast these findings to the EAE literature.

4.3. Methods

4.3.1. Electronic search

We identified studies reporting the use of a dopamine agonist in an animal model of PD by electronic searching of Pubmed, ISI Web of Science and Embase in September 2009. Our search terms were: [Parkinson's disease] AND ([1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine ORMPTP OR 1-methyl 4-phenyl pyridinium OR MPP+ OR 6-hydroxydopamine OR 6-OHDA OR Paraquat OR Maneb OR Rotenone OR 3-nitrotyrosine OR Alpha-synuclein OR Reserpine OR Methamphetamine]). Two investigators (ER & HV) independently screened all references, with differences clarified by discussion with a third investigator (ES).

4.3.2. Inclusion and exclusion criteria

We included publications in the systematic review if they described the use of a dopamine agonist in an animal model of PD where efficacy was measured against a neurobehavioural outcome. Outcomes were included in the meta-analysis if the number of animals per group, mean outcome and its variance (SEM or SD) were reported. We defined a dopamine agonist as a drug with reported agonism at at least one class of dopamine receptor irrespective of actions at other dopamine or other receptor classes. We therefore made no judgement as to whether dopamine agonism was the principal mechanism of action. Indirect dopamine agonists (e.g. the dopamine precursor L-DOPA) were specifically excluded. We also excluded studies where apomorphine was used exclusively to confirm successful lesioning as part of an experimental protocol not testing the efficacy of dopamine agonists.

4.3.3. Data Extraction

Neurobehavioural outcome measures used were categorised into one of seven groupings for further analyses (Table 4.1). Where outcomes were measured repeatedly we chose the time at which efficacy was greatest. Information was extracted for aspects of quality (see section 4.3.4) and experimental design (animal species and strain, sex, intervention tested, anaesthetic used during disease induction). For neurobehavioural outcomes the number of animals, mean and variance (standard error of the mean or

standard deviation) for the treatment and control group were extracted as well as the dose, route of administration and time of administration and assessment. The time of lesioning was set to zero and the time of drug administration expressed relative to this.

Neurobehavioural Outcome	Description
Motor activity requiring sensory input (MASI)	Number of mistakes or "no response" errors; pellets eaten; steps reached; reaction time (correct responses); startle response.
Spontaneous activity	Locomotor/spontaneous activity (measured as beam crossings); time spent in: body displacement, shuffling, head movement, locomotor activity, grooming, jumping, rearing.
Skilled motor activity	Catalepsy; errors per step, number of steps or time to traverse on a beam; retention time on rotarod; initiation time for stepping; grasping time or hanging time.
Rotational Behaviour	Number of spontaneous or drug induced rotations.
Limb asymmetry	Right biased swing; goal directed limb movements; contralateral turns or pivots; adjusting steps in backhand or forehand direction; turns to the right in a maze; ipsilateral rotations; right hand use.
Parkinson's disability rating	Akinesia score; Parkinson's rating score (usually out of 5); disability score; bradykinesia score.
Balance and gait	Stepping length or width (gait); ankle extension or flexion; posture; balance; rigidity.

Table 4.1. Grouping of the different outcome measures to one of six categories for analysis.

4.3.4. Methodological quality

We assessed the quality of included studies against our six point checklist as described in Chapter 2 (section 2.1.3).

4.3.5. Data analysis

We calculated SMD effect sizes (section 2.2.2) and pooled these using the random effects model (section 2.2.4). To assess the impact of study quality and design characteristics we took all neurobehavioural outcomes together and used stratified

meta-analysis (Section 2.3.2). Our pre-specified analysis included testing the impact of: species, sex, route of administration, time of administration, anaesthetic used during lesioning, sample size, aggregate quality score, random allocation to group, blinded assessment of outcome, method of lesioning, the intervention tested and the neurobehavioural score used. For either random allocation to group or blinded assessment of outcome we pre-specified that if either had a significant impact on efficacy in the stratified meta-analysis we would use meta-regression to explore whether these had a particular influence on specific outcome measures.

To assess for publication bias we used funnel plotting, Egger regression and trim and fill on pre-nested data (section 2.5). We adjusted our significance level to $p<0.004$ for 12 comparisons.

4.4. Results

4.4.1. Search results

We identified 252 published articles (215 full publications and 37 abstracts) from the electronic search, and hand searching identified one unpublished thesis (Appendix 3). This review includes data from articles published between 1975 and September 2009, with the greatest number published in 2008 (Figure 4.1). Together these reported the use of 74 unique dopamine agonists in animal models of PD (Figure 4.2). We were unable to include data from 132 publications in the meta-analysis because: (1) they did not report critical information such as results from a control group (82 publications); data were insufficient or had subsequently been published in greater detail (37 publications, mostly abstracts), or they used apomorphine as a screening tool to assess the level of dopamine depletion (13 publications). The remaining 121 publications (116 full publications and 5 abstracts) using 47 dopamine agonists reported at least one neurobehavioural outcome in sufficient detail to allow meta-analysis. 46 of 121 publications described crossover studies, where each animal served as its own control, with performance under control conditions generally assessed before the treatment phase. This review is therefore based on data from 253 sources, and we have been able to perform meta-analysis on a subset of 121 publications which included data from 601 experiments involving 4181 animals.

Ten interventions with at least some dopaminergic activity have been, or are in current clinical use for PD. Interestingly, for all but pramipexole, data on its use in human clinical trials of PD were published before data from animal models of PD (Table 4.2).

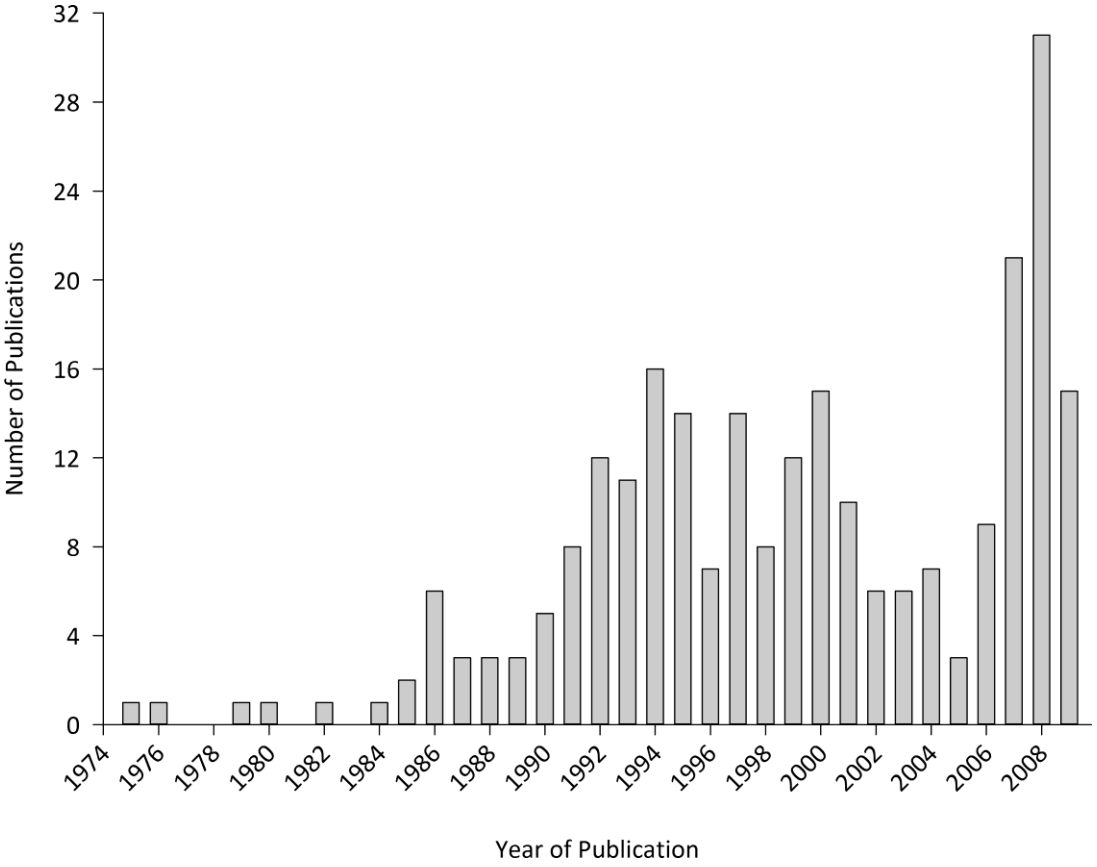


Figure 4.1. Time course of publications. A histogram showing the number of included articles published by year

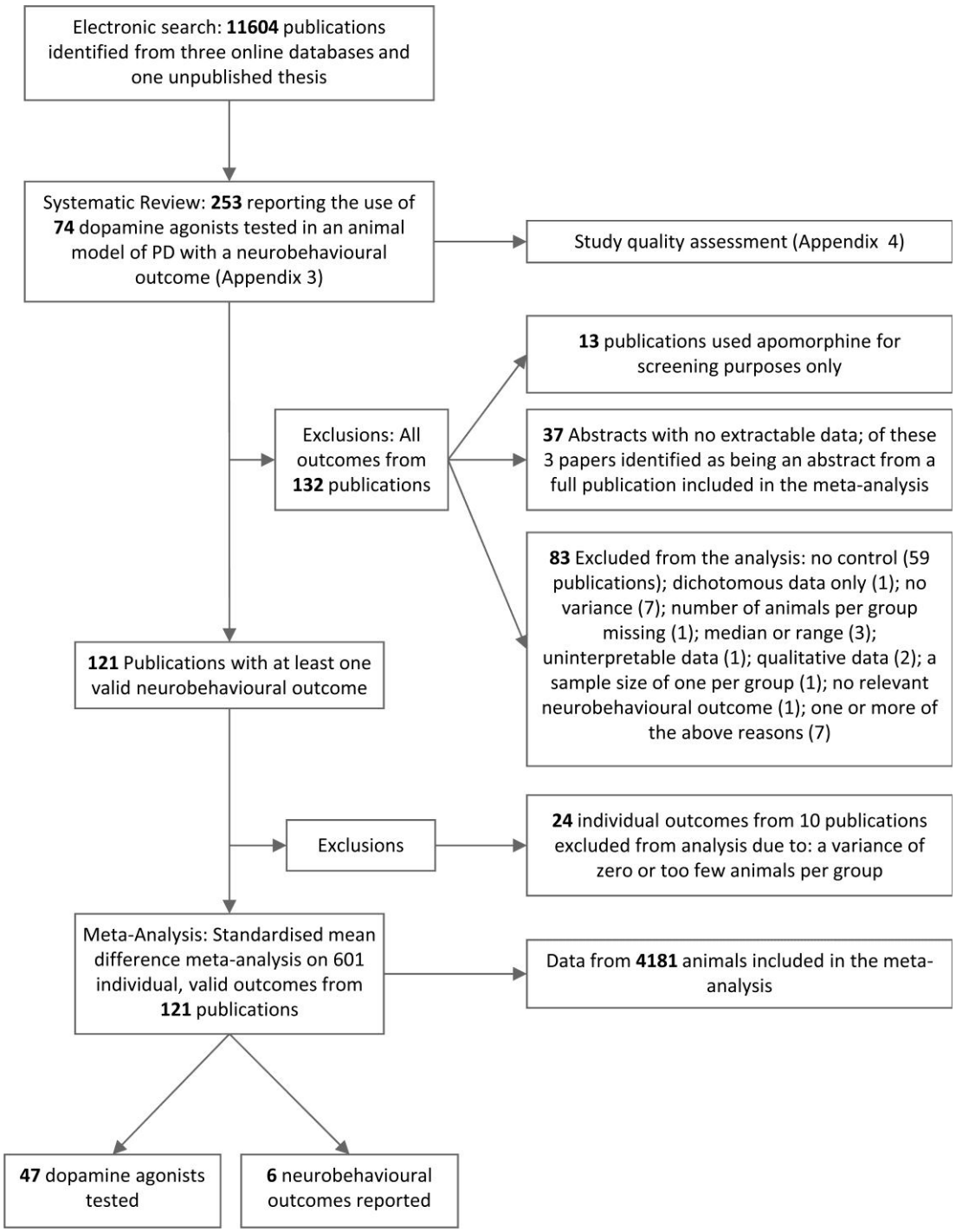


Figure 4.2. Quorum chart showing the progression from the literature search to the meta-analysis

4.4.2. Efficacy of dopamine agonists

Overall, neurobehavioural outcome was improved by 1.10 SD (95% CI 0.99 to 1.22; n=601 comparisons). The efficacy of 47 individual interventions ranged from an improvement of 6.57 SDs (0.75 to 12.4) for BAM-1110 to a significant worsening of -1.35 (-2.49 to -0.21) for Amantadine (Figure 4.3 and Appendix 5). Overall 29 interventions significantly improved outcome, only 1 made it significantly worse, and 17 drugs had no significant effect on outcome. We grouped the outcome measures used into seven broad categories (Table 4.1), and these accounted for a significant proportion of the between study heterogeneity, with largest effects seen when outcome was measured on various Parkinsonism disability rating scales (χ^2= 136.6, df=6, p<0.004, Figure 4.4A).

For the majority of the ten interventions which are in clinical use, we were able to identify a relatively large dataset on their use (Table 4.2). However, we were only able to identify one source on amantadine. Data from this publication was suitable for meta-analysis, although the overall effect size was negative (-1.35 SD (95% CI -2.49 to -0.12)). Cabergoline was also found to show no overall improvement. The other 8 interventions had positive estimates of efficacy although the average quality score was low across all interventions.

Intervention	No. Of Publications[1] (Experiments)	Average Quality Score (out of 6)	Estimate of Efficacy (95% CI)	First Published Animal PD Study	First Published Human PD Trial[2]
Amantadine	1 (4)	1	-1.35 (-2.49 to -0.21)	2008	1969 (Schwab et al.)
Apomorphine	123 (89)	0.6	1.54 (1.19 to 1.9)	1975	1951 (Schwab et al.)
Bromocriptine	32 (58)	0.4	0.96 (0.73 to 1.19)	1982	1976 (Lieberman et al.)
Cabergoline	11 (13)	0.6	0.73 (-0.24 to 1.7)	1994	1990 (Jori et al.)
Lisuride	8 (10)	0.1	1.5 (0.98 to 2.03)	1984	1979 (Lieberman et al.)
Pergolide	13 (14)	0.5	1.01 (0.26 to 1.76)	1980	1979 (Lieberman et al.)
Piribedil	8 (26)	0.8	1.07 (0.48 to 1.66)	1992	1974 (Sweet et al.)
Pramipexole	7 (14)	0.6	1.31 (0.67 to 1.96)	1992	1995 (Hubble et al.)
Ropinirole	16 (23)	0.7	1.85 (1.39 to 2.32)	1991	1989 (Kapoor et al.)
Rotigotine	4 (10)	1.5	1.8 (1.1 to 2.51)	2007	2003 (Blindauer et al.)

Table 4.2. A summary of the evidence from animal studies on interventions with some dopaminergic activity which are in clinical use. [1]For references see Appendix 3. [2]Includes any trial of the intervention in PD subjects regardless of size or quality.

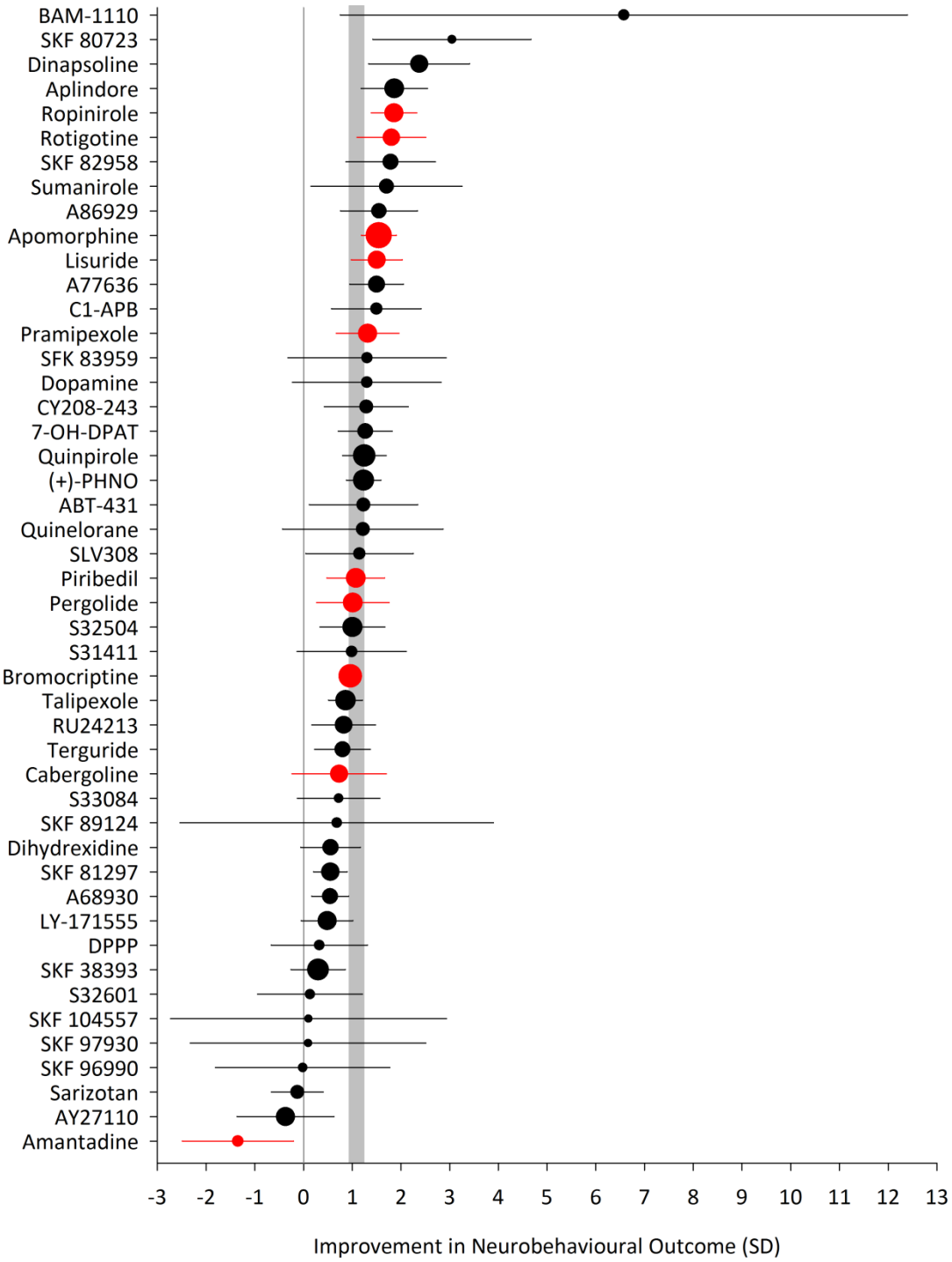


Figure 4.3. Estimates of efficacy of 47 dopamine agonists. The vertical grey bar represents the global estimate of effect size and its 95% CI. Horizontal error bars represent 95% CI and symbol sizes represent the log of the number of animals for that intervention. Interventions shown in red are those used clinically.

4.4.3. Methodological quality

Few studies reported measures to avoid bias (Table 4.3); the median number of quality items scored was 2 out of a possible 6 (interquartile range 1-2) (Appendix 4). Of 253 publications included in our systematic review, 207 publications (81%) were published in a peer reviewed journal, random allocation to group was reported by 40 publications (16%), blinded assessment of outcome by 38 publications (15%), and a sample size calculation by only 1 publication (<1%). Compliance with animal welfare regulations was reported by 100 publications (40%) and a potential conflict of interest by 6 publications (2%).

	PD (253)	**EAE (1464)**	**FCI (260)**	**AD (427)**
Random allocation to group	16%	11%	36%	16%
Blinded assessment of outcome	15%	30%*	29%	22%
Compliance with animal welfare regulations	40%	34%	57%	56%
Sample size calculation	<1%	<1%	3%	0%
Conflict of interest statement	2%	7%	23%	13%

Table 4.3. Study quality assessment. The percentage of publications reporting to meet each quality item in the preclinical literature on four neurological diseases, including PD, EAE, focal cerebral ischaemia (FCI; (Sena et al., 2007a)) and Alzheimer's disease (AD; Egan et al, manuscript in preparation). The number of publications included in the systematic review for each disease is shown in parentheses at the top of each column. *17% of 1446 publications reporting neurobehavioural outcomes and 17% of 1044 reporting histological outcomes.

Collectively for all neurobehavioural outcomes there was an inverse relationship between study quality and effect size (Figure 4.4B) (χ^2=102.3, df=4, p<0.004). Reporting of blinded assessment of outcome was associated with significantly smaller effect sizes (0.85 SD, 95% CI 0.64 to 1.07, 144 comparisons) than those that did not (1.18 SD, 95% CI 1.05 to 1.31, 457 comparisons; χ^2=64.4, df=1, p<0.004). Using meta-regression we found that blinding had a different impact on each outcomes measure with the biggest differences seen between skilled motor activity and spontaneous activity (Figure 4.4C). Randomisation did not impact on reported efficacy and was not explored further.

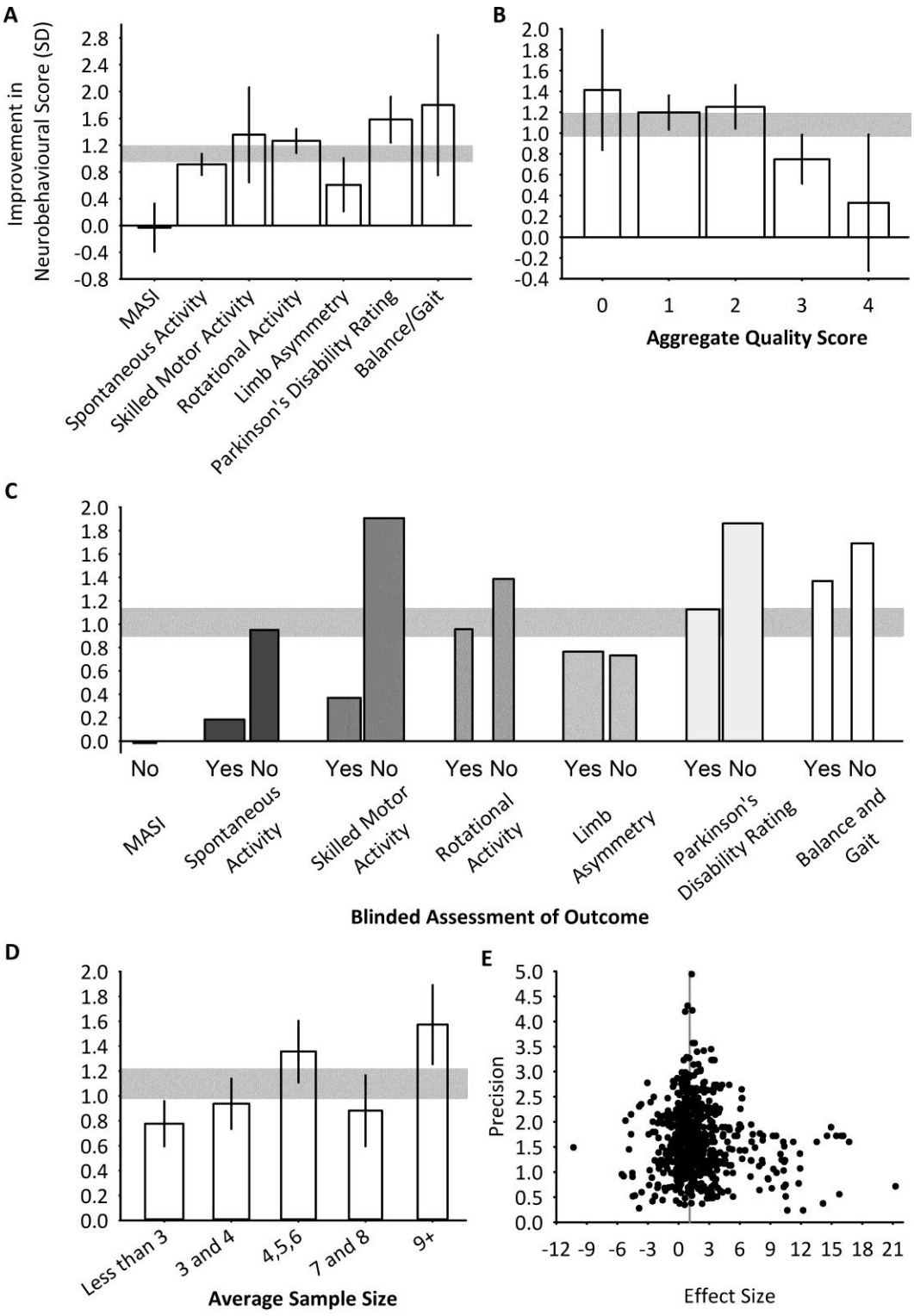


Figure 4.4. The improvement in different neurobehavioural outcomes (A), and the effect of aggregate quality score (B) blinded assessment of outcome (C) and mean sample size (D) on the estimates of effect size, and a funnel plot (E) to test for the presence of publication bias. In A-D horizontal error bars represents the 95% CI of overall efficacy; bar width reflects the number of animals used. In E the vertical grey bar represents the global estimate of efficacy.

4.4.4. Sample size

The median number of animals was 5 in the treatment group (IQR 4 to 8) and 2 in the control group (IQR 1 to 4) giving a median total number of animals per group as 8 (IQR 5 to 12). The number of animals per group accounted for a significant proportion of between group heterogeneity (χ^2=57.4, df=4, p<0.004); however there was no clear trend between the sample size and reported effect size (Figure 4.4D).

4.4.5. Publication bias

Our analysis on publication bias was conducted on effect sizes calculated from 876 pre-nested experiments. Funnel plot inspection and Egger regression suggested a preponderance of imprecise studies overstating efficacy which is consistent with publication bias (Figure 4.4E), but this was not confirmed by the "trim and fill" iterative approach.

4.4.6. Study design characteristics

vii. Parkinson's disease model

Of the 253 publications identified in the systematic review, ten different methods of inducing experimental PD were reported. The most common were: 6-hydroxydopamine striatal lesioning was reported in 136 publications, followed by MPTP (105) and reserpine (22). Seven lesioning methods were used in the 121 studies included in the meta-analysis, and the method of lesioning accounted for a significant proportion of the between study heterogeneity (χ^2=197.7, df=6, p<0.004); interventions were most effective when disease was modelled by rotenone lesioning, whereas dopamine agonists did not improve outcome when the lesion was induced in a transgenic mouse model by over-expression of mutated alpha synuclein (Figure 4.5).

viii. Species

Dopamine agonists were tested in rats (141 publications), non-human primates (101), mice (21) and guinea pigs (1) and in one publication the species used was not reported.

The animal species accounted for a significant proportion of between study heterogeneity (χ^2=44.1, df=3, Figure 4.5B); however effect sizes were comparable across all species apart from experiments using guinea pigs which was likely due to the small sample size.

ix. Sex

Experiments were most commonly conducted using male animals (130 publications), followed by both males and females (31 publications) and females alone (30 publications). A further 69 publications did not report the sex used. Overall the sex of the animals accounted for a significant proportion of between study heterogeneity (χ^2=58.7, df=3, Figure 4.5C); effect sizes were largest when males were used or when the sex was not reported. However the latter may be more of a reflection of study quality.

x. Anaesthetic

Eleven anaesthetics (or combinations) were used during the induction of lesioning for experiments with data included in the meta-analysis and these accounted for a significant proportion of between study heterogeneity (χ^2=52.1, df=10, Figure 4.5D); isoflurane was associated with the largest effect sizes, and diazapem & ketamine when used in combination were associated with an overall worsening in outcome. Across all of the publications in the systematic review, the majority of experiments were conducted without using an anaesthetic (71 publications). For 67 publications the lesioning method used would suggest that an anaesthetic would have been administered, but for these publications it was not reported. The next most common anaesthetics included pentobarbital (40 publications), chloral hydrate (22) and ketamine (21).

Time of administration

The median interval between lesioning and administration of treatment was 28 days (IQR 13 to 70) and this accounted for a significant proportion of between study

heterogeneity (χ^2=35.4, df=6, Figure 4.5E). However there was no clear trend between the age of the lesion and efficacy.

xi. Route of administration

For 121 publications with data suitable for meta-analysis, the subcutaneous route of delivery was most commonly used (63 publications), followed by intraperitoneal (38), oral (19), intramuscular (10), dermal (5), striatal (2) and intracerebroventricularly (1) and 3 publications did not report the route of delivery. Route of delivery accounted for a significant proportion of between study heterogeneity (χ^2=25.7, df=7, p<0.004, Figure 4.5F). Of the four most commonly used routes of delivery, subcutaneous injection was associated with the largest effect sizes.

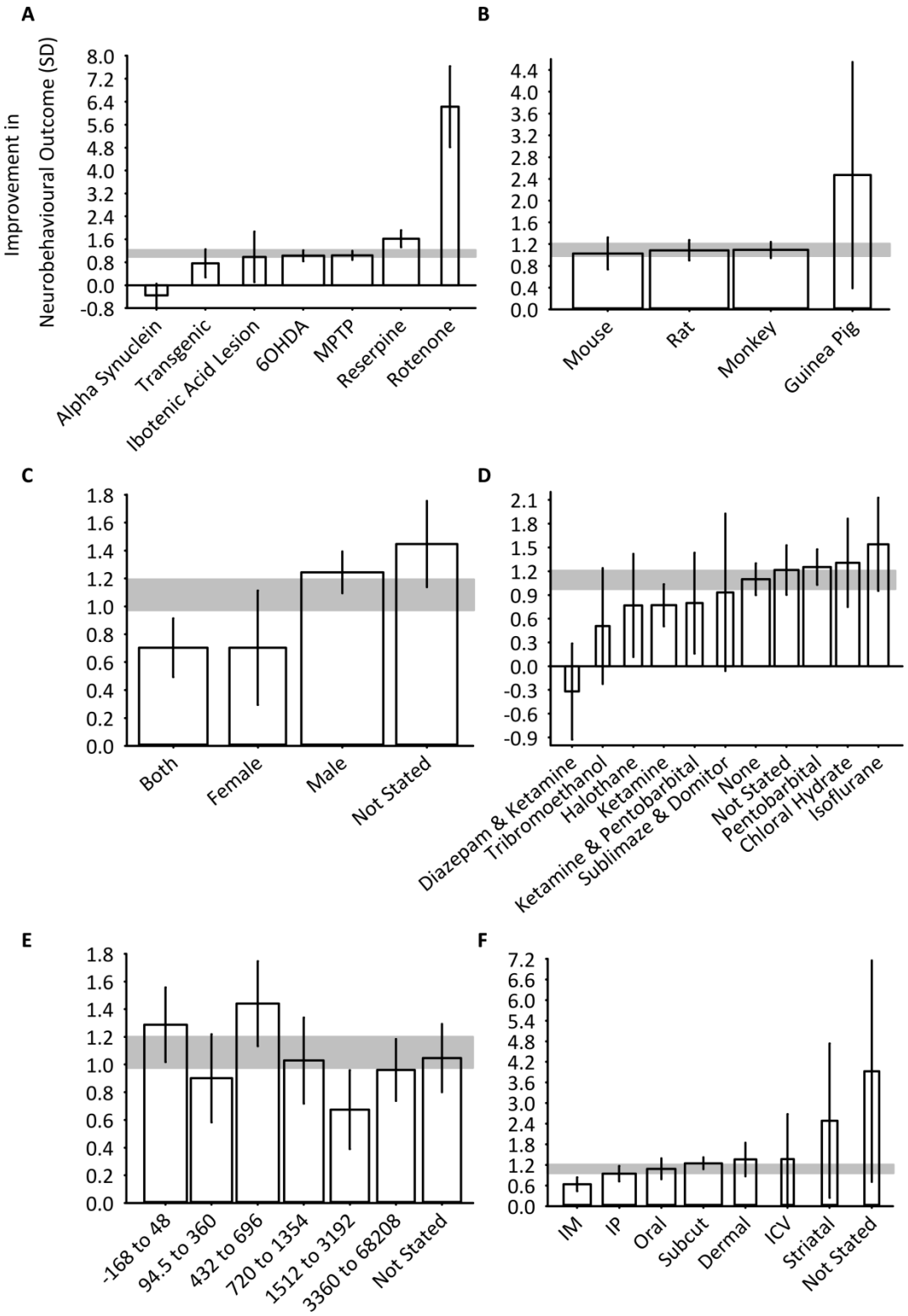


Figure 4.5. The impact of the method of induction of injury (A), animal species (B), sex (C), anaesthetic used during lesioning (D), time to treatment following lesioning (E) and route of intervention administration (F) on the estimates of efficacy. Horizontal error bars represents the 95% CI; vertical grey bar represents the global estimate of efficacy and its 95% CI; symbol size represents the log of the number of animals for that intervention.

4.5. Discussion

4.5.1. Efficacy of dopamine agonists

Dopamine agonists are routinely used in the management of PD, and we have shown here that several have substantial reported efficacy in relevant animal models. Of the ten interventions with at least some dopamine agonist activity used clinically (amantadine, apomorphine, bromocriptine, cabergoline, lisuride, pergolide, peribidel, pramipexole, ropinirole and rotigotine), eight had significant efficacy; cabergoline was without effect and amantadine resulted in a significant worsening in outcome. Interventions with the highest (BAM-110) and lowest (amantadine) efficacy each were reported in only one publication, and because of this and the absence of head-to-head comparisons no reliable conclusions about the rank order of potency can be drawn.

It is possible that since this analysis was conducted, further research on amantadine in animal models has been conducted. Moreover, our search strategy was broad but not deep which may have missed relevant publications from our final list, including those on amantadine. Interestingly however, a systematic review of amantadine in clinical trials found no reliable effect (Crosby et al., 2003). Conversely, rotigotine had higher efficacy and relatively high study quality in the animal models, and moreover, rotigotine appears to be a good exemplar of animal data supporting a successful clinical treatment as it has shown to be effective in humans (Blindauer et al., 2003).

4.5.2. Study Characteristics

Our results suggest that dopamine agonists were most potent when tested in male animals (discussed in section 4.5.6), in guinea pigs, using the subcutaneous route of delivery and when rotenone was used as the experimental model and when isoflurane, chloral hydrate or pentobarbital anaesthesia was used. No improvement was seen in the alpha-synuclein transgenic model; however it is unclear whether this is a biological phenomenon, or these associations are confounded by the quality of the literature.

4.5.3. Study Quality

Measures to avoid bias were infrequently reported. While it is possible that some authors might have taken such measures but not reported them, in the experimental stroke literature there were no significant differences between actual and reported study quality (Samaranayake, 2006), and the same may hold here. This is important because we have shown that across a range of animal experiments modelling stroke and multiple sclerosis, publications which do not report such measures substantially overstate efficacy (Macleod et al., 2008, Macleod et al., 2005c, Sena et al., 2007b, Vesterinen et al., 2010). Here we have shown that the same holds for animal experiments modelling PD. Because of this our findings for efficacy should be interpreted with some caution, and a more detailed review would be required fully to assess the impact of these factors.

In addition to these concerns about the quality of studies included in the review a further 83 publications could not be included because they had no control group, they reported data without reporting its variance, it was not possible to interpret the data as presented or too few animals were used per group for an effect size to be calculated.

We hypothesised that study quality would be increasing over time and conducted a *post-hoc* regression analysis to test this (in Sigmaplot Version 11). Encouragingly we identified that there was a significant trend with a point increase in quality every 18 years.

4.5.4. Sample Size

Animal experiments should be designed to be large enough to have a reasonable prospect of detecting a biologically significant difference yet small enough to minimise unnecessary use of animals. The required size can be estimated using a sample size or "power" calculation, but only one publication reported a sample size calculation. Overall the median number of animals per group was five for the treatment groups (IQR 4-8) and 2 for the control groups (IQR 1-4). As mentioned in Chapter 3, *post-hoc* power calculations have limited validity, but with a median effect size of 1.12 SD and a pooled variance of 0.648, 50% of experiments included in this analysis were powered

at 40% or less, that is to say they only had a two in five chance of detecting the outcomes reported.

Taken together, these findings provide further support for the development of guidelines regarding the conduct (van der Worp et al., 2010a) and reporting (Kilkenny et al., 2010) of animal studies.

4.5.5. Publication Bias

Both funnel plotting and Egger regression suggested publication bias, but this was not confirmed by "trim and fill" analysis, in contrast to the experimental stroke literature (Sena et al., 2010). This analysis is based on the subset of 121 studies included in the meta-analysis, and it may be that were it possible to include the other studies then publication bias might indeed have been found. Furthermore, it has been suggested that trim and fill is an overly conservative statistical approach to the detection of publication bias (Schwarzer et al., 2010), and it may be that with other techniques such as the Copas selection model, or a larger dataset, publication bias would be seen. Research summaries and considerations about taking novel treatments to clinical trial can only assess available data, and given the suggestion that publication bias may exist in this literature we advocate the development of research registries similar to those adopted in clinical research, that such unpublished sources of data might be identified in the development of research summaries.

4.5.6. Comparison with pre-clinical EAE literature

There were some similarities and differences across the experimental PD and EAE literature (Table 4.4). The median quality score were the same and the sample size comparable - albeit slightly smaller in pre-clinical PD experiments. However this may be explained by the substantially larger proportion of non-human primates used in the PD literature (38%) compared to EAE literature (2%). Notable differences included the sex ratios and the median time to treatment. The use of females was over four times more prevalent in the preclinical EAE literature compared to males which reflects the differences in the human condition. Although the evidence has not always been

consistent, particularly in predicting the sex ratio, there is substantial evidence from epidemiological studies that MS is more prevalent in females and PD is generally considered more prevalent in males (Burn, 2007).

Whereas the time to treatment in the EAE literature was commonly on or before the time of EAE induction, it was commonly given a month after lesioning in the preclinical PD literature. Interventions in MS are aimed at halting progression (disease modifying drugs) in a disease marked by neurodegeneration, and outcome is therefore typically measured over a long period of time in clinical trials. Conversely in clinical trials of PD, interventions are typically aimed at short-term relief from motor symptoms. Thus in the EAE literature, the time of assessment relative to intervention administration should be, and is, far longer than in experiment PD models, where the assessment can be made within minutes of drug administration and measured over the course of minutes of hours. However, even relatively short times of assessment relative to drug administration adequately reflect a key area of PD research - targeting immediate relief from the motor symptoms – as long as the time of administration relative to lesioning is long enough to reflect the neurodegeneration in humans. Conversely, the shorter times of administration relative to EAE induction are arguably of limited clinical value when the key area for research nowadays is neuroprotection.

4.5.7. Limitations

As mentioned in Chapter 3, there are a number of limitations to our approach. Firstly, as described above, our analysis can only include published data, and since positive studies are more likely to be published, it is conceivable that our estimates of effect size reported here are overstated. In addition, although we have accounted for multiple comparisons in our statistical evaluation, it is possible that some results occurred by chance.

	EAE	PD
Number of publications in the systematic review (SR) and meta-analysis (MA)	SR (1646); MA (834)	SR (243); MA (121)
Median study quality (IRQ)*	2 (1-2)	2 (1-2)
Time to treatment (median day)**	Neurobehavioural scores & inflammation (0) Demyelination (5) Axon loss (7)	28
Median sample size across both groups**	Neurobehavioural scores (12) Inflammation (9) Demyelination (10) Axon loss (9)	8
Sex**	Female (793; 53%) Male (230; 15%) Both (99; 7%) Not stated (379; 25%)	Female (30; 12%) Male (130; 50%) Both (31; 12%) Not stated (69; 27%)
Publication bias?**	Funnel plot, Egger regression and trim and fill for three neurobehavioural and three histological outcomes	Funnel plot and Egger regression. Not confirmed with trim and fill.

Table 4.4. A comparison between the preclinical literature on drugs tested in EAE and dopamine agonists in EAE. *Of publications in the systematic review. **Of publications in the meta-analysis.

4.5.8. Conclusions

Here we have shown that several dopamine agonists have efficacy in animal models of PD including a number which are not currently in clinical use. However, we found reported study quality to be limited, and that reported efficacy fell as reported study quality increased. We have also found evidence suggesting the presence of publication bias, although we have not been able to quantify its impact. The use of systematic review and meta-analysis and the data presented here provide a framework for an

evidence based approach to the development of new treatments for PD and for the design of future animal and clinical studies. In addition we have shown that the limitations to clinical efficacy in the EAE literature are prevalent here. However, further work is required to fully to elucidate the impact of study quality and design factors on the animal modelling of PD.

5. Assessment of study quality, statistical analysis, and reporting of studies across a field of research: a systematic survey of the 2008 volume of the Journal of Cerebral Blood Flow and Metabolism

I acknowledge the following for their contributions to this research: Kieren Egan (KE) for second screening the publications against the checklist; Peter Schlattmann (PS) for assessing the statistical design reported in each publication; Ulrich Dirnagl (UD) and Malcolm Macleod (MM) for overseeing the study design; and Amelie Deister (AD) for obtaining the PDFs.

5.1. Background

As described in the Chapter 1, drug efficacy identified in animal studies of MS has not always translated into clinically effective treatments (Chapter 3, Vesterinen et al., 2010). This "translational roadblock" is also particularly evident in the cerebrovascular research field, where despite numerous promising preclinical trials, only a few treatments of proven efficacy are available (Dirnagl, 2006, Macleod et al., 2009a, O'Collins et al., 2006). Moreover, a number of systematic reviews and meta-analyses on the preclinical research in this field have demonstrated that low study quality at various stages in the research process might have reduced their internal validity, leading to falsely positive findings (Macleod et al., 2004, Macleod et al., 2005b, Macleod et al., 2005c, Macleod et al., 2005a, Sena and Macleod, 2007, Sena et al., 2007b, Wheble et al., 2008, Macleod et al., 2008, van der Worp et al., 2010a, Dirnagl, 2006, Banwell et al., 2009, Frantzias et al., 2011).

An extensive literature has accumulated with a primary focus of quality assessment of clinical trials, specifically assessing study design, statistical analysis, and trial reporting (Altman, 1998, Sarter and Fritschy, 2008, Glantz, 1980). This paved the way for establishment of standards for conducting and reporting clinical trials—namely the initialisation and implementation of practices such as Cochrane

(http://www.cochrane.org), CONsolidated Standards of Reporting Trials (CONSORT) (http://www.consort-statement.org), web-based trial databases (e.g., http://www.clinicaltrials.gov, http://www.controlled-trials.com), and STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (http://www.strobe-statement.org) (Moher et al., 2001b, Moher et al., 2001a, Bellolio et al., 2008). These measures have vastly improved the validity of clinical trials and ultimately their impact on patients (Moher et al., 2001a). However, in the translational preclinical realm, and particularly in translational cerebrovascular medicine, such approaches have been advocated more recently, e.g., Stroke Academia Industry Roundtable (STAIR) (http://www.thestair.org) and Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES, http://www.camarades.info) (Macleod et al., 2009b, Dirnagl, 2006). Despite the lessons learned through clinical trial quality assessment, few studies have formally investigated such factors in the basic science and translational preclinical trial realms (Dirnagl, 2006). Those that have, included publications from more than one scientific journal and assessed publications across various research fields (Kilkenny et al., 2009, Ioannidis, 2005, Nieminen et al., 2006, Schroter et al., 2008). To our knowledge, no systematic investigation focusing on study design, statistical analysis, and reporting in the field of translational cerebrovascular research has been carried out.

5.2. Aims

The aim of this study was to establish a baseline for the changes which might occur as a result of the adoption of reporting guidelines. To achieve this we chose to assess articles in the Journal of Cerebral Blood Flow and Metabolism (JCBFM) which is a leading journal of the International Society for Cerebral Blood Flow and Metabolism, as it stands at the interface between basic and clinical neurovascular research. Specifically our objectives were to compile a comprehensive checklist and apply this to assess the scientific reporting, experimental design and statistical analysis of all original articles published in the 2008 volume of the JCBFM.

The JCBFM is a relatively high impact journal (5.008), and is ranked 20th of 121 journals in endocrinology and metabolism, and 11th out of 68 in hematology and 14th out of 243

in neuroscience (Thomson Reuters, 2011). Therefore we hypothesised that the overall quality of the studies would be high, reflecting the journals' position in this field.

5.3. Methods

5.3.1. Search strategy

We downloaded electronic copies of all full publications in volume 28 of JCBFM (issue 1, January 2008 to issue 12, December 2008 inclusive). We screened each publication and categorised them according to study type: animal (including rodents, primates, canines, and birds), *in vitro*, or human studies, review articles, commentaries, communications, errata, and corrigenda.

5.3.2. Inclusion and exclusion criteria

Review articles (8 publications), commentaries or communications (21), or errata and corrigenda (8) were excluded from further analysis.

5.3.3. Study questionnaire

We developed a comprehensive study quality checklist to capture the key aspects of the reporting of (1) experimental design, (2) experimental analysis and statistics, and (3) the overall quality of reporting. Such checklists for reporting standards are commonly used in other research domains (particularly in clinical trials), and we began by creating a catalogue of possible checklist items from publications in these other domains. Some items thus identified were clearly not relevant to original articles in JCBFM, and after exclusion of these, we selected 15 main items and 9 supplementary items which, in our view, captured most of the important aspects of study reporting, which might reasonably be expected from publications in JCBFM (Table 5.1).

5.3.4. Assessment process

For all items apart from the reporting of specific test statistics (question 8) and the appropriateness of the statistical tests used (question 8a; see next section), two nonblinded reviewers (H.V. and K.E.) independently assessed each publication against the questionnaire. For each question it was reported whether the publication met the criteria (yes), did not meet the criteria (no), the criteria was not applicable to that publication (n/a), or insufficient information was given to assess the criteria (unknown).

5.3.5. Assessing test statistics

An independent, expert reviewer (P.S.), blinded to the authors and their institutes, assessed for the presence of specific test statistics (question 8) and whether the analytical test statistics were appropriate for the underlying experimental design (question 8a). In a statistical analysis, the method of choice depends on the type of data, e.g., numerical or categorical, as well as on the structure and distribution of data. Thus, it was investigated whether the chosen analysis was suitable for data presented. For example, for a comparison of three groups with repeated continuous measurements, it was checked whether an appropriate method, such as an analysis of variance with repeated measures was chosen. To do so, statistical details reported in the selected publications were extracted and given to the reviewer alongside the publications. Moreover, the order in which publications were presented was randomised and the reviewer was blinded to authors, institution, journal, volume number, and digital object identifier number of the publications. Inter-observer agreement κ-Statistics, representing the extent of agreement between the two scorers (H.V. and K.E.), were calculated for each item, except for 8a. As κ is highly affected by the prevalence of t-positive scores, we also calculated separate indices of the proportionate agreement in the observers' positive ("yes") and negative ("no") decisions (Feinstein and Cicchetti, 1990; Cicchetti and Feinstein, 1990).

		Question
Design	1	Was a primary/research hypothesis stated?
	1a	Was an aim/purpose of study stated?
	2	Was the design randomised? (Dirnagl, 2006)
	3	Was allocation concealed?
	4	Was outcome assessment blinded?
	5	Was a statement about sample size given? (e.g., a priori power analysis) (Altman, 2002)
	6	Was study design stated? (Andersen, 1990). Assessed from the abstract e.g. randomised controlled trial; crossover trial.
	7	Were inclusion and exclusion criteria stated? (Altman et al, 1983; Andersen, 1990)
Analysis and statistics	8	Were specific test statistics reported? (Altman, 2002)
	8a	Were statistical tests appropriate for study design?
	9	Was a measure of variance reported? (Andersen, 1990)
	9a	Were S.D. reported?
	9b	Were S.E.M. reported?
	9c	Were confidence intervals reported?
	10	Were the units of analysis specified? (Andersen, 1990; Altman, 2002). I.e. can we tell which animals contributed to each endpoint?
	10a	Were individual data points reported (e.g., in a plot)?
	10b	Were raw data given?
Reporting	11	Were numerical values only given in graphs? (regarding primary hypothesis/main experiment) (Altman, 1998)
	12	Was mortality/number of dead quantified and stated? (Andersen, 1990)
	13	Was the source of experimental organism/cells given? (species, strain, etc.)
	13a	Was the laboratory/company stated where experimental organism was acquired from?
	13b	Was the age of the experimental organism given?
	13c	Was the weight of the experimental organism stated?
	14	Was a control group reported? (Andersen, 1990)
	15	Was a conflict of interest statement given?

Table 5.1. The study questionnaire used to assess the design, analysis and statistics, and reporting of studies in JCBFM.

5.4. Results

A total of 193 original scientific publications were published in JCBFM in the year 2008. Of these, 95 (49%) described animal studies, 49 (25%) described *in vitro* experiments, 34 (18%) included human participants, 8 (4%) were review articles, and 29 (15%) were of other types. Of the 193 total publications, 156 were original studies. Quality assessment of these studies was performed using the checklist presented in Table 5.1. The proportion of animal, cell culture, and human studies meeting each of the checklist items is given in Table 5.2, and is summarised in Figure 5.1. Further summary statistics are given alongside their interpretation in the discussion.

Question			Animal (n=190)			*In Vitro* (n=98)			Human (n=68)			Overall (n=312)		
			Yes	n/a	U	Yes	n/a	U	Yes	n/a	U	Yes	n/a	U
Design	1	Primary/Research Hypothesis stated?	51 (27)	-	-	32 (33)	-	-	24 (35)	-	-	93 (30)	-	-
	1a	Aim/Purpose of study stated?	181 (95)	-	-	90 (92)	-	-	67 (99)	-	-	300 (96)	-	-
	2	Randomisation?	39 (22)	13 (7)	-	14 (15)	3 (3)	-	5 (8)	6 (9)	-	46 (15)	13 (4)	7 (2)
	3	Allocation concealment?	14 (8)	6 (3)	-	2 (2)	3 (3)	-	3 (5)	3 (4)	-	17 (6)	10 (3)	-
	4	Blinded assessment of outcome?	28 (15)	-	-	13 (13)	-	-	17 (25)	-	-	46 (15)	-	-
	5	Statement about sample size given	2 (1)	1 (1)	-	2 (2)	1 (1)	-	0 (0)	-	-	2 (1)	1 (0)	-
	6	Is study design stated?	6 (3)	-	-	2 (2)	-	-	9 (13)	-	-	16 (5)	-	-
	7	Are inclusion and exclusion criteria stated?	26 (14)	-	-	11 (11)	-	-	29 (43)	-	-	58 (19)	-	-
Analysis & Statistics	8	Are specific test statistics reported?	84 (88)	-	-	36 (73)	-	-	31 (91)	-	-	132 (85)	-	-
	8a	Are applied statistical tests appropriate for	73 (77)	-	-	42 (88)	1 (2)	-	30 (88)	-	-	127 (81)	-	-
	9	Measure of variance reported?	183 (97)	2 (1)	-	95 (99)	2 (2)	-	66 (99)	1 (1)	3 (4)	302 (97)	2 (1)	-
	9a	Standard deviation (s.d.) reported?	86 (47)	8 (4)	-	36 (38)	2 (2)	14 (15)	44 (66)	1 (1)	3 (4)	150 (50)	9 (3)	25 (8)
	9b	Standard error of the mean (s.e.m.) reported?	92 (51)	8 (4)	-	47 (49)	2 (2)	14 (15)	24 (36)	1 (1)	3 (4)	140 (46)	9 (3)	25 (8)
	9c	Confidence interval (C.I.) reported?	5 (3)	8 (4)	-	1 (1)	2 (2)	14 (15)	5 (7)	-	-	10 (3)	9 (3)	25 (8)
	10	Units of analysis given?	85 (34)	1 (1)	-	37 (38)	1 (1)	-	40 (62)	3 (4)	-	140 (46)	5 (2)	-
	10a	Are individual data points reported	24 (13)	-	-	16 (16)	-	-	22 (32)	-	-	59 (19)	-	-
	10b	Are raw data given?	13 (7)	-	-	11 (11)	-	-	13 (19)	-	-	34 (11)	-	-
Reporting	11	Numerical values only given in graphs?	110 (59)	2 (1)	-	50 (52)	2 (2)	-	28 (41)	-	-	163 (53)	2 (1)	-
	12	Mortality/Number of dead stated?	16 (9)	19 (10)	-	6 (8)	24 (24)	-	4 (8)	19 (28)	-	22 (8)	53 (17)	-
	13	Source of experimental organism/cells	158 (92)	19 (10)	-	82 (93)	10 (10)	-	23 (100)	45 (66)	-	224 (93)	71 (23)	-
	13a	Laboratory/Company stated where	91 (53)	19 (10)	-	51 (57)	9 (9)	-	13 (54)	44 (65)	-	133 (55)	68 (22)	-
	13b	Age of experimental organism given?	75 (42)	11 (6)	-	38 (46)	16 (16)	-	50 (77)	3 (4)	-	145 (50)	23 (7)	-
	13c	Weight of experimental organism stated?	108 (60)	11 (6)	-	38 (46)	16 (16)	-	19 (29)	3 (4)	-	149 (52)	23 (7)	-
	14	Is a control group reported?	162 (86)	1 (1)	-	80 (82)	1 (1)	-	49 (73)	1 (1)	-	254 (82)	3 (1)	-
	15	Conflict of interest statement given?	54 (28)	-	-	23 (23)	-	-	31 (46)	-	-	94 (30)	-	-

Table 5.2. The total number of animal, *in vitro*, and human studies meeting each of the checklist items (yes, not applicable (n.a.), and unknown (U)) as assessed by both reviewers in relevant publications (those which were not n.a.). Some publications reported more than one type of subject (animal, *in vitro*, and human) and are therefore represented more than once. Values in brackets represent percentages. Only one reviewer assessed questions 8 and 8a, and therefore, values are for half the sample size given in column headings.

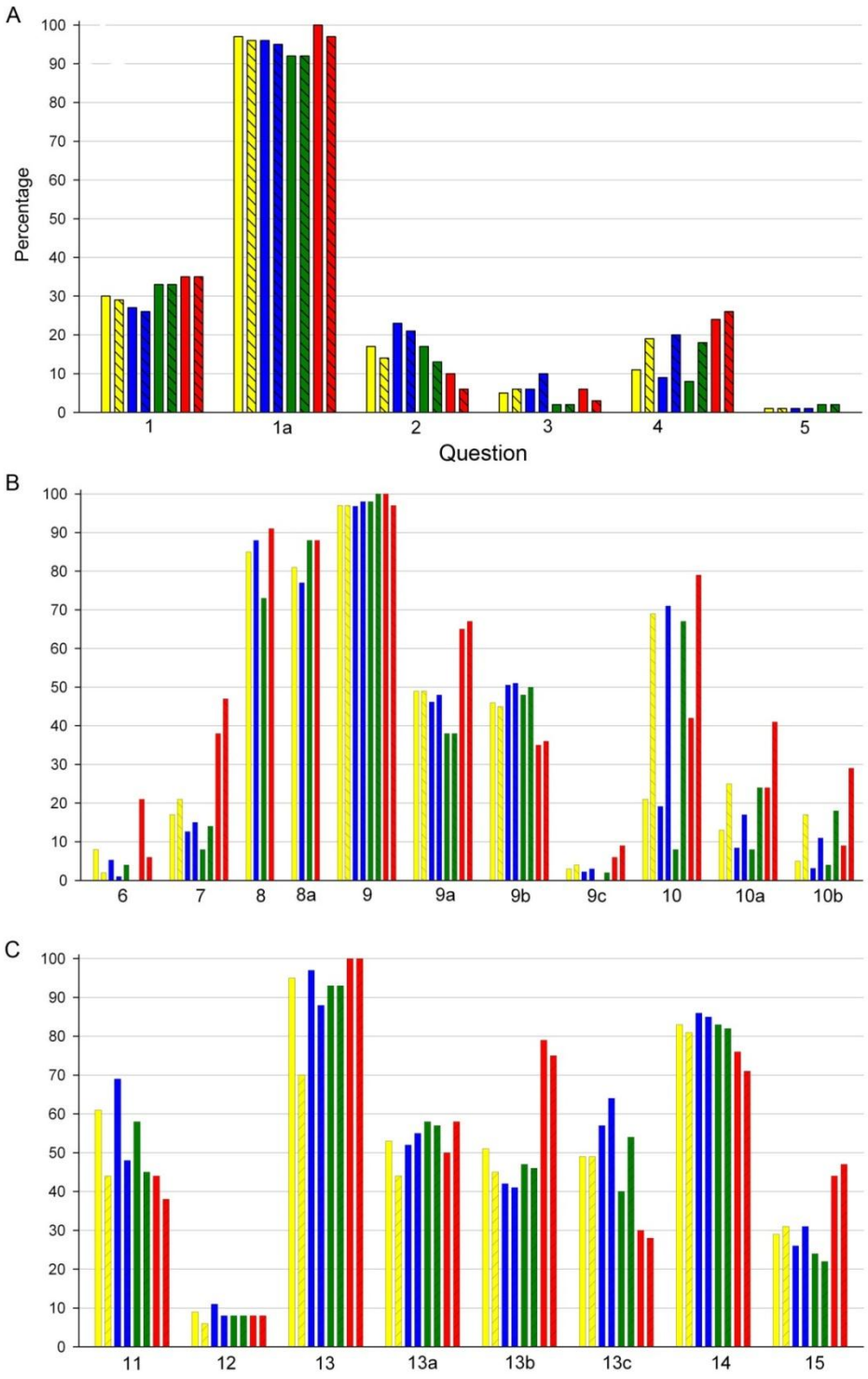


Figure 5.1. Comparison of the results obtained by two reviewers (HV: solid colour; KE: diagonal stripes) assessing the publications presenting all included publications (N=156, yellow), animal studies (N=95, blue), *in vitro* studies (N=49, green), and those involving human participation (N=34, red). X axis values indicate the corresponding question number as it appeared on the questionnaire (see Table 5.1. The study questionnaire used to assess the design, analysis and statistics, and reporting of studies in JCBFM), and y axis values represent the number of publications expressed in percentages (0% to 100%). For numerical values, see Table 5.2.

5.5. Discussion

In this systematic survey of 156 original research articles published in JCBFM in 2008 we identified a number of potential shortcomings in their reporting, study design and statistical analyses.

Scientific findings are disseminated to the public domain predominately via publication in relevant journals; thus adequate reporting is essential. Articles should be the primary source of information necessary to replicate the experiment and/or assess its internal and external validity. However, issues relating to poor methodology and reporting are prevalent across the field of preclinical cerebrovascular research and these are thought to contribute to the translational failures (Dirnagl, 2006, Sena et al., 2007a, Phillips et al., 2008, Fisher et al., 2009, Crossley et al., 2008, Jerndal et al., 2010, Dirnagl and Macleod, 2009). Moreover, these concerns are not unique to this field. As I described in Chapter 3, inadequate reporting was extremely prevalent in the preclinical EAE literature, and study quality was poor. Moreover, others have found similar results when surveying animal experiments in general (Kilkenny et al., 2009), medical research in general (Altman, 2002), and statistics in experimental and clinical medical papers (Holmes, 2004, Zinsmelster and Connor, 2008, Phillips et al., 2008, Glantz, 1980, Hoffmann, 1984, Garcia-Berthou and Alcaraz, 2004)

Ethical considerations regarding the use of animals in research and the well-being of patients dictate that experiments be conducted and analysed according to good laboratory or clinical practice (GLP, GCP), and that reporting of the results be comprehensive, accurate, and transparent. More than a decade ago, following an analysis of deficiencies in the quality and reporting of randomised clinical trials, journal editors, epidemiologists, and statisticians have published the CONSORT statement and the CONSORT checklist of items to include when reporting a randomised trial (Moher et al., 2001b). Since then, the quality of reporting and quality in general of randomised clinical trials has greatly improved, which has at least in part been attributed to this process (Plint et al., 2006, Hopewell et al., 2010). The current study was conducted to further raise the awareness of quality issues in neuroscience research, and to further the implementation of a CONSORT-like statement in experimental medical research.

5.5.1. Specific Checklist Items

xii. Purpose/aim and hypothesis

A clear statement on the objective of a study or its main hypothesis being tested is critical for the reader to assess the appropriateness of the study design, methods, analysis, and implications. We found 30% of publications explicitly stated a primary research hypothesis; however, 97% indicated the aim or purpose; 44% indicated both, and only 3% gave neither a hypothesis nor an aim (percentages given herein represent the mean of both reviewers). Interestingly, the reporting of these was only slightly higher in human clinical studies where the regulatory environment is stricter than experimental or *in vitro* studies (see Figure 5.1, Table 5.2). Where a study hypothesis is well defined and an analysis protocol agreed in advance of experiments being conducted, the risk of chance associations being considered of significance are diminished. Moreover, this is the laboratory equivalent of the *post-hoc* subgroup analysis of clinical trial data, which can at best be considered hypothesis generating only. Where a clear hypothesis is stated, data presented that are not relevant to this can be interpreted appropriately (Andersen, 1990).

xiii. Randomisation, allocation concealment, blinded assessment of outcomes

The importance of taking adequate measures to reduce bias – and thus to improve the internal validity of a study – has been described extensively in the clinical and preclinical literature. Where these are not reported, there is consistent evidence to suggest that effect sizes are overinflated, and moreover that these contribute to translational failures. In the present study, fewer than 20% of publications reported three key measures to reduce bias, namely randomisation, allocation concealment and blinded assessment of outcome. This is broadly similar preclinical MS and PD literature (Chapter 3 and 4 respectively) for which we have data for the prevalence of reporting of randomisation and blinded assessment of outcome (for comparison see Table 4.3 in Chapter 4). In the few publications in the present study in which randomisation was mentioned, it was unclear whether proper procedures were followed. Moreover, in some studies, randomisation or blinded assessment may not have been feasible, or indicated. However, as reporting of these items is not common, it is often not possible

for readers to assess whether such studies are indeed flawed. It should be noted that in two recent studies focusing on experimental stroke studies, roughly 50% of the included studies reported randomisation (Minnerup et al., 2010, Philip et al., 2009).

xiv. Sample size

Only 1% of the studies reported either sample size calculations or power analyses, or the effect size that could have been detected, given the variance of data and the preset levels for α (risk of committing a type I error, or false positive) and β (risk of committing a type II error, or false negative) (Sterne et al., 2001, Mulaik, 1997, Schlattmann and Dirnagl, 2010b). Again this percentage is broadly similar to that of the preclinical MS and PD literature and provides further evidence that sample size calculations are rarely conducted across the field of preclinical experiments. The statistical power of a study informs us not only about the risk of false negatives but it is also directly related to the reproducibility and positive-predictive value of the experimental results (Ioannidis, 2005). Again, in some of the studies in this survey, a priori sample size calculations would not have made sense. However, for the majority of studies, they would have been helpful in designing experiments. Most studies included here were in fact grossly underpowered; with sample sizes of 10 per group (which is at the high end of sample sizes found), an α-value of 0.05 and a β-value of 0.8, effect sizes of 1.33 times the SD can be detected (two-sided, independent samples t-test). As variance in most of the reported experiments is quite high (e.g., SD 30% of the mean), this implies that these studies are only powered reliably to detect a 32% mean change in outcomes, such as infarct volume or neurobehavioral score.

xv. Study design

We established the design of the study if it was reported in the abstract. However, the process of categorising and assessing the study design of the included publications was not trivial. In fact this was not so much due to problems with individual manuscripts, but rather because well-established nomenclature is only available for clinical trials (e.g. randomised control trial, cohort study, phase 1 trial, etc…). The implementation of an analogous terminology for the field of experimental research would be of substantial aid in understanding the design and implications of a study. Interestingly however,

despite a range of analogous terminology available to describe the design of human studies, this information was missing almost as often as in the experimental studies.

xvi. Inclusion and exclusion criteria, mortality, control group

Reporting inclusion and exclusion criteria in the 'Methods' section, and exclusions, dropouts, or mortality (including the reasons behind it) of the experimental groups in the 'Results' section is another key element to prevent bias and to improve the internal validity of a study. We found that <20% (29/156) of the publications reported inclusion and exclusion criteria. Mortality was reported in only 8% (20/129) of studies in which it was relevant; a further 27 studies reported for instance imaging findings, human participants, or purely *in vitro* experiments. We propose that it should be made mandatory to publish mortality rates in animal experiments, as this would prevent the masking of a severe bias which could, e.g., result from excluding severely affected animals in only one of the experimental groups. Control groups are crucial measures to safeguard that an effect is a true effect of the manipulation or condition under study, and to minimise the effect of other, unintended variables on the results. More than 80% of the publications reported the use of control groups. Assuming that in a fraction of articles, control groups would not have made sense, this figure is comforting as it points to a widespread use of this key element of the scientific method.

xvii. Experimental animals and study subjects:

Adequate reporting of the specific characteristics of a study (including the animal species, strain, sex, sub-strain, supplier, genetic background, age, weight, comorbidities etc…) is necessary both to be able to replicate the experiment, and to assess the implications of the study. In a systematic review and meta-analysis of NXY059 or nicotinamide in experimental stroke, performance was significantly higher in animals without comorbidities (Macleod et al., 2004, Macleod et al., 2008). These models are of limited value for a disease commonly associated with comorbidities such as hypertension and diabetes.

xviii. General reporting of statistical analysis

Specific test statistics were reported in 85% of the assessed publications. Of those, expert statistical assessment revealed that 81% (127/156 relevant publications) of the studies used appropriate approaches and test. The remaining articles either used inappropriate statistical analyses or did not supply the reader with sufficient information to comprehend the reported results. The lack of information made it difficult to evaluate the appropriateness of given statistical tests, and moreover, of the 156 assessed studies, 3 did not provide enough information to judge the methodological quality. When performing statistical analysis, the method of choice depends on the type of data, e.g., numerical or categorical, as well as on the structure and distribution of data. In all studies assessed, the choice of statistical method was appropriate for the type of data under study. However, in terms of structure, the results were different. Among others factors, the structure of the data is given by the number of groups considered, e.g., one, two, or more than two groups. If the number of groups is larger than two, applying multiple t-tests without correcting for multiple comparisons is not appropriate. This error occurred in 4 of the 156 studies reviewed. Often, a more complex design is chosen, e.g., when several measurements per animal or subject are taken. In this case, the data points are dependent as we are measuring on the same subject. This introduces a correlation between individual measurements. In such cases, statistical tests that require independent data, such as the unpaired t-test or an analysis of variance, are not appropriate. This error occurred in 22 of the 156 assessed studies.

xix. Measure of variance

A high proportion of publications included a measure of variance (151/155; 97%). Authors most commonly chose to report SDs (49%), followed by SEM (46%) with far fewer choosing confidence intervals (4%). A further 9% of relevant publications did not state the type of variance reported. Although popular because it produces smaller whiskers in graphs for descriptive purposes, SEM is not considered an acceptable measure. The latter is an estimate for the precision of estimating the mean, not a description of the sample (Altman and Bland, 2005, Schlattmann and Dirnagl, 2010a).

xx. Units of analysis, data points

Most of the assessed studies represent data numerically, and more or less directly indicate the unit of analysis (e.g., an Eppendorf tube, right or left hemisphere, a single animal, a group or a cage of animals). Nonetheless, in some cases, the experimental unit/unit of analysis could not be identified. Data for individual study objects (instead of only presenting group data) were found in 30 publications, and raw data were provided in 17 publications. Reporting raw data and individual data points can help the reader to assess the quality and dispersion of results. As most studies were reporting on rather low numbers of subjects, and because most journals allow almost unlimited publication of additional data as Supplementary material on the website of the journal, we strongly encourage authors to provide as much detailed information as useful and possible. This, in many cases, includes the plotting of individual data points in scatter plots and the listing of numerical values in tables (Schlattmann and Dirnagl, 2010a).

5.5.2. Limitations

Our survey has a number of limitations. None of the dichotomised percentages (yes/no) of the items of our questionnaire (Table 5.1) can be interpreted as quality statements in themselves. For example, if it is said that 85% of all studies did not use allocation concealment, then it must be kept in mind that not all studies may have allowed designs in which allocation could be concealed, or allocation concealment may have not made sense. We have repeatedly alluded to this constraint in the above discussion. In any case, these numbers present a first overview on the reporting and statistics practices of the surveyed volume. Our approach was to define criteria and then apply them to all publication categories (such as experimental, animal, and clinical) rather than to define criteria specific to each. Although there might be concerns that not all criteria would be appropriate in each publication category, in fact this was not the case; each criterion was scored as being present in at least one publication from each category and at worse, one-third of publications in a category could be scored (source of experimental organism, human studies). Even with criteria specific to each publication category, we would have some in which criteria were not appropriate, and we believe that our approach has the benefit of being simple and broadly applicable. It might be argued that some of the questions used in this survey may not be answered in an unambiguous manner. For example, we might have

answered question 1: Primary/ research hypothesis stated? with 'no', because the hypothesis was not explicitly phrased as such ('In our study we tested the hypothesis that.'), but the author of the study might object because he might insist that the hypothesis reveals itself allusively from the text. However, we argue that a suitably skilled reader should be clearly presented with all the relevant information of a scientific communication, which includes aims, purpose, and hypotheses, to be able to understand, analyse, and potentially replicate the findings. To assess potential bias of the assessor, we used two assessors, and found a very high degree of inter-rater agreement. In all categories, questions were more often answered by the scorers with 'no' than with 'yes'. For many questions, a score of 'yes' was low. This in some instances lead to low κ -values despite high agreement between scorers, as κ is not reliable for rare observations because it is affected by the prevalence of observations. Restricting our analysis to JCBFM may introduce bias, which precludes generalisation of our results to studies published in other journals. This is very unlikely, as JCBFM is one of the top-ranked journals in the field of experimental cerebrovascular and stroke research. Standards for publication, authors, reviewers, etc., are similar to other journals in the field, such as Stroke. We have opted to restrict our analysis to this journal, as its scope was ideally suited to survey experimental studies and clinical proof-of-concept studies. We hypothesise that surveying related journals, and even scientific journals in other experimental-translational areas in life sciences would yield very similar results.

5.5.3. Conclusions

In this systematic survey, we found indicators for deficiencies in the design, reporting, and statistical analysis of the original articles in a recent volume of JCBFM, one of the leading journals in the cerebrovascular field. There is ample indirect and direct evidence that this is not a problem unique to this particular journal, or even research field. We, along with others (Kilkenny et al., 2009, e.g. Fisher et al., 2009, Macleod et al., 2009b, Percie du Sert, 2011, du Sert, 2011), believe that quality issues in experimental life sciences are an important reason for why we are currently facing roadblocks to translation from bench to bedside (and vice versa). Only a joint effort of the scientific community (authors, readers, reviewers, editors, professional societies, etc.) can improve the current situation. The results of our study, together with a thorough analysis of the measures that were successfully taken in clinical medicine to improve

study quality, indicate some of the action points. We propose that, in analogy to the CONSORT statement, a set of standards for reporting of experimental studies in biomedicine is used. Like with CONSORT, journal editors need to adopt these standards. Journals need to educate their readers and create awareness in areas, such as proper study design and analysis. Indeed, Kilkenny et al (2011) have recently proposed such reporting guidelines (Animal Research Reporting In Vivo Experiments, ARRIVE; http://www.nc3rs.org/ARRIVE) using the CONSORT statement as a foundation. Reviewers need to be more critical regarding missing hypotheses, deficiencies of experimental design, insufficient statistical power, or inadequate information in the submitted articles.

6. The relationship between treatment related effects on neurobehavioural and histological outcomes in EAE: a systematic approach to regression and path analyses

I acknowledge the contribution of Malcolm Macleod and Emily Sena for help with the study design and interpretation of results.

6.1. Introduction

Inflammation is widely considered to be the driving force behind the classic relapsing-remitting MS (RRMS) disease course which the majority (70%) of patients follow. However, 65% of these patients transition to secondary progressive MS (SPMS) (Compston and Coles, 2008), and 10-15% first present with a progressive disease course (Miller and Leary, 2007). For both of these the permanent and increasing disability is thought to be caused by axon loss (Trapp et al., 1999), which can occur independently from inflammation and demyelination (Bruck, 2005). With this in mind, it is perhaps not surprising that the clinically available disease modifying interventions, all of which are immune-modulatory or immunosuppressive are biased towards the treatment of RRMS (Lim and Constantinescu, 2010).

As described in Chapter 3, the vast majority of experiments on EAE measure efficacy as a change in neurobehavioural score which is typically measured on a 0 (healthy) to 5 (moribund or death) scale. This grades the characteristic ascending paralysis seen in most varieties of EAE. Previously we have used systematic review and meta-analysis to summarise the efficacy of interventions when they have been measured against neurobehavioural (Vesterinen et al., 2010) and histological outcomes including axon loss, demyelination and inflammation (Chapter 3). With axon loss being a target for current drug research, we aimed to use this systematic approach to assess the extent to which axon loss is being measured in publications, and to assess the relationship between different outcome measures.

Specifically our objective were to: (1) summarise the outcome measures which are reported in the preclinical literature reporting interventions tested in EAE; (2) pool data from experiments where more than one outcome are measured in the same cohort of animals; (3) use meta-regression to assess the extent to which treatment related effects in one outcome measures are associated with the treatment related effects in another; and (3) use meta-pathway-analysis to hypothesise the sequence of treatment related histological events which lead to the improvement in neurobehavioural scores.

6.2. Methods

6.2.1. Dataset

The present analysis was carried out on a subset of the data previously extracted onto the CAMARADES Data-Manager which are described in Chapter 3. Specifically, we included in this analysis publications reporting valid (see below), quantitative data for two or more outcomes which included axon loss, demyelination, inflammation or neurobehavioural scores where these were measured in the same cohort of animals. Outcomes were valid if we could extract the number of animals, a mean score and its variance (SEM or SD).

Any neurobehavioural outcome measured on a clinical scale was valid for inclusion. In initial analyses we grouped these into three categories which were later combined for the purposes of assessing the effect of time to treatment: (1) mean severity scores (mean severity score, the product of mean severity and duration, the product of mean severity plus number of exacerbations); (2) mean clinical scores and mean cumulative scores; (3) the clinical score on the day that the histological outcome was quantified. For publications reporting quantifiable histological data, we included any outcome measured as change in axon loss, demyelination and/or inflammation whereby these were measured directly; thus we excluded publications where the researcher manipulated the system for measurement using methods other than staining e.g. change in DNA expression of inflammatory markers, results from a FACS or ELISA analysis. Some publications reported a “histological score” which combined data from inflammation and demyelination, and we excluded these from our analyses.

6.2.2. Data Analysis

For individual comparisons we calculated effect sizes as SMDs to account for the lack of reported data for sham animals for a large proportion of comparisons (see section 2.2.2). We used meta-regression to identify the relationship between treatment related variations in different outcome measures. We conducted the meta-regression analyses in Stata (section 2.3.2) which gave us adjusted R^2 values which we have expressed as percentages and hereafter refer to as R^2. We made the assumption that the changes in neurobehavioural scores are a consequence of changes in EAE which might be detected in histological outcomes. Therefore we took the effect sizes for neurobehavioural scores as the dependent variable. Where the relationship between different histological outcome measures was being assessed we took inflammation as the independent variable; and where we assessed the relationship between axon loss and demyelination we conducted two regression analyses so that both were treated as the dependent and independent variables in turn.

We considered values of R^2>1% and <9 to be small effects (weak relationships), >9 and <25 to be medium sized effects (moderate), and >25 to be large effects (strong). These are based on the estimates for the strength of correlation coefficients described by Cohen (1988) which we squared to represent the equivalent values for R^2.

6.2.3. Path Analysis

We used the adjusted R^2 values from the results of the meta-regression analysis to predict the pathway to improvement in neurobehavioural scores. Our aim was to assess the extent to which improvements in neurobehavioural scores, individually or in combination, are mediated through any of the three histological outcomes. Attempts to assess the impact of interventions on the pathway of improvement by categorising into anti-inflammatory and neuroprotective agents was not carried out because it was predicted that the vast majority of interventions would be anti-inflammatory; furthermore, because there were so many interventions tested the number of comparisons available would be too low to make any meaningful judgements.

The strength of the association between treatment related effects for each of two outcome measures represents the *total effect* (X_{TOTAL}) for that pair. That is, X_{TOTAL} is the R^2 value calculated in section 6.2.2 for that pair of outcome measures. This value includes both direct and indirect pathways. For example, the impact of inflammation on neurobehavioural scores may be mediated by the *direct effects* of improvement in inflammation, or this process may be mediated by *indirect effects* through demyelination and/or axon loss; or some combination of the above. The meta-pathway analysis thus allows us to compute the strength of these direct and indirect relationships and use these to build a model of the pathway to improvement in neurobehavioural scores.

We first computed the *direct effect* (X_{DIRECT}) of treatment related improvements in one outcome measure to improvements in another outcome measure. Thus for each pair of outcome measures, X_{DIRECT} is the residual variance calculated by subtracting the strength of the indirect pathway from the known total variance, X_{TOTAL} (Equation 6.1). To calculate the strength of the indirect relationships between outcome measures we multiplied the R^2 values for the steps in the indirect pathway. For example, if the relationship between A and B is 0.6, and between B and C is 0.6, the strength of the indirect pathway between A and C is 0.36.

Equation 6.1

$$\mathrm{X}_{TOTAL} = X_{DIRECT} + SUM(X_{INDIRECT})$$

And thus,

$$\mathrm{X}_{DIRECT} = X_{TOTAL} - SUM(X_{INDIRECT})$$

Where X_{TOTAL} is the R^2 value for the strength of the association between that pair of outcome measures, and $X_{INDIRECT}$ is calculated as the sum of each individual indirect pathway, shown in Figure 6.1.

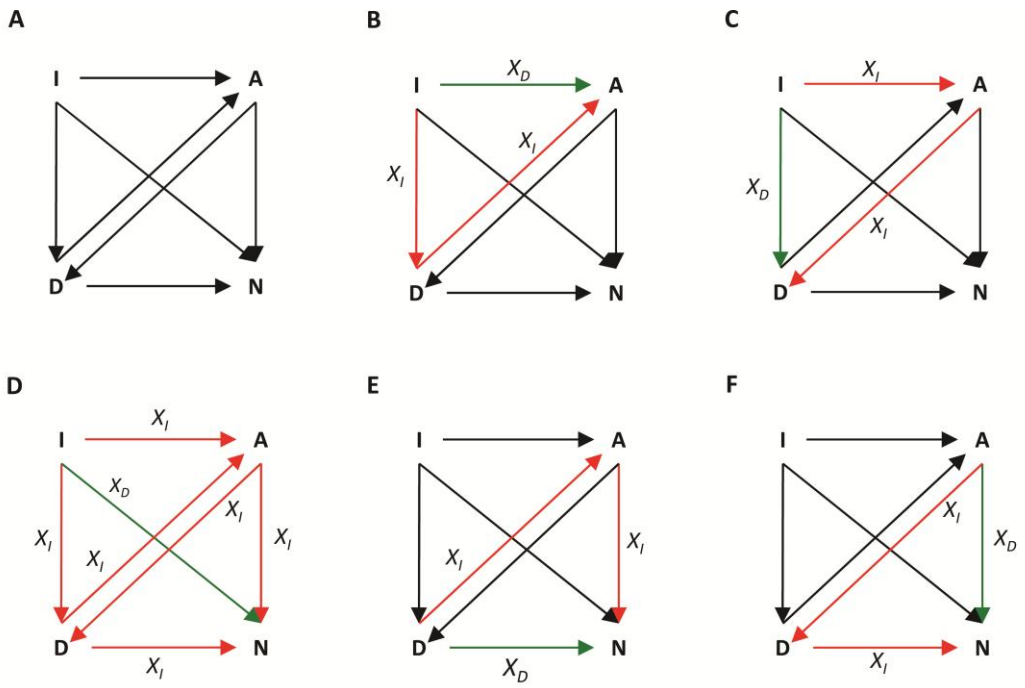
To build the model of the pathway to improvements in neurobehavioural score we made two initial assumptions: firstly, that inflammation is the first step in the model and neurobehavioural scores are the last step in the model; and secondly that a relationship exists between every pair of outcome measures. We sought to establish

whether evidence exists to retain these relationships or to exclude them by calculating the direct effects between each pair of outcome measures in the following order:

1. inflammation and axon loss: this was assumed to be either direct, or mediated through improvements in inflammation on demyelination or axon loss (Figure 6.1B);
2. inflammation and demyelination: this was assumed to be direct or mediated through improvement in axon loss (Figure 6.1C);
3. inflammation and neurobehavioural scores: this was assumed to be direct or mediated through: (i) inflammation on demyelination, and demyelination on axon loss); (ii) inflammation on axon loss; (iii) inflammation on demyelination; (iv) inflammation on axon loss, and axon loss on demyelination (Figure 6.1D);
4. demyelination and neurobehavioural scores: this was assumed to be direct or mediated through effects of demyelination on axon loss (Figure 6.1E);
5. axon loss and neurobehavioural scores: this was assumed to be direct or mediated through axon loss on demyelination (Figure 6.1F).

After each step we excluded the direct pathway in subsequent steps if the strength of the association ($X_{DIRECET}$) was less than 1%. For example, if X_{DIRECT} between inflammation and demyelination is less than 1%, the mediated effects of (I-A-D) would be deleted from step 3, such that the direct effect of inflammation on demyelinating is the same as the R^2 value calculated previously.

We predicted that the strength of the relationship between different outcome measures would change depending on the time of drug administration. Therefore we categorised the data into four broad times of administration and carried out the path analysis on each of the following datasets: (1) grouping all times of administration together; (2) prior-treatment: where the drug was administered on or before day 0; (3) early treatment: where drugs were administered between day 1 and day 8; late treatment: where the drug was administered after day 8. Additionally we took the meta-regression estimate for the strength of the relationship between outcomes for rolling six day epochs. Six days was the lowest epoch for which data were available to investigate the strength of the relationship between the independent and dependent variable. We used linear regression in Sigmaplot (Version 11) to illustrate the strength of relationships.



Equations:

Step B: $X_{DIRECT}(IA) = X_{TOTAL}(IA) - X_{INDIRECT}(I*D) - X_{INDIRECT}(D*A)$

Step C: $X_{DIRECT}(ID) = X_{TOTAL}(ID) - X_{INDIRECT}(I*A*D)$

Step D: $X_{DIRECT}(IN) = X_{TOTAL}(IN) - X_{INDIRECT}(I*D*A*N) - X_{INDIRECT}(I*A*N) - X_{INDIRECT}(I*D*N) - X_{INDIRECT}(I*D*A*N)$

Step E: $X_{DIRECT}(DN) = X_{TOTAL}(DN) - X_{INDIRECT}(D*A*N)$

Step F: $X_{DIRECT}(AN) = X_{TOTAL}(AN) - X_{INDIRECT}(A*D*N)$

Figure 6.1. Steps taken in the meta-pathway analysis, shown in order from A to F. We used the equations shown to calculate the strength of the direct pathway (X_D; green arrows) by substituting in R^2 values which correspond to the overall strength of the association between those two outcome measures (X_{TOTAL}). Where an indirect path ($X_{INDIRECT}$; red arrows) consisted of more than one pair of outcomes, for example, going from inflammation to demyelination to axon loss to neurobehavioural scores (denoted here as I*D*A*N), we multiplied the R^2 values (which in this example would be (X_{TOTAL}(ID) * X_{TOTAL}(DA) * X_{TOTAL}(AN)). The direct effect is the total association strength minus the sum of the association strength in each indirect pathway. If X_D<1% for a relationship between two outcome measures, it was excluded from subsequent steps.

6.3. Results

6.3.1. Extracted Data

We had previously identified 1464 publications on drugs tested in EAE. Of these, 1036 publications reporting more than one outcome measure, regardless of the type of data

(quantitative or qualitative) or the validity of the outcome (whether required information for inclusion in a meta-analysis was reported, i.e. the number of animals, mean score and its variance) or whether the outcomes were measured in the same cohort of animals (Figure 6.2). 99% of publications reported neurobehavioural outcomes (1446/1464), either as the only outcome measure (420/1464) or in combination with other endpoints (1026/1464).

Histological endpoints were reported in 1044 publications, of which the majority used change in inflammation as their endpoint, either alone (618/1044) or in combination with either axon loss and/or demyelination (386/1044). In total, axon loss was reported in 117 (of 1464) publications and demyelination by 388 publications. Of the 1036 publications reporting more than one outcome measure, 291 publications reported more than one *valid* outcome suitable for meta-analysis from the same cohort of animals of which there were 620 individual cohorts. The majority of cohorts had two outcomes reported (437/620 cohorts; 198/291 publications), followed by three outcomes (118/620 cohorts; 63/291 publications) and substantially fewer cohorts had four outcomes reported (65/620 cohorts; 30/292 publications, Figure 6.2).

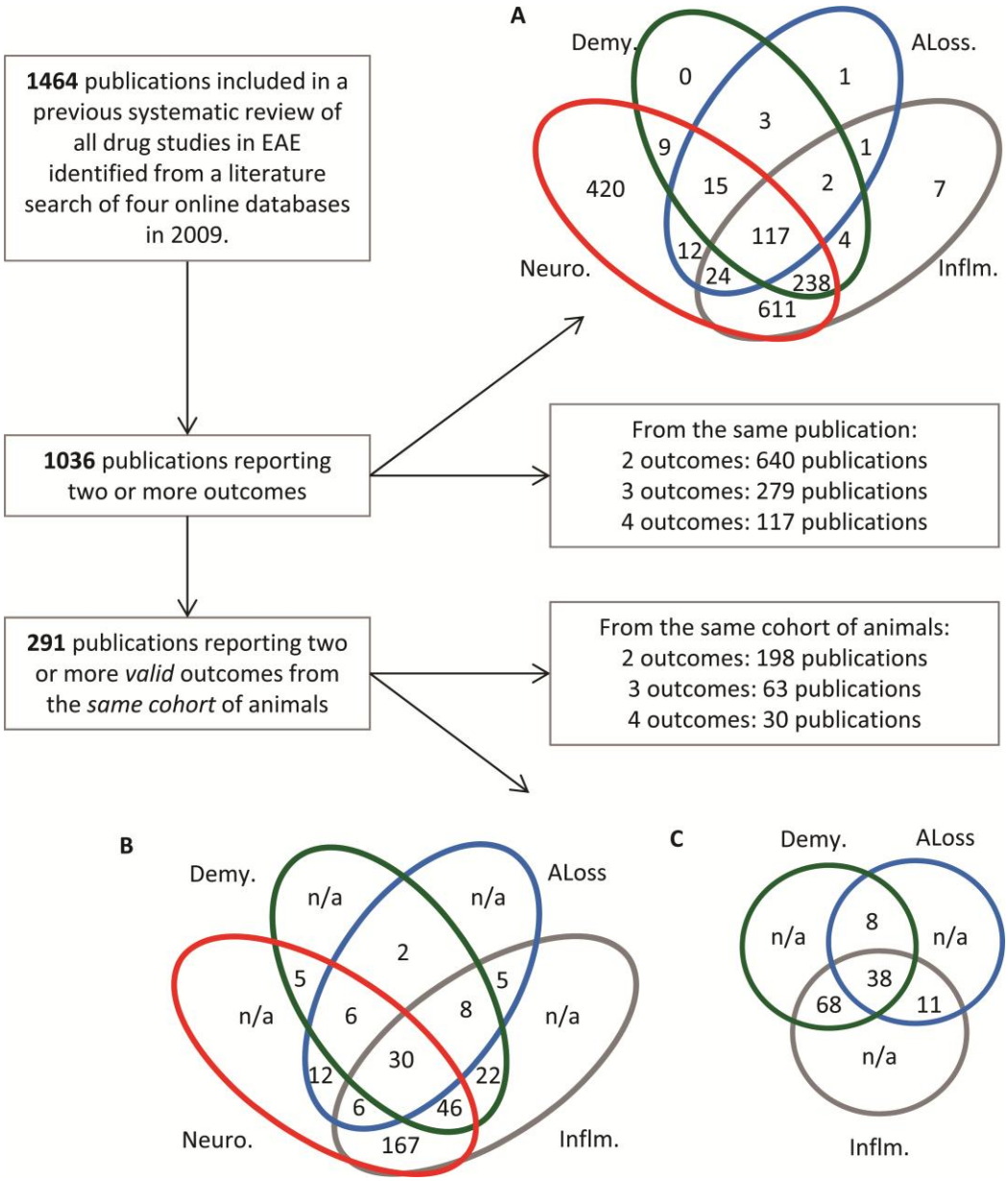


Figure 6.2. Quorum chart of the progression from our original literature search for drug studies in EAE to the publications used in the analysis presented here. The Venn diagrams represent (A) the number of publications reporting any data for any combination of reported outcome measures; (B) valid data for two or more outcomes from the same cohort of animals, taking into account neurobehavioural scores; or (C) only taking into account reporting of valid data in the same cohort where histological outcomes are measured. Neurobehavioural scores (Neuro.) are shown in red, demyelination (demy.) in green, axon loss (ALoss) in blue and inflammation (Inflm.) in grey. 16 publications reported data for a different combination of outcome measures in unique cohorts of animals and are therefore represented more than once in B and C (corresponding to a total extra of 18). Note that the Venn diagram in A is reported in Chapter 3.

6.3.2. Relationship between outcome measures

xxi. Different neurobehavioural scores; combined treatment times (Figure 6.3)

Our dataset includes 248 nested outcomes for mean severity scores; 173 nested outcomes for mean clinical and mean cumulative scores; and 336 outcomes for the clinical score on the day of histological assessment. Taking all times of drug administration together, histological outcomes appeared to be the most strongly associated with the change in mean severity scores, and most weakly associated with the change in clinical score on the day that histological changes were quantified (Figure 6.3). Axon loss was relatively weakly associated with changes in all three neurobehavioural scores compared to inflammation; however it was interesting to note that of the three histological outcomes it was the outcome most strongly associated with the changes in the clinical score on the day that histological outcome was quantified. In total 5 of 9 of our analyses were classified as strong (R^2>25%: all three histological outcome measures versus mean severity scores; and inflammation or demyelination versus mean clinical and cumulative scores), and 4 were considered moderate in strength (R^2>9 and <25%: axon loss versus mean clinical and cumulative scores, and all three histological outcomes versus the clinical score on the day of histological assessment; summarised in Table 6.1).

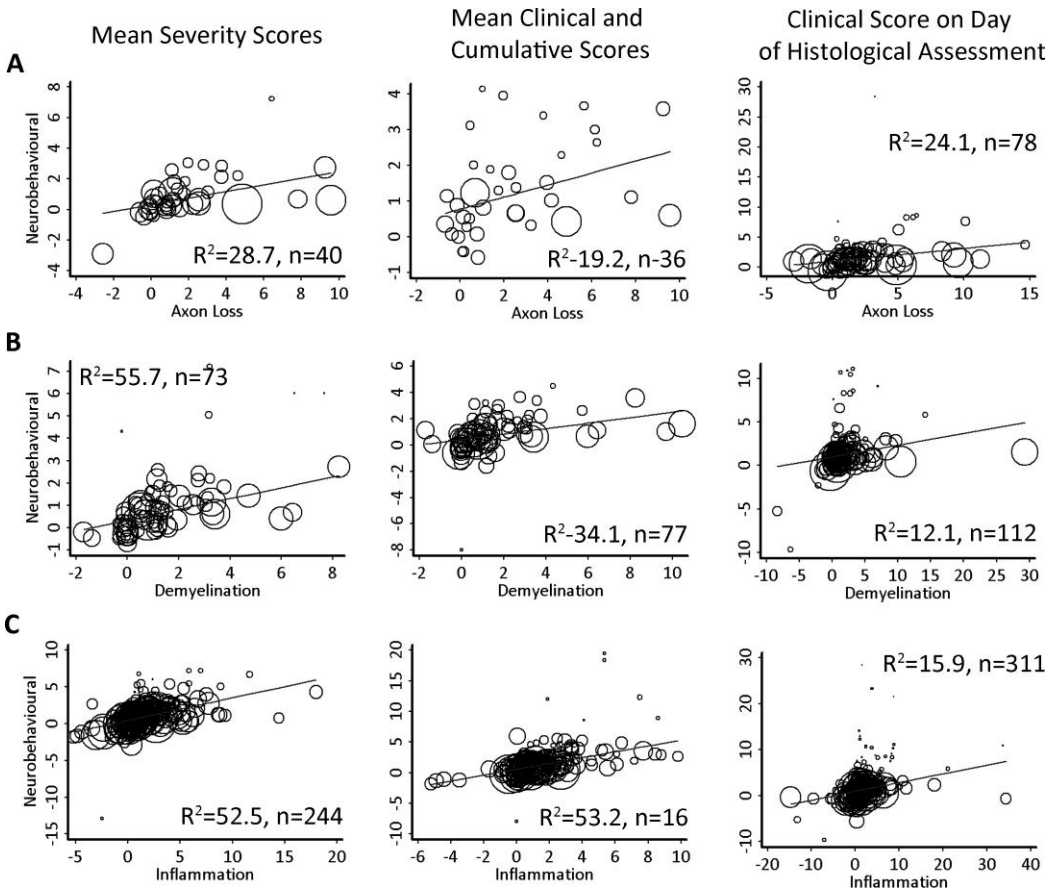


Figure 6.3. The relationship between improvement in (A) axon loss, (B) demyelination or (C) inflammation with improvement in: neurobehavioural score on the mean severity score (left hand panels); the mean clinical cumulative score (middle panels); and the day that histological changes were measured (right hand panel). The relationships were assessed using meta-regression between each pair of outcomes where they were measured in the same cohort of animals. The adjusted R-squared and the number of comparisons are shown on the graphs for each pair of outcome measures. Symbol size represents the precision of the dependent variable.

xxii. Combined neurobehavioural scores; combined treatment times (Figure 6.4)

Taking all times of administration together and all neurobehavioural outcomes together, the strongest relationship was between the improvement in inflammation and demyelination (R2=84.5%; Figure 6.4). In total, 5 of 6 pairs of outcome measures were considered to have strong relationships and one was classified as moderate (demyelination versus neurobehavioural scores).

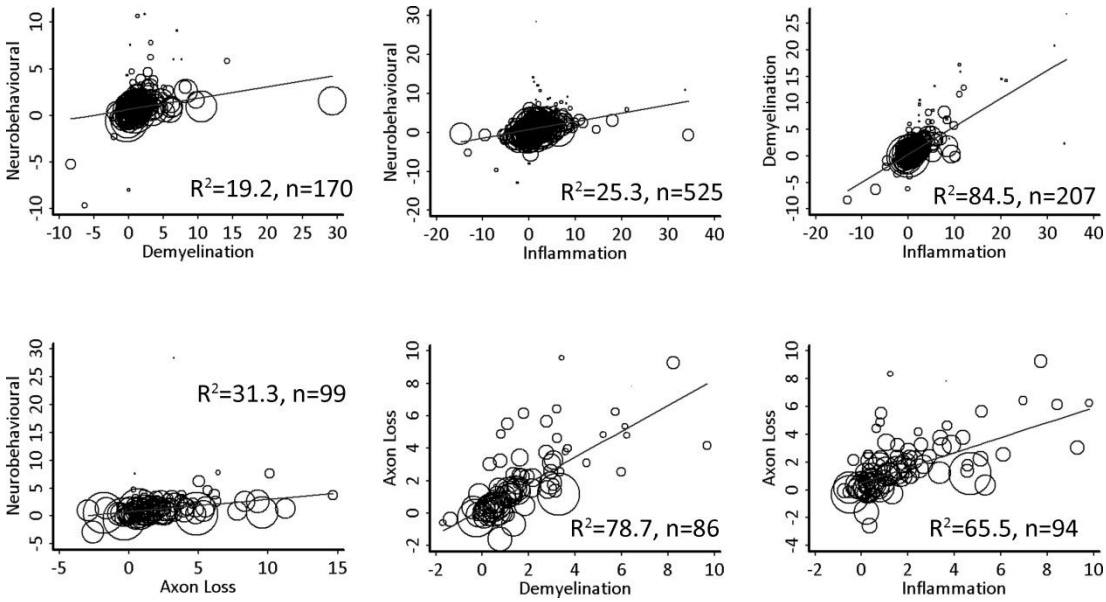


Figure 6.4. The relationship between different outcome measures when all different times of administration are taken together. See **Figure 6.3** for more details.

xxiii. Combined neurobehavioural scores; prior-treatment (Figure 6.5, top panels)

We assessed the relationship between outcome measures where the time of administration was either before or on the day or EAE induction. The strongest relationship was identified between the improvement in inflammation and demyelination, and the weakest between axon loss and neurobehavioural scores. In total 3 of 6 pairs of outcomes were considered to have strong relationships (inflammation versus demyelination; demyelination versus axon loss; inflammation versus axon loss) and the remaining three were considered to have moderate relationships. Thus histological outcome measures accounted for a greater proportion of variation in other histological outcome measures than neurobehavioural scores.

xxiv. Combined neurobehavioural scores; early treatment (Figure 6.5, middle panels)

Taking the data from studies where the drugs were administered from day 1 to 8 inclusive ("early treatment"), we found a stronger relationship between all outcome

measures in comparison to the prior treatment. We found that all of the pairs of outcomes had strong relationships (R^2>25%).

xxv. Combined neurobehavioural scores; late treatment (Figure 6.5, lower panels)

For studies which administered interventions from day 9, we identified a strong relationship between all pairs of outcome measures (Table 6.1) with the strongest between improvement in inflammation versus demyelination, and inflammation or demyelination versus axon loss.

		Axon Loss	Demyelination	Inflammation
All Times	**Neurobehavioural Scores**			
	Axon Loss	n/a		
	Demyelination	n/a	n/a	
Prior	**Neurobehavioural Scores**			
	Axon Loss	n/a		
	Demyelination	n/a	n/a	
Early	**Neurobehavioural Scores**			
	Axon Loss	n/a		
	Demyelination	n/a	n/a	
Late	**Neurobehavioural Scores**			
	Axon Loss	n/a		
	Demyelination	n/a	n/a	

Table 6.1. A heat map of the strength of relationships between outcome measures when improvement was measured in the same cohort of animals. Strong relationships (R^2>50%) are shown in green, moderate relationships (R^2>20% and <50%) are shown in orange and weak relationships (R^2>10% and <20%) are shown in red.

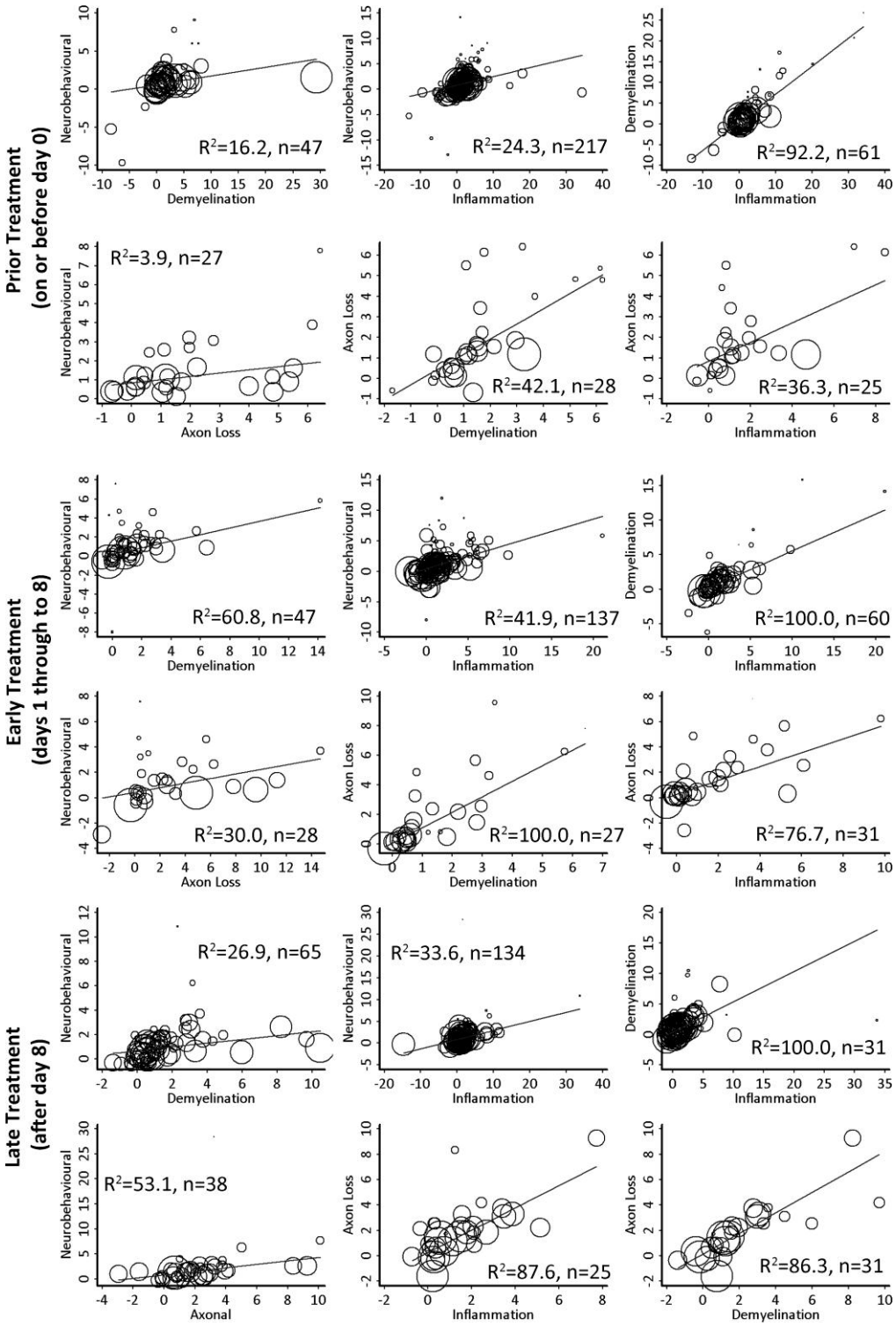


Figure 6.5. The relationship between different outcome measures when drugs are administered prior to EAE induction (upper two pannels), as early treatments after EAE induction (middle pannels) or as late treatments (lower two panels). See Figure 6.3 for more details.

6.3.3. Pathway to improvement in neurobehavioural scores

Using meta-pathway analysis we first assessed the pathway to improvement in neurobehavioural score when we grouped all times of administration together. As shown in Figure 6.6A, all of the effects on neurobehavioural score appear to be mediated through effects of inflammation on demyelination, and demyelination on axon loss.

We expected that the pathway would be sensitive to the time of drug administration and so we next assessed the pathway for drugs administered at prior-treatment times (on or before day zero). We identified a weak relationship between inflammation and neurobehavioural scores, and axon loss and neurobehavioural scores. The majority of the effects on neurobehavioural scores appeared to be mediated via improvements in demyelination (Figure 6.6B) which equated to greater than two thirds of the overall effects (Table 6.2). For early treatments (between day 1 and 8 inclusive), there was a strong relationship between inflammation and demyelination through which a large proportion of the effects on neurobehavioural outcome were mediated through the effects of inflammation on demyelination (Figure 6.6C). For late treatments (administered after day 8), the improvement in neurobehavioural was partly mediated through the effect of inflammation on demyelination, and demyelination on axon loss and the direct effect of axon loss (53.1%; Figure 6.6D).

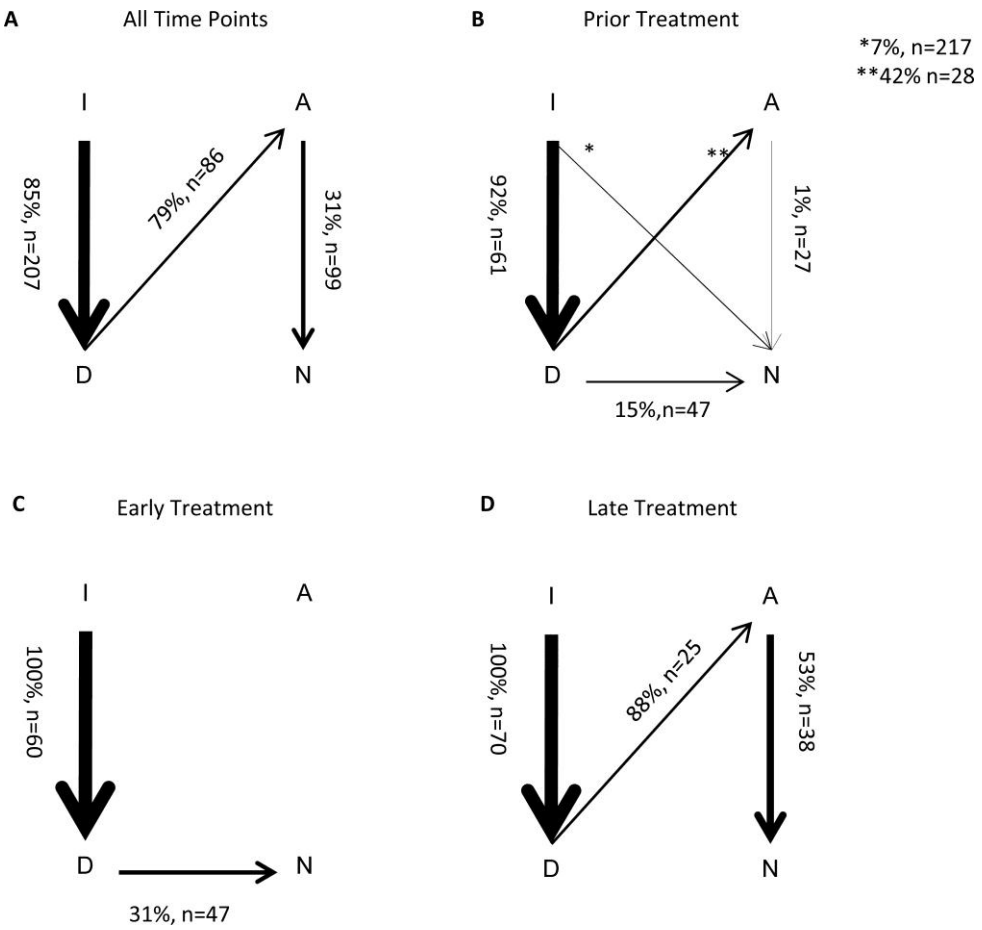


Figure 6.6. The proposed pathways to improvement in neurobehavioural scores for all times of administration (A), prior treatment or on the day of EAE induction (B), early treatment between days 1 and 8 (C) or late treatment from day 9 (D). Percentages represent X_{DIRECT} calculated as shown in Figure 6.1 along with the number of comparisons. The width of the arrow is the relative strength of the relationship. * and ** represent the strength of the relationship between inflammation and neurobehavioural scores, and demyelination and axon loss respectively for the prior treatment times (for the purpose of clarity these are not shown on their corresponding arrows).

		Inflammation	Demyelination	Axon Loss
Treatment Times	**Prior**	<1/3	>2/3	>0
	Early	0	1	0
	Late	0	0	1

Table 6.2. The proportion of the variation in neurobehavioural scores which can be explained by change in inflammation, demyelination or axon loss. All values are rounded to the nearest third. For example, from Figure 6.6, a very small proportion of variation in axon loss (direct or mediated) can explain variation in neurobehavioural scores; a larger proportion (7% which have labelled here as less than a third) is via direct effects, and the remaining variation is explained by variation in demyelination, either directly or mediated through variation in inflammation.

6.3.4. Time of administration

By grouping the meta-regression data into 6-day rolling epochs for the time of administration, we identified a poor relationship between both the improvement in inflammation and neurobehavioural scores (R2=6%) and between demyelination and neurobehavioural scores with increasing times of administration (R2=5%). However the strength of the relationship between improvement in axon loss and neurobehavioural scores increased with later times of administration (R2=81%; Figure 6.7).

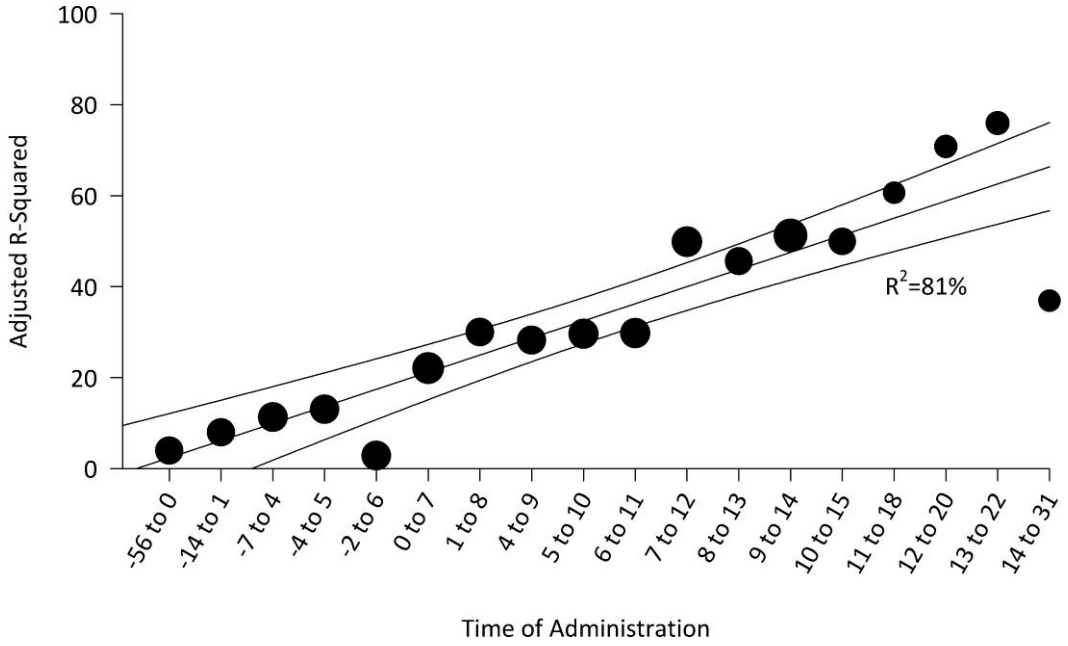


Figure 6.7. The strength of the relationship between axon loss and neurobehavioural scores over time. Relationship strength was assessed by meta-regression on effect sizes over 6 day rolling epochs. The symbol size represents the log of the number of comparisons.

6.4. Discussion

Here we have described the relationship between treatment related improvements in four outcome measures using novel methodology based on a systematic approach. Beyond the limitations of this study (described below), this approach was used to minimise bias and it provides further insights into the usefulness of a repository of data from animal studies.

6.4.1. Outcome measure reporting

Roughly 70% of publications on drug efficacy in EAE conduct their analysis using more than one endpoint (1036/1464 publications). Over 98% include change in neurobehavioural scores as one (or all) of their measures of efficacy. Axon loss is the least reported measure of efficacy; however this dataset also includes publications dating back to the early 1960's, when there were high expectations for anti-inflammatory medications – a trend which lasted until the end of the 20th century when the importance of axon loss became far clearer.

6.4.2. Relationship between outcome measures: treatment related improvements

The treatment related improvements in the three histological outcomes and neurobehavioural scores appears to depend on the method of measuring the neurobehavioural score. There was a particularly poor correlation when the outcomes were measured on the same day. Moreover, the relationship with change in inflammation was especially weak, whereas the strongest relationship was with the change in axon loss. This is perhaps reflected by an early improvement in inflammation, which diminishes with time as more consequential pathological changes are emerging (i.e. axon loss) and thus when they are both measured at the same (later) time point, the improvement in neurobehavioural score is not reflected by the treatment effect on inflammation. Interestingly the relationship with axon loss appears to not change substantially between different measures of neurobehavioural score. However, from these data the relationship between neurobehavioural scores and axon loss or demyelination is not clear. In animal models and humans, demyelination can undergo some repair, mediated by oligodendrocytes. Conversely, endogenous repair mechanisms do not seem to act on axon loss (Xie and Zheng, 2008). Moreover, a simple observation of the magnitude of the axis of the graphs presented in this analysis shows that interventions had the least benefit in reducing axon loss compared to other outcome measures.

6.4.3. Time to treatment and path analysis

The categories for time to treatment were chosen based on subjective biological plausibility, and to ensure roughly equal group sizes. Our analysis suggests that pre-treatment of EAE leads to a relatively weaker association between changes in histological and neurobehavioural outcome measures, and that they are even relatively weak correlates of improvement in each other. The meta-pathway analysis suggests that the route to improvement in neurobehavioural scores may be mediated through direct effects on inflammation, as well as its mediation through demyelination and that improving axon loss plays a minimal role in mediating these effects. We were unable to ascertain the strength of the direct effects of change in axon loss on neurobehavioural outcomes and therefore it is possible that interventions simply prevent axon loss from occuring. The particularly poor relationship between improvement in

neurobehavioural scores and axon loss is possibly indicative that this pathological change hasn't occurred before both are assessed. In fact there appears to be no role for axon loss when we analysed data from experiments which gave early treatments with all the effects coming from improvement in inflammation which is either mediated, or through direct improvement in demyelination. Improvement in axon loss appears to be more important at later time points in terms of its ability to affect neurobehavioural scores; shown also in Figure 6.7. This is perhaps not surprising given that axon loss is thought to be the cause of permanent disability; thus at later time points, if axon loss has improved it is feasible to expect neurobehavioural scores to also improve. At earlier time points it is conceivably far more difficult to disentangle the complex relationship between endogenous and exogenous repair mechanisms on inflammation and demyelination and the subsequent interaction with neurobehavioural scores. We found that the relationship between inflammation or demyelination and neurobehavioural scores did not change as the time of administration increased. These data therefore support the notion that axon loss should be a key target for drug research.

6.4.4. Limitations

An important limitation to this study is that aggregating data from such a wide range of disease models and study design paradigms can mask important observations which are unique to certain experiments. For example we have grouped together different EAE models (which may have different clinical and histological responses) and different drugs (which may have different drug targets, such as inflammation or neurodegeneration). Secondly, meta-analysis relies on adequate reporting of crucial information (number of animals, mean and variance per group) and thus we had to exclude a large volume of data on this basis. Moreover, this analysis was based on the relationship between outcomes where they were reported from the same cohort of animals; however, we were at times unable to ascertain whether this was the case. Thirdly, our approach is hypothesis generating and based on observation only (described in more detail in Chapter 9). Therefore we urge caution when using these data to make interpretations about the relationship between outcomes and the pathway to improvement in neurobehavioural scores, and highlight that our interpretation is merely subjective.

Lastly, we have shown that publication bias is an issue in the preclinical EAE literature (see Chapter 3). Consequently our analyses may be subject to two types of positive reporting bias: (1) studies which reported negative results across all outcomes may not be in the public domain at all; and (2) where interventions had a non-significant impact on one outcome measure, and a significant impact on the other, it may be that only sufficient data was reported for the significant outcome which would not be eligible for inclusion in our study. The latter could result in the relationship strengths being overstated. In addition, as I mentioned in the discussion of Chapter3, where demyelination is reported without mention of the presence of axons, we cannot ascertain whether primary demyelination has occurred, or whether axons have simply been displaced by the inflammatory environment. Thus the relationship between demyelination and inflammation described in this analysis may be confounded by this.

In addition to these concerns, we made the observation that for some pairs of outcome measures, all of the variation in one could be explained by the variation in the other (adjusted R^2 of 100%). Careful inspection of the data revealed that this was due to there being such low heterogeneity in the dependent variable (tau^2 was less than 1) and so all of it could be explained by variation in the independent variable. These results should therefore be interpreted with caution.

6.4.5. Conclusions

Our novel methodology demonstrates how meta-analysis estimates of efficacy can be used to unpick the pathways to improvement in a disease model. The findings that we have reported are assumption free, apart from our chosen start point (reduction of inflammation) and end point (improvement in neurobehavioural scores). Using these methods we observe that variation in the change in neurobehavioural scores can be explained in part by variation in axon loss, and moreover, that the strength of the relationship increases over time. Our data support the rationale that axon loss is a key therapeutic target for the improvement in disability in EAE.

7. Assessing methodological differences in meta-analysis of data from preclinical trials

7.1. Background

An effect size is the quantifiable magnitude of the relationship between two groups (e.g. a control and treatment group). There are a number of methods available to quantify this relationship and extensive literature on their merits and conditions with which each is appropriate (for example see: Nakagawa and Cuthill, 2007, Baguley, 2009, Durlak, 2009). Typically these methods fall into one of three categories: effect sizes for correlations, odds ratios and differences between means (Borenstein, 2009), the latter of which has been used in this thesis. Within each of these categories, there are yet further methods to choose from. Herein, I will only refer to some of the methods used to calculate effect sizes for the difference between means.

Standardised effect sizes are commonly referred to as the *d* family of calculations. This is named after Jacob Cohen, whose effect size calculation, Cohen's *d*, or just *d* for short, was the first of any effect size described (Cohen, 1962). In this thesis I have used Hedge's g which is essentially the same as Cohen's *d* but takes into account a correction factor for small sample sizes, which were found to be common in the dataset I extracted (the median sample sizes were less than ten for both the preclinical research on EAE and PD). The correction factor lies between >0 and <1, with larger sample sizes tending towards 1, which are therefore more closely in line with the value for Cohen's *d* (Cooper et al., 2009).

The classic alternative to the SMD is the *raw difference in means*, in which the calculation method is, as the name suggests, simply the difference between the mean in the control group and the treatment group. With SMDs, problems can arise during the process of standardisation, and thus the advantage of raw differences in means is that their calculation does not rely on variance. Additionally, the unit of the effect size is in the same scale as the original units which are intuitive to interpret. The unit of SMD is standard deviations (SDs) which are not as easy to interpret; for example a change of 1

SD is not necessarily clear in terms of drug efficacy (Bond, 2003, Baguley, 2004). It has also been suggested that the unit of an SMD is less meaningful if the reader does not know how they were calculated or what factors influence them (Baguley, 2009). However, the clear disadvantage of this approach is that the scale must be identical across every outcome measure in the dataset. Thus, despite its merits, it is sometimes not appropriate to meta-analyse raw differences in means.

In Chapter 2, I introduced an alternative metric, the normalised mean difference (NMD; section 2.2.2i) where the mean outcome in the group with the smallest deviation from the mean in the sham group is expressed as a proportion of the mean score which has the greatest deviation from the mean in the sham group. Similarly, the standard deviation (SD) for each group is recalculated as a proportion of this same mean value. This approach has similar benefits to the raw difference in means and has the advantage of being more widely applicable. In fact the normalised mean difference can be calculated for any data where the mean score for an unlesioned animal is either reported or can be inferred, as this calculation relies on converting all values to the same scale for which the baseline is required. However, this also provides a disadvantage to this approach; in our experience data for the sham group are often not reported when it is required (described in further detail in the results section) and therefore we cannot always calculate this effect size.

Meta-analysis involves aggregating effect sizes from a number of studies. Where these are calculated on data from different study designs and therefore where the underlying treatment effect may be different, it is both useful and often strongly advised to conduct a formal assessment on the potential sources of heterogeneity (Thompson, 1994, Thompson and Sharp, 1999, Higgins and Thompson, 2002). As described in Chapter 2, we used two methods to calculate heterogeneity: Cochrans Q and the newer I^2 value (section 2.3). Cochrans Q can be used to stratify heterogeneity (herein referred to as stratified meta-analysis; section 2.3.2i). On this we can calculate a p value for the likelihood that the amount of heterogeneity is due to chance alone; that is, confirming the null hypothesis that the samples are from the same population. However, Q is documented as being underpowered in the test for heterogeneity where sample sizes are small, and over-powered to detect a significant result when there are many studies,

a situation which cannot be ruled out in the dataset described in this thesis (Hardy and Thompson, 1998).

At different stages in this thesis we have applied two methods to calculate effect sizes: NMDs and SMDs. All things being equal, our preference has been to calculate NMDs as the effect sizes are more intuitive to interpret. However, under certain circumstances we have been unable to calculate NMDs because too few experiments reported data for sham or it could not be inferred. Thus for the EAE literature we calculated NMDs as data for sham were largely available, and for the preclinical PD literature where these data were rarely reported and could not be inferred we calculated SMDs.

We also used two methods to perform assessments on heterogeneity: meta-regression and stratified meta-analysis. For the preclinical PD literature we performed stratified meta-analysis because this approach reflected the common practice at the time that the pre-specified analysis methods were chosen. We performed meta-regression on the data from EAE studies because this is a more recent method and we have made the observation that it is also more conservative than stratified meta-analysis. However, to our knowledge, this assumption (that meta-regression is a more conservative approach) has not been formally investigated on a large collection of real data from animal studies which are heterogeneous.

7.2. Aims and objective

In this study I set out to explore and describe the differences between the main methodological choices available in the meta-analysis of data from animal studies. Specifically my objectives were to use the same dataset to: (1) explore the differences between estimates of effect size calculated as NMDs and SMDs; (2) explore the differences in performance of meta-regression and stratified meta-analysis in estimating differences between strata; and (3) explore the impact that the two effect size calculations have on the assessment of publication bias.

	Summary of use	Strengths/Weaknesses
Standardised mean difference	Place all measures of outcome onto a single, standardised scale by dividing the difference in means by a measure of the standard deviation in one or both groups.	Applies to a wide range of research. Does not require data for a sham group.
Raw difference in means	Simply the difference between mean in the control group and mean in the treatment group.	Only applicable if the measurement scales are the same. However, it is the most intuitive measure of effect size if it is able to be applied to the data. Does not require data for a sham group.
Normalised mean difference	The effect size is the proportion of the mean value in one group against the mean score in the other group.	Unit of effect size is intuitive (% change). However, value for the mean in the sham group must be reported or able to be inferred.

Table 7.1. Difference between three methods to calculate effect sizes on data from preclinical experiments.

7.3. Methods

We used all of the available data from all drug studies on EAE published prior to October 2009 and calculated both an NMD and a Hedge's *g* SMD effect size for each comparison. Both of these calculations have unique situations in which the effect size cannot be calculated (described in Table 7.1); therefore we only included data where both could be successfully computed.

Because our aim was to explore methodological differences only, we randomly relabelled the values for each of the groupings in our analysis. That is, for example for blinded assessment of outcomes which has two possibilities, "yes" and "no", we randomly relabelled these as "blinded 1" and "blinded 2". The relabeling was consistent across each analysis such that for example "blinded 1" always coded for the same value.

We carried out analyses on three types of neurobehavioural score: (1) mean severity scores (mean severity score, the product of mean severity and duration, the product of mean severity plus number of exacerbations); (2) mean clinical scores and mean

cumulative scores taken together; (3) the clinical score on the last day of observation; and three measures of histological outcome: (1) inflammation; (2) demyelination; and (3) axon loss.

7.3.1. Comparing effect size calculations and methods of exploring heterogeneity

To explore sources of significant heterogeneity we used the methods described in Chapter 2 (section 2.3.2). Specifically we explored the impact of the following variables on each outcome measure: (1) route of drug delivery; (2) species; (3) sex; (4) time of drug administration; (5) time of outcome assessment; (6) the mean number of animals in the nested comparison; (7) quality score based on our 6 point checklist (section 2.1.3); (8) blinded assessment of outcome; (9) random allocation to group; and (10) for three histological outcomes we assessed the impact of the CNS section observed.

In meta-regression, data for continuous variables can be entered directly, and produces an equation of the line of best fit. To allow for comparison with stratified meta-analysis we converted variables on a continuous scale into categorical variables (Table 7.2).

Study Design Characteristic	Raw Data Type	Categories
Blinded assessment of outcome	Dichotomous	2 (yes; no)
Random allocation to group	Dichotomous	2 (yes; no)
Overall quality score	Ordinal	6 (maximum checklist items)
Route of drug delivery	Categorical	40 identified
Animal species	Categorical	8 identified
Animal sex	Categorical	4 (male; female; both; unknown)
Time of administration (days)	Continuous scale	7 (day <0; 0; 1-7; 8-14; >15; day of onset or other; unknown)
Number of animals per Group	Continuous scale	4 (1-4; 5 or 6; 7-9; 10+)
Time of assessment (days)	Continuous scale	5 (<16 days; 16 to 30; 31 to 45; >45; unknown)
Histological section analysed	Categorical	4 (spinal cord; brain; brain & spinal cord; unknown)

Table 7.2. The categories that each study design characteristic were split into for the analysis on sources of heterogeneity.

7.3.2. Publication bias

We assessed for publication bias using effect sizes calculated as both NMDs. We used funnel plotting, Egger regression and trim and fill (section 2.5).

7.3.3. Statistics

Our analyses were purely observational and therefore we only report descriptive statistics and three levels of significance for our assessment of heterogeneity using meta-regression and stratified meta-analysis ($p<0.005$ shown in green; $p<0.01$ shown in orange; $p<0.05$ shown in red). We performed no formal comparison of the number of significant differences between methods.

7.4. Results

7.4.1. Included and excluded data

Our initial dataset included 1464 publications from which we were able to extract 6709 individual comparisons on 6 outcome measures from 881 publications. For this analysis we excluded 773 outcomes from 189 publications because they did not describe data for a sham group and they could not be inferred. However, of these 773 publications 172 still had at least one outcome suitable for meta-analysis, and hence 5935 outcomes from 864 publications were carried forward. Of these, we excluded a further 449 comparisons from 167 publications which could have neither an SMD or NMD calculated. These were excluded when the measure of variance in both the control and treatment group was zero and thus the calculations for effect size and standard error of the comparison therefore include a division by zero. We excluded a further 89 comparisons from 20 publications because an SMD could not be calculated. Of the 187 publications with data excluded at this stage, 155 still had at least one outcome suitable for meta-analysis. Thus our final analysis included 5395 un-nested outcomes from 832 publications on which we could calculate both an SMD and NMD effect size (Figure 7.1).

We performed random effects meta-analysis and analyses on heterogeneity on nested data comprising: 1866 comparisons on mean severities, 1064 on mean clinical & mean cumulative score, 1198 on the clinical score on the last day of observation, 495 on inflammation, 239 on demyelination, and 113 on axon loss. On these we performed a total of 698 random effects meta-analyses (349 each for NMDs and SMDs, shown in Table 7.3) exploring the variables described in Table 7.2.

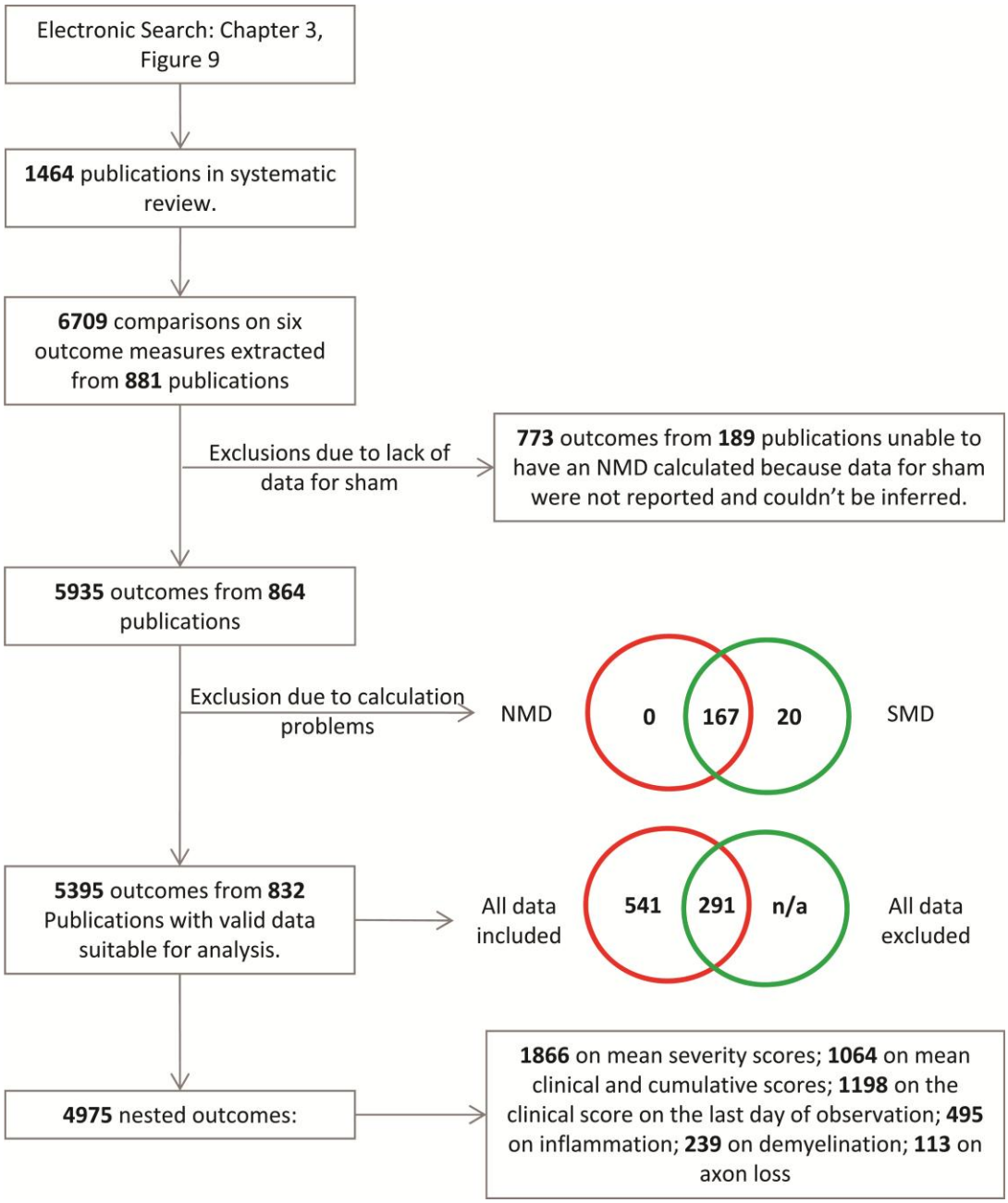


Figure 7.1. Quorum chart of the progression from the literature search and inclusion in the systematic review (described in more detail in Chapter 3) to the analysis on methodological differences. *The Venn diagram shows the number of publications excluded from the meta-analysis for either not being able to have an NMD calculated (red circle), not being able to have an SMD calculated (green circle; 89 comparisons) or neither calculated (overlap between circles; 452 comparisons). Further exclusions of data are described in Chapter 3. The number of comparisons refers to un-nested data. Some publications still had at least one outcome suitable for inclusion in subsequent stages.

	MSS	MCSS	CSLD	Inflm	Demy	ALoss
Blinded assessment of outcome	2	2	2	2	2	2
Random allocation to group	2	2	2	2	2	2
Overall quality score	5	6	5	4	4	4
Route of drug delivery	31	23	32	20	15	11
Animal species	8	5	6	6	5	4
Animal sex	4	4	4	4	4	4
Time of administration (days)	7	7	7	7	7	7
Number of animals per Group	4	4	4	4	4	4
Time of assessment (days)	5	5	5	5	5	5
Histological section analysed	n/a	n/a	n/a	4	4	3
Total number of Analyses	68	58	67	58	52	46

Table 7.3. The number of strata within each category shown in Table 7.2 for which we calculated a random effects meta-analysis effect size using both NMDs and SMDs. The total number of calculations equals 349. Abbreviations: MSS, mean severity scores; MCS, mean clinical and cumulative scores; CSLD, clinical score on the last day of observation; Inflm, inflammation; Demy, demyelination; and ALoss, axon loss.

7.4.2. Global effect size calculations

Global estimates of efficacy are shown with their 95% confidence intervals in Table 7.4. For each outcome measure the direction of effect was positive. For both methods of effect size calculation, axon loss had the highest magnitude of efficacy, followed by demyelination, the clinical score on the last day of observation, inflammation, mean clinical & cumulative scores, and mean severity scores. We calculated Z scores (effect size/standard error) to compare the precision of our estimates and found that global effect sizes calculated on NMDs were more precise.

	NMD			SMD		
	Global Estimate	**95% CI**	**Z score**	**Global Estimate**	**95% CI**	**Z score**
Mean severity score	33.0	31.0-35.0	32.6	0.85	0.79-0.90	29.9
Mean clinical & cumulative score	38.8	36.0-41.5	27.3	0.99	0.92-1.07	25.1
Clinical score on last day of observation	41.5	38.6-44.3	28.8	1.05	0.98-1.13	27.1
Inflammation	39.5	2.20-35.2	18.0	1.03	0.90-1.15	16.3
Demyelination	43.2	37.6-37.6	15.1	1.13	0.94-1.32	11.6
Axon loss	51.6	3.72-44.4	13.9	1.48	1.22-1.74	11.1

Table 7.4. The random effects meta-analysis estimate of global efficacy, 95% CI and Z score for effect sizes calculated as NMDs and SMDs.

7.4.3. Effect sizes in strata

Across the 349 comparisons made between random effects estimates of effect sizes calculated for NMDs and SMDs, we observed that the majority (89%) were in concordance in terms of their direction of effect size (positive, negative or neutral) as shown in Table 7.5. Just 39 comparisons were not in concordance with their direction of effect.

		SMD		
		Positive	**Neutral**	**Negative**
NMD	**Positive**	240	36	0
	Neutral	3	69	0
	Negative	0	0	1

Table 7.5. The number of matching positive, negative and neutral random-effects effect sizes calculated as NMDs and SMDs. The shaded grey boxes are those which are concordant between SMD and NMD effect sizes.

7.4.4. Exploring sources of heterogeneity

Across all six outcome measures a total of 55 out of a possible 57 analyses were significant when effect sizes were calculated as NMDs and heterogeneity was assessed by one or other method (Table 6, 7 and 8). All 55 of these were identified as significant using stratified meta-analysis and 15 of these were significant using either method. All analyses which were significant using meta-regression were also identified as significant using stratified meta-analysis.

When effect sizes were calculated as SMDs, 38 of 57 analyses were significant where heterogeneity was assessed using one or other method. Just two analyses were significant using meta-regression where they were not significant using stratified meta-analysis: blinded assessment of outcome for inflammation and the histological section analysed for demyelination were significant using meta-regression only.

A total of 15 analyses were significant where we used meta-regression with effect sizes calculated using one or other method. All 15 were significant where effect sizes were calculated as NMDs, and 4 of these were also significant for SMD effect sizes. All of the significant analyses on SMD effect sizes were also significant on NMD effect sizes. 56 of the possible 57 analyses were significant when we used stratified meta-analysis on effect sizes calculated by one or other method. 55 of these were significant for NMD effect sizes, and 38 were significant for SMD effect sizes. Only one of the 36 analyses which was significant using SMD effect sizes was not significant using NMD effect sizes (Figure 7.2).

	Normalised Mean Difference	Standardised Mean Difference	TOTAL
Meta-Regression	15 (26%)	4 (7%)	15/57
Stratified Meta-Analysis	55 (95%)	36 (63%)	56/57
TOTAL*	55/57	38/57	56/57

Table 7.6. Summary statistics for the number of study design characteristics which were statistically significant when effect sizes were measured as NMDs or SMDs and heterogeneity assessed using meta-regression or stratified meta-analysis. Percentages of the total number of analyses are shown in parentheses. *The total number of unique study design characteristics which were significant across one or other method.

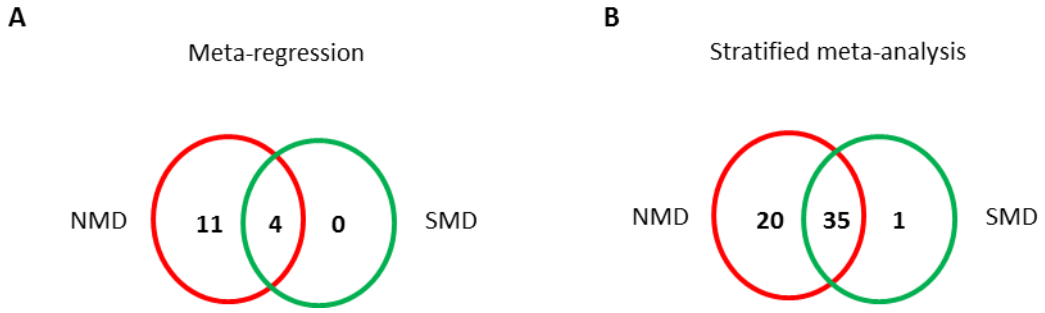


Figure 7.2. Venn diagrams of the number of significant findings identified using (A) meta-regression and (B) stratified meta-analysis on NMD (red) and SMD (green) effect sizes.

Meta-Regression		Mean Severity (n=1866)	Mean Clinical & Cumulative Scores (n=1064)	Clinical Score on Last Day of Observation (n=1198)	Inflammation (n=495)	Demyelination (n=239)	Axon Loss (n=113)
Normalised Mean Difference	Blinded Assessment of Outcome						
	Random Allocation to Group						
	Overall Quality Score						
	Route of Drug Delivery						
	Animal Species						
	Animal Sex						
	Time of Administration (Days)						
	Number of Animals per Group						
	Time of Assessment (Days)						
	Histological Section Analysed	N/A	N/A	N/A			
Standardised Mean Difference	Blinded Assessment of Outcome						
	Random Allocation to Group						
	Overall Quality Score						
	Route of Drug Delivery						
	Animal Species						
	Animal Sex						
	Time of Administration (Days)						
	Number of Animals per Group						
	Time of Assessment (Days)						
	Histological Section Analysed	N/A	N/A	N/A			

Table 7.7. A heat map of the number of study design characteristics which accounted for a significant proportion of between study heterogeneity across six outcomes using *meta-regression* on normalised mean differences and standardised mean differences. Colour coded p valued: green $p<0.005$, orange $p<0.01$ and red $p<0.05$.

Stratified Meta-Analysis		Mean Severity (n=1866)	Mean Clinical & Cumulative Scores (n=1064)	Clinical Score on Last Day of Observation (n=1198)	Inflammation (n=495)	Demyelination (n=239)	Axon Loss (n=113)
Normalised Mean Difference	Blinded Assessment of Outcome						
	Random Allocation to Group						
	Overall Quality Score						
	Route of Drug Delivery						
	Animal Species						
	Animal Sex						
	Time of Administration (Days)						
	Number of Animals per Group						
	Time of Assessment (Days)						
	Histological Section Analysed	N/A	N/A	N/A			
Standardised Mean Difference	Blinded Assessment of Outcome						
	Random Allocation to Group						
	Overall Quality Score						
	Route of Drug Delivery						
	Animal Species						
	Animal Sex						
	Time of Administration (Days)						
	Number of Animals per Group						
	Time of Assessment (Days)						
	Histological Section Analysed	N/A	N/A	N/A			

Table 7.8. A heat map of the number of study design characteristics which accounted for a significant proportion of between study heterogeneity across six outcomes using *stratified meta-analysis* on normalised mean differences and standardised mean differences. Colour coded p valued: green $p<0.005$, orange $p<0.01$ and red $p<0.05$.

7.4.5. Impact of group sample size

We used hypothetical data to demonstrate the impact of the sample size on effect sizes when calculated as SMDs. As shown in Figure 7.3, for different raw data the computed effect size is only stable when there are roughly ten or more animals per group. Additionally the data range which effect sizes are constrained to depends on the values for the mean scores and variance. The greater the difference between the mean scores, and the smaller the variance, the broader the range of effect sizes that they are constrained to.

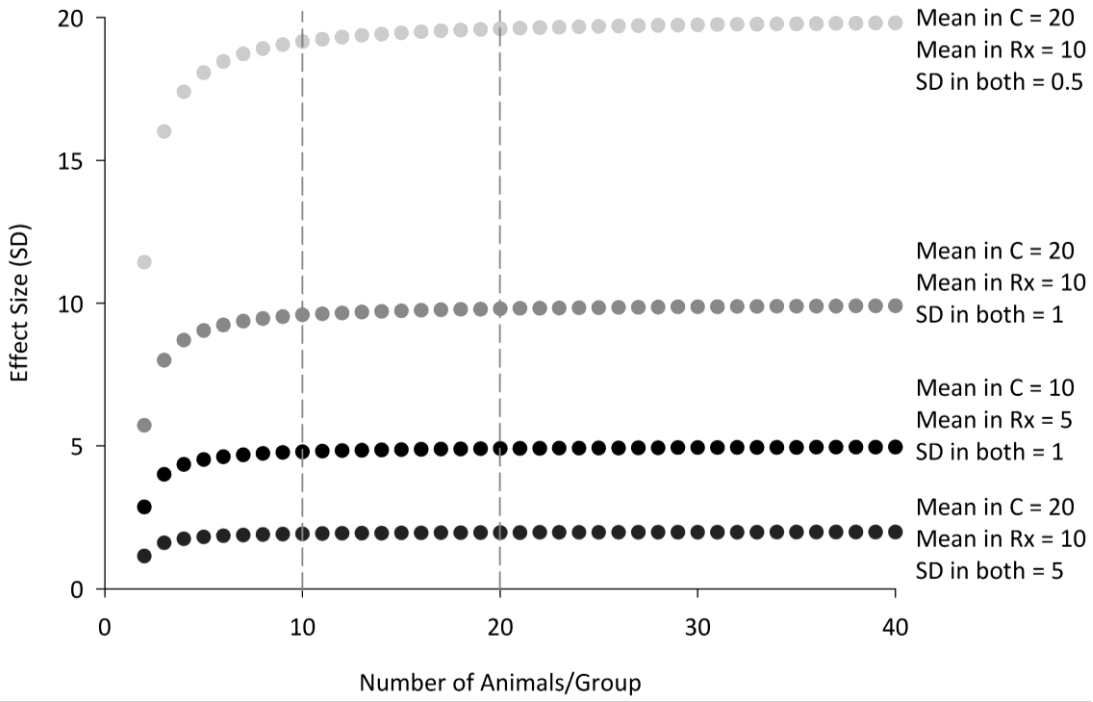


Figure 7.3. The effect size for Hedges G is dependent on the number of animals when the mean in both groups and the variance are fixed. All data are hypothetical.

7.4.6. Impact on publication bias

For the purposes of this exploratory analysis we grouped neurobehavioural outcomes together.

xxvi. Funnel plotting

We identified a clear publication bias using funnel plotting for all four outcome measures where effect sizes were calculated as SMDs (Figure 7.4). Funnel plotting on NMD effect sizes produced less clearly defined funnel shapes, whether taking into account potential skew which would occur with publication bias or not. Where a scale is used to grade animals, with zero representing the value for sham, there is a reasonable likelihood that some interventions or experimental designs will result in an effect size of 100% when calculated as an NMD; that is, the treatment animal is scored as zero, and the control animal is scored as anything greater than zero. Contrastingly, there is no upper or lower limit for SMDs, and two sets of animals with the same scores can have different effect sizes as it depends on more than just the mean scores in either group. Thus, the funnel plots for NMD effect sizes show a clear ceiling and floor effect, whereby a reasonably large proportion of studies reach 100% improvement which skews the funnel shape.

It can be seen in Figure 7.4D (NMD effect sizes, left hand panel) that the percentage improvement was greater than 100% for some comparisons. Lesioned animals can conceivably perform better than unlesioned, sham animals. For example, if the outcome measure is “number of axons”, there is no upper limit for this outcome measure and so lesioned animals could have more axons than the unlesioned sham group.

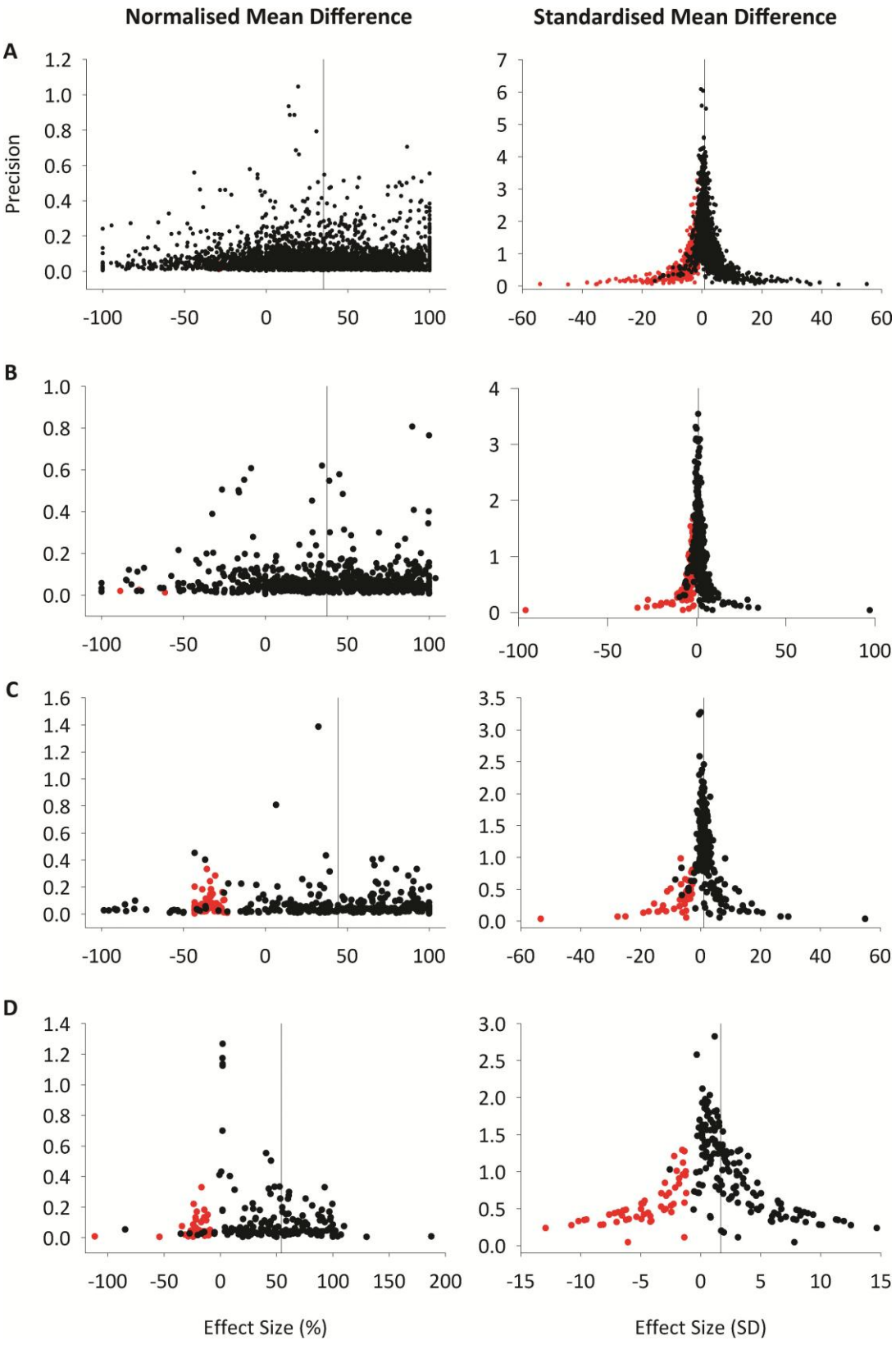


Figure 7.4. Funnel plots of normalised mean differences (left hand panels) and standardised mean differences (right hand panels) plotted against precision for (A) neurobehavioural scores, (B) inflammation, (C) demyelination and (D) axon loss. Extracted data are shown as black symbols and missing studies identified with a trim and fill analysis are shown in red.

xxvii. Egger regression

For both NMD and SMD effect sizes the intercept of the regression line with the origin was positive, indicative of a preponderance of small, positive studies (Figure 7.5).

We assessed the goodness of fit of the regression line by comparing R^2 values. For each outcome measure the R^2 value was smaller for SMD data (shown in Figure 7.5), suggesting that the regression model was less robust on these data. In addition to this, when we conducted Egger regression on SMD data, we observed distinctive arcs in the graph. The number of animals per group has a bearing on the estimate for standard error of the comparison for both NMD and SMD effect sizes. However, it also has a bearing on the estimate of effect size for SMD, constraining it to certain values, seen as these distinctive arcs (see section 7.4.5). This is more easily demonstrated using a large dataset and thus we have plotted examples of this using real data (Figure 7.6).

For these reasons we would typically use the formula shown in the methods chapter as our estimate of the precision (see section 2.5.2). This generates a pooled standard deviation based on the difference in means.

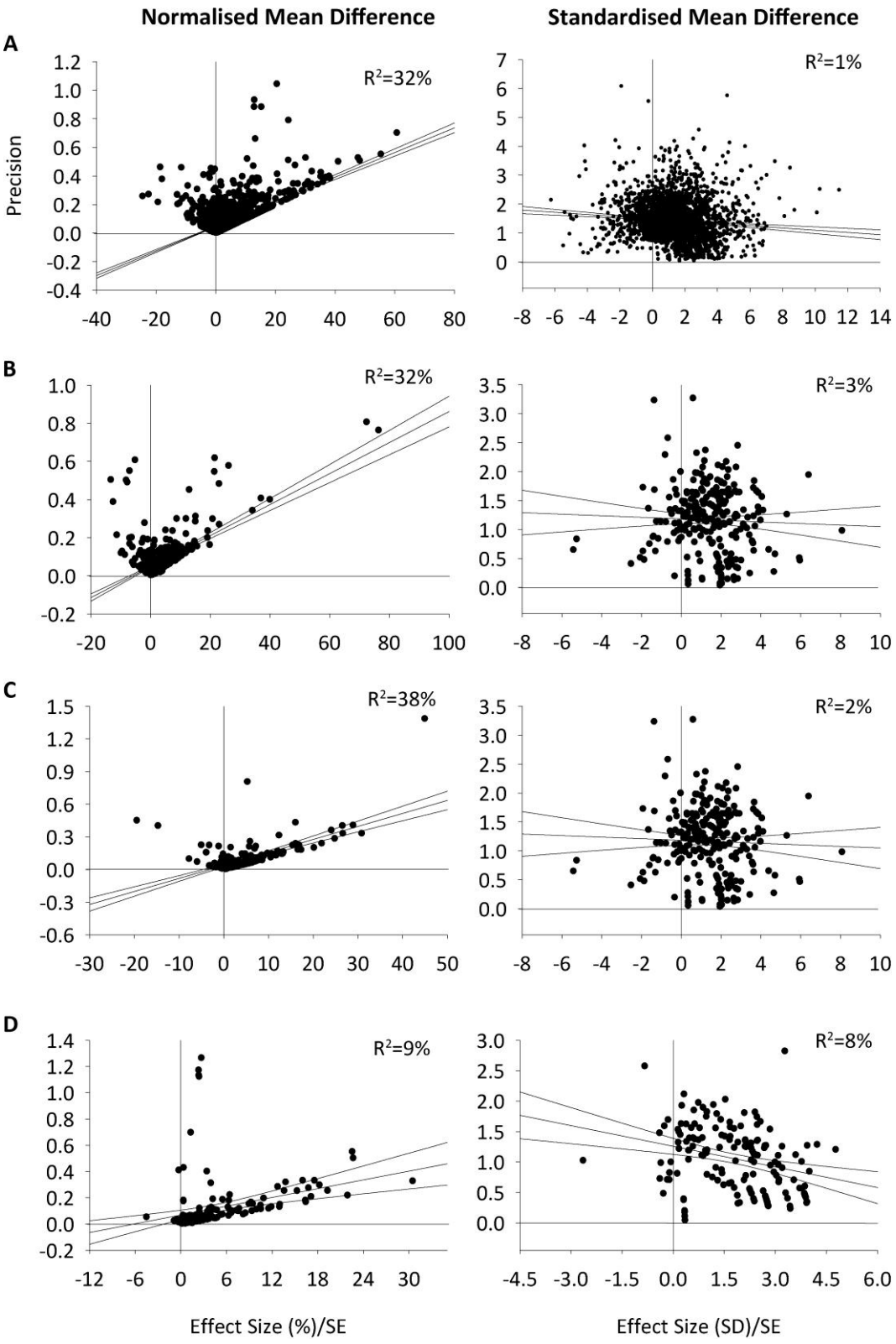


Figure 7.5. Assessment of publication bias using Egger regression of normalised mean differences (left hand panels) and standardised mean differences effect sizes (right hand panels) calculated on (A) neurobehavioural outcomes, (B) inflammation, (C) demyelination and (D) axon loss.

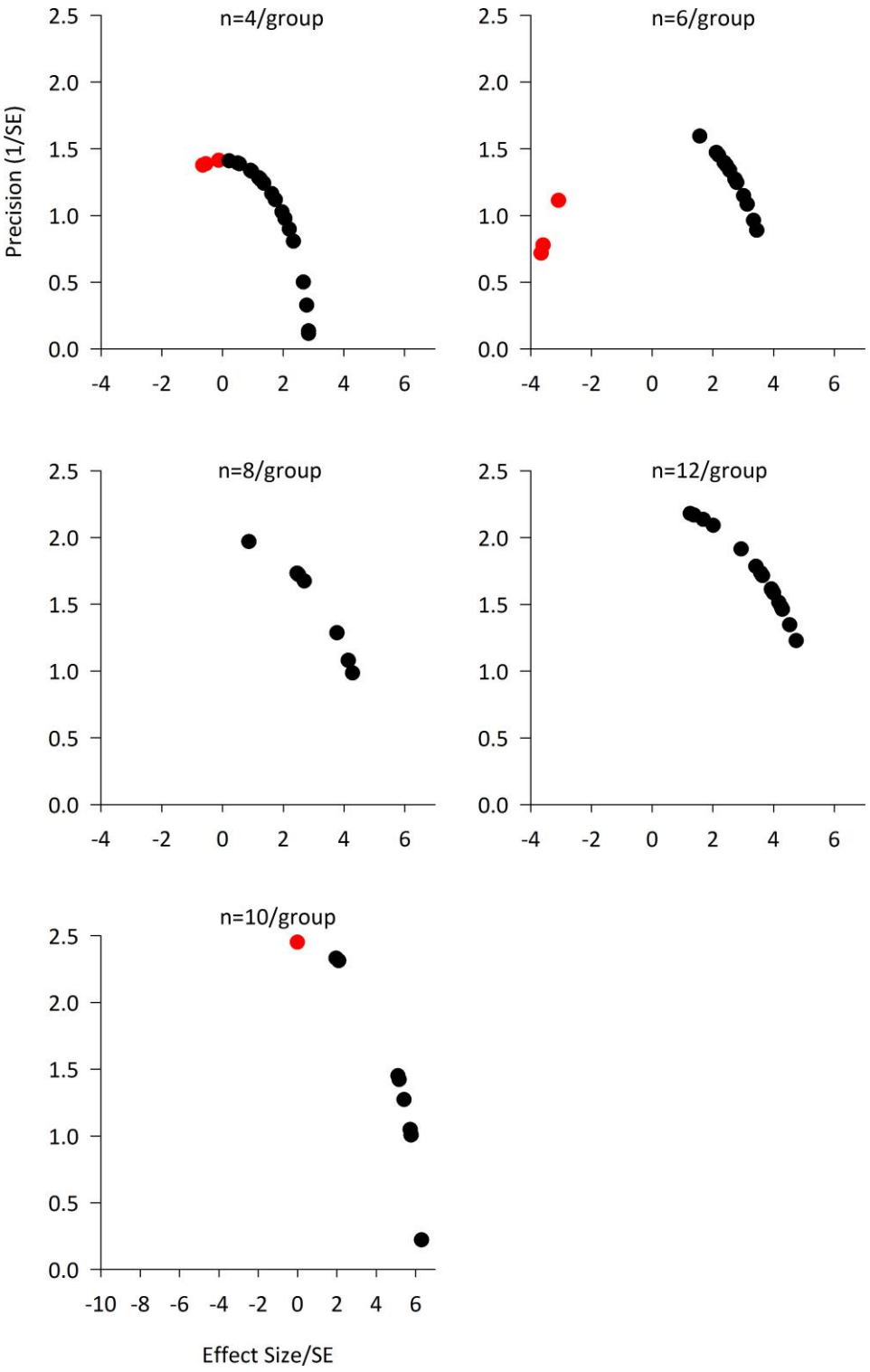


Figure 7.6. Data used for Egger regression when the pooled standard error is used. The data form arcs which depend on the number of animals per group. Symbols in red represent negative effect sizes.

xxviii. Trim and fill

For neurobehavioural and inflammation outcomes, trim and fill identified a substantially higher number of missing studies for SMD effect sizes (893 versus 199 respectively for neurobehavioural scores and 149 versus 3 for inflammation). Contrastingly, for demyelination and axon loss, the results were comparable across both NMD and SMD effect sizes; and both showed the same relatively large decrease in effect size when the predicted missing studies were taken into account.

		N (n=4158)	I (n=789)	D (n=283)	AL (n=165)
Normalised Mean Difference	Global effect size (95% CI)	36.9 (35.5-38.4)	37.8 (34.2-41.3)	44.4 (39.1-49.7)	54.3 (48.8-59.8)
	Missing studies	199	3	57	45
	Effect size after trim and fill	35.1 (33.7-36.5)	37.5 (34.0-41.1)	30.4 (25.2-35.6)	40.4 (34.8-46.0)
	Absolute difference in effect size (%)	1.8	0.3	14	13.9
	Relative difference in effect size (%)	5	0.80	37.4	29.4
	Relative difference in number of studies (%)	4.67	0.38	18.3	24.0
Standardised Mean Difference	Global effect size (95% CI)	0.94 (0.90-0.98)	0.98 (0.88-1.08)	1.12 (0.95-1.30)	1.68 (1.43-1.92)
	Missing studies	893	149	42	52
	Effect size after trim and fill	0.50 (0.46-0.55)	0.60 (0.49-0.72)	0.87 (0.67-1.06)	0.95 (0.67-1.23)
	Absolute difference in effect size (SD)	0.44	0.38	0.26	0.73
	Relative difference in effect size (%)	61.1	48.1	25.1	55.5
	Relative difference in number of studies (%)	19.4	17.3	13.8	27.2

Table 7.9. Assessment of publication bias using effect sizes calculated as NMDs and SMDs across four outcome measures. The number of publications contributing to each analysis is given in the column headers. Abbreviations: N, neurobehavioural scores; I, inflammation; D, demyelination; and AL, axon loss.

7.5. Discussion

In this assessment of methodological differences in meta-analysis, we have used the dataset from the largest meta-analysis of preclinical studies. With a number of methods available to choose from, it is not always clear in which circumstances each should be used. We have attempted to model the differences between the two most common methods of calculating effect sizes and assessing sources of heterogeneity in the data from animal studies, namely SMD and NMD, and meta-regression and stratified meta-analysis respectively.

7.5.1. Effect size calculations

We observed that there was a discrepancy between data that could have an SMD and NMD effect size calculated. Our pre-specified protocol was to use data which could have both effect sizes calculated; thus we had to exclude a substantial proportion of experiments because they did not report sham data or it could not be inferred. This provides evidence for a situation in which using SMDs is preferable – that is, upon inspection of the extracted data, prior to running any assessments of heterogeneity, if there are a number of comparisons for which sham data is required but not available, calculating SMDs may be a preferred option. However, it should be noted that a larger number of comparisons could not have SMDs calculated due to calculation errors (such as there being too few animals per group, or components of the equation cancelling each other out to result in a value of zero as a numerator). Therefore if all else is equal, the choice between the two effect sizes could be justified based on the proportion of comparisons which can be included in either analysis.

7.5.2. Publication Bias

We identified publication bias on both SMD and NMD effect sizes using all three methods. Trim and fill identified a greater proportion of missing studies on SMD effect sizes. It could therefore be considered more conservative to assess publication bias on NMD effect sizes as fewer missing studies are identified. However, it could equally be considered more conservative to use SMD effect sizes as they would generate a more conservative estimate of the overall global estimate of efficacy when the hypothesised

missing studies are taken into account. In addition it is likely that NMD effect sizes might be less likely to identify publication bias because the effect sizes are constrained by a ceiling and floor effect (typically -100% to +100%).

In addition, we found that Egger regression was not as robust using SMD effect sizes. Furthermore, we found that if we use the standard error in our measure of precision, we observed clear arcs in the data which may limit the validity of this test.

7.5.3. Assessing sources of heterogeneity

Our analysis suggests that meta-regression is more conservative as we found that substantially more study design characteristics accounted for a significant proportion of heterogeneity when assessed using stratified meta-analysis. However, our approach was not able to determine whether stratified meta-analysis is in fact accurate, and whether meta-regression is overly conservative.

7.5.4. Limitations and Future directions

Our analysis has provided empirical evidence for some of the key differences between two common methods of calculating effect sizes and assessing sources of heterogeneity. However, the main limitation to our approach is that we have been unable to provide empirical evidence for the circumstances in which one method may be superior to another. To explore this in more detail we propose to conduct a bootstrapping analysis. Since we know the distribution of data for a particular test (e.g. blinded assessment of outcome where the distribution is roughly 20% yes to 80% no), we can generate random samples from our dataset which follow this distribution. Thus if we run stratified meta-analysis and meta-regression on e.g. 1000 samples of 10% of the total dataset we can establish whether the analyses report significant differences at the 5% level for these randomly constructed contrasts, or whether they are more conservative than this.

A second limitation to our analysis is the likelihood of spurious findings. We calculated a total of 114 tests on heterogeneity (9 variables for all six outcome measures and an

additional variable, the histological section analysed, on three histological outcomes, calculated on both SMD and NMD effect sizes). Taking a cut-off p value of 0.05, we would expect to have found roughly 6 spurious results. However, the number of significant findings for these approaches was so large that we do not think that this is an important weakness.

7.5.5. Conclusions

Our analysis has demonstrated the fundamental differences which are observed when different methods are used to calculate an effect size for a meta-analysis and when we assess sources of heterogeneity on data from animal studies. We have not provided details on which method a researcher should use, but rather provide a transparent and objective comparison. Based on these observations, we have found that NMDs appear to give more precise estimates of global effect size. In addition we found that meta-regression was more conservative than stratified meta-analysis, although again we have not assessed the sensitivity and specificity of these tests. Despite this limitation, researchers should bear in mind these differences when conducting meta-analyses on data from animal experiments.

8. A systematic approach to identify putative drugs for a clinical trial of secondary progressive multiple sclerosis

This study was conducted in collaboration with the following: Siddharthan Chandran (SC) Emily Sena (ES), Malcolm Macleod (MM), Kieren Egan (KE), Cadi Irvine (CI), Afiyah Tariq (AT), Gary Carmichael (GC) and Jeremy Chataway (JC).

The drug selection committee meeting included the following: David Baker (DBa), Gina Cranswick (GC), Doug Brown (DBr), Graziella Filippini (GF), Gavin Giovannoni (GG), Andy Haines (AH), Lorraine Smith (LS), Sue Pavitt (SP), Ursula Utz (UU), Christopher Weir (CW).

My contributions include involvement in the study design & data extraction, all of the data analysis, and overseeing the implementation of the study when conducted by others.

8.1. Background

Secondary progressive multiple sclerosis (SPMS) represents an unmet target of drug research, with no proven disease modifying treatments available (Humphries, 2012). Efforts to slow progression over the last 20 years have been resoundingly negative with immunosuppressive (eg cyclophosphamide, cyclosporine), immunomodulatory (eg beta-interferon) and immunotolerance (eg myelin basic protein) (Ulzheimer et al., 2010). More effective trial designs have been developed incorporating multi-arm, multistage and adaptive approaches, but clearly are of no value without potentially effective drugs being tested. Moreover, a better understanding of the pathophysiology underpinning the transition from RRMS to SPMS highlights the need to identify potential neuroprotective agents, rather than immunomodulatory agents which are probably more suited to treat the inflammatory driven processes of RRMS (see Chapter 6).

Recently there has been increased interest in providing safe and efficacious therapies which can be administered orally. Prior to the clinical approval of fingolimod (FTY720), all disease modifying treatments (DMTs) were administered by injection, which over a long period of time can lead to poor compliance (Cox and Stone, 2006, Treadaway et al., 2009). Investigations of other potential orally active agents are underway (e.g. cladribine, laquinimod and teriflunomide) (Rammohan and Shoemaker, 2010, Gold, 2011); however it remains important to continue trying to identify oral interventions which will halt, or at the very least slow down, the neurodegeneration in SPMS.

Clinical trial design should either be based on sufficient evidence from animal studies, or there should be sufficient evidence of safety and predicted efficacy from other clinical trials. Systematic review and meta-analysis are useful for providing a comprehensive overview of a field of research. They have been extensively applied to clinical research (most notably by the Cochrane collaboration) to provide an objective overview of the evidence for safety and efficacy of specific interventions for specific diseases. They have also been applied to preclinical research (most notably by the Camarades collaboration) to identify limits to efficacy and provide evidence for the best design of clinical trials.

8.2. Aims

Our primary aim was to identify putative, orally administered interventions which might target SPMS, using systematic review and meta-analysis. We applied these techniques to the available evidence from clinical trials on four other neurodegenerative diseases: Alzheimers disease (AD), motor neuron disease (MND), Parkinson's disease (PD) and Huntingdon's disease (HD). We shortlisted interventions for further analysis of their safety, efficacy and quality if they had: been tested in one MS trial and at least one other disease; at least one MS trial; or not been tested in MS but had been tested in at least 3 other diseases. These were also checked for efficacy in the most common animal model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE). To our knowledge, this is the first time such an approach has been used to identify putative interventions for a clinical trial.

8.3. Methods

8.3.1. Search strategy

To identify all of the clinical trials in HD, PD, AD, MND and MS, we searched three online databases (PubMed, ISI Web of Knowledge and Embase) as well as the UK clinical trials database (www.clinicaltrials.gov, accessed August 2011); additionally we screened the MS database held by the Cochrane group to identify any further clinical trials on MS. We used the following search terms with results not limited by language or date: [multiple sclerosis OR Alzheimer's disease OR motor neuron disease OR Parkinson's OR Huntington]. We included case reports, uncontrolled case series, non-randomised parallel group studies, crossover studies and randomised controlled trials which reported efficacy or safety. References were exported to Reference Manager and three reviewers (CI, AT & GC) independently excluded duplicates and screened titles and abstracts for relevance against our pre-defined inclusion and exclusion criteria (Table 8.1), with differences resolved by discussion with a fourth reviewer (HV).

8.3.2. Hierarchy to short list interventions

At each stage of the short listing process, data were extracted and analysed using a Microsoft Access Database held by CAMARADES[6]. Six steps, outlined below, were taken to identify the final short-list of candidate interventions for SPMS.

i. Summary of interventions tested in clinical trials

To summarise the number of interventions tested orally in any of the five diseases, we extracted basic information from each publication including: publication ID, author year of publication, intervention tested and disease (MS, PD, HD, MND or AD).

[6] www.camarades.info

Inclusion Criteria	Exclusion Criteria
• Reporting primary data. • Reports of qualitative or quantitative data on either safety or efficacy for an intervention, treatment or pharmacological agent delivered orally in all types of human clinical trial design. • Studies reporting any change in clinical status (relapse frequency, disability progression, behavioural symptoms) or changes in biomarkers of clinical status (magnetic resonance imaging (MRI), blood, cerebral spinal fluid (CSF)) • Publications reporting on oral interventions in combination with other oral agents • Reports on MS must describe patients with any form of progressive disease.	• Publications reporting secondary analysis of previously published clinical trial data. • Non pharmacologic agents such as acupuncture, aromatherapy, physiotherapy, or exercise. • Reports on interventions already in clinical use for MS which are administered by any route including orally (i.e. methylprednisolone; interferon beta-1a; interferon beta-1b; mitoxantrone; natalizumab; glatiramer acetate). • Reports on Fingolimod as it has recently been approved for oral administration in humans. • Reports on levodopa treatment for Parkinson's disease. • Protocols for potential clinical trials. • Articles on relapsing-remitting MS. • Combination treatments where an oral and a non-oral intervention are administered.

Table 8.1. Inclusion and exclusion criteria used to assess the relevance of each report.

ii. Selection of interventions for further investigation

We carried forward interventions for further investigation if they had either been tested in MS at least once, or had been tested in at least 3 of 4 other diseases. Two clinicians independently (SS and JC) reviewed the long-list of interventions to exclude all interventions which met predefined exclusion criteria (Table 8.2).

Exclusion Criteria	Code for Subsequent Tables
Lack of evidence of efficacy/biological plausibility	A
Immune-suppressant	B
Steroid	C
Combination drug	D
Symptomatic relief only	E
Ongoing/ recently completed late trial	F
Better same class alternative	G
Adverse side effect profile.	H

Table 8.2. The criteria used to exclude the long list of drugs which met the inclusion criteria shown in Table 1 and had either been tested in MS at least once, or had been tested in at least 3 of 4 other diseases.

iii. Evidence for efficacy, safety and study quality

One author (MM) assessed all of the reports on the short-listed candidate interventions identified in the previous step against pre-defined criteria. Each report was graded on a scale of one (worst) to four (best) for their reported evidence on each of: quality (Table 8.3), efficacy and safety (Table 8.4). The four point scales for safety and efficacy was defined using criteria agreed upon by three clinicians (MM, SC and JC). Study quality was assessed against a combination of criteria defined by GRADE (Verhagen et al, 1998), CAMARADES (Macleod et al, 2004) and through a Delphi process (Atkins et al, 2004), to give a potential maximum score of 21 points from which a final quality score of 1 to 4 was allocated based on median and interquartile ranges. We additionally categorised the size of each study on a 1-4 scale (Table 8.4), and this was used in the calculation for the overall score assigned to each drug. In addition, we extracted the following information: clinical trial type (e.g. RCT, un-controlled, cross-over etc), clinical trial phase, mean age of the patients, sex of the patients, dose, duration of treatment, multi-centre or single centre study and the funding source.

iv. Evidence of efficacy from preclinical studies

We screened the short-listed interventions against our updated database, funded by the MS-Society, containing systematically identified reports of drugs tested in EAE, the most common animal model of MS. Where available, we generated summary estimates of efficacy for each intervention, measured as a standardised mean difference change in neurobehavioural scores, axon loss, demyelination and inflammation which were pooled using random effects meta-analysis. Additionally we assessed the publications against our 6 point quality checklist (Vesterinen et al., 2010), comprising of: (1) publication in a peer reviewed journal; and reporting of: (2) random allocation to group; (3) blinded assessment of outcomes; (4) a sample size calculation; (5) compliance with animal welfare regulations; and (6) a statement of any potential conflicts of interest.

v. Summary estimates

We generated summaries for each intervention including: clinical trial type, type of disease, median efficacy, safety and quality scores, the number of patients, study duration, dose, and overall score for the publication. Additionally we tabulated the number of publications awarded each of grades 1-4 for efficacy versus safety, efficacy versus quality and safety versus quality.

The overall score for each publication was calculated as the product of the scores for efficacy, quality, safety and study size and of the log of the number of publications identified plus 1.

STUDY QUALITY

Tick boxes: Yes (1 point); No (0 points)

- Peer Review Publication[1]
- Statement of Potential Conflicts of Interest[1]
- Sample Size Calculation[1]
- Random Allocation to Group[1,3]
- Allocation Concealment[1,2,3]
- Blinded Assessment on Outcome[1,2]
- Outcome Assessor Blinded[3]
- Patient Blinded[3]
- Care provider Blinded[3]

Options: Yes (1 point); No (0 points); Not Clear (0.5 points)

- Were the groups similar at baseline regarding the most important prognostic indicators?[3]
- Were the eligibility criteria specified?[3]
- Were point estimates and measures of variability presented for the primary outcome measures?[3]
- Was there an intention to treat analysis?[3]
- Complete accounting of patient and outcome events?[2]
- Non-selective Outcome Reporting[3]
- No other limitations[3]

Options: N/A; Definitely Yes (Low risk of bias; 1 point); Probably Yes (0.75 points); Probably No (0.25 points); Definitely No (High Risk of Bias; 0 points)

- Was selection of treatment and control groups drawn from the same population?[2]
- Can we be confident that patients received the allocation treatment?[2]
- Can we be confident that the outcome of interest was not present at start of the study?[2]
- Did the study stratify on variables associated with the outcome of interest or did the analysis take this into account?[2]
- Can we be confident in the assessment of the presence or absence of prognostic factors?[2]
- Can we be confident in the assessment of outcome?[2]
- Was the follow up of cohorts adequate?[2]
- Were co-interventions similar between groups?[2]

Table 8.3. The criteria adapted from the CAMARADES quality checklist[1], GRADE[2] and Delphi[3] to assess study quality.

SAFETY
Not Described (1 point)
SUSARs (suspected unexpected serious adverse reaction) or mortality (1 point)
SAE's (Severe adverse events) only(2 points)
AE's only (3 points)
No adverse effects reported (4 points)
EFFICACY
Not presented (1 point)
Definite worsening (1 point)
Neutral (2 points)
Non-significant improvement (3 points)
Significant improvement (4 points)
PATIENT SAMPLE SIZE
1-10 patients (1 point)
11-100 patients (2 points)
101-1000 patients (3 points)
1001+ patients (4 points)

Table 8.4. The criteria used to assess safety, efficacy and patient sample size.

vi. Candidate drug selection committee

The final short-list of candidate oral interventions was discussed in a face-to-face meeting with a panel of experts including: 5 neurologists, 1 MS patient representative, 1 member of the MS-Society research committee, 1 expert on the animal models of MS and 3 scientists that conducted part of the research and analysis. Interventions were scrutinised in detail with an emphasis on safety, efficacy, biological plausibility, pharmacological criteria such as CNS penetration as well as mechanistic class of action. Animal data were also considered where the clinical data were supportive.

After each of three rounds of reviewing, a number of candidate interventions were excluded from further consideration based on a lack of evidence for any of safety, efficacy or biological plausibility (Table 8.2).

8.4. Results

8.4.1. Search Results

Our initial electronic search of Pubmed identified 10,969 publications of which 956 met out inclusion criteria (Figure 8.1). Subsequent searches of other online databases and the Cochrane database of clinical trials of MS identified a further 419 publications meeting our inclusion criteria. In total this analysis is based on 1375 publications which reported an orally administered drug in a clinical trial of MS, AD, PD, HD or MND.

Of these 1375 publications, 13 interventions from 93 publications were tested in one MS clinical trial and at least one other disease; 21 interventions from 336 publications were tested in two or more MS clinical trials; 76 interventions from 144 publications were tested in one MS clinical trial; and 10 interventions from 102 publications were not tested in any MS clinical trials but were tested in at least three other diseases. The remaining 700 publications were not carried forward for further analysis.

8.4.2. Selection of interventions for further analysis

Our criteria above gave a long-list of 120 candidate interventions from 675 publications. All 120 interventions were screened against the exclusion criteria in Table 8.2. 68 interventions from 247 publications fell into one or more of the exclusion categories (Table 8.5), leaving 52 interventions from 428 publications in the short-list which we applied our detailed appraisal of safety, efficacy and quality.

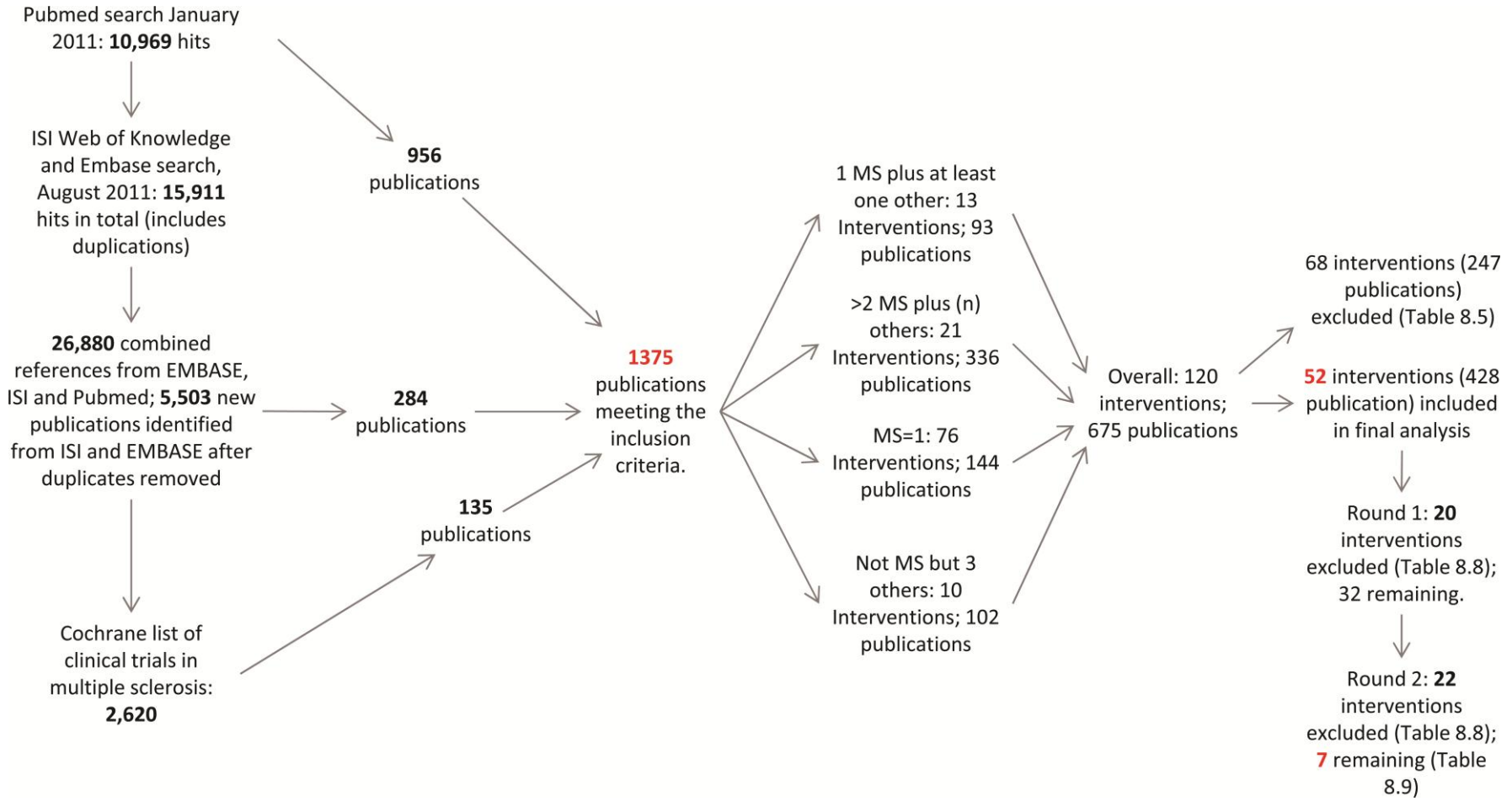


Figure 8.1. A quorum chart of the progression from the literature search to the final selection of seven candidate interventions. Round 1 and 2 refer to the two discussion sessions held with a panel of experts.

Drug	Exclusion Criteria Code
MK-677	A
15+- Dexoxyspergualin	B
4 Ammonium Phosphate	A
Adrenocorticotropic Hormone	C
Adrenocorticotropic Hormone 1-17	C
Amantidine/Isoprinosine	D
Anastal	No meaningful data
Antithymocyte Globulin	B
Arachidonic Acid	A
Azathioprine	B
Azathioprine & Prednisolone	B/D
Azathioprine/6-mercaptopurine	B/D
Baclofen	E
BHT-3009	A
Cannabidiol/Tetrahydrocannabinol	F
Cannabis extract	F
Cannabis Oil	F
Chlorambucil	B
Cladribine	F
Clofibrate	G
Cranberry Juice	A
Cyclophosphamide	B
Cyclophosphamide/predisone	B
Cyclosporin A	B
D1	A
Dantrolene Sodium	E
Delta-9-tetrahydrocannabinol	F
Desmopressin	A
Di Huang Cong Ji	A
Donepezil	H
D-penicillamine & Metacycline	B/D
DS103-282	E
Efamol	A
Estrogen	A
Fatty Acids	G
Fumarate (BG00012)	F
IFN-beta 1b	A/F
Indoramin	A
Isoprinosine	A/F
Lamotrigine	F/G
Laquinomod	F
Lycopid	B
Methotrexate	B
Mitoxantrone	B
Mizoribine	B
MMF (Mycophenolate-mofentil)	B
MS14	A
Oxybutynin	E

Padma 28	A
paroxetine	G
Piracetam/Cinnarizine	A/D
Prednisolone	C
Prednisolone/Levamisole	C
Prucalopride	E
Pyrogenalum/Flower	A
Rivastigmine	H
Ruta graveolens	A
Sulfasalazine	B/D
Tacrine	H
Tetrahydrocannabinol	F/G
Tizanidine	E
Tolperisone	E
Tolterodine	E
Triamcinolon	C
Tripterygium Wilpordii	A
Vigabatrin	H
Vitamin D/Calcium/Magnesium	D

Table 8.5. The category each intervention fell into for exclusion. See Table 8.2 for codes.

8.4.3. Summarising the evidence

Across the 52 candidate interventions, the median overall drug score was 13.6 (interquartile range (IQR) 8.9-27.3). Dextromethorphan/quinidine had the highest overall score with 56.2, followed by amantadine (55.2) and memantine (51.6). Conversely, the lowest scoring drugs were cyproheptadine (0.9), diazepam (1.8) and atromid (2.4; Table 8.6).

vii. Quality

The median quality score was 2.3 (IQR 2 to 3). Three interventions were given the highest score (4) for quality: ibudilast, dextromethorphan/ quinidine and L-amphetamine sulphate. All three received relatively high overall drug scores: dextromethorphan received the highest score of all 52 interventions, ibudilast and L-amphetamine sulfate were both reported in one publication each but had an overall score of 25.3 and 32.5 respectively, reflecting relatively high grades across each assessment criteria.

viii. Efficacy

The median efficacy score was 2.6 (IQR 2.1-3). Three interventions received the highest efficacy grade (4): misoprostal, oxcarbazepine and moclobemide. However these all received overall drug scores in the lowest quartile because they were reported in just one publication each. The drugs assigned the lowest scores for efficacy were rolipram (1.5), omega 3 fatty acid (1.8) and pentoxifylline (1.8).

ix. Safety

The median safety grade was 2.3 (IQR 2-3). Vitamin D/calcium, carbamazepine and myelin were the only interventions to receive grades of 4. Each drug was reported in one publication but vitamin D/calcium had a relatively high overall score reflecting high scores across each assessment criteria (3 for efficacy, 4 for quality and 2 for the patient sample size). Carbamazepine and myelin scored 3.6 and 12 overall.

x. Patient Sample Size

The median grade for the patient sample size was 2 (IQR 1.9-2.3). No clinical trial included in our analysis used more than 1000 patients and so the highest grade achieved by any intervention was 3 which was assigned to L-amphetamine sulphate, dextromethorphan/quinidine, ibudiblast and MaxEPA oil. Interventions tested in the smallest clinical trials in terms of patient sample sizes included cyprheptadine, isoniazid and rolipram, moclobemide and carbamazepine which all used between one and ten patients, thus scoring 1 point each.

8.4.4. Evidence from EAE studies

We identified pre-clinical literature on 34 of the 52 candidate interventions tested in EAE. The majority of the literature was on myelin basic protein (126 publications), followed by vitamin D (17), minocycline (12) and rolipram (10). The median quality score, measured against our 6 point quality checklist was 1 (IQR 1 to 2). Reporting of random allocation to group and blinded assessment of outcome was generally low but for many interventions it was difficult to make inferences on study quality as they were reported in so few publications (Table 8.7).

	N	Efficacy Score	Safety Score	Quality Score	Patient Sample Size Score	Overall Drug Score
3,4-Diaminopyridine	3	2.3	2.3	2.7	1.3	11.4
4-Aminopyridine	10	2.7	2.5	3.0	2.1	44.4
Amantadine	57	3.1	2.4	2.2	1.9	55.2
Aspirin	2	2.0	1.5	3.0	2.5	10.7
Atomoxetine	3	2.7	3.3	3.0	1.7	26.8
Atromid	1	2.0	1.0	2.0	2.0	2.4
Bromocriptine	4	1.9	2.5	1.8	1.5	8.6
Carbamazepine	1	3.0	4.0	1.0	1.0	3.6
Coenzyme Q10	9	2.2	1.9	3.2	2.3	30.6
Creatine	12	2.1	2.3	2.7	2.4	35.9
Cyproheptadine	1	3.0	1.0	1.0	1.0	0.9
dextromethorphan	7	2.5	2.7	2.3	1.9	26.2
Dextromethorphan/ Quinidine	3	3.3	2.3	4.0	3.0	56.2
Diazepam	1	3.0	1.0	1.0	2.0	1.8
Fluoxetine	5	2.4	2.2	2.6	1.6	17.1
Gabapentin	8	2.7	2.5	2.9	2.5	46.7
Ginseng	1	3.3	3.0	2.0	2.0	12.0
Glucosamine Sulfate	1	2.5	3.0	4.0	2.0	18.1
Hydroxyzine/Caffeine	1	3.0	3.0	1.0	2.0	5.4
Ibudilast	1	3.5	2.0	4.0	3.0	25.3
Imipramine	2	2.0	2.0	3.0	2.0	11.5
Isoniazid	4	2.8	2.5	2.3	1.0	10.8
L-amphetamine sulfate	1	3.0	3.0	4.0	3.0	32.5
Levamisole	2	3.2	2.0	3.0	2.0	18.1
Levetiracetam	3	3.7	2.0	1.7	2.0	14.7
Linoleic Acid	4	2.5	1.0	2.3	2.5	9.8
Linomide	3	3.0	1.3	2.7	2.3	15.0
lipoic acid	2	2.0	2.0	2.0	2.0	7.6
Lithium	11	2.0	1.4	2.4	1.5	10.2
MaxEPA Oil	1	3.0	1.0	3.0	3.0	8.1
Melatonin	7	2.1	2.6	2.1	2.0	21.2
Memantine	34	2.7	2.0	2.6	2.4	51.6
Milacemide	4	2.0	2.3	2.5	2.0	15.7
Minocycline	11	2.3	2.6	2.3	2.2	31.9

Misoprostol	1	4.0	3.0	1.0	2.0	7.2
Moclobemide	1	4.0	3.0	1.0	1.0	3.6
Modafinil	8	2.9	2.4	3.1	2.1	44.4
Myelin	1	2.5	4.0	2.0	2.0	12.0
Naltrexone	8	2.2	2.6	2.1	1.8	20.6
Omega 3 Fatty Acid	2	1.8	3.0	2.0	2.0	10.0
Oxcarbazepine	1	4.0	2.0	1.0	2.0	4.8
Pemoline	2	2.0	2.0	2.5	2.0	9.5
Pentoxifylline	2	1.8	1.0	2.5	2.5	5.5
Pirfenidone	3	3.1	3.0	2.3	2.0	25.8
Riluzole	16	2.4	1.8	2.4	2.0	24.6
Rolipram	2	1.5	3.0	1.5	1.0	3.2
Selegiline	11	2.7	1.9	2.7	2.3	34.2
Tolbutamide	1	3.0	3.0	2.0	2.0	10.8
Tranylcypromine	2	2.5	3.5	2.0	1.5	12.5
Vinpocetin / Propentofylline / Theofylline	1	2.5	3.0	2.0	2.0	9.0
Vitamin D/Calcium	1	3.0	4.0	4.0	2.0	28.9
Vitamin E	9	2.1	2.0	3.0	2.4	31.1
Median (IQR)	3 (1-7)	3 (2-3)	2 (2-3)	2 (2-3)	2 (2-2)	14 (9-27)

Table 8.6. The summary statistics on safety, efficacy and quality for 52 candidate interventions. N represents the number of publications identified for each intervention.

Drug	Publications	Average Quality Score	Random Alloc.	Blinded Assess.	Improvement in:			
					Neurobehavioural Score	Axon Loss	Demyelination	Inflammation
4-Aminopyridine	1	1.0	0	0	n/a	n/a	n/a	n/a
Amiloride	2	1.5	0	1	1.3 (0.9 to 1.7; n=4; 123 animals)	0.2 (-4.5 to 4.8; n=2; 22 animals)	-1.4 (-2.7 to -0.1; n=1;12 animals)	n/a
Amphetamine	1	1.0	0	1	-0.6 (-1.5 to 0.3; n=2;30 animals)	n/a	n/a	13.5 (-6 to32.9; n=4; 30 animals)
Aspirin	3	1.7	2	0	n/a	n/a	n/a	n/a
Atomoxetine	1	1.0	0	1	0.8 (-0.4 to 2.0; n=1; 12 animals)	n/a	n/a	n/a
Bromocriptine	2	1.0	0	1	0.9 (0.4 to 1.4; n=3; 70 animals)	n/a	n/a	n/a
Caffeic Acid Phenethyl Ester	1	2.0	0	0	-1.5 (-2.4 to -0.5; n=1; 24 animals)	n/a	n/a	n/a
Calcium	2	1.5	0	0	n/a	n/a	n/a	n/a
Calcium + Vitamin D	1	1.0	0	0	n/a	n/a	n/a	n/a
Carbamazepine	1	2.0	0	0	1.2 (-1.7 to 4.1; n=2; 24 animals)	n/a	n/a	n/a
Cyproheptadine	3	1.3	1	1	6.5 (1.7 to 11.4; n=4; 32 animals)	n/a	n/a	n/a
Dextromethorphan	1	1.0	0	1	0.1 (-0.2 to 0.5; n=4; 133 animals)	n/a	n/a	n/a
Essential Fatty	1	0.0	0	1	n/a	n/a	n/a	n/a

Acids								
Ginseng	1	2.0	0	0	4.7 (3.1 to 6.2; n=1; 28 animals)	n/a	n/a	n/a
Glucosamine	1	2.0	0	1	n/a	n/a	0.7 (-0.3 to 1.8; n=3; 20 animals)	0.6 (-0.4 to 1.7; n=3; 20 animals)
Imipramine Hydrochloride	2	1.0	0	0	n/a	n/a	n/a	n/a
Levamisole	3	1.3	2	1	0.8 (0.1 to 1.4; n=8; 84 animals)	n/a	n/a	-0.5 (-1.9-0.8; n=1;10 animals)
Linoleic Acid	4	0.0	0	2	0.1 (-0.4 to 0.7; n=10; 88 animals)	n/a	n/a	n/a
Linolenic Acid	1	1.0	0	1		n/a	1.5 (0.6-2.3; n=4;80 animals)	n/a
Linomide	5	0.8	0	2	1.5 (-0.3 to 3.2; n=8; 192 animals)	n/a	n/a	1.8 (1-2.5; n=4;51 animals)
Lipoic Acid	6	1.7	2	2	1.2 (0.7 to 1.6; n=15;188 animals)	n/a	1.1 (0.5-1.7; n=2;45 animals)	1 (-0.7-2.6; n=3;53 animals)
Lithium	3	1.7	0	0	1.7 (0.5 to 2.9; n=4; 80 animals)	n/a	n/a	n/a
MBP	126	1.1	8	38	0.9 (0.7 to 1.1; n=140; 1880 animals)	n/a	n/a	1.9 (1.5-2.4; n=38;509 animals)
Melatonin	1	1.0	0	0	1.1 (0.1 to 2.2; n=1; 17 animals)	n/a	n/a	n/a
Memantine	2	2.0	0	1	2.7 (1.6 to 3.7; n=13; 156 animals)	n/a	n/a	2.2 (0.9-3.5; n=6;61 animals)

Minocycline	12	1.6	3	6	0.9 (0.6 to 1.3; n=23; 311 animals)	0.3 (-0.6-1.2; n=3;31 animals)	0.5 (-0.2-1.1; n=7;76 animals)	0.8 (0.3-1.3; n=9;93 animals)
Myelin	9	1.4	2	1	0.7 (-0.5 to 1.9; n=8; 130 animals)	n/a	0.8 (0.2-1.5; n=5;53 animals)	1 (0.4-1.5; n=6;68 animals)
Pentoxifylline	6	1.3	2	1	0.2 (-0.3 to 0.7; n=13; 170 animals)	n/a	n/a	4 (2-6.1; n=1;14 animals)
Propentofylline	1	1.0	0	1	n/a	n/a	n/a	n/a
Riluzole	2	1.0	0	1	3.5 (2.3 to 4.8; n=7; 119 animals)	4.4 (1.3-7.6; n=1;10 animals)	n/a	0.6 (-0.6-1.9; n=1;10 animals)
Rivastigmine	1	2.0	0	0	1.4 (0.8 to 2.1; n=2; 56 animals)	1.2 (0-2.5; n=1;13 animals)	1.1 (-0.1-2.3; n=1;13 animals)	1.6 (0.2-2.9; n=1;13 animals)
Rolipram	10	1.2	1	5	0.8 (0.3 to 1.4; n=22; 528 animals)	1.2 (-0.2-2.7; n=1;12 animals)	n/a	1.5 (0.1-2.9; n=9;77 animals)
Vitamin D	17	1.6	5	4	0.9 (0.5 to 1.4; n=26; 670 animals)	n/a	n/a	1.8 (1.1-2.5; n=6;74 animals)
Vitamin E	1	1.0	0	0	n/a	n/a	n/a	n/a

Table 8.7. Summary data for 34 of the 52 candidate interventions which had been tested in EAE including: the number of publications which randomly allocated to group and/or blinded their assessment of outcome; and summary estimates for effect size, presented as: (random effects estimate of efficacy (L95% CI – U95% CI; number of comparisons; number of animals).

8.4.5. Drug Selection Meeting

Detailed discussions of each of the 52 drugs were first undertaken based on individual drug summaries using the core selection / exclusion criteria (Table 8.2) with particular emphasis on safety and efficacy. This led to 20 drugs being excluded (Table 8.8). The remaining drugs then underwent further scrutiny including examination of source publications by the whole group as well as NIH clinical trials site and animal data where relevant. Again using the core criteria 25 further drugs were excluded (Table 8.8).

After the two rounds of discussion the candidate interventions for a clinical trial were narrowed down to a final list of seven (Table 8.9) which had been selected based on sufficient evidence of efficacy, safety and quality and an appraisal of the preclinical data. The final list included: oxycarbamazepine, amiloride, fluoxetine, pirfenidone, PUFA class (poly unsaturated fatty acids which include linoleic Acid, lipoic acid; MaxEPA and omega-3), ibudilast and riluzole.

	Drug	Exclusion Criteria Code
Exclusion after round 1 of discussion	3,4-Diaminopyridine	A
	4-Aminopyridine	A
	Atomoxetine	H
	Clofibrate (trade name Atromid)	H
	Bromocriptine	H and G
	Dextromethorphan	D
	Diazepam	H
	Ginseng	A
	Imipramine	A and H
	Isoniazid	E
	Levamisole	H
	Linomide	H
	Lithium	A
	Melatonin	A
	Milacemide	A
	Myelin	A
	Naltrexone	A
	Pemoline	A
	Tolbutamide	A and H
	Vitamin E	A
Exclusion after round 1 of discussion	Amantadine	A
	Aspirin	A
	Carbamazepine	G and H
	Coenzyme Q10	A
	Creatine	E and H
	Cyproheptamine	A and E
	Dextromethorphan/ quinidine	E
	Gabapentin	G
	Glucosamine sulfate	A
	Hydroxyzine/caffeine	A
	L-amphetamine sulfate	H
	Levetiracetam	A
	Memantine	A and E
	Minocycline	F
	Misoprostol	E
	Moclobemide	E
	Modafinil	E
	Pentoxifylline	G
	Rolipram	G
	Tranycypromine	A and H
	Vinpocetin/Propentofylline/ Theofylline	G
	Vitamin D/ Calcium	A

Table 8.8. Interventions excluded after round 1 and 2 of discussion with a panel of experts. For the codes see Table 8.2 legend.

Intervention	Class of action
Amiloride	Acid sensing ion channel 1 blocker, potassium sparing diuretic
Fluoxetine	SSRI, antidepressant
Ibudilast	PDE(4)I
Oxycarbamazepine	Voltage sensitive sodium channel blocker, anticonvulsant
Pirfenidone	Antagonises synthesis of TGF-beta & TNF-alpha; antifibrotic/anti-inflammatory
PUFA class (Linoleic Acid, Lipoic acid; MaxEPA, Omega3)	Complex group of dietary supplement
Riluzole	Glutamate release inhibitor/inactivation of voltage-dependent sodium channels

Table 8.9. The 7 remaining candidate interventions after 2 rounds of discussion with a panel of experts.

8.5. Discussion

In this chapter I have described the process of using systematic review and meta-analysis to select and critically appraise publications on clinical trials, leading to a final shortlist of seven candidate interventions which may be suitable for a clinical trial of SPMS.

8.5.1. Systematic approach to drug selection for clinical trials

Systematic review and meta-analysis have been used extensively in the life sciences and beyond. They have established themselves as important tools for assessing the efficacy of interventions in preclinical and clinical trials, as well as predicting limits to efficacy such as the influence of study design characteristics and the internal & external validity of included studies. Moreover, in Chapter 6 I described a novel use of these tools in establishing the relationships between outcome measures, and the pathway to improvement in one outcome via mediation of other disease mechanisms. In this study these methods have been applied in another unique way.

The necessary applications to proceed to clinical trial are traditionally put forward by research groups or pharmaceutical companies who have evidence of efficacy from animal studies on the drug of interest. Furthermore, the choice of drug selection in preclinical trials is based simply on the research directions of that group, or via large scale pharmacologic screening based on, for example, knowledge of specific receptors or targets of interest for a particular disease. Our approach is both unique for two reasons. Firstly, our approach includes potential useful clinical trials which may have been lost in the midst of, for example, inadequate funding to continue research. Secondly, using data from clinical trials which have already taken place, and by having adequate evidence of safety as one our criteria for inclusion in the final shortlist, we are potentially able to bypass much, or all of the preclinical testing phases. Typically it takes more than five years to reach FDA approval from animal testing and so our approach is useful to be able to reduce this time gap.

8.5.2. Short-listed interventions

From our initial literature search of over 15,000 publications, our selection process narrowed down 1375 potentially relevant publications to seven interventions which met all of the critical criteria. Initially we generated a long-list of interventions; these were drugs which had been tested either in MS at least once, or in two or more other diseases. Because our aim was to identify a drug which could be taken forward to a large scale clinical trial, we only carried forward interventions which had at least been tested in MS as these are more likely to meet the necessarily approval from regulatory boards, and thus potentially minimise the time to clinical approval. However, the drugs which did not meet these selection criteria are listed as they present a useful range of interventions which may warrant further investigation, either in adequately designed preclinical trials, or smaller phase one clinical trials.

8.5.3. Limitations

As described in previous chapters, there are a number of limitations of systematic review and meta-analysis in general. Importantly, these are methods hypothesis generating only and are not deemed as a substitute for a high quality, adequately powered, multi-centre study in a clinically relevant cohort of patients. However, our

approach is potentially useful for designing such a trial. Secondly, to our knowledge we included all the available evidence, and moreover we tried to increase the sensitivity and specificity of our search strategy by including broad search terms and by multiple researchers going through the same reference lists. However, as publication bias is prevalent in clinical research (Dwan et al., 2008, Hopewell et al., 2009), it is possible that our analysis did not include all of the negative or non-significant studies. We attempted to minimise this bias in two ways. Firstly, we included the reference library from the Cochrane collaboration which has all of the clinical trials they have identified, including hand searched research which is not in the public domain. Secondly, our discussions with the panel of experts included knowledge of any potentially missing studies, or of any research groups which may have conducted research on the short-listed interventions.

8.5.4. Conclusions

We have identified and described a novel method to identify putative drugs for clinical trial which may be useful for the development of further clinical trials. Furthermore, our approach narrowed down the focus of investigation to seven drugs with adequate evidence of safety and efficacy from high quality clinical trials which may be useful for a clinical trial of SPMS.

9. Discussion

At the start of this thesis I summarised some of the issues surrounding translational failures in the life sciences. My focus was on MS for which there are major treatment gaps. The primary objective of this thesis was to describe the application of systematic review and meta-analysis to the preclinical literature on EAE to summarise the scope of the literature and to try and identify potential reasons for the failure to translate reliably the efficacy from bench to beside. Other objectives were: to compare the findings in the EAE literature to the literature on another neurological disease with limited translational success (PD); explore the relationship between different measures of drug efficacy in EAE; to explore the differences between the methods I used; and to describe my experience of using systematic review and meta-analysis to identify putative interventions for SPMS. The following sections summarise the main questions I have tried to address, the conclusions I have drawn, the limitations to my approach, and some potential avenues for future research.

9.1. Why have interventions for MS failed to translate from EAE to the clinic?

9.1.1. What was known prior to this research?

> "An animal model is defined as an animal that has a disease or injury similar to the human condition. Ideally, it should have a similar aetiology and function to the human equivalent, and it is necessary that as many aspects of the disease are replicated as possible to avoid confounding and misleading results, which in turn may hinder the development of new therapeutic approaches" (Lane and Dunnett, 2008)

MS is a complex and heterogeneous disease. More than a century after its formal recognition by Charcot, there are still a number of fundamental unknowns; for example we do not know with any certainty what causes MS and how the pathophysiological processes interact to cause neurological impairment. Owing to this it has been argued by some in the MS research community that while EAE is a very good model of

autoimmunity, it does not adequately recapitulate the complexities and true nature of MS. Therefore it could be argued that EAE may be violating the conditions described by Lane and Dunnett in the above quote. In fact there is large community that believe that MS is not an autoimmune disease at all, and that inflammatory processes are secondary to neurodegeneration (Stys et al., 2012). The biological underpinnings of MS and EAE, and their differences, are beyond the scope of this thesis; however, while the findings I summarise below make little inferences to the role that biological factors play, it is important to keep in mind that these are clearly important.

9.1.2. The importance of adequate study quality

There has been extensive literature published on the inadequacies of clinical trials, from their methodological design and implementation to their reporting (described in Chapter 5). In more recent years there has been increased momentum in exploring whether these inadequacies exist in the preclinical literature as it is clear that animal studies may bear some of the clues to translational failures. Systematic review and meta-analysis of preclinical studies of stroke, glioma, Alzheimer's disease, intracerebral haemorrhage (ICH) (Frantzias et al., 2011, Sena et al., 2007a, Egan et al. under review, Hirst et al. under review) and more broadly (Kilkenny et al., 2009) have generally found study quality to be poor. Importantly, I have found the same trend across 1464 publications on EAE, 253 publications on experimental PD studies, and 95 publications on animal experiments in the 2008 volume of JCBFM.

Two aspects of study quality were of particular concern. Firstly, measures to reduce bias were rarely reported in the preclinical literature on EAE, PD and in the 2008 volume of the JCBFM. For the preclinical EAE studies, where outcome was measured as the reduction in inflammation, I found that efficacy was substantially overstated in studies which did not report blinding their assessment of outcome. This finding was also found in the preclinical PD studies where improvement was measured as change in neurobehavioural outcomes. We have also previously shown that for the publications which report the most commonly tested interventions in EAE, lack of reporting of both randomisation and blinded assessment of outcome led to substantial overstatements of efficacy measured as improvement in neurobehavioural outcomes (Vesterinen et al., 2010).

The importance of randomisation of animals prior to experimentation is perhaps not as obvious as the importance of blinding the assessment of outcome, particularly when the animals are genetically inbred, commercially sourced, and group-allocation is done prior to disease induction. However, because animals respond differently to their environment it may be more difficult to "catch" a more active animal in a cage – perhaps an indication of the animal's health and stress levels at the start of the trial. Thus active and docile animals may end up being treated in a manner that is not entirely random.

Secondly, across all of the publications reviewed in this thesis (1464 on EAE, 253 on PD, and 312 from the JCBFM) just 7 reported a sample size calculation. Although it provides little comfort, this trend is the same across the preclinical literature as a whole (Kilkenny et al, 2009, Baginskaite unpublished findings). It is not clear why so few publications report sample size calculations, however it is clear that there are a number of incentives to keep the numbers low: ethics, cost and time.

Calculating the required sample size is not a trivial matter, and this may go some way to explain why they are so rarely conducted. A sample size calculation is conducted to estimate the probability that if there is a true treatment effect of a given size, the statistical test will detect it. Calculating the minimum required sample size involves careful consideration of a number of factors, as well as their predicted values. These include: the type 1 error (alpha; the predicted rate of picking up a false-positive effect which is usually pre-set at 0.05), the power (1-beta; the predicted rate of avoiding picking up a false-negative effect, which is often set at 80%), the smallest effect of interest (the minimum difference between the treatment and control group which would be of biological/clinical relevance), and the variability (usually expressed as the standard deviation of the treatment effect) (for more details see: Noordzij et al., 2010). Nowadays several tools are available to aid in these calculations including online resources (Lenth, 2007, Lenth, 2006-9) and publications describing calculation methods and the practical issues that may arise (for example see: Chapman and Seidel, 2008, Dirnagl, 2010).

We have used post-hoc power calculations to give a rough estimate of the power to detect differences between the treatment and control group for the preclinical EAE and PD literature. Although post-hoc power calculations comes with their limitations (Hoenig and Heisey, 2001), our estimates suggest that the median study is powered at 64% for EAE studies and 40% for PD studies. However if we also take into account the probability that a substantial proportion of experiments on which we based these calculations reported inflated estimates of efficacy (because they did not randomise or blind their assessment of outcome), then it is likely that for high quality studies which have taken these measures, our power calculations underestimate the number of animals required.

9.1.3. The importance of adequate reporting

Experiments should be replicable and robustly designed to minimise the risk of false findings which may be exceptionally common (Ioannidis, 2005). Being able to replicate and assess the robustness of an experiment relies on adequate reporting. We identified a number of areas for concern. In particular in the EAE literature a large proportion of studies across the dataset did not report the number of animals, the variance, or the type of variance reported. These are all crucial for assessing the robustness of a study, and we urge caution in interpreting data from studies which do not report these. Kilkenny et al, (2009) have found a similar trend across a range of preclinical literature, with 4% of 271 publications not reporting the number of animals in either the methods or the results section.

The ARRIVE guidelines (Kilkenny et al., 2010) aim to pave the way for improvements in the conduct and reporting of preclinical experiments in the same way that the CONSORT statement has improved these in clinical trials (Plint et al., 2006). This thesis has provided a foundation for such guidelines to exist in the field of preclinical research as I have provided empirical evidence from the largest systematic review of preclinical experiments to show that the issues addressed in these guidelines are likely to be contributing to the bottleneck in translational medicine.

To further reduce the impact of bias, it has been proposed that multi-centre animal studies be set up (Bath et al., 2009). There are a number of advantages to this approach. First and foremost, scientific research should be collaborative as this sparks new ideas and may improve study design. Lastly, adequate sample sizes may be difficult to achieve due to limited resources. In our group, we found that we would need over 300 animals per group (using a sample size calculation) to conduct a specific preclinical stroke experiment. With limited resources and funding the project progressed no further. However, taking a multi-centred approach, the number of animals required could be shared between centres, reducing the resources required by each research group.

9.1.4. The impact of publication bias

We identified a substantial publication bias in the EAE literature using three approaches including a quantitative analysis to predict the number of missing studies and their impact on the global estimate of efficacy. In addition, two out of the three approaches identified publication bias in the preclinical PD literature.

Where studies are small and give imprecise estimates of treatment effects, some will overstate efficacy and some will understate efficacy. This provides the background for publication bias, such that there is a bias towards publication of the small, imprecise, positive studies rather than the small, imprecise, neutral studies. Two important considerations are raised from these observations. Firstly, it is ethically questionable to use animals for research which will never reach the public domain. Even if these studies are underpowered, it does not mean that they are not valuable to others conducting a trial on the same intervention. For example, case studies and pilot studies are both important contributors. It is important however that such a limitation is mentioned in a publication so results can be interpreted in this context. Secondly, publication bias can lead to the overstatement of efficacy in meta-analyses. An advantage of meta-analysis is that they include all available evidence and where the sample size is small, less weight will be given in the overall estimate of efficacy. Crucially, even larger negative studies are less likely to be published, and so a drug may be taken forward for clinical trial based on incomplete evidence.

Publication bias was described by Rosenthal in 1979, and has since been formally identified in both clinical (Easterbrook et al., 1991, Hopewell et al., 2009, Dwan et al., 2008) and animal experiments (Sena et al., 2010). The identification of this in clinical research came first, and has since led to registries of clinical trials. These registries allow investigators to know whether a drug has been tested and where the study has been conducted. However, there is no such registry of animal experiments, and therefore personal communication and/or publication are the only methods of finding out whether a study has been conducted. The solution to this problem is not immediately apparent. Ideally, all animal experiments would be pre-registered on a central database; however this raises the issue of intellectual property. A solution to this problem may be to register core information such as the class of drug under investigation.

With no immediate solution to hand, our approach is to continue to raise awareness of the issue of publication bias by providing empirical evidence for its existence and impact. Our hope is that this will encourage more researchers to be transparent in their approach, and for prestigious journals to encourage preregistration of animal studies in the same way that this has occurred in clinical research.

9.2. How else can systematic review and meta-analysis be used to improve translational efficacy?

In this thesis I have described two novel uses of systematic review and meta-analysis. In Chapter 6 I described how they can be used to assess the relationship between different outcome measures in the preclinical literature; and in Chapter 8 I described how these were used to identify putative candidate drugs for a clinical trial of SPMS. Conclusions from these are described in turn below.

9.2.1. Identifying drug targets

We found that the majority of publications on EAE report neurobehavioural outcomes, most commonly as a mean severity score, a mean clinical score, a mean cumulative score, and/or the data for these are shown graphically. Fewer publications report

histological outcomes which are considered to be key drug targets, namely demyelination and/or axon loss. We found that neurobehavioural scores were not always strong correlates of changes in histological outcomes, and moreover that histological outcomes were not always strong correlates of each other. This implies that these may represent different underlying pathological processes. Interestingly however, we also found that the relationship between the improvement in axon loss and neurobehavioural scores increased with later times of administration. This provides empirical evidence to support the idea that axon loss is a key drug target to successfully alter disability when more clinically relevant times of administration are used. We conclude that drugs targeting axon loss when administered at a clinically relevant time point may offer substantial hope for successful translation to the clinic.

9.2.2. Evidence based clinical trial design

In our interest to explore further the potential uses of systematic review and meta-analysis we applied these to clinical literature to identify putative interventions for a clinical trial of SPMS. The methods were designed using all of our experience in conducting systematic reviews of animal studies and the key aspect to this was the collaborative approach. Whilst all of the data extraction and analyses were conducted in Edinburgh, the feedback on the protocol and the final drug selection committee was multi-national. This included a member of the MS Cochrane group which provided useful feedback from the perspective of an expert in the field of systematic review and meta-analysis of clinical research. By identifying all of the relevant clinical trials on a number of other neurodegenerative diseases as well as MS, and assessing their evidence for safety, efficacy and quality, we have been able to identify seven interventions which have sufficient high-quality evidence to warrant further investigation and potentially be taken forward to a clinical trial.

9.3. Which are the most suitable methods for the systematic review and meta-analysis of preclinical studies?

To provide a more solid foundation to the choices of methods used in this research, we explored the differences between NMD and SMD effect sizes, and stratified meta-analysis and meta-regression for exploring sources of heterogeneity. Previously we

have preferentially chosen NMDs over SMDs as the unit of NMDs are intuitive (percentage change). In addition, when meta-regression became more accessible to use in statistical software and it was shown to be robust, this was our preferred choice as it is a more conservative approach than stratified meta-analysis. Our exploratory analyses on these methods demonstrated the similarities and differences using real data. The advantage of this is that hypothetical data do not necessarily take into account the impact of outliers and unusual situations, for example when a control group performs better than a sham group. We found that in general NMD effect sizes were more precise, and Egger regression was more robust on these effect sizes. We also found that meta-regression was substantially more conservative, and particularly on SMD effect sizes.

A limitation to this analysis is that it was descriptive and therefore no firm conclusions could be drawn. However in Chapter 7 I proposed a series of steps which could be taken to formally and empirically assess our hypotheses.

9.4. Limitations

There are a number of limitations to our approach which are described below.

9.4.1. Systematic review

As mentioned in Chapter 1, systematic reviews should be transparent, replicable and efforts should be taken to avoid bias. Transparency refers to reporting of clear methodology and this has been made more straightforward in recent years by the publication of the PRISMA checklist and flow-chart (Moher et al., 2009). These publications came out after the initiation of the research in this thesis, and thus the flow diagram is not easily applied to the systematic reviews of EAE studies in this thesis as it is based on multiple searches. Owing to the large number of hits in the literature search it was also not possible to give a reason for exclusion of articles which is a PRISMA-checklist item. Indeed, while we have made efforts to ensure the reporting of our methodology was clear, the replicability may be affected by not reporting clear reasons for each study's exclusion.

We attempted to minimise selection bias by using multiple electronic databases for our initial literature search which was screened by at least two independent reviewers for all but the updated literature search on EAE studies. However, although our initial search strategy for EAE studies (on Pubmed in 2007) was broad, it was not deep and thus we may have initially missed relevant publications. Our updated literature search was broader, but while we made every attempt to identify all relevant studies it is nonetheless possible that relevant studies were not identified. However, while there may be some missing studies, these are likely to affect only our estimates of efficacy where we have reported these for individual drugs. However, where a systematic review and meta-analysis of an individual drug or drug group is conducted, the literature search should be more focused and include an attempt to identify unpublished research.

9.4.2. Meta-analysis

Meta-analyses are post-hoc, observational studies and therefore only hypothesis generating. While we have made a number of interesting observations relating to the EAE and PD literature, such as the differences between routes of delivery, they should be used merely to inform the design of future studies. Furthermore, discussion about study quality and its potential impact on reporting effect sizes is only intended to be thought provoking, and to raise further awareness that these issues are relevant to animal studies.

Our estimates of efficacy, both globally and for individual strata should be interpreted with caution for several reasons. Firstly, it is possible that our observations that efficacy is higher under certain study design conditions may in fact be statistical artefact or due to collinearity with other study design variables, or both. Secondly a meta-analysis can involve conducting large numbers of exploratory analyses of heterogeneity. In this thesis we avoided large numbers of analyses as it raises the likelihood of a type 1 error. We pre-specified our analyses based on biological relevance and scientific interest. In addition we used Bonferroni correction to adjust our p value for the number of variables we assessed. Secondly, taking any meaning

from our estimates of efficacy for individual interventions relies on the assumption that the outcome measure is clinically relevant, or that it is a suitable surrogate marker for a relevant outcome. Indeed, it may be that neurobehavioural outcomes are not relevant measures of drug efficacy. Our approach is to be transparent and to simply summarise the available data. Thus we have summarised the four outcome measures most commonly reported without any prior assumptions about their clinical relevance.

9.4.3. Lumping oranges and giraffes[7]

Another criticism of meta-analyses is the lumping together of studies which are fundamentally different. Main concerns relate to the grouping of: different models which behave differently in terms of clinical and/or pathological manifestations; different interventions which may have different physiological targets; and studies with different aims, such as those which target the prevention of disease versus those which target established disease.

All of the results we have presented from meta-analyses of preclinical studies should be interpreted with these concerns in mind. However, in order to group only similar studies together, we would need to make prior assumptions. In our experience this is too difficult to perform adequately. For example, assigning each individual intervention to a drug group would perhaps be useful, but arguably most drugs could fall into more than one category, and developing a systematic and robust approach to drug classification is difficult. Additionally, whilst we could for example separate individual EAE or PD models into the method used to induce them, perhaps along with the specific species used, there could essentially be no limit to this disaggregation. It is our belief that one advantage of meta-analysis is that these prior assumptions are not made.

Nonetheless, particular animal models or interventions may be targeted towards specific aspects of the clinical disease, and grouping these different studies together will inevitably mask these crucial nuances. We propose that whilst this is a criticism of the current work, it may be useful to conduct systematic reviews and meta-analyses on

[7] SENA, E., VAN DER WORP, H. B., HOWELLS, D. & MACLEOD, M. 2007a. How can we improve the pre-clinical development of drugs for stroke? *Trends in Neurosciences*, 30**,** 433-439.

individual drugs. This would allow for a far more in depth analysis on the effect of these study design characteristics. Furthermore, we propose that such analyses would be most valuable for interventions which have been or are in clinical use (either licensed or in clinical trials) as we can gain insights into which experiments have translated most successfully to the clinic.

9.5. Future Directions

This thesis has provided a firm foundation for assessing the improvements which may come about as a result of relevant reporting guidelines. In our experience, some journal editors are extremely accommodating and actively encourage the critical appraisal of their journals so that they can set foundations for improvement. Indeed the review of JCBFM in Chapter 4 was conducted at the request of the editor with the aim of repeating this analysis at a later time to establish whether the improvements have occurred as a result of publication guidelines adopted by the journal. We propose that such an analysis may be a useful contribution to the journals which publish EAE studies. An approach to this may be to assess a proportion of the journals which publish the greatest volume of EAE literature against the ARRIVE guidelines and the more specific guidelines proposed for EAE research (Baker and Amor, 2012). Such an analysis would provide a useful baseline for the changes which might occur and further reveal the current state of reporting which may have already improved since more journals have adopted the ARRIVE guidelines.

Another potentially interesting avenue for further research is in the revealing characteristics about the choice of language in reviews. For example, in discussing how EAE has been used for the successful translation of efficacy of natalizumab, it has been noted that "it substantially reduced EAE when administered before and even during clinical disease" (Wekerle, 2008); and it was "thereby effective in preventing EAE" (Mix et al., 2010). Minor distinctions in the choice of language are either accidental or may reflect the opinion of the author. In the case of the first quote above, it is perhaps implied that it is unexpected, or perhaps a bonus that the intervention was efficacious at a later time of administration. The second quote makes the same point, and in this case the author makes no reference to the drugs' success at a later time of administration in EAE, implying that its attainment in preventing EAE is reflective of

the translational success. Thus it may be useful to systematically assess the reviews on, for example, a particular drug in a disease model to assess which evidence authors provide for the reasons for translational success or failure. The data in this thesis have provided a framework for critically analysing original preclinical research; however, the research I have proposed would provide another aspect of critically appraising review articles with a view to encouraging readers not to take published literature at face value.

Our assessment of quality was based on a broad checklist of items which made it possible to assess a large number of publications as none of our items were open to subjective interpretation (they were either reported or not). Newer reporting guidelines (e.g. ARRIVE) advocate the assessment of, for example, the suitability of the title or the use of adequate statistics. Since these are now recognised as the gold standard quality assessment items it would be beneficial to further assess these against the preclinical EAE literature. As a criticism to our approach here, it could be argued that it is unreasonable to assess publications from earlier epochs against the guidelines of the current scientific era; however, it is interesting to note that randomisation, blinding and compliance with animal welfare regulations were each reported in at least one of 32 included publications from the 1960's (the earliest decade of research included in our analysis). Not unexpectedly, neither a sample size calculation nor a statement of a potential conflict of interest were reported in this decade.

9.6. Recommendations for future EAE studies

All of the analyses described in the prior chapters have demonstrated the usefulness of a large repository of data from animal studies for which this is just one of many in this field. Beyond the limitations of the these studies, we believe that there is now sufficient evidence, from both here and elsewhere, to recommend that studies testing the efficacy of candidate drugs in animal models of MS should take (and report) measures to improve their internal validity, such as randomisation and the blinded assessment of outcome; that sample size calculations should be performed and reported; and that the preclinical testing should focus on testing efficacy under clinically relevant conditions including the initiation of treatment at some time after the induction of injury, using models which are specifically designed to reflect the complexities of the human disease.

Although high-quality, pragmatically designed studies do exist, and their researchers should be commended as such, evidence from this thesis show that they are too few and far between and thus they may be difficult to identify.

9.7. Conclusion

An on-going debate in MS research is whether EAE is useful for predicting therapeutic success in the clinic. The translational success rate has not been promising and this has led some to believe that EAE is not relevant at a pathophysiological level. As a consequence of the secondary analyses I have conducted and described on data from EAE studies, it is my opinion that the translational limitations are at least in part due to study design rather than biological underpinnings. EAE is a model of neuroinflammation and autoimmunity and it is considered that these two processes occur in MS to some extent. For realistic expectations of how interventions will perform in humans we would firstly need to try to align the pathophysiological process being targeted in EAE with the corresponding pathophysiology of the human disease. Secondly interventions should be tested at times which reflect what we achieve in the clinic. Thirdly, efforts should be made to use EAE models to their potential by, at the very least, taking measures to reduce bias and reporting the experiment with sufficient detail to assess their internal and external validity. Finally I would reason that there will be far more weight to the debate on EAE's utility when we have evidence from high quality, pragmatically designed experiments using a model of EAE which reflects an appropriate pathophysiological process.

References

ALEXANDROV, A. V. 2004. How to write a research paper. *Cerebrovascular Diseases,* 18**,** 135-138.

ALONSO, A. & HERNAN, M. A. 2008. Temporal trends in the incidence of multiple sclerosis. *Neurology,* 71**,** 129-135.

ALTMAN, D. G. 1998. Statistical reviewing for medical journals. *Stat Med,* 17**,** 2661-74.

ALTMAN, D. G. 2002. Poor-quality medical research - What can journals do? *Jama-Journal of the American Medical Association,* 287**,** 2765-2767.

ALTMAN, D. G. & BLAND, J. M. 2005. Statistics notes - Standard deviations and standard errors. *British Medical Journal,* 331**,** 903-903.

ALVORD, E. C., JAHNKE, U., FISCHER, E. H., KIES, M. W., DRISCOLL, B. F. & COMPSTON, D. A. S. 1987. THE MULTIPLE CAUSES OF MULTIPLE-SCLEROSIS - THE IMPORTANCE OF AGE OF INFECTIONS IN CHILDHOOD. *Journal of Child Neurology,* 2**,** 313-321.

ANDERSEN, B. 1990. *Methodological Errors in Medical Research,* Oxford, UK, Blackwell Science Ltd.

ANTMAN, E. M., LAU, J., KUPELNICK, B., MOSTELLER, F. & CHALMERS, T. C. 1992. A COMPARISON OF RESULTS OF META-ANALYSES OF RANDOMIZED CONTROL TRIALS AND RECOMMENDATIONS OF CLINICAL EXPERTS - TREATMENTS FOR MYOCARDIAL-INFARCTION. *Jama-Journal of the American Medical Association,* 268**,** 240-248.

ANTONINI, A., TOLOSA, E., MIZUNO, Y., YAMAMOTO, M. & POEWE, W. H. 2009. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. *Lancet Neurol,* 8**,** 929-37.

ASCHERIO, A. & MUNCH, M. 2000. Epstein-Barr virus and multiple sclerosis. *Epidemiology,* 11**,** 220-4.

ASCHERIO, A. & MUNGER, K. L. 2007a. Environmental risk factors for multiple sclerosis. Part I: The role of infection. *Annals of Neurology,* 61**,** 288-299.

ASCHERIO, A. & MUNGER, K. L. 2007b. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. *Annals of Neurology,* 61**,** 504-513.

ASCHERIO, A. & MUNGER, K. L. 2010. Epstein-barr virus infection and multiple sclerosis: a review. *J Neuroimmune Pharmacol,* 5**,** 271-7.

ASCHERIO, A., MUNGER, K. L. & SIMON, K. C. 2010. Vitamin D and multiple sclerosis. *Lancet Neurology,* 9**,** 599-612.

BAGINSKAITE, J. 2012. Scientific quality issues in the design and reporting of bioscience research: a systematic study of randomly selected original in vitro, in vivo and human study articles listed in the PubMed database. The University of Edinburgh.

BAGINSKAITĖ, J. 2012. Scientific quality issues in the design and reporting of bioscience research: a systematic study of randomly selected original in vitro, in vivo and human study articles listed in the PubMed database. *Unpublished.*

BAGOS, P. G., NIKOLOPOULOS, G. & IOANNIDIS, A. 2006. Chlamydia pneumoniae infection and the risk of multiple sclerosis: a meta-analysis. *Multiple Sclerosis,* 12**,** 397-411.

BAGULEY, T. 2004. Understanding statistical power in the context of applied research. *Applied Ergonomics,* 35**,** 73-80.

BAGULEY, T. 2009. Standardized or simple effect size: what should be reported? *British journal of psychology (London, England : 1953),* 100**,** 603-17.

BAKER, D. & AMOR, S. 2012. Publication guidelines for refereeing and reporting on animal use in experimental autoimmune encephalomyelitis. *J Neuroimmunol*.

BAKER, D., GERRITSEN, W., RUNDLE, J. & AMOR, S. 2011. Critical appraisal of animal models of multiple sclerosis. *Multiple Sclerosis Journal,* 17**,** 647-657.

BANWELL, V., SENA, E. S. & MACLEOD, M. R. 2009. Systematic Review and Stratified Meta-analysis of the Efficacy of Interleukin-1 Receptor Antagonist in Animal Models of Stroke. *Journal of Stroke & Cerebrovascular Diseases,* 18**,** 269-276.

BARKHOF, F., FILIPPI, M., MILLER, D. H., SCHELTENS, P., CAMPI, A., POLMAN, C. H., COMI, G., ADER, H. J., LOSSEFF, N. & VALK, J. 1997. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain,* 120**,** 2059-2069.

BATH, P. M. W., MACLEOD, M. R. & GREEN, A. R. 2009. Emulating multicentre clinical stroke trials: a new paradigm for studying novel interventions in experimental models of stroke. *International Journal of Stroke,* 4**,** 471-479.

BEGG, C., CHO, M., EASTWOOD, S., HORTON, R., MOHER, D., OLKIN, I., PITKIN, R., RENNIE, D., SCHULZ, K. F., SIMEL, D. & STROUP, D. F. 1996. Improving the quality of reporting of randomized controlled trials - The CONSORT statement. *Jama-Journal of the American Medical Association,* 276**,** 637-639.

BELLOLIO, M. F., SERRANO, L. A. & STEAD, L. G. 2008. Understanding statistical tests in the medical literature: which test should I use? *Int J Emerg Med,* 1**,** 197-9.

BENATAR, M. 2007. Lost in translation: Treatment trials in the SOD1 mouse and in human ALS. *Neurobiology of Disease,* 26**,** 1-13.

BEZARD, E. & PRZEDBORSKI, S. 2011. A Tale on Animal Models of Parkinson's Disease. *Movement Disorders,* 26**,** 993-1002.

BIOGEN IDEC. 2012. *A clinical study of the efficacy of natalizumab on reducing disability progression in subjects with SPMS (ASCEND IN SPMS)* [Online]. Available: http://clinicaltrials.gov/ct2/show/NCT01416181?term=natalizumab&rank=1 [Accessed 01/08/2012].

BLINDAUER, K., SHOULSON, I., KIEBURTZ, K., MCDERMOTT, M., GARDINER, I., KAMP, C., MARSHALL, F., ZHANG, L., SHINAMAN, M. A., FAHN, S., SUCHOWERSKY, O., WOOTEN, F. G., FREI, K., PATHAK, M., LUONG, N., TUITE, P., SCHACHERER, R., JENNINGS, D., STAVRIS, K., WOJCIESZEK, J., ELMER, L., AIKEN, L., RAJPUT, A., EWANISHIN, M., SHIRLEY, T., GOLBE, L., CAPUTO, D., DEWEY, R., ESTES, B., DEMARCAIDA, T., COUNIHAN, T., DEELEY, C., JANKOVIC, J., HUNTER, C., FERNANDEZ, H. H., LANNON, M. C., HUBBLE, J., LA FONTAINE, A. L., PANTELLA, C., DERWENT, L., CALABRESE, V., ROBERGE, P., LOU, J. S., ANDREWS, P., NIEVES, A., SIME, E., SHULTS, C., FONTAINE, D., RACETTE, B., COOPER, P., WELSH, M., KAWAI, C., WATERS, C., HAUSER, R., GAUGER, L., PANISSET, M., HALL, J., O'BRIEN, C., JUDD, D., DALVI, A., SCHWIETEREN, D., MAHANT, P., WILLIAMSON, K., CHRISTINE, C., HEVEZI, J., KANG, U. J., RICHMAN, J., KOMPOLITI, K., JAGLIN, J., TRUGMAN, J., ROST-RUFFNER, E., GRIMES, D., COLCHER, A., REICHWEIN, S., TARSY, D., RYAN, P., BERTONI, J., PETERSON, C., ATCHISON, P., ALLEN, C., CURRAN, T., BAILEY, S., BROCHT, A., HODGEMAN, K., JOSEPHSON, L., LENIO, E., O'CONNELL, C., ROTHENBURGH, K., RUMFOLA, L., WATTS, A., WEAVER, C., TARIOT, P., RAUBERTAS, R., CHASE, T., GOODIN, T., BIANCHINE, J., WOLTERING, F., MENDZELEVSKI, B., PARKINSON STUDY, G., STEERING, C., et al. 2003. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Archives of Neurology,* 60**,** 1721-1728.

BLOOMGREN, G., RICHMAN, S., HOTERMANS, C., SUBRAMANYAM, M., GOELZ, S., NATARAJAN, A., LEE, S., PLAVINA, T., SCANLON, J. V., SANDROCK, A. & BOZIC, C. 2012. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *The New England journal of medicine,* 366**,** 1870-80.

BOLTON, C. 2007. The translation of drug efficacy from in vivo models to human disease with special reference to experimental autoimmune encephalomyelitis and multiple sclerosis. *Inflammopharmacology,* 15**,** 183-7.

BOND, F. C. 2003. Meta-analysis of raw mean differencea. *Psychological Methods*.
BONESCHI, M. F., ROVARIS, M., CAPRA, R. & COMI, G. 2005. Mitoxantrone for multiple sclerosis. *Cochrane Database Syst Rev*, CD002127.
BONUCCELLI, U., DEL DOTTO, P. & RASCOL, O. 2009. Role of dopamine receptor agonists in the treatment of early Parkinson's disease. *Parkinsonism Relat Disord,* 15 Suppl 4, S44-53.
BORENSTEIN, M. 2009. *Introduction to meta-analysis,* Chichester, U.K., John Wiley & Sons.
BRUCK, W. 2005. Inflammatory demyelination is not central to the pathogenesis of multiple sclerosis. *J Neurol,* 252 Suppl 5, v10-5.
BURN, D. J. 2007. Sex and Parkinson's disease: a world of difference? *J Neurol Neurosurg Psychiatry,* 78, 787.
CHAN, A. & GOLD, R. 2007. Lessons from the past: failed MS trials. *Int MS J,* 14, 3-4.
CHAPMAN, P. L. & SEIDEL, G. E. 2008. Experimental design, power and sample size for animal reproduction experiments. *Reproduction Fertility and Development,* 20, 33-44.
CLARKE, C. E. & GUTTMAN, M. 2002. Dopamine agonist monotherapy in Parkinson's disease. *Lancet,* 360, 1767-1769.
COCHRAN, W. G. 1954. The Combination of Estimates from Different Experiments. *Biometrics,* 10, 101-129.
COHEN, J. 1962. The statistical power of abnormal-social psychological research: a review. *J Abnorm Soc Psychol,* 65, 145-53.
COHEN, J. 1988. *Statistical power analysis for the behavioral sciences,* Hillsdale, N.J., L. Erlbaum Associates.
COHEN, J. I. 2000. Epstein-Barr virus infection. *The New England journal of medicine,* 343, 481-92.
COMPSTON, A. & COLES, A. 2002. Multiple sclerosis. *Lancet,* 359, 1221-31.
COMPSTON, A. & COLES, A. 2008. Multiple sclerosis. *Lancet,* 372, 1502-1517.
CONFAVREUX, C. & VUKUSIC, S. 2006. Natural history of multiple sclerosis: a unifying concept. *Brain,* 129, 606-616.
COOK, D. J., MULROW, C. D. & HAYNES, R. B. 1997. Systematic reviews: Synthesis of best evidence for clinical decisions. *Annals of Internal Medicine,* 126, 376-380.
COOPER, H. M., HEDGES, L. V. & VALENTINE, J. C. 2009. *The handbook of research synthesis and meta-analysis,* New York, Russell Sage Foundation.
COX, D. & STONE, J. 2006. Managing self-injection difficulties in patients with relapsing-remitting multiple sclerosis. *The Journal of neuroscience nursing : journal of the American Association of Neuroscience Nurses,* 38, 167-71.
CROSBY, N., DEANE, K. H. & CLARKE, C. E. 2003. Amantadine in Parkinson's disease. *Cochrane Database Syst Rev*, CD003468.
CROSSLEY, N. A., SENA, E., GOEHLER, J., HORN, J., VAN DER WORP, B., BATH, P. M. W., MACLEOD, M. & DIRNAGL, U. 2008. Empirical evidence of bias in the design of experimental stroke studies - A metaepidemiologic approach. *Stroke,* 39, 929-934.
DALTON, C. M., CHARD, D. T., DAVIES, G. R., MISZKIEL, K. A., ALTMANN, D. R., FERNANDO, K., PLANT, G. T., THOMPSON, A. J. & MILLER, D. H. 2004. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. *Brain,* 127, 1101-1107.
DE LAU, L. M. & BRETELER, M. M. 2006a. Epidemiology of Parkinson's disease. *Lancet Neurol,* 5, 525-35.
DE LAU, L. M. L. & BRETELER, M. M. B. 2006b. Epidemiology of Parkinson's disease. *Lancet Neurology,* 5, 525-535.

DENIC, A., JOHNSON, A. J., BIEBER, A. J., WARRINGTON, A. E., RODRIGUEZ, M. & PIRKO, I. 2011. The relevance of animal models in multiple sclerosis research. *Pathophysiology : the official journal of the International Society for Pathophysiology / ISP,* 18**,** 21-9.

DERSIMONIAN, R. & LAIRD, N. 1986. Metaanalysis in Clinical-Trials. *Controlled Clinical Trials,* 7**,** 177-188.

DEVONSHIRE, V., HAVRDOVA, E., RADUE, E. W., O'CONNOR, P., ZHANG-AUBERSON, L., AGOROPOULOU, C., HAERING, D. A., FRANCIS, G., KAPPOS, L. & GRP, F. S. 2012. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. *Lancet Neurology,* 11**,** 420-428.

DIRNAGL, U. 2006. Bench to bedside: the quest for quality in experimental stroke research. *Journal of Cerebral Blood Flow and Metabolism,* 26**,** 1465-1478.

DIRNAGL, U. 2010. Statistics in Experimental Stroke Research: From Sample Size Calculation to Data Description and Significance Testing. *In:* DIRNAGL, U. (ed.) *Rodent Models of Stroke.* Totowa: Humana Press Inc.

DIRNAGL, U. & MACLEOD, M. R. 2009. Stroke research at a road block: the streets from adversity should be paved with meta-analysis and good laboratory practice. *British Journal of Pharmacology,* 157**,** 1154-1156.

DU SERT, N. P. 2011. Improving the reporting of animal research: when will we ARRIVE? *Disease Models & Mechanisms,* 4**,** 281-282.

DURLAK, J. A. 2009. How to Select, Calculate, and Interpret Effect Sizes. *Journal of Pediatric Psychology,* 34**,** 917-928.

DUTY, S. & JENNER, P. 2011. Animal models of Parkinson's disease: a source of novel treatments and clues to the cause of the disease. *British Journal of Pharmacology,* 164**,** 1357-1391.

DUVAL, S. & TWEEDIE, R. 2000. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *Journal of the American Statistical Association,* 95**,** 89-98.

DWAN, K., ALTMAN, D. G., ARNAIZ, J. A., BLOOM, J., CHAN, A. W., CRONIN, E., DECULLIER, E., EASTERBROOK, P. J., VON ELM, E., GAMBLE, C., GHERSI, D., IOANNIDIS, J. P. A., SIMES, J. & WILLIAMSON, P. R. 2008. Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias. *Plos One,* 3.

EASTERBROOK, P. J., BERLIN, J. A., GOPALAN, R. & MATTHEWS, D. R. 1991. PUBLICATION BIAS IN CLINICAL RESEARCH. *Lancet,* 337**,** 867-872.

EBERS, G. C., SADOVNICK, A. D., RISCH, N. J., BULMAN, D., RICE, G. P. A., HASHIMOTO, S. A., PATY, D., OGER, J. J. F., METZ, L., BELL, R., WARREN, S., HADER, W., AUTY, T., NATH, A., GRAY, T., OCONNOR, P., NELSON, R., FREEDMAN, M., BRUNET, D., PAULSETH, R., FRANCIS, G., DUQUETTE, P., MURRAY, T. J., BAHN, V. & PRYSEPHILLIPS, W. 1995. A GENETIC-BASIS FOR FAMILIAL AGGREGATION IN MULTIPLE-SCLEROSIS. *Nature,* 377**,** 150-151.

EGAN, K., BEGLOPOULOS, V., SENA, E., VESTERINEN, H. M. & MACLEOD, M. 2012. From a mouse: improving the prospects for translational success in Alzheimer's disease. *(Under Review)*.

EGGER, M., SMITH, G. D. & ALTMAN, D. G. 2001. *Systematic reviews in health care: meta-analysis in context.,* London, UK, BMJ Publishing Group.

EGGER, M., SMITH, G. D., SCHNEIDER, M. & MINDER, C. 1997. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal,* 315**,** 629-634.

ELBERS, C. C., VAN EIJK, K. R., FRANKE, L., MULDER, F., VAN DER SCHOUW, Y. T., WIJMENGA, C. & ONLAND-MORET, N. C. 2009. Using Genome-Wide Pathway

Analysis to Unravel the Etiology of Complex Diseases. *Genetic Epidemiology,* 33**,** 419-431.
FAHN, S., SHOULSON, I., KIEBURTZ, K., RUDOLPH, A., LANG, A., OLANOW, C. W., TANNER, C., MAREK, K. & PARKINSON STUDY, G. 2004. Levodopa and the progression of Parkinson's disease. *New England Journal of Medicine,* 351**,** 2498-2508.
FAINARDI, E., CASTELLAZZI, M., SERACENI, S., GRANIERI, E. & CONTINI, C. 2008. Under the microscope: Focus on Chlamydia pneumoniae infection and multiple sclerosis. *Current Neurovascular Research,* 5**,** 60-70.
FALCHUK, Z. M., ROGENTINE, G. N. & STROBER, W. 1972. Predominance of histocompatibility antigen HL-A8 in patients with gluten-sensitive enteropathy. *J Clin Invest,* 51**,** 1602-5.
FEINSTEIN, A. 1997. Multiple sclerosis, depression, and suicide - Clinicians should pay more attention to psychopathology. *British Medical Journal,* 315**,** 691-692.
FEINSTEIN, A. 2002. An examination of suicidal intent in patients with multiple sclerosis. *Neurology,* 59**,** 674-678.
FEINSTEIN, A. 2011. Multiple sclerosis and depression. *Mult Scler,* 17**,** 1276-81.
FERGUSON, B., MATYSZAK, M. K., ESIRI, M. M. & PERRY, V. H. 1997. Axonal damage in acute multiple sclerosis lesions. *Brain,* 120**,** 393-399.
FISHER, M., FEUERSTEIN, G., HOWELLS, D. W., HURN, P. D., KENT, T. A., SAVITZ, S. I., LO, E. H. & GRP, S. 2009. Update of the Stroke Therapy Academic Industry Roundtable Preclinical Recommendations. *Stroke,* 40**,** 2244-2250.
FRANKLIN, R. J. M. & FFRENCH-CONSTANT, C. 2008. Remyelination in the CNS: from biology to therapy. *Nature Reviews Neuroscience,* 9**,** 839-855.
FRANKLIN, R. J. M. & KOTTER, M. R. 2008. The biology of CNS remyelination - The key to therapeutic advances. *Journal of Neurology,* 255**,** 19-25.
FRANTZIAS, J., SENA, E. S., MACLEOD, M. R. & SALMAN, R. A.-S. 2011. Treatment of Intracerebral Hemorrhage in Animal Models: Meta-Analysis. *Annals of Neurology,* 69**,** 389-399.
FUJINAMI, R. S., VON HERRATH, M. G., CHRISTEN, U. & WHITTON, J. L. 2006. Molecular mimicry, bystander activation, or viral persistence: Infections and autoimmune disease. *Clinical Microbiology Reviews,* 19**,** 80-+.
GALEA, I., BECHMANN, I. & PERRY, V. H. 2007. What is immune privilege (not)? *Trends in Immunology,* 28**,** 12-18.
GARCIA-BERTHOU, E. & ALCARAZ, C. 2004. Incongruence between test statistics and P values in medical papers. *BMC Med Res Methodol,* 4**,** 13.
GLANTZ, S. A. 1980. Biostatistics - How to Detect, Correct and Prevent Errors in the Medical Literature. *Circulation,* 61**,** 1-7.
GLUUD, L. L. 2006. Bias in clinical intervention research. *American Journal of Epidemiology,* 163**,** 493-501.
GOLD, R. 2011. Oral Therapies for Multiple Sclerosis A Review of Agents in Phase III Development or Recently Approved. *Cns Drugs,* 25**,** 37-52.
GOLD, R., LININGTON, C. & LASSMANN, H. 2006. Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research. *Brain,* 129**,** 1953-1971.
GOLDBERG, P. 1974. Multiple Sclerosis - Vitamin D and Calcium as Environmental Determinants of Prevalence (a Viewpoint) .1. Sunlight, Dietary Factors and Epidemiology. *International Journal of Environmental Studies,* 6**,** 19-27.
GOLDE, T. E. 2009. The therapeutic importance of understanding mechanisms of neuronal cell death in neurodegenerative disease. *Molecular Neurodegeneration,* 4.

GOURRAUD, P.-A., HARBO, H. F., HAUSER, S. L. & BARANZINI, S. E. 2012. The genetics of multiple sclerosis: an up-to-date review. *Immunological Reviews,* 248**,** 87-103.
GREENHALGH, T. 1997. How to read a paper: Papers that summarise other papers (systematic reviews and meta-analyses). *British Medical Journal,* 315**,** 672-675.
HAFLER, D. A., COMPSTON, A., SAWCER, S., LANDER, E. S., DALY, M. J., DE JAGER, P. L., DE BAKKER, P. I. W., GABRIEL, S. B., MIREL, D. B., IVINSON, A. J., PERICAK-VANCE, M. A., GREGORY, S. G., RIOUX, J. D., MCCAULEY, J. L., HAINES, J. L., BARCELLOS, L. F., CREE, B., OKSENBERG, J. R., HAUSER, S. L. & INT MULTIPLE SCLEROSIS GENETICS, C. 2007. Risk alleles for multiple sclerosis identified by a genomewide study. *New England Journal of Medicine,* 357**,** 851-862.
HANDEL, A. E., WILLIAMSON, A. J., DISANTO, G., DOBSON, R., GIOVANNONI, G. & RAMAGOPALAN, S. V. 2011. Smoking and multiple sclerosis: an updated meta-analysis. *Plos One,* 6**,** e16149.
HARDY, R. J. & THOMPSON, S. G. 1998. Detecting and describing heterogeneity in meta-analysis. *Statistics in Medicine,* 17**,** 841-856.
HEDGES, L. V. & OLKIN, I. 1985. *Statistical methods for meta-analysis,* Orlando, Academic Press.
HEDSTROM, A. K., BAARNHIELM, M., OLSSON, T. & ALFREDSSON, L. 2011. Exposure to environmental tobacco smoke is associated with increased risk for multiple sclerosis. *Multiple Sclerosis Journal,* 17**,** 788-793.
HERNAN, M. A., JICK, S. S., LOGROSCINO, G., OLEK, M. J., ASCHERIO, A. & JICK, H. 2005. Cigarette smoking and the progression of multiple sclerosis. *Brain,* 128**,** 1461-1465.
HERNAN, M. A., ZHANG, S. M., LIPWORTH, L., OLEK, M. J. & ASCHERIO, A. 2001. Multiple sclerosis and age at infection with common viruses. *Epidemiology,* 12**,** 301-306.
HIGGINS, J. P. T. & THOMPSON, S. G. 2002. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine,* 21**,** 1539-1558.
HIGGINS, J. P. T., THOMPSON, S. G., DEEKS, J. J. & ALTMAN, D. G. 2003. Measuring inconsistency in meta-analyses. *British Medical Journal,* 327**,** 557-560.
HIRST, T. C., VESTERINEN, H. M., SENA, E. S., EGAN, K. J., MACLEOD, M. R. & WHITTLE, I. R. 2012. Systematic review and meta-analysis of temozolomide in animal models of glioma: was clinical efficacy predicted? *Under review*.
HOENIG, J. M. & HEISEY, D. M. 2001. The abuse of power: The pervasive fallacy of power calculations for data analysis. *American Statistician,* 55**,** 19-24.
HOFFMANN, O. 1984. Application of Statistics and Frequency of Statistical Errors in Articles in Acta Neurochirurgica. *Acta Neurochirurgica,* 71**,** 307-315.
HOLMES, T. H. 2004. Ten categories of statistical errors: a guide for research in endocrinology and metabolism. *American Journal of Physiology-Endocrinology and Metabolism,* 286**,** E495-E501.
HOPEWELL, S., DUTTON, S., YU, L. M., CHAN, A. W. & ALTMAN, D. G. 2010. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *British Medical Journal,* 340.
HOPEWELL, S., LOUDON, K., CLARKE, M. J., OXMAN, A. D. & DICKERSIN, K. 2009. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database of Systematic Reviews*.
HUBBLE, J. P., KOLLER, W. C., CUTLER, N. R., SRAMEK, J. J., FRIEDMAN, J., GOETZ, C., RANHOSKY, A., KORTS, D. & ELVIN, A. 1995. PRAMIPEXOLE IN PATIENTS WITH EARLY PARKINSONS-DISEASE. *Clinical Neuropharmacology,* 18**,** 338-347.
HUMPHRIES, C. 2012. Progressive multiple sclerosis: The treatment gap. *Nature,* 484**,** S10.
HUTCHINSON, M. 2011. Controversies in multiple sclerosis: a series of debates. *Multiple sclerosis (Houndmills, Basingstoke, England),* 17**,** 1170.

HUTCHINSON, M., KAPPOS, L., CALABRESI, P. A., CONFAVREUX, C., GIOVANNONI, G., GALETTA, S. L., HAVRDOVA, E., LUBLIN, F. D., MILLER, D. H., O'CONNOR, P. W., PHILLIPS, J. T., POLMAN, C. H., RADUE, E.-W., RUDICK, R. A., STUART, W. H., WAJGT, A., WEINSTOCK-GUTTMAN, B., WYNN, D. R., LYNN, F., PANZARA, M. A. & INVESTIGATORS, A. S. 2009. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *Journal of Neurology,* 256**,** 405-415.

IOANNIDIS, J. P. A. 2005. Why most published research findings are false. *Plos Medicine,* 2**,** 696-701.

IOANNIDIS, J. P. A. 2008. Why most discovered true associations are inflated. *Epidemiology,* 19**,** 640-648.

JACKSON-LEWIS, V., BLESA, J. & PRZEDBORSKI, S. 2012. Animal models of Parkinson's disease. *Parkinsonism & Related Disorders,* 18 Suppl 1**,** S183-5.

JANKOVIC, J. 2008. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry,* 79**,** 368-76.

JERNDAL, M., FORSBERG, K., SENA, E. S., MACLEOD, M. R., O'COLLINS, V. E., LINDEN, T., NILSSON, M. & HOWELLS, D. W. 2010. A systematic review and meta-analysis of erythropoietin in experimental stroke. *Journal of Cerebral Blood Flow and Metabolism,* 30**,** 961-968.

JORI, M. C., FRANCESCHI, M., GIUSTI, M. C., CANAL, N., PIOLTI, R., FRATTOLA, L., BASSI, S., CALLONI, E., MAMOLI, A. & CAMERLINGO, M. 1990. *CLINICAL-EXPERIENCE WITH CABERGOLINE, A NEW ERGOLINE DERIVATIVE, IN THE TREATMENT OF PARKINSONS-DISEASE*.

KABAT, E. A., WOLF, A. & BEZER, A. E. 1947. THE RAPID PRODUCTION OF ACUTE DISSEMINATED ENCEPHALOMYELITIS IN RHESUS MONKEYS BY INJECTION OF HETEROLOGOUS AND HOMOLOGOUS BRAIN TISSUE WITH ADJUVANTS. *Journal of Experimental Medicine,* 85**,** 117-&.

KAMPMAN, M. T., STEFFENSEN, L. H., MELLGREN, S. I. & JORGENSEN, L. 2012. Effect of vitamin D3 supplementation on relapses, disease progression and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. *Mult Scler*.

KAPOOR, R., PIRTOSEK, Z., FRANKEL, J. P., STERN, G. M., LEES, A. J., BOTTOMLEY, J. M. & HARAN, N. S. 1989. TREATMENT OF PARKINSONS-DISEASE WITH NOVEL DOPAMINE-D2 AGONIST SK-AND-F-101468. *Lancet,* 1**,** 1445-1446.

KAPPOS, L., ANTEL, J., COMI, G., MONTALBAN, X., O'CONNOR, P., POLMAN, C. H., HAAS, T., KORN, A. A., KARLSSON, G., RADUE, E. W. & GRP, F. D. S. 2006. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *New England Journal of Medicine,* 355**,** 1124-1140.

KAPPOS, L., RADUE, E. W., O'CONNOR, P., POLMAN, C., HOHLFELD, R., CALABRESI, P., SELMAJ, K., AGOROPOULOU, C., LEYK, M., ZHANG-AUBERSON, L., BURTIN, P. & GRP, F. S. 2010. A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis. *New England Journal of Medicine,* 362**,** 387-401.

KHAJA, A. M. & GROTTA, J. C. 2007. Established treatments for acute ischaemic stroke. *Lancet,* 369**,** 319-330.

KILKENNY, C., BROWNE, W., CUTHILL, I. C., EMERSON, M. & ALTMAN, D. G. Animal research: reporting in vivo experiments--the ARRIVE guidelines. *J Cereb Blood Flow Metab,* 31**,** 991-3.

KILKENNY, C., BROWNE, W., CUTHILL, I. C., EMERSON, M. & ALTMAN, D. G. 2011. Animal research: reporting in vivo experiments--the ARRIVE guidelines. *J Cereb Blood Flow Metab,* 31**,** 991-3.

KILKENNY, C., BROWNE, W. J., CUTHILL, I. C., EMERSON, M. & ALTMAN, D. G. 2010. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biol,* 8**,** e1000412.

KILKENNY, C., PARSONS, N., KADYSZEWSKI, E., FESTING, M. F. W., CUTHILL, I. C., FRY, D., HUTTON, J. & ALTMAN, D. G. 2009. Survey of the Quality of Experimental Design, Statistical Analysis and Reporting of Research Using Animals. *Plos One,* 4.

KILLESTEIN, J. & POLMAN, C. H. 2011. Determinants of interferon beta efficacy in patients with multiple sclerosis. *Nature Reviews Neurology,* 7**,** 221-228.

KLEINSCHMIDT-DEMASTERS, B. K. & TYLER, K. L. 2005. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *The New England journal of medicine,* 353**,** 369-74.

KOCH, M., VAN HARTEN, A. & DE KEYSER, J. 2007. Cigarette smoking and progression in multiple sclerosis. *Neurology,* 69**,** 1515-1520.

KURTZKE, J. F. 1983. RATING NEUROLOGIC IMPAIRMENT IN MULTIPLE-SCLEROSIS - AN EXPANDED DISABILITY STATUS SCALE (EDSS). *Neurology,* 33**,** 1444-1452.

KURTZKE, J. F. 1993. Epidemiologic evidence for multiple sclerosis as an infection. *Clinical Microbiology Reviews,* 6**,** 382-427.

LA MANTIA, L., MUNARI, L. M. & LOVATI, R. 2010. Glatiramer acetate for multiple sclerosis. *Cochrane Database Syst Rev***,** CD004678.

LANE, E. & DUNNETT, S. 2008. Animal models of Parkinson's disease and L-dopa induced dyskinesia: How close are we to the clinic? *Psychopharmacology,* 199**,** 303-312.

LAU, J., ANTMAN, E. M., JIMENEZ-SILVA, J., KUPELNICK, B., MOSTELLER, F. & CHALMERS, T. C. 1992. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *The New England journal of medicine,* 327**,** 248-54.

LAURIE, C. C., DOHENY, K. F., MIREL, D. B., PUGH, E. W., BIERUT, L. J., BHANGALE, T., BOEHM, F., CAPORASO, N. E., CORNELIS, M. C., EDENBERG, H. J., GABRIEL, S. B., HARRIS, E. L., HU, F. B., JACOBS, K. B., KRAFT, P., LANDI, M. T., LUMLEY, T., MANOLIO, T. A., MCHUGH, C., PAINTER, I., PASCHALL, J., RICE, J. P., RICE, K. M., ZHENG, X. W., WEIR, B. S. & INVESTIGATORS, G. 2010. Quality Control and Quality Assurance in Genotypic Data for Genome-Wide Association Studies. *Genetic Epidemiology,* 34**,** 591-602.

LAVI, E. & CONSTANTINESCU, C. S. 2005. *Experimental Models of Multiple Sclerosis,* New York, Springer Science + Business Media.

LEES, A. J., HARDY, J. & REVESZ, T. 2009. Parkinson's disease. *Lancet,* 373**,** 2055-2066.

LENTH, R. V. 2006-9. Java Applets for Power and Sample Size [Computer software].

LENTH, R. V. 2007. Statistical power calculations. *J Anim Sci,* 85**,** E24-9.

LEVIN, L. I., MUNGER, K. L., O'REILLY, E. J., FALK, K. I. & ASCHERIO, A. 2010. Primary infection with the Epstein-Barr virus and risk of multiple sclerosis. *Ann Neurol,* 67**,** 824-30.

LIEBERMAN, A., KUPERSMITH, M., ESTEY, E. & GOLDSTEIN, M. 1976. TREATMENT OF PARKINSONS-DISEASE WITH BROMOCRIPTINE. *New England Journal of Medicine,* 295**,** 1400-1404.

LIEBERMAN, A. N., LEIBOWITZ, M., NEOPHYTIDES, A., KUPERSMITH, M., MEHL, S., KLEINBERG, D., SERBY, M. & GOLDSTEIN, M. 1979. PERGOLIDE AND LISURIDE FOR PARKINSONS-DISEASE. *Lancet,* 2**,** 1129-1130.

LIGHT, R. J. & PILLEMER, D. B. 1984. *Summing up. The science of reviewing research.,* Cambrige, MA, Harvard University Press.

LIM, S. Y. & CONSTANTINESCU, C. S. 2010. Current and future disease-modifying therapies in multiple sclerosis. *International Journal of Clinical Practice,* 64**,** 637-650.

LINK, H. & HUANG, Y. M. 2006. Oligoclonal bands in multiple sclerosis cerebrospinal fluid: An update on methodology and clinical usefulness. *Journal of Neuroimmunology,* 180**,** 17-28.

LUBLIN, F. D. & REINGOLD, S. C. 1996. Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology,* 46**,** 907-911.

LUCCHINETTI, C., BRUCK, W., PARISI, J., SCHEITHAUER, B., RODRIGUEZ, M. & LASSMANN, H. 2000. Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination. *Annals of Neurology,* 47**,** 707-717.

MACLEOD, M. R., BRISCOE, C. L. & SANDERCOCK, P. A. G. 2005a. Systematic review and meta-analysis of the efficacy of tPA in experimental stroke. *Journal of the Neurological Sciences,* 238**,** S73-S73.

MACLEOD, M. R., FISHER, M., O'COLLINS, V., SENA, E. S., DIRNAGL, U., BATH, P. M. W., BUCHAN, A., VAN DER WORP, H. B., TRAYSTMAN, R., MINEMATSU, K., DONNAN, G. A. & HOWELLS, D. W. 2009a. Good Laboratory Practice Preventing Introduction of Bias at the Bench. *Stroke,* 40**,** E50-E52.

MACLEOD, M. R., FISHER, M., O'COLLINS, V., SENA, E. S., DIRNAGL, U., BATH, P. M. W., BUCHAN, A., VAN DER WORP, H. B., TRAYSTMAN, R. J., MINEMATSU, K., DONNAN, G. A. & HOWELLS, D. W. 2009b. Reprint: Good laboratory practice: preventing introduction of bias at the bench. *Journal of Cerebral Blood Flow and Metabolism,* 29**,** 221-223.

MACLEOD, M. R., O'COLLINS, T., HORKY, L. L., HOWELLS, D. W. & DONNAN, G. A. 2005b. Systematic review and meta-analysis of the efficacy of melatonin in experimental stroke. *Journal of Pineal Research,* 38**,** 35-41.

MACLEOD, M. R., O'COLLINS, T., HORKY, L. L., HOWELLS, D. W. & DONNAN, G. A. 2005c. Systematic review and metaanalysis of the efficacy of FK506 in experimental stroke. *Journal of Cerebral Blood Flow and Metabolism,* 25**,** 713-721.

MACLEOD, M. R., O'COLLINS, T., HOWELLS, D. W. & DONNAN, G. A. 2004. Pooling of animal experimental data reveals influence of study design and publication bias. *Stroke,* 35**,** 1203-1208.

MACLEOD, M. R., PETERSSON, J., NORRVING, B., HACKE, W., DIRNAGL, U., WAGNER, M., SCHWAB, S. & EUROPEAN HYPOTHERMIA STROKE RES, W. 2010. Hypothermia for Stroke: call to action 2010. *International Journal of Stroke,* 5**,** 489-492.

MACLEOD, M. R., VAN DER WORP, H. B., SENA, E. S., HOWELLS, D. W., DIRNAGL, U. & DONNAN, G. A. 2008. Evidence for the efficacy of NXY-059 in experimental focal cerebral ischaemia is confounded by study quality. *Stroke,* 39**,** 2824-2829.

MCDONALD, W. I., COMPSTON, A., EDAN, G., GOODKIN, D., HARTUNG, H. P., LUBLIN, F. D., MCFARLAND, H. F., PATY, D. W., POLMAN, C. H., REINGOLD, S. C., SANDBERG-WOLLHEIM, M., SIBLEY, W., THOMPSON, A. J., VAN DEN NOORT, S., WEINSHENKER, B. Y. & WOLINSKY, J. S. 2001. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Annals of Neurology,* 50**,** 121-127.

MEERPOHL, J. J., HERRLE, F., ANTES, G. & VON ELM, E. 2012. Scientific value of systematic reviews: survey of editors of core clinical journals. *Plos One,* 7**,** e35732.

MEUTH, S. G., BITTNER, S., ULZHEIMER, J. C., KLEINSCHNITZ, C., KIESEIER, B. C. & WIENDL, H. 2010. Therapeutic approaches to multiple sclerosis: an update on failed, interrupted, or inconclusive trials of neuroprotective and alternative treatment strategies. *Biodrugs,* 24**,** 317-30.

MILLER, D., BARKHOF, F., MONTALBAN, X., THOMPSON, A. & FILIPPI, M. 2005. Clinically isolated syndromes suggestive of multiple sclerosis, part 1: natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurology,* 4**,** 281-288.

MILLER, D. H., CHARD, D. T. & CICCARELLI, O. 2012. Clinically isolated syndromes. *Lancet Neurology,* 11**,** 157-169.

MILLER, D. H. & LEARY, S. M. 2007. Primary-progressive multiple sclerosis. *Lancet Neurology,* 6**,** 903-912.

MILO, R. & KAHANA, E. 2010. Multiple sclerosis: Geoepidemiology, genetics and the environment. *Autoimmunity reviews,* 9**,** A387-A394.

MINNERUP, J., WERSCHING, H., DIEDERICH, K., SCHILLING, M., RINGELSTEIN, E. B., WELLMANN, J. & SCHABITZ, W.-R. 2010. Methodological quality of preclinical stroke studies is not required for publication in high-impact journals. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* 30**,** 1619-24.

MIX, E., MEYER-RIENECKER, H., HARTUNG, H. P. & ZETTL, U. K. 2010. Animal models of multiple sclerosis--potentials and limitations. *Prog Neurobiol,* 92**,** 386-404.

MOHER, D., JONES, A., LEPAGE, L. & GRP, C. 2001a. Use of the CONSORT statement and quality of reports of randomized trials - A comparative before-and-after evaluation. *Jama-Journal of the American Medical Association,* 285**,** 1992-1995.

MOHER, D., LIBERATI, A., TETZLAFF, J. & ALTMAN, D. G. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med,* 6**,** e1000097.

MOHER, D., SCHULZ, K. F., ALTMAN, D. G. & GRP, C. 2001b. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet,* 357**,** 1191-1194.

MOHER, D., TETZLAFF, J., TRICCO, A. C., SAMPSON, M. & ALTMAN, D. G. 2007. Epidemiology and reporting characteristics of systematic reviews. *Plos Medicine,* 4**,** 447-455.

MOSAYEBI, G., GHAZAVI, A., GHASAMI, K., JAND, Y. & KOKHAEI, P. 2011. Therapeutic Effect of Vitamin D3 in Multiple Sclerosis Patients. *Immunological Investigations,* 40**,** 627-639.

MULAIK, S. A. 1997. There is a time and a place for significance testing. *In:* HARLOW, L., MULAIK, S. A. & STEIGER, J. H. (eds.) *What If There were No Significance Tests.* London: Lawrence Erlbaum Associates.

MURRAY, T. J. 2009. The history of multiple sclerosis: the changing frame of the disease over the centuries. *Journal of the Neurological Sciences,* 277 Suppl 1**,** S3-8.

NAKAGAWA, S. & CUTHILL, I. C. 2007. Effect size, confidence interval and statistical significance: a practical guide for biologists. *Biological Reviews,* 82**,** 591-605.

NIEMINEN, P., CARPENTER, J., RUCKER, G. & SCHUMACHER, M. 2006. The relationship between quality of research and citation frequency. *BMC medical research methodology,* 6**,** 42.

NIKFAR, S., RAHIMI, R. & ABDOLLAHI, M. 2010. A Meta-Analysis of the Efficacy and Tolerability of Interferon-beta in Multiple Sclerosis, Overall and by Drug and Disease Type. *Clinical Therapeutics,* 32**,** 1871-1888.

NOORDZIJ, M., TRIPEPI, G., DEKKER, F. W., ZOCCALI, C., TANCK, M. W. & JAGER, K. J. 2010. Sample size calculations: basic principles and common pitfalls. *Nephrology Dialysis Transplantation,* 25**,** 1388-1393.

O'COLLINS, V. E., MACLEOD, M. R., DONNAN, G. A., HORKY, L. L., VAN DER WORP, B. H. & HOWELLS, D. W. 2006. 1,026 experimental treatments in acute stroke. *Annals of Neurology,* 59**,** 467-477.

O'CONNOR, P. W., GOODMAN, A., WILLMER-HULME, A. J., LIBONATI, M. A., METZ, L., MURRAY, R. S., SHEREMATA, W. A., VOLLMER, T. L., STONE, L. A. & NATALIZUMAB MULTIPLE SCLEROSIS, T. 2004. Randomized multicenter trial of natalizumab in acute MS relapses - Clinical and MRI effects. *Neurology,* 62**,** 2038-2043.

O'RIORDAN, J. I., THOMPSON, A. J., KINGSLEY, D. P. E., MACMANUS, D. G., KENDALL, B. E., RUDGE, P., MCDONALD, W. I. & MILLER, D. H. 1998. The prognostic value of brain MRI in clinically isolated syndromes of the CNS - A 10-year follow-up. *Brain,* 121**,** 495-503.

O'ROURKE, K. 2007. An historical perspective on meta-analysis: dealing quantitatively with varying study results. *Journal of the Royal Society of Medicine,* 100**,** 579-582.

OLIVER, B. J., KOHLI, E. & KASPER, L. H. 2011. Interferon therapy in relapsing-remitting multiple sclerosis: a systematic review and meta-analysis of the comparative trials. *J Neurol Sci,* 302**,** 96-105.

PALACIOS, N., ALONSO, A., BRONNUM-HANSEN, H. & ASCHERIO, A. 2011. Smoking and Increased Risk of Multiple Sclerosis: Parallel Trends in the Sex Ratio Reinforce the Evidence. *Annals of Epidemiology,* 21**,** 536-542.

PATRIKIOS, P., STADELMANN, C., KUTZELNIGG, A., RAUSCHKA, H., SCHMIDBAUER, M., LAURSEN, H., SORENSEN, P. S., BRUECK, W., LUCCHINETTI, C. & LASSMANN, H. 2006. Remyelination is extensive in a subset of multiple sclerosis patients. *Brain,* 129**,** 3165-3172.

PEARSON, T. A. & MANOLIO, T. A. 2008. How to interpret a genome-wide association study. *Jama-Journal of the American Medical Association,* 299**,** 1335-1344.

PERCIE DU SERT, N. 2011. Systematic review and meta-analysis of pre-clinical research: the need for reporting guidelines. *European Heart Journal,* 32**,** 2340.

PEREL, P., ROBERTS, I., SENA, E., WHEBLE, P., BRISCOE, C., SANDERCOCK, P., MACLEOD, M., MIGNINI, L. E., JAYARAM, P. & KHAN, K. S. 2007. Comparison of treatment effects between animal experiments and clinical trials: systematic review. *British Medical Journal,* 334**,** 197-200.

PETERSON, L. K. & FUJINAMI, R. S. 2007. Inflammation, demyelination, neurodegeneration and neuroprotection in the pathogenesis of multiple sclerosis. *J Neuroimmunol,* 184**,** 37-44.

PHILIP, M., BENATAR, M., FISHER, M. & SAVITZ, S. I. 2009. Methodological Quality of Animal Studies of Neuroprotective Agents Currently in Phase II/III Acute Ischemic Stroke Trials. *Stroke,* 40**,** 577-581.

PHILLIPS, C. V., MACLEHOSE, R. F. & KAUFMAN, J. S. 2008. (Errors in statistical tests)3. *Emerging themes in epidemiology,* 5**,** 9.

PLINT, A. C., MOHER, D., MORRISON, A., SCHULZ, K., ALTMAN, D. G., HILL, C. & GABOURY, I. 2006. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *Medical Journal of Australia,* 185**,** 263-267.

PLUZHNIKOV, A., BELOW, J. E., KONKASHBAEV, A., TIKHOMIROV, A., KISTNER-GRIFFIN, E., ROE, C. A., NICOLAE, D. L. & COX, N. J. 2010. Spoiling the Whole Bunch: Quality Control Aimed at Preserving the Integrity of High-Throughput Genotyping. *American Journal of Human Genetics,* 87**,** 123-128.

POLMAN, C. H., REINGOLD, S. C., BANWELL, B., CLANET, M., COHEN, J. A., FILIPPI, M., FUJIHARA, K., HAVRDOVA, E., HUTCHINSON, M., KAPPOS, L., LUBLIN, F. D., MONTALBAN, X., O'CONNOR, P., SANDBERG-WOLLHEIM, M., THOMPSON, A. J., WAUBANT, E., WEINSHENKER, B. & WOLINSKY, J. S. 2011. Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria. *Annals of Neurology,* 69**,** 292-302.

POSER, C. M., PATY, D. W., SCHEINBERG, L., MCDONALD, W. I., DAVIS, F. A., EBERS, G. C., JOHNSON, K. P., SIBLEY, W. A., SILBERBERG, D. H. & TOURTELLOTTE, W. W. 1983. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol,* 13**,** 227-31.

PUTMAN, T. J. 1938. The Centenary of Multiple Sclerosis. *Archives of Neurology & Psychiatry,* 40**,** 806-313.

RACKE, M. K., LOVETT-RACKE, A. E. & KARANDIKAR, N. J. 2010. The mechanism of action of glatiramer acetate treatment in multiple sclerosis. *Neurology,* 74**,** S25-S30.

RAMAGOPALAN, S. V., DOBSON, R., MEIER, U. C. & GIOVANNONI, G. 2010. Multiple sclerosis: risk factors, prodromes, and potential causal pathways. *Lancet Neurology,* 9**,** 727-739.

RAMAGOPALAN, S. V., MAUGERI, N. J., HANDUNNETTHI, L., LINCOLN, M. R., ORTON, S. M., DYMENT, D. A., DELUCA, G. C., HERRERA, B. M., CHAO, M. J., SADOVNICK, A. D., EBERS, G. C. & KNIGHT, J. C. 2009. Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D. *PLoS Genet,* 5**,** e1000369.

RAMMOHAN, K. W. & SHOEMAKER, J. 2010. Emerging multiple sclerosis oral therapies. *Neurology,* 74**,** S47-S53.

RASCOL, O., LOZANO, A., STERN, M. & POEWE, W. 2011. Milestones in Parkinson's Disease Therapeutics. *Movement Disorders,* 26**,** 1072-1082.

RIVERS, T. M., SPRUNT, D. H. & BERRY, G. P. 1933. Observations on attempts to produce acute disseminated encephalomyelitis in monkeys. *Journal of Experimental Medicine,* 58**,** 39-U58.

ROBINSON, G. W. 1929. Eight cases of multiple sclerosis in three generations of one family. *Journal of the American Medical Association,* 92**,** 892-893.

ROLAK, L. A. & FLEMING, J. O. 2007. The differential diagnosis of multiple sclerosis. *Neurologist,* 13**,** 57-72.

ROSATI, G. 2001. The prevalence of multiple sclerosis in the world: an update. *Neurol Sci,* 22**,** 117-39.

RUDICK, R. A., STUART, W. H., CALABRESI, P. A., CONFAVREUX, C., GALETTA, S. L., RADUE, E. W., LUBLIN, F. D., WEINSTOCK-GUTTMAN, B., WYNN, D. R., LYNN, F., PANZARA, M. A., SANDROCK, A. W. & INVESTIGATORS, S. 2006. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *New England Journal of Medicine,* 354**,** 911-923.

RUSSELL, T. J., SCHULTES, L. M. & KUBAN, D. J. 1972. Histocompatibility (HL-A) antigens associated with psoriasis. *The New England journal of medicine,* 287**,** 738-40.

SAMARANAYAKE, S. 2006. Study quality in experimental stroke. *CAMARADES Monograph No 2.* The University of Edinburgh.

SARTER, M. & FRITSCHY, J. M. 2008. Reporting statistical methods and statistical results in EJN. *European Journal of Neuroscience,* 28**,** 2363-2364.

SAWCER, S., HELLENTHAL, G., PIRINEN, M., SPENCER, C. C. A., PATSOPOULOS, N. A., MOUTSIANAS, L., DILTHEY, A., SU, Z., FREEMAN, C., HUNT, S. E., EDKINS, S., GRAY, E., BOOTH, D. R., POTTER, S. C., GORIS, A., BAND, G., OTURAI, A. B., STRANGE, A., SAARELA, J., BELLENGUEZ, C., FONTAINE, B., GILLMAN, M., HEMMER, B., GWILLIAM, R., ZIPP, F., JAYAKUMAR, A., MARTIN, R., LESLIE, S., HAWKINS, S., GIANNOULATOU, E., D'ALFONSO, S., BLACKBURN, H., BONESCHI, F. M., LIDDLE, J., HARBO, H. F., PEREZ, M. L., SPURKLAND, A., WALLER, M. J., MYCKO, M. P., RICKETTS, M., COMABELLA, M., HAMMOND, N., KOCKUM, I., MCCANN, O. T., BAN, M., WHITTAKER, P., KEMPPINEN, A., WESTON, P., HAWKINS, C., WIDAA, S., ZAJICEK, J., DRONOV, S., ROBERTSON, N., BUMPSTEAD, S. J., BARCELLOS, L. F., RAVINDRARAJAH, R., ABRAHAM, R., ALFREDSSON, L., ARDLIE, K., AUBIN, C., BAKER, A., BAKER, K., BARANZINI, S. E., BERGAMASCHI, L., BERGAMASCHI, R., BERNSTEIN, A., BERTHELE, A., BOGGILD, M., BRADFIELD, J. P., BRASSAT, D., BROADLEY, S. A., BUCK, D., BUTZKUEVEN, H., CAPRA, R., CARROLL, W. M., CAVALLA, P., CELIUS, E. G., CEPOK, S., CHIAVACCI, R., CLERGET-DARPOUX, F., CLYSTERS, K., COMI, G.,

COSSBURN, M., COURNU-REBEIX, I., COX, M. B., COZEN, W., CREE, B. A. C., CROSS, A. H., CUSI, D., DALY, M. J., DAVIS, E., DE BAKKER, P. I. W., DEBOUVERIE, M., D'HOOGHE, M. B., DIXON, K., DOBOSI, R., DUBOIS, B., ELLINGHAUS, D., ELOVAARA, I., ESPOSITO, F., et al. 2011. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature,* 476**,** 214-219.

SCHAPIRA, A. H. & JENNER, P. 2011. Etiology and Pathogenesis of Parkinson's Disease. *Movement Disorders,* 26**,** 1049-1055.

SCHLATTMANN, P. & DIRNAGL, U. 2010a. Statistics in experimental cerebrovascular research-comparison of two groups with a continuous outcome variable. *J Cereb Blood Flow Metab,* 30**,** 474-9.

SCHLATTMANN, P. & DIRNAGL, U. 2010b. Statistics in experimental cerebrovascular research: comparison of more than two groups with a continuous outcome variable. *J Cereb Blood Flow Metab,* 30**,** 1558-63.

SCHROTER, S., BLACK, N., EVANS, S., GODLEE, F., OSORIO, L. & SMITH, R. 2008. What errors do peer reviewers detect, and does training improve their ability to detect them? *Journal of the Royal Society of Medicine,* 101**,** 507-14.

SCHUMACKER, G. A., BEEBE, G., KIBLER, R. F., KURLAND, L. T., KURTZKE, J. F., MCDOWELL, F., NAGLER, B., SIBLEY, W. A., TOURTELLOTTE, W. W. & WILLMON, T. L. 1965. Problems of Experimental Trials of Therapy in Multiple Sclerosis: Report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis. *Ann N Y Acad Sci,* 122**,** 552-68.

SCHWAB, R. S., AMADOR, L. V. & LETTVIN, J. Y. 1951. Apomorphine in Parkinson's disease. *Transactions of the American Neurological Association,* 56**,** 251-3.

SCHWAB, R. S., ENGLAND, A. C., POSKANZE.DC & YOUNG, R. R. 1969. AMANTADINE IN TREATMENT OF PARKINSONS DISEASE. *Journal of the American Medical Association,* 208**,** 1168-&.

SCHWARZER, G., CARPENTER, J. & RUCKER, G. 2010. Empirical evaluation suggests Copas selection model preferable to trim-and-fill method for selection bias in meta-analysis. *Journal of Clinical Epidemiology,* 63**,** 282-288.

SENA, E., VAN DER WORP, H. B., HOWELLS, D. & MACLEOD, M. 2007a. How can we improve the pre-clinical development of drugs for stroke? *Trends in Neurosciences,* 30**,** 433-439.

SENA, E., WHEBLE, P., SANDERCOCK, P. & MACLEOD, M. 2007b. Systematic review and meta-analysis of the efficacy of tirilazad in experimental stroke. *Stroke,* 38**,** 388-394.

SENA, E. S. & MACLEOD, M. R. 2007. Concordance between laboratory and clinical drug efficacy: Lessons from systematic review and meta-analysis. *Stroke,* 38**,** 502-502.

SENA, E. S., VAN DER WORP, H. B., BATH, P. M. W., HOWELLS, D. W. & MACLEOD, M. R. 2010. Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy. *Plos Biology,* 8, e1000344.

SIMPSON, S., JR., BLIZZARD, L., OTAHAL, P., VAN DER MEI, I. & TAYLOR, B. 2011. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *Journal of neurology, neurosurgery, and psychiatry,* 82**,** 1132-41.

SOILU-HANNINEN, M., AIVO, J., LINDSTROM, B. M., ELOVAARA, I., SUMELAHTI, M. L., FARKKILA, M., TIENARI, P., ATULA, S., SARASOJA, T., HERRALA, L., KESKINARKAUS, I., KRUGER, J., KALLIO, T., ROCCA, M. A. & FILIPPI, M. 2012. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry,* 83**,** 565-71.

SRIRAM, S. & STEINER, I. 2005. Experimental allergic encephalomyelitis: A misleading model of multiple sclerosis. *Annals of Neurology,* 58**,** 939-945.
SRIRAM, S. & STEINER, I. 2006. Chlamydia pneumoniae: a candidate pathogen. *Lancet Neurology,* 5**,** 891-892.
STADELMANN, C. & BRUCK, W. 2008. Interplay between mechanisms of damage and repair in multiple sclerosis. *Journal of Neurology,* 255**,** 12-18.
STEINMAN, L. & ZAMVIL, S. S. 2006. How to successfully apply animal studies in experimental allergic encephalomyelitis to research on multiple sclerosis. *Annals of Neurology,* 60**,** 12-21.
STERNE, J. A. C., EGGER, M. & SMITH, G. D. 2001. Systematic reviews in health care - Investigating and dealing with publication and other biases in meta-analysis. *British Medical Journal,* 323**,** 101-105.
STOWE, R. L., IVES, N. J., CLARKE, C., VAN, H. J., FERREIRA, J., HAWKER, R. J., SHAH, L., WHEATLEY, K. & GRAY, R. 2008. Dopamine agonist therapy in early Parkinson's disease. *Cochrane Database of Systematic Reviews*.
STUART, G. & KRIKORIAN, K. S. 1928. The neuro-paralytic accidents of anti-rabies treatment. *Annals of Tropical Medicine and Parastitology,* 22**,** 327-377.
STYS, P. K., ZAMPONI, G. W., VAN MINNEN, J. & GEURTS, J. J. 2012. Will the real multiple sclerosis please stand up? *Nat Rev Neurosci,* 13**,** 507-14.
SUMAYA, C. V., MYERS, L. W. & ELLISON, G. W. 1980. EPSTEIN-BARR VIRUS-ANTIBODIES IN MULTIPLE-SCLEROSIS. *Archives of Neurology,* 37**,** 94-96.
SUNDSTROM, P., NYSTROM, L. & HALLMANS, G. 2008. Smoke exposure increases the risk for multiple sclerosis. *European Journal of Neurology,* 15**,** 579-583.
SVEJGAARD, A. 2008. The immunogenetics of multiple sclerosis. *Immunogenetics,* 60**,** 275-86.
SWANBORG, R. H., WHITTUM-HUDSON, J. A. & HUDSON, A. P. 2003. Infectious agents and multiple sclerosis - are Chlamydia pneumoniae and human herpes virus 6 involved? *Journal of Neuroimmunology,* 136**,** 1-8.
SWEET, R. D., WASTERLA.CG & MCDOWELL, F. H. 1974. PIRIBEDIL, A DOPAMINE AGONIST, IN PARKINSONS-DISEASE. *Clinical Pharmacology & Therapeutics,* 16**,** 1077-1082.
THANVI, B. R. & LO, T. C. N. 2004. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgraduate Medical Journal,* 80**,** 452-458.
THOMPSON, S. G. 1994. SYSTEMATIC REVIEW - WHY SOURCES OF HETEROGENEITY IN METAANALYSIS SHOULD BE INVESTIGATED. *British Medical Journal,* 309**,** 1351-1355.
THOMPSON, S. G. & HIGGINS, J. P. T. 2002. How should meta-regression analyses be undertaken and interpreted? *Statistics in Medicine,* 21**,** 1559-1573.
THOMPSON, S. G. & SHARP, S. J. 1999. Explaining heterogeneity in meta-analysis: A comparison of methods. *Statistics in Medicine,* 18**,** 2693-2708.
THROWER, B. W. 2007. Clinically isolated syndromes - Predicting and delaying multiple sclerosis. *Neurology,* 68**,** S12-S15.
TINTORE, M., ROVIRA, A., RIO, J., TUR, C., PELAYO, R., NOS, C., TELLEZ, N., PERKAL, H., COMABELLA, M., SASTRE-GARRIGA, J. & MONTALBAN, X. 2008. Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? *Neurology,* 70**,** 1079-1083.
TRAPP, B. D. & NAVE, K. A. 2008. Multiple sclerosis: An immune or neurodegenerative disorder? *Annual Review of Neuroscience.* Palo Alto: Annual Reviews.

TRAPP, B. D., PETERSON, J., RANSOHOFF, R. M., RUDICK, R., MORK, S. & BO, L. 1998. Axonal transection in the lesions of multiple sclerosis. *New England Journal of Medicine,* 338**,** 278-285.

TRAPP, B. D., RANSOHOFF, R. & RUDICK, R. 1999. Axonal pathology in multiple sclerosis: relationship to neurologic disability. *Curr Opin Neurol,* 12**,** 295-302.

TREADAWAY, K., CUTTER, G., SALTER, A., LYNCH, S., SIMSARIAN, J., CORBOY, J., JEFFERY, D., COHEN, B., MANKOWSKI, K., GUARNACCIA, J., SCHAEFFER, L., KANTER, R., BRANDES, D., KAUFMAN, C., DUNCAN, D., MARDER, E., ALLEN, A., HARNEY, J., COOPER, J., WOO, D., STUVE, O., RACKE, M. & FROHMAN, E. M. 2009. Factors that influence adherence with disease-modifying therapy in MS. *Journal of Neurology,* 256**,** 568-576.

ULZHEIMER, J. C., MEUTH, S. G., BITTNER, S., KLEINSCHNITZ, C., KIESEIER, B. C. & WIENDL, H. 2010. Therapeutic approaches to multiple sclerosis: an update on failed, interrupted, or inconclusive trials of immunomodulatory treatment strategies. *Biodrugs,* 24**,** 249-74.

VAN DER WORP, H. B., HOWELLS, D. W., SENA, E. S., PORRITT, M. J., REWELL, S., O'COLLINS, V. & MACLEOD, M. R. 2010a. Can Animal Models of Disease Reliably Inform Human Studies? *Plos Medicine,* 7, e1000245.

VAN DER WORP, H. B. & MACLEOD, M. R. 2011. Preclinical studies of human disease: Time to take methodological quality seriously. *Journal of Molecular and Cellular Cardiology,* 51**,** 449-450.

VAN DER WORP, H. B., MACLEOD, M. R., KOLLMAR, R. & EUROPEAN STROKE RES NETWORK, H. 2010b. Therapeutic hypothermia for acute ischemic stroke: ready to start large randomized trials? *Journal of Cerebral Blood Flow and Metabolism,* 30**,** 1079-1093.

VAN DER WORP, H. B., SENA, E. S., DONNAN, G. A., HOWELLS, D. W. & MACLEOD, M. R. 2007. Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis. *Brain,* 130**,** 3063-3074.

VAN EPPS, H. L. 2005. Thomas Rivers and the EAE model. *Journal of Experimental Medicine,* 202**,** 4-4.

VESTERINEN, H. M., SENA, E. S., FFRENCH-CONSTANT, C., WILLIAMS, A., CHANDRAN, S. & MACLEOD, M. R. 2010. Improving the translational hit of experimental treatments in multiple sclerosis. *Multiple Sclerosis Journal,* 16**,** 1044-1055.

WEKERLE, H. 2008. Lessons from multiple sclerosis: models, concepts, observations. *Annals of the Rheumatic Diseases,* 67**,** 56-60.

WHEBLE, P. C. R., SENA, E. S. & MACLEOD, M. R. 2008. A systematic review and meta-analysis of the efficacy of piracetam and piracetam-like compounds in experimental stroke. *Cerebrovascular Diseases,* 25**,** 5-11.

WYNIA, K., MIDDEL, B., VAN DIJK, J. P., DE KEYSER, J. H. A. & REIJNEVELD, S. A. 2008. The impact of disabilities on quality of life in people with multiple sclerosis. *Multiple Sclerosis,* 14**,** 972-980.

XIE, F. & ZHENG, B. 2008. White matter inhibitors in CNS axon regeneration failure. *Exp Neurol,* 209**,** 302-12.

ZHONG, H. & PRENTICE, R. L. 2008. Bias-reduced estimators and confidence intervals for odds ratios in genome-wide association studies. *Biostatistics,* 9**,** 621-634.

ZIEMSSEN, T. 2008. What can we learn from failed clinical trials in multiple sclerosis? *Journal of Neurology,* 255**,** 97-101.

ZINSMELSTER, A. R. & CONNOR, J. I. 2008. Ten common statistical errors and how to avoid them. *American Journal of Gastroenterology,* 103**,** 262-266.

ZIPP, F. & AKTAS, O. 2006. The brain as a target of inflammation: common pathways link inflammatory and neurodegenerative diseases. *Trends in Neurosciences,* 29**,** 518-527

Appendix 1. References used in the systematic review and meta-analysis of interventions tested in EAE

't Hart, B. A., Blezer, E. L., Brok, H. P., Boon, L., de, B. M., Bauer, J., & Laman, J. D. 2005a, "Treatment with chimeric anti-human CD40 antibody suppresses MRI-detectable inflammation and enlargement of pre-existing brain lesions in common marmosets affected by MOG-induced EAE", J.Neuroimmunol., vol. 163, no. 1-2, pp. 31-39.

't Hart, B. A., Brok, H. P., Remarque, E., Benson, J., Treacy, G., Amor, S., Hintzen, R. Q., Laman, J. D., Bauer, J., & Blezer, E. L. 2005b, "Suppression of ongoing disease in a nonhuman primate model of multiple sclerosis by a human-anti-human IL-12p40 antibody", J.Immunol., vol. 175, no. 7, pp. 4761-4768.

Abdarasulova, I. N., Serdiuk, S. E., & Gmiro, V. E. 2007, "[Combined blockade of GluR1 AMPA and NMDA receptors effectively eliminates neurological disorders in rats with experimental allergic encephalomyelitis]", Eksp.Klin.Farmakol., vol. 70, no. 4, pp. 15-19.

Abramsky, O., Brenner, T., Mizrachi, R., & Soffer, D. 1982, "Alpha-fetoprotein suppresses experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 2, no. 1, pp. 1-7.

Abramsky, O., Karussis, D. M., Mizrachi-Koll, R., & Lehmann, D. 1994, "Inoculation of BCL1 lymphoma cells into CSJL/J F1 mice inhibits acute experimental autoimmune encephalomyelitis", Isr.J.Med.Sci., vol. 30, no. 1, pp. 1-6.

Abramsky, O., Wertman, E., Reches, A., Brenner, T., & Ovadia, H. 1987, "Effect of hypothalamic lesions on experimental autoimmune diseases in rats", Ann.N.Y.Acad.Sci., vol. 496, pp. 360-365.

Abreu, S. L. 1982, "Suppression of experimental allergic encephalomyelitis by interferon", Immunol.Commun., vol. 11, no. 1, pp. 1-7.

Abreu, S. L., Thampoe, I., & Kaplan, P. 1986, "Interferon in experimental autoimmune encephalomyelitis: intraventricular administration", J.Interferon Res., vol. 6, no. 6, pp. 627-632.

Achiron, A., Gilad, R., Margalit, R., Gabbay, U., Sarova-Pinhas, I., Cohen, I. R., Melamed, E., Lider, O., Noy, S., & Ziv, I. 1994a, "Intravenous gammaglobulin treatment in multiple sclerosis and experimental autoimmune encephalomyelitis: delineation of usage and mode of action", J.Neurol.Neurosurg.Psychiatry, vol. 57 Suppl, pp. 57-61.

Achiron, A., Margalit, R., Hershkoviz, R., Markovits, D., Reshef, T., Melamed, E., Cohen, I. R., & Lider, O. 1994b, "Intravenous immunoglobulin treatment of experimental T cell-mediated autoimmune disease. Upregulation of T cell proliferation and downregulation of tumor necrosis factor alpha secretion", J.Clin.Invest, vol. 93, no. 2, pp. 600-605.

Achiron, A., Miron, S., Lavie, V., Margalit, R., & Biegon, A. 2000a, "Dexanabinol (HU-211) effect on experimental autoimmune encephalomyelitis: implications for the treatment of acute relapses of multiple sclerosis", J.Neuroimmunol., vol. 102, no. 1, pp. 26-31.

Achiron, A., Mor, F., Margalit, R., Cohen, I. R., Lider, O., & Miron, S. 2000b, "Suppression of experimental autoimmune encephalomyelitis by intravenously administered polyclonal immunoglobulins", J.Autoimmun., vol. 15, no. 3, pp. 323-330.

Adams, R. A., Schachtrup, C., Bauer, J., Flick, M. J., Lassmann, H., Degen, J. L., & Akassoglou, K. 2007, "Fibrinogen as a signaling molecule and therapeutic target for inflammation and neuroprotection in multiple sclerosis", Multiple Sclerosis, vol. 13, no. 9, p. 24.

Adamus, G., Manczak, M., & Machnicki, M. 2001, "Expression of CC chemokines and their receptors in the eye in autoimmune anterior uveitis associated with EAE", Invest Ophthalmol.Vis.Sci., vol. 42, no. 12, pp. 2894-2903.

Adda, D. H., Beraud, E., & Depieds, R. 1977, "[Suppressor cells in allergic encephalomyelitis]", Ann.Immunol.(Paris), vol. 128, no. 1-2, pp. 241-242.

Agnello, D., Bigini, P., Villa, P., Mennini, T., Cerami, A., Brines, M. L., & Ghezzi, P. 2002, "Erythropoietin exerts an anti-inflammatory effect on the CNS in a model of experimental autoimmune encephalomyelitis", Brain Res., vol. 952, no. 1, pp. 128-134.

Agnello, D., Carvelli, L., Muzio, V., Villa, P., Bottazzi, B., Polentarutti, N., Mennini, T., Mantovani, A., & Ghezzi, P. 2000, "Increased peripheral benzodiazepine binding sites and pentraxin 3 expression in the spinal cord during EAE: relation to inflammatory cytokines and modulation by dexamethasone and rolipram", J.Neuroimmunol., vol. 109, no. 2, pp. 105-111.

Aharoni, R., Arnon, R., & Eilam, R. 2005, "Neurogenesis and neuroprotection induced by peripheral immunomodulatory treatment of experimental autoimmune encephalomyelitis", J.Neurosci., vol. 25, no. 36, pp. 8217-8228.

Aharoni, R., Eilam, R., Domev, H., Labunskay, G., Sela, M., & Arnon, R. 2005, "The immunomodulator glatiramer acetate augments the expression of neurotrophic factors in brains of experimental autoimmune encephalomyelitis mice", Proc.Natl.Acad.Sci.U.S.A, vol. 102, no. 52, pp. 19045-19050.

Aharoni, R., Teitelbaum, D., & Arnon, R. 1993, "T suppressor hybridomas and interleukin-2-dependent lines induced by copolymer 1 or by spinal cord homogenate down-regulate experimental allergic encephalomyelitis", Eur.J.Immunol., vol. 23, no. 1, pp. 17-25.

Aharoni, R., Herschkovitz, A., Eilam, R., Blumberg-Hazan, M., Sela, M., Bruck, W., & Arnon, R. 2008, "Demyelination arrest and remyelination induced by glatiramer acetate treatment of experimental autoimmune encephalomyelitis", Proc Natl Acad Sci U S A, vol. 105, no. 32.

Aharonowiz, M., Einstein, O., Fainstein, N., Lassmann, H., Reubinoff, B., & Ben Hur, T. 2008, "Neuroprotective effect of transplanted human embryonic stem cell-derived neural precursors in an animal model of multiple sclerosis", PLoS.ONE., vol. 3, no. 9, p. e3145.

Ahmed, Z., Gveric, D., Pryce, G., Baker, D., Leonard, J. P., & Cuzner, M. L. 2001, "Myelin/axonal pathology in interleukin-12 induced serial relapses of experimental allergic encephalomyelitis in the Lewis rat", American Journal of Pathology.158(6)()(pp 2127-2138), 2001.Date of Publication: 2001. no. 6, pp. 2127-2138.

Aikawa, Y., Tanuma, N., Shin, T., Makino, S., Tanaka, K., & Matsumoto, Y. 1998, "A new anti-rheumatic drug, T-614, effectively suppresses the development of autoimmune encephalomyelitis", J.Neuroimmunol., vol. 89, no. 1-2, pp. 35-42.

Akabane, H., Miyagawa, N., Nii, H., Inami, Y., Togawa, M., Tanaka, H., Inagaki, N., & Nagai, H. 2004, "The effect of a newly synthesized indazole compound, TAS-3-124, on experimental autoimmune disease", Biol.Pharm.Bull., vol. 27, no. 8, pp. 1218-1223.

Akiyama, K., Murakami, T., Nomaguchi, T. A., & Nagai, Y. 1981, "Complete Freund's adjuvant-induced immune prevention against experimental allergic encephalomyelitis in guinea pigs: early appearance of anti-myelin basic protein antibody", Jpn.J.Exp.Med., vol. 51, no. 2, pp. 137-139.

Aktas, O., Brocke, S., Smorodchenko, A., Osmanova, V., Prozorovski, T., Bechmann, I., Beyer, M., Infante-Duarte, C., Nitsch, R., & Zipp, F. 2002, "Therapeutic Blockade of Trail - Induced Neuronal Cell Death in Autoimmune Encephalomyelitis", Society for Neuroscience Abstract Viewer and Itinerary Planner, vol. 2002.

Aktas, O., Prozorovski, T., Smorodchenko, A., Savaskan, N. E., Lauster, R., Kloetzel, P. M., Infante-Duarte, C., Brocke, S., & Zipp, F. 2004, "Green tea epigallocatechin-3-gallate mediates T cellular NF-kappa B inhibition and exerts neuroprotection in autoimmune encephalomyelitis", J.Immunol., vol. 173, no. 9, pp. 5794-5800.

Aktas, O., Smorodchenko, A., Brocke, S., Infante-Duarte, C., Topphoff, U. S., Vogt, J., Prozorovski, T., Meier, S., Osmanova, V., Pohl, E., Bechmann, I., Nitsch, R., & Zipp, F. 2005a, "Neuronal damage in autoimmune neuroinflammation mediated by the death ligand TRAIL", Neuron, vol. 46, pp. 421-432.

Aktas, O., Waiczies, S., Smorodchenko, A., Dorr, J., Seeger, B., Prozorovski, T., Sallach, S., Endres, M., Brocke, S., Nitsch, R., & Zipp, F. 2003, "Treatment of relapsing paralysis in experimental encephalomyelitis by targeting Th1 cells through atorvastatin", J.Exp.Med., vol. 197, no. 6, pp. 725-733.

Aktas, O., Prozorovski, T., Smorodchenko, A., Savaskan, N. E., Lauster, R., Kloetzel, P. M., Infante-Duarte, C., Brocke, S., & Zipp, F. 2005b, "Independent anti-inflammatory and neuroprotective effects of oral green tea epigallocatechin-3-gallate (EGCG) in experimental autoimmune encephalomyelitis", Neurology, vol. 64, no. 6, Suppl. 1.

Al-Sabbagh, A., Miller, A., Santos, L. M., & Weiner, H. L. 1994, "Antigen-driven tissue-specific suppression following oral tolerance: orally administered myelin basic protein suppresses proteolipid protein-induced experimental autoimmune encephalomyelitis in the SJL mouse", Eur.J.Immunol., vol. 24, no. 9, pp. 2104-2109.

Al-Sabbagh, A., Nelson, P. A., Akselband, Y., Sobel, R. A., & Weiner, H. L. 1996, "Antigen-driven peripheral immune tolerance: suppression of experimental autoimmmune encephalomyelitis and collagen-induced arthritis by aerosol administration of myelin basic protein or type II collagen", Cell Immunol., vol. 171, no. 1, pp. 111-119.

al-Sabbagh, A. M., Goad, E. P., Weiner, H. L., & Nelson, P. A. 1996, "Decreased CNS inflammation and absence of clinical exacerbation of disease after six months oral administration of bovine myelin in diseased SJL/J mice with chronic relapsing experimental autoimmune encephalomyelitis", J.Neurosci.Res., vol. 45, no. 4, pp. 424-429.

Alvord, E. C., Jr., Shaw, C. M., & Hruby, S. 1979, "Myelin basic protein treatment of experimental allergic encephalomyelitis in monkeys", Ann.Neurol., vol. 6, no. 6, pp. 469-473.

Anane, R., Geffard, M., Taxile, M., Bodet, D., Billaudel, B., Dulou, P. E., & Veyret, B. 2003, "Effects of GSM-900 microwaves on the experimental allergic encephalomyelitis (EAE) rat model of multiple sclerosis", Bioelectromagnetics, vol. 24, no. 3, pp. 211-213.

Anderton, S. M. & Wraith, D. C. 1998, "Hierarchy in the ability of T cell epitopes to induce peripheral tolerance to antigens from myelin", Eur.J.Immunol., vol. 28, no. 4, pp. 1251-1261.

Anghelescu, N., Petrescu, A., & Chimion, D. 1979, "Experimental allergic encephalomyelitis. V. Therapeutic attempts with immunosuppressive and antiinflammatory drugs", Neurol.Psychiatr.(Bucur.), vol. 17, no. 2, pp. 99-105.

Aoyagi, T., Wada, T., Nagai, M., Sakaguchi, H., Osanai, T., Nagai, Y., & Umezawa, H. 1984, "Low-molecular-weight enzyme inhibitors suppress the development of experimental allergic encephalomyelitis", Experientia, vol. 40, no. 12, pp. 1405-1407.

Archelos, J. J., Jung, S., Maurer, M., Schmied, M., Lassmann, H., Tamatani, T., Miyasaka, M., Toyka, K. V., & Hartung, H. P. 1993, "Inhibition of experimental autoimmune encephalomyelitis by an antibody to the intercellular adhesion molecule ICAM-1", Ann.Neurol., vol. 34, no. 2, pp. 145-154.

Archelos, J. J., Jung, S., Rinner, W., Lassmann, H., Miyasaka, M., & Hartung, H. P. 1998, "Role of the leukocyte-adhesion molecule L-selectin in experimental autoimmune encephalomyelitis", J.Neurol.Sci., vol. 159, no. 2, pp. 127-134.

Arima, T., Rehman, A., Hickey, W. F., & Flye, M. W. 1996, "Inhibition by CTLA4Ig of experimental allergic encephalomyelitis", J.Immunol., vol. 156, no. 12, pp. 4916-4924.

Arnason, B. G. & Richman, D. P. 1969, "Effect of oral contraceptives on experimental demyelinating disease", Arch.Neurol., vol. 21, no. 1, pp. 103-108.

Aroeira, L. S. 2006, "TCR vaccination in aluminum adjuvant protects against autoimmune encephalomyelitis", Clin.Immunol., vol. 119, no. 3, pp. 252-260.

Arredondo, L. R., Deng, C., Ratts, R. B., Lovett-Racke, A. E., Holtzman, D. M., & Racke, M. K. 2001, "Role of nerve growth factor in experimental autoimmune encephalomyelitis", Eur.J.Immunol., vol. 31, no. 2, pp. 625-633.

Auci, D., Nicoletti, F., Mangano, K., Pieters, R., Nierkens, S., Morgan, L., Offner, H., Frincke, J., & Reading, C. 2005, "Anti-inflammatory and immune regulatory properties of 5-androsten-3beta, 17beta-diol (HE2100), and synthetic analogue HE3204: implications for treatment of autoimmune diseases", Ann.N Y Acad Sci, vol. 1051, pp. 730-742.

Avrilionis, K. & Boggs, J. M. 1991, "Suppression of experimental allergic encephalomyelitis by the encephalitogenic peptide, in solution or bound to liposomes", J.Neuroimmunol., vol. 35, no. 1-3, pp. 201-210.

Babington, R. G. & Wedeking, P. W. 1971, "The influence of cinanserin and selected pharmacologic agents on experimental allergic encephalomyelitis (EAE)", J.Pharmacol.Exp.Ther., vol. 177, no. 2, pp. 454-460.

Badger, A. M., DiMartino, M. J., Talmadge, J. E., Picker, D. H., Schwartz, D. A., Dorman, J. W., Mirabelli, C. K., & Hanna, N. 1989, "Inhibition of animal models of autoimmune disease and the induction of non-specific suppressor cells by SK&F 105685 and related azaspiranes", Int.J.Immunopharmacol., vol. 11, no. 7, pp. 839-846.

Badmaev, V., Kozlowski, P. B., Schuller-Levis, G. B., & Wisniewski, H. M. 1999, "The therapeutic effect of an herbal formula Badmaev 28 (padma 28) on experimental allergic encephalomyelitis (EAE) in SJL/J mice", Phytother.Res., vol. 13, no. 3, pp. 218-221.

Badovinac, V., Mostarica-Stojkovic, M., Dinarello, C. A., & Stosic-Grujicic, S. 1998, "Interleukin-1 receptor antagonist suppresses experimental autoimmune encephalomyelitis (EAE) in rats by influencing the activation and proliferation of encephalitogenic cells", J.Neuroimmunol., vol. 85, no. 1, pp. 87-95.

Bai, X. F., Li, H. L., Shi, F. D., Liu, J. Q., Xiao, B. G., van der Meide, P. H., & Link, H. 1998, "Complexities of applying nasal tolerance induction as a therapy for ongoing relapsing experimental autoimmune encephalomyelitis (EAE) in DA rats", Clin.Exp.Immunol., vol. 111, no. 1, pp. 205-210.

Bai, X. F., Shi, F. D., Xiao, B. G., Li, H. L., van der Meide, P. H., & Link, H. 1997, "Nasal administration of myelin basic protein prevents relapsing experimental autoimmune encephalomyelitis in DA rats by activating regulatory cells expressing IL-4 and TGF-beta mRNA", J Neuroimmunol, vol. 80, no. 1-2, pp. 65-75.

Baker, D., Butler, D., Scallon, B. J., O'Neill, J. K., Turk, J. L., & Feldmann, M. 1994, "Control of established experimental allergic encephalomyelitis by inhibition of tumor necrosis factor (TNF) activity within the central nervous system using monoclonal antibodies and TNF receptor-immunoglobulin fusion proteins", Eur.J.Immunol., vol. 24, no. 9, pp. 2040-2048.

Baker, D., O'Neill, J. K., Amor, S., Khamashta, M. A., & Turk, J. L. 1991, "Inhibition of chronic relapsing experimental allergic encephalomyelitis in the mouse by the alkyl-lysophospholipid ET-18-OCH3", Int.J.Immunopharmacol., vol. 13, no. 4, pp. 385-392.

Baker, D., O'Neill, J. K., Davison, A. N., & Turk, J. L. 1992, "Control of immune-mediated disease of the central nervous system requires the use of a neuroactive agent: elucidation by the action of mitoxantrone", Clin.Exp.Immunol., vol. 90, no. 1, pp. 124-128.

Baker, D., Pryce, G., Croxford, J. L., Brown, P., Pertwee, R. G., Huffman, J. W., & Layward, L. 2000, "Cannabinoids control spasticity and tremor in a multiple sclerosis model", Nature, vol. 404, no. 6773, pp. 84-87.

Baker, D., Pryce, G., Croxford, J. L., Brown, P., Pertwee, R. G., Makriyannis, A., Khanolkar, A., Layward, L., Fezza, F., Bisogno, T., & Di, M. 2001, "Endocannabinoids control spasticity in a multiple sclerosis model", FASEB J, vol. 15, no. 2.

Bakker, J. M., Kavelaars, A., Kamphuis, P. J., Cobelens, P. M., van Vugt, H. H., van, B. F., & Heijnen, C. J. 2000, "Neonatal dexamethasone treatment increases susceptibility to experimental autoimmune disease in adult rats", J.Immunol., vol. 165, no. 10, pp. 5932-5937.

Balatoni, B., Storch, M. K., Swoboda, E. M., Schonborn, V., Koziel, A., Lambrou, G. N., Hiestand, P. C., Weissert, R., & Foster, C. A. 2007, "FTY720 sustains and restores neuronal function in the DA rat model of MOG-induced experimental autoimmune encephalomyelitis", Brain Res.Bull., vol. 74, no. 5, pp. 307-316.

Barnard, A. L., Chidgey, A. P., Bernard, C. C., & Boyd, R. L. 2009, "Androgen depletion increases the efficacy of bone marrow transplantation in ameliorating experimental autoimmune encephalomyelitis", Blood, vol. 113, no. 1.

Basso, A. S., Frenkel, D., Petrovic-Stojkovic, S., Monsonego, A., Puckett, L., Gozin, M., Weiner, H., & Kroc, R. L. 2007a, "Treatment with a fullerene derivative (ABS-75) reduces disease progression and axonal loss in MOG-induced progressive EAE in NOD mice", Clinical Immunology, vol. 123, p. S151.

Basso, A. S., Frenkel, D., Quintana, F. J., Costa-Pinto, F. A., Petrovic-Stojkovic, S., Puckett, L., Monsonego, A., Bar-Shir, A., Engel, Y., Gozin, M., & Weiner, H. L. 2008, "Reversal of axonal loss and disability in a mouse model of progressive multiple sclerosis", Journal of Clinical Investigation, vol. 118, no. 4, pp. 1532-1543.

Basso, A. S., Frenkel, D., Petrovic-Stojkovic, S., Puckett, L., Monsonego, A., Gozin, M., & Weiner, H. 2007b, "Fullerene (ABS-75) treatment reduces disease progression and axonal loss in MOG-induced progressive EAE in NOD mice", Neurology, vol. 68, no. 12, Suppl. 1.

Bauer, J., Huitinga, I., Zhao, W., Lassmann, H., Hickey, W. F., & Dijkstra, C. D. 1995, "The role of macrophages, perivascular cells, and microglial cells in the pathogenesis of experimental autoimmune encephalomyelitis", Glia, vol. 15, no. 4, pp. 437-446.

Bebo, B. F., Jr., Adlard, K., Schuster, J. C., Unsicker, L., Vandenbark, A. A., & Offner, H. 1999, "Gender differences in protection from EAE induced by oral tolerance with a peptide analogue of MBP-Ac1-11", J Neurosci Res, vol. 55, no. 4, pp. 432-440.

Bebo, B. F., Jr., Fyfe-Johnson, A., Adlard, K., Beam, A. G., Vandenbark, A. A., & Offner, H. 2001, "Low-dose estrogen therapy ameliorates experimental autoimmune encephalomyelitis in two different inbred mouse strains", J.Immunol., vol. 166, no. 3, pp. 2080-2089.

Bebo, J., Dehghani, B., Foster, S., Kurniawan, A., Lopez, F. J., & Sherman, L. S. 2009, "Treatment with selective estrogen receptor modulators regulates myelin specific T-cells and suppresses experimental autoimmune encephalomyelitis", GLIA.57(7)()(pp 777-790), 2009.Date of Publication: 2009. no. 7, pp. 777-790.

Bechtold, D., Kapoor, R., & Smith, K. 2002, "Axonal Protection in Experimental Inflammatory Demyelinating Disease Achieved by Flecainide Therapy", Society for Neuroscience Abstract Viewer and Itinerary Planner, vol. 2002.

Bechtold, D. A., Kapoor, R., & Smith, K. J. 2004, "Axonal protection using flecainide in experimental autoimmune encephalomyelitis", Ann.Neurol., vol. 55, no. 5, pp. 607-616.

Bechtold, D. A., Miller, S. J., Dawson, A. C., Sun, Y., Kapoor, R., Berry, D., & Smith, K. J. 2006, "Axonal protection achieved in a model of multiple sclerosis using lamotrigine", Journal of Neurology, vol. 253, no. 12, pp. 1542-1551.

Beck, F. W. & Whitehouse, M. W. 1975, "Modified EAE as an assay for immunosuppressant drugs", Proc.West Pharmacol.Soc., vol. 18, pp. 136-140.

Becklund, B. R., Hansen, D. W., Jr., & Deluca, H. F. 2009, "Enhancement of 1,25-dihydroxyvitamin D3-mediated suppression of experimental autoimmune encephalomyelitis by calcitonin", Proc Natl Acad Sci U S A, vol. 106, no. 13, pp. 5276-5281.

Bedoui, S., Miyake, S., Lin, Y., Miyamoto, K., Oki, S., Kawamura, N., Beck-Sickinger, A., von, H. S., & Yamamura, T. 2003, "Neuropeptide Y (NPY) suppresses experimental autoimmune encephalomyelitis: NPY1 receptor-specific inhibition of autoreactive Th1 responses in vivo", J.Immunol., vol. 171, no. 7, pp. 3451-3458.

Beeton, C., Barbaria, J., Giraud, P., Devaux, J., Benoliel, A. M., Gola, M., Sabatier, J. M., Bernard, D., Crest, M., & Beraud, E. 2001a, "Selective blocking of voltage-gated K+ channels improves experimental autoimmune encephalomyelitis and inhibits T cell activation", J.Immunol., vol. 166, no. 2, pp. 936-944.

Beeton, C., Wulff, H., Barbaria, J., Clot-Faybesse, O., Pennington, M., Bernard, D., Cahalan, M. D., Chandy, K. G., & Beraud, E. 2001b, "Selective blockade of T lymphocyte K(+) channels ameliorates experimental autoimmune encephalomyelitis, a model for multiple sclerosis", Proc.Natl.Acad.Sci.U.S.A, vol. 98, no. 24, pp. 13942-13947.

Belik, I., Terletskaia, I., Kozulina, E. P., Syrovatskaia, L. P., & Gershkovich, A. A. 1978, "[Therapeutic effect of myelin basic protein and synthetic encephalitogenic peptide in guinea pigs with experimental allergic encephalomyelitis]", Vopr.Med.Khim., vol. 24, no. 3, pp. 372-377.

Bell, J. J., Divekar, R. D., Ellis, J. S., Cascio, J. A., Haymaker, C. L., Jain, R., Tartar, D. M., Hoeman, C. M., Hardaway, J. C., & Zaghouani, H. 2008, "In trans T cell tolerance diminishes autoantibody responses and exacerbates experimental allergic encephalomyelitis", J.Immunol., vol. 180, no. 3, pp. 1508-1516.

Ben Nun, A. & Cohen, I. R. 1981, "Vaccination against autoimmune encephalomyelitis (EAE): attenuated autoimmune T lymphocytes confer resistance to induction of active EAE but not to EAE mediated by the intact T lymphocyte line", Eur J Immunol, vol. 11, no. 11, pp. 949-952.

Ben-Nun, A., Mendel, I., Sappler, G., & Kerlero de, R. N. 1995, "A 12-kDa protein of Mycobacterium tuberculosis protects mice against experimental autoimmune encephalomyelitis. Protection in the absence of shared T cell epitopes with encephalitogenic proteins", J.Immunol., vol. 154, no. 6, pp. 2939-2948.

Ben-Nun, A., Wekerle, H., & Cohen, I. R. 1981, "Vaccination against autoimmune encephalomyelitis with T-lymphocyte line cells reactive against myelin basic protein", Nature, vol. 292, no. 5818, pp. 60-61.

Ben-Nun, A. & Yossefi, S. 1990, "Reversal of autoimmune encephalomyelitis by membranes presenting myelin basic protein-associated class II MHC molecule as an approach to immunotherapy of organ-specific autoimmune diseases", Eur.J.Immunol., vol. 20, no. 2, pp. 357-361.

Ben-Nun, A., Yossefi, S., & Lehmann, D. 1993, "Protection against autoimmune disease by bacterial agents. II. PPD and pertussis toxin as proteins active in protecting mice against experimental autoimmune encephalomyelitis", Eur.J.Immunol., vol. 23, no. 3, pp. 689-696.

Benou, C., Wang, Y., Imitola, J., VanVlerken, L., Chandras, C., Karalis, K. P., & Khoury, S. J. 2005, "Corticotropin-releasing hormone contributes to the peripheral inflammatory response in experimental autoimmune encephalomyelitis", J.Immunol., vol. 174, no. 9, pp. 5407-5413.

Benson, J. M., Stuckman, S. S., Cox, K. L., Wardrop, R. M., Gienapp, I. E., Cross, A. H., Trotter, J. L., & Whitacre, C. C. 1999, "Oral administration of myelin basic protein is superior to myelin in suppressing

established relapsing experimental autoimmune encephalomyelitis", J.Immunol., vol. 162, no. 10, pp. 6247-6254.

Beraud, E., Lider, O., Baharav, E., Reshef, T., & Cohen, I. R. 1989, "Vaccination against experimental autoimmune encephalomyelitis using a subencephalitogenic dose of autoimmune effector cells (1). Characteristics of vaccination", J.Autoimmun., vol. 2, no. 1, pp. 75-86.

Beraud, E., Lorberboum-Galski, H., Chan, C. C., Fitzgerald, D., Pastan, I., & Nussenblatt, R. B. 1991, "Immunospecific suppression of encephalitogenic-activated T lymphocytes by chimeric cytotoxin IL-2-PE40", Cell Immunol., vol. 133, no. 2, pp. 379-389.

Beraud, E., Varriale, S., Farnarier, C., & Bernard, D. 1982, "Suppressor cells in Lewis rats with experimental allergic encephalomyelitis: prevention of the disease and inhibition of lymphocyte proliferation by the suppressor cells or their products", Eur.J.Immunol., vol. 12, no. 11, pp. 926-930.

Beraud, E., Viola, A., Regaya, I., Confort-Gouny, S., Siaud, P., Ibarrola, D., Le Fur, Y., Barbaria, J., Pellissier, J. F., Sabatier, J. M., Medina, I., & Cozzone, P. J. 2006, "Block of neural Kv1.1 potassium channels for neuroinflammatory disease therapy", Ann Neurol, vol. 60, no. 5.

Bergstrand, H. 1976, "Blocking the encephalitogenic activity of the C-terminal part of the basic myelin protein in rabbits by treatment with serum", Immunology, vol. 30, no. 4, p. UNKNOWN.

Berman, Z., Techetchik, & Stern, N. 1977, "[D. Effect of high molecular levan on experimental allergic encephalitis]", Harefuah, vol. 93, no. 11, pp. 340-343.

Bernard, C. C. 1977, "Suppressor T cells prevent experimental autoimmune encephalomyelitis in mice", Clin.Exp.Immunol., vol. 29, no. 1, pp. 100-109.

Bernard, C. C., Leydon, J., & Mackay, I. R. 1977, "Anti-T cell activity of niridazole in experimental autoimmune encephalomyelitis", Int.Arch.Allergy Appl.Immunol., vol. 53, no. 6, pp. 555-559.

Bernard, C. C., Mackay, I. R., Whittingham, S., & Brous, P. 1976, "Durability of immune protection against experimental autoimmune encephalomyelitis", Cell Immunol, vol. 22, no. 2, pp. 297-310.

Bernard, C. C. A., Leydon, J., & Mackay, I. R. 1976, "Thymus Derived Cell Necessity in the Pathogenesis of Experimental Auto Immune Encephalo Myelitis in Mice", European Journal of Immunology, vol. 6, no. 9, pp. 655-660.

Besong, G., Battaglia, G., D'Onofrio, M., Di, M. R., Ngomba, R. T., Storto, M., Castiglione, M., Mangano, K., Busceti, C. L., Nicoletti, F. R., Bacon, K., Tusche, M., Valenti, O., Conn, P. J., Bruno, V., & Nicoletti, F. 2002, "Activation of group III metabotropic glutamate receptors inhibits the production of RANTES in glial cell cultures", J.Neurosci., vol. 22, no. 13, pp. 5403-5411.

Beyersdorf, N., Gaupp, S., Balbach, K., Schmidt, J., Toyka, K. V., Lin, C. H., Hanke, T., Hunig, T., Kerkau, T., & Gold, R. 2005, "Selective targeting of regulatory T cells with CD28 superagonists allows effective therapy of experimental autoimmune encephalomyelitis", J.Exp.Med., vol. 202, no. 3, pp. 445-455.

Bhasin, M., Wu, M., & Tsirka, S. E. 2007, "Modulation of microglial/macrophage activation by macrophage inhibitory factor (TKP) or tuftsin (TKPR) attenuates the disease course of experimental autoimmune encephalomyelitis", BMC.Immunol., vol. 8, p. 10.

Biasi, G., Facchinetti, A., Monastra, G., Mezzalira, S., Sivieri, S., Tavolato, B., & Gallo, P. 1997, "Protection from experimental autoimmune encephalomyelitis (EAE): non-depleting anti-CD4 mAb treatment induces peripheral T-cell tolerance to MBP in PL/J mice", J.Neuroimmunol., vol. 73, no. 1-2, pp. 117-123.

Birnbaum, G., Kotilinek, L., Schlievert, P., Clark, H. B., Trotter, J., Horvath, E., Gao, E., Cox, M., & Braun, P. E. 1996, "Heat shock proteins and experimental autoimmune encephalomyelitis (EAE): I. Immunization with a peptide of the myelin protein 2',3' cyclic nucleotide 3' phosphodiesterase that is cross-reactive with a heat shock protein alters the course of EAE", J.Neurosci.Res., vol. 44, no. 4, pp. 381-396.

Bitar, D. M. & Whitacre, C. C. 1988, "Suppression of experimental autoimmune encephalomyelitis by the oral administration of myelin basic protein", Cell Immunol., vol. 112, no. 2, pp. 364-370.

Blaber, S. I., Ciric, B., Christophi, G. P., Bernett, M. J., Blaber, M., Rodriguez, M., & Scarisbrick, I. A. 2004, "Targeting kallikrein 6-proteolysis attenuates CNS inflammatory disease", Faseb Journal, vol. 18, no. 3, p. 920-+.

Black, J. A., Liu, S., Carrithers, M., Carrithers, L. M., & Waxman, S. G. 2007, "Exacerbation of experimental autoimmune encephalomyelitis after withdrawal of phenytoin and carbamazepine", Ann.Neurol., vol. 62, no. 1, pp. 21-33.

Black, J. A., Liu, S., Hains, B. C., Saab, C. Y., & Waxman, S. G. 2006, "Long-term protection of central axons with phenytoin in monophasic and chronic-relapsing EAE", Brain, vol. 129, no. Pt 12, pp. 3196-3208.

Blaszczyk, B., Gieldanowski, J., & Karakoz, I. 1978, "Experimental allergic encephalomyelitis in chickens", Arch.Immunol.Ther.Exp.(Warsz.), vol. 26, no. 1-6, pp. 743-746.

Boehme, D. H., Umezawa, H., Hashim, G., & Marks, N. 1978, "Treatment of experimental allergic encephalomyelitis with an inhibitor of cathepsin D (pepstatin)", Neurochem.Res., vol. 3, no. 2, pp. 185-194.

Bolton, C., Allsopp, G., & Cuzner, M. L. 1982, "The effect of cyclosporin A on the adoptive transfer of experimental allergic encephalomyelitis in the Lewis rat", Clin.Exp.Immunol., vol. 47, no. 1, pp. 127-132.

Bolton, C., Borel, J. F., Cuzner, M. L., Davison, A. N., & Turner, A. M. 1982, "Immunosuppression by cyclosporin A of experimental allergic encephalomyelitis", J.Neurol.Sci., vol. 56, no. 2-3, pp. 147-153.

Bolton, C. & Paul, C. 1997, "MK-801 limits neurovascular dysfunction during experimental allergic encephalomyelitis", J.Pharmacol.Exp.Ther., vol. 282, no. 1, pp. 397-402.

Bolton, C., Scott, G. S., Smith, T., & Flower, R. J. 2008, "The acute and chronic phases of chronic relapsing experimental autoimmune encephalomyelitis (CR EAE) are ameliorated by the peroxynitrite decomposition catalyst, 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrinatoiron (III) chloride, (FeTPPS)", European Journal of Pharmacology, vol. 601, no. 1-3, pp. 88-93.

Boon, L., Brok, H. P., Bauer, J., Ortiz-Buijsse, A., Schellekens, M. M., Ramdien-Murli, S., Blezer, E., van, M. M., Ceuppens, J., de, B. M., 't Hart, B. A., & Laman, J. D. 2001, "Prevention of experimental autoimmune encephalomyelitis in the common marmoset (Callithrix jacchus) using a chimeric antagonist monoclonal antibody against human CD40 is associated with altered B cell responses", J.Immunol., vol. 167, no. 5, pp. 2942-2949.

Borel, J. F., Feurer, C., Gubler, H. U., & Stahelin, H. 1976, "Biological effects of cyclosporin A: a new antilymphocytic agent", Agents Actions, vol. 6, no. 4, pp. 468-475.

Bouerat, L., Fensholdt, J., Liang, X., Havez, S., Nielsen, S. F., Hansen, J. R., Bolvig, S., & Andersson, C. 2005, "Indolin-2-ones with high in vivo efficacy in a model for multiple sclerosis", J.Med.Chem., vol. 48, no. 17, pp. 5412-5414.

Bourquin, C., Iglesias, A., Berger, T., Wekerle, H., & Linington, C. 2000, "Myelin oligodendrocyte glycoprotein-DNA vaccination induces antibody-mediated autoaggression in experimental autoimmune encephalomyelitis", European Journal of Immunology.30(12)()(pp 3663-3671), 2000.Date of Publication: 2000. no. 12, pp. 3663-3671.

Bourrie, B., Bribes, E., Esclangon, M., Garcia, L., Marchand, J., Thomas, C., Maffrand, J. P., & Casellas, P. 1999, "The neuroprotective agent SR 57746A abrogates experimental autoimmune encephalomyelitis and impairs associated blood-brain barrier disruption: implications for multiple sclerosis treatment", Proc.Natl.Acad.Sci.U.S.A, vol. 96, no. 22, pp. 12855-12859.

Bowern, N., Ramshaw, I. A., Clark, I. A., & Doherty, P. C. 1984, "Inhibition of autoimmune neuropathological process by treatment with an iron-chelating agent", J.Exp.Med., vol. 160, no. 5, pp. 1532-1543.

Brahmachari, S. & Pahan, K. 2007, "Sodium benzoate, a food additive and a metabolite of cinnamon, modifies T cells at multiple steps and inhibits adoptive transfer of experimental allergic encephalomyelitis", J.Immunol., vol. 179, no. 1, pp. 275-283.

Brand-Schieber, E. & Werner, P. 2004, "Calcium channel blockers ameliorate disease in a mouse model of multiple sclerosis", Exp.Neurol., vol. 189, no. 1, pp. 5-9.

Brandt, A., Giessler, J., Schmidt, K., & Hirschelmann, R. 1993, "Megadose glucocorticoid therapy: investigations in rat anaphylactic shock and experimental allergic encephalomyelitis", Agents Actions, vol. 38 Spec No, p. C108-C111.

Branisteanu, D. D., Mathieu, C., & Bouillon, R. 1997, "Synergism between sirolimus and 1,25-dihydroxyvitamin D3 in vitro and in vivo", J.Neuroimmunol., vol. 79, no. 2, pp. 138-147.

Brenner, T., Brocke, S., Szafer, F., Sobel, R. A., Parkinson, J. F., Perez, D. H., & Steinman, L. 1997, "Inhibition of nitric oxide synthase for treatment of experimental autoimmune encephalomyelitis", J.Immunol., vol. 158, no. 6, pp. 2940-2946.

Brenner, T., Evron, S., Soffer, D., & Abramsky, O. 1985, "Treatment of experimental allergic encephalomyelitis in rabbits with alpha-fetoprotein", Isr.J.Med.Sci., vol. 21, no. 12, pp. 945-949.

Brenner, T., Poradosu, E., Soffer, D., Sicsic, C., Gazit, A., & Levitzki, A. 1998, "Suppression of experimental autoimmune encephalomyelitis by tyrphostin AG-556", Exp.Neurol., vol. 154, no. 2, pp. 489-498.

Brenner, T., Steinberger, I., Soffer, D., Beraud, E., Ben-Nun, A., & Lorberboum-Galski, H. 1999, "A novel antigen-toxin chimeric protein: myelin basic protein-pseudomonas exotoxin (MBP-PE 40) for treatment of experimental autoimmune encephalomyelitis", Immunol.Lett., vol. 68, no. 2-3, pp. 403-410.

Bright, J. J., Du, C., Coon, M., Sriram, S., & Klaus, S. J. 1998, "Prevention of experimental allergic encephalomyelitis via inhibition of IL-12 signaling and IL-12-mediated Th1 differentiation: an effect of the novel anti-inflammatory drug lisofylline", J.Immunol., vol. 161, no. 12, pp. 7015-7022.

Bright, J. J., Du, C., & Sriram, S. 1999, "Tyrphostin B42 inhibits IL-12-induced tyrosine phosphorylation and activation of Janus kinase-2 and prevents experimental allergic encephalomyelitis", J.Immunol., vol. 162, no. 10, pp. 6255-6262.

Brini, E., Ruffini, F., Bergami, A., Brambilla, E., Dati, G., Greco, B., Cirillo, R., Proudfoot, A. E., Comi, G., Furlan, R., Zaratin, P., & Martino, G. 2009, "Administration of a monomeric CCL2 variant to EAE mice inhibits inflammatory cell recruitment and protects from demyelination and axonal loss", J Neuroimmunol, vol. 209, no. 1-2, pp. 33-39.

Brini, E., Ruffini, F., Bergami, A., Brambilla, E., Dati, G., Greco, B., Cirillo, R., Proudfoot, A. I. E., Furlan, R., Zaratin, P., & Martino, G. 2008, "Administration of an MCP-1 variant to EAE mice prevents inflammatory cell recruitment and protects from demyelination and axonal loss", Journal of Neuroimmunology, vol. 203, no. 2, p. 142.

Brinkman, C. J., Ter Laak, H. J., & Hommes, O. R. 1985, "Modulation of experimental allergic encephalomyelitis in Lewis rats by monoclonal anti-T cell antibodies", J.Neuroimmunol., vol. 7, no. 4, pp. 231-238.

Broberg, E., Setala, N., Roytta, M., Salmi, A., Eralinna, J. P., He, B., Roizman, B., & Hukkanen, V. 2001, "Expression of interleukin-4 but not of interleukin-10 from a replicative herpes simplex virus type 1 viral vector precludes experimental allergic encephalomyelitis", Gene Ther, vol. 8, no. 10, pp. 769-777.

Brocke, S., Piercy, C., Steinman, L., Weissman, I. L., & Veromaa, T. 1999, "Antibodies to CD44 and integrin alpha4, but not L-selectin, prevent central nervous system inflammation and experimental encephalomyelitis by blocking secondary leukocyte recruitment", Proc Natl Acad Sci U S A, vol. 96, no. 12, pp. 6896-6901.

Brod, S. A., Al-Sabbagh, A., Sobel, R. A., Hafler, D. A., & Weiner, H. L. 1991, "Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin antigens: IV. Suppression of chronic relapsing disease in the Lewis rat and strain 13 guinea pig", Ann.Neurol., vol. 29, no. 6, pp. 615-622.

Brod, S. A. & Burns, D. K. 1994, "Suppression of relapsing experimental autoimmune encephalomyelitis in the SJL/J mouse by oral administration of type I interferons", Neurology, vol. 44, no. 6, pp. 1144-1148.

Brod, S. A. & Hood, Z. 2007, "Ingested (oral) SIRS peptide 1-21 inhibits acute EAE by inducing Th2-like cytokines", J.Neuroimmunol., vol. 183, no. 1-2, pp. 89-95.

Brod, S. A. & Hood, Z. M. 2008, "Ingested (oral) alpha-MSH inhibits acute EAE", J.Neuroimmunol., vol. 193, no. 1-2, pp. 106-112.

Brod, S. A., Khan, M., Kerman, R. H., & Pappolla, M. 1995a, "Oral administration of human or murine interferon alpha suppresses relapses and modifies adoptive transfer in experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 58, no. 1, pp. 61-69.

Brod, S. A., Lindsey, J. W., & Wolinsky, J. S. 2000, "Combination therapy with glatiramer acetate (copolymer-1) and a type I interferon (IFN-alpha) does not improve experimental autoimmune encephalomyelitis", Ann.Neurol., vol. 47, no. 1, pp. 127-131.

Brod, S. A., Nelson, L., Jin, R., & Wolinsky, J. S. 1999, "Ingested interferon alpha induces Mx mRNA", Cytokine, vol. 11, no. 7, pp. 492-499.

Brod, S. A., Scott, M., Burns, D. K., & Phillips, J. T. 1995b, "Modification of acute experimental autoimmune encephalomyelitis in the Lewis rat by oral administration of type 1 interferons", J.Interferon Cytokine Res., vol. 15, no. 2, pp. 115-122.

Brodmerkel, C. M., Huber, R., Covington, M., Diamond, S., Hall, L., Collins, R., Leffet, L., Gallagher, K., Feldman, P., Collier, P., Stow, M., Gu, X., Baribaud, F., Shin, N., Thomas, B., Burn, T., Hollis, G., Yeleswaram, S., Solomon, K., Friedman, S., Wang, A., Xue, C. B., Newton, R. C., Scherle, P., & Vaddi, K. 2005, "Discovery and pharmacological characterization of a novel rodent-active CCR2 antagonist, INCB3344", J.Immunol., vol. 175, no. 8, pp. 5370-5378.

Brok, H. P., van, M. M., Blezer, E., Schantz, A., Peritt, D., Treacy, G., Laman, J. D., Bauer, J., & 't Hart, B. A. 2002, "Prevention of experimental autoimmune encephalomyelitis in common marmosets using an anti-IL-12p40 monoclonal antibody", J.Immunol., vol. 169, no. 11, pp. 6554-6563.

Brooks, J. W., Pryce, G., Bisogno, T., Jaggar, S. I., Hankey, D. J., Brown, P., Bridges, D., Ledent, C., Bifulco, M., Rice, A. S., Di, M., V, & Baker, D. 2002, "Arvanil-induced inhibition of spasticity and persistent pain: evidence for therapeutic sites of action different from the vanilloid VR1 receptor and cannabinoid CB(1)/CB(2) receptors", Eur.J.Pharmacol., vol. 439, no. 1-3, pp. 83-92.

Brosnan, C. F., Cammer, W., Norton, W. T., & Bloom, B. R. 1980, "Proteinase inhibitors suppress the development of experimental allergic encephalomyelitis", Nature, vol. 285, no. 5762, pp. 235-237.

Brosnan, C. F., Goldmuntz, E. A., Cammer, W., Factor, S. M., Bloom, B. R., & Norton, W. T. 1985, "Prazosin, an alpha 1-adrenergic receptor antagonist, suppresses experimental autoimmune encephalomyelitis in the Lewis rat", Proc.Natl.Acad.Sci.U.S.A, vol. 82, no. 17, pp. 5915-5919.

Brosnan, C. F., Sacks, H. J., Goldschmidt, R. C., Goldmuntz, E. A., & Norton, W. T. 1986, "Prazosin treatment during the effector stage of disease suppresses experimental autoimmune encephalomyelitis in the Lewis rat", J.Immunol., vol. 137, no. 11, pp. 3451-3456.

Brostoff, S. W. & Mason, D. W. 1984, "Experimental allergic encephalomyelitis: successful treatment in vivo with a monoclonal antibody that recognizes T helper cells", J.Immunol., vol. 133, no. 4, pp. 1938-1942.

Brostoff, S. W. & Mason, D. W. 1986, "The role of lymphocyte subpopulations in the transfer of rat EAE", J.Neuroimmunol., vol. 10, no. 4, pp. 331-340.

Brostoff, S. W. & White, T. M. 1986, "Treatment of clinical experimental allergic encephalomyelitis in the rat with monoclonal antibodies", J.Neuroimmunol., vol. 13, no. 2, pp. 233-240.

Brostoff, S. W., White, T. M., & Powers, J. M. 1988, "Treatment of clinical experimental allergic encephalomyelitis in the rat using fragments and combinations of monoclonal antibodies", J.Neuroimmunol., vol. 17, no. 2, pp. 167-173.

Brucchieri, A. & Grasso, A. M. 1966, "[The immune behavior of animals treated with mycetes. Apropos of yeast therapy in multiple sclerosis]", Acta Neurol.(Napoli), vol. 21, no. 2, pp. 158-162.

Bruck, W., Kaye, J., Fine, T., & Mayk, A. 2007, "Laquinimod modulates inflammation and prevents demyelination in MOG-induced EAE: A novel wet SEM technology showing potential neuroprotective effect", Neurology, vol. 68, no. 12, p. A318.

Brundula, V., Rewcastle, N. B., Metz, L. M., Bernard, C. C., & Yong, V. W. 2002, "Targeting leukocyte MMPs and transmigration: minocycline as a potential therapy for multiple sclerosis", Brain, vol. 125, no. Pt 6, pp. 1297-1308.

Brunmark, C., Runstrom, A., Ohlsson, L., Sparre, B., Brodin, T., Astrom, M., & Hedlund, G. 2002, "The new orally active immunoregulator laquinimod (ABR-215062) effectively inhibits development and relapses of experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 130, no. 1-2, pp. 163-172.

Bucher, A. E., Maccioni, M., Rivero, V. E., Riera, C. M., & Roth, G. A. 1996, "Experimental autoimmune encephalomyelitis: antigen-induced inhibition of biochemical and immunohistological alterations", J.Neurosci.Res., vol. 46, no. 3, pp. 367-374.

Buenafe, A. C. & Bourdette, D. N. 2007, "Lipopolysaccharide pretreatment modulates the disease course in experimental autoimmune encephalomyelitis", Journal of Neuroimmunology.182(1-2)()(pp 32-40), 2007.Date of Publication: Jan 2007. no. 1-2, pp. 32-40.

Buenafe, A. C., Vainiene, M., Celnik, B., Vandenbark, A. A., & Offner, H. 1995, "Analysis of V beta 8.2 CDR3 sequences from spinal cord T cells of Lewis rats vaccinated or treated with TCR V beta 8.2-39-59 peptide", J.Immunol., vol. 155, no. 3, pp. 1556-1564.

Burrows, G. G., Adlard, K. L., Bebo, B. F., Jr., Chang, J. W., Tenditnyy, K., Vandenbark, A. A., & Offner, H. 2000, "Regulation of encephalitogenic T cells with recombinant TCR ligands", J Immunol, vol. 164, no. 12, pp. 6366-6371.

Burrows, G. G., Bebo, B. F., Jr., Adlard, K. L., Vandenbark, A. A., & Offner, H. 1998, "Two-domain MHC class II molecules form stable complexes with myelin basic protein 69-89 peptide that detect and inhibit rat encephalitogenic T cells and treat experimental autoimmune encephalomyelitis", J.Immunol., vol. 161, no. 11, pp. 5987-5996.

Burt, R., Burns, W., Ruvolo, P., Fischer, A., Shiao, C., Guimaraes, A., Barrett, J., & Hess, A. 1995, "Syngeneic bone marrow transplantation eliminates V-beta-8.2 T lymphocytes from the spinal cord of Lewis rats with experimental allergic encephalomyelitis", Journal of Neuroscience Research, vol. 41, no. 4, pp. 526-531.

Burt, R., Padilla, J., Dal Canto, M., & Miller, S. 1996, "Remission of relapsing experimental autoimmune encephalomyelitis by immune ablation and bone marrow transplantation", Blood, vol. 88, no. 10 SUPPL. 1 PART 1-2.

Burt, R., Padilla, J., Dal Canto, M., & Miller, S. 1997, "Reversal of neurologic deficits after bone marrow transplantation in relapsing-experimental autoimmune encephalomyelitis: Effect of disease duration", Journal of the Neurological Sciences, vol. 150, no. SUPPL..

Burt, R. K., Padilla, J., Begolka, W. S., Canto, M. C., & Miller, S. D. 1998, "Effect of disease stage on clinical outcome after syngeneic bone marrow transplantation for relapsing experimental autoimmune encephalomyelitis", Blood, vol. 91, no. 7, pp. 2609-2616.

Butovsky, O., Landa, G., Kunis, G., Ziv, Y., Avidan, H., Greenberg, N., Schwartz, A., Smirnov, I., Pollack, A., Jung, S., & Schwartz, M. 2006, "Induction and blockage of oligodendrogenesis by differently activated microglia in an animal model of multiple sclerosis", J.Clin.Invest, vol. 116, no. 4, pp. 905-915.

Butzkueven, H., Emery, B., Cipriani, T., Marriott, M. P., & Kilpatrick, T. J. 2006, "Endogenous leukemia inhibitory factor production limits autoimmune demyelination and oligodendrocyte loss", GLIA.53(7)()(pp 696-703), 2006.Date of Publication: May 2006. no. 7, pp. 696-703.

Butzkueven, H., Zhang, J. G., Soilu-Hanninen, M., Hochrein, H., Chionh, F., Shipham, K. A., Emery, B., Turnley, A. M., Petratos, S., Ernst, M., Bartlett, P. F., & Kilpatrick, T. J. 2002, "LIF receptor signaling limits immune-mediated demyelination by enhancing oligodendrocyte survival", Nat.Med., vol. 8, no. 6, pp. 613-619.

Bynoe, M. S., Evans, J. T., Viret, C., & Janeway, C. A., Jr. 2003, "Epicutaneous immunization with autoantigenic peptides induces T suppressor cells that prevent experimental allergic encephalomyelitis", Immunity, vol. 19, no. 3, pp. 317-328.

Byrne, F. R., Winters, A., Brankow, D., Hu, S., Juan, T., Steavenson, S., Doellgast, G., Kuchimanchi, K., Brown, H., Anderson, S., Smelt, S., Sullivan, T., Alcorn, D., Tocker, J., Dean, C., Jr., Macmaster, J., Kirchner, J., Buys, J., Manoukian, R., Jiao, E., Zou, X., Campanella, G. S., & Siu, G. 2009, "An antibody to IP-10 is a potent antagonist of cell migration in vitro and in vivo and does not affect disease in several animal models of inflammation", Autoimmunity, vol. 42, no. 3, pp. 171-182.

Cabranes, A., Venderova, K., de, L. E., Fezza, F., Sanchez, A., Mestre, L., Valenti, M., Garcia-Merino, A., Ramos, J. A., Di, M., V, & Fernandez-Ruiz, J. 2005, "Decreased endocannabinoid levels in the brain and beneficial effects of agents activating cannabinoid and/or vanilloid receptors in a rat model of multiple sclerosis", Neurobiol.Dis., vol. 20, no. 2, pp. 207-217.

Cabrelle, A., Dell'Aica, I., Melchiori, L., Carraro, S., Brunetta, E., Niero, R., Scquizzato, E., D'Intino, G., Calza, L., Garbisa, S., & Agostini, C. 2008, "Hyperforin down-regulates effector function of activated T lymphocytes and shows efficacy against Th1-triggered CNS inflammatory-demyelinating disease", J Leukoc Biol, vol. 83, no. 1.

Camelo, S., Iglesias, A. H., Hwang, D., Due, B., Ryu, H., Smith, K., Gray, S. G., Imitola, J., Duran, G., Assaf, B., Langley, B., Khoury, S. J., Stephanopoulos, G., De Girolami, U., Ratan, R. R., Ferrante, R. J., & Dangond, F. 2005, "Transcriptional therapy with the histone deacetylase inhibitor trichostatin A ameliorates experimental autoimmune encephalomyelitis", J Neuroimmunol, vol. 164, no. 1-2.

Cammisuli, S. & Feurer, C. 1984, "The effect of cyclosporin-A and dihydrocyclosporin-D on the therapy and prophylaxis of experimental allergic encephalomyelitis", Prog.Clin.Biol.Res., vol. 146, pp. 415-421.

Cannella, B., Cross, A. H., & Raine, C. S. 1993, "Anti-adhesion molecule therapy in experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 46, no. 1-2, pp. 43-55.

Cannella, B., Gao, Y. L., Brosnan, C., & Raine, C. S. 1996, "IL-10 fails to abrogate experimental autoimmune encephalomyelitis", J.Neurosci.Res., vol. 45, no. 6, pp. 735-746.

Cannella, B., Gaupp, S., Tilton, R. G., & Raine, C. S. 2003, "Differential efficacy of a synthetic antagonist of VLA-4 during the course of chronic relapsing experimental autoimmune encephalomyelitis", J.Neurosci.Res., vol. 71, no. 3, pp. 407-416.

Cannella, B., Hoban, C. J., Gao, Y. L., Garcia-Arenas, R., Lawson, D., Marchionni, M., Gwynne, D., & Raine, C. S. 1998, "The neuregulin, glial growth factor 2, diminishes autoimmune demyelination and enhances remyelination in a chronic relapsing model for multiple sclerosis", Proc.Natl.Acad.Sci.U.S.A, vol. 95, no. 17, pp. 10100-10105.

Cannella, B., Pitt, D., Capello, E., & Raine, C. S. 2000, "Insulin-like growth factor-1 fails to enhance central nervous system myelin repair during autoimmune demyelination", Am.J.Pathol., vol. 157, no. 3, pp. 933-943.

Canonico, P. L., Sortino, M. A., Favit, A., Aleppo, G., & Scapagnini, U. 1993, "Dihydroergocryptine protects from acute experimental allergic encephalomyelitis in the rat", Funct.Neurol., vol. 8, no. 3, pp. 183-188.

Cantorna, M. T., Hayes, C. E., & Deluca, H. F. 1996, "1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis", Proc.Natl.Acad.Sci.U.S.A, vol. 93, no. 15, pp. 7861-7864.

Cantorna, M. T., Humpal-Winter, J., & Deluca, H. F. 1999, "Dietary calcium is a major factor in 1,25-dihydroxycholecalciferol suppression of experimental autoimmune encephalomyelitis in mice", J.Nutr., vol. 129, no. 11, pp. 1966-1971.

Cantorna, M. T., Humpal-Winter, J., & Deluca, H. F. 2000, "In vivo upregulation of interleukin-4 is one mechanism underlying the immunoregulatory effects of 1,25-dihydroxyvitamin D(3)", Arch.Biochem.Biophys., vol. 377, no. 1, pp. 135-138.

Cao, L., Sun, D., Cruz, T., Moscarello, M. A., Ludwin, S. K., & Whitaker, J. N. 2000, "Inhibition of experimental allergic encephalomyelitis in the Lewis rat by paclitaxel", Journal of Neuroimmunology.108(1-2)()(pp 103-111), 2000.Date of Publication: 01 Aug 2000. no. 1-2, pp. 103-111.

Caputo, D., Altamura, C., Bisaccia, G., Ghezzi, A., Manara, F., & Zibetti, A. 1978, "2 [(methylsulfinyl) acetyl] pyridine (Oxisuran): a new immunosuppressive agent in EAE", Boll.Ist.Sieroter.Milan, vol. 57, no. 4, pp. 422-427.

Carlson, R. P., Datko, L. J., O'Neill-Davis, L., & Lewis, A. J. 1986, "Immunomodulating activity of Wy-41,770 (5H-dibenzo[A,D]cyclohepten-5-ylidene) acetic acid", J.Immunopharmacol., vol. 8, no. 2, pp. 205-221.

Cash, E., Minty, A., Ferrara, P., Caput, D., Fradelizi, D., & Rott, O. 1994, "Macrophage-inactivating IL-13 suppresses experimental autoimmune encephalomyelitis in rats", J.Immunol., vol. 153, no. 9, pp. 4258-4267.

Caspary, E. A. & Hughes, D. 1977, "Experimental allergic encephalomyelitis in the guinea pig. Failure to suppress with crude human chorionic gonadotrophin", J.Neurol.Sci., vol. 34, no. 1, pp. 53-62.

Cassiani-Ingoni, R., Muraro, P. A., Magnus, T., Reichert-Scrivner, S., Schmidt, J., Huh, J., Quandt, J. A., Bratincsak, A., Shahar, T., Eusebi, F., Sherman, L. S., Mattson, M. P., Martin, R., & Rao, M. S. 2007, "Disease progression after bone marrow transplantation in a model of multiple sclerosis is associated with chronic microglial and glial progenitor response", J.Neuropathol.Exp.Neurol., vol. 66, no. 7, pp. 637-649.

Castedo, M., Pelletier, L., Rossert, J., Pasquier, R., Villarroya, H., & Druet, P. 1993, "Mercury-induced autoreactive anti-class II T cell line protects from experimental autoimmune encephalomyelitis by the bias of CD8+ antiergotypic cells in Lewis rats", J.Exp.Med., vol. 177, no. 4, pp. 881-889.

Cavaletti, G., Cavalletti, E., Crippa, L., Di, L. E., Oggioni, N., Mazzanti, B., Biagioli, T., Sala, F., Sala, V., Frigo, M., Rota, S., Tagliabue, E., Stanzani, L., Galbiati, S., Rigolio, R., Zoia, C., Tredici, G., Perseghin, P., Dassi, M., Riccio, P., & Lolli, F. 2004a, "Pixantrone (BBR2778) reduces the severity of experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 151, no. 1-2, pp. 55-65.

Cavaletti, G., Perseghin, P., Buscemi, F., Dassi, M., Oggioni, N., Sala, F., Lolli, F., Liuzzi, G. M., Riccio, P., Frattola, L., & Tredici, G. 2001, "Immunomodulating effects of extracorporeal photochemotherapy in rat experimental allergic encephalomyelitis", Int.J.Tissue React., vol. 23, no. 1, pp. 21-31.

Cavaletti, G., Perseghin, P., Dassi, M., Oggioni, N., Sala, F., Braga, M., Lolli, F., Riccio, P., Carlone, G., Zoia, C., Tagliabue, E., Stanzani, L., Galbiati, S., Rigamonti, L., Marmiroli, P., Ferrarese, C., Frattola, L., & Tredici, G. 2004b, "Extracorporeal photochemotherapy reduces the severity of Lewis rat experimental allergic encephalomyelitis through a modulation of the function of peripheral blood mononuclear cells", J.Biol.Regul.Homeost.Agents, vol. 18, no. 1, pp. 9-17.

Ceroni, M., Camana, C., Franciotta, D. M., Savoldi, F., Scelsi, R., & Fumagalli, M. 1988, "Acute experimental allergic encephalitis. Treatment with fungal polysaccharides", Farmaco [Sci.], vol. 43, no. 4, pp. 381-387.

Chabannes, D., Besnier, D. P., & Esnault, V. L. 2002, "Photopheresis affects the course of experimental allergic encephalomyelitis in Lewis rat", Photodermatol.Photoimmunol.Photomed., vol. 18, no. 5, pp. 238-243.

Chabannes, D., Ryffel, B., & Borel, J. F. 1992, "SRI 62-834, a cyclic ether analogue of the phospholipid ET-18-OCH3, displays long-lasting beneficial effect in chronic relapsing experimental allergic encephalomyelitis in the Lewis rat. Comparison with cyclosporin and (Val2)-dihydrocyclosporin effects in clinical, functional and histological studies", J.Autoimmun., vol. 5, no. 2, pp. 199-211.

Chakravarti, S., Sabatos, C. A., Xiao, S., Illes, Z., Cha, E. K., Sobel, R. A., Zheng, X. X., Strom, T. B., & Kuchroo, V. K. 2005, "Tim-2 regulates T helper type 2 responses and autoimmunity", J.Exp.Med., vol. 202, no. 3, pp. 437-444.

Chan, J., Ban, E. J., Chun, K. H., Wang, S., Backstrom, B. T., Bernard, C. C., Toh, B. H., & Alderuccio, F. 2008a, "Transplantation of bone marrow transduced to express self-antigen establishes deletional tolerance and permanently remits autoimmune disease", J Immunol, vol. 181, no. 11, pp. 7571-7580.

Chan, J., Ban, E. J., Chun, K. H., Wang, S., McQualter, J., Bernard, C., Toh, B. H., & Alderuccio, F. 2008b, "Methylprednisolone induces reversible clinical and pathological remission and loss of lymphocyte reactivity to myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis", Autoimmunity, vol. 41, no. 5.

Chaudhary, P., Marracci, G. H., & Bourdette, D. N. 2006, "Lipoic acid inhibits expression of ICAM-1 and VCAM-1 by CNS endothelial cells and T cell migration into the spinal cord in experimental autoimmune encephalomyelitis", J Neuroimmunol, vol. 175, no. 1-2, pp. 87-96.

Chelmicka-Schorr, E., Checinski, M., & Arnason, B. G. 1988, "Sympathectomy augments the severity of experimental allergic encephalomyelitis in rats", Ann.N.Y.Acad.Sci., vol. 540, pp. 707-708.

Chelmicka-Schorr, E., Kwasniewski, M. N., Thomas, B. E., & Arnason, B. G. 1989, "The beta-adrenergic agonist isoproterenol suppresses experimental allergic encephalomyelitis in Lewis rats", J.Neuroimmunol., vol. 25, no. 2-3, pp. 203-207.

Chelmicka-Schorr, E., Wiegmann, K., Wollmann, R., Arnason, B. G., & Kim, D. H. 1998, "Immunoaugmenting effect of FK 506 on experimental allergic encephalomyelitis in Lewis rats", J.Autoimmun., vol. 11, no. 4, pp. 329-334.

Chelmicka-Szorc, E. & Arnason, B. G. 1972, "Partial suppression of experimental allergic encephalomyelitis with heparin", Arch.Neurol., vol. 27, no. 2, pp. 153-158.

Chelmicka-Szorc, E. & Arnason, B. G. 1975, "Suppression of experimental allergic encephalomyelitis in guinea-pigs with poly-L-lysine", Clin.Exp.Immunol., vol. 22, no. 3, pp. 539-545.

Chen, C., Rivera, A., Ron, N., Dougherty, J. P., & Ron, Y. 2001, "A gene therapy approach for treating T-cell-mediated autoimmune diseases", Blood, vol. 97, no. 4, pp. 886-894.

Chen, C. C., Rivera, A., Dougherty, J. P., & Ron, Y. 2004, "Complete protection from relapsing experimental autoimmune encephalomyelitis induced by syngeneic B cells expressing the autoantigen", Blood, vol. 103, no. 12, pp. 4616-4618.

Chen, W., Li, H., Jia, Y., Li, M., Jiang, Z., Lu, M., & Zhang, L. 2007a, "[An expression plasmid encoding recombinant immunotoxin IP10-DT390 suppresses the experimental autoimmune encephalomyelitis]", Sheng Wu Yi Xue Gong.Cheng Xue Za Zhi, vol. 24, no. 5, pp. 1118-1122.

Chen, W., Li, H., Jia, Y., Lv, M., Li, M., Feng, P., Hu, H., & Zhang, L. 2007b, "In vivo administration of plasmid DNA encoding recombinant immunotoxin DT390-IP-10 attenuates experimental autoimmune encephalomyelitis", J.Autoimmun., vol. 28, no. 1, pp. 30-40.

Chen, X., Hu, X., Zou, Y., Pi, R., Wang, T., Zheng, X., Liu, M., Lin, M., Liu, P., & Tao, L. 2009, "Combined treatment with minocycline and prednisone attenuates experimental autoimmune encephalomyelitis in C57 BL/6 mice", Journal of Neuroimmunology.210(1-2)()(pp 22-29), 2009.Date of Publication: 29 May 2009. no. 1-2, pp. 22-29.

Chen, X., Oppenheim, J. J., Winkler-Pickett, R. T., Ortaldo, J. R., & Howard, O. M. 2006a, "Glucocorticoid amplifies IL-2-dependent expansion of functional FoxP3(+)CD4(+)CD25(+) T regulatory cells in vivo and enhances their capacity to suppress EAE", Eur.J.Immunol., vol. 36, no. 8, pp. 2139-2149.

Chen, Y., Kuchroo, V. K., Inobe, J., Hafler, D. A., & Weiner, H. L. 1994, "Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis", Science, vol. 265, no. 5176, pp. 1237-1240.

Chen, Y., Langrish, C. L., McKenzie, B., Joyce-Shaikh, B., Stumhofer, J. S., McClanahan, T., Blumenschein, W., Churakovsa, T., Low, J., Presta, L., Hunter, C. A., Kastelein, R. A., & Cua, D. J. 2006b, "Anti-IL-23 therapy inhibits multiple inflammatory pathways and ameliorates autoimmune encephalomyelitis", J.Clin.Invest, vol. 116, no. 5, pp. 1317-1326.

Cheng, X., Zhao, Z., Ventura, E., Gran, B., Shindler, K. S., & Rostami, A. 2007, "The PD-1/PD-L pathway is up-regulated during IL-12-induced suppression of EAE mediated by IFN-gamma", J.Neuroimmunol., vol. 185, no. 1-2, pp. 75-86.

Chiarugi, A. 2002, "Inhibitors of poly(ADP-ribose) polymerase-1 suppress transcriptional activation in lymphocytes and ameliorate autoimmune encephalomyelitis in rats", Br.J.Pharmacol., vol. 137, no. 6, pp. 761-770.

Chora, A. A., Fontoura, P., Cunha, A., Pais, T. F., Cardoso, S., Ho, P. P., Lee, L. Y., Sobel, R. A., Steinman, L., & Soares, M. P. 2007, "Heme oxygenase-1 and carbon monoxide suppress autoimmune neuroinflammation", J.Clin.Invest, vol. 117, no. 2, pp. 438-447.

Chorny, A., Gonzalez-Rey, E., Ganea, D., & Delgado, M. 2006, "Vasoactive intestinal peptide generates CD4+CD25+ regulatory T cells in vivo: therapeutic applications in autoimmunity and transplantation", Ann.N.Y.Acad.Sci., vol. 1070, pp. 190-195.

Chou, F. C., Chou, C. H., Fritz, R. B., & Kibler, R. F. 1980, "Prevention of experimental allergic encephalomyelitis in Lewis rats with peptide 68-88 of guinea pig myelin basic protein", Ann.Neurol., vol. 7, no. 4, pp. 336-339.

Chow, L. H., Feurer, C., & Borel, J. F. 1988, "Chronic relapsing experimental allergic encephalomyelitis in the Lewis rat: studies on immune regulation", J.Neuroimmunol., vol. 19, no. 4, pp. 329-338.

Chung, D. T., Korn, T., Richard, J., Ruzek, M., Kohm, A. P., Miller, S., Nahill, S., & Oukka, M. 2007, "Anti-thymocyte globulin (ATG) prevents autoimmune encephalomyelitis by expanding myelin antigen-specific Foxp3+ regulatory T cells", Int.Immunol., vol. 19, no. 8, pp. 1003-1010.

Ciusani, E., Gelati, M., Frigerio, S., Pollo, B., Massa, G., Sacerdote, P., Panerai, A. E., & Salmaggi, A. 2001, "Modulation of experimental allergic encephalomyelitis in Lewis rats by administration of a peptide of Fas ligand", J.Autoimmun., vol. 17, no. 4, pp. 273-280.

Claudio, L. & Brosnan, C. F. 1992, "Effects of prazosin on the blood-brain barrier during experimental autoimmune encephalomyelitis", Brain Res., vol. 594, no. 2, pp. 233-243.

Clayton, J. P., Gammon, G. M., Ando, D. G., Kono, D. H., Hood, L., & Sercarz, E. E. 1989, "Peptide-specific prevention of experimental allergic encephalomyelitis. Neonatal tolerance induced to the dominant T cell determinant of myelin basic protein", J.Exp.Med., vol. 169, no. 5, pp. 1681-1691.

Clements, J. M., Cossins, J. A., Wells, G. M., Corkill, D. J., Helfrich, K., Wood, L. M., Pigott, R., Stabler, G., Ward, G. A., Gearing, A. J., & Miller, K. M. 1997, "Matrix metalloproteinase expression during experimental autoimmune encephalomyelitis and effects of a combined matrix metalloproteinase and tumour necrosis factor-alpha inhibitor", J.Neuroimmunol., vol. 74, no. 1-2, pp. 85-94.

Coates, A., Mackay, I. R., & Crawford, M. 1974, "Immune protection against experimental autoimmune encephalomyelitis: optimal conditions and analysis of mechanism", Cell Immunol., vol. 12, no. 3, pp. 370-381.

Columba-Cabezas, S., Griguoli, M., Rosicarelli, B., Magliozzi, R., Ria, F., Serafini, B., & Aloisi, F. 2006, "Suppression of established experimental autoimmune encephalomyelitis and formation of meningeal lymphoid follicles by lymphotoxin beta receptor-Ig fusion protein", J.Neuroimmunol., vol. 179, no. 1-2, pp. 76-86.

Constantin, G., Brocke, S., Izikson, A., Laudanna, C., & Butcher, E. C. 1998, "Tyrphostin AG490, a tyrosine kinase inhibitor, blocks actively induced experimental autoimmune encephalomyelitis", Eur.J.Immunol., vol. 28, no. 11, pp. 3523-3529.

Constantin, G., Laudanna, C., Brocke, S., & Butcher, E. C. 1999, "Inhibition of experimental autoimmune encephalomyelitis by a tyrosine kinase inhibitor", J.Immunol., vol. 162, no. 2, pp. 1144-1149.

Constantinescu, C., Ventura, E., Hilliard, B., & Rostami, A. 1995a, "Effect of Angiotensin Converting Enzyme (ACE) Inhibitor Captopril on Experimental Autoimmune Encephalomyelitis (EAE)", Neurology, vol. 45, no. 4 SUPPL. 4.

Constantinescu, C. S., Hilliard, B., Ventura, E., & Rostami, A. 1997, "Luzindole, a melatonin receptor antagonist, suppresses experimental autoimmune encephalomyelitis", Pathobiology, vol. 65, no. 4, pp. 190-194.

Constantinescu, C. S., Hilliard, B., Ventura, E., Wysocka, M., Showe, L., Lavi, E., Fujioka, T., Scott, P., Trinchieri, G., & Rostami, A. 2001, "Modulation of susceptibility and resistance to an autoimmune model of multiple sclerosis in prototypically susceptible and resistant strains by neutralization of interleukin-12 and interleukin-4, respectively", Clin Immunol, vol. 98, no. 1, pp. 23-30.

Constantinescu, C. S., Ventura, E., Hilliard, B., & Rostami, A. 1995b, "Effects of the angiotensin converting enzyme inhibitor captopril on experimental autoimmune encephalomyelitis", Immunopharmacol Immunotoxicol, vol. 17, no. 3, pp. 471-491.

Constantinescu, C. S., Wysocka, M., Hilliard, B., Ventura, E. S., Lavi, E., Trinchieri, G., & Rostami, A. 1998, "Antibodies against IL-12 prevent superantigen-induced and spontaneous relapses of experimental autoimmune encephalomyelitis", J Immunol, vol. 161, no. 9, pp. 5097-5104.

Correale, J., Olsson, T., Bjork, J., Smedegard, G., Hojeberg, B., & Link, H. 1991, "Sulfasalazine aggravates experimental autoimmune encephalomyelitis and causes an increase in the number of autoreactive T cells", J.Neuroimmunol., vol. 34, no. 2-3, pp. 109-120.

Cowing, C. O. & Rauch, H. C. 1974, "Immunologic responses of guinea pigs treated with phytohemagglutinin", Int.Arch.Allergy Appl.Immunol., vol. 47, no. 3, pp. 440-450.

Craner, M. J., Damarjian, T. G., Liu, S., Hains, B. C., Lo, A. C., Black, J. A., Newcombe, J., Cuzner, M. L., & Waxman, S. G. 2005, "Sodium channels contribute to microglia/macrophage activation and function in EAE and MS", Glia, vol. 49, no. 2, pp. 220-229.

Cretney, E., McQualter, J. L., Kayagaki, N., Yagita, H., Bernard, C. C. A., Grewal, I. S., Ashkenazi, A., & Smyth, M. J. 2005, "TNF-related apoptosis-inducing ligand (TRAIL)/Apo2L suppresses experimental autoimmune encephalomyelitis in mice", Immunology and Cell Biology.83(5)()(pp 511-519), 2005.Date of Publication: Oct 2005. no. 5, pp. 511-519.

Crisi, G. M., Santambrogio, L., Hochwald, G. M., Smith, S. R., Carlino, J. A., & Thorbecke, G. J. 1995, "Staphylococcal enterotoxin B and tumor-necrosis factor-alpha-induced relapses of experimental allergic encephalomyelitis: protection by transforming growth factor-beta and interleukin-10", Eur J Immunol, vol. 25, no. 11, pp. 3035-3040.

Critchfield, J. M., Racke, M. K., Zuniga-Pflucker, J. C., Cannella, B., Raine, C. S., Goverman, J., & Lenardo, M. J. 1994, "T cell deletion in high antigen dose therapy of autoimmune encephalomyelitis", Science, vol. 263, no. 5150, pp. 1139-1143.

Cross, A., Misko, T., Keeling, R., & San, M. 1998, "A catalyst of peroxynitrite decomposition inhibits EAE, indicating a key role for peroxynitrite in CNS inflammatory demyelination", Journal of Neuroimmunology, vol. 90, no. 1.

Cross, A. H., Misko, T. P., Lin, R. F., Hickey, W. F., Trotter, J. L., & Tilton, R. G. 1994, "Aminoguanidine, an inhibitor of inducible nitric oxide synthase, ameliorates experimental autoimmune encephalomyelitis in SJL mice", J.Clin.Invest, vol. 93, no. 6, pp. 2684-2690.

Cross, A. H., San, M., Keeling, R. M., & Karr, R. W. 1999, "CTLA-4-Fc treatment of ongoing EAE improves recovery, but has no effect upon relapse rate. Implications for the mechanisms involved in disease perpetuation", J.Neuroimmunol., vol. 96, no. 2, pp. 144-147.

Cross, A. H., San, M., Stern, M. K., Keeling, R. M., Salvemini, D., & Misko, T. P. 2000, "A catalyst of peroxynitrite decomposition inhibits murine experimental autoimmune encephalomyelitis", J Neuroimmunol, vol. 107, no. 1, pp. 21-28.

Cross, A. H., Girard, T. J., Giacoletto, K. S., Evans, R. J., Keeling, R. M., Lin, R. F., Trotter, J. L., & Karr, R. W. 1995, "Long-term inhibition of murine experimental autoimmune encephalomyelitis using CTLA-4-Fc supports a key role for CD28 costimulation", Journal of Clinical Investigation, vol. 95, no. 6, pp. 2783-2789.

Croxford, J. L., Feldmann, M., Chernajovsky, Y., & Baker, D. 2001, "Different therapeutic outcomes in experimental allergic encephalomyelitis dependent upon the mode of delivery of IL-10: a comparison of the effects of protein, adenoviral or retroviral IL-10 delivery into the central nervous system", J.Immunol., vol. 166, no. 6, pp. 4124-4130.

Croxford, J. L., Pryce, G., Jackson, S. J., Ledent, C., Giovannoni, G., Pertwee, R. G., Yamamura, T., & Baker, D. 2008, "Cannabinoid-mediated neuroprotection, not immunosuppression, may be more relevant to multiple sclerosis", J.Neuroimmunol., vol. 193, no. 1-2, pp. 120-129.

Croxford, J. L., Triantaphyllopoulos, K., Podhajcer, O. L., Feldmann, M., Baker, D., & Chernajovsky, Y. 1998, "Cytokine gene therapy in experimental allergic encephalomyelitis by injection of plasmid DNA-cationic liposome complex into the central nervous system", J.Immunol., vol. 160, no. 10, pp. 5181-5187.

Croxford, J. L., Triantaphyllopoulos, K. A., Neve, R. M., Feldmann, M., Chernajovsky, Y., & Baker, D. 2000, "Gene therapy for chronic relapsing experimental allergic encephalomyelitis using cells expressing a novel soluble p75 dimeric TNF receptor", J.Immunol., vol. 164, no. 5, pp. 2776-2781.

Cua, D. J., Hutchins, B., LaFace, D. M., Stohlman, S. A., & Coffman, R. L. 2001, "Central nervous system expression of IL-10 inhibits autoimmune encephalomyelitis", J Immunol, vol. 166, no. 1, pp. 602-608.

Dahlen, E., Andersson, M., Dawe, K., Tellander, A. C., Brunmark, C., Bjork, A., & Hedlund, G. 2000, "Inhibition of autoimmune disease by the immunomodulator linomide correlates with the ability to activate macrophages", Autoimmunity, vol. 32, no. 3, pp. 199-211.

Dai, L. M., Chen, M. Z., & Xu, S. Y. 1982, "[The therapeutic effect of the Chinese drug Yu-Jin (Curcuma aromatica salisb) on experimental allergic encephalomyelitis of the guinea pig]", Yao Xue.Xue.Bao., vol. 17, no. 9, pp. 692-695.

Dal Canto, R. A., Costa, G., Shaw, M. D., Seroogy, C., Nolan, G. P., & Fathman, C. G. 1998, "Local delivery of cytokines by retrovirally transduced antigen-specific TCR+ hybridoma cells in experimental autoimmune encephalomyelitis", Eur Cytokine Netw., vol. 9, no. 3 Suppl, pp. 83-91.

Danilov, A. I., Jagodic, M., Wiklund, N. P., Olsson, T., & Brundin, L. 2005, "Effects of long term NOS inhibition on disease and the immune system in MOG induced EAE", Nitric.Oxide., vol. 13, no. 3, pp. 188-195.

Danusevich, I. K., Korin, M. M., Nedz'ved', G. K., Shal'kevich, V. B., & Alpatova, A. I. 1975, "[Study of the mechanism of action of tegretol in experimental allergic encephalomyelitis]", Farmakol.Toksikol., vol. 38, no. 2, pp. 210-214.

Dasgupta, S., Roy, A., Jana, M., Hartley, D. M., & Pahan, K. 2007, "Gemfibrozil ameliorates relapsing-remitting experimental autoimmune encephalomyelitis independent of peroxisome proliferator-activated receptor-alpha", Mol.Pharmacol., vol. 72, no. 4, pp. 934-946.

Dasgupta, S., Zhou, Y., Jana, M., Banik, N. L., & Pahan, K. 2003, "Sodium phenylacetate inhibits adoptive transfer of experimental allergic encephalomyelitis in SJL/J mice at multiple steps", J.Immunol., vol. 170, no. 7, pp. 3874-3882.

de Brito, F. B. & Hanahoe, T. H. 1984, "The effects of cyclophosphamide on delayed hypersensitivity in rats", Int.Arch.Allergy Appl.Immunol., vol. 73, no. 1, pp. 92-94.

de Graaf, K. L., Barth, S., Herrmann, M. M., Storch, M. K., Otto, C., Olsson, T., Melms, A., Jung, G., Wiesmuller, K. H., & Weissert, R. 2004, "MHC class II isotype- and allele-specific attenuation of experimental autoimmune encephalomyelitis", J.Immunol., vol. 173, no. 4, pp. 2792-2802.

De Sarno, P., Axtell, R. C., Raman, C., Roth, K. A., Alessi, D. R., & Jope, R. S. 2008, "Lithium prevents and ameliorates experimental autoimmune encephalomyelitis", J Immunol, vol. 181, no. 1.

de Vries, E., Hendriks, J., Alblas, J., van der Pol, S., van Tol, E., & Dijkstra, C. 2004, "Flavonoids are protective in animal models for multiple sclerosis", Immunobiology, vol. 209, no. 4-6, pp. 372-373.

de, L. E., Fernandez-Ruiz, J., Ortega-Gutierrez, S., Cabranes, A., Pryce, G., Baker, D., Lopez-Rodriguez, M., & Ramos, J. A. 2006, "UCM707, an inhibitor of the anandamide uptake, behaves as a symptom control agent in models of Huntington's disease and multiple sclerosis, but fails to delay/arrest the progression of different motor-related disorders", Eur.Neuropsychopharmacol., vol. 16, no. 1, pp. 7-18.

de, L. E., Ligresti, A., Ortar, G., Morera, E., Cabranes, A., Pryce, G., Bifulco, M., Baker, D., Fernandez-Ruiz, J., & Di, M., V 2004, "In vivo pharmacological actions of two novel inhibitors of anandamide cellular uptake", Eur.J.Pharmacol., vol. 484, no. 2-3, pp. 249-257.

De, R., V, Procaccini, C., La, C. A., Chieffi, P., Nicoletti, G. F., Fontana, S., Zappacosta, S., & Matarese, G. 2006, "Leptin neutralization interferes with pathogenic T cell autoreactivity in autoimmune encephalomyelitis", J.Clin.Invest, vol. 116, no. 2, pp. 447-455.

Degano, A. L., Bucher, A. E., & Roth, G. A. 1998, "Suppression of acute experimental allergic encephalomyelitis by intraperitoneal administration of synaptosomal antigens", J.Neurosci.Res., vol. 53, no. 2, pp. 187-194.

Degano, A. L., Ditamo, Y., & Roth, G. A. 2004, "Neuronal antigens modulate the immune response associated with experimental autoimmune encephalomyelitis", Immunol Cell Biol, vol. 82, no. 1, pp. 17-23.

Deguchi, K., Takeuchi, H., Miki, H., Yamada, A., Touge, T., Terada, S., & Nishioka, M. 1990, "[Effects of novel immunosuppressant FK 506 in acute experimental allergic encephalomyelitis]", No To Shinkei, vol. 42, no. 4, pp. 391-397.

Deguchi, K., Takeuchi, H., Miki, H., Yamada, A., Touge, T., Terada, S., & Nishioka, M. 1991, "Effects of FK 506 on acute experimental allergic encephalomyelitis", Transplant.Proc., vol. 23, no. 6, pp. 3360-3362.

Dello, R. C., Polak, P. E., Mercado, P. R., Spagnolo, A., Sharp, A., Murphy, P., Kamal, A., Burrows, F. J., Fritz, L. C., & Feinstein, D. L. 2006, "The heat-shock protein 90 inhibitor 17-allylamino-17-demethoxygeldanamycin suppresses glial inflammatory responses and ameliorates experimental autoimmune encephalomyelitis", J Neurochem, vol. 99, no. 5, pp. 1351-1362.

Deloire, M. S., Touil, T., Brochet, B., Dousset, V., Caille, J. M., & Petry, K. G. 2004, "Macrophage brain infiltration in experimental autoimmune encephalomyelitis is not completely compromised by suppressed T-cell invasion: in vivo magnetic resonance imaging illustration in effective anti-VLA-4 antibody treatment", Mult.Scler., vol. 10, no. 5, pp. 540-548.

Denkinger, C. M., Denkinger, M., Kort, J. J., Metz, C., & Forsthuber, T. G. 2003, "In vivo blockade of macrophage migration inhibitory factor ameliorates acute experimental autoimmune encephalomyelitis by impairing the homing of encephalitogenic T cells to the central nervous system", J.Immunol., vol. 170, no. 3, pp. 1274-1282.

Desai, S. & Barton, R. 1989, "Pharmacological comparison of active and passive experimental allergic encephalomyelitis in the rat", Agents Actions, vol. 27, no. 3-4, pp. 351-355.

Desplat-Jego, S., Creidy, R., Varriale, S., Allaire, N., Luo, Y., Bernard, D., Hahm, K., Burkly, L., & Boucraut, J. 2005, "Anti-TWEAK monoclonal antibodies reduce immune cell infiltration in the central nervous system and severity of experimental autoimmune encephalomyelitis", Clin.Immunol., vol. 117, no. 1, pp. 15-23.

Devaux, B., Enderlin, F., Wallner, B., & Smilek, D. E. 1997, "Induction of EAE in mice with recombinant human MOG, and treatment of EAE with a MOG peptide", J.Neuroimmunol., vol. 75, no. 1-2, pp. 169-173.

Devaux, J., Beeton, C., Beraud, E., & Crest, M. 2004, "Ion channels and clemyelination: basis of a treatment of experimental autoimmune encephalomyelitis (EAE) by potassium channel blockers", Revue Neurologique, vol. 160, no. 5, p. S16-S27.

DeVry, C. G., Valdez, M., Gao, L., Wang, J., Kotsch, K., Volk, H. D., Bechmann, I., Buelow, R., & Iyer, S. 2004, "RDP58, a novel immunomodulatory peptide, ameliorates clinical signs of disease in the Lewis rat model of acute experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 152, no. 1-2, pp. 33-43.

Di, M. R., Khademi, M., Wallstrom, E., Iacobaeus, E., Salvaggio, A., Caracappa, S., Papoian, R., Nicoletti, F., & Olsson, T. 2001a, "Curative effects of recombinant human Interleukin-6 in DA rats with protracted relapsing experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 116, no. 2, pp. 168-177.

Di, M. R., Puglisi, G., Papaccio, G., Nicoletti, A., Patti, F., Reggio, A., Bendtzen, K., & Nicoletti, F. 2001b, "Sodium fusidate (fusidin) ameliorates the course of monophasic experimental allergic encephalomyelitis in the Lewis rat", Mult.Scler., vol. 7, no. 2, pp. 101-104.

Diab, A., Deng, C., Smith, J. D., Hussain, R. Z., Phanavanh, B., Lovett-Racke, A. E., Drew, P. D., & Racke, M. K. 2002, "Peroxisome proliferator-activated receptor-gamma agonist 15-deoxy-Delta(12,14)-prostaglandin J(2) ameliorates experimental autoimmune encephalomyelitis", J Immunol, vol. 168, no. 5, pp. 2508-2515.

Diab, A., Hussain, R. Z., Lovett-Racke, A. E., Chavis, J. A., Drew, P. D., & Racke, M. K. 2004, "Ligands for the peroxisome proliferator-activated receptor-gamma and the retinoid X receptor exert additive anti-inflammatory effects on experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 148, no. 1-2, pp. 116-126.

Diab, A., Michael, L., Wahren, B., Deng, G. M., Bjork, J., Hedlund, G., & Zhu, J. 1998, "Linomide suppresses acute experimental autoimmune encephalomyelitis in Lewis rats by counter-acting the imbalance of pro-inflammatory versus anti-inflammatory cytokines", J.Neuroimmunol., vol. 85, no. 2, pp. 146-154.

Diaz-Bardales, B. M., Novaski, S. M., Goes, A. E., Castro, G. M., Mengel, J., & Santos, L. M. 2001, "Modulation of the severity of experimental autoimmune encephalomyelitis by gammadelta T lymphocytes activated by mycobacterial antigens", Immunol.Invest, vol. 30, no. 3, pp. 245-258.

Diem, R., Sattler, M. B., Merkler, D., Demmer, I., Maier, K., Stadelmann, C., Ehrenreich, H., & Bahr, M. 2005, "Combined therapy with methylprednisolone and erythropoietin in a model of multiple sclerosis", Brain, vol. 128, no. Pt 2, pp. 375-385.

Diem, R. r. d., Hobom, M., Maier, K., Weissert, R., Storch, M. K., Meyer, R., & Baehr, M. 2003, "Methylprednisolone increases neuronal apoptosis during autoimmune CNS inflammation by inhibition of an endogenous neuroprotective pathway", Journal of Neuroscience, vol. 23, no. 18, pp. 6993-7000.

Dietsch, G. N. & Hinrichs, D. J. 1989, "The role of mast cells in the elicitation of experimental allergic encephalomyelitis", J.Immunol., vol. 142, no. 5, pp. 1476-1481.

Dijkstra, C. D., De Groot, C. J., Koetsier, J. C., Matthaei, I., Polman, C. H., & Sminia, T. 1988, "Low-dose cyclosporin A induces relapsing experimental allergic encephalomyelitis in the Lewis rat", Ann.N.Y.Acad.Sci., vol. 540, pp. 549-550.

Dijkstra, C. D., van, d., V, De Groot, C. J., Huitinga, I., Uitdehaag, B. M., Polman, C. H., & Berkenbosch, F. 1994, "Therapeutic effect of the D2-dopamine agonist bromocriptine on acute and relapsing experimental allergic encephalomyelitis", Psychoneuroendocrinology, vol. 19, no. 2, pp. 135-142.

Dijkstra, S., Kooij, G., Verbeek, R., van der Pol, S. M. A., Amor, S., Geisert, J., Dijkstra, C. D., van Noort, J. M., & Vries, H. E. 2008, "Targeting the tetraspanin CD81 blocks monocyte transmigration and ameliorates EAE", Neurobiology of Disease.31(3)()(pp 413-421), 2008.Date of Publication: September 2008. no. 3, pp. 413-421.

DiMartino, M. J., Wolff, C. E., Campbell, G. K., Jr., & Hanna, N. 1988, "Inhibition of experimental allergic encephalomyelitis by a new anti-inflammatory compound--SK&F 86002", Ann.N.Y.Acad.Sci., vol. 540, pp. 578-580.

Dimitrijevic, M., Rauski, A., Radojevic, K., Kosec, D., Stanojevic, S., Pilipovic, I., & Leposavic, G. 2007, "Beta-adrenoceptor blockade ameliorates the clinical course of experimental allergic encephalomyelitis and diminishes its aggravation in adrenalectomized rats", Eur.J.Pharmacol., vol. 577, no. 1-3, pp. 170-182.

Ding, M., Zhang, M., Wong, J. L., Rogers, N. E., Ignarro, L. J., & Voskuhl, R. R. 1998, "Antisense knockdown of inducible nitric oxide synthase inhibits induction of experimental autoimmune encephalomyelitis in SJL/J mice", J.Immunol., vol. 160, no. 6, pp. 2560-2564.

Driscoll, B. F., Kies, M. W., & Alvord, E. C., Jr. 1974, "Successful treatment of experimental allergic encephalomyelitis (EAE) in guinea pigs with homologous myelin basic protein", J.Immunol., vol. 112, no. 1, pp. 392-397.

Driscoll, B. F., Kies, M. W., & Alvord, E. C., Jr. 1976, "Protection against experimental allergic encephalomyelitis with peptides derived from myelin basic protein: presence of intact encephalitogenic site is essential", J.Immunol., vol. 117, no. 1, pp. 110-114.

Driscoll, B. F., Kies, M. W., & Alvord, E. C., Jr. 1982, "Suppression of acute experimental allergic encephalomyelitis in guinea pigs by prior transfer of suboptimal numbers of EAE-effector cells: induction of chronic EAE in whole tissue-sensitized guinea pigs", J.Immunol., vol. 128, no. 2, pp. 635-638.

Du, C., Cooper, J. C., Klaus, S. J., & Sriram, S. 2000, "Amelioration of CR-EAE with lisofylline: effects on mRNA levels of IL-12 and IFN-gamma in the CNS", J.Neuroimmunol., vol. 110, no. 1-2, pp. 13-19.

Du, C., Khalil, M. W., & Sriram, S. 2001, "Administration of dehydroepiandrosterone suppresses experimental allergic encephalomyelitis in SJL/J mice", J.Immunol., vol. 167, no. 12, pp. 7094-7101.

Duckers, H. J., Muller, H. J., Verhaagen, J., Nicolay, K., & Gispen, W. H. 1997, "Longitudinal in vivo magnetic resonance imaging studies in experimental allergic encephalomyelitis: effect of a neurotrophic treatment on cortical lesion development", Neuroscience, vol. 77, no. 4, pp. 1163-1173.

Duckers, H. J., van Dokkum, R. P., Verhaagen, J., Lopes da Silva, F. H., & Gispen, W. H. 1996, "Functional and neurophysiological evidence of the efficacy of trophic pharmacotherapy using an adrenocorticotrophic hormone4-9 analog in experimental allergic encephalomyelitis, an animal model of multiple sclerosis", Neuroscience, vol. 71, no. 2, pp. 507-521.

Duckers, H. J., van Dokkum, R. P., Verhaagen, J., van Luijtelaar, E. L., Coenen, A. M., Lopes da Silva, F. H., & Gispen, W. H. 1998, "Neurotrophic ACTH4-9 analogue therapy normalizes electroencephalographic alterations in chronic experimental allergic encephalomyelitis", Eur.J.Neurosci., vol. 10, no. 12, pp. 3709-3720.

Duong, T. T., Finkelman, F. D., Singh, B., & Strejan, G. H. 1994, "Effect of anti-interferon-gamma monoclonal antibody treatment on the development of experimental allergic encephalomyelitis in resistant mouse strains", J.Neuroimmunol., vol. 53, no. 1, pp. 101-107.

Duong, T. T., St Louis, J., Gilbert, J. J., Finkelman, F. D., & Strejan, G. H. 1992, "Effect of anti-interferon-gamma and anti-interleukin-2 monoclonal antibody treatment on the development of actively and passively induced experimental allergic encephalomyelitis in the SJL/J mouse", J Neuroimmunol, vol. 36, no. 2-3, pp. 105-115.

Duplan, V., Beriou, G., Heslan, J. M., Bruand, C., Dutartre, P., Mars, L. T., Liblau, R. S., Cuturi, M. C., & Saoudi, A. 2006, "LF 15-0195 treatment protects against central nervous system autoimmunity by favoring the development of Foxp3-expressing regulatory CD4 T cells", J.Immunol., vol. 176, no. 2, pp. 839-847.

Duplan, V., Dutartre, P., Mars, L. T., Liblau, R. S., Druet, P., & Saoudi, A. 2003, "LF 15-0195 inhibits the development of rat central nervous system autoimmunity by inducing long-lasting tolerance in autoreactive CD4 T cells", J.Immunol., vol. 170, no. 4, pp. 2179-2185.

Duplan, V., Stennevin, A., Ipinazar, K., Druet, P., Dutartre, P., & Saoudi, A. 2002, "Beneficial effect of the immunosuppressant LF 15-0195 on passively induced rat experimental autoimmune encephalomyelitis", Transplant.Proc., vol. 34, no. 7, pp. 2966-2969.

Edling, A. E., Choksi, S., Huang, Z., & Korngold, R. 2001, "Effect of a cyclic heptapeptide based on the human CD4 domain 1 CC' loop region on murine experimental allergic encephalomyelitis: inhibition of both primary and secondary responses", J.Neuroimmunol., vol. 112, no. 1-2, pp. 115-128.

Edling, A. E., Choksi, S., Huang, Z., & Korngold, R. 2002, "An organic CD4 inhibitor reduces the clinical and pathological symptoms of acute experimental allergic encephalomyelitis", J.Autoimmun., vol. 18, no. 2, pp. 169-179.

Einstein, E. R., Chao, L. P., & Csejtey, J. 1972, "Suppression of experimental allergic encephalomyelitis by chemically modified encephalitogen", Immunochemistry., vol. 9, no. 10, pp. 1013-1019.

Einstein, O., Fainstein, N., Vaknin, I., Mizrachi-Kol, R., Reihartz, E., Grigoriadis, N., Lavon, I., Baniyash, M., Lassmann, H., & Ben Hur, T. 2007, "Neural precursors attenuate autoimmune encephalomyelitis by peripheral immunosuppression", Ann.Neurol., vol. 61, no. 3, pp. 209-218.

Einstein, O., Grigoriadis, N., Mizrachi-Kol, R., Reinhartz, E., Polyzoidou, E., Lavon, I., Milonas, I., Karussis, D., Abramsky, O., & Ben-Hur, T. 2006, "Transplanted neural precursor cells reduce brain inflammation to attenuate chronic experimental autoimmune encephalomyelitis", Exp.Neurol., vol. 198, no. 2, pp. 275-284.

Einstein, O., Karussis, D., Grigoriadis, N., Mizrachi-Kol, R., Reinhartz, E., Abramsky, O., & Ben Hur, T. 2003, "Intraventricular transplantation of neural precursor cell spheres attenuates acute experimental allergic encephalomyelitis", Molecular and Cellular Neuroscience.24(4)()(pp 1074-1082), 2003.Date of Publication: Dec 2003. no. 4, pp. 1074-1082.

El Gouhary, I., Mohamed, A., Suleiman, S., & Benghuzzi, H. 2005, "Comparison of the amelioration effects of two enzyme inducers on the inflammatory process of experimental allergic encephalitis (EAE) using immunohistochemical technique", Biomed Sci Instrum, vol. 41, pp. 376-381.

Elkin, R., Lyman, W. D., Brosnan, C. F., & Bornstein, M. B. 1987, "Delta-9 Tetrahydrocannabinol A Novel Treatment for Inflammatory Demyelination", Federation Proceedings, vol. 46, no. 4.

Elliott, E. A., Cofiell, R., Wilkins, J. A., Raine, C. S., Matis, L. A., & Mueller, J. P. 1997, "Immune tolerance mediated by recombinant proteolipid protein prevents experimental autoimmune encephalomyelitis", Journal of Neuroimmunology.79(1)()(pp 1-11), 1997.Date of Publication: Oct 1997. no. 1, pp. 1-11.

Elliott, E. A., McFarland, H. I., Nye, S. H., Cofiell, R., Wilson, T. M., Wilkins, J. A., Squinto, S. P., Matis, L. A., & Mueller, J. P. 1996, "Treatment of experimental encephalomyelitis with a novel chimeric fusion protein of myelin basic protein and proteolipid protein", J.Clin.Invest, vol. 98, no. 7, pp. 1602-1612.

Elliott, G. A., Gibbons, A. J., & Greig, M. E. 1973a, "A comparison of the effects of melengestrol acetate with a combination of hydrocortisone acetate and medroxyprogesterone acetate and with other steroids in the treatment of experimental alleric encephalomyelitis in Wistar rats", Acta Neuropathol.(Berl), vol. 23, no. 2, pp. 95-104.

Elliott, G. A., Gibbons, A. J., & Greig, M. E. 1973b, "Therapeutic effects of melengestrol acetate, cyclophosphamide and palmitoyl cytarabine in established experimental allergic encephalomyelitis of rats", Arch.Int.Pharmacodyn.Ther., vol. 204, no. 1, pp. 62-76.

Ellison, G. W. & Waksman, B. H. 1970, "Role of the thymus in tolerance. IX. Inhibition of experimental autoallergic encephalomyelitis by intrathymic injection of encephalitogen", J.Immunol., vol. 105, no. 2, pp. 322-326.

Elyaman, W., Bradshaw, E. M., Wang, Y., Oukka, M., Kivisakk, P., Chiba, S., Yagita, H., & Khoury, S. J. 2007, "JAGGED1 and delta1 differentially regulate the outcome of experimental autoimmune encephalomyelitis", J.Immunol., vol. 179, no. 9, pp. 5990-5998.

Emerson, M. R., Biswas, S., & LeVine, S. M. 2001, "Cuprizone and piperonyl butoxide, proposed inhibitors of T-cell function, attenuate experimental allergic encephalomyelitis in SJL mice", J.Neuroimmunol., vol. 119, no. 2, pp. 205-213.

Emerson, M. R., Orentas, D. M., Lynch, S. G., & LeVine, S. M. 2002, "Activation of histamine H2 receptors ameliorates experimental allergic encephalomyelitis", Neuroreport, vol. 13, no. 11, pp. 1407-1410.

Endoh, M. & Tabira, T. 1990, "Effect of thymic hormones on induction of experimental allergic encephalomyelitis in old mice", Tohoku J Exp Med, vol. 161, no. 4, pp. 303-309.

Engelhardt, B., Diamantstein, T., & Wekerle, H. 1989, "Immunotherapy of experimental autoimmune encephalomyelitis (EAE): differential effect of anti-IL-2 receptor antibody therapy on actively induced and T-line mediated EAE of the Lewis rat", J.Autoimmun., vol. 2, no. 1, pp. 61-73.

Englert, D. & Hempel, K. 1981, "Suppression of experimental allergic encephalomyelitis by transfer of lymph node cells from Lewis rats pretreated with complete Freund's adjuvant", Int.Arch.Allergy Appl.Immunol., vol. 66, no. 3, pp. 326-331.

Ephrem, A., Chamat, S., Miquel, C., Fisson, S., Mouthon, L., Caligiuri, G., Delignat, S., Elluru, S., Bayry, J., Lacroix-Desmazes, S., Cohen, J. L., Salomon, B. L., Kazatchkine, M. D., Kaveri, S. V., & Misra, N. 2008, "Expansion of CD4+CD25+ regulatory T cells by intravenous immunoglobulin: a critical factor in controlling experimental autoimmune encephalomyelitis", Blood, vol. 111, no. 2, pp. 715-722.

Eralinna, J., Setala, N., Roytta, M., Soppi, E., Salmi, A., Panelius, M., & Salonen, R. 1997, "Anti-oxidant therapy with tirilazad mesylate reduces autoimmune CNS demyelination in experimental allergic encephalomyelitis (EAE)", Journal of the Neurological Sciences, vol. 150, no. SUPPL..

Eralinna, J., Toytta, M., Hukkanen, V., Zinhu, D., Salmi, A., & Salonen, R. 1998, "Selective downregulation of Th1 response by Linomide reduces autoimmunity but increase susceptibility to viral infection in BALB/c and SJL mice", Journal of Neuroimmunology, vol. 88, no. 1-2, pp. 165-176.

Esquifino, A. I., Cano, P., Jimenez-Ortega, V., Fernandez-Mateos, M. P., & Cardinali, D. P. 2007, "Immune response after experimental allergic encephalomyelitis in rats subjected to calorie restriction", J.Neuroinflammation., vol. 4, p. 6.

Eylar, E. H., Jackson, J., Rothenberg, B., & Brostoff, S. W. 1972, "Suppression of the immune response: reversal of the disease state with antigen in allergic encephalomyelitis", Nature, vol. 236, no. 5341, pp. 74-76.

Eylar, E. H., Jackson, J. J., & Kniskern, P. J. 1979, "Suppression and reversal of allergic encephalomyelitis in rhesus monkeys with basic protein and peptides", Neurochem.Res., vol. 4, no. 2, pp. 249-258.

Ezendam, J. & van Loveren, H. 2008, "Lactobacillus casei Shirota administered during lactation increases the duration of autoimmunity in rats and enhances lung inflammation in mice", Br J Nutr, vol. 99, no. 1, pp. 83-90.

Falk, G. A., Kies, M. W., & Alvord, E. C., Jr. 1969, "Passive transfer of experimental allergic encephalomyelitis: mechanisms of suppression", J.Immunol., vol. 103, no. 6, pp. 1248-1253.

Falk, K., Rotzschke, O., Santambrogio, L., Dorf, M. E., Brosnan, C., & Strominger, J. L. 2000, "Induction and suppression of an autoimmune disease by oligomerized T cell epitopes: enhanced in vivo potency of encephalitogenic peptides", J Exp Med, vol. 191, no. 4, pp. 717-730.

Faunce, D. E., Terajewicz, A., & Stein-Streilein, J. 2004, "Cutting edge: in vitro-generated tolerogenic APC induce CD8+ T regulatory cells that can suppress ongoing experimental autoimmune encephalomyelitis", J.Immunol., vol. 172, no. 4, pp. 1991-1995.

Feinstein, D. L., Galea, E., Gavrilyuk, V., Brosnan, C. F., Whitacre, C. C., Dumitrescu-Ozimek, L., Landreth, G. E., Pershadsingh, H. A., Weinberg, G., & Heneka, M. T. 2002, "Peroxisome proliferator-activated receptor-gamma agonists prevent experimental autoimmune encephalomyelitis", Ann.Neurol., vol. 51, no. 6, pp. 694-702.

Fernandez, M., Giuliani, A., Pirondi, S., D'Intino, G., Giardino, L., Aloe, L., Levi-Montalcini, R., & Calza, L. 2004, "Thyroid hormone administration enhances remyelination in chronic demyelinating inflammatory disease", Proc.Natl.Acad.Sci.U.S.A, vol. 101, no. 46, pp. 16363-16368.

Feurer, C., Chow, L. H., & Borel, J. F. 1988, "Preventive and therapeutic effects of cyclosporin and valine2-dihydro-cyclosporin in chronic relapsing experimental allergic encephalomyelitis in the Lewis rat", Immunology, vol. 63, no. 2, pp. 219-223.

Field, E. J. 1967, "Effect of imuran (azathioprine) on susceptibility of guinea pigs to allergic encephalomyelitis", Arch.Int.Pharmacodyn.Ther., vol. 165, no. 1, pp. 138-141.

Field, E. J. 1969, "Antilymphocytic serum in experimental allergic encephalomyelitis", Br.Med.J., vol. 3, no. 5673, pp. 758-760.

Fife, B. T., Kennedy, K. J., Paniagua, M. C., Lukacs, N. W., Kunkel, S. L., Luster, A. D., & Karpus, W. J. 2001, "CXCL10 (IFN-gamma-inducible protein-10) control of encephalitogenic CD4+ T cell accumulation in the central nervous system during experimental autoimmune encephalomyelitis", J Immunol, vol. 166, no. 12, pp. 7617-7624.

Filipp, G., Zimmerman, G., & Biro, G. 1981, "Suppression of experimental allergic encephalomyelitis by previous intracardial application of hot-labelled basic myelin protein", Allergologia et Immunopathologia.9(3)()(pp 229-232), 1981.Date of Publication: 1981. no. 3, pp. 229-232.

Fischer, W. & Muller, J. 1970, "[The suppression of experimental allergic encephalomyelitis by heterologous antilymphocyte serum and antimetabolites]", Acta Biol.Med.Ger, vol. 25, no. 1, pp. 197-200.

Flanagan, E. M., Erickson, J. B., Viveros, O. H., Chang, S. Y., & Reinhard, J. 1995, "Neurotoxin quinolinic acid is selectively elevated in spinal cords of rats with experimental allergic encephalomyelitis", Journal of Neurochemistry.64(3)()(pp 1192-1196), 1995.Date of Publication: Mar 1995. no. 3, pp. 1192-1196.

Floris, S., Blezer, E. L., Schreibelt, G., Dopp, E., van der Pol, S. M., Schadee-Eestermans, I. L., Nicolay, K., Dijkstra, C. D., & de Vries, H. E. 2004, "Blood-brain barrier permeability and monocyte infiltration in experimental allergic encephalomyelitis: a quantitative MRI study", Brain, vol. 127, no. Pt 3, pp. 616-627.

Floris, S., Ruuls, S. R., Wierinckx, A., van der Pol, S. M., Dopp, E., van der Meide, P. H., Dijkstra, C. D., & de Vries, H. E. 2002, "Interferon-beta directly influences monocyte infiltration into the central nervous system", J Neuroimmunol, vol. 127, no. 1-2, pp. 69-79.

Folcik, V. A., Smith, T., O'Bryant, S., Kawczak, J. A., Zhu, B., Sakurai, H., Kajiwara, A., Staddon, J. M., Glabinski, A., Chernosky, A. L., Tani, M., Johnson, J. M., Tuohy, V. K., Rubin, L. L., & Ransohoff, R. M. 1999, "Treatment with BBB022A or rolipram stabilizes the blood-brain barrier in experimental autoimmune encephalomyelitis: an additional mechanism for the therapeutic effect of type IV phosphodiesterase inhibitors", J.Neuroimmunol., vol. 97, no. 1-2, pp. 119-128.

Foster, C. A., Howard, L. M., Schweitzer, A., Persohn, E., Hiestand, P. C., Balatoni, B., Reuschel, R., Beerli, C., Schwartz, M., & Billich, A. 2007, "Brain penetration of the oral immunomodulatory drug FTY720 and its phosphorylation in the central nervous system during experimental autoimmune encephalomyelitis: consequences for mode of action in multiple sclerosis", J.Pharmacol.Exp.Ther., vol. 323, no. 2, pp. 469-475.

Foster, C. A., Mechtcheriakova, D., Storch, M. K., Balatoni, B., Howard, L. M., Bornancin, F., Wlachos, A., Sobanov, J., Kinnunen, A., & Baumruker, T. 2009, "FTY720 rescue therapy in the dark agouti rat model of experimental autoimmune encephalomyelitis: Expression of central nervous system genes and reversal of blood-brain-barrier damage", Brain Pathology.19(2)()(pp 254-266), 2009.Date of Publication: April 2009. no. 2, pp. 254-266.

Foster, C. & Mechtcheriakova, D. 2008, "Effects of FTY720 rescue therapy on active inflammation, myelin damage and repair in the DA rat model of experimental autoimmune encephalomyelitis", Neurology, vol. 70, no. 11, Suppl. 1.

Franco, A., Southwood, S., Arrhenius, T., Kuchroo, V. K., Grey, H. M., Sette, A., & Ishioka, G. Y. 1994, "T cell receptor antagonist peptides are highly effective inhibitors of experimental allergic encephalomyelitis", Eur.J.Immunol., vol. 24, no. 4, pp. 940-946.

Fredane, L. M., Hashim, G. A., & McCabe, R. E. 1983, "The effect of cyclosporine on lymphocyte subsets in experimental allergic encephalomyelitis: Functional loss of disease-suppressing cells in vivo", Transplantation Proceedings.15(4 SUPPL.1-2)()(pp 2909-2913), 1983.Date of Publication: 1983. no. 4 SUPPL. 1-2, pp. 2909-2913.

Freire-Garabal, M., Nunez, M. J., Balboa, J., Garcia-Vallejo, L. A., Argibay, S., Rodrigo, E., & Rey-Mendez, M. 2003, "Administration of the 5-hydroxytryptamine(1A) receptor antagonist WAY100635 suppresses acute experimental allergic encephalomyelitis in Lewis rats", Neurosci.Lett., vol. 342, no. 1-2, pp. 33-36.

Frenkel, D., Puckett, L., Yang, K., Peron, J. P., & Weiner, H. 2007, "Nasal MOG (35-55) reduces disease progression and axonal damage in a model of chronic progressive EAE", Neurology, vol. 68, no. 12, Suppl. 1.

Fretland, D. J., Widomski, D. L., Shone, R. L., Levin, S., & Gaginella, T. S. 1991, "Effect of the leukotriene B4 receptor antagonist, SC-41930, on experimental allergic encephalomyelitis (EAE) in the guinea pig", Agents Actions, vol. 34, no. 1-2, pp. 172-174.

Friese, M. A., Craner, M. J., Etzensperger, R., Vergo, S., Wemmie, J. A., Welsh, M. J., Vincent, A., & Fugger, L. 2007, "Acid-sensing ion channel-1 contributes to axonal degeneration in autoimmune inflammation of the central nervous system", Nat.Med., vol. 13, no. 12, pp. 1483-1489.

Frost, H. & Swanborg, R. H. 1980, "Suppression of experimental allergic encephalomyelitis with thoracic duct lymphocytes", Int.Arch.Allergy Appl.Immunol., vol. 63, no. 2, pp. 153-158.

Fu, Y. F., Zhu, Y. N., Ni, J., Zhong, X. G., Tang, W., Re, Y. D., Shi, L. P., Wan, J., Yang, Y. F., Yuan, C., Nan, F. J., Lawson, B. R., & Zuo, J. P. 2006a, "A reversible S-adenosyl-L-homocysteine hydrolase inhibitor ameliorates experimental autoimmune encephalomyelitis by inhibiting T cell activation", J.Pharmacol.Exp.Ther., vol. 319, no. 2, pp. 799-808.

Fu, Y. F., Zhu, Y. N., Ni, J., Zhong, X. G., Tang, W., Zhou, R., Zhou, Y., Dong, J. R., He, P. L., Wan, H., Li, Y. C., Yang, Y. F., & Zuo, J. P. 2006b, "(5R)-5-hydroxytriptolide (LLDT-8), a novel triptolide derivative, prevents experimental autoimmune encephalomyelitis via inhibiting T cell activation", J.Neuroimmunol., vol. 175, no. 1-2, pp. 142-151.

Fujino, M., Funeshima, N., Kitazawa, Y., Kimura, H., Amemiya, H., Suzuki, S., & Li, X. K. 2003, "Amelioration of experimental autoimmune encephalomyelitis in Lewis rats by FTY720 treatment", J.Pharmacol.Exp.Ther., vol. 305, no. 1, pp. 70-77.

Fukumoto, N., Shimaoka, T., Fujimura, H., Sakoda, S., Tanaka, M., Kita, T., & Yonehara, S. 2004, "Critical roles of CXC chemokine ligand 16/scavenger receptor that binds phosphatidylserine and oxidized lipoprotein in the pathogenesis of both acute and adoptive transfer experimental autoimmune encephalomyelitis", J Immunol, vol. 173, no. 3, pp. 1620-1627.

Fuller, K. A., Pearl, D., & Whitacre, C. C. 1990, "Oral tolerance in experimental autoimmune encephalomyelitis: serum and salivary antibody responses", J.Neuroimmunol., vol. 28, no. 1, pp. 15-26.

Furlan, R., Bergami, A., Brambilla, E., Butti, E., De Simoni, M. G., Campagnoli, M., Marconi, P., Comi, G., & Martino, G. 2007, "HSV-1-mediated IL-1 receptor antagonist gene therapy ameliorates MOG(35-55)-induced experimental autoimmune encephalomyelitis in C57BL/6 mice", Gene Ther, vol. 14, no. 1, pp. 93-98.

Furlan, R., Bergami, A., Cantarella, D., Brambilla, E., Taniguchi, M., Dellabona, P., Casorati, G., & Martino, G. 2003, "Activation of invariant NKT cells by alphaGalCer administration protects mice from MOG35-55-induced EAE: critical roles for administration route and IFN-gamma", Eur.J.Immunol., vol. 33, no. 7, pp. 1830-1838.

Furlan, R., Brambilla, E., Ruffini, F., Poliani, P. L., Bergami, A., Marconi, P. C., Franciotta, D. M., Penna, G., Comi, G., Adorini, L., & Martino, G. 2001a, "Intrathecal delivery of IFN-gamma protects C57BL/6 mice from chronic-progressive experimental autoimmune encephalomyelitis by increasing apoptosis of central nervous system-infiltrating lymphocytes", J.Immunol., vol. 167, no. 3, pp. 1821-1829.

Furlan, R., Kurne, A., Bergami, A., Brambilla, E., Maucci, R., Gasparini, L., Butti, E., Comi, G., Ongini, E., & Martino, G. 2004, "A nitric oxide releasing derivative of flurbiprofen inhibits experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 150, no. 1-2, pp. 10-19.

Furlan, R., Martino, G., Galbiati, F., Poliani, P. L., Smiroldo, S., Bergami, A., Desina, G., Comi, G., Flavell, R., Su, M. S., & Adorini, L. 1999, "Caspase-1 regulates the inflammatory process leading to autoimmune demyelination", Journal of Immunology.163(5)()(pp 2403-2409), 1999.Date of Publication: 01 Sep 1999. no. 5, pp. 2403-2409.

Furlan, R., Poliani, P. L., Galbiati, F., Bergami, A., Grimaldi, L. M., Comi, G., Adorini, L., & Martino, G. 1998, "Central nervous system delivery of interleukin 4 by a nonreplicative herpes simplex type 1 viral vector ameliorates autoimmune demyelination", Hum.Gene Ther., vol. 9, no. 17, pp. 2605-2617.

Furlan, R., Poliani, P. L., Marconi, P. C., Bergami, A., Ruffini, F., Adorini, L., Glorioso, J. C., Comi, G., & Martino, G. 2001b, "Central nervous system gene therapy with interleukin-4 inhibits progression of ongoing relapsing-remitting autoimmune encephalomyelitis in Biozzi AB/H mice", Gene Ther., vol. 8, no. 1, pp. 13-19.

Galazka, G., Jurewicz, A., Orlowski, W., Stasiolek, M., Brosnan, C. F., Raine, C. S., & Selmaj, K. 2007, "EAE tolerance induction with Hsp70-peptide complexes depends on H60 and NKG2D activity", J.Immunol., vol. 179, no. 7, pp. 4503-4512.

Galazka, G., Stasiolek, M., Walczak, A., Jurewicz, A., Zylicz, A., Brosnan, C. F., Raine, C. S., & Selmaj, K. W. 2006, "Brain-derived heat shock protein 70-peptide complexes induce NK cell-dependent tolerance to experimental autoimmune encephalomyelitis", J Immunol, vol. 176, no. 3, pp. 1588-1599.

Galazka, G., Walczak, A., Berkowicz, T., & Selmaj, K. 2001, "Effect of Hsp70-peptide complexes generated in vivo on modulation EAE", Adv.Exp.Med.Biol., vol. 495, pp. 227-230.

Galle, P., Jensen, L., Andersson, C., Cuzzocrea, S., Di Paola, R., Nicoletti, F., Svenson, M., Bendtzen, K., Thomsen, A. R., & Hansen, M. B. 2007, "Vaccination with IL-6 analogues induces autoantibodies to IL-6 and influences experimentally induced inflammation", Int.Immunopharmacol., vol. 7, no. 13, pp. 1704-1713.

Garay, L., Deniselle, M. C., Lima, A., Roig, P., & De Nicola, A. F. 2007, "Effects of progesterone in the spinal cord of a mouse model of multiple sclerosis", J.Steroid Biochem.Mol.Biol., vol. 107, no. 3-5, pp. 228-237.

Garcion, E., Sindji, L., Nataf, S., Brachet, P., Darcy, F., & Montero-Menei, C. N. 2003, "Treatment of experimental autoimmune encephalomyelitis in rat by 1,25-dihydroxyvitamin D3 leads to early effects within the central nervous system", Acta Neuropathol.(Berl), vol. 105, no. 5, pp. 438-448.

Garin, T., Rubinstein, A., Grigoriadis, N., Nedvetzki, S., Abramsky, O., Mizrachi-Koll, R., Hand, C., Naor, D., & Karussis, D. 2007, "CD44 variant DNA vaccination with virtual lymph node ameliorates experimental autoimmune encephalomyelitis through the induction of apoptosis", J.Neurol.Sci., vol. 258, no. 1-2, pp. 17-26.

Garren, H., Ruiz, P. J., Watkins, T. A., Fontoura, P., Nguyen, L. T., Estline, E. R., Hirschberg, D. L., & Steinman, L. 2001, "Combination of gene delivery and DNA vaccination to protect from and reverse Th1 autoimmune disease via deviation to the Th2 pathway", Immunity., vol. 15, no. 1, pp. 15-22.

Gaur, A., Boehme, S. A., Chalmers, D., Crowe, P. D., Pahuja, A., Ling, N., Brocke, S., Steinman, L., & Conlon, P. J. 1997, "Amelioration of relapsing experimental autoimmune encephalomyelitis with altered myelin basic protein peptides involves different cellular mechanisms", J Neuroimmunol, vol. 74, no. 1-2, pp. 149-158.

Gaur, A., Fathman, C. G., Steinman, L., & Brocke, S. 1993, "SEB induced anergy: modulation of immune response to T cell determinants of myoglobin and myelin basic protein", J.Immunol., vol. 150, no. 7, pp. 3062-3069.

Gaur, A., Wiers, B., Liu, A., Rothbard, J., & Fathman, C. G. 1992, "Amelioration of autoimmune encephalomyelitis by myelin basic protein synthetic peptide-induced anergy", Science, vol. 258, no. 5087, pp. 1491-1494.

Gautam, A. M. 1995, "Self and non-self peptides treat autoimmune encephalomyelitis: T cell anergy or competition for major histocompatibility complex class II binding?", Eur.J.Immunol., vol. 25, no. 7, pp. 2059-2063.

Gautam, A. M. & Glynn, P. 1990, "Competition between foreign and self proteins in antigen presentation. Ovalbumin can inhibit activation of myelin basic protein-specific T cells", J.Immunol., vol. 144, no. 4, pp. 1177-1180.

Gautam, A. M., Pearson, C. I., Sinha, A. A., Smilek, D. E., Steinman, L., & McDevitt, H. O. 1992, "Inhibition of experimental autoimmune encephalomyelitis by a nonimmunogenic non-self peptide that binds to I-Au", J.Immunol., vol. 148, no. 10, pp. 3049-3054.

Genain, C. P., Gritz, L., Joshi, N., Panicali, D., Davis, R. L., Whitaker, J. N., Letvin, N. L., & Hauser, S. L. 1997, "Inhibition of allergic encephalomyelitis in marmosets by vaccination with recombinant vaccinia virus encoding for myelin basic protein", J.Neuroimmunol., vol. 79, no. 2, pp. 119-128.

Genoud, S., Maricic, I., Kumar, V., & Gage, F. H. 2005, "Targeted expression of IGF-1 in the central nervous system fails to protect mice from experimental autoimmune encephalomyelitis", Journal of Neuroimmunology, vol. 168, no. 1-2, pp. 40-45.

Gerber, R. C., Whitehouse, M. W., & Orr, K. J. 1972, "Effect of gold preparations on the development and passive transfer of experimental allergic encephalomyelitis in rats. 1", Proc.Soc.Exp.Biol.Med., vol. 140, no. 4, pp. 1379-1384.

Gerdoni, E., Gallo, B., Casazza, S., Musio, S., Bonanni, I., Pedemonte, E., Mantegazza, R., Frassoni, F., Mancardi, G., Pedotti, R., & Uccelli, A. 2007, "Mesenchymal stem cells effectively modulate pathogenic immune response in experimental autoimmune encephalomyelitis", Ann.Neurol., vol. 61, no. 3, pp. 219-227.

Gerdoni, E., Gallo, B., Casazza, S., Pedemonte, E., Musio, S., Frassoni, F., Mancardi, G., Pedotti, R., & Uccelli, A. 2006a, "Mesenchymal stem cells treat CNS autoimmunity through a dual effect on inflammation and tissue damage", Bone Marrow Transplantation, vol. 37, no. Suppl. 1.

Gerdoni, E., Gallo, B., Casazza, S., Pedemonte, E., Musio, S., Mancardi, G. L., Pedotti, R., & Uccelli, A. 2006b, "Mesenchymal stem cells treat relapsing-remitting experimental autoimmune encephalomyelitis through a dual effect on inflammation and tissue damage", Journal of Neuroimmunology, vol. 178, p. 75.

Gienapp, I., Cox, K., Javed, N., & Whitacre, C. 1996, "Oral tolerance in autoimmune encephalomyelitis. In vivo reversal of anergy", Ann.N.Y.Acad.Sci., vol. 778, pp. 382-383.

Gijbels, K., Brocke, S., Abrams, J. S., & Steinman, L. 1995, "Administration of neutralizing antibodies to interleukin-6 (IL-6) reduces experimental autoimmune encephalomyelitis and is associated with elevated levels of IL-6 bioactivity in central nervous system and circulation", Mol Med, vol. 1, no. 7, pp. 795-805.

Gijbels, K., Galardy, R. E., & Steinman, L. 1994, "Reversal of experimental autoimmune encephalomyelitis with a hydroxamate inhibitor of matrix metalloproteases", J.Clin.Invest, vol. 94, no. 6, pp. 2177-2182.

Gilgun-Sherki, Y., Panet, H., Holdengreber, V., Mosberg-Galili, R., & Offen, D. 2003a, "Axonal damage is reduced following glatiramer acetate treatment in C57/bl mice with chronic-induced experimental autoimmune encephalomyelitis", Neurosci.Res., vol. 47, no. 2, pp. 201-207.

Gilgun-Sherki, Y., Panet, H., Melamed, E., & Offen, D. 2003b, "Riluzole suppresses experimental autoimmune encephalomyelitis: implications for the treatment of multiple sclerosis", Brain Res., vol. 989, no. 2, pp. 196-204.

Gilgun-Sherki, Y., Barhum, Y., Atlas, D., Melamed, E., & Offen, D. 2005, "Analysis of gene expression in MOG-induced experimental autoimmune encephalomyelitis after treatment with a novel brain-penetrating antioxidant", J Mol Neurosci, vol. 27, no. 1.

Gilgun-Sherki, Y., Offen, D., Panet, H., Mosberg-Galili, R., & Melamed, E. 2002, "Riluzole improves motor function in experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis", Neurology, vol. 58, no. 7 Supplement 3, p. A386-A387.

Gilman, S. C., Carlson, R. P., & Lewis, A. J. 1985, "Immunomodulatory activity of Wy-18,251 (3-(p-chlorophenyl)thiazolo[3,2-a]benzimidazole-2-acetic acid)", J.Immunopharmacol., vol. 7, no. 1, pp. 79-98.

Giuliani, F., Fu, S. A., Metz, L. M., & Yong, V. W. 2005a, "Effective combination of minocycline and interferon-beta in a model of multiple sclerosis", J.Neuroimmunol., vol. 165, no. 1-2, pp. 83-91.

Giuliani, F., Metz, L. M., Wilson, T., Fan, Y., Bar-Or, A., & Yong, V. W. 2005b, "Additive effect of the combination of glatiramer acetate and minocycline in a model of MS", J Neuroimmunol, vol. 158, no. 1-2, pp. 213-221.

Glabinski, A. R., Bielecki, B., Kawczak, J. A., Tuohy, V. K., Selmaj, K., & Ransohoff, R. M. 2004, "Treatment with soluble tumor necrosis factor receptor (sTNFR):Fc/p80 fusion protein ameliorates relapsing-remitting experimental autoimmune encephalomyelitis and decreases chemokine expression", Autoimmunity, vol. 37, no. 6-7, pp. 465-471.

Gladue, R. P. & Newborg, M. F. 1991, "The Protective Effects of the Thromboxane Synthetase Inhibitor Dazmegrel on Nephrotoxicity in Cyclosporine-Treated Rats", Transplantation, vol. 52, no. 5, pp. 837-841.

Glenn, E. M., Lyster, S. C., & Rohloff, N. A. 1971, "Antiarthritic effects of the antispermatogenic agent 2,3-dihydro-(1-naphthyl)-4-(1H)-quinazolinone (U-29,409)", Proc.Soc.Exp.Biol.Med., vol. 138, no. 1, pp. 244-248.

Gocke, A. R., Cravens, P. D., Ben, L. H., Hussain, R. Z., Northrop, S. C., Racke, M. K., & Lovett-Racke, A. E. 2007, "T-bet regulates the fate of Th1 and Th17 lymphocytes in autoimmunity", J.Immunol., vol. 178, no. 3, pp. 1341-1348.

Goihman-Yahr, M., Requena, M. A., Vallecalle-Suegart, E., & Convit, J. 1974, "Autoimmune diseases and thalidomide. II. Adjuvant disease, experimental allergic encephalomyelitis and experimental allergic neuritis of the rat", Int.J.Lepr.Other Mycobact.Dis., vol. 42, no. 3, pp. 266-275.

Gold, B. G., Voda, J., Yu, X., McKeon, G., & Bourdette, D. N. 2004, "FK506 and a nonimmunosuppressant derivative reduce axonal and myelin damage in experimental autoimmune encephalomyelitis: neuroimmunophilin ligand-mediated neuroprotection in a model of multiple sclerosis", J.Neurosci.Res., vol. 77, no. 3, pp. 367-377.

Goldberg, R., Zohar, Y., Wildbaum, G., Geron, Y., Maor, G., & Karin, N. 2004, "Suppression of ongoing experimental autoimmune encephalomyelitis by neutralizing the function of the p28 subunit of IL-27", J.Immunol., vol. 173, no. 10, pp. 6465-6471.

Goldenberg, M. M., Boise, K. L., & Ilse, A. C. 1980, "Evaluation of a new anti-inflammatory/analgesic compound F-776, 5-(4-chlorophenyl)-beta-hydroxy-2-furanpropanoic acid", Arch Int Pharmacodyn.Ther, vol. 243, no. 2, pp. 331-350.

Goldmuntz, E. A., Brosnan, C. F., & Norton, W. T. 1986, "Prazosin treatment suppresses increased vascular permeability in both acute and passively transferred experimental autoimmune encephalomyelitis in the Lewis rat", J.Immunol., vol. 137, no. 11, pp. 3444-3450.

Goldowitz, D., Knobler, R. L., & Lublin, F. D. 1987, "Heterotopic brain transplants in the study of experimental allergic encephalomyelitis", Exp Neurol, vol. 97, no. 3, pp. 653-661.

Gonzalez-Rey, E., Fernandez-Martin, A., Chorny, A., Martin, J., Pozo, D., Ganea, D., & Delgado, M. 2006, "Therapeutic effect of vasoactive intestinal peptide on experimental autoimmune encephalomyelitis: down-regulation of inflammatory and autoimmune responses", Am.J.Pathol., vol. 168, no. 4, pp. 1179-1188.

Goss, J. A., Nakafusa, Y., Roland, C. R., Hickey, W. F., & Flye, M. W. 1994, "Immunological tolerance to a defined myelin basic protein antigen administered intrathymically", J.Immunol., vol. 153, no. 9, pp. 3890-3898.

Gozes, I., Zaltzman, R., Giladi, E., Grigoriadis, N., Brenneman, D., Melamed, E., & Offen, D. 2003, "Treatment of experimental encephalomyelitis by intranasal application of the ADNP peptide, NAP", Society for Neuroscience Abstract Viewer and Itinerary Planner, vol. 2003.

Graham, D. I., Gonatas, N. K., & Gasser, D. L. 1974, "Experimental allergic encephalomyelitis in triethyltin sulfate-treated brown Norwegian and Lewis rats", Lab Invest, vol. 31, no. 1, pp. 24-28.

Gran, B., Chu, N., Zhang, G. X., Yu, S., Li, Y., Chen, X. H., Kamoun, M., & Rostami, A. 2004, "Early administration of IL-12 suppresses EAE through induction of interferon-gamma", J.Neuroimmunol., vol. 156, no. 1-2, pp. 123-131.

Gran, B., Tabibzadeh, N., Martin, A., Ventura, E. S., Ware, J. H., Zhang, G.-X., Parr, J. L., Kennedy, A. R., & Rostami, A. M. 2006, "The protease inhibitor, Bowman-Birk Inhibitor, suppresses experimental autoimmune encephalomyelitis: A potential oral therapy for multiple sclerosis", Multiple Sclerosis.12(6)()(pp 688-697), 2006.Date of Publication: Dec 2006. no. 6, pp. 688-697.

Grant, S. M., Wiesinger, J. A., Beard, J. L., & Cantorna, M. T. 2003, "Iron-deficient mice fail to develop autoimmune encephalomyelitis", J.Nutr., vol. 133, no. 8, pp. 2635-2638.

Grassin, M., Brochet, B., Coussemacq, M., & Brochet, H. 1998, "Controlled therapeutic trials of pentoxifylline in relapsing-experimental auto-immune encephalomyelitis", Acta Neurol.Scand., vol. 97, no. 6, pp. 404-408.

Greenwood, J., Walters, C. E., Pryce, G., Kanuga, N., Beraud, E., Baker, D., & Adamson, P. 2003, "Lovastatin inhibits brain endothelial cell Rho-mediated lymphocyte migration and attenuates experimental autoimmune encephalomyelitis", FASEB J., vol. 17, no. 8, pp. 905-907.

Greig, M. E. & Gibbons, A. J. 1969, "Effects of cytarabine and adamantoyl cytarabine on experimental allergic encephalomyelitis in rats", Arch.Int.Pharmacodyn.Ther., vol. 182, no. 2, pp. 364-369.

Griffiths, M. R., Neal, J. W., Fontaine, M., Das, T., & Gasque, P. 2009, "Complement factor H, a marker of self protects against experimental autoimmune encephalomyelitis", J Immunol, vol. 182, no. 7, pp. 4368-4377.

Gruenewald, R., Levine, S., & Sowinski, R. 1977, "Experimental allergic encephalomyelitis in the rat: enhancement and suppression by synthetic polyribonucleotides", Proc.Soc.Exp.Biol.Med., vol. 154, no. 2, pp. 175-179.

Guo, S.-G., Jin, F., Tang, Z.-P., Wang, C.-J., Chen, H., & Zhang, S.-M. 2006, "An experimental study on the effect of olfactory ensheathing cells transplantation on autoimmune encephalomyelitis. [Chinese]", Chinese Journal of Neurology.39(5)()(pp 328-331), 2006.Date of Publication: May 2006. no. 5, pp. 328-331.

Guo, X., Nakamura, K., Kohyama, K., Harada, C., Behanna, H. A., Watterson, D. M., Matsumoto, Y., & Harada, T. 2007, "Inhibition of glial cell activation ameliorates the severity of experimental autoimmune encephalomyelitis", Neurosci.Res., vol. 59, no. 4, pp. 457-466.

Guy, J., Ellis, E. A., Hope, G. M., & Rao, N. A. 1989, "Antioxidant enzyme suppression of demyelination in experimental optic neuritis", Curr.Eye Res., vol. 8, no. 5, pp. 467-477.

Guy, J., McGorray, S., Qi, X., Fitzsimmons, J., Mancuso, A., & Rao, N. 1994, "Conjugated deferoxamine reduces blood-brain barrier disruption in experimental optic neuritis", Ophthalmic Res., vol. 26, no. 5, pp. 310-323.

Guy, J., Qi, X., & Hauswirth, W. W. 1998, "Adeno-associated viral-mediated catalase expression suppresses optic neuritis in experimental allergic encephalomyelitis", Proc.Natl.Acad.Sci.U.S.A, vol. 95, no. 23, pp. 13847-13852.

Guyton, M., Rohrer, B., Azuma, M., Inoue, J., Ray, S., & Banik, N. 2005, "Calpain inhibition attenuates loss of retinal function in experimantal optic neuritis", Iovs, vol. 46, no. Suppl. S.

Guyton, M. K., Das, A., Matzelle, D. D., Samantaray, S., Azuma, M., Inoue, J., Ray, S. K., & Banik, N. L. 2006, "SJA6017 attenuates immune cell infiltration and neurodegeneration in EAE", 8Th International Congress of Neuroimmunology pp. 107-112.

Hallal, D. E., Farias, A. S., Oliveira, E. C., Diaz-Bardales, B. M., Brandao, C. O., Protti, G. G., Pereira, F. G., Metze, I. L., & Santos, L. M. 2003, "Costimulatory molecule expression on leukocytes from mice with experimental autoimmune encephalomyelitis treated with IFN-beta", J Interferon Cytokine Res, vol. 23, no. 6, pp. 293-298.

Han, D., Tian, Y., Zhang, M., Zhou, Z., & Lu, J. 2007, "Prevention and treatment of experimental autoimmune encephalomyelitis with recombinant adeno-associated virus-mediated alpha-melanocyte-stimulating hormone-transduced PLP139-151-specific T cells", Gene Ther., vol. 14, no. 5, pp. 383-395.

Harbige, L. S., Layward, L., Morris, M., & Amor, S. 1997, "Protective mechanisms by omega-6 lipids in experimental autoimmune encephalomyelitis (EAE) are associated with cytokines and eicosanoids", Biochem.Soc.Trans., vol. 25, no. 2, p. 342S.

Harbige, L. S., Layward, L., Morris-Downes, M. M., Dumonde, D. C., & Amor, S. 2000, "The protective effects of omega-6 fatty acids in experimental autoimmune encephalomyelitis (EAE) in relation to transforming growth factor-beta 1 (TGF-beta1) up-regulation and increased prostaglandin E2 (PGE2) production", Clin.Exp.Immunol., vol. 122, no. 3, pp. 445-452.

Harling-Berg, C. J., Knopf, P. M., & Cserr, H. F. 1991, "Myelin basic protein infused into cerebrospinal fluid suppresses experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 35, no. 1-3, pp. 45-51.

Harness, J., Cavanagh, A., Morton, H., & McCombe, P. 2003, "A protective effect of early pregnancy factor on experimental autoimmune encephalomyelitis induced in Lewis rats by inoculation with myelin basic protein", J Neurol Sci, vol. 216, no. 1, pp. 33-41.

Hashim, G. A. 1975, "Non-encephalitogenic antigen-induced suppression and reversal of allergic encephalomyelitis", Nature, vol. 256, no. 5518, pp. 953-955.

Hashim, G. A. 1980, "Failure of myelin basic protein to prevent or suppress experimental allergic encephalomyelitis in guinea pigs", Neurochem.Res., vol. 5, no. 2, pp. 101-113.

Hashim, G. A. 1981a, "Experimental allergic encephalomyelitis: activation of suppressor T lymphocytes by a modified sequence of the T effector determinant", J Immunol, vol. 126, no. 2, pp. 419-423.

Hashim, G. A. 1981b, "Successful immunization against experimental allergic encephalomyelitis with myelin basic protein-sensitized allogeneic lymphocytes", Neurochem.Res., vol. 6, no. 6, pp. 699-718.

Hashim, G. A. & Schilling, F. J. 1973, "Prevention of experimental allergic encephalomyelitis by nonencephalitogenic basic peptides", Arch.Biochem.Biophys., vol. 156, no. 1, pp. 287-297.

Hashim, G. A., Sharpe, R. D., Carvalho, E. F., & Stevens, L. E. 1976, "Suppression and reversal of allergic encephalomyelitis in guinea pigs with a non-encephalitogenic analogue of the tryptophan region of the myelin basic protein", J.Immunol., vol. 116, no. 1, pp. 126-130.

Hashim, G. A., Vandenbark, A. A., Galang, A. B., Diamanduros, T., Carvalho, E., Srinivasan, J., Jones, R., Vainiene, M., Morrison, W. J., & Offner, H. 1990, "Antibodies specific for VB8 receptor peptide suppress experimental autoimmune encephalomyelitis", J.Immunol., vol. 144, no. 12, pp. 4621-4627.

Hassen, G. W., Feliberti, J., Kesner, L., Stracher, A., & Mokhtarian, F. 2006, "A novel calpain inhibitor for the treatment of acute experimental autoimmune encephalomyelitis", Journal of Neuroimmunology, vol. 180, no. 1-2, pp. 135-146.

Hauser, S. L., Weiner, H. L., Che, M., Shapiro, M. E., Gilles, F., & Letvin, N. L. 1984, "Prevention of experimental allergic encephalomyelitis (EAE) in the SJL/J mouse by whole body ultraviolet irradiation", J.Immunol., vol. 132, no. 3, pp. 1276-1281.

Hayashi, T., Gray, C. S., Chan, M., Tawatao, R. I., Ronacher, L., McGargill, M. A., Datta, S. K., Carson, D. A., & Corr, M. 2009, "Prevention of autoimmune disease by induction of tolerance to Toll-like receptor 7", Proc Natl Acad Sci U S A, vol. 106, no. 8, pp. 2764-2769.

Hayosh, N. S. & Swanborg, R. H. 1987, "Autoimmune effector cells. IX. Inhibition of adoptive transfer of autoimmune encephalomyelitis with a monoclonal antibody specific for interleukin 2 receptors", J.Immunol., vol. 138, no. 11, pp. 3771-3775.

Held, K. S., Glass, W. G., Orlovsky, Y. I., Shamberger, K. A., Petley, T. D., Branigan, P. J., Carton, J. M., Beck, H. S., Cunningham, M. R., Benson, J. M., & Lane, T. E. 2008, "Generation of a protective T-cell response following coronavirus infection of the central nervous system is not dependent on IL-12/23 signaling", Viral Immunology, vol. 21, no. 2, pp. 173-187.

Hempel, K., Freitag, A., Freitag, B., Endres, B., & Mai, B. 1984, "Complete Freund's adjuvants (CFA) induced unresponsiveness to EAE in Lewis rats", Prog Clin Biol Res, vol. 146, pp. 407-414.

Hempel, K., Freitag, A., Freitag, B., Endres, B., Mai, B., & Liebaldt, G. 1985, "Unresponsiveness to experimental allergic encephalomyelitis in Lewis rats pretreated with complete Freund's adjuvant", Int.Arch.Allergy Appl.Immunol., vol. 76, no. 3, pp. 193-199.

Hendriks, J. J., Alblas, J., van der Pol, S. M., van Tol, E. A., Dijkstra, C. D., & de Vries, H. E. 2004, "Flavonoids influence monocytic GTPase activity and are protective in experimental allergic encephalitis", J.Exp.Med., vol. 200, no. 12, pp. 1667-1672.

Heneka, M. T., Sharp, A., Murphy, P., Lyons, J. A., Dumitrescu, L., & Feinstein, D. L. 2001, "The heat shock response reduces myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis in mice", J.Neurochem., vol. 77, no. 2, pp. 568-579.

Henson, E. C. & Brunson, J. G. 1969, "Prevention of experimental allergic encephalomyelitis by combination of epinephrine and a phenothiazine derivative, propiomazine", Proc.Soc.Exp.Biol.Med., vol. 131, no. 3, pp. 752-755.

Herrmann, I., Kellert, M., Schmidt, H., Mildner, A., Hanisch, U. K., Bruck, W., Prinz, M., & Nau, R. 2006, "Streptococcus pneumoniae infection aggravates experimental autoimmune encephalomyelitis via toll-like receptor 2", Infection and Immunity.74(8)()(pp 4841-4848), 2006.Date of Publication: Aug 2006. no. 8, pp. 4841-4848.

Herrmann, M. M., Gaertner, S., Stadelmann, C., van den, B. J., Boscke, R., Budach, W., Reichardt, H. M., & Weissert, R. 2005, "Tolerance induction by bone marrow transplantation in a multiple sclerosis model", Blood, vol. 106, no. 5, pp. 1875-1883.

Hewson, A. K., Smith, T., Leonard, J. P., & Cuzner, M. L. 1995, "Suppression of experimental allergic encephalomyelitis in the Lewis rat by the matrix metalloproteinase inhibitor Ro31-9790", Inflamm.Res., vol. 44, no. 8, pp. 345-349.

Hiestand, P. C., Graber, M., Hurtenbach, U., Herrmann, P., Cammisuli, S., Richardson, B. P., Eberle, M. K., & Borel, J. F. 1992, "The new cyclosporine derivative, SDZ IMM 125: in vitro and in vivo pharmacologic effects", Transplant.Proc., vol. 24, no. 4 Suppl 2, pp. 31-38.

Higgins, P. J. & Weiner, H. L. 1988, "Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein and its fragments", J.Immunol., vol. 140, no. 2, pp. 440-445.

Hilliard, B., Ventura, E. S., & Rostami, A. 1999, "Effect of timing of intravenous administration of myelin basic protein on the induction of tolerance in experimental allergic encephalomyelitis", Mult Scler, vol. 5, no. 1, pp. 2-9.

Hilliard, B., Wilmen, A., Seidel, C., Liu, T. S., Goke, R., & Chen, Y. 2001, "Roles of TNF-related apoptosis-inducing ligand in experimental autoimmune encephalomyelitis", J Immunol, vol. 166, no. 2, pp. 1314-1319.

Hindinger, C., Hinton, D. R., Kirwin, S. J., Atkinson, R. D., Burnett, M. E., Bergmann, C. C., & Stohlman, S. A. 2006, "Liver X receptor activation decreases the severity of experimental autoimmune encephalomyelitis", J.Neurosci.Res., vol. 84, no. 6, pp. 1225-1234.

Hinrichs, D. J., Wegmann, K. W., & Peters, B. A. 1983, "The influence of cyclosporin A on the development of actively induced and passively transferred experimental allergic encephalomyelitis", Cell Immunol., vol. 77, no. 1, pp. 202-209.

Hirata, S., Matsuyoshi, H., Fukuma, D., Kurisaki, A., Uemura, Y., Nishimura, Y., & Senju, S. 2007, "Involvement of regulatory T cells in the experimental autoimmune encephalomyelitis-preventive effect of dendritic cells expressing myelin oligodendrocyte glycoprotein plus TRAIL", J.Immunol., vol. 178, no. 2, pp. 918-925.

Hirata, S., Senju, S., Matsuyoshi, H., Fukuma, D., Uemura, Y., & Nishimura, Y. 2005, "Prevention of experimental autoimmune encephalomyelitis by transfer of embryonic stem cell-derived dendritic cells expressing myelin oligodendrocyte glycoprotein peptide along with TRAIL or programmed death-1 ligand", J.Immunol., vol. 174, no. 4, pp. 1888-1897.

Ho, P. P., Fontoura, P., Platten, M., Sobel, R. A., DeVoss, J. J., Lee, L. Y., Kidd, B. A., Tomooka, B. H., Capers, J., Agrawal, A., Gupta, R., Zernik, J., Yee, M. K., Lee, B. J., Garren, H., Robinson, W. H., & Steinman, L. 2005, "A suppressive oligodeoxynucleotide enhances the efficacy of myelin cocktail/IL-4-tolerizing DNA vaccination and treats autoimmune disease", J.Immunol., vol. 175, no. 9, pp. 6226-6234.

Ho, S. H., Lee, H. J., Kim, D. S., Jeong, J. G., Kim, S., Yu, S. S., Jin, Z., Kim, S., & Kim, J. M. 2006, "Intrasplenic electro-transfer of IL-4 encoding plasmid DNA efficiently inhibits rat experimental allergic encephalomyelitis", Biochem.Biophys.Res.Commun., vol. 343, no. 3, pp. 816-824.

Holoshitz, J., Frenkel, A., Ben-Nun, A., & Cohen, I. R. 1983, "Autoimmune encephalomyelitis (EAE) mediated or prevented by T lymphocyte lines directed against diverse antigenic determinants of myelin basic protein. Vaccination is determinant specific", J.Immunol., vol. 131, no. 6, pp. 2810-2813.

Hooper, D. C., Scott, G. S., Zborek, A., Mikheeva, T., Kean, R. B., Koprowski, H., & Spitsin, S. V. 2000, "Uric acid, a peroxynitrite scavenger, inhibits CNS inflammation, blood-CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis", FASEB J., vol. 14, no. 5, pp. 691-698.

Hooper, D. C., Spitsin, S., Kean, R. B., Champion, J. M., Dickson, G. M., Chaudhry, I., & Koprowski, H. 1998, "Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and multiple sclerosis", Proc.Natl.Acad.Sci.U.S.A, vol. 95, no. 2, pp. 675-680.

Horie, T., Shen, Y., Kajino, K., Gaubin, M., Bonomi, G., Mani, J. C., Berezov, A., Piatier-Tonneau, D., Guardiola, J., Hillard, B., Rostami, A., Greene, M., & Murali, R. 2002, "Study of disabling T-cell activation and inhibiting T-cell-mediated immunopathology reveals a possible inverse agonist activity of CD4 peptidomimetics", Exp.Mol.Pathol., vol. 73, no. 2, pp. 93-103.

Hosseini, H., Andre, P., Lefevre, N., Viala, L., Walzer, T., Peschanski, M., & Lotteau, V. 2001, "Protection against experimental autoimmune encephalomyelitis by a proteasome modulator", J.Neuroimmunol., vol. 118, no. 2, pp. 233-244.

Hou, G., Abrams, G. D., Dick, R., & Brewer, G. J. 2008, "Efficacy of tetrathiomolybdate in a mouse model of multiple sclerosis", Translational Research.152(5)()(pp 239-244), 2008.Date of Publication: November 2008. no. 5, pp. 239-244.

Howard, L. M., Dal Canto, M. C., & Miller, S. D. 2002, "Transient anti-CD154-mediated immunotherapy of ongoing relapsing experimental autoimmune encephalomyelitis induces long-term inhibition of disease relapses", J.Neuroimmunol., vol. 129, no. 1-2, pp. 58-65.

Howard, L. M., Miga, A. J., Vanderlugt, C. L., Dal Canto, M. C., Laman, J. D., Noelle, R. J., & Miller, S. D. 1999, "Mechanisms of immunotherapeutic intervention by anti-CD40L (CD154) antibody in an animal model of multiple sclerosis", J.Clin.Invest, vol. 103, no. 2, pp. 281-290.

Howard, L. M., Ostrovidov, S., Smith, C. E., Dal Canto, M. C., & Miller, S. D. 2002, "Normal Th1 development following long-term therapeutic blockade of CD154-CD40 in experimental autoimmune encephalomyelitis", J.Clin.Invest, vol. 109, no. 2, pp. 233-241.

Howat, D. W., Chand, N., Braquet, P., & Willoughby, D. A. 1989, "An investigation into the possible involvement of platelet activating factor in experimental allergic encephalomyelitis in rats", Agents Actions, vol. 27, no. 3-4, pp. 473-476.

Howell, M. D., Winters, S. T., Olee, T., Powell, H. C., Carlo, D. J., & Brostoff, S. W. 1989, "Vaccination against experimental allergic encephalomyelitis with T cell receptor peptides", Science, vol. 246, no. 4930, pp. 668-670.

Hu, H., Stavrou, S., Cairns, B. B., Tornatore, C., Scharff, J., Okunieff, P., & Neville, D. M., Jr. 1997, "Depletion of T lymphocytes with immunotoxin retards the progress of experimental allergic encephalomyelitis in rhesus monkeys", Cell Immunol, vol. 177, no. 1, pp. 26-34.

Huan, J., Subramanian, S., Jones, R., Rich, C., Link, J., Mooney, J., Bourdette, D. N., Vandenbark, A. A., Burrows, G. G., & Offner, H. 2004, "Monomeric recombinant TCR ligand reduces relapse rate and severity of experimental autoimmune encephalomyelitis in SJL/J mice through cytokine switch", J.Immunol., vol. 172, no. 7, pp. 4556-4566.

Hudson, R. A., Montgomery, I. N., & Rauch, H. C. 1983, "Experimental allergic encephalomyelitis: prevention with a nontoxic derivative of a cobra neurotoxin", Mol.Immunol., vol. 20, no. 2, pp. 229-232.

Hugh, A. R., Simmons, R. D., & Willenborg, D. O. 1989, "Immediate, long-lasting suppression of autoimmune encephalomyelitis by cell-bound neuroantigen", Cell Immunol., vol. 123, no. 1, pp. 108-117.

Hughes, D., Keith, A. B., Mertin, J., & Caspary, E. A. 1980, "Linoleic acid therapy in severe experimental allergic encephalomyelitis in the guinea-pig: suppression by continuous treatment", Clin.Exp.Immunol., vol. 40, no. 3, pp. 523-531.

Hughes, R. A. 1974, "Protection of rats from experimental allergic encephalomyelitis with antiserum to guinea-pig spinal cord", Immunology, vol. 26, no. 4, pp. 703-711.

Huitinga, I., Bauer, J., Strijbos, P. J., Rothwell, N. J., Dijkstra, C. D., & Tilders, F. J. 1998, "Effect of annexin-1 on experimental autoimmune encephalomyelitis (EAE) in the rat", Clin.Exp.Immunol., vol. 111, no. 1, pp. 198-204.

Huitinga, I., Damoiseaux, J. G., Dopp, E. A., & Dijkstra, C. D. 1993, "Treatment with anti-CR3 antibodies ED7 and ED8 suppresses experimental allergic encephalomyelitis in Lewis rats", Eur.J.Immunol., vol. 23, no. 3, pp. 709-715.

Huitinga, I., Ruuls, S. R., Jung, S., van Rooijen, N., Hartung, H.-P., & Dijkstra, C. D. 1995, "Macrophages in T cell line-mediated, demyelinating, and chronic relapsing experimental autoimmune encephalomyelitis in Lewis rats", Clinical and Experimental Immunology.100(2)()(pp 344-351), 1995.Date of Publication: 1995. no. 2, pp. 344-351.

Huitinga, I., Schmidt, E. D., van der Cammen, M. J., Binnekade, R., & Tilders, F. J. 2000, "Priming with interleukin-1beta suppresses experimental allergic encephalomyelitis in the Lewis rat", J.Neuroendocrinol., vol. 12, no. 12, pp. 1186-1193.

Huitinga, I., van, R. N., De Groot, C. J., Uitdehaag, B. M., & Dijkstra, C. D. 1990, "Suppression of experimental allergic encephalomyelitis in Lewis rats after elimination of macrophages", J.Exp.Med., vol. 172, no. 4, pp. 1025-1033.

Hultqvist, M., Nandakumar, K. S., Bjorklund, U., & Holmdahl, R. 2009, "The novel small molecule drug Rabeximod is effective in reducing disease severity of mouse models of autoimmune disorders", Ann Rheum Dis, vol. 68, no. 1, pp. 130-135.

Hunter, N., Weston, K. M., & Bowern, N. A. 1991, "Suppression of experimental allergic encephalomyelitis by alpha 2-macroglobulin", Immunology, vol. 73, no. 1, pp. 58-63.

Huntington, N. D., Tomioka, R., Clavarino, C., Chow, A. M., Linares, D., Mana, P., Rossjohn, J., Cachero, T. G., Qian, F., Kalled, S. L., Bernard, C. C., & Reid, H. H. 2006, "A BAFF antagonist suppresses experimental autoimmune encephalomyelitis by targeting cell-mediated and humoral immune responses", Int.Immunol., vol. 18, no. 10, pp. 1473-1485.

Ichikawa, M., Koh, C. S., Inoue, A., Tsuyusaki, J., Yamazaki, M., Inaba, Y., Sekiguchi, Y., Itoh, M., Yagita, H., & Komiyama, A. 2000, "Anti-IL-12 antibody prevents the development and progression of multiple sclerosis-like relapsing--remitting demyelinating disease in NOD mice induced with myelin oligodendrocyte glycoprotein peptide", J Neuroimmunol, vol. 102, no. 1, pp. 56-66.

Ilhan, A., Akyol, O., Gurel, A., Armutcu, F., Iraz, M., & Oztas, E. 2004, "Protective effects of caffeic acid phenethyl ester against experimental allergic encephalomyelitis-induced oxidative stress in rats", Free Radic.Biol.Med., vol. 37, no. 3, pp. 386-394.

Imrich, H., Kugler, C., Torres-Nagel, N., Dorries, R., & Hunig, T. 1995, "Prevention and treatment of Lewis rat experimental allergic encephalomyelitis with a monoclonal antibody to the T cell receptor V beta 8.2 segment", Eur.J.Immunol., vol. 25, no. 7, pp. 1960-1964.

Inaba, Y., Ichikawa, M., Koh, C. S., Inoue, A., Itoh, M., Kyogashima, M., & Komiyama, A. 1999, "Suppression of experimental autoimmune encephalomyelitis by dermatan sulfate", Cell Immunol., vol. 198, no. 2, pp. 96-102.

Inada, T. & Mims, C. A. 1986, "Infection of mice with lactic dehydrogenase virus prevents development of experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 11, no. 1, pp. 53-56.

Inobe, J., Slavin, A. J., Komagata, Y., Chen, Y., Liu, L., & Weiner, H. L. 1998, "IL-4 is a differentiation factor for transforming growth factor-beta secreting Th3 cells and oral administration of IL-4 enhances oral tolerance in experimental allergic encephalomyelitis", Eur J Immunol, vol. 28, no. 9, pp. 2780-2790.

Inobe, J. I., Chen, Y., & Weiner, H. L. 1996, "In vivo administration of IL-4 induces TGF-beta-producing cells and protects animals from experimental autoimmune encephalomyelitis", Ann.N.Y.Acad.Sci., vol. 778, pp. 390-392.

Inoue, A., Koh, C. S., Shimada, K., Yanagisawa, N., & Yoshimura, K. 1996, "Suppression of cell-transferred experimental autoimmune encephalomyelitis in defibrinated Lewis rats", J.Neuroimmunol., vol. 71, no. 1-2, pp. 131-137.

Inuzuka, T., Sato, S., Baba, H., & Miyatake, T. 1988, "Suppressive effect of camostat mesilate (FOY 305) on acute experimental allergic encephalomyelitis (EAE)", Neurochem.Res., vol. 13, no. 3, pp. 225-228.

Irony-Tur-Sinai, M., Grigoriadis, N., Lourbopoulos, A., Pinto-Maaravi, F., Abramsky, O., & Brenner, T. 2006, "Amelioration of autoimmune neuroinflammation by recombinant human alpha-fetoprotein", Exp.Neurol., vol. 198, no. 1, pp. 136-144.

Irony-Tur-Sinai, M., Vlodavsky, I., Ben-Sasson, S. A., Pinto, F., Sicsic, C., & Brenner, T. 2003, "A synthetic heparin-mimicking polyanionic compound inhibits central nervous system inflammation", J.Neurol.Sci., vol. 206, no. 1, pp. 49-57.

Iruretagoyena, M. I., Sepulveda, S. E., Lezana, J. P., Hermoso, M., Bronfman, M., Gutierrez, M. A., Jacobelli, S. H., & Kalergis, A. M. 2006, "Inhibition of nuclear factor-kappa B enhances the capacity of immature dendritic cells to induce antigen-specific tolerance in experimental autoimmune encephalomyelitis", J Pharmacol Exp Ther, vol. 318, no. 1, pp. 59-67.

Iruretagoyena, M. I., Tobar, J. A., Gonzalez, P. A., Sepulveda, S. E., Figueroa, C. A., Burgos, R. A., Hancke, J. L., & Kalergis, A. M. 2005, "Andrographolide interferes with T cell activation and reduces experimental autoimmune encephalomyelitis in the mouse", J.Pharmacol.Exp.Ther., vol. 312, no. 1, pp. 366-372.

Isetta, A. M., Ferrari, M., Fornasiero, M. C., & Trizio, D. 1991, "Effects of the new immunoactive compound FCE 20696 on rat and murine models of autoimmune diseases", Immunopharmacol.Immunotoxicol., vol. 13, no. 4, pp. 499-511.

Ishigami, T., White, C. A., & Pender, M. P. 1998, "Soluble antigen therapy induces apoptosis of autoreactive T cells preferentially in the target organ rather than in the peripheral lymphoid organs", Eur.J.Immunol., vol. 28, no. 5, pp. 1626-1635.

Ishikawa, M., Jin, Y., Guo, H., Link, H., & Xiao, B. G. 1999, "Nasal administration of transforming growth factor-beta1 induces dendritic cells and inhibits protracted-relapsing experimental allergic encephalomyelitis", Mult.Scler., vol. 5, no. 3, pp. 184-191.

Issekutz, T. B., Sporici, R., & Mohan, K. 2005, "Antibody blockade of chemokine receptor CXCR3 inhibits T lymphocyte migration to the CNS in experimental autoimmune encephalomyelitis (EAE) and prevents induction of EAE by adoptively transferred immune T cells", Faseb Journal, vol. 19, no. 5, Suppl. S, Part 2.

Ito, A., Bebo, B. F., Jr., Matejuk, A., Zamora, A., Silverman, M., Fyfe-Johnson, A., & Offner, H. 2001, "Estrogen treatment down-regulates TNF-alpha production and reduces the severity of experimental autoimmune encephalomyelitis in cytokine knockout mice", J.Immunol., vol. 167, no. 1, pp. 542-552.

Ito, A., Matejuk, A., Hopke, C., Drought, H., Dwyer, J., Zamora, A., Subramanian, S., Vandenbark, A. A., & Offner, H. 2003, "Transfer of severe experimental autoimmune encephalomyelitis by IL-12- and IL-18-potentiated T cells is estrogen sensitive", J.Immunol., vol. 170, no. 9, pp. 4802-4809.

Jackson, S., Al Izik, S., Pryce, G., Giovannoni, G., & Baker, D. 2008, "Fingolimod reduces axonal loss in relapsing secondary progressive experimental autoimmune encephalomyelitis", Multiple Sclerosis, vol. 14, p. S80-S81.

Jacobs, C. A., Baker, P. E., Roux, E. R., Picha, K. S., Toivola, B., Waugh, S., & Kennedy, M. K. 1991, "Experimental autoimmune encephalomyelitis is exacerbated by IL-1 alpha and suppressed by soluble IL-1 receptor", J.Immunol., vol. 146, no. 9, pp. 2983-2989.

Jaini, R., Hannaman, D., Johnson, J. M., Bernard, R. M., Altuntas, C. Z., Delasalas, M. M., Kesaraju, P., Luxembourg, A., Evans, C. F., & Tuohy, V. K. 2006, "Gene-based intramuscular interferon-beta therapy for experimental autoimmune encephalomyelitis", Mol.Ther., vol. 14, no. 3, pp. 416-422.

Jameson, B. A., McDonnell, J. M., Marini, J. C., & Korngold, R. 1994, "A rationally designed CD4 analogue inhibits experimental allergic encephalomyelitis", Nature, vol. 368, no. 6473, pp. 744-746.

Jankovic, B. D. & Maric, D. 1987, "Enkephalins and autoimmunity: differential effect of methionine-enkephalin on experimental allergic encephalomyelitis in Wistar and Lewis rats", J.Neurosci.Res., vol. 18, no. 1, pp. 88-94.

Jansson, L., Olsson, T., & Holmdahl, R. 1994, "Estrogen induces a potent suppression of experimental autoimmune encephalomyelitis and collagen-induced arthritis in mice", J.Neuroimmunol., vol. 53, no. 2, pp. 203-207.

Javed, N. H., Gienapp, I. E., Cox, K. L., & Whitacre, C. C. 1995, "Exquisite peptide specificity of oral tolerance in experimental autoimmune encephalomyelitis", J.Immunol., vol. 155, no. 3, pp. 1599-1605.

Jee, Y., Liu, R., Bai, X. F., Campagnolo, D. I., Shi, F. D., & Vollmer, T. L. 2006, "Do Th2 cells mediate the effects of glatiramer acetate in experimental autoimmune encephalomyelitis?", Int.Immunol., vol. 18, no. 4, pp. 537-544.

Jee, Y., Piao, W. H., Liu, R., Bai, X. F., Rhodes, S., Rodebaugh, R., Campagnolo, D. I., Shi, F. D., & Vollmer, T. L. 2007, "CD4(+)CD25(+) regulatory T cells contribute to the therapeutic effects of glatiramer acetate in experimental autoimmune encephalomyelitis", Clin.Immunol., vol. 125, no. 1, pp. 34-42.

Jerusalmi, A., Morris-Downes, M. M., Sheahan, B. J., & Atkins, G. J. 2003, "Effect of intranasal administration of Semliki Forest virus recombinant particles expressing reporter and cytokine genes on the progression of experimental autoimmune encephalomyelitis", Mol.Ther., vol. 8, no. 6, pp. 886-894.

Jia, J., Li, H., Tai, S., Lv, M., Liao, M., Yang, Z., Zhang, B., Zhou, B., Zhang, G., & Zhang, L. 2008, "Construction and preliminary investigation of a plasmid containing a novel immunotoxin DT390-IL-18 gene for the prevention of murine experimental autoimmune encephalomyelitis", DNA Cell Biol, vol. 27, no. 5, pp. 279-285.

Jia, Y., Li, H., Chen, W., Li, M., Lv, M., Feng, P., Hu, H., & Zhang, L. 2006, "Prevention of murine experimental autoimmune encephalomyelitis by in vivo expression of a novel recombinant immunotoxin DT390-RANTES", Gene Ther, vol. 13, no. 18, pp. 1351-1359.

Jia, Y., Li, H., Chen, W. J., Lu, M. L., Li, M. Y., Jiang, Z. H., & Zhang, L. 2007, "[Primary study of the recombinant immunotoxin DT390-mRantes in EAE therapy]", Xi Bao Yu Fen.Zi.Mian.Yi Xue Za Zhi, vol. 23, no. 3, pp. 236-239.

Jiang, Z., Li, H., Fitzgerald, D. C., Zhang, G. X., & Rostami, A. 2009, "MOG(35-55) i.v suppresses experimental autoimmune encephalomyelitis partially through modulation of Th17 and JAK/STAT pathways", Eur J Immunol, vol. 39, no. 3, pp. 789-799.

Jiao, Z. M., Fu, Y. H., Fu, J., Zhang, F., & Wang, W. Z. 2008, "[1, 25-dihydroxyvitamin D3 promotes the apoptosis of inflammatory cells in acute experimental autoimmune encephalomyelitis: experiment with rats]", Zhonghua Yi Xue Za Zhi, vol. 88, no. 33, pp. 2350-2354.

Jin, S. J., Takeuchi, H., Yawata, I., Harada, Y., Sonobe, Y., Doi, Y., Liang, J. F., Hua, L., Yasuoka, S., Zhou, Y., Noda, M., Kawanokuchi, J., Mizuno, T., & Suzumura, A. 2009, "Blockade of Glutamate Release from Microglia Attenuates Experimental Autoimmune Encephalomyelitis in Mice", Tohoku Journal of Experimental Medicine, vol. 217, no. 2, pp. 87-92.

Johns, L. D., Flanders, K. C., Ranges, G. E., & Sriram, S. 1991, "Successful treatment of experimental allergic encephalomyelitis with transforming growth factor-beta 1", J.Immunol., vol. 147, no. 6, pp. 1792-1796.

Jolivalt, C. G., Howard, R. B., Chen, L. S., Mizisin, A. P., & Lai, C. S. 2003, "A novel nitric oxide scavenger in combination with cyclosporine A ameliorates experimental autoimmune encephalomyelitis progression in mice", J.Neuroimmunol., vol. 138, no. 1-2, pp. 56-64.

Jonker, M., van, L. R., Mitchell, D. J., Durham, S. K., & Steinman, L. 1988, "Successful treatment of EAE in rhesus monkeys with MHC class II specific monoclonal antibodies", J.Autoimmun., vol. 1, no. 5, pp. 399-414.

Jonsson, S., Andersson, G., Fex, T., Fristedt, T., Hedlund, G., Jansson, K., Abramo, L., Fritzson, I., Pekarski, O., Runstrom, A., Sandin, H., Thuvesson, I., & Bjork, A. 2004, "Synthesis and biological evaluation of new 1,2-dihydro-4-hydroxy-2-oxo-3-quinolinecarboxamides for treatment of autoimmune disorders: structure-activity relationship", J.Med.Chem., vol. 47, no. 8, pp. 2075-2088.

Jorgensen, S. H., Jensen, P. E., Laursen, H., & Sorensen, P. S. 2005, "Intravenous immunoglobulin ameliorates experimental autoimmune encephalomyelitis and reduces neuropathological abnormalities when administered prophylactically", Neurol.Res., vol. 27, no. 6, pp. 591-597.

Jun, S., Gilmore, W., Callis, G., Rynda, A., Haddad, A., & Pascual, D. W. 2005, "A live diarrheal vaccine imprints a Th2 cell bias and acts as an anti-inflammatory vaccine", J.Immunol., vol. 175, no. 10, pp. 6733-6740.

Jun, S. M., Callis, G., & Pascual, D. W. 2005, "Antigen-independent suppression of experimental autoimmune encephalomyelitis (EAE) by a Salmonella vaccine expressing enterotoxigenic E. coli colonization factor antigen I (CFA/I)", Faseb Journal, vol. 19, no. 4, Suppl. S, Part 1, p. A3-A4.

Jung, S., Donhauser, T., Toyka, K. V., & Hartung, H. P. 1997, "Propentofylline and iloprost suppress the production of TNF-alpha by macrophages but fail to ameliorate experimental autoimmune encephalomyelitis in Lewis rats", J.Autoimmun., vol. 10, no. 6, pp. 519-529.

Jung, S., Schluesener, H. J., Toyka, K. V., & Hartung, H. P. 1993, "Modulation of EAE by vaccination with T cell receptor peptides: V beta 8 T cell receptor peptide-specific CD4+ lymphocytes lack direct immunoregulatory activity", J.Neuroimmunol., vol. 45, no. 1-2, pp. 15-22.

Jung, S., Toyka, K., & Hartung, H. P. 1995, "Suppression of experimental autoimmune encephalomyelitis in Lewis rats by antibodies against CD2", Eur.J.Immunol., vol. 25, no. 5, pp. 1391-1398.

Jurynczyk, M., Jurewicz, A., Bielecki, B., Raine, C. S., & Selmaj, K. 2005, "Inhibition of Notch signaling enhances tissue repair in an animal model of multiple sclerosis", J.Neuroimmunol., vol. 170, no. 1-2, pp. 3-10.

Jurynczyk, M., Jurewicz, A., Bielecki, B., Raine, C. S., & Selmaj, K. 2008a, "Overcoming failure to repair demyelination in EAE: gamma-secretase inhibition of Notch signaling", J.Neurol.Sci., vol. 265, no. 1-2, pp. 5-11.

Jurynczyk, M., Jurewicz, A., Raine, C. S., & Selmaj, K. 2008b, "Notch3 inhibition in myelin-reactive T cells down-regulates protein kinase C theta and attenuates experimental autoimmune encephalomyelitis", J Immunol., vol. 180, no. 4, pp. 2634-2640.

Jyothi, M. D., Flavell, R. A., & Geiger, T. L. 2002, "Targeting autoantigen-specific T cells and suppression of autoimmune encephalomyelitis with receptor-modified T lymphocytes", Nat.Biotechnol., vol. 20, no. 12, pp. 1215-1220.

Kahl, K. G., Zielasek, J., Uttenthal, L. O., Rodrigo, J., Toyka, K. V., & Schmidt, H. H. H. W. 2003, "Protective role of the cytokine-inducible isoform of nitric oxide synthase induction and nitrosative stress in experimental autoimmune encephalomyelitis of the DA rat", Journal of Neuroscience Research.73(2)()(pp 198-205), 2003.Date of Publication: 15 Jul 2003. no. 2, pp. 198-205.

Kallen, B., Dohlsten, M., & Klementsson, H. 1986, "Effect of cyclophosphamide pretreatment on autoimmune encephalomyelitis in rats", Acta Neurol.Scand., vol. 73, no. 4, pp. 338-344.

Kalyvas, A., Baskakis, C., Magrioti, V., Constantinou-Kokotou, V., Stephens, D., Lpez-Vales, R., Lu, J.-Q., Yong, V. W., Dennis, E. A., Kokotos, G., & David, S. 2009, "Differing roles for members of the phospholipase A2 superfamily in experimental autoimmune encephalomyelitis", Brain.132(5)()(pp 1221-1235), 2009.Date of Publication: May 2009. no. 5, pp. 1221-1235.

Kalyvas, A. & David, S. 2004, "Cytosolic phospholipase A2 plays a key role in the pathogenesis of multiple sclerosis-like disease", Neuron, vol. 41, no. 3, pp. 323-335.

Kanchurin, A. K. & Umerov, Z. 1972, "[The effect of antilymphocytic serum on experimental allergic pertussis encephalomyelitis]", Patol.Fiziol.Eksp.Ter., vol. 16, no. 3, pp. 52-54.

Kaneko, H., Iizuka, K., Kokai, Y., Fujimoto, J. I., Hirasawa, A., Tsujimoto, G., Koike, H., Torres-Nagel, N., Hunig, T., & Kimura, H. 1995, "Vaccination with a synthetic T-cell receptor V-region peptide: immunomodulation or vaccination", Transplant.Proc., vol. 27, no. 2, pp. 1539-1542.

Kaneko, S., Wang, J., Kaneko, M., Yiu, G., Hurrell, J. M., Chitnis, T., Khoury, S. J., & He, Z. 2006, "Protecting axonal degeneration by increasing nicotinamide adenine dinucleotide levels in experimental autoimmune encephalomyelitis models", J.Neurosci., vol. 26, no. 38, pp. 9794-9804.

Kang, J. C., Ahn, M., Kim, Y. S., Moon, C., Lee, Y., Wie, M. B., Lee, Y. J., & Shin, T. 2001, "Melatonin ameliorates autoimmune encephalomyelitis through suppression of intercellular adhesion molecule-1", J.Vet.Sci., vol. 2, no. 2, pp. 85-89.

Kang, S. Y., Kang, J. H., Choi, J. C., Lee, J. S., Lee, C. S., & Shin, T. 2009, "Expression of Erythropoietin in the Spinal Cord of Lewis Rats with Experimental Autoimmune Encephalomyelitis", Journal of Clinical Neurology, vol. 5, no. 1, pp. 39-45.

Kanwar, J., Kanwar, R., & Krissansen, G. 2005, "Successes in repairing and reversing the loss of axonal and oligodendrocytes damage of CNS in experimental autoimmune encephalomyelitis (EAE) - an animal model of multiple sclerosis (MS)", Tissue Antigens, vol. 66, no. 5.

Kanwar, J. R., Harrison, J. E., Wang, D., Leung, E., Mueller, W., Wagner, N., & Krissansen, G. W. 2000a, "Beta7 integrins contribute to demyelinating disease of the central nervous system", J Neuroimmunol, vol. 103, no. 2, pp. 146-152.

Kanwar, J. R., Kanwar, R. K., & Krissansen, G. W. 2004, "Simultaneous neuroprotection and blockade of inflammation reverses autoimmune encephalomyelitis", Brain, vol. 127, no. Pt 6, pp. 1313-1331.

Kanwar, J. R., Kanwar, R. K., Wang, D., & Krissansen, G. W. 2000b, "Prevention of a chronic progressive form of experimental autoimmune encephalomyelitis by an antibody against mucosal addressin cell adhesion molecule-1, given early in the course of disease progression", Immunol.Cell Biol., vol. 78, no. 6, pp. 641-645.

Kardys, E. & Hashim, G. A. 1981, "Experimental allergic encephalomyelitis in Lewis rats: immunoregulation of disease by a single amino acid substitution in the disease-inducing determinant", J.Immunol., vol. 127, no. 3, pp. 862-866.

Karlik, S., Keszthelyi, E., & Horner, H. 1995, "Anti-alpha-4 treatment reverses active EAE 28 days following disease appearance", Society for Neuroscience Abstracts, vol. 21, no. 1-3.

Karlik, S. J., Grant, E., Norley, C., & Hall, E. D. 1991, "Attenuation of Experimental Allergic Encephalomyelitis Eae by the 21 Aminosteroid Tirilazad Mesylate U-74006F", Society for Neuroscience Abstracts, vol. 17, no. 1-2.

Karlik, S. J., Munoz, D., St, L. J., & Strejan, G. 1999, "Correlation between MRI and clinico-pathological manifestations in Lewis rats protected from experimental allergic encephalomyelitis by acylated synthetic peptide of myelin basic protein", Magn Reson.Imaging, vol. 17, no. 5, pp. 731-737.

Karlik, S. J., Stavraky, R. T., & Hall, E. D. 1996, "Comparison of tirilazad mesylate (U-74006F) and methylprednisolone sodium succinate treatments in experimental allergic encephalomyelitis in the guinea pig", Mult.Scler., vol. 1, no. 4, pp. 228-235.

Karpus, W. J., Kennedy, K. J., Smith, W. S., & Miller, S. D. 1996, "Inhibition of relapsing experimental autoimmune encephalomyelitis in SJL mice by feeding the immunodominant PLP139-151 peptide", J.Neurosci.Res., vol. 45, no. 4, pp. 410-423.

Karpus, W. J., Konkol, R. J., & Killen, J. A. 1988, "Central catecholamine neurotoxin administration. 1. Immunological changes associated with the suppression of experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 18, no. 1, pp. 61-73.

Karpus, W. J., Lukacs, N. W., McRae, B. L., Strieter, R. M., Kunkel, S. L., & Miller, S. D. 1995, "An important role for the chemokine macrophage inflammatory protein-1 alpha in the pathogenesis of the T cell-mediated autoimmune disease, experimental autoimmune encephalomyelitis", J Immunol, vol. 155, no. 10, pp. 5003-5010.

Karpus, W. J. & Swanborg, R. H. 1991, "Protection against experimental autoimmune encephalomyelitis requires both CD4+ T suppressor cells and myelin basic protein-primed B cells", J.Neuroimmunol., vol. 33, no. 2, pp. 173-177.

Karussis, D., Abramsky, O., Grigoriadis, N., Chapman, J., Mizrachi-Koll, R., Niv, H., & Kloog, Y. 2001, "The Ras-pathway inhibitor, S-trans-trans-farnesylthiosalicylic acid, suppresses experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 120, no. 1-2, pp. 1-9.

Karussis, D., Vourka-Karussis, U., Mizrachi-Koll, R., & Abramsky, O. 1999, "Acute/relapsing experimental autoimmune encephalomyelitis: induction of long lasting, antigen-specific tolerance by syngeneic bone marrow transplantation", Mult Scler, vol. 5, no. 1, pp. 17-21.

Karussis, D. M., Lehmann, D., Slavin, S., Ben Nun, A., & Abramsky, O. 1991a, "Immunosuppression by High-Dose Cytoreductive Therapy and Bone Marrow Transplantation Bmt As A Therapeutic Approach in Chronic-Relapsing Autoimmune Encephalomyelitis Cr-Eae", Neurology, vol. 41, no. 3 SUPPL. 1.

Karussis, D. M., Lehmann, D., Slavin, S., Vourka-Karussis, U., Mizrachi-Koll, R., Ovadia, H., Ben-Nun, A., Kalland, T., & Abramsky, O. 1993a, "Inhibition of acute, experimental autoimmune encephalomyelitis by the synthetic immunomodulator linomide", Ann.Neurol., vol. 34, no. 5, pp. 654-660.

Karussis, D. M., Lehmann, D., Slavin, S., Vourka-Karussis, U., Mizrachi-Koll, R., Ovadia, H., Kalland, T., & Abramsky, O. 1993b, "Treatment of chronic-relapsing experimental autoimmune encephalomyelitis with the synthetic immunomodulator linomide (quinoline-3-carboxamide)", Proc.Natl.Acad.Sci.U.S.A, vol. 90, no. 14, pp. 6400-6404.

Karussis, D. M., Slavin, S., Ben Nun, A., Lehman, D., Mizrachi-Kol, R., & Abramsky, O. 1991b, "Induction of Tolerance to Self Antigens Through Bone Marrow Transplantation Bmt As A Therapeutic Approach in Acute and Chronic Relapsing Cr-Eae Experimental Autoimmune Encephalomyelitis", Journal of Neuroimmunology no. SUPPL. 1.

Karussis, D. M., Slavin, S., Ben-Nun, A., Ovadia, H., Vourka-Karussis, U., Lehmann, D., Mizrachi-Kol, R., & Abramsky, O. 1992a, "Chronic-relapsing experimental autoimmune encephalomyelitis (CR-EAE): treatment and induction of tolerance, with high dose cyclophosphamide followed by syngeneic bone marrow transplantation", J.Neuroimmunol., vol. 39, no. 3, pp. 201-210.

Karussis, D. M., Slavin, S., Lehmann, D., Mizrachi-Koll, R., Abramsky, O., & Ben-Nun, A. 1992b, "Prevention of experimental autoimmune encephalomyelitis and induction of tolerance with acute immunosuppression followed by syngeneic bone marrow transplantation", J.Immunol., vol. 148, no. 6, pp. 1693-1698.

Karussis, D. M., Vourka-Karussis, U., Lehmann, D., Ovadia, H., Mizrachi-Koll, R., Ben-Nun, A., Abramsky, O., & Slavin, S. 1993c, "Prevention and reversal of adoptively transferred, chronic relapsing experimental autoimmune encephalomyelitis with a single high dose cytoreductive treatment followed by syngeneic bone marrow transplantation", J.Clin.Invest, vol. 92, no. 2, pp. 765-772.

Kasckow, J. W., Tabira, T., Itoyama, Y., Kuroiwa, Y., Takenaka, A., & Nagai, Y. 1981, "Experimental allergic encephalomyelitis: suppression with SD-170, a new synthetic drug", Jpn.J.Exp.Med., vol. 51, no. 5, pp. 293-298.

Kassabova, T., Staykova, M., Balevska, P., Atanassov, B., & Goranov, I. 1990, "Anti-oxidant capacity of spinal cord and erythrocytes of guinea pigs in case of experimental allergic encephalomyelitis and after disease suppression", Acta Neurol.Scand., vol. 82, no. 2, pp. 116-120.

Kassis, I., Grigoriadis, N., Gowda-Kurkalli, B., Mizrachi-Kol, R., Ben Hur, T., Slavin, S., Abramsky, O., & Karussis, D. 2008, "Neuroprotection and immunomodulation with mesenchymal stem cells in chronic experimental autoimmune encephalomyelitis", Arch Neurol, vol. 65, no. 6.

Kataoka, H., Sugahara, K., Shimano, K., Maeda, Y., Koyama, M., Fukunari, A., & Chiba, K. 2006, "Fingolimod (FTY720), sphingosine 1-phosphate receptor modulator, ameliorates experimental autoimmune encephalomyelitis (EAE) I. Effect of FTY720 and FTY720-phosphate on myelin proteolipid protein-induced EAE in SJL/J mice", 8Th International Congress of Neuroimmunology pp. 117-120.

Kataoka, H., Sugahara, K., Shimano, K., Teshima, K., Koyama, M., Fukunari, A., & Chiba, K. 2005, "FTY720, sphingosine 1-phosphate receptor modulator, ameliorates experimental autoimmune encephalomyelitis by inhibition of T cell infiltration", Cell Mol.Immunol., vol. 2, no. 6, pp. 439-448.

Kato, H., Ito, A., Kawanokuchi, J., Jin, S., Mizuno, T., Ojika, K., Ueda, R., & Suzumura, A. 2004, "Pituitary adenylate cyclase-activating polypeptide (PACAP) ameliorates experimental autoimmune encephalomyelitis by suppressing the functions of antigen presenting cells", Mult.Scler., vol. 10, no. 6, pp. 651-659.

Kato, S. & Nakamura, H. 1988, "Suppression of acute experimental allergic encephalomyelitis by synthetic serum thymic factor. Clinical, histopathological, and immunohistochemical studies", Acta Neuropathol.(Berl), vol. 75, no. 4, pp. 337-344.

Kato, S., Nakamura, H., Naiki, M., Takeoka, Y., & Suehiro, S. 1991, "Suppression of acute experimental allergic encephalomyelitis by neurotropin: clinical, histopathologic, immunologic and immunohistochemical studies", J.Neuroimmunol., vol. 35, no. 1-3, pp. 237-245.

Kaushansky, N., Zilkha-Falb, R., Hemo, R., Lassman, H., Eisenstein, M., Sas, A., & Ben Nun, A. 2007, "Pathogenic T cells in MOBP-induced murine EAE are predominantly focused to recognition of MOBP21F and MOBP27P epitopic residues", Eur.J.Immunol., vol. 37, no. 11, pp. 3281-3292.

Kawaguchi, Y. 1999, "A gene therapy or purified CTLA4IgG treatment of experimental allergic encephalomyelitis", Hokkaido Igaku Zasshi, vol. 74, no. 6, pp. 467-475.

Kawai, K., Kobayashi, Y., Shiratori, M., Sobue, G., Tamatani, T., Miyasaka, M., & Yoshikai, Y. 1996, "Intrathecal administration of antibodies against LFA-1 and against ICAM-1 suppresses experimental allergic encephalomyelitis in rats", Cell Immunol., vol. 171, no. 2, pp. 262-268.

Kayhan, B., Aharoni, R., & Arnon, R. 2003, "Glatiramer acetate (Copaxone) regulates nitric oxide and related cytokine secretion in experimental autoimmune encephalomyelitis", Immunol.Lett., vol. 88, no. 3, pp. 185-192.

Keith, A. B., Arnon, R., Teitelbaum, D., Caspary, E. A., & Wisniewski, H. M. 1979, "The effect of Cop 1, a synthetic polypeptide, on chronic relapsing experimental allergic encephalomyelitis in guinea pigs", J.Neurol.Sci., vol. 42, no. 2, pp. 267-274.

Kelemen, J., Feszt, T., Becus-Laurentiu, M., & Gyergyay, F. 1970, "[Research on experimental encephalopathies. 28. Action of chlorpromazine associated with promethazine on the course of experimental allergic encephalomyelitis]", Stud.Cercet.Neurol., vol. 15, no. 2, pp. 85-93.

Kelly, K. A. & Whitacre, C. C. 1996, "Oral tolerance in EAE: reversal of tolerance by T helper cell cytokines", J.Neuroimmunol., vol. 66, no. 1-2, pp. 77-84.

Kennedy, K. J., Smith, W. S., Miller, S. D., & Karpus, W. J. 1997, "Induction of antigen-specific tolerance for the treatment of ongoing, relapsing autoimmune encephalomyelitis: a comparison between oral and peripheral tolerance", J.Immunol., vol. 159, no. 2, pp. 1036-1044.

Kennedy, M. K., Dal Canto, M. C., Trotter, J. L., & Miller, S. D. 1988, "Specific immune regulation of chronic-relapsing experimental allergic encephalomyelitis in mice", J.Immunol., vol. 141, no. 9, pp. 2986-2993.

Kennedy, M. K., Tan, L. J., Dal Canto, M. C., & Miller, S. D. 1990a, "Regulation of the effector stages of experimental autoimmune encephalomyelitis via neuroantigen-specific tolerance induction", J.Immunol., vol. 145, no. 1, pp. 117-126.

Kennedy, M. K., Tan, L. J., Dal Canto, M. C., Tuohy, V. K., Lu, Z. J., Trotter, J. L., & Miller, S. D. 1990b, "Inhibition of murine relapsing experimental autoimmune encephalomyelitis by immune tolerance to proteolipid protein and its encephalitogenic peptides", J.Immunol., vol. 144, no. 3, pp. 909-915.

Kent, S. J., Karlik, S. J., Rice, G. P., & Horner, H. C. 1995, "A monoclonal antibody to alpha 4-integrin reverses the MR-detectable signs of experimental allergic encephalomyelitis in the guinea pig", J.Magn Reson.Imaging, vol. 5, no. 5, pp. 535-540.

Kerfoot, S. M., Norman, M. U., Lapointe, B. M., Bonder, C. S., Zbytnuik, L., & Kubes, P. 2006, "Reevaluation of P-selectin and alpha 4 integrin as targets for the treatment of experimental autoimmune encephalomyelitis", J.Immunol., vol. 176, no. 10, pp. 6225-6234.

Keszthelyi, E., Karlik, S., Hyduk, S., Rice, G., Gordon, G., Yednock, T., & Horner, H. 1996, "Evidence for a prolonged role of alpha-4 integrin throughout active experimental allergic encephalomyelitis", Neurology, vol. 47, no. 4, pp. 1053-1059.

Khan, A., Hill, J. M., & Adachi, M. 1970, "L-asparaginase in experimental auto-immune disease: inhibition of allergic encephalomyelitis", J.Immunol., vol. 105, no. 1, pp. 256-258.

Khan, A. & Levine, S. 1974, "Further studies on the inhibition of allergic encephalomyelitis by L-asparaginase", J.Immunol., vol. 113, no. 1, pp. 367-370.

Khoury, S. J., Gallon, L., Chen, W., Betres, K., Russell, M. E., Hancock, W. W., Carpenter, C. B., Sayegh, M. H., & Weiner, H. L. 1995, "Mechanisms of acquired thymic tolerance in experimental autoimmune encephalomyelitis: thymic dendritic-enriched cells induce specific peripheral T cell unresponsiveness in vivo", J.Exp.Med., vol. 182, no. 2, pp. 357-366.

Khoury, S. J., Gallon, L., Verburg, R. R., Chandraker, A., Peach, R., Linsley, P. S., Turka, L. A., Hancock, W. W., & Sayegh, M. H. 1996, "Ex vivo treatment of antigen-presenting cells with CTLA4Ig and encephalitogenic peptide prevents experimental autoimmune encephalomyelitis in the Lewis rat", J.Immunol., vol. 157, no. 8, pp. 3700-3705.

Khoury, S. J., Lider, O., Al-Sabbagh, A., & Weiner, H. L. 1990, "Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein. III. Synergistic effect of lipopolysaccharide", Cell Immunol., vol. 131, no. 2, pp. 302-310.

Khoury, S. J., Sayegh, M. H., Hancock, W. W., Gallon, L., Carpenter, C. B., & Weiner, H. L. 1993, "Acquired tolerance to experimental autoimmune encephalomyelitis by intrathymic injection of myelin basic protein or its major encephalitogenic peptide", J.Exp.Med., vol. 178, no. 2, pp. 559-566.

Kikukawa, A., Peterson, B. S., & Deutsch, H. F. 1988, "Attempts to suppress experimental allergic encephalomyelitis in rats with alpha fetoprotein", Tumour.Biol., vol. 9, no. 2-3, pp. 84-94.

Kim, S., Liva, S. M., Dalal, M. A., Verity, M. A., & Voskuhl, R. R. 1999, "Estriol ameliorates autoimmune demyelinating disease: implications for multiple sclerosis", Neurology, vol. 52, no. 6, pp. 1230-1238.

Kinoshameg, S. A. & Persinger, M. A. 2004, "Suppression of experimental allergic encephalomyelitis in rats by 50-nT, 7-Hz amplitude-modulated nocturnal magnetic fields depends on when after inoculation the fields are applied", Neurosci.Lett., vol. 370, no. 2-3, pp. 166-170.

Kipper-Galperin, M., Galilly, R., Danenberg, H. D., & Brenner, T. 1999, "Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interlukin-6] in astrocytes", Int.J.Dev.Neurosci., vol. 17, no. 8, pp. 765-775.

Klein-Franke, A. & Munder, P. G. 1992, "Alkyllysophospholipid prevents induction of experimental allergic encephalomyelitis", J.Autoimmun., vol. 5, no. 1, pp. 83-91.

Klemann, C., Raveney, B. J., Klemann, A. K., Ozawa, T., von Horsten, S., Shudo, K., Oki, S., & Yamamura, T. 2009, "Synthetic retinoid AM80 inhibits Th17 cells and ameliorates experimental autoimmune encephalomyelitis", Am J Pathol, vol. 174, no. 6, pp. 2234-2245.

Klinkert, W. E. F., Kojima, K., Lesslauer, W., Rinner, W., Lassmann, H., & Wekerle, H. 1997, "TNF-alpha receptor fusion protein prevents experimental auto-immune encephalomyelitis and demyelination in Lewis rats: An overview", Journal of Neuroimmunology.72(2)()(pp 163-168), 1997.Date of Publication: Feb 1997. no. 2, pp. 163-168.

Kobayashi, N., Kobayashi, H., Gu, L., Malefyt, T., & Siahaan, T. J. 2007, "Antigen-specific suppression of experimental autoimmune encephalomyelitis by a novel bifunctional peptide inhibitor", J.Pharmacol.Exp.Ther., vol. 322, no. 2, pp. 879-886.

Koh, C. S. & Paterson, P. Y. 1987, "Suppression of clinical signs of cell-transferred experimental allergic encephalomyelitis and altered cerebrovascular permeability in Lewis rats treated with a plasminogen activator inhibitor", Cell Immunol., vol. 107, no. 1, pp. 52-63.

Kohm, A. P., Carpentier, P. A., Anger, H. A., & Miller, S. D. 2002, "Cutting edge: CD4+CD25+ regulatory T cells suppress antigen-specific autoreactive immune responses and central nervous system inflammation during active experimental autoimmune encephalomyelitis", J Immunol, vol. 169, no. 9, pp. 4712-4716.

Kohm, A. P., Williams, J. S., Bickford, A. L., McMahon, J. S., Chatenoud, L., Bach, J. F., Bluestone, J. A., & Miller, S. D. 2005, "Treatment with nonmitogenic anti-CD3 monoclonal antibody induces CD4+ T cell unresponsiveness and functional reversal of established experimental autoimmune encephalomyelitis", J.Immunol., vol. 174, no. 8, pp. 4525-4534.

Komarek, A. & Dietrich, F. M. 1971, "Chemical prevention of experimental allergic encephalomyelitis in rats: a quantitative evaluation of steroids and various non-steroid drugs", Arch.Int.Pharmacodyn.Ther., vol. 193, no. 2, pp. 249-257.

Konkol, R. J., Wesselmann, U., Karpus, W. J., Leo, G. L., Killen, J. A., & Roerig, D. L. 1990, "Suppression of clinical weakness in experimental autoimmune encephalomyelitis associated with weight changes, and post-decapitation convulsions after intracisternal-ventricular administration of 6-hydroxydopamine", J.Neuroimmunol., vol. 26, no. 1, pp. 25-34.

Korn, T., Magnus, T., Toyka, K., & Jung, S. 2004, "Modulation of effector cell functions in experimental autoimmune encephalomyelitis by leflunomide--mechanisms independent of pyrimidine depletion", J.Leukoc.Biol., vol. 76, no. 5, pp. 950-960.

Korner, H., Lemckert, F. A., Chaudhri, G., Etteldorf, S., & Sedgwick, J. D. 1997, "Tumor necrosis factor blockade in actively induced experimental autoimmune encephalomyelitis prevents clinical disease despite activated T cell infiltration to the central nervous system", Eur.J.Immunol., vol. 27, no. 8, pp. 1973-1981.

Kovarik, J., Chabannes, D., & Borel, J. F. 1995, "Immunoregulation and drug treatment in chronic relapsing experimental allergic encephalomyelitis in the Lewis rat", Int.J.Immunopharmacol., vol. 17, no. 4, pp. 255-263.

Kryzhanovskii, G. N., Vilkov, G. A., & Stepanenko, E. M. 1984, "[Protective action of antioxidant preparations on the development of experimental allergic encephalomyelitis in guinea pigs]", Biull.Eksp.Biol.Med., vol. 98, no. 11, pp. 527-530.

Kuchroo, V., Greer, J., Kaul, D., Ishoka, G., Franco, A., Sette, A., Sobel, R., & Lees, M. 1994a, "A T cell receptor (TcR) antagonist peptide prevents experimental allergic encephalomyelitis (EAE) mediated by a diverse T cell repertoire", Faseb Journal, vol. 8, no. 4-5.

Kuchroo, V. K., Das, M. P., Brown, J. A., Ranger, A. M., Zamvil, S. S., Sobel, R. A., Weiner, H. L., Nabavi, N., & Glimcher, L. H. 1995, "B7-1 and B7-2 costimulatory molecules activate differentially the Th1/Th2 developmental pathways: application to autoimmune disease therapy", Cell, vol. 80, no. 5, pp. 707-718.

Kuchroo, V. K., Greer, J. M., Kaul, D., Ishioka, G., Franco, A., Sette, A., Sobel, R. A., & Lees, M. B. 1994b, "A single TCR antagonist peptide inhibits experimental allergic encephalomyelitis mediated by a diverse T cell repertoire", J.Immunol., vol. 153, no. 7, pp. 3326-3336.

Kuhlmann, T., Remington, L., Cognet, I., Bourbonniere, L., Zehntner, S., Guilhot, F., Herman, A., Guay-Giroux, A., Antel, J. P., Owens, T., & Gauchat, J. F. 2006, "Continued administration of ciliary neurotrophic factor protects mice from inflammatory pathology in experimental autoimmune encephalomyelitis", Am.J.Pathol., vol. 169, no. 2, pp. 584-598.

Kuhns, M. S., Epshteyn, V., Sobel, R. A., & Allison, J. P. 2000, "Cytotoxic T lymphocyte antigen-4 (CTLA-4) regulates the size, reactivity, and function of a primed pool of CD4+ T cells", Proc Natl Acad Sci U S A, vol. 97, no. 23, pp. 12711-12716.

Kumar, V., Coulsell, E., Ober, B., Hubbard, G., Sercarz, E., & Ward, E. S. 1997, "Recombinant T cell receptor molecules can prevent and reverse experimental autoimmune encephalomyelitis: dose effects and involvement of both CD4 and CD8 T cells", J.Immunol., vol. 159, no. 10, pp. 5150-5156.

Kumar, V., Maglione, J., Thatte, J., Pederson, B., Sercarz, E., & Ward, E. S. 2001, "Induction of a type 1 regulatory CD4 T cell response following V beta 8.2 DNA vaccination results in immune deviation and protection from experimental autoimmune encephalomyelitis", Int.Immunol., vol. 13, no. 6, pp. 835-841.

Kupfer, M., Kupfer, G., & Berger, U. 1969, "[Immunoactivation with ethylnitrosourea]", Naturwissenschaften, vol. 56, no. 4, p. 216.

Kuroda, Y. 1979, "[Immunological studies on experimental allergic encephalomyelitis--suppression by concanavalin A (author's transl)]", Fukuoka Igaku Zasshi, vol. 70, no. 9, pp. 513-528.

Kuroda, Y., Mori, R., & Aoki, T. 1980, "Concanavalin A inhibits the development of experimental allergic encephalomyelitis in guinea pigs", Int.Arch.Allergy Appl.Immunol., vol. 61, no. 3, pp. 308-320.

Kuruvilla, A. P., Shah, R., Hochwald, G. M., Liggitt, H. D., Palladino, M. A., & Thorbecke, G. J. 1991, "Protective effect of transforming growth factor beta 1 on experimental autoimmune diseases in mice", Proc.Natl.Acad.Sci.U.S.A, vol. 88, no. 7, pp. 2918-2921.

Kwak, H. J., Pae, H. O., Oh, G. S., Choi, B. M., Jang, S. I., Jung, S., & Chung, H. T. 2003, "Molsidomine ameliorates experimental allergic encephalomyelitis in Lewis rats", Immunopharmacol.Immunotoxicol., vol. 25, no. 1, pp. 41-52.

Kwiatkowska-Patzer, B., Walski, M., Frontczak-Baniewicz, M., Zalewska, T., Baranowska, B., & Lipkowski, A. W. 2004, "Matrix metalloproteases activity and ultrastructural changes in the early phase of experimental allergic encephalomyelitis. The effect of oral treatment with spinal cord hydrolisate proteins in Lewis rat. The pilot study", Folia Neuropathologica.42(2)()(pp 107-111), 2004.Date of Publication: 2004. no. 2, pp. 107-111.

Kwidzinski, E., Bunse, J., Aktas, O., Richter, D., Mutlu, L., Zipp, F., Nitsch, R., & Bechmann, I. 2005, "Indolamine 2,3-dioxygenase is expressed in the CNS and down-regulates autoimmune inflammation", FASEB J, vol. 19, no. 10, pp. 1347-1349.

Kwidzinski, E., Bunse, J., Kovac, A. D., Ullrich, O., Zipp, F., Nitsch, R., & Bechmann, I. 2003, "IDO (indolamine 2,3-dioxygenase) expression and function in the CNS", Advances in Experimental Medicine and Biology.527()(pp 113-118), 2003.Date of Publication: 2003. pp. 113-118.

Kwon, S. S., Kim, N., & Yoo, T. J. 2005, "The effects of intradermal vaccination with DNA encoding for the T-cell receptor on the induction of experimental autoimmune encephalomyelitis in B10.PL mice", J.Korean Med.Sci., vol. 20, no. 6, pp. 1039-1045.

La Flamme, A. C., Harvie, M., McNeill, A., Goldsack, L., Tierney, J. B., & Backstrom, B. T. 2006, "Fcgamma receptor-ligating complexes improve the course of experimental autoimmune encephalomyelitis by enhancing basal Th2 responses", Immunol.Cell Biol., vol. 84, no. 6, pp. 522-529.

Laman, J. D., 't Hart, B. A., Brok, H., Meurs, M., Schellekens, M. M., Kasran, A., Boon, L., Bauer, J., Boer, M., & Ceuppens, J. 2002, "Protection of marmoset monkeys against EAE by treatment with a murine antibody blocking CD40 (mu5D12)", Eur.J.Immunol., vol. 32, no. 8, pp. 2218-2228.

Laman, J. D., Maassen, C. B., Schellekens, M. M., Visser, L., Kap, M., de, J. E., van, P. M., van Stipdonk, M. J., van, M. M., Schwarzler, C., & Gunthert, U. 1998, "Therapy with antibodies against CD40L (CD154) and CD44-variant isoforms reduces experimental autoimmune encephalomyelitis induced by a proteolipid protein peptide", Mult.Scler., vol. 4, no. 3, pp. 147-153.

Lamont, A. G., Sette, A., Fujinami, R., Colon, S. M., Miles, C., & Grey, H. M. 1990, "Inhibition of experimental autoimmune encephalomyelitis induction in SJL/J mice by using a peptide with high affinity for IAs molecules", J.Immunol., vol. 145, no. 6, pp. 1687-1693.

Land, W., Frick, E., Brendel, W., Roscher, R., & Pichlmayr, R. 1968, "[Experimental allergic encephalomyelitis: a study model for testing the effects of an heterologous antilymphocyte serum on the cellular immune reaction]", Langenbecks Arch.Chir, vol. 322, pp. 525-528.

Lando, Z., Dori, Y., Teitelbamum, D., & Arnon, R. 1981, "Unresponsiveness to experimental allergic encephalomyelitis in mice: replacement of suppressor cells by a soluble factor", J.Immunol., vol. 127, no. 5, pp. 1915-1919.

Lando, Z., Teitelbaum, D., & Arnon, R. 1979a, "Effect of Cyclo Phosphamide on Suppressor Cell Activity in Mice Unresponsive to Experimental Allergic Encephalo Myelitis", Journal of Immunology, vol. 123, no. 5, pp. 2156-2160.

Lando, Z., Teitelbaum, D., & Arnon, R. 1979b, "Effect of cyclophosphamide on suppressor cell activity in mice unresponsive to EAE", J.Immunol., vol. 123, no. 5, pp. 2156-2160.

Lange, F., Bajtner, E., Rintisch, C., Nandakumar, K. S., Sack, U., & Holmdahl, R. 2005, "Methotrexate ameliorates T cell dependent autoimmune arthritis and encephalomyelitis but not antibody induced or fibroblast induced arthritis", Ann.Rheum.Dis., vol. 64, no. 4, pp. 599-605.

Lassmann, H., Brunner, C., Bradl, M., & Linington, C. 1988, "Experimental allergic encephalomyelitis: the balance between encephalitogenic T lymphocytes and demyelinating antibodies determines size and structure of demyelinated lesions", Acta Neuropathol.(Berl), vol. 75, no. 6, pp. 566-576.

Lavasani, S., Dzhambazov, B., & Andersson, M. 2007, "Monoclonal antibody against T-cell receptor alphabeta induces self-tolerance in chronic experimental autoimmune encephalomyelitis", Scand J Immunol, vol. 65, no. 1, pp. 39-47.

Lavrnja, I., Stojkov, D., Pekovic, S., Subasic, S., Mostarica-Stojkovic, M., Stosic-Grujicic, S., Nedeljkovic, N., Medic-Mijacevic, L., Rakic, L., & Stojiljkovi, M. 2005, "Combination of nucleoside analogues tiazofurin and ribavirin downregulates experimental autoimmune encephalomyelitis", Ann.N.Y.Acad.Sci., vol. 1048, pp. 392-395.

Lawson, B. R., Manenkova, Y., Ahamed, J., Chen, X., Zou, J. P., Baccala, R., Theofilopoulos, A. N., & Yuan, C. 2007, "Inhibition of transmethylation down-regulates CD4 T cell activation and curtails development of autoimmunity in a model system", J Immunol, vol. 178, no. 8, pp. 5366-5374.

Leadbetter, E. A., Bourque, C. R., Devaux, B., Olson, C. D., Sunshine, G. H., Hirani, S., Wallner, B. P., Smilek, D. E., & Happ, M. P. 1998, "Experimental autoimmune encephalomyelitis induced with a combination of myelin basic protein and myelin oligodendrocyte glycoprotein is ameliorated by administration of a single myelin basic protein peptide", J.Immunol., vol. 161, no. 1, pp. 504-512.

Lee, Y. H., Ishida, Y., Rifa'i, M., Shi, Z., Isobe, K., & Suzuki, H. 2008, "Essential role of CD8+CD122+ regulatory T cells in the recovery from experimental autoimmune encephalomyelitis", J.Immunol., vol. 180, no. 2, pp. 825-832.

Leech, M. D., Chung, C. Y., Culshaw, A., & Anderton, S. M. 2007, "Peptide-based immunotherapy of experimental autoimmune encephalomyelitis without anaphylaxis", Eur.J.Immunol., vol. 37, no. 12, pp. 3576-3581.

Leger, O. J., Yednock, T. A., Tanner, L., Horner, H. C., Hines, D. K., Keen, S., Saldanha, J., Jones, S. T., Fritz, L. C., & Bendig, M. M. 1997, "Humanization of a mouse antibody against human alpha-4 integrin: a potential therapeutic for the treatment of multiple sclerosis", Hum.Antibodies, vol. 8, no. 1, pp. 3-16.

Legge, K. L., Min, B., Bell, J. J., Caprio, J. C., Li, L., Gregg, R. K., & Zaghouani, H. 2000, "Coupling of peripheral tolerance to endogenous interleukin 10 promotes effective modulation of myelin-activated T cells and ameliorates experimental allergic encephalomyelitis", J Exp Med, vol. 191, no. 12, pp. 2039-2052.

Lehmann, D. & Ben-Nun, A. 1992, "Bacterial agents protect against autoimmune disease. I. Mice pre-exposed to Bordetella pertussis or Mycobacterium tuberculosis are highly refractory to induction of experimental autoimmune encephalomyelitis", J.Autoimmun., vol. 5, no. 6, pp. 675-690.

Lehmann, D., Karussis, D., Misrachi-Koll, R., Shezen, E., Ovadia, H., & Abramsky, O. 1994, "Oral administration of the oxidant-scavenger N-acetyl-L-cysteine inhibits acute experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 50, no. 1, pp. 35-42.

Lehmann, D., Karussis, D. M., Fluresco, D., Mizrachi-Koll, R., Ovadia, H., Shezen, E., Kalland, T., & Abramsky, O. 1997, "Immunomodulation of autoimmunity by linomide: inhibition of antigen presentation through down regulation of macrophage activity in the model of experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 74, no. 1-2, pp. 102-110.

Lehmann, D., Karussis, D. M., Slavin, S., Abramsky, O., & Ben Nun, A. 1991, "Radical Immunosuppression and Bone Marrow Transplantation Bmt As A Therapeutic Approach in Acute Autoimmune Encephalomyelitis Eae", Neurology, vol. 41, no. 3 SUPPL. 1.

Leibowitz, S. 1968, "Antilymphocyte serum in the later stages of experimental allergic encephalomyelitis", Lancet, vol. 7542, pp. 569-570.

Leibowitz, S., Lessof, M. H., & Kennedy, L. A. 1968, "The effect of anti-lymphocyte serum on experimental allergic encephalomyelitis in the guinea-pig", Clin.Exp.Immunol., vol. 3, no. 8, pp. 753-760.

Lemire, J. M. & Archer, D. C. 1991, "1,25-dihydroxyvitamin D3 prevents the in vivo induction of murine experimental autoimmune encephalomyelitis", J.Clin.Invest, vol. 87, no. 3, pp. 1103-1107.

Lemire, J. M., Archer, D. C., & Reddy, G. S. 1994, "1,25-Dihydroxy-24-OXO-16ene-vitamin D3, a renal metabolite of the vitamin D analog 1,25-dihydroxy-16ene-vitamin D3, exerts immunosuppressive activity equal to its parent without causing hypercalcemia in vivo", Endocrinology, vol. 135, no. 6, pp. 2818-2821.

Leonard, J. P., Waldburger, K. E., & Goldman, S. J. 1995, "Prevention of experimental autoimmune encephalomyelitis by antibodies against interleukin 12", J.Exp.Med., vol. 181, no. 1, pp. 381-386.

Leone, D. R., Giza, K., Gill, A., Dolinski, B. M., Yang, W., Perper, S., Scott, D. M., Lee, W. C., Cornebise, M., Wortham, K., Nickerson-Nutter, C., Chen, L. L., Lepage, D., Spell, J. C., Whalley, E. T., Petter, R. C., Adams, S. P., Lobb, R. R., & Pepinsky, R. B. 2003, "An assessment of the mechanistic differences between two integrin alpha 4 beta 1 inhibitors, the monoclonal antibody TA-2 and the small molecule BIO5192, in rat experimental autoimmune encephalomyelitis", J.Pharmacol.Exp.Ther., vol. 305, no. 3, pp. 1150-1162.

Leong, S., Chan, A. H., Levy, J. G., & Hunt, D. W. 1996, "Transcutaneous photodynamic therapy alters the development of an adoptively transferred form of murine experimental autoimmune encephalomyelitis", Photochem.Photobiol., vol. 64, no. 5, pp. 751-757.

Levi-Schaffer, F., Riesel, N., Soffer, D., Abramsky, O., & Brenner, T. 1991, "Mast cell activity in experimental allergic encephalomyelitis", Mol Chem Neuropathol, vol. 15, no. 2, pp. 173-184.

Levine, S., Cochrane, C. G., Carpenter, C. B., & Behan, P. O. 1971, "Allergic encephalomyelitis: effect of complement depletion with cobra venom", Proc.Soc.Exp.Biol.Med., vol. 138, no. 1, pp. 285-289.

Levine, S., Hoenig, E. M., & Kies, M. W. 1970, "Allergic encephalomyelitis: immunologically specific inhibition of cellular passive transfer by encephalitogenic basic proteins", Clin.Exp.Immunol., vol. 6, no. 4, pp. 503-517.

Levine, S., Prineas, J., & Scheinberg, L. C. 1969, "Allergic encephalomyelitis: inhibition of cellular passive transfer by x-irradiation", Proc.Soc.Exp.Biol.Med., vol. 131, no. 3, pp. 986-990.

Levine, S. & Saltzman, A. 1986, "Regional suppression, therapy after onset and prevention of relapses in experimental allergic encephalomyelitis by mitoxantrone", J.Neuroimmunol., vol. 13, no. 2, pp. 175-181.

Levine, S. & Saltzman, A. 1989, "Suppression of experimental allergic encephalomyelitis in rats by mercuric chloride", Chem.Biol.Interact., vol. 69, no. 1, pp. 17-21.

Levine, S. & Saltzman, A. 1991, "Inhibition of experimental allergic encephalomyelitis by lithium chloride: specific effect or nonspecific stress?", Immunopharmacology, vol. 22, no. 3, pp. 207-213.

Levine, S. & Sowinski, R. 1976, "Necrotic myelopathy (myelomalacia) in rats with allergic encephalomyelitis treated with tilorone", Am J Pathol, vol. 82, no. 2, pp. 381-392.

Levine, S. & Sowinski, R. 1977a, "Effects of cycloleucine on macrophages and on experimental allergic encephalomyelitis", Exp.Mol.Pathol., vol. 26, no. 1, pp. 103-112.

Levine, S. & Sowinski, R. 1977b, "Suppression of the hyperacute form of experimental allergic encephalomyelitis by drugs", Arch Int Pharmacodyn.Ther, vol. 230, no. 2, pp. 309-318.

Levine, S. & Sowinski, R. 1977c, "Synergistic suppression of the hyperacute form of experimental allergic encephalomyelitis by tilorone and cycloleucine", Proc.Soc.Exp.Biol.Med., vol. 156, no. 3, pp. 457-460.

Levine, S. & Sowinski, R. 1978, "Suppression of experimental allergic encephalomyelitis by 6-hydroxyphthalaldehydic acid, O-(p-chlorobenzyl)oxime (EN3638)", J.Immunol., vol. 120, no. 2, pp. 602-606.

Levine, S. & Sowinski, R. 1979, "Suppression of experimental allergic encephalomyelitis by EN3638: dependence on adjuvants and treatment schedules", J.Immunopharmacol., vol. 1, no. 4, pp. 547-557.

Levine, S. & Sowinski, R. 1980, "Effect of essential fatty acid deficiency on experimental allergic encephalomyelitis in rats", J Nutr, vol. 110, no. 5, pp. 891-896.

Levine, S., Sowinski, R., & Abreu, S. L. 1983, "Suppression of experimental allergic encephalomyelitis by tilorone: cell transfer and interferon studies", Immunopharmacology, vol. 6, no. 1, pp. 23-30.

Levine, S., Sowinski, R., & Kies, M. W. 1972, "Treatment of experimental allergic encephalomyelitis with encephalitogenic basic proteins", Proc.Soc.Exp.Biol.Med., vol. 139, no. 2, pp. 506-510.

Li, C. G. 1989, "[Histopathologic observation on the therapeutic effect of Tripterygium wilfordii in treating experimental allergic encephalomyelitis]", Zhong.Xi.Yi.Jie.He.Za Zhi., vol. 9, no. 2, pp. 98-9, 70.

Li, F. Q., Sempowski, G. D., McKenna, S. E., Laskowitz, D. T., Colton, C. A., & Vitek, M. P. 2006a, "Apolipoprotein E-derived peptides ameliorate clinical disability and inflammatory infiltrates into the spinal cord in a murine model of multiple sclerosis", J.Pharmacol.Exp.Ther., vol. 318, no. 3, pp. 956-965.

Li, H., Mei, Y., Wang, Y., & Xu, L. 2006b, "Vasoactive intestinal polypeptide suppressed experimental autoimmune encephalomyelitis by inhibiting T helper 1 responses", J.Clin.Immunol., vol. 26, no. 5, pp. 430-437.

Li, H., Zhang, G. X., Chen, Y., Xu, H., Fitzgerald, D. C., Zhao, Z., & Rostami, A. 2008, "CD11c+CD11b+ dendritic cells play an important role in intravenous tolerance and the suppression of experimental autoimmune encephalomyelitis", J Immunol, vol. 181, no. 4, pp. 2483-2493.

Li, H. L., Liu, J. Q., Bai, X. F., vn der Meide, P. H., & Link, H. 1998a, "Dose-dependent mechanisms relate to nasal tolerance induction and protection against experimental autoimmune encephalomyelitis in Lewis rats", Immunology, vol. 94, no. 3, pp. 431-437.

Li, W., Maeda, Y., Yuan, R. R., Elkabes, S., Cook, S., & Dowling, P. 2004, "Beneficial effect of erythropoietin on experimental allergic encephalomyelitis", Ann.Neurol., vol. 56, no. 6, pp. 767-777.

Li, W., Quigley, L., Yao, D. L., Hudson, L. D., Brenner, M., Zhang, B. J., Brocke, S., McFarland, H. F., & Webster, H. D. 1998b, "Chronic relapsing experimental autoimmune encephalomyelitis: effects of insulin-like growth factor-I treatment on clinical deficits, lesion severity, glial responses, and blood brain barrier defects", J.Neuropathol.Exp.Neurol., vol. 57, no. 5, pp. 426-438.

Li, X., Yu, K., & Li, Z. 2008, "Effect of neuropeptide Y on white matter demyelination and serum interleukin-4 and gamma-interferon levels in the guinea pig with experimental allergic encephalomyelitis", Neural Regeneration Research.3(5)()(pp 554-557), 2008.Date of Publication: May 2008. no. 5, pp. 554-557.

Li, X. B. & Schluesener, H. J. 2006, "Therapeutic effects of cisplatin on rat experimental autoimmune encephalomyelitis", Arch.Immunol.Ther.Exp.(Warsz.), vol. 54, no. 1, pp. 51-53.

Liang, M., Mallari, C., Rosser, M., Ng, H. P., May, K., Monahan, S., Bauman, J. G., Islam, I., Ghannam, A., Buckman, B., Shaw, K., Wei, G. P., Xu, W., Zhao, Z., Ho, E., Shen, J., Oanh, H., Subramanyam, B., Vergona, R., Taub, D., Dunning, L., Harvey, S., Snider, R. M., Hesselgesser, J., Morrissey, M. M., & Perez, H. D. 2000, "Identification and characterization of a potent, selective, and orally active antagonist of the CC chemokine receptor-1", J.Biol.Chem., vol. 275, no. 25, pp. 19000-19008.

Lichtenegger, F. S., Kuerten, S., Faas, S., Boehm, B. O., Tary-Lehmann, M., & Lehmann, P. V. 2007, "Dissociation of experimental allergic encephalomyelitis protective effect and allergic side reactions in tolerization with neuroantigen", J.Immunol., vol. 178, no. 8, pp. 4749-4756.

Lider, O., Reshef, T., Beraud, E., Ben-Nun, A., & Cohen, I. R. 1988, "Anti-idiotypic network induced by T cell vaccination against experimental autoimmune encephalomyelitis", Science, vol. 239, no. 4836, pp. 181-183.

Lider, O., Santos, L. M., Lee, C. S., Higgins, P. J., & Weiner, H. L. 1989, "Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein. II. Suppression of disease and in vitro immune responses is mediated by antigen-specific CD8+ T lymphocytes", J.Immunol., vol. 142, no. 3, pp. 748-752.

Lider, O., Shinitzky, M., & Cohen, I. R. 1986, "Vaccination against experimental autoimmune diseases using T lymphocytes treated with hydrostatic pressure", Ann.N.Y.Acad.Sci., vol. 475, pp. 267-273.

Liedtke, W., Cannella, B., Mazzaccaro, R. J., Clements, J. M., Miller, K. M., Wucherpfennig, K. W., Gearing, A. J., & Raine, C. S. 1998, "Effective treatment of models of multiple sclerosis by matrix metalloproteinase inhibitors", Ann.Neurol., vol. 44, no. 1, pp. 35-46.

Linington, C., Bradl, M., Lassmann, H., Brunner, C., & Vass, K. 1988, "Augmentation of demyelination in rat acute allergic encephalomyelitis by circulating mouse monoclonal antibodies directed against a myelin/oligodendrocyte glycoprotein", American Journal of Pathology.130(3)()(pp 443-454), 1988.Date of Publication: 1988. no. 3, pp. 443-454.

Linington, C., Morgan, B. P., Scolding, N. J., Wilkins, P., Piddlesden, S., & Compston, D. A. 1989, "The role of complement in the pathogenesis of experimental allergic encephalomyelitis", Brain, vol. 112 (Pt 4), pp. 895-911.

Linker, R. A., Luhder, F., Kallen, K. J., Lee, D. H., Engelhardt, B., Rose-John, S., & Gold, R. 2008a, "IL-6 transsignalling modulates the early effector phase of EAE and targets the blood-brain barrier", J Neuroimmunol, vol. 205, no. 1-2, pp. 64-72.

Linker, R. A., Weller, C., Luhder, F., Mohr, A., Schmidt, J., Knauth, M., Metselaar, J. M., & Gold, R. 2008b, "Liposomal glucocorticosteroids in treatment of chronic autoimmune demyelination: long-term protective effects and enhanced efficacy of methylprednisolone formulations", Exp Neurol, vol. 211, no. 2.

Lisak, R. P., Falk, G. A., Heinze, R. G., Kies, M. W., & Alvord, E. C., Jr. 1970, "Dissociation of antibody production from disease suppression in the inhibition of allergic encephalomyelitis by myelin basic protein", J.Immunol., vol. 104, no. 6, pp. 1435-1446.

Lisak, R. P. & Kies, M. W. 1968, "Mycobacterial suppression of delayed hypersensitivity in experimental allergic encephalomyelitis", Proc.Soc.Exp.Biol.Med., vol. 128, no. 1, pp. 214-218.

Lisak, R. P. & Zweiman, B. 1974, "Immune responses to myelin basic protein in mycobacterial-induced suppression of experimental allergic encephalomyelitis", Cell Immunol., vol. 14, no. 2, pp. 242-254.

Lisak, R. P., Zweiman, B., Blanchard, N., & Rorke, L. B. 1983, "Effect of treatment with Copolymer 1 (Cop-1) on the in vivo and in vitro manifestations of experimental allergic encephalomyelitis (EAE)", J.Neurol.Sci., vol. 62, no. 1-3, pp. 281-293.

Lisak, R. P., Zweiman, B., Dzida, L., Rosenblum, F., Rorke, L. B., & Barger, G. 1980, "In vitro response to basic protein in experimental allergic encephalomyelitis: effect of pretreatment with basic protein in incomplete adjuvant", Cell Immunol., vol. 52, no. 2, pp. 443-450.

Liu, G. Y. & Wraith, D. C. 1995, "Affinity for class II MHC determines the extent to which soluble peptides tolerize autoreactive T cells in naive and primed adult mice--implications for autoimmunity", Int.Immunol., vol. 7, no. 8, pp. 1255-1263.

Liu, J. Q., Bai, X. F., Shi, F. D., Xiao, B. G., Li, H. L., Levi, M., Mustafa, M., Wahren, B., & Link, H. 1998, "Inhibition of experimental autoimmune encephalomyelitis in Lewis rats by nasal administration of encephalitogenic MBP peptides: synergistic effects of MBP 68-86 and 87-99", Int.Immunol., vol. 10, no. 8, pp. 1139-1148.

Liu, X., Fan, Y., Wang, L., Cui, Y., & Gong, H. 2007, "Effect of erhuangfang on cerebral and spinal demyelination and regeneration as well as expression of glial fibrillary acidic protein in rats with experimental allergic encephalomyelitis", Neural Regeneration Research.2(8)()(pp 491-496), 2007.Date of Publication: Aug 2007. no. 8, pp. 491-496.

Liu, X., Linnington, C., Webster, H. D., Lassmann, S., Yao, D. L., Hudson, L. D., Wekerle, H., & Kreutzberg, G. W. 1997, "Insulin-like growth factor-I treatment reduces immune cell responses in acute non-demyelinative experimental autoimmune encephalomyelitis", J.Neurosci.Res., vol. 47, no. 5, pp. 531-538.

Liu, X., Yao, D. L., & Webster, H. 1995, "Insulin-like growth factor I treatment reduces clinical deficits and lesion severity in acute demyelinating experimental autoimmune encephalomyelitis", Mult.Scler., vol. 1, no. 1, pp. 2-9.

Liu, Y., Liu, J., Tetzlaff, W., Paty, D. W., & Cynader, M. S. 2006, "Biliverdin reductase, a major physiologic cytoprotectant, suppresses experimental autoimmune encephalomyelitis", Free Radic.Biol.Med., vol. 40, no. 6, pp. 960-967.

Liu, Y., Zhu, B., Wang, X., Luo, L., Li, P., Paty, D. W., & Cynader, M. S. 2003, "Bilirubin as a potent antioxidant suppresses experimental autoimmune encephalomyelitis: implications for the role of oxidative stress in the development of multiple sclerosis", J.Neuroimmunol., vol. 139, no. 1-2, pp. 27-35.

Livine, S., Hoenig, E. M., & Kies, M. W. 1967, "Allergic encephalomyelitis. Passive transfer prevented by encephalitogen", Science, vol. 161, no. 846, pp. 1155-1157.

Lo, A. C., Black, J. A., & Waxman, S. G. 2002, "Neuroprotection of axons with phenytoin in experimental allergic encephalomyelitis", Neuroreport, vol. 13, no. 15, pp. 1909-1912.

Lo, A. C., Saab, C. Y., Black, J. A., & Waxman, S. G. 2003, "Phenytoin protects spinal cord axons and preserves axonal conduction and neurological function in a model of neuroinflammation in vivo", J.Neurophysiol., vol. 90, no. 5, pp. 3566-3571.

Lobell, A., Weissert, R., Eltayeb, S., de Graaf, K. L., Wefer, J., Storch, M. K., Lassmann, H., Wigzell, H., & Olsson, T. 2003, "Suppressive DNA vaccination in myelin oligodendrocyte glycoprotein peptide-induced

experimental autoimmune encephalomyelitis involves a T1-biased immune response", J.Immunol., vol. 170, no. 4, pp. 1806-1813.

Lobell, A., Weissert, R., Eltayeb, S., Svanholm, C., Olsson, T., & Wigzell, H. 1999, "Presence of CpG DNA and the local cytokine milieu determine the efficacy of suppressive DNA vaccination in experimental autoimmune encephalomyelitis", J.Immunol., vol. 163, no. 9, pp. 4754-4762.

Lobell, A., Weissert, R., Storch, M. K., Svanholm, C., de Graaf, K. L., Lassmann, H., Andersson, R., Olsson, T., & Wigzell, H. 1998, "Vaccination with DNA encoding an immunodominant myelin basic protein peptide targeted to Fc of immunoglobulin G suppresses experimental autoimmune encephalomyelitis", J.Exp.Med., vol. 187, no. 9, pp. 1543-1548.

Lohse, A. W., Mor, F., Karin, N., & Cohen, I. R. 1989, "Control of experimental autoimmune encephalomyelitis by T cells responding to activated T cells", Science, vol. 244, no. 4906, pp. 820-822.

Loria, F., Docagne, F., Clemente, D., Correa, F., Hernangomez, M., Mestre, L., & Guaza, C. 2007, "Neuroprotective effects of cannabinoids against axonal damage in a viral model of multiple sclerosis", Journal of Neurochemistry, vol. 101, no. Suppl. 1.

Louie, K. A., Weiner, L. P., Du, J., Kochounian, H. H., Fling, S. P., Wei, W., & McMillan, M. 2005, "Cell-based gene therapy experiments in murine experimental autoimmune encephalomyelitis", Gene Ther., vol. 12, no. 14, pp. 1145-1153.

Love, S., Wiley, C. A., Fujinami, R. S., & Lampert, P. W. 1987, "Effects of regional spinal X-irradiation on demyelinating disease caused by Theiler's virus, mouse hepatitis virus or experimental allergic encephalomyelitis", Journal of Neuroimmunology.14(1)()(pp 19-33), 1987.Date of Publication: 1987. no. 1, pp. 19-33.

Lovett-Racke, A. E., Bittner, P., Cross, A. H., Carlino, J. A., & Racke, M. K. 1998, "Regulation of experimental autoimmune encephalomyelitis with insulin-like growth factor (IGF-1) and IGF-1/IGF-binding protein-3 complex (IGF-1/IGFBP3)", J.Clin.Invest, vol. 101, no. 8, pp. 1797-1804.

Lovett-Racke, A. E., Rocchini, A. E., Choy, J., Northrop, S. C., Hussain, R. Z., Ratts, R. B., Sikder, D., & Racke, M. K. 2004, "Silencing T-bet defines a critical role in the differentiation of autoreactive T lymphocytes", Immunity, vol. 21, no. 5, pp. 719-731.

Lowe, V. C. & Noronha-Blob, L. 1993, "Prevention and suppression of experimental allergic encephalomyelitis by an orally active leukocyte recruitment inhibitor, NPC 16570", Agents Actions, vol. 39 Spec No, p. C83-C85.

Lu, P.-Y., Song, C.-F., Koh, C.-S., & Inoue, A. 2003, "Suppression of active experimental autoimmune encephalomyelitis in Lewis rats by using compound ONO-4817, a new inhibitor of matrix metalloproteinases. [Chinese]", Chinese Pharmaceutical Journal.38(1)()(pp 28-31), 2003.Date of Publication: 01 Jan 2003. no. 1, pp. 28-31.

Lublin, F. D. 1984, "Immunomodulation of relapsing experimental allergic encephalomyelitis", Neurology, vol. 34, no. 12, pp. 1615-1617.

Lublin, F. D., Knobler, R. L., Kalman, B., Goldhaber, M., Marini, J., Perrault, M., D'Imperio, C., Joseph, J., Alkan, S. S., & Korngold, R. 1993, "Monoclonal anti-gamma interferon antibodies enhance experimental allergic encephalomyelitis", Autoimmunity, vol. 16, no. 4, pp. 267-274.

Lublin, F. D., Lavasa, M., Viti, C., & Knobler, R. L. 1987, "Suppression of acute and relapsing experimental allergic encephalomyelitis with mitoxantrone", Clin.Immunol.Immunopathol., vol. 45, no. 1, pp. 122-128.

Luca, M. E., Visser, L., Lucas, C. J., & Nagelkerken, L. 1999, "IFN-beta modulates specific T cell responses in vitro but does not affect Experimental Autoimmune Encephalomyelitis in the SJL mouse", J.Neuroimmunol., vol. 100, no. 1-2, pp. 190-196.

Luccarini, I., Ballerini, C., Biagioli, T., Biamonte, F., Bellucci, A., Rosi, M. C., Grossi, C., Massacesi, L., & Casamenti, F. 2008, "Combined treatment with atorvastatin and minocycline suppresses severity of EAE", Exp Neurol, vol. 211, no. 1.

Lyman, W. D., Sonett, J. R., Brosnan, C. F., Elkin, R., & Bornstein, M. B. 1989, "Delta 9-tetrahydrocannabinol: a novel treatment for experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 23, no. 1, pp. 73-81.

Lyons, M. J., Amador, R., Petito, C., Nagashima, K., Weinreb, H., & Zabriskie, J. B. 1986, "Inhibition of acute experimental allergic encephalomyelitis in mice by colchicine", J.Exp.Med., vol. 164, no. 5, pp. 1803-1808.

Maassen, C. B., Laman, J. D., van Holten-Neelen, C., Hoogteijling, L., Groenewegen, L., Visser, L., Schellekens, M. M., Boersma, W. J., & Claassen, E. 2003, "Reduced experimental autoimmune encephalomyelitis after intranasal and oral administration of recombinant lactobacilli expressing myelin antigens", Vaccine, vol. 21, no. 32, pp. 4685-4693.

Maccio, D. R., Calfa, G., & Roth, G. A. 2005, "Oral testosterone in male rats and the development of experimental autoimmune encephalomyelitis", Neuroimmunomodulation., vol. 12, no. 4, pp. 246-254.

Maccioni, M., Riera, C. M., & Rivero, V. E. 1999, "Peritoneal antigen-presenting cells pulsed in vivo with myelin basic protein induce the suppression of experimental autoimmune encephalomyelitis (EAE) in Wistar rats", J Neuroimmunol, vol. 96, no. 1, pp. 46-56.

MacKenzie, A. R., Sibley, P. R., & White, B. P. 1979, "Differential suppression of experimental allergic diseases in rats infected with trypanosomes", Parasite Immunol., vol. 1, no. 1, pp. 49-59.

MacPhee, I. A., Day, M. J., & Mason, D. W. 1990, "The role of serum factors in the suppression of experimental allergic encephalomyelitis: evidence for immunoregulation by antibody to the encephalitogenic peptide", Immunology, vol. 70, no. 4, pp. 527-534.

MacPhee, I. A. & Mason, D. W. 1988, "Evidence for an immunosuppressive autoantibody in experimental allergic encephalomyelitis", Ann.N.Y.Acad.Sci., vol. 540, pp. 718-719.

MacPhee, I. A., Turner, D. R., Yagita, H., & Oliveira, D. B. 2001, "CD80(B7.1) and CD86(B7.2) do not have distinct roles in setting the Th1/Th2 balance in autoimmunity in rats", Scand.J.Immunol., vol. 54, no. 5, pp. 486-494.

MacPherson, C. F. 1980, "Suppression and treatment of experimental allergic encephalitis in guinea-pigs with the bovine spinal cord protein (BSCP)", Immunology, vol. 40, no. 3, pp. 377-383.

MacPherson, C. F. & Armstrong, H. 1977, "Prevention of experimental allergic encephalitis in Lewis rats by rat and bovine spinal cord proteins", Nature, vol. 266, no. 5601, pp. 459-461.

MacPherson, C. F., Armstrong, H., & Tan, O. 1977, "Prevention of experimental allergic encephalitis in guinea-pigs with spinal cord protein: optimum pretreatment schedules and appraisal of plausible mechanisms", Immunology, vol. 33, no. 2, pp. 161-166.

MacPherson, C. F. & Yo, S. L. 1973, "Studies on brain antigens. VI. Prevention of experimental allergic encephalomyelitis by a water-soluble spinal cord protein, 1 -SCP", J.Immunol., vol. 110, no. 5, pp. 1371-1375.

Maier, K., Kuhnert, A. V., Taheri, N., Sattler, M. B., Storch, M. K., Williams, S. K., Bahr, M., & Diem, R. 2006, "Effects of glatiramer acetate and interferon-beta on neurodegeneration in a model of multiple sclerosis: a comparative study", Am.J.Pathol., vol. 169, no. 4, pp. 1353-1364.

Maier, K., Merkler, D., Gerber, J., Taheri, N., Kuhnert, A. V., Williams, S. K., Neusch, C., Bahr, M., & Diem, R. 2007, "Multiple neuroprotective mechanisms of minocycline in autoimmune CNS inflammation", Neurobiol.Dis, vol. 25, no. 3, pp. 514-525.

Maier, K., Rau, C. R., Storch, M. K., Sattler, M. B., Demmer, I., Weissert, R., Taheri, N., Kuhnert, A. V., Bahr, M., & Diem, R. 2004, "Ciliary neurotrophic factor protects retinal ganglion cells from secondary cell death during acute autoimmune optic neuritis in rats", Brain Pathol., vol. 14, no. 4, pp. 378-387.

Makar, T. K., Bever, C. T., Singh, I. S., Royal, W., Sahu, S. N., Sura, T. P., Sultana, S., Sura, K. T., Patel, N., Dhib-Jalbut, S., & Trisler, D. 2009, "Brain-derived neurotrophic factor gene delivery in an animal model of multiple sclerosis using bone marrow stem cells as a vehicle", Journal of Neuroimmunology.210(1-2)()(pp 40-51), 2009.Date of Publication: 29 May 2009. no. 1-2, pp. 40-51.

Makar, T. K., Trisler, D., Bever, C. T., Goolsby, J. E., Sura, K. T., Balasubramanian, S., Sultana, S., Patel, N., Ford, D., Singh, I. S., Gupta, A., Valenzuela, R. M., & Dhib-Jalbut, S. 2008a, "Stem cell based delivery of IFN-beta reduces relapses in experimental autoimmune encephalomyelitis", Journal of Neuroimmunology.196(1-2)()(pp 67-81), 2008.Date of Publication: 30 May 2008. no. 1-2, pp. 67-81.

Makar, T. K., Trisler, D., Sura, K. T., Sultana, S., Patel, N., & Bever, C. T. 2008b, "Brain derived neurotrophic factor treatment reduces inflammation and apoptosis in experimental allergic encephalomyelitis",

Journal of the Neurological Sciences.270(1-2)()(pp 70-76), 2008.Date of Publication: 15 Jul 2008. no. 1-2, pp. 70-76.

Makar, T. K., Trisler, D., Royal, W., Dhib-Jalbut, S., Sura, T., Sahu, S. N., & Bever, C. T. 2008c, "The effect of BDNF delivery on demyelination and remyelination in a mouse model of multiple sclerosis", Annals of Neurology, vol. 64, no. Suppl. 12.

Malfitano, A. M., Matarese, G., Pisanti, S., Grimaldi, C., Laezza, C., Bisogno, T., Di, M., V, Lechler, R. I., & Bifulco, M. 2006, "Arvanil inhibits T lymphocyte activation and ameliorates autoimmune encephalomyelitis", J.Neuroimmunol., vol. 171, no. 1-2, pp. 110-119.

Malfroy, B., Doctrow, S. R., Orr, P. L., Tocco, G., Fedoseyeva, E. V., & Benichou, G. 1997, "Prevention and suppression of autoimmune encephalomyelitis by EUK-8, a synthetic catalytic scavenger of oxygen-reactive metabolites", Cell Immunol., vol. 177, no. 1, pp. 62-68.

Malotky, M. K., Pope, L., & Miller, S. D. 1994, "Epitope and functional specificity of peripheral tolerance induction in experimental autoimmune encephalomyelitis in adult Lewis rats", J.Immunol., vol. 153, no. 2, pp. 841-851.

Mana, P., Goodyear, M., Bernard, C., Tomioka, R., Freire-Garabal, M., & Linares, D. 2004, "Tolerance induction by molecular mimicry: prevention and suppression of experimental autoimmune encephalomyelitis with the milk protein butyrophilin", Int.Immunol., vol. 16, no. 3, pp. 489-499.

Mannie, M. D. & Abbott, D. J. 2007, "A fusion protein consisting of IL-16 and the encephalitogenic peptide of myelin basic protein constitutes an antigen-specific tolerogenic vaccine that inhibits experimental autoimmune encephalomyelitis", J.Immunol., vol. 179, no. 3, pp. 1458-1465.

Marchionni, M. A., Cannella, B., Hoban, C., Gao, Y. L., Garcia-Arenas, R., Lawson, D., Happel, E., Noel, F., Tofilon, P., Gwynne, D., & Raine, C. S. 1999, "Neuregulin in neuron/glial interactions in the central nervous system. GGF2 diminishes autoimmune demyelination, promotes oligodendrocyte progenitor expansion, and enhances remyelination", Adv.Exp.Med.Biol., vol. 468, pp. 283-295.

Margot, C. D., Ford, M. L., & Evavold, B. D. 2005, "Amelioration of established experimental autoimmune encephalomyelitis by an MHC anchor-substituted variant of proteolipid protein 139-151", J.Immunol., vol. 174, no. 6, pp. 3352-3358.

Maricic, I., Halder, R., Wu, D., Wong, C. H., Beeston, T., & Kumar, V. 2005, "Treatment of chronic-relapsing EAE by targeting sulfatide-reactive T cells", Faseb Journal, vol. 19, no. 4, Suppl. S, Part 1.

Marini, J. C., Jameson, B. A., Lublin, F. D., & Korngold, R. 1996, "A CD4-CDR3 peptide analog inhibits both primary and secondary autoreactive CD4+ T cell responses in experimental allergic encephalomyelitis", J.Immunol., vol. 157, no. 8, pp. 3706-3715.

Marino, M., Ippolito, A., & Fassina, G. 1999, "Inhibition of experimental autoimmune encephalomyelitis in SJL mice by oral administration of retro-inverso derivative of encephalitogenic epitope P87-99", Eur.J.Immunol., vol. 29, no. 8, pp. 2560-2566.

Marino, M., Ippolito, A., Ruvo, M., Scarallo, A., Volpe, S., & Fassina, G. 2000, "Prevention of experimental autoimmune encephalomyelitis by encephalitogenic epitope sequence simplified derivatives", Mol.Immunol., vol. 37, no. 16, pp. 951-960.

Marques, K. B., Scorisa, J. M., Zanon, R., Freria, C. M., Santos, L. M. B., Damasceno, B. P., & Oliveira, A. L. R. 2009, "The immunomodulator glatiramer acetate influences spinal motoneuron plasticity during the course of multiple sclerosis in an animal model", Brazilian Journal of Medical and Biological Research.42(2)()(pp 179-188), 2009.Date of Publication: 2009. no. 2, pp. 179-188.

Marracci, G. H., Jones, R. E., McKeon, G. P., & Bourdette, D. N. 2002, "Alpha lipoic acid inhibits T cell migration into the spinal cord and suppresses and treats experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 131, no. 1-2, pp. 104-114.

Martel, R. R., Klicius, J., & Galet, S. 1977, "Inhibition of the immune response by rapamycin, a new antifungal antibiotic", Can.J.Physiol Pharmacol., vol. 55, no. 1, pp. 48-51.

Martin, D., Near, S. L., Bendele, A., & Russell, D. A. 1995, "Inhibition of tumor necrosis factor is protective against neurologic dysfunction after active immunization of Lewis rats with myelin basic protein", Exp.Neurol., vol. 131, no. 2, pp. 221-228.

Martin-Saavedra, F. M., Flores, N., Dorado, B., Eguiluz, C., Bravo, B., Garcia-Merino, A., & Ballester, S. 2007, "Beta-interferon unbalances the peripheral T cell proinflammatory response in experimental autoimmune encephalomyelitis", Mol.Immunol., vol. 44, no. 14, pp. 3597-3607.

Martiney, J. A., Rajan, A. J., Charles, P. C., Cerami, A., Ulrich, P. C., Macphail, S., Tracey, K. J., & Brosnan, C. F. 1998, "Prevention and treatment of experimental autoimmune encephalomyelitis by CNI-1493, a macrophage-deactivating agent", J.Immunol., vol. 160, no. 11, pp. 5588-5595.

Martinez, I., Puerta, C., Redondo, C., & Garcia-Merino, A. 1999, "Type IV phosphodiesterase inhibition in experimental allergic encephalomyelitis of Lewis rats: sequential gene expression analysis of cytokines, adhesion molecules and the inducible nitric oxide synthase", J.Neurol.Sci., vol. 164, no. 1, pp. 13-23.

Marusic, S., Thakker, P., Pelker, J. W., Stedman, N. L., Lee, K. L., McKew, J. C., Han, L., Xu, X., Wolf, S. F., Borey, A. J., Cui, J., Shen, M. W., Donahue, F., Hassan-Zahraee, M., Leach, M. W., Shimizu, T., & Clark, J. D. 2008, "Blockade of cytosolic phospholipase A2 alpha prevents experimental autoimmune encephalomyelitis and diminishes development of Th1 and Th17 responses", J Neuroimmunol, vol. 204, no. 1-2, pp. 29-37.

Massacesi, L., Abbamondi, A. L., Giorgi, C., Sarlo, F., Lolli, F., & Amaducci, L. 1987a, "Suppression of experimental allergic encephalomyelitis by retinoic acid", J.Neurol.Sci., vol. 80, no. 1, pp. 55-64.

Massacesi, L., Abbamondi, A. L., Sarlo, F., & Amaducci, L. 1987b, "The control of experimental allergic encephalomyelitis with retinoic acid. Further studies", Riv.Neurol., vol. 57, no. 3, pp. 166-169.

Massacesi, L., Castigli, E., Vergelli, M., Olivotto, J., Abbamondi, A. L., Sarlo, F., & Amaducci, L. 1991, "Immunosuppressive activity of 13-cis-retinoic acid and prevention of experimental autoimmune encephalomyelitis in rats", J.Clin.Invest, vol. 88, no. 4, pp. 1331-1337.

Mastronardi, F. G., Min, W., Wang, H., Winer, S., Dosch, M., Boggs, J. M., & Moscarello, M. A. 2004, "Attenuation of experimental autoimmune encephalomyelitis and nonimmune demyelination by IFN-beta plus vitamin B12: treatment to modify notch-1/sonic hedgehog balance", J.Immunol., vol. 172, no. 10, pp. 6418-6426.

Mastronardi, F. G., Tsui, H., Winer, S., Wood, D. D., Selvanantham, T., Galligan, C., Fish, E. N., Dosch, H. M., & Moscarello, M. A. 2007, "Synergy between paclitaxel plus an exogenous methyl donor in the suppression of murine demyelinating diseases", Mult.Scler., vol. 13, no. 5, pp. 596-609.

Matarese, G., Carrieri, P. B., La Cava, A., Perna, F., Sanna, V., De, R., V, Aufiero, D., Fontana, S., & Zappacosta, S. 2005, "Leptin increase in multiple sclerosis associates with reduced number of CD4(+)CD25+ regulatory T cells", Proc Natl Acad Sci U S A, vol. 102, no. 14, pp. 5150-5155.

Matarese, G., Sanna, V., Di, G. A., Lord, G. M., Howard, J. K., Bloom, S. R., Lechler, R. I., Fontana, S., & Zappacosta, S. 2001, "Leptin potentiates experimental autoimmune encephalomyelitis in SJL female mice and confers susceptibility to males", Eur.J.Immunol., vol. 31, no. 5, pp. 1324-1332.

Matejuk, A., Dwyer, J., Hopke, C., Vandenbark, A. A., & Offner, H. 2004, "Opposing roles for TGF-beta1 and TGF-beta3 isoforms in experimental autoimmune encephalomyelitis", Cytokine, vol. 25, no. 2, pp. 45-51.

Matejuk, A., Hopke, C., Vandenbark, A. A., Hurn, P. D., & Offner, H. 2005, "Middle-age male mice have increased severity of experimental autoimmune encephalomyelitis and are unresponsive to testosterone therapy", J.Immunol., vol. 174, no. 4, pp. 2387-2395.

Mathey, E. K., Derfuss, T., Storch, M. K., Williams, K. R., Hales, K., Woolley, D. R., Al Hayani, A., Davies, S. N., Rasband, M. N., Olsson, T., Moldenhauer, A., Velhin, S., Hohlfeld, R., Meinl, E., & Linington, C. 2007, "Neurofascin as a novel target for autoantibody-mediated axonal injury", Journal of Experimental Medicine, vol. 204, no. 10, pp. 2363-2372.

Mathisen, P., Yu, M., Johnson, J., Drazba, J., & Tuohy, V. 1997a, "Prevention and treatment of experimental autoimmune encephalomyelitis (EAE) with genetically modified autoreactive T cells", Journal of Allergy and Clinical Immunology, vol. 99, no. 1 PART 2.

Mathisen, P. M., Yu, M., Johnson, J. M., Drazba, J. A., & Tuohy, V. K. 1997b, "Treatment of experimental autoimmune encephalomyelitis with genetically modified memory T cells", J.Exp.Med., vol. 186, no. 1, pp. 159-164.

Matous-Malbohan, I., Holub, M., Mares, V., & Lodin, Z. 1976, "Experimental allergic encephalomyelitis.-- The effect of dexamethasone on growth and proliferation in the draining lymph node", Exp.Pathol.(Jena), vol. 12, no. 6, pp. 295-300.

Matsui, M., Weaver, J., Proudfoot, A. E., Wujek, J. R., Wei, T., Richer, E., Trapp, B. D., Rao, A., & Ransohoff, R. M. 2002, "Treatment of experimental autoimmune encephalomyelitis with the chemokine receptor antagonist Met-RANTES", J.Neuroimmunol., vol. 128, no. 1-2, pp. 16-22.

Matsumo, Y., Sakuma, H., Miyakoshi, A., Tsukada, Y., Kohyama, K., Park, I. K., & Tanuma, N. 2005, "Characterization of relapsing autoimmune encephalomyelitis and its treatment with decoy chemokine receptor genes", J.Neuroimmunol., vol. 170, no. 1-2, pp. 49-61.

Matsumoto, Y. & Jee, Y. 2001, "Characterization of T cells that are activated after depletion of major encephalitogenic T cells in rat autoimmune encephalomyelitis", J.Neuroimmunol., vol. 114, no. 1-2, pp. 89-98.

Matsumoto, Y., Tsuchida, M., Hanawa, H., & Abo, T. 1994a, "Successful prevention and treatment of autoimmune encephalomyelitis by short-term administration of anti-T-cell receptor alpha beta antibody", Immunology, vol. 81, no. 1, pp. 1-7.

Matsumoto, Y., Tsuchida, M., Hanawa, H., & Abo, T. 1994b, "T cell receptor peptide therapy for autoimmune encephalomyelitis: stronger immunization is necessary for effective vaccination", Cell Immunol., vol. 153, no. 2, pp. 468-478.

Matsuo, H., Ichinose, K., Ohtsuru, I., Fujishita, S., Onodera, H., Suematsu, J., Yoshida, M., Yamawaki, N., & Shibuya, N. 1997, "Treatment of experimental allergic encephalomyelitis by selective removal of CD4+ T cells", Ther.Apher., vol. 1, no. 2, pp. 165-168.

Matsushima, S., Yoshitoshi, T., Mahalak, S. M., & Shichi, H. 1990, "Immunosuppressive effect of gramicidin S on experimental ocular neuritis and allergic encephalomyelitis", Jpn.J.Ophthalmol., vol. 34, no. 3, pp. 306-313.

Matsushima, S., Yoshitoshi, T., & Shichi, H. 1990, "Immunosuppression by gramicidin S of experimental autoimmune uveoretinitis, pinealitis and autoimmune encephalomyelitis", J.Ocul.Pharmacol., vol. 6, no. 3, pp. 219-226.

Mattner, F., Smiroldo, S., Galbiati, F., Muller, M., Di, L. P., Poliani, P. L., Martino, G., Panina-Bordignon, P., & Adorini, L. 2000, "Inhibition of Th1 development and treatment of chronic-relapsing experimental allergic encephalomyelitis by a non-hypercalcemic analogue of 1,25-dihydroxyvitamin D(3)", Eur.J.Immunol., vol. 30, no. 2, pp. 498-508.

Matute, C., Torre, I., Perez-Cerda, F., Perez-Samartin, A., Alberdi, E., Etxebarria, E., Arranz, A. M., Ravid, R., Rodriguez-Antiguedad, A., Sanchez-Gomez, M., & Domercq, M. 2007, "P2X(7) receptor blockade prevents ATP excitotoxicity in oligodendrocytes and ameliorates experimental autoimmune encephalomyelitis", J.Neurosci., vol. 27, no. 35, pp. 9525-9533.

Maverakis, E., van den Elzen, P., Sercarz, E., & Stevens, D. 2001, "Loss of a driver clone correlates with protection against experimental autoimmune encephalomeylitis", Faseb Journal, vol. 15, no. 5.

McCandless, E. E., Wang, Q., Mark, W. B., Harper, J. M., & Klein, R. S. 2006, "CXCL12 limits inflammation by localizing mononuclear infiltrates to the perivascular space during experimental autoimmune encephalomyelitis", Journal of Immunology.177(11)()(pp 8053-8064), 2006.Date of Publication: 01 Dec 2006. no. 11, pp. 8053-8064.

McCombe, P. A., Harness, J., & Pender, M. P. 1999, "Effects of cyclosporin A treatment on clinical course and inflammatory cell apoptosis in experimental autoimmune encephalomyelitis induced in Lewis rats by inoculation with myelin basic protein", J.Neuroimmunol., vol. 97, no. 1-2, pp. 60-69.

McCombe, P. A., Nickson, I., Tabi, Z., & Pender, M. P. 1996, "Corticosteroid treatment of experimental autoimmune encephalomyelitis in the Lewis rat results in loss of V beta 8.2+ and myelin basic protein-reactive cells from the spinal cord, with increased total T-cell apoptosis but reduced apoptosis of V beta 8.2+ cells", J.Neuroimmunol., vol. 70, no. 2, pp. 93-101.

McCreary, P. A., Battifora, H. A., Laing, G. H., & Hass, G. M. 1966, "Protective effect of magnesium deficiency on experimental allergic encephalomyelitis in the rat", Proc.Soc.Exp.Biol.Med., vol. 121, no. 4, pp. 1130-1133.

McDermott, J. R. & Keith, A. B. 1979, "Relative effectiveness of spinal cord and purified myelin basic protein in producing resistance to experimental allergic encephalomyelitis", Eur.Neurol., vol. 18, no. 2, pp. 136-139.

McFarland, H. I., Lobito, A. A., Johnson, M. M., Palardy, G. R., Yee, C. S., Jordan, E. K., Frank, J. A., Tresser, N., Genain, C. P., Mueller, J. P., Matis, L. A., & Lenardo, M. J. 2001, "Effective antigen-specific immunotherapy in the marmoset model of multiple sclerosis", J.Immunol., vol. 166, no. 3, pp. 2116-2121.

McIlhenny, H. M., Levine, S., Wiseman, E. H., & Sowinski, R. 1978, "Disposition and activity in experimental allergic encephalomyelitis of flumizole, a nonacidic, nonsteroidal, anti-inflammatory agent", Exp.Neurol., vol. 58, no. 1, pp. 126-137.

McKenna, R. M., Carter, B. G., Paterson, J. A., & Sehon, A. H. 1983, "The suppression of experimental allergic encephalomyelitis in Lewis rats by treatment with myelin basic protein-cell conjugates", Cell Immunol., vol. 81, no. 2, pp. 391-402.

McKenna, R. M., Carter, B. G., & Sehon, A. H. 1984, "Studies on the mechanism of suppression of experimental allergic encephalomyelitis induced by myelin basic protein-cell conjugates", Cell Immunol., vol. 88, no. 2, pp. 251-259.

McRae, B. L., Vanderlugt, C. L., Dal Canto, M. C., & Miller, S. D. 1995, "Functional evidence for epitope spreading in the relapsing pathology of experimental autoimmune encephalomyelitis", Journal of Experimental Medicine.182(1)()(pp 75-85), 1995.Date of Publication: 01 Jul 1995. no. 1, pp. 75-85.

Meade, C. J., Mertin, J., Sheena, J., & Hunt, R. 1977, "How linoleic acid (C18:2) affects the response of guinea pigs to basic protein", Proc.Nutr.Soc., vol. 36, no. 3, p. 131A.

Meade, C. J., Mertin, J., Sheena, J., & Hunt, R. 1978, "Reduction by linoleic acid of the severity of experimental allergic encephalomyelitis in the guinea pig", J.Neurol.Sci., vol. 35, no. 2-3, pp. 291-308.

Meehan, T. F. & Deluca, H. F. 2002, "CD8(+) T cells are not necessary for 1 alpha,25-dihydroxyvitamin D(3) to suppress experimental autoimmune encephalomyelitis in mice", Proc.Natl.Acad.Sci.U.S.A, vol. 99, no. 8, pp. 5557-5560.

Megel, H., Raychaudhuri, A., Bayer, M., & Beaver, T. H. 1978, "The immunopharmacologic and anti-inflammatory properties of RMI 9563 with special reference to its effect on the complement system", Agents Actions, vol. 8, no. 3, pp. 218-228.

Meiron, M., Zohar, Y., Anunu, R., Wildbaum, G., & Karin, N. 2008, "CXCL12 (SDF-1alpha) suppresses ongoing experimental autoimmune encephalomyelitis by selecting antigen-specific regulatory T cells", J Exp Med, vol. 205, no. 11, pp. 2643-2655.

Mekala, D. J., Alli, R. S., & Geiger, T. L. 2005, "IL-10-dependent suppression of experimental allergic encephalomyelitis by Th2-differentiated, anti-TCR redirected T lymphocytes", J.Immunol., vol. 174, no. 6, pp. 3789-3797.

Mekala, D. J. & Geiger, T. L. 2005, "Immunotherapy of autoimmune encephalomyelitis with redirected CD4+CD25+ T lymphocytes", Blood, vol. 105, no. 5, pp. 2090-2092.

Mel'nyk, V. O., Lisianyi, M. I., Biel's'ka LM, & Shniakin, S. A. 2005, "[Effectiveness of immunoglobulin treatment in rats with experimental allergic encephalomyelitis]", Fiziol.Zh., vol. 51, no. 6, pp. 37-39.

Merendino, A., Vecchi, A., Spreafico, F., Sironi, M., Borrelli, F., Antonetti, F., Cantelmo, A., & Falchetti, R. 1987, "Effect of thymostimulin in models of cell-mediated and humoral autoreactivity and on T-dependent suppression", Int.J.Immunopharmacol., vol. 9, no. 8, pp. 937-945.

Merrill, J. E., Hanak, S., Pu, S.-F., Liang, J., Dang, C., Iglesias-Bregna, D., Harvey, B., Zhu, B., & McMonagle-Strucko, K. 2009, "Teriflunomide reduces behavioral, electrophysiological, and histopathological deficits in the Dark Agouti rat model of experimental autoimmune encephalomyelitis", Journal of Neurology.256(1)()(pp 89-103), 2009.Date of Publication: January 2009. no. 1, pp. 89-103.

Mertin, J. & Hunt, R. 1976, "Hyperphenylalaninaemia and experimental allergic encephalomyelitis", J Neurol Sci, vol. 29, no. 2-4, pp. 351-359.

Mertin, J. & Stackpoole, A. 1978, "Suppression by essential fatty acids of experimental allergic encephalomyelitis is abolished by indomethacin", Prostaglandins Med., vol. 1, no. 4, pp. 283-291.

Metzler, B. & Wraith, D. C. 1993, "Inhibition of experimental autoimmune encephalomyelitis by inhalation but not oral administration of the encephalitogenic peptide: influence of MHC binding affinity", Int.Immunol., vol. 5, no. 9, pp. 1159-1165.

Metzler, B. & Wraith, D. C. 1996, "Mucosal tolerance in a murine model of experimental autoimmune encephalomyelitis", Ann.N.Y.Acad.Sci., vol. 778, pp. 228-242.

Meuth, S. G., Simon, O. J., Grimm, A., Melzer, N., Herrmann, A. M., Spitzer, P., Landgraf, P., & Wiendl, H. 2008, "CNS inflammation and neuronal degeneration is aggravated by impaired CD200-CD200R-mediated macrophage silencing", Journal of Neuroimmunology.194(1-2)()(pp 62-69), 2008.Date of Publication: Feb 2008. no. 1-2, pp. 62-69.

Meyer, A. L., Benson, J. M., Gienapp, I. E., Cox, K. L., & Whitacre, C. C. 1996, "Suppression of murine chronic relapsing experimental autoimmune encephalomyelitis by the oral administration of myelin basic protein", J.Immunol., vol. 157, no. 9, pp. 4230-4238.

Mi, S., Hu, B., Hahm, K., Luo, Y., Kam Hui, E. S., Yuan, Q., Wong, W. M., Wang, L., Su, H., Chu, T. H., Guo, J., Zhang, W., So, K. F., Pepinsky, B., Shao, Z., Graff, C., Garber, E., Jung, V., Wu, E. X., & Wu, W. 2007, "LINGO-1 antagonist promotes spinal cord remyelination and axonal integrity in MOG-induced experimental autoimmune encephalomyelitis", Nat.Med., vol. 13, no. 10, pp. 1228-1233.

Milford, C. M., Lynch, S. G., Cross, R. S., & LeVine, S. M. 1995, "Testing lazaroids U-74389G and U-83836E for therapeutic value in experimental allergic encephalomyelitis in the Lewis rat", Res.Commun.Mol.Pathol.Pharmacol., vol. 87, no. 3, pp. 353-358.

Milicevic, I., Pekovic, S., Subasic, S., Mostarica-Stojkovic, M., Stosic-Grujicic, S., Medic-Mijacevic, L., Pejanovic, V., Rakic, L., & Stojiljkovic, M. 2003, "Ribavirin reduces clinical signs and pathological changes of experimental autoimmune encephalomyelitis in Dark Agouti rats", J.Neurosci.Res., vol. 72, no. 2, pp. 268-278.

Miller, A., Al-Sabbagh, A., Santos, L. M., Das, M. P., & Weiner, H. L. 1993a, "Epitopes of myelin basic protein that trigger TGF-beta release after oral tolerization are distinct from encephalitogenic epitopes and mediate epitope-driven bystander suppression", J.Immunol., vol. 151, no. 12, pp. 7307-7315.

Miller, A., Lider, O., Abramsky, O., & Weiner, H. L. 1994, "Orally administered myelin basic protein in neonates primes for immune responses and enhances experimental autoimmune encephalomyelitis in adult animals", Eur.J.Immunol., vol. 24, no. 5, pp. 1026-1032.

Miller, A., Lider, O., Al-Sabbagh, A., & Weiner, H. L. 1992a, "Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein. V. Hierarchy of suppression by myelin basic protein from different species", J.Neuroimmunol., vol. 39, no. 3, pp. 243-250.

Miller, A., Lider, O., Roberts, A. B., Sporn, M. B., & Weiner, H. L. 1992b, "Suppressor T cells generated by oral tolerization to myelin basic protein suppress both in vitro and in vivo immune responses by the release of transforming growth factor beta after antigen-specific triggering", Proc.Natl.Acad.Sci.U.S.A, vol. 89, no. 1, pp. 421-425.

Miller, A., Lider, O., & Weiner, H. L. 1991, "Antigen-driven bystander suppression after oral administration of antigens", J.Exp.Med., vol. 174, no. 4, pp. 791-798.

Miller, A., Zhang, Z. J., Sobel, R. A., Al-Sabbagh, A., & Weiner, H. L. 1993b, "Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein. VI. Suppression of adoptively transferred disease and differential effects of oral vs. intravenous tolerization", J.Neuroimmunol., vol. 46, no. 1-2, pp. 73-82.

Miller, D. J., Bright, J. J., Sriram, S., & Rodriguez, M. 1997, "Successful treatment of established relapsing experimental autoimmune encephalomyelitis in mice with a monoclonal natural autoantibody", J.Neuroimmunol., vol. 75, no. 1-2, pp. 204-209.

Miller, S. D., Tan, L. J., Kennedy, M. K., & Dal Canto, M. C. 1991, "Specific immunoregulation of the induction and effector stages of relapsing EAE via neuroantigen-specific tolerance induction", Ann.N.Y.Acad.Sci., vol. 636, pp. 79-94.

Min, B., Legge, K. L., Caprio, J. C., Li, L., Gregg, R., & Zaghouani, H. 2000, "Differential control of neonatal tolerance by antigen dose versus extended exposure and adjuvant", Cell Immunol, vol. 200, no. 1, pp. 45-55.

Min, B., Legge, K. L., Pack, C., & Zaghouani, H. 1998, "Neonatal exposure to a self-peptide-immunoglobulin chimera circumvents the use of adjuvant and confers resistance to autoimmune disease by a novel mechanism involving interleukin 4 lymph node deviation and interferon gamma-mediated splenic anergy", J.Exp.Med., vol. 188, no. 11, pp. 2007-2017.

Min, K., Yoon, W. K., Kim, S. K., & Kim, B. H. 2007, "Immunosuppressive effect of silibinin in experimental autoimmune encephalomyelitis", Arch.Pharm.Res., vol. 30, no. 10, pp. 1265-1272.

Minagawa, H., Takenaka, A., Itoyama, Y., & Mori, R. 1987, "Experimental Allergic Encephalomyelitis in the Lewis Rat A Model of Predictable Relapse by Cyclophosphamide", Journal of the Neurological Sciences, vol. 78, no. 2, pp. 225-235.

Minter, L. M., Turley, D. M., Das, P., Shin, H. M., Joshi, I., Lawlor, R. G., Cho, O. H., Palaga, T., Gottipati, S., Telfer, J. C., Kostura, L., Fauq, A. H., Simpson, K., Such, K. A., Miele, L., Golde, T. E., Miller, S. D., & Osborne, B. A. 2005, "Inhibitors of gamma-secretase block in vivo and in vitro T helper type 1 polarization by preventing Notch upregulation of Tbx21", Nat.Immunol., vol. 6, no. 7, pp. 680-688.

Mirshafiey, A., Cuzzocrea, S., Rehm, B. H., & Matsuo, H. 2005a, "M2000: a revolution in pharmacology", Med.Sci.Monit., vol. 11, no. 8, p. I53-I63.

Mirshafiey, A., Matsuo, H., Nakane, S., Rehm, B. H., Koh, C. S., & Miyoshi, S. 2005b, "Novel immunosuppressive therapy by M2000 in experimental multiple sclerosis", Immunopharmacol.Immunotoxicol., vol. 27, no. 2, pp. 255-265.

Misiewicz, B., Poltorak, M., Wright, R., Szczepanowski, R., Freed, W., & Sternberg, E. 1996, "Intracerebroventricular transplantation differentially affects experimental allergic encephalomyelitis and peripheral inflammation", Society for Neuroscience Abstracts, vol. 22, no. 1-3.

Miskolczy, D., Feszt, T., Gyergyay, F., Szabo, S., & Gundisch, M. 1965, "[Research on the action of hyaluronic acid on the development of experimental allergic encephalomy- elitis]", Stud.Cercet.Neurol., vol. 10, no. 5, pp. 493-497.

Mitchell, K. M., Dotson, A. L., Cool, K. M., Chakrabarty, A., Benedict, S. H., & LeVine, S. M. 2007, "Deferiprone, an orally deliverable iron chelator, ameliorates experimental autoimmune encephalomyelitis", Mult.Scler., vol. 13, no. 9, pp. 1118-1126.

Mitsuzawa, E., Yasuda, T., Tamura, N., & Ohtani, S. 1984, "Pretreatment with antigen or adjuvant, and the preventability of allergic encephalomyelitis induced by basic protein with synthetic muramyl dipeptide in comparison with Freund's complete adjuvant", Jpn.J.Exp.Med., vol. 54, no. 3, pp. 97-107.

Miyagawa, N., Homma, T., Kagechika, H., Shudo, K., & Nagai, H. 2003, "Effect of synthetic retinoid, TAC-101, on experimental autoimmune disease", Pharmacology, vol. 67, no. 1, pp. 21-31.

Miyake, M., Sasaki, K., Ide, K., Matsukura, Y., Shijima, K., & Fujiwara, D. 2006, "Highly oligomeric procyanidins ameliorate experimental autoimmune encephalomyelitis via suppression of Th1 immunity", J.Immunol., vol. 176, no. 10, pp. 5797-5804.

Miyamoto, K., Kingsley, C. I., Zhang, X., Jabs, C., Izikson, L., Sobel, R. A., Weiner, H. L., Kuchroo, V. K., & Sharpe, A. H. 2005, "The ICOS molecule plays a crucial role in the development of mucosal tolerance", J Immunol, vol. 175, no. 11, pp. 7341-7347.

Miyamoto, K., Miyake, S., Mizuno, M., Oka, N., Kusunoki, S., & Yamamura, T. 2006, "Selective COX-2 inhibitor celecoxib prevents experimental autoimmune encephalomyelitis through COX-2-independent pathway", Brain, vol. 129, no. Pt 8, pp. 1984-1992.

Miyamoto, K., Miyake, S., & Yamamura, T. 2001, "A synthetic glycolipid prevents autoimmune encephalomyelitis by inducing TH2 bias of natural killer T cells", Nature, vol. 413, no. 6855, pp. 531-534.

Mizobuchi, M., Iwasaki, Y., Sako, K., & Kaneko, Y. 1997, "Suppression of acute experimental allergic encephalomyelitis in Lewis rats with a mycophenolic acid derivative", Tohoku J.Exp.Med., vol. 182, no. 3, pp. 217-229.

Mohamed, A., Afridi, D. M., Garani, O., & Tucci, M. 2005, "Thymoquinone inhibits the activation of NF-kappaB in the brain and spinal cord of experimental autoimmune encephalomyelitis", Biomed.Sci.Instrum., vol. 41, pp. 388-393.

Mohamed, A., Reid, P. F., Raymond, L., & Dufan, T. 2006, "Amelioration of acute and relapsing stages of the experimental allergic encephalomyelitis by cobra toxins", Biomed.Sci.Instrum., vol. 42, pp. 399-404.

Mohamed, A., Shoker, A., Bendjelloul, F., Mare, A., Alzrigh, M., Benghuzzi, H., & Desin, T. 2003, "Improvement of experimental allergic encephalomyelitis (EAE) by thymoquinone; an oxidative stress inhibitor", Biomed.Sci.Instrum., vol. 39, pp. 440-445.

Mohamed, A., Waris, H. M., Ramadan, H., Qureshi, M., & Kalra, J. 2009, "Amelioration of Chronic Relapsing Experimental autoimmune encephalomyelitis (CR-EAE) using thymoquinone", Biomedical Sciences Instrumentation.45()(pp 274-279), 2009.Date of Publication: 2009. pp. 274-279.

Mohamed, A. A., Avila, J. G., Schultke, E., Kamencic, H., Skihar, V., Obayan, A., & Juurlink, B. H. 2002, "Amelioration of experimental allergic encephalitis (EAE) through phase 2 enzyme induction", Biomed.Sci.Instrum., vol. 38, pp. 9-13.

Mokhtarian, F. 1988, "Role of Ia antigen in the induction of adoptively transferred acute and chronic relapsing demyelinating disease in mice", Clin Immunol Immunopathol, vol. 49, no. 2, pp. 308-317.

Mokhtarian, F., Shirazian, T., Batuman, O., & Shi, Y. 1996, "The effects of oral myelin basic protein and dexamethasone treatment on experimental autoimmune encephalomyelitis", Ann.N.Y.Acad.Sci., vol. 778, pp. 414-417.

Monastra, G., Cross, A. H., Bruni, A., & Raine, C. S. 1991, "Phosphatidylserine-Induced Inhibition of Experimental Auto-Immune Encephalomyelitis Eae in Mice", Journal of Neuroimmunology no. SUPPL. 1.

Monastra, G., Cross, A. H., Bruni, A., & Raine, C. S. 1993, "Phosphatidylserine, a putative inhibitor of tumor necrosis factor, prevents autoimmune demyelination", Neurology, vol. 43, no. 1, pp. 153-163.

Mondal, S., Roy, A., & Pahan, K. 2009, "Functional Blocking Monoclonal Antibodies against IL-12p40 Homodimer Inhibit Adoptive Transfer of Experimental Allergic Encephalomyelitis", Journal of Immunology, vol. 182, no. 8, pp. 5013-5023.

Montero, E., Alonso, L., Perez, R., & Lage, A. 2007, "Interleukin-2 mastering regulation in cancer and autoimmunity", Ann.N.Y.Acad.Sci., vol. 1107, pp. 239-250.

Montgomery, I. N. & Rauch, H. C. 1980, "Bovine-derived spinal cord protein (SCP) protects guinea pigs from experimental allergic encephalomyelitis (EAE) - a confirmatory report", Immunol.Commun., vol. 9, no. 3, pp. 289-295.

Moon, C., Ahn, M., Jee, Y., Heo, S., Kim, S., Kim, H., Sim, K. B., Koh, C. S., Shin, Y. G., & Shin, T. 2004, "Sodium salicylate-induced amelioration of experimental autoimmune encephalomyelitis in Lewis rats is associated with the suppression of inducible nitric oxide synthase and cyclooxygenases", Neurosci.Lett., vol. 356, no. 2, pp. 123-126.

Moon, C., Ahn, M., Wie, M. B., Kim, H. M., Koh, C. S., Hong, S. C., Kim, M. D., Tanuma, N., Matsumoto, Y., & Shin, T. 2005, "Phenidone, a dual inhibitor of cyclooxygenases and lipoxygenases, ameliorates rat paralysis in experimental autoimmune encephalomyelitis by suppressing its target enzymes", Brain Res., vol. 1035, no. 2, pp. 206-210.

Moore, C. S., Earl, N., Frenette, R., Styhler, A., Mancini, J. A., Nicholson, D. W., Hebb, A. L., Owens, T., & Robertson, G. S. 2006, "Peripheral phosphodiesterase 4 inhibition produced by 4-[2-(3,4-Bis-difluoromethoxyphenyl)-2-[4-(1,1,1,3,3,3-hexafluoro-2-hydrox ypropan-2-yl)-phenyl]-ethyl]-3-methylpyridine-1-oxide (L-826,141) prevents experimental autoimmune encephalomyelitis", J.Pharmacol.Exp.Ther., vol. 319, no. 1, pp. 63-72.

Moore, M. J., Matthews, J. M., Matthews, T. K., Behan, P. O., & Kies, M. W. 1974, "Reaginic antibody in experimental allergic encephalomyelitis. II. Histamine and serotonin blockade", Res Commun.Chem Pathol Pharmacol, vol. 9, no. 1, pp. 133-144.

Morariu, M. A. & Dalmasso, A. P. 1978, "Experimental allergic encephalomyelitis in cobra venom factor-treated and C4-deficient guinea pigs", Ann.Neurol., vol. 4, no. 5, pp. 427-430.

Moreno, B., Hevia, H., Santamaria, M., Sepulcre, J., Munoz, J., Garcia-Trevijano, E. R., Berasain, C., Corrales, F. J., Avila, M. A., & Villoslada, P. 2006, "Methylthioadenosine reverses brain autoimmune disease", Ann.Neurol., vol. 60, no. 3, pp. 323-334.

Morgan, B. P., Griffiths, M., Khanom, H., Taylor, S. M., & Neal, J. W. 2004, "Blockade of the C5a receptor fails to protect against experimental autoimmune encephalomyelitis in rats", Clin.Exp.Immunol., vol. 138, no. 3, pp. 430-438.

Morini, M., Roccatagliata, L., Dell'Eva, R., Pedemonte, E., Furlan, R., Minghelli, S., Giunti, D., Pfeffer, U., Marchese, M., Noonan, D., Mancardi, G., Albini, A., & Uccelli, A. 2004, "Alpha-lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 148, no. 1-2, pp. 146-153.

Moriya, M., Nakatsuji, Y., Okuno, T., Hamasaki, T., Sawada, M., & Sakoda, S. 2005, "Vitamin K2 ameliorates experimental autoimmune encephalomyelitis in Lewis rats", J.Neuroimmunol., vol. 170, no. 1-2, pp. 11-20.

Morris, M., Piddlesden, S., Groome, N., & Amor, S. 1996, "Anti-myelin antibodies modulated EAE in Biozzi ABH mice", Immunology, vol. 89, no. SUPPL. 1.

Morris, M. M., Piddlesden, S., Groome, N., & Amor, S. 1997, "Anti-myelin antibodies modulate experimental allergic encephalomyelitis in Biozzi ABH mice", Biochem.Soc.Trans., vol. 25, no. 2, p. 168S.

Morrissey, S. P., Deichmann, R., Syha, J., Simonis, C., Zettl, U., Archelos, J. J., Jung, S., Stodal, H., Lassmann, H., Toyka, K. V., Haase, A., & Hartung, H. P. 1996, "Partial inhibition of AT-EAE by an antibody to ICAM-1: clinico-histological and MRI studies", J.Neuroimmunol., vol. 69, no. 1-2, pp. 85-93.

Mosayebi, G., Ghazavi, A., Salehi, H., Payani, M. A., & Khazae, M. R. 2007, "Effect of sesame oil on the inhibition of experimental autoimmune encephalomyelitis in C57BL/6 mice", Pak.J Biol Sci, vol. 10, no. 11, pp. 1790-1796.

Mostarica-Stojkovic, M., Petrovic, M., & Lukic, M. L. 1982, "Resistance to the induction of EAE in AO rats: its prevention by the pre-treatment with cyclophosphamide or low dose of irradiation", Clin.Exp.Immunol., vol. 50, no. 2, pp. 311-317.

Mostarica-Stojkovic, M., Vukmanovic, S., Petrovic, M., Ramic, Z., & Lukic, M. L. 1988, "Dissection of adjuvant and suppressive effects of mycobacteria in experimental allergic encephalomyelitis production", Int.Arch.Allergy Appl.Immunol., vol. 85, no. 1, pp. 82-86.

Moulias, R. & Peetoom, F. 1968, "[Studies of the protective effect of hyperimmune anti-nervous system serum against experimental allergic encephalomyelitis]", Pathol.Biol., vol. 16, no. 19, pp. 859-863.

Mueller, A. M., Pedre, X., Kleiter, I., Hornberg, M., Steinbrecher, A., & Giegerich, G. 2005, "Targeting fibroblast growth factor-inducible-14 signaling protects from chronic relapsing experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 159, no. 1-2, pp. 55-65.

Muhvic, D., Radosevic-Stasic, B., Pugel, E., Rukavina, D., Sepcic, J., & Efendic, S. 1992, "Modulation of experimental allergic encephalomyelitis by somatostatin", Ann.N.Y.Acad.Sci., vol. 650, pp. 170-178.

Mujtaba, M. G., Flowers, L. O., Patel, C. B., Patel, R. A., Haider, M. I., & Johnson, H. M. 2005, "Treatment of mice with the suppressor of cytokine signaling-1 mimetic peptide, tyrosine kinase inhibitor peptide, prevents development of the acute form of experimental allergic encephalomyelitis and induces stable remission in the chronic relapsing/remitting form", J.Immunol., vol. 175, no. 8, pp. 5077-5086.

Mujtaba, M. G., Streit, W. J., & Johnson, H. M. 1998, "IFN-tau suppresses both the autoreactive humoral and cellular immune responses and induces stable remission in mice with chronic experimental allergic encephalomyelitis", Cell Immunol., vol. 186, no. 2, pp. 94-102.

Mullin, B. R., Patrick, D. H., Poore, C. M., Rupp, B. H., & Smith, M. T. 1986, "Prevention of experimental allergic encephalomyelitis by ganglioside GM4. A follow-up study", J.Neurol.Sci., vol. 73, no. 1, pp. 55-60.

Mullin, B. R., Patrick, D. H., Poore, C. M., & Smith, M. T. 1984, "Prevention of experimental allergic encephalomyelitis by ganglioside GM4", Brain Res., vol. 296, no. 1, pp. 174-176.

Murphy, P., Sharp, A., Shin, J., Gavrilyuk, V., Dello, R. C., Weinberg, G., Sharp, F. R., Lu, A., Heneka, M. T., & Feinstein, D. L. 2002, "Suppressive effects of ansamycins on inducible nitric oxide synthase expression and the development of experimental autoimmune encephalomyelitis", J.Neurosci.Res., vol. 67, no. 4, pp. 461-470.

Mustafa, M., Diener, P., Sun, J. B., Link, H., & Olsson, T. 1993, "Immunopharmacologic modulation of experimental allergic encephalomyelitis: low-dose cyclosporin-A treatment causes disease relapse and increased systemic T and B cell-mediated myelin-directed autoimmunity", Scand J Immunol, vol. 38, no. 6, pp. 499-507.

Muthian, G. & Bright, J. J. 2004, "Quercetin, a flavonoid phytoestrogen, ameliorates experimental allergic encephalomyelitis by blocking IL-12 signaling through JAK-STAT pathway in T lymphocyte", J.Clin.Immunol., vol. 24, no. 5, pp. 542-552.

Nagai, Y., Osanai, T., & Sakakibara, K. 1982, "Intensive suppression of experimental allergic encephalomyelitis (EAE) by serum thymic factor and therapeutic implication for multiple sclerosis", Jpn.J.Exp.Med., vol. 52, no. 4, pp. 213-219.

Nagasawa, K. 1976, "[Immunological studies on experimental allergic encephalomyelitis (EAE). Protection against EAE (author's transl)]", Fukuoka Igaku Zasshi, vol. 67, no. 6, pp. 220-233.

Nagasawa, K. & Mori, R. 1976, "Inhibition of experimental allergic encephalomyelitis in guinea pigs by administration of bacterial lipopolysaccharide", Neurology, vol. 26, no. 6 PT 2, pp. 64-65.

Nagasawa, K. & Mori, R. 1977, "Protection against experimental allergic encephalomyelitis in guinea pigs by bacterial lipopolysaccharide", Int.Arch.Allergy Appl.Immunol., vol. 55, no. 1-6, pp. 332-342.

Nagasawa, K., Mori, R., Kondo, S., & Hisatsune, K. 1979, "Correlation between the capacity of bacterial lipopolysaccharide to supress experimental allergic encephalomyelitis and its mitogenic activity for lymph node cells in guinea pigs", J.Neurol.Sci., vol. 42, no. 3, pp. 417-427.

Nagelkerken, L., Blauw, B., & Tielemans, M. 1997, "IL-4 abrogates the inhibitory effect of IL-10 on the development of experimental allergic encephalomyelitis in SJL mice", Int.Immunol., vol. 9, no. 9, pp. 1243-1251.

Nagelkerken, L., Haspels, I., van, R. W., Blauw, B., Ferrant, J. L., Hess, D. M., Garber, E. A., Taylor, F. R., & Burkly, L. C. 2004, "FcR interactions do not play a major role in inhibition of experimental autoimmune encephalomyelitis by anti-CD154 monoclonal antibodies", J.Immunol., vol. 173, no. 2, pp. 993-999.

Naiki, M., Takeoka, Y., Kurimoto, Y., Matsuoka, T., Suehiro, S., Imai, Y., Osawa, T., & Gershwin, M. E. 1991, "Neurotropin inhibits experimental allergic encephalomyelitis (EAE) in Lewis rats", Int.J.Immunopharmacol., vol. 13, no. 2-3, pp. 235-243.

Nakajima, A., Oshima, H., Nohara, C., Morimoto, S., Yoshino, S., Kobata, T., Yagita, H., & Okumura, K. 2000, "Involvement of CD70-CD27 interactions in the induction of experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 109, no. 2, pp. 188-196.

Nakane, S., Matsuo, H., Goto, H., Yoshinaga-Matsumoto, M., Ohtsuru, I., Ichinose, K., Onodera, H., Yoshida, M., & Shibuya, N. 2003, "Cytapheresis with a filter for selective removal of CD4+ T cells in experimental autoimmune encephalomyelitis", Mult.Scler., vol. 9, no. 6, pp. 579-584.

Namer, I. J., Steibel, J., Poulet, P., Mauss, Y., Armspach, J. P., Eclancher, B., & Chambron, J. 1994, "Hyperbaric oxygen treatment in acute experimental allergic encephalomyelitis. Contribution of magnetic resonance imaging study", Neuroimage., vol. 1, no. 4, pp. 308-312.

Narumi, S., Kaburaki, T., Yoneyama, H., Iwamura, H., Kobayashi, Y., & Matsushima, K. 2002, "Neutralization of IFN-inducible protein 10/CXCL10 exacerbates experimental autoimmune encephalomyelitis", Eur.J.Immunol., vol. 32, no. 6, pp. 1784-1791.

Nashold, F. E., Hoag, K. A., Goverman, J., & Hayes, C. E. 2001, "Rag-1-dependent cells are necessary for 1,25-dihydroxyvitamin D(3) prevention of experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 119, no. 1, pp. 16-29.

Nashold, F. E., Miller, D. J., & Hayes, C. E. 2000, "1,25-dihydroxyvitamin D3 treatment decreases macrophage accumulation in the CNS of mice with experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 103, no. 2, pp. 171-179.

Nataf, S., Garcion, E., Darcy, F., Chabannes, D., Muller, J. Y., & Brachet, P. 1996, "1,25 Dihydroxyvitamin D3 exerts regional effects in the central nervous system during experimental allergic encephalomyelitis", J.Neuropathol.Exp.Neurol., vol. 55, no. 8, pp. 904-914.

Nataf, S., Louboutin, J. P., Chabannes, D., Feve, J. R., & Muller, J. Y. 1993, "Pentoxifylline inhibits experimental allergic encephalomyelitis", Acta Neurol.Scand., vol. 88, no. 2, pp. 97-99.

Natarajan, C. & Bright, J. J. 2002a, "Curcumin inhibits experimental allergic encephalomyelitis by blocking IL-12 signaling through Janus kinase-STAT pathway in T lymphocytes", J.Immunol., vol. 168, no. 12, pp. 6506-6513.

Natarajan, C. & Bright, J. J. 2002b, "Peroxisome proliferator-activated receptor-gamma agonists inhibit experimental allergic encephalomyelitis by blocking IL-12 production, IL-12 signaling and Th1 differentiation", Genes Immun., vol. 3, no. 2, pp. 59-70.

Nath, N., Giri, S., Prasad, R., Salem, M. L., Singh, A. K., & Singh, I. 2005, "5-aminoimidazole-4-carboxamide ribonucleoside: a novel immunomodulator with therapeutic efficacy in experimental autoimmune encephalomyelitis", J.Immunol., vol. 175, no. 1, pp. 566-574.

Nath, N., Giri, S., Prasad, R., Singh, A. K., & Singh, I. 2004, "Potential targets of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor for multiple sclerosis therapy", J.Immunol., vol. 172, no. 2, pp. 1273-1286.

Nath, N., Khan, M., Paintlia, M. K., Hoda, M. N., & Giri, S. 2009, "Metformin attenuated the autoimmune disease of the central nervous system in animal models of multiple sclerosis", J Immunol, vol. 182, no. 12, pp. 8005-8014.

Nelson, P., La Ronde, A., Rego, J., Coppola, A., Weiner, H., & Al Sabbagh, A. 1996a, "Prolonged oral administration of bovine myelin suppresses CNS inflammation and demyelination foci in SJL/J mice with chronic relapsing EAE", Faseb Journal, vol. 10, no. 6.

Nelson, P. A., Akselband, Y., Dearborn, S. M., Al-Sabbagh, A., Tian, Z. J., Gonnella, P. A., Zamvil, S. S., Chen, Y., & Weiner, H. L. 1996b, "Effect of oral beta interferon on subsequent immune responsiveness", Ann.N.Y.Acad.Sci., vol. 778, pp. 145-155.

Nemoto, K., Abe, F., Takita, T., Nakamura, T., Takeuchi, T., & Umezawa, H. 1987, "Suppression of experimental allergic encephalomyelitis in guinea pigs by spergualin and 15-deoxyspergualin", J.Antibiot.(Tokyo), vol. 40, no. 8, pp. 1193-1194.

Nessler, S., Stadelmann, C., Bittner, A., Schlegel, K., Gronen, F., Brueck, W., Hemmer, B., & Sommer, N. 2006, "Suppression of autoimmune encephalomyelitis by a neurokinin-1 receptor antagonist--a putative role for substance P in CNS inflammation", J.Neuroimmunol., vol. 179, no. 1-2, pp. 1-8.

Neu, I. S., Wildfeuer, A., Mallinger, J., & Mehlber, L. 1992, "Suppression of experimental autoimmune encephalomyelitis by a new specific inhibitor of leukotriene biosynthesis", Arzneimittelforschung., vol. 42, no. 9, pp. 1083-1086.

Nguyen, K. B., McCombe, P. A., & Pender, M. P. 1997, "Increased apoptosis of T lymphocytes and macrophages in the central and peripheral nervous systems of Lewis rats with experimental autoimmune encephalomyelitis treated with dexamethasone", J.Neuropathol.Exp.Neurol., vol. 56, no. 1, pp. 58-69.

Ni, J., Shu, Y. Y., Zhu, Y. N., Fu, Y. F., Tang, W., Zhong, X. G., Wang, H., Yang, Y. F., Ren, J., Wang, M. W., & Zuo, J. P. 2007, "COX-2 inhibitors ameliorate experimental autoimmune encephalomyelitis through modulating IFN-gamma and IL-10 production by inhibiting T-bet expression", J.Neuroimmunol., vol. 186, no. 1-2, pp. 94-103.

Ni, X., Geller, E. B., Eppihimer, M. J., Eisenstein, T. K., Adler, M. W., & Tuma, R. F. 2004, "Win 55212-2, a cannabinoid receptor agonist, attenuates leukocyte/endothelial interactions in an experimental autoimmune encephalomyelitis model", Mult Scler, vol. 10, no. 2, pp. 158-164.

Ni, X., Gu, Y., Eppihimer, M., & Tuma, R. F. 2002, "Evidence that anti-VIL-4 attenuates leukocyte/endothelial interactions in experimental autoimmune encephalomyelitis", Faseb Journal, vol. 16, no. 5.

Nicholson, L. B., Greer, J. M., Sobel, R. A., Lees, M. B., & Kuchroo, V. K. 1995, "An altered peptide ligand mediates immune deviation and prevents autoimmune encephalomyelitis", Immunity., vol. 3, no. 4, pp. 397-405.

Niedieck, B. & Kuck, U. 1967, "[On the protective effect of cerebroside injections on experimental allergic encephalomyelitis]", Z.Immunitatsforsch.Allerg.Klin.Immunol., vol. 133, no. 1, pp. 43-49.

Niino, M., Iwabuchi, K., Kikuchi, S., Ato, M., Morohashi, T., Ogata, A., Tashiro, K., & Onoe, K. 2001, "Amelioration of experimental autoimmune encephalomyelitis in C57BL/6 mice by an agonist of peroxisome proliferator-activated receptor-gamma", J.Neuroimmunol., vol. 116, no. 1, pp. 40-48.

Nikodemova, M., Watters, J. J., Jackson, S. J., Yang, S. K., & Duncan, I. D. 2007, "Minocycline down-regulates MHC II expression in microglia and macrophages through inhibition of IRF-1 and protein kinase C (PKC)alpha/betaII", J.Biol.Chem., vol. 282, no. 20, pp. 15208-15216.

Nikolajeva, V., Eze, D., Petrina, Z., & Muiznieks, I. 2000, "Treatment of experimental autoimmune encephalomyelitis with adenylate deaminase from Penicillium lanoso-viride", J.Autoimmun., vol. 14, no. 2, pp. 107-113.

Nizri, E., Adani, R., Meshulam, H., Amitai, G., & Brenner, T. 2005, "Bifunctional compounds eliciting both anti-inflammatory and cholinergic activity as potential drugs for neuroinflammatory impairments", Neurosci.Lett., vol. 376, no. 1, pp. 46-50.

Nizri, E., Hamra-Amitay, Y., Sicsic, C., Lavon, I., & Brenner, T. 2006, "Anti-inflammatory properties of cholinergic up-regulation: A new role for acetylcholinesterase inhibitors", Neuropharmacology, vol. 50, no. 5, pp. 540-547.

Nizri, E., Irony-Tur-Sinai, M., Lavon, I., Meshulam, H., Amitai, G., & Brenner, T. 2007, "IBU-octyl-cytisine, a novel bifunctional compound eliciting anti-inflammatory and cholinergic activity, ameliorates CNS inflammation by inhibition of T-cell activity", Int.Immunopharmacol., vol. 7, no. 9, pp. 1129-1139.

Nizri, E., Irony-Tur-Sinai, M., Faranesh, N., Lavon, I., Lavi, E., Weinstock, M., & Brenner, T. 2008, "Suppression of neuroinflammation and immunomodulation by the acetylcholinesterase inhibitor rivastigmine", J Neuroimmunol, vol. 203, no. 1.

Norga, K., Paemen, L., Masure, S., Dillen, C., Heremans, H., Billiau, A., Carton, H., Cuzner, L., Olsson, T., Van, D. J., & . 1995, "Prevention of acute autoimmune encephalomyelitis and abrogation of relapses in murine models of multiple sclerosis by the protease inhibitor D-penicillamine", Inflamm.Res., vol. 44, no. 12, pp. 529-534.

Nunez, M. J., Balboa, J., Rey-Mendez, M., Brenlla, J., Gonzalez-Peteiro, M., Rodrigo, E., & Freire-Garabal, M. 2007, "Effects of amphetamine and cocaine on the development of acute experimental allergic encephalomyelitis in Lewis rats", Hum.Exp.Toxicol., vol. 26, no. 8, pp. 637-643.

O'Brien, N. C., Charlton, B., Cowden, W. B., & Willenborg, D. O. 1999, "Nitric oxide plays a critical role in the recovery of Lewis rats from experimental autoimmune encephalomyelitis and the maintenance of resistance to reinduction", J Immunol, vol. 163, no. 12, pp. 6841-6847.

O'Neill, E. J., Day, M. J., & Wraith, D. C. 2006, "IL-10 is essential for disease protection following intranasal peptide administration in the C57BL/6 model of EAE", J.Neuroimmunol., vol. 178, no. 1-2, pp. 1-8.

O'Neill, J. K., Baker, D., Davison, A. N., Allen, S. J., Butter, C., Waldmann, H., & Turk, J. L. 1993, "Control of immune-mediated disease of the central nervous system with monoclonal (CD4-specific) antibodies", J.Neuroimmunol., vol. 45, no. 1-2, pp. 1-14.

O'Neill, J. K., Baker, D., Davison, A. N., Maggon, K. K., Jaffee, B. D., & Turk, J. L. 1992, "Therapy of chronic relapsing experimental allergic encephalomyelitis and the role of the blood-brain barrier: elucidation by the action of Brequinar sodium", J.Neuroimmunol., vol. 38, no. 1-2, pp. 53-62.

O'Neill, J. K., Baker, D., & Turk, J. L. 1992, "Inhibition of chronic relapsing experimental allergic encephalomyelitis in the Biozzi AB/H mouse", J Neuroimmunol, vol. 41, no. 2, pp. 177-187.

O'Rourke, A. M., Wang, E. Y., Salter-Cid, L., Huang, L., Miller, A., Podar, E., Gao, H. F., Jones, D. S., & Linnik, M. D. 2007, "Benefit of inhibiting SSAO in relapsing experimental autoimmune encephalomyelitis", J.Neural Transm., vol. 114, no. 6, pp. 845-849.

Ochi, H., Abraham, M., Ishikawa, H., Frenkel, D., Yang, K., Basso, A. S., Wu, H., Chen, M. L., Gandhi, R., Miller, A., Maron, R., & Weiner, H. L. 2006, "Oral CD3-specific antibody suppresses autoimmune encephalomyelitis by inducing CD4+", Nat.Med., vol. 12, no. 6, pp. 627-635.

Ochoa-Reparaz, J., Riccardi, C., Rynda, A., Jun, S., Callis, G., & Pascual, D. W. 2007, "Regulatory T cell vaccination without autoantigen protects against experimental autoimmune encephalomyelitis", J.Immunol., vol. 178, no. 3, pp. 1791-1799.

Odoardi, F., Kawakami, N., Klinkert, W. E., Wekerle, H., & Flugel, A. 2007, "Blood-borne soluble protein antigen intensifies T cell activation in autoimmune CNS lesions and exacerbates clinical disease", Proc.Natl.Acad.Sci.U.S.A, vol. 104, no. 47, pp. 18625-18630.

Offen, D., Gilgun-Sherki, Y., Barhum, Y., Benhar, M., Grinberg, L., Reich, R., Melamed, E., & Atlas, D. 2004, "A low molecular weight copper chelator crosses the blood-brain barrier and attenuates experimental autoimmune encephalomyelitis", J.Neurochem., vol. 89, no. 5, pp. 1241-1251.

Offner, H., Celnik, B., Bringman, T. S., Casentini-Borocz, D., Nedwin, G. E., & Vandenbark, A. A. 1990, "Recombinant human beta-galactoside binding lectin suppresses clinical and histological signs of experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 28, no. 2, pp. 177-184.

Offner, H., Hashim, G. A., & Vandenbark, A. A. 1991, "T cell receptor peptide therapy triggers autoregulation of experimental encephalomyelitis", Science, vol. 251, no. 4992, pp. 430-432.

Offner, H., Jones, R., Celnik, B., & Vandenbark, A. A. 1989, "Lymphocyte vaccination against experimental autoimmune encephalomyelitis: evaluation of vaccination protocols", J.Neuroimmunol., vol. 21, no. 1, pp. 13-22.

Offner, H., Jones, R., & Vandenbark, A. A. 1988, "Attenuated T-lymphocyte lines as vaccinating agents against experimental autoimmune encephalomyelitis", Ann.N.Y.Acad.Sci., vol. 540, pp. 540-542.

Offner, H., Malotky, M. K., Pope, L., Vainiene, M., Celnik, B., Miller, S. D., & Vandenbark, A. A. 1995, "Increased severity of experimental autoimmune encephalomyelitis in rats tolerized as adults but not neonatally to a protective TCR V beta 8 CDR2 idiotope", J.Immunol., vol. 154, no. 2, pp. 928-935.

Offner, H., Subramanian, S., Wang, C., Afentoulis, M., Vandenbark, A. A., Huan, J., & Burrows, G. G. 2005, "Treatment of passive experimental autoimmune encephalomyelitis in SJL mice with a recombinant TCR ligand induces IL-13 and prevents axonal injury", J.Immunol., vol. 175, no. 6, pp. 4103-4111.

Offner, H., Vainiene, M., Celnik, B., Weinberg, A. D., Buenafe, A., & Vandenbark, A. A. 1994, "Coculture of TCR peptide-specific T cells with basic protein-specific T cells inhibits proliferation, IL-3 mRNA, and transfer of experimental autoimmune encephalomyelitis", J.Immunol., vol. 153, no. 11, pp. 4988-4996.

Offner, H., Vainiene, M., Gold, D. P., Morrison, W. J., Wang, R. Y., Hashim, G. A., & Vandenbark, A. A. 1991, "Protection against experimental encephalomyelitis. Idiotypic autoregulation induced by a nonencephalitogenic T cell clone expressing a cross-reactive T cell receptor V gene", J.Immunol., vol. 146, no. 12, pp. 4165-4172.

Offner, H., Zamora, A., Drought, H., Matejuk, A., Auci, D. L., Morgan, E. E., Vandenbark, A. A., & Reading, C. L. 2002, "A synthetic androstene derivative and a natural androstene metabolite inhibit relapsing-remitting EAE", J.Neuroimmunol., vol. 130, no. 1-2, pp. 128-139.

Ofosu-Appiah, W. & Mokhtarian, F. 1991, "Characterization of a T suppressor cell line that downgrades experimental allergic encephalomyelitis in mice", Cell Immunol, vol. 135, no. 1, pp. 143-153.

Ohta, Y., Fukuda, S., & Makino, H. 1997, "Reduction of disease causative T-cells in experimental autoimmune disease models by a new antirheumatic drug, TAK-603", Immunopharmacology, vol. 37, no. 2-3, pp. 167-174.

Okuda, Y., Sakoda, S., Fujimura, H., & Yanagihara, T. 1996, "Pentoxifylline delays the onset of experimental allergic encephalomyelitis in mice by modulating cytokine production in peripheral blood mononuclear cells", Immunopharmacology, vol. 35, no. 2, pp. 141-148.

Okuda, Y., Sakoda, S., Fujimura, H., & Yanagihara, T. 1998, "Aminoguanidine, a selective inhibitor of the inducible nitric oxide synthase, has different effects on experimental allergic encephalomyelitis in the induction and progression phase", J Neuroimmunol, vol. 81, no. 1-2, pp. 201-210.

Okuda, Y., Sakoda, S., Fujimura, H., & Yanagihara, T. 2000, "The effect of apoptosis inhibitors on experimental autoimmune encephalomyelitis: apoptosis as a regulatory factor", Biochem.Biophys.Res.Commun., vol. 267, no. 3, pp. 826-830.

Olive, C. 1997, "Modulation of experimental allergic encephalomyelitis in mice by immunization with a peptide specific for the gamma delta T cell receptor", Immunol Cell Biol, vol. 75, no. 1, pp. 102-106.

Osanai, T. & Nagai, Y. 1984, "Suppression of experimental allergic encephalomyelitis (EAE) with liposome-encapsulated protease inhibitor: therapy through the blood-brain barrier", Neurochem.Res., vol. 9, no. 10, pp. 1407-1416.

Otero, D. A. & O'Brien, J. S. 1998, "Intramuscular treatment with a prosaptide mimetic promotes recovery of EAE", Society for Neuroscience Abstracts, vol. 24, no. 1-2.

Ousman, S. S., Tomooka, B. H., van Noort, J. M., Wawrousek, E. F., O'Connor, K. C., Hafler, D. A., Sobel, R. A., Robinson, W. H., & Steinman, L. 2007, "Protective and therapeutic role for alphaB-crystallin in autoimmune demyelination", Nature, vol. 448, no. 7152, pp. 474-479.

Ovadia, H. & Paterson, P. Y. 1982, "Effect of indomethacin treatment upon actively-induced and transferred experimental allergic encephalomyelitis (EAE) in Lewis rats", Clin.Exp.Immunol., vol. 49, no. 2, pp. 386-392.

Ovadia, H., Lehmann, D., Kol-Mizrachi, R., & Abramsky, O. 1994, "Inhibition of experimental allergic encephalomyelitis by nitric oxide synthase inhibitor", Neurology, vol. 44, no. 4 SUPPL. 2.

Pabst, H., Day, N. K., Gewurz, H., & Good, R. A. 1971, "Prevention of experimental allergic encephalomyelitis with cobra venom factor", Proc.Soc.Exp.Biol.Med., vol. 136, no. 2, pp. 555-560.

Paintlia, A. S., Paintlia, M. K., Khan, M., Vollmer, T., Singh, A. K., & Singh, I. 2005, "HMG-CoA reductase inhibitor augments survival and differentiation of oligodendrocyte progenitors in animal model of multiple sclerosis", FASEB J., vol. 19, no. 11, pp. 1407-1421.

Paintlia, A. S., Paintlia, M. K., Singh, A. K., Stanislaus, R., Gilg, A. G., Barbosa, E., & Singh, I. 2004, "Regulation of gene expression associated with acute experimental autoimmune encephalomyelitis by Lovastatin", J.Neurosci.Res., vol. 77, no. 1, pp. 63-81.

Paintlia, A. S., Paintlia, M. K., Singh, I., & Singh, A. K. 2006a, "Immunomodulatory effect of combination therapy with lovastatin and 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside alleviates neurodegeneration in experimental autoimmune encephalomyelitis", Am.J.Pathol., vol. 169, no. 3, pp. 1012-1025.

Paintlia, A. S., Paintlia, M. K., Singh, I., & Singh, A. K. 2008a, "Combined medication of lovastatin with rolipram suppresses severity of experimental autoimmune encephalomyelitis", Exp Neurol, vol. 214, no. 2.

Paintlia, A. S., Paintlia, M. K., Singh, I., Skoff, R. B., & Singh, A. K. 2009, "Combination therapy of lovastatin and rolipram provides neuroprotection and promotes neurorepair in inflammatory demyelination model of multiple sclerosis", Glia, vol. 57, no. 2.

Paintlia, A. S., Paintlia, M. K., Singh, A. K., & Singh, I. 2006b, "Concurrent treatment with Lovastatin and 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside provides neuroprotection and alleviate neurodegeneration in experimental autoimmune encephalomyelitis", Faseb Journal, vol. 20, no. 5, Part 2.

Paintlia, A. S., Paintlia, M. K., Singh, A. K., & Singh, I. 2008b, "Inhibition of rho family functions by lovastatin promotes myelin repair in ameliorating experimental autoimmune encephalomyelitis", Mol Pharmacol, vol. 73, no. 5.

Pal, E. & Tabira, T. 2002, "Autonomic regulation of experimental autoimmune encephalomyelitis: the role of interferon-gamma", Neuroimmunomodulation, vol. 10, no. 2, pp. 80-84.

Palaszynski, K. M., Liu, H., Loo, K. K., & Voskuhl, R. R. 2004, "Estriol treatment ameliorates disease in males with experimental autoimmune encephalomyelitis: implications for multiple sclerosis", J.Neuroimmunol., vol. 149, no. 1-2, pp. 84-89.

Papenfuss, T. L., Kithcart, A. P., Powell, N. D., McClain, M. A., Gienapp, I. E., Shawler, T. M., & Whitacre, C. C. 2007, "Disease-modifying capability of murine Flt3-ligand DCs in experimental autoimmune encephalomyelitis", J.Leukoc.Biol., vol. 82, no. 6, pp. 1510-1518.

Park, I. K., Hiraki, K., Kohyama, K., & Matsumoto, Y. 2008, "Differential effects of decoy chemokine (7ND) gene therapy on acute, biphasic and chronic autoimmune encephalomyelitis: implication for pathomechanisms of lesion formation", J Neuroimmunol, vol. 194, no. 1-2, pp. 34-43.

Pashov, A., Bellon, B., Kaveri, S. V., & Kazatchkine, M. D. 1997, "A shift in encephalitogenic T cell cytokine pattern is associated with suppression of EAE by intravenous immunoglobulins (IVIg)", Mult.Scler., vol. 3, no. 2, pp. 153-156.

Pashov, A., Dubey, C., Kaveri, S. V., Lectard, B., Huang, Y. M., Kazatchkine, M. D., & Bellon, B. 1998, "Normal immunoglobulin G protects against experimental allergic encephalomyelitis by inducing transferable T cell unresponsiveness to myelin basic protein", Eur J Immunol, vol. 28, no. 6, pp. 1823-1831.

Paterson, P. Y. 1971, "Cyclophosphamide treatment of experimental allergic encephalomyelitis in Lewis rats", J.Immunol., vol. 106, no. 6, pp. 1473-1479.

Paterson, P. Y. & Drobish, D. G. 1969, "Cyclophosphamide: effect on experimental allergic encephalomyelitis in Lewis rats", Science, vol. 165, no. 889, pp. 191-192.

Paterson, P. Y. & Hanson, M. A. 1969a, "Cyclophosphamide inhibition of experimental allergic encephalomyelitis and cellular transfer of the disease in Lewis rats", J.Immunol., vol. 103, no. 6, pp. 1311-1316.

Paterson, P. Y. & Hanson, M. A. 1969b, "Studies of cyclophosphamide suppression of experimental allergic encephalomyelitis in Wistar rats", J.Immunol., vol. 103, no. 4, pp. 795-803.

Paterson, P. Y., Harvey, J. M., & Webster, L. T., Jr. 1977, "Niridazole suppression of experimental allergic encephalomyelitis in Lewis rats", J.Immunol., vol. 118, no. 6, pp. 2151-2154.

Paul, C. & Bolton, C. 2002, "Modulation of blood-brain barrier dysfunction and neurological deficits during acute experimental allergic encephalomyelitis by the N-methyl-D-aspartate receptor antagonist memantine", J.Pharmacol.Exp.Ther., vol. 302, no. 1, pp. 50-57.

Pedchenko, T. V. & LeVine, S. M. 1998, "Desferrioxamine suppresses experimental allergic encephalomyelitis induced by MBP in SJL mice", J.Neuroimmunol., vol. 84, no. 2, pp. 188-197.

Pedemonte, E., Benvenuto, F., Casazza, S., Mancardi, G., Oksenberg, J. R., Uccelli, A., & Baranzini, S. E. 2007, "The molecular signature of therapeutic mesenchymal stem cells exposes the architecture of the hematopoietic stem cell niche synapse", BMC.Genomics, vol. 8, p. 65.

Pedotti, R., DeVoss, J. J., Youssef, S., Mitchell, D., Wedemeyer, J., Madanat, R., Garren, H., Fontoura, P., Tsai, M., Galli, S. J., Sobel, R. A., & Steinman, L. 2003, "Multiple elements of the allergic arm of the immune response modulate autoimmune demyelination", Proc.Natl.Acad.Sci.U.S.A, vol. 100, no. 4, pp. 1867-1872.

Peers, S. H., Duncan, G. S., Flower, R. J., & Bolton, C. 1995, "Endogenous corticosteroids modulate lymphoproliferation and susceptibility to experimental allergic encephalomyelitis in the Brown Norway rat", Int Arch Allergy Immunol, vol. 106, no. 1, pp. 20-24.

Peiris, M., Monteith, G. R., Roberts-Thomson, S. J., & Cabot, P. J. 2007, "A model of experimental autoimmune encephalomyelitis (EAE) in C57BL/6 mice for the characterisation of intervention therapies", J.Neurosci.Methods, vol. 163, no. 2, pp. 245-254.

Pekarski, O., Bjork, J., Hedlund, G., & Andersson, G. 1998, "The inhibitory effect in experimental autoimmune encephalomyelitis by the immunomodulatory drug Linomide (PNU-212616) is not mediated via release of endogenous glucocorticoids", Autoimmunity, vol. 28, no. 4, pp. 235-241.

Pellet, H., Brun, M., Camargo, R., & Girard, P. 1968, "[Prevention of experimental allergic encephalomyelitis by immunological technics]", Rev.Neurol.(Paris), vol. 118, no. 2, pp. 133-140.

Pelletier, L., Rossert, J., Pasquier, R., Villarroya, H., Belair, M. F., Vial, M. C., Oriol, R., & Druet, P. 1988, "Effect of HgCl2 on experimental allergic encephalomyelitis in Lewis rats. HgCl2-induced down-modulation of the disease", Eur.J.Immunol., vol. 18, no. 2, pp. 243-247.

Pender, M. P., Stanley, G. P., Yoong, G., & Nguyen, K. B. 1990, "The neuropathology of chronic relapsing experimental allergic encephalomyelitis induced in the Lewis rat by inoculation with whole spinal cord and treatment with cyclosporin A", Acta Neuropathol, vol. 80, no. 2.

Penkowa, M. & Hidalgo, J. 2001, "Metallothionein treatment reduces proinflammatory cytokines IL-6 and TNF-alpha and apoptotic cell death during experimental autoimmune encephalomyelitis (EAE)", Exp.Neurol., vol. 170, no. 1, pp. 1-14.

Penkowa, M. & Hidalgo, J. 2003, "Treatment with metallothionein prevents demyelination and axonal damage and increases oligodendrocyte precursors and tissue repair during experimental autoimmune encephalomyelitis", J.Neurosci.Res., vol. 72, no. 5, pp. 574-586.

Pepinsky, R. B., Lee, W. C., Cornebise, M., Gill, A., Wortham, K., Chen, L. L., Leone, D. R., Giza, K., Dolinski, B. M., Perper, S., Nickerson-Nutter, C., Lepage, D., Chakraborty, A., Whalley, E. T., Petter, R. C., Adams, S. P., Lobb, R. R., & Scott, D. M. 2005, "Design, synthesis, and analysis of a polyethelene glycol-modified (PEGylated) small molecule inhibitor of integrin {alpha}4{beta}1 with improved pharmaceutical properties", J Pharmacol Exp Ther, vol. 312, no. 2, pp. 742-750.

Perper, S., Nickerson-Nutter, C., & Benjamin, C. D. 1999, "Impact of an anti-rat CD40L antibody on rat EAE", Arthritis and Rheumatism, vol. 42, no. 9 SUPPL..

Perrin, P., Racke, M., Davis, T., June, C., & Scott, D. 1995, "Differential roles of the CTLA-4 ligands CD80(B7-1) and CD86(B7-2) in the induction of experimental allergic encephalomyelitis", Faseb Journal, vol. 9, no. 4.

Perrin, P. J., June, C. H., Maldonado, J. H., Ratts, R. B., & Racke, M. K. 1999, "Blockade of CD28 during in vitro activation of encephalitogenic T cells or after disease onset ameliorates experimental autoimmune encephalomyelitis", J.Immunol., vol. 163, no. 3, pp. 1704-1710.

Perruche, S., Zhang, P., Liu, Y., Saas, P., Bluestone, J. A., & Chen, W. 2008, "CD3-specific antibody-induced immune tolerance involves transforming growth factor-beta from phagocytes digesting apoptotic T cells", Nat Med, vol. 14, no. 5, pp. 528-535.

Persinger, M. A., Cook, L. L., & Koren, S. A. 2000, "Suppression of experimental allergic encephalomyelitis in rats exposed nocturnally to magnetic fields", Int.J.Neurosci., vol. 100, no. 1-4, pp. 107-116.

Pesoa, S. A., Hayosh, N. S., & Swanborg, R. H. 1984, "Regulation of experimental allergic encephalomyelitis. Part 5. Role of the recipient in suppressor cell induction", J.Neuroimmunol., vol. 7, no. 2-3, pp. 131-135.

Peterson, L. K., Tsunoda, I., & Fujinami, R. S. 2008, "Role of CD5+ B-1 cells in EAE pathogenesis", Autoimmunity, vol. 41, no. 5.

Pettersson, A., Ciumas, C., Chirsky, V., Link, H., Huang, Y. M., & Xiao, B. G. 2004a, "Dendritic cells exposed to estrogen in vitro exhibit therapeutic effects in ongoing experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 156, no. 1-2, pp. 58-65.

Pettersson, A., Wu, X. C., Ciumas, C., Lian, H., Chirsky, V., Huang, Y. M., Bjelke, B., Link, H., & Xiao, B. G. 2004b, "CD8alpha dendritic cells and immune protection from experimental allergic encephalomyelitis", Clin.Exp.Immunol., vol. 137, no. 3, pp. 486-495.

Phillips, S. M., Bhopale, M. K., Constantinescu, C. S., Ciric, B., Hilliard, B., Ventura, E., Lavi, E., & Rostami, A. 2007, "Effect of DAB(389)IL-2 immunotoxin on the course of experimental autoimmune encephalomyelitis in Lewis rats", J.Neurol.Sci., vol. 263, no. 1-2, pp. 59-69.

Piao, W. H., Jee, Y. H., Liu, R. L., Coons, S. W., Kala, M., Collins, M., Young, D. A., Campagnolo, D. I., Vollmer, T. L., Bai, X. F., La Cava, A., & Shi, F. D. 2008, "IL-21 modulates CD4+ CD25+ regulatory T-cell homeostasis in experimental autoimmune encephalomyelitis", Scand.J.Immunol., vol. 67, no. 1, pp. 37-46.

Piao, W. H., Wong, R., Bai, X. F., Huang, J., Campagnolo, D. I., Dorr, R. T., Vollmer, T. L., & Shi, F. D. 2007, "Therapeutic effect of anthracene-based anticancer agent ethonafide in an animal model of multiple sclerosis", J.Immunol., vol. 179, no. 11, pp. 7415-7423.

Piccio, L., Buonsanti, C., Mariani, M., Cella, M., Gilfillan, S., Cross, A. H., Colonna, M., & Panina-Bordignon, P. 2007, "Blockade of TREM-2 exacerbates experimental autoimmune encephalomyelitis", European Journal of Immunology.37(5)()(pp 1290-1301), 2007.Date of Publication: May 2007. no. 5, pp. 1290-1301.

Piccio, L., Stark, J. L., & Cross, A. H. 2008, "Chronic calorie restriction attenuates experimental autoimmune encephalomyelitis", Journal of Leukocyte Biology.84(4)()(pp 940-948), 2008.Date of Publication: 01 Oct 2008. no. 4, pp. 940-948.

Piccirillo, C. A. & Prud'homme, G. J. 1999, "Prevention of experimental allergic encephalomyelitis by intramuscular gene transfer with cytokine-encoding plasmid vectors", Hum.Gene Ther., vol. 10, no. 12, pp. 1915-1922.

Piddlesden, S., Lassmann, H., Laffafian, I., Morgan, B. P., & Linington, C. 1991, "Antibody-mediated demyelination in experimental allergic encephalomyelitis is independent of complement membrane attack complex formation", Clin.Exp.Immunol., vol. 83, no. 2, pp. 245-250.

Piddlesden, S. J., Storch, M. K., Hibbs, M., Freeman, A. M., Lassmann, H., & Morgan, B. P. 1994, "Soluble recombinant complement receptor 1 inhibits inflammation and demyelination in antibody-mediated demyelinating experimental allergic encephalomyelitis", J.Immunol., vol. 152, no. 11, pp. 5477-5484.

Pietropaolo, M., Olson, C. D., Reiseter, B. S., Kasaian, M. T., & Happ, M. P. 2000, "Intratracheal administration to the lung enhances therapeutic benefit of an MBP peptide in the treatment of murine experimental autoimmune encephalomyelitis", Clin.Immunol., vol. 95, no. 2, pp. 104-116.

Pinto, F., Brenner, T., Dan, P., Krimsky, M., & Yedgar, S. 2003, "Extracellular phospholipase A2 inhibitors suppress central nervous system inflammation", Glia, vol. 44, no. 3, pp. 275-282.

Piraino, P. S., Yednock, T. A., Freedman, S. B., Messersmith, E. K., Pleiss, M. A., & Karlik, S. J. 2005a, "Suppression of acute experimental allergic encephalomyelitis with a small molecule inhibitor of alpha4 integrin", Mult.Scler., vol. 11, no. 6, pp. 683-690.

Piraino, P. S., Yednock, T. A., Freedman, S. B., Messersmith, E. K., Pleiss, M. A., Vandevert, C., Thorsett, E. D., & Karlik, S. J. 2002, "Prolonged reversal of chronic experimental allergic encephalomyelitis using a small molecule inhibitor of alpha4 integrin", J.Neuroimmunol., vol. 131, no. 1-2, pp. 147-159.

Piraino, P. S., Yednock, T. A., Messersmith, E. K., Pleiss, M. A., Freedman, S. B., Hammond, R. R., & Karlik, S. J. 2005b, "Spontaneous remyelination following prolonged inhibition of alpha4 integrin in chronic EAE", J Neuroimmunol, vol. 167, no. 1-2.

Pitt, D., Werner, P., & Raine, C. 1999, "The AMPA/kainate antagonist NBQX protects against oligodendroglial and axonal damage in experimental autoimmune encephalomyelitis (EAE)", Society for Neuroscience Abstracts, vol. 25, no. 1-2.

Pitt, D., Werner, P., & Raine, C. S. 2000, "Glutamate excitotoxicity in a model of multiple sclerosis", Nat.Med., vol. 6, no. 1, pp. 67-70.

Platten, M., Ho, P. P., Youssef, S., Fontoura, P., Garren, H., Hur, E. M., Gupta, R., Lee, L. Y., Kidd, B. A., Robinson, W. H., Sobel, R. A., Selley, M. L., & Steinman, L. 2005, "Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite", Science, vol. 310, no. 5749, pp. 850-855.

Pluchino, S., Quattrini, A., Brambilla, E., Gritti, A., Salani, G., Dina, G., Galli, R., Del Carro, U., Amadio, S., Bergami, A., Furlan, R., Comi, G., Vescovi, A. L., & Martino, G. 2003, "Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis", Nature, vol. 422, no. 6933.

Podojil, J. R., Kohm, A. P., & Miller, S. D. 2006, "CD4+ T cell expressed CD80 regulates central nervous system effector function and survival during experimental autoimmune encephalomyelitis", J.Immunol., vol. 177, no. 5, pp. 2948-2958.

Polak, P. E., Kalinin, S., Dello, R. C., Gavrilyuk, V., Sharp, A., Peters, J. M., Richardson, J., Willson, T. M., Weinberg, G., & Feinstein, D. L. 2005, "Protective effects of a peroxisome proliferator-activated receptor-beta/delta agonist in experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 168, no. 1-2, pp. 65-75.

Poliani, P. L., Brok, H., Furlan, R., Ruffini, F., Bergami, A., Desina, G., Marconi, P. C., Rovaris, M., Uccelli, A., Glorioso, J. C., Penna, G., Adorini, L., Comi, G., 't, H. B., & Martino, G. 2001, "Delivery to the central nervous system of a nonreplicative herpes simplex type 1 vector engineered with the interleukin 4 gene protects rhesus monkeys from hyperacute autoimmune encephalomyelitis", Human Gene Therapy.12(8)()(pp 905-920), 2001.Date of Publication: 2001. no. 8, pp. 905-920.

Pollak, Y., Ovadia, H., Orion, E., & Yirmiya, R. 2003, "The EAE-associated behavioral syndrome: II. Modulation by anti-inflammatory treatments", J.Neuroimmunol., vol. 137, no. 1-2, pp. 100-108.

Pope, L., Paterson, P. Y., & Miller, S. D. 1992, "Antigen-specific inhibition of the adoptive transfer of experimental autoimmune encephalomyelitis in Lewis rats", J.Neuroimmunol., vol. 37, no. 3, pp. 177-189.

Popovic, N., Schubart, A., Goetz, B. D., Zhang, S. C., Linington, C., & Duncan, I. D. 2002, "Inhibition of autoimmune encephalomyelitis by a tetracycline", Ann.Neurol., vol. 51, no. 2, pp. 215-223.

Popovich, P. G., Yu, J. Y., & Whitacre, C. C. 1997, "Spinal cord neuropathology in rat experimental autoimmune encephalomyelitis: modulation by oral administration of myelin basic protein", J Neuropathol Exp Neurol, vol. 56, no. 12, pp. 1323-1338.

Pozza, M., Bettelli, C., Aloe, L., Giardino, L., & Calza, L. 2000, "Further evidence for a role of nitric oxide in experimental allergic encephalomyelitis: aminoguanidine treatment modifies its clinical evolution", Brain Res., vol. 855, no. 1, pp. 39-46.

Prasad, D. V., Nguyen, T., Li, Z., Yang, Y., Duong, J., Wang, Y., & Dong, C. 2004, "Murine B7-H3 is a negative regulator of T cells", J.Immunol., vol. 173, no. 4, pp. 2500-2506.

Prasad, R., Giri, S., Nath, N., Singh, I., & Singh, A. K. 2007, "GSNO attenuates EAE disease by S-nitrosylation-mediated modulation of endothelial-monocyte interactions", Glia, vol. 55, no. 1, pp. 65-77.

Prockop, L. D. & Grasso, R. J. 1978, "Ameliorating effects of hyperbaric oxygenation on experimental allergic encephalomyelitis", Brain Res.Bull., vol. 3, no. 3, pp. 221-225.

Prosiegel, M., Neu, I., Mallinger, J., Wildfeuer, A., Mehlber, L., Vogl, S., Hoffmann, G., & Ruhenstroth-Bauer, G. 1989, "Suppression of experimental autoimmune encephalomyelitis by dual cyclo-oxygenase and 5-lipoxygenase inhibition", Acta Neurol.Scand., vol. 79, no. 3, pp. 223-226.

Prosiegel, M., Neu, I., Vogl, S., Hoffmann, G., Wildfeuer, A., & Ruhenstroth-Bauer, G. 1990, "Suppression of experimental autoimmune encephalomyelitis by sulfasalazine", Acta Neurol.Scand., vol. 81, no. 3, pp. 237-238.

Pryce, G., O'Neill, J. K., Croxford, J. L., Amor, S., Hankey, D. J., East, E., Giovannoni, G., & Baker, D. 2005, "Autoimmune tolerance eliminates relapses but fails to halt progression in a model of multiple sclerosis", J Neuroimmunol., vol. 165, no. 1-2, pp. 41-52.

Przuntek, H., Westarp, M. E., Vohl, M. L., Gerlach, M., Jutzi, P., & Wekerle, H. 1987, "The effect of silyl substituted methotrexate in the treatment of experimental allergic encephalomyelitis in rats mediated by T-line cells", Neuropharmacology, vol. 26, no. 2-3, pp. 255-260.

Puerta, C., Martinez, I., Baranda, P., Blasco, M. R., Castejon, R., Vargas, J. A., & Garcia-Merino, A. 2000, "Aminoguanidine reduces apoptosis of circulating V Beta 8.2 T lymphocytes in Lewis rats with actively induced

experimental autoimmune encephalomyelitis. Association with persistent inflammation of the central nervous system and lack of recovery", J Neuroimmunol, vol. 110, no. 1-2, pp. 140-150.

Qi, X., Sun, L., Lewin, A. S., Hauswirth, W. W., & Guy, J. 2007, "Long-term suppression of neurodegeneration in chronic experimental optic neuritis: antioxidant gene therapy", Invest Ophthalmol.Vis.Sci, vol. 48, no. 12, pp. 5360-5370.

Qin, Y. F., Sun, D. M., Goto, M., Meyermann, R., & Wekerle, H. 1989, "Resistance to experimental autoimmune encephalomyelitis induced by neonatal tolerization to myelin basic protein: clonal elimination vs. regulation of autoaggressive lymphocytes", Eur.J.Immunol., vol. 19, no. 2, pp. 373-380.

Quinn, K., Galbraith, S., Sheahan, B., & Atkins, G. 2008, "Effect of intranasal administration of Semliki Forest virus recombinant particles expressing interferon-B on the progression of experimental autoimmune encephalomyelitis", Molecular Medicine Reports, vol. 1, no. 3, pp. 335-342.

Rabin, B. S. 1983, "Inhibition of experimentally induced autoimmunity in rats by biotin deficiency", J.Nutr., vol. 113, no. 11, pp. 2316-2322.

Racke, M. K., Bonomo, A., Scott, D. E., Cannella, B., Levine, A., Raine, C. S., Shevach, E. M., & Rocken, M. 1994a, "Cytokine-induced immune deviation as a therapy for inflammatory autoimmune disease", J.Exp.Med., vol. 180, no. 5, pp. 1961-1966.

Racke, M. K., Burnett, D., Pak, S. H., Albert, P. S., Cannella, B., Raine, C. S., McFarlin, D. E., & Scott, D. E. 1995, "Retinoid treatment of experimental allergic encephalomyelitis. IL-4 production correlates with improved disease course", J.Immunol., vol. 154, no. 1, pp. 450-458.

Racke, M. K., Cannella, B., Albert, P., Sporn, M., Raine, C. S., & McFarlin, D. E. 1992, "Evidence of endogenous regulatory function of transforming growth factor-beta 1 in experimental allergic encephalomyelitis", Int Immunol, vol. 4, no. 5, pp. 615-620.

Racke, M. K., Critchfield, J. M., Quigley, L., Cannella, B., Raine, C. S., McFarland, H. F., & Lenardo, M. J. 1996, "Intravenous antigen administration as a therapy for autoimmune demyelinating disease", Ann.Neurol., vol. 39, no. 1, pp. 46-56.

Racke, M. K., Dhib-Jalbut, S., Cannella, B., Albert, P. S., Raine, C. S., & McFarlin, D. E. 1991, "Prevention and treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-beta 1", J.Immunol., vol. 146, no. 9, pp. 3012-3017.

Racke, M. K., Quigley, L., Cannella, B., Raine, C. S., McFarlin, D. E., & Scott, D. E. 1994b, "Superantigen modulation of experimental allergic encephalomyelitis: activation of anergy determines outcome", J.Immunol., vol. 152, no. 4, pp. 2051-2059.

Racke, M. K., Sriram, S., Carlino, J., Cannella, B., Raine, C. S., & McFarlin, D. E. 1993, "Long-term treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-beta 2", J.Neuroimmunol., vol. 46, no. 1-2, pp. 175-183.

Racke, M. K., Hussain, R. Z., Northrup, S., Diab, A., & Lovett-Racke, A. E. 2003, "PPARalpha agonists as therapy for autoimmune demyelination", Neurology, vol. 60, no. 5 Supplement 1.

Raikwar, H. P., Muthian, G., Rajasingh, J., Johnson, C., & Bright, J. 2005, "PPAR gamma antagonists exacerbate neural antigen-specific TH1 response and experimental allergic encephalomyelitis", Journal of Neuroimmunology, vol. 167, pp. 99-107.

Raikwar, H. P., Muthian, G., Rajasingh, J., Johnson, C. N., & Bright, J. J. 2006, "PPARgamma antagonists reverse the inhibition of neural antigen-specific Th1 response and experimental allergic encephalomyelitis by Ciglitazone and 15-deoxy-Delta12,14-prostaglandin J2", J.Neuroimmunol., vol. 178, no. 1-2, pp. 76-86.

Raine, C. S., Snyder, D. H., Stone, S. H., & Bornstein, M. B. 1977, "Suppression of acute and chronic experimental allergic encephalomyelitis in Strain 13 guinea pigs. A clinical and pathological study", J.Neurol.Sci., vol. 31, no. 3, pp. 355-367.

Raine, C. S. & Traugott, U. 1983, "Chronic relapsing experimental autoimmune encephalomyelitis. Ultrastructure of the central nervous system of animals treated with combinations of myelin components", Laboratory Investigation.48(3)()(pp 275-284), 1983.Date of Publication: 1983. no. 3, pp. 275-284.

Raine, C. S., Traugott, U., & Stone, S. H. 1978a, "Chronic relapsing experimental allergic encephalomyelitis: CNS plaque development in unsuppressed and suppressed animals", Acta Neuropathol.(Berl), vol. 43, no. 1-2, pp. 43-53.

Raine, C. S., Traugott, U., & Stone, S. H. 1978b, "Suppression of chronic allergic encephalomyelitis: relevance to multiple sclerosis", Science, vol. 201, no. 4354, pp. 445-448.

Rajan, A. J., Gao, Y. L., Raine, C. S., & Brosnan, C. F. 1996, "A pathogenic role for gamma delta T cells in relapsing-remitting experimental allergic encephalomyelitis in the SJL mouse", J Immunol, vol. 157, no. 2, pp. 941-949.

Rajan, A. J., Klein, J. D., & Brosnan, C. F. 1998, "The effect of gammadelta T cell depletion on cytokine gene expression in experimental allergic encephalomyelitis", J Immunol, vol. 160, no. 12, pp. 5955-5962.

Rauch, H. C. & Einstein, E. R. 1974, "Induction and suppression of experimental allergic encephalomyelitis in the non-human primate", J.Neurol.Sci., vol. 23, no. 1, pp. 99-116.

Rauch, H. C., Einstein, E. R., Csejtey, J., & Davis, W. J. 1968, "Protective action of the encephalitogen and other basic proteins in experimental allergic encephalomyelitis", Immunochemistry., vol. 5, no. 6, pp. 567-575.

Rauch, H. C., Montgomery, I. N., & Swanborg, R. H. 1981, "Inhibition of experimental allergic encephalomyelitis by carrier administered prior to challenge with encephalitogenic peptide-carrier conjugate", Eur.J.Immunol., vol. 11, no. 4, pp. 335-338.

Rauch, H. C. & Tom, B. H. 1980, "Immunosuppression of experimental allergic encephalomyelitis in guinea pigs by antibrain and antithymocyte heteroantisera", J.Neurol.Sci., vol. 44, no. 2-3, pp. 265-272.

Rauch, H. C., Wilson, B., & Malley, A. 1979, "Induction of allergic encephalomyelitis in rhesus monkeys treated with anti monkey thymocyte sera", J.Neurol.Sci., vol. 44, no. 1, pp. 135-144.

Rausch, M., Hiestand, P., Foster, C. A., Baumann, D. R., Cannet, C., & Rudin, M. 2004, "Predictability of FTY720 efficacy in experimental autoimmune encephalomyelitis by in vivo macrophage tracking: clinical implications for ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging", J.Magn Reson.Imaging, vol. 20, no. 1, pp. 16-24.

Rausch, M., Kindler, D., Bolliger, S., & Hiestand, P. 2005, "Demonstration of the efficacy of FTY720 in acute EAE: analysis of lesion load using USPIO- and gadolinium- enhanced MRI and correlation with neurological readouts", Multiple Sclerosis, vol. 11, no. S1, p. 64.

Ravkina, L., Rogova, V., & Lazarenko, L. 1978, "Chronic Experimental Allergic Encephalo Myelitis in Rhesus Monkeys and Its Modification by Treatment", Journal of the Neurological Sciences, vol. 38, no. 3, pp. 281-294.

Raziuddin, S., Kibler, R. F., & Morrison, D. C. 1981, "Experimental allergic encephalomyelitis in Lewis rats: inhibition by bacterial lipopolysaccharides and acquired resistance to reinduction by challenge with myelin basic protein", J.Immunol., vol. 127, no. 1, pp. 16-20.

Raziuddin, S. & Morrison, D. C. 1982, "Prolonged suppression of experimental allergic encephalomyelitis in the Lewis rats: the effect of lipopolysaccharides", J.Immunol., vol. 128, no. 3, pp. 1486-1489.

Razmara, M., Hilliard, B., Ziarani, A. K., Murali, R., Yellayi, S., Ghazanfar, M., Chen, Y. H., & Tykocinski, M. L. 2009, "Fn14-TRAIL, a chimeric intercellular signal exchanger, attenuates experimental autoimmune encephalomyelitis", Am J Pathol, vol. 174, no. 2, pp. 460-474.

Reber, N. V. 1971, "[Development of immunological tolerance to brain antigens as a means of specific prevention and treatment of experimental allergic encephalomyelitis]", Biull.Eksp.Biol.Med., vol. 72, no. 11, pp. 69-73.

Reber, N. V. 1973, "[Prevention and depression of experimental allergic encephalomyelitis by the administration of brain antigens and barbamyl]", Patol.Fiziol.Eksp.Ter., vol. 17, no. 1, pp. 65-67.

Reder, A. T., Thapar, M., & Jensen, M. A. 1994, "A reduction in serum glucocorticoids provokes experimental allergic encephalomyelitis: implications for treatment of inflammatory brain disease", Neurology, vol. 44, no. 12, pp. 2289-2294.

Reiber, H. & Suckling, A. J. 1986, "Cyclosporin-A treatment of experimental allergic encephalomyelitis: changes in immunological regulation and blood-CSF barrier function", J.Neuroimmunol., vol. 12, no. 2, pp. 121-130.

Reichert, F. & Rotshenker, S. 1999, "Galectin-3/MAC-2 in experimental allergic encephalomyelitis", Experimental Neurology.160(2)()(pp 508-514), 1999.Date of Publication: Dec 1999. no. 2, pp. 508-514.

Reinke, E. K., Johnson, M. J., Ling, C., Karman, J., Lee, J., Weinstock, J. V., Sandor, M., & Fabry, Z. 2006, "Substance P receptor mediated maintenance of chronic inflammation in EAE", J Neuroimmunol, vol. 180, no. 1-2, pp. 117-125.

Reinke, E. K., Lee, J., Zozulya, A., Karman, J., Muller, W. A., Sandor, M., & Fabry, Z. 2007, "Short-term sPECAM-Fc treatment ameliorates EAE while chronic use hastens onset of symptoms", J.Neuroimmunol., vol. 186, no. 1-2, pp. 86-93.

Reiseter, B. S., Miller, G. T., Happ, M. P., & Kasaian, M. T. 1998, "Treatment of murine experimental autoimmune encephalomyelitis with a myelin basic protein peptide analog alters the cellular composition of leukocytes infiltrating the cerebrospinal fluid", Journal of Neuroimmunology.91(1-2)()(pp 156-170), 1998.Date of Publication: 02 Nov 1998. no. 1-2, pp. 156-170.

Richert, J. R., Namikawa, T., Kies, M. W., & Alvord, E. C., Jr. 1982, "Failure of serum from recovered rats to prevent enhanced adoptive transfer of experimental allergic encephalomyelitis", J.Neurol.Sci., vol. 53, no. 2, pp. 225-232.

Ridge, S. C., Sloboda, A. E., McReynolds, R. A., Levine, S., Oronsky, A. L., & Kerwar, S. S. 1985, "Suppression of experimental allergic encephalomyelitis by mitoxantrone", Clin.Immunol.Immunopathol., vol. 35, no. 1, pp. 35-42.

Riskind, P. N., Massacesi, L., Doolittle, T. H., & Hauser, S. L. 1991, "The role of prolactin in autoimmune demyelination: suppression of experimental allergic encephalomyelitis by bromocriptine", Ann.Neurol., vol. 29, no. 5, pp. 542-547.

Rivero, V. E., Maccioni, M., Bucher, A. E., Roth, G. A., & Riera, C. M. 1997, "Suppression of experimental autoimmune encephalomyelitis (EAE) by intraperitoneal administration of soluble myelin antigens in Wistar rats", J.Neuroimmunol., vol. 72, no. 1, pp. 3-10.

Rolls, A., Cahalon, L., Bakalash, S., Avidan, H., Lider, O., & Schwartz, M. 2006, "A sulfated disaccharide derived from chondroitin sulfate proteoglycan protects against inflammation-associated neurodegeneration", FASEB J, vol. 20, no. 3.

Root-Bernstein, R. S., Yurochko, F., & Westall, F. C. 1986, "Clinical suppression of experimental allergic encephalomyelitis by muramyl dipeptide "adjuvant"", Brain Res.Bull., vol. 17, no. 4, pp. 473-476.

Roscoe, W. A., Messersmith, E., Meyer-Franke, A., Wipke, B., & Karlik, S. J. 2007, "Connexin 43 gap junction proteins are up-regulated in remyelinating spinal cord", J.Neurosci.Res., vol. 85, no. 5, pp. 945-953.

Rose, J. W., Lorberbou-Galski, H., Fitzgerald, D., McCarron, R., Hill, K., Townsend, J. J., & Pastan, I. 1991a, "Effects of Chimeric Cytotoxin Il2-Pe40 on Adoptively Transferred Experimental Allergic Encephalomyelitis", Journal of Cellular Biochemistry Supplement, vol. 15, no. PART E.

Rose, J. W., Lorberboum-Galski, H., Fitzgerald, D., McCarron, R., Hill, K. E., Townsend, J. J., & Pastan, I. 1991b, "Chimeric cytotoxin IL2-PE40 inhibits relapsing experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 32, no. 3, pp. 209-217.

Rose, L. M., Alvord, E. C., Jr., Hruby, S., Jackevicius, S., Petersen, R., Warner, N., & Clark, E. A. 1987, "In vivo administration of anti-CD4 monoclonal antibody prolongs survival in longtailed macaques with experimental allergic encephalomyelitis", Clin.Immunol.Immunopathol., vol. 45, no. 3, pp. 405-423.

Rose, L. M., Alvord, E. C., Jr., Hruby, S., Jackevicius, S. L., Petersen, R., Warner, N., & Clark, E. A. 1988, "Anti-CD4 monoclonal antibody therapy of experimental allergic encephalomyelitis in longtailed macaques", Ann.N.Y.Acad.Sci., vol. 540, pp. 581-584.

Rose, L. M., Richards, T. L., Peterson, J., Petersen, R., & Alvord, E. C., Jr. 1997, "Resolution of CNS lesions following treatment of experimental allergic encephalomyelitis in macaques with monoclonal antibody to the CD18 leukocyte integrin", Mult.Scler., vol. 2, no. 6, pp. 259-266.

Rosenthale, M. E., Datko, L. J., Kassarich, J., & Rosanoff, E. I. 1972, "Immunopharmacologic effects of cycloleucine", J.Pharmacol.Exp.Ther., vol. 180, no. 2, pp. 501-513.

Rosenthale, M. E., Datko, L. J., Kassarich, J., & Schneider, F. 1969, "Chemotherapy of experimental allergic encephalomyelitis (EAE)", Arch.Int.Pharmacodyn.Ther., vol. 179, no. 2, pp. 251-275.

Rosenthale, M. E. & Margules, D. L. 1969, "Failure of hypothalamic lesions to protect against experimental allergic encephalomyelitis (EAE) in the rat", Proc.Soc.Exp.Biol.Med., vol. 130, no. 1, pp. 339-342.

Rosenthale, M. E. & Nagra, C. L. 1967, "Comparative effects of some immunosuppressive and anti-inflammotory drugs on allergic encephalomyelitis and adjuvant arthritis", Proc.Soc.Exp.Biol.Med., vol. 125, no. 1, pp. 149-153.

Roth, G. A., Monferran, C. G., Maggio, B., & Cumar, F. A. 1982, "Central nervous system lipid alterations in rats with experimental allergic encephalomyelitis and its suppression by immunosuppressive drugs", Life Sci., vol. 30, no. 10, pp. 859-866.

Rott, O., Cash, E., & Fleischer, B. 1993, "Phosphodiesterase inhibitor pentoxifylline, a selective suppressor of T helper type 1- but not type 2-associated lymphokine production, prevents induction of experimental autoimmune encephalomyelitis in Lewis rats", Eur.J.Immunol., vol. 23, no. 8, pp. 1745-1751.

Rott, O., Fleischer, B., & Cash, E. 1994, "Interleukin-10 prevents experimental allergic encephalomyelitis in rats", Eur.J.Immunol., vol. 24, no. 6, pp. 1434-1440.

Rottman, J. B., Smith, T., Tonra, J. R., Ganley, K., Bloom, T., Silva, R., Pierce, B., Gutierrez-Ramos, J. C., Ozkaynak, E., & Coyle, A. J. 2001, "The costimulatory molecule ICOS plays an important role in the immunopathogenesis of EAE", Nat Immunol, vol. 2, no. 7, pp. 605-611.

Ruddle, N. H., Bergman, C. M., McGrath, K. M., Lingenheld, E. G., Grunnet, M. L., Padula, S. J., & Clark, R. B. 1990, "An antibody to lymphotoxin and tumor necrosis factor prevents transfer of experimental allergic encephalomyelitis", J.Exp.Med., vol. 172, no. 4, pp. 1193-1200.

Ruffini, F., Furlan, R., Poliani, P. L., Brambilla, E., Marconi, P. C., Bergami, A., Desina, G., Glorioso, J. C., Comi, G., & Martino, G. 2001, "Fibroblast growth factor-II gene therapy reverts the clinical course and the pathological signs of chronic experimental autoimmune encephalomyelitis in C57BL/6 mice", Gene Ther., vol. 8, no. 16, pp. 1207-1213.

Ruiz, P. J., Garren, H., Ruiz, I. U., Hirschberg, D. L., Nguyen, L. V., Karpuj, M. V., Cooper, M. T., Mitchell, D. J., Fathman, C. G., & Steinman, L. 1999, "Suppressive immunization with DNA encoding a self-peptide prevents autoimmune disease: modulation of T cell costimulation", J.Immunol., vol. 162, no. 6, pp. 3336-3341.

Ruocco, H. H., Fernandes, G. A., Namer, I. J., Depaulis, A., & Levy, S. 2004, "Hypothalamic response to experimental allergic encephalomyelitis: role of substance P", Neuroimmunomodulation, vol. 11, no. 1, pp. 28-35.

Ruuls, S. R., Bauer, J., Sontrop, K., Huitinga, I., 't Hart, B. A., & Dijkstra, C. D. 1995, "Reactive oxygen species are involved in the pathogenesis of experimental allergic encephalomyelitis in Lewis rats", Journal of Neuroimmunology.56(2)()(pp 207-217), 1995.Date of Publication: 1995. no. 2, pp. 207-217.

Ruuls, S. R., de Labie, M. C., Weber, K. S., Botman, C. A., Groenestein, R. J., Dijkstra, C. D., Olsson, T., & van der Meide, P. H. 1996, "The length of treatment determines whether IFN-beta prevents or aggravates experimental autoimmune encephalomyelitis in Lewis rats", J.Immunol., vol. 157, no. 12, pp. 5721-5731.

Ryffel, B., Feurer, C., Heuberger, B., & Borel, J. F. 1982, "Immunosuppressive effect of cyclosporin A in two lymphocyte transfer models in rats: comparison of in vivo and in vitro treatment", Immunobiology, vol. 163, no. 5, pp. 470-483.

Ryskova, O., Zhitnuhin, Y., & Chizhnyak, M. G. 1988, "Effect of levamisole and etimisole on the development of experimental allergic encephalomeylitis", J.Hyg.Epidemiol.Microbiol.Immunol., vol. 32, no. 1, pp. 105-112.

Sacks, H. J., Braunstein, V., & Brosnan, C. F. 1987, "Preliminary study on the suppression of experimental autoimmune encephalomyelitis in the Lewis rat with spirogermanium", J.Neuropathol.Exp.Neurol., vol. 46, no. 3, pp. 250-261.

Sakai, K., Zamvil, S. S., Mitchell, D. J., Hodgkinson, S., Rothbard, J. B., & Steinman, L. 1989, "Prevention of experimental encephalomyelitis with peptides that block interaction of T cells with major histocompatibility complex proteins", Proc.Natl.Acad.Sci.U.S.A, vol. 86, no. 23, pp. 9470-9474.

Sakurai, K., Zou, J. P., Tschetter, J. R., Ward, J. M., & Shearer, G. M. 2002, "Effect of indoleamine 2,3-dioxygenase on induction of experimental autoimmune encephalomyelitis", J Neuroimmunol, vol. 129, no. 1-2, pp. 186-196.

Samoilova, E. B., Horton, J. L., Zhang, H., & Chen, Y. 1997, "CD40L blockade prevents autoimmune encephalomyelitis and hampers TH1 but not TH2 pathway of T cell differentiation", J.Mol.Med., vol. 75, no. 8, pp. 603-608.

Samson, M. F. & Smilek, D. E. 1995, "Reversal of acute experimental autoimmune encephalomyelitis and prevention of relapses by treatment with a myelin basic protein peptide analogue modified to form long-lived peptide-MHC complexes", J.Immunol., vol. 155, no. 5, pp. 2737-2746.

Sanchez, A. J., Gonzalez-Perez, P., Galve-Roperh, I., & Garcia-Merino, A. 2006, "R-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphtalenylmethanone (WIN-2) ameliorates experimental autoimmune encephalomyelitis and induces encephalitogenic T cell apoptosis: Partial involvement of the CB₂ receptor", Biochemical Pharmacology.72(12)()(pp 1697-1706), 2006.Date of Publication: 15 Dec 2006. no. 12, pp. 1697-1706.

Santambrogio, L., Crisi, G. M., Leu, J., Hochwald, G. M., Ryan, T., & Thorbecke, G. J. 1995, "Tolerogenic forms of auto-antigens and cytokines in the induction of resistance to experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 58, no. 2, pp. 211-222.

Santambrogio, L., Hochwald, G. M., Leu, C. H., & Thorbecke, G. J. 1993a, "Antagonistic effects of endogenous and exogenous TGF-beta and TNF on auto-immune diseases in mice", Immunopharmacol.Immunotoxicol., vol. 15, no. 4, pp. 461-478.

Santambrogio, L., Hochwald, G. M., Saxena, B., Leu, C. H., Martz, J. E., Carlino, J. A., Ruddle, N. H., Palladino, M. A., Gold, L. I., & Thorbecke, G. J. 1993b, "Studies on the mechanisms by which transforming growth factor-beta (TGF-beta) protects against allergic encephalomyelitis. Antagonism between TGF-beta and tumor necrosis factor", J.Immunol., vol. 151, no. 2, pp. 1116-1127.

Santos, L. M., Al-Sabbagh, A., Londono, A., & Weiner, H. L. 1994, "Oral tolerance to myelin basic protein induces regulatory TGF-beta-secreting T cells in Peyer's patches of SJL mice", Cell Immunol., vol. 157, no. 2, pp. 439-447.

Saoudi, A., Simmonds, S., Huitinga, I., & Mason, D. 1995, "Prevention of experimental allergic encephalomyelitis in rats by targeting autoantigen to B cells: evidence that the protective mechanism depends on changes in the cytokine response and migratory properties of the autoantigen-specific T cells", J.Exp.Med., vol. 182, no. 2, pp. 335-344.

Satoh, J., Kunishita, T., & Tabira, T. 1988, "In vivo and in vitro studies of the prevention of proteolipid apoprotein-induced murine experimental allergic encephalomyelitis by monoclonal antibody against L3T4", J.Neuroimmunol., vol. 18, no. 2, pp. 105-116.

Sattler, M. B., Demmer, I., Williams, S. K., Maier, K., Merkler, D., Gadjanski, I., Stadelmann, C., Bahr, M., & Diem, R. 2006, "Effects of interferon-beta-1a on neuronal survival under autoimmune inflammatory conditions", Exp.Neurol., vol. 201, no. 1, pp. 172-181.

Sattler, M. B., Diem, R., Merkler, D., Demmer, I., Boger, I., Stadelmann, C., & Bahr, M. 2005, "Simvastatin treatment does not protect retinal ganglion cells from degeneration in a rat model of autoimmune optic neuritis", Exp Neurol, vol. 193, no. 1.

Sattler, M. B., Williams, S. K., Neusch, C., Otto, M., Pehlke, J. R., Bahr, M., & Diem, R. 2008, "Flupirtine as neuroprotective add-on therapy in autoimmune optic neuritis", Am J Pathol, vol. 173, no. 5.

Savino, C., Pedotti, R., Baggi, F., Ubiali, F., Gallo, B., Nava, S., Bigini, P., Barbera, S., Fumagalli, E., Mennini, T., Vezzani, A., Rizzi, M., Coleman, T., Cerami, A., Brines, M., Ghezzi, P., & Bianchi, R. 2006, "Delayed administration of erythropoietin and its non-erythropoietic derivatives ameliorates chronic murine autoimmune encephalomyelitis", J.Neuroimmunol., vol. 172, no. 1-2, pp. 27-37.

Scelsi, R., Franciotta, D. M., Camana, C., Savoldi, F., & Allegrini, M. 1989, "Suppression of Experimental Allergic Encephalomyelitis After Dietary Zinc Deprivation in Guinea-Pigs", Nutrition Research, vol. 9, no. 12, pp. 1345-1354.

Scelsi, R., Savoldi, F., Ceroni, M., Allegrini, M., & Poggi, P. 1983, "Selenium and Experimental Allergic Encephalo Myelitis Effects of Different Levels of Dietary Selenium on Clinico Pathological Findings", Journal of the Neurological Sciences, vol. 61, no. 3, pp. 369-380.

Schaefer, C., Hidalgo, T. R., Cashion, L., Petry, H., Brooks, A., Szymanski, P., Qian, H. S., Gross, C., Wang, P., Liu, P., Goldman, C., Rubanyi, G. M., & Harkins, R. N. 2006, "Gene-based delivery of IFN-beta is efficacious in a murine model of experimental allergic encephalomyelitis", J.Interferon Cytokine Res., vol. 26, no. 7, pp. 449-454.

Schaub, M., Issazadeh, S., Stadlbauer, T. H., Peach, R., Sayegh, M. H., & Khoury, S. J. 1999, "Costimulatory signal blockade in murine relapsing experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 96, no. 2, pp. 158-166.

Scheinberg, L. C., Lee, J. M., & Taylor, J. M. 1967, "Suppression of experimental allergic encephalomyelitis in mice by irradiation of the target organ", Nature, vol. 216, no. 5118, pp. 924-925.

Scherer, R., Simon, J., bd-el-Fattah, M., & Ruhenstroth-Bauer, G. 1980, "The effect of fibrinopeptides A and B on experimental allergic encephalomyelitis", Clin.Exp.Immunol., vol. 40, no. 1, pp. 49-59.

Schif-Zuck, S., Wildbaum, G., & Karin, N. 2006, "Coadministration of plasmid DNA constructs encoding an encephalitogenic determinant and IL-10 elicits regulatory T cell-mediated protective immunity in the central nervous system", J Immunol, vol. 177, no. 11, pp. 8241-8247.

Schiffenbauer, J., Butfiloski, E., Hanley, G., Sobel, E. S., Streit, W. J., & Lazarovits, A. 1998, "Prevention of experimental allergic encephalomyelitis by an antibody to CD45RB", Cell Immunol., vol. 190, no. 2, pp. 173-182.

Schiffer, R. B., Herndon, R. M., & Eskin, T. 1990, "Effects of altered dietary trace metals upon experimental allergic encephalomyelitis", Neurotoxicology, vol. 11, no. 3, pp. 443-450.

Schilling, S., Goelz, S., Linker, R., Luehder, F., & Gold, R. 2006, "Fumaric acid esters are effective in chronic experimental autoimmune encephalomyelitis and suppress macrophage infiltration", Clin.Exp.Immunol., vol. 145, no. 1, pp. 101-107.

Schluesener, H., Brunner, C., Vass, K., & Lassmann, H. 1986, "Therapy of rat autoimmune disease by a monoclonal antibody specific for T lymphoblasts", J.Immunol., vol. 137, no. 12, pp. 3814-3820.

Schluesener, H. J. 1987, "T cell line-mediated EAE: prevention and therapy by a monoclonal antibody specific for T lymphoblasts", J.Neuroimmunol., vol. 14, no. 3, pp. 339-343.

Schluesener, H. J. & Meyermann, R. 1989, "T cell vaccination in monoclonal antibody-induced hyperacute experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 24, no. 3, pp. 233-238.

Schluesener, H. J., Seid, K., & Meyermann, R. 1999, "Effects of autoantigen and dexamethasone treatment on expression of endothelial-monocyte activating polypeptide II and allograft-inflammatory factor-1 by activated macrophages and microglial cells in lesions of experimental autoimmune encephalomyelitis, neuritis and uveitis", Acta Neuropathol.(Berl), vol. 97, no. 2, pp. 119-126.

Schluesener, H. J., Sobel, R. A., & Weiner, H. L. 1988, "Demyelinating experimental allergic encephalomyelitis (EAE) in the rat: treatment with a monoclonal antibody against activated T cells", J.Neuroimmunol., vol. 18, no. 4, pp. 341-351.

Schmidt, J., Metselaar, J. M., & Gold, R. 2003, "Intravenous liposomal prednisolone downregulates in situ TNF-alpha production by T-cells in experimental autoimmune encephalomyelitis", J.Histochem.Cytochem., vol. 51, no. 9, pp. 1241-1244.

Schmidt, J., Metselaar, J. M., Wauben, M. H., Toyka, K. V., Storm, G., & Gold, R. 2003, "Drug targeting by long-circulating liposomal glucocorticosteroids increases therapeutic efficacy in a model of multiple sclerosis", Brain, vol. 126, no. Pt 8, pp. 1895-1904.

Schmitz, D. N., Hofmann, N., Tomov, T. L., Kovac, A. D., Neiss, W. F., & Angelov, D. N. 2003, "The correlation between severity of paraparesis and reduced density of resident antigen-presenting cells implicates an unknown role for the spinal perivascular macrophages in experimental autoimmune encephalomyelitis in rats", J.Neuroimmunol., vol. 142, no. 1-2, pp. 31-46.

Schorlemmer, H. U. & Bartlett, R. R. 1997a, "Malononitrilamides (MNA 279 and MNA 715) have therapeutic activity in acute and chronic relapsing experimental allergic encephalomyelitis (EAE)", Inflamm.Res., vol. 46 Suppl 2, p. S163-S164.

Schorlemmer, H. U. & Bartlett, R. R. 1997b, "Therapeutic activity of malononitrilamides (MNA 279 and MNA 715) on acute and chronic, relapsing, experimental, allergic encephalomyelitis (EAE)", Drugs Exp.Clin.Res., vol. 23, no. 5-6, pp. 175-181.

Schorlemmer, H. U., Dickneite, G., Haenel, H., Duerckheimer, W., & Sedlacek, H. H. 1989, "Immunomodulation by the New Synthetic Thiazole Derivative Tiprotimod 3Rd Communication Influence on Host Resistance to Microorganisms Tumors and on Experimental Immune Disorders", Arzneimittel-Forschung, vol. 39, no. 10, pp. 1235-1239.

Schorlemmer, H. U., Kanzy, E. J., Kurrle, R., & Seiler, F. R. 1990, "Inhibition of Various Experimental Autoimmune Diseases by the Anti-Rat-Tcr Monoclonal Antibody R73", Immunobiology, vol. 181, no. 2-3, pp. 222-223.

Schorlemmer, H. U., Kanzy, E. J., Kurrle, R., & Seiler, F. R. 1991, "Inhibitory effects of the anti-rat T-cell receptor (TCR) monoclonal antibody (MAb) R73 on various experimental autoimmune diseases", Agents Actions, vol. 34, no. 1-2, pp. 161-164.

Schorlemmer, H. U. & Seiler, F. R. 1991a, "15-Deoxyspergualin (15-DOS) for therapy in an animal model of multiple sclerosis (MS): disease modifying activity on acute and chronic relapsing experimental allergic encephalomyelitis (EAE)", Agents Actions, vol. 34, no. 1-2, pp. 156-160.

Schorlemmer, H. U. & Seiler, F. R. 1991b, "Therapeutic effects of 15-deoxyspergualin in acute and chronic relapsing experimental allergic encephalomyelitis (EAE) as models for multiple sclerosis (MS)", Drugs Exp.Clin.Res., vol. 17, no. 10-11, pp. 461-469.

Schreibelt, G., Musters, R. J., Reijerkerk, A., de Groot, L. R., van der Pol, S. M., Hendrikx, E. M., Dopp, E. D., Dijkstra, C. D., Drukarch, B., & de Vries, H. E. 2006, "Lipoic acid affects cellular migration into the central nervous system and stabilizes blood-brain barrier integrity", J.Immunol., vol. 177, no. 4, pp. 2630-2637.

Schubart, A. S., Howard, L., Seabrook, T., Lange, T., Rausch, M., & Mir, A. K. 2008, "FTY720 suppresses ongoing EAE and promotes a remyelinating environment preventing axonal degeneration within the CNS", Neurology, vol. 70, no. 11, Suppl. 1.

Schuller-Levis, G. B., Kozlowski, P. B., & Wisniewski, H. M. 1986, "Cyclosporin A treatment of an induced attack in a chronic relapsing model of experimental allergic encephalomyelitis", Clin.Immunol.Immunopathol., vol. 40, no. 2, pp. 244-252.

Scott, C. F., Jr., Cashman, N., & Spitler, L. E. 1982a, "Experimental Allergic Encephalitis Treatment with Drugs Which Alter Central Nervous System Serotonin Levels", Journal of Immunopharmacology, vol. 4, no. 3, pp. 153-162.

Scott, C. F., Jr., Cashman, N., & Spitler, L. E. 1982b, "Experimental allergic encephalitis; treatment with drugs which alter CNS serotonin levels", J.Immunopharmacol., vol. 4, no. 3, pp. 153-162.

Scott, G. S. & Bolton, C. 2000, "L-arginine modifies free radical production and the development of experimental allergic encephalomyelitis", Inflamm.Res., vol. 49, no. 12, pp. 720-726.

Scott, G. S., Kean, R. B., Mikheeva, T., Fabis, M. J., Mabley, J. G., Szabo, C., & Hooper, D. C. 2004, "The therapeutic effects of PJ34 [N-(6-oxo-5,6-dihydrophenanthridin-2-yl)-N,N-dimethylacetamide.HCl], a selective inhibitor of poly(ADP-ribose) polymerase, in experimental allergic encephalomyelitis are associated with immunomodulation", J.Pharmacol.Exp.Ther., vol. 310, no. 3, pp. 1053-1061.

Scott, G. S., Kean, R. B., Southan, G. J., Szabo, C., & Hooper, D. C. 2001, "Effect of mercaptoethylguanidine scavengers of peroxynitrite on the development of experimental allergic encephalomyelitis in PLSJL mice", Neurosci.Lett., vol. 311, no. 2, pp. 125-128.

Scott, G. S., Spitsin, S. V., Kean, R. B., Mikheeva, T., Koprowski, H., & Hooper, D. C. 2002, "Therapeutic intervention in experimental allergic encephalomyelitis by administration of uric acid precursors", Proc.Natl.Acad.Sci.U.S.A, vol. 99, no. 25, pp. 16303-16308.

Scott, G. S., Williams, K. I., & Bolton, C. 1996, "A pharmacological study on the role of nitric oxide in the pathogenesis of experimental allergic encephalomyelitis", Inflamm.Res., vol. 45, no. 10, pp. 524-529.

Sedgwick, J. D. & Mason, D. W. 1986, "The mechanism of inhibition of experimental allergic encephalomyelitis in the rat by monoclonal antibody against CD4", J.Neuroimmunol., vol. 13, no. 2, pp. 217-232.

Seki, N., Kataoka, H., Ohtsuki, M., Sato, N., Fukunari, A., & Chiba, K. 2006, "FTY720, sphinogosine 1-phosphate modulator, ameliorates experimental autoimmune encephalomyelitis (EAE). II. Effect of FTY720 on myelin oligodendrocyte glcoprotein-induced EAE in C57BL/6 mice", Journal of Neuroimmunology, vol. 178, p. 161.

Sekiguchi, Y., Ichikawa, M., Inoue, A., Itoh, M., & Koh, C. S. 2001, "Brain-derived gangliosides suppress the chronic relapsing-remitting experimental autoimmune encephalomyelitis in NOD mice induced with myelin oligodendrocyte glycoprotein peptide", J.Neuroimmunol., vol. 116, no. 2, pp. 196-205.

Selivonchick, D. P. & Johnston, P. V. 1975, "Fat deficiency in rats during development of the central nervous system and susceptibility to experimental allergic encephalomyelitis", J Nutr, vol. 105, no. 3, pp. 288-300.

Selmai, K., Cross, A. H., & Raine, C. S. 1991, "Anti-Tumor Necrosis Factor Anti-Tnf Therapy Abrogates Autoimmune Demyelination New Therapeutic Implications for Multiple Sclerosis", Journal of Neuroimmunology no. SUPPL. 1.

Selmaj, K., Kowal, C., Walczak, A., Nowicka, J., & Raine, C. S. 2000, "Naked DNA vaccination differentially modulates autoimmune responses in experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 111, no. 1-2, pp. 34-44.

Selmaj, K., Papierz, W., Glabinski, A., & Kohno, T. 1995, "Prevention of chronic relapsing experimental autoimmune encephalomyelitis by soluble tumor necrosis factor receptor I", J.Neuroimmunol., vol. 56, no. 2, pp. 135-141.

Selmaj, K., Raine, C. S., & Cross, A. H. 1991, "Anti-tumor necrosis factor therapy abrogates autoimmune demyelination", Ann.Neurol., vol. 30, no. 5, pp. 694-700.

Selmaj, K., Walczak, A., Mycko, M., Berkowicz, T., Kohno, T., & Raine, C. S. 1998, "Suppression of experimental autoimmune encephalomyelitis with a TNF binding protein (TNFbp) correlates with down-regulation of VCAM-1/VLA-4", Eur J Immunol, vol. 28, no. 6, pp. 2035-2044.

Senices, M., Dussault, N., Harding, K., Sobel, R., O'Hara, R. M., Collins, M., & Young, D. 2001, "Rapamycin inhibits adoptive transfer and prevents relapses in experimental autoimmune encephalomyelitis", Faseb Journal, vol. 15, no. 5.

Sewell, D., Qing, Z., Reinke, E., Elliot, D., Weinstock, J., Sandor, M., & Fabry, Z. 2003a, "Immunomodulation of experimental autoimmune encephalomyelitis by helminth ova immunization", Int.Immunol., vol. 15, no. 1, pp. 59-69.

Sewell, D. L., Reinke, E. K., Co, D. O., Hogan, L. H., Fritz, R. B., Sandor, M., & Fabry, Z. 2003b, "Infection with Mycobacterium bovis BCG diverts traffic of myelin oligodendroglial glycoprotein autoantigen-specific T cells away from the central nervous system and ameliorates experimental autoimmune encephalomyelitis", Clin Diagn Lab Immunol, vol. 10, no. 4, pp. 564-572.

Sewell, D. L., Zhu, Q., Elliot, D., Weinstock, J., Sandor, M., & Fabry, Z. 2000, "Parasite induced protection from Experimental Autoimmune Encephalomyelitis", Faseb Journal, vol. 14, no. 6.

Shankaran, M., Marino, M. E., Busch, R., Keim, C., King, C., Lee, J., Killion, S., Awada, M., & Hellerstein, M. K. 2007, "Measurement of brain microglial proliferation rates in vivo in response to neuroinflammatory stimuli: application to drug discovery", J.Neurosci.Res., vol. 85, no. 11, pp. 2374-2384.

Sharma, S. D., Nag, B., Su, X. M., Green, D., Spack, E., Clark, B. R., & Sriram, S. 1991, "Antigen-specific therapy of experimental allergic encephalomyelitis by soluble class II major histocompatibility complex-peptide complexes", Proc.Natl.Acad.Sci.U.S.A, vol. 88, no. 24, pp. 11465-11469.

Shaw, M. K., Lorens, J. B., Dhawan, A., DalCanto, R., Tse, H. Y., Tran, A. B., Bonpane, C., Eswaran, S. L., Brocke, S., Sarvetnick, N., Steinman, L., Nolan, G. P., & Fathman, C. G. 1997, "Local delivery of interleukin 4 by retrovirus-transduced T lymphocytes ameliorates experimental autoimmune encephalomyelitis", J.Exp.Med., vol. 185, no. 9, pp. 1711-1714.

Shi, F. D., Bai, X. F., Xiao, B. G., van der Meide, P. H., & Link, H. 1998, "Nasal administration of multiple antigens suppresses experimental autoimmune myasthenia gravis, encephalomyelitis and neuritis", J.Neurol.Sci., vol. 155, no. 1, pp. 1-12.

Shimada, K., Koh, C. S., Uemura, K., & Yanagisawa, N. 1994, "Suppression of experimental allergic encephalomyelitis in Lewis rats by administration of gangliosides", Cell Immunol., vol. 154, no. 1, pp. 231-239.

Shin, T. 2001, "Increased expression of neuronal nitric oxide synthase in astrocytes and macrophages in the spinal cord of Lewis rats with autoimmune encephalomyelitis", J Vet Sci, vol. 2, no. 3, pp. 195-199.

Shin, T., Kang, B., Tanuma, N., Matsumoto, Y., Wie, M., Ahn, M., & Kang, J. 2001, "Intrathecal administration of endothelin-1 receptor antagonist ameliorates autoimmune encephalomyelitis in Lewis rats", Neuroreport, vol. 12, no. 7, pp. 1465-1468.

Shin, T., Kim, S., Moon, C., Wie, M., & Kim, H. 2000, "Aminoguanidine-induced amelioration of autoimmune encephalomyelitis is mediated by reduced expression of inducible nitric oxide synthase in the spinal cord", Immunol.Invest, vol. 29, no. 3, pp. 233-241.

Shindler, K. S., Ventura, E., Rex, T. S., Elliott, P., & Rostami, A. 2007, "SIRT1 activation confers neuroprotection in experimental optic neuritis", Invest Ophthalmol.Vis.Sci, vol. 48, no. 8, pp. 3602-3609.

Sibley, W. A., Kiernat, J., & Laguna, J. F. 1978, "The modification of experimental allergic encephalomyelitis with epsilon aminocaproic acid", Neurology, vol. 28, no. 9 Pt 2, pp. 102-105.

Simmons, R. D., Buzbee, T. M., & Linthicum, D. S. 1989, "Methysergide, a serotonin antagonist, does not inhibit the expression of autoimmune encephalomyelitis in the rabbit", J.Neuroimmunol., vol. 22, no. 1, pp. 77-79.

Simmons, R. D., Hugh, A. R., Willenborg, D. O., & Cowden, W. B. 1992, "Suppression of active but not passive autoimmune encephalomyelitis by dual cyclo-oxygenase and 5-lipoxygenase inhibition", Acta Neurol.Scand., vol. 85, no. 3, pp. 197-199.

Simon, J., Contag, I., & Pollinger, G. 1979, "Inhibition by polyunsaturated phospholipids of experimental allergic encephalomyelitis in the guinea pig", J.Neurol.Sci., vol. 40, no. 2-3, pp. 113-122.

Simon, J. & Nowoczek, G. 1978, "Protective effect of competitive target structure on experimental allergic encephalomyelitis", J.Neurol.Sci., vol. 38, no. 3, pp. 383-389.

Singh, I., Paintlia, A. S., Khan, M., Stanislaus, R., Paintlia, M. K., Haq, E., Singh, A. K., & Contreras, M. A. 2004, "Impaired peroxisomal function in the central nervous system with inflammatory disease of experimental autoimmune encephalomyelitis animals and protection by lovastatin treatment", Brain Res., vol. 1022, no. 1-2, pp. 1-11.

Singh, M. P., Meyer zu, H. G., Hu, W., Mausberg, A. K., Cravens, P. D., Eagar, T., Lober, S., Klingenstein, R., Gmeiner, P., Korth, C., Kieseier, B. C., & Stuve, O. 2009, "Quinpramine is a novel compound effective in ameliorating brain autoimmune disease", Exp Neurol, vol. 215, no. 2, pp. 397-400.

Singh, N. P., Hegde, V. L., Hofseth, L. J., Nagarkatti, M., & Nagarkatti, P. 2007, "Resveratrol (trans-3,5,4'-trihydroxystilbene) ameliorates experimental allergic encephalomyelitis, primarily via induction of apoptosis in T cells involving activation of aryl hydrocarbon receptor and estrogen receptor", Mol.Pharmacol., vol. 72, no. 6, pp. 1508-1521.

Sinha, S., Subramanian, S., Miller, L., Proctor, T. M., Roberts, C., Burrows, G. G., Vandenbark, A. A., & Offner, H. 2009, "Cytokine switch and bystander suppression of autoimmune responses to multiple antigens in experimental autoimmune encephalomyelitis by a single recombinant T-cell receptor ligand", J Neurosci, vol. 29, no. 12, pp. 3816-3823.

Sinha, S., Subramanian, S., Proctor, T. M., Kaler, L. J., Grafe, M., Dahan, R., Huan, J., Vandenbark, A. A., Burrows, G. G., & Offner, H. 2007, "A promising therapeutic approach for multiple sclerosis: recombinant T-cell receptor ligands modulate experimental autoimmune encephalomyelitis by reducing interleukin-17 production and inhibiting migration of encephalitogenic cells into the CNS", J.Neurosci., vol. 27, no. 46, pp. 12531-12539.

Skundric, D., Dai, R., Skoff, R., Bessert, D., Cruikshank, W., & Kurjakovic, Z. 2005a, "Neutralization of IL-16 reduces inflammation, demyelination, axonal damage, and reverses paralysis during relapsing-remitting EAE", Journal of Neurochemistry, vol. 94, no. Suppl. 1.

Skundric, D. S., Dai, R., Zakarian, V. L., Bessert, D., Skoff, R. P., Cruikshank, W. W., & Kurjakovic, Z. 2005b, "Anti-IL-16 therapy reduces CD4+ T-cell infiltration and improves paralysis and histopathology of relapsing EAE", J.Neurosci.Res., vol. 79, no. 5, pp. 680-693.

Slavin, A. J., Maron, R., & Weiner, H. L. 2001, "Mucosal administration of IL-10 enhances oral tolerance in autoimmune encephalomyelitis and diabetes", Int.Immunol., vol. 13, no. 6, pp. 825-833.

Sloane, E., Ledeboer, A., Seibert, W., Coats, B., van Strien, M., Maier, S. F., Johnson, K. W., Chavez, R., Watkins, L. R., Leinwand, L., Milligan, E. D., & Van Dam, A. M. 2009, "Anti-inflammatory cytokine gene therapy decreases sensory and motor dysfunction in experimental Multiple Sclerosis: MOG-EAE behavioral and anatomical symptom treatment with cytokine gene therapy", Brain Behav Immun, vol. 23, no. 1.

Smilek, D. E., Wraith, D. C., Hodgkinson, S., Dwivedy, S., Steinman, L., & McDevitt, H. O. 1991, "A single amino acid change in a myelin basic protein peptide confers the capacity to prevent rather than induce experimental autoimmune encephalomyelitis", Proc.Natl.Acad.Sci.U.S.A, vol. 88, no. 21, pp. 9633-9637.

Smith, C. E. & Miller, S. D. 2006, "Multi-peptide coupled-cell tolerance ameliorates ongoing relapsing EAE associated with multiple pathogenic autoreactivities", J Autoimmun, vol. 27, no. 4, pp. 218-231.

Smith, M. E. & Amaducci, L. A. 1982, "Observations on the effects of protease inhibitors on the suppression of experimental allergic encephalomyelitis", Neurochem.Res., vol. 7, no. 5, pp. 541-554.

Smith, R. M., Morgan, A., & Wraith, D. C. 1994, "Anti-class II MHC antibodies prevent and treat EAE without APC depletion", Immunology, vol. 83, no. 1, pp. 1-8.

Smith, S. R., Terminelli, C., Epps, S., Watnick, A., & Umland, S. 1987, "A study of the immunosuppressive properties of Sch 24937", Immunopharmacol.Immunotoxicol., vol. 9, no. 2-3, pp. 333-359.

Smith, S. R., Watnick, A. S., Kung, T., & Siegel, M. I. 1993, "In vitro and in vivo immunopharmacological profile of Sch 40120", Immunopharmacol.Immunotoxicol., vol. 15, no. 1, pp. 13-44.

Smith, T., Groom, A., Rivers, L., & Yamanishi, Y. 2002a, "Synergistic Effect of the Ampa Receptor Antagonist, E2007 and Interferon-Beta in Ameliorating Experimental Autoimmune Encephalomyelitis (Eae)", Society for Neuroscience Abstract Viewer and Itinerary Planner, vol. 2002.

Smith, T., Groom, A., Zhu, B., & Turski, L. 2000, "Autoimmune encephalomyelitis ameliorated by AMPA antagonists", Nat.Med., vol. 6, no. 1, pp. 62-66.

Smith, T., Yamauchi, T., Groom, A., Rivers, L., Hanada, T., Nishizawa, Y., & Yamamishi, Y. 2002b, "The Ampa Receptor Antagonist, E2007, Ameliorates Experimental Autoimmune Encephalomyelitis (Eae)", Society for Neuroscience Abstract Viewer and Itinerary Planner, vol. 2002.

Snyder, A. R. & Levine, S. 1980, "Modulation of experimental allergic encephalomyelitis with yeast glucan and methyl palmitate to alter the activity of the reticuloendothelial system", J.Reticuloendothel.Soc., vol. 28, no. 1, pp. 49-54.

Sobel, R. A., Blanchette, B. W., Russo, M. A., Williams, A. M., & Colvin, R. B. 1987, "Anti-T cell monoclonal antibodies in vivo. II. Modulation of acute and chronic experimental allergic encephalomyelitis (EAE) in guinea pigs", J.Immunol., vol. 138, no. 8, pp. 2507-2513.

Soilu-Hanninen, M., Epa, R., Shipham, K., Butzkueven, H., Bucci, T., Barrett, G., Bartlett, P. F., & Kilpatrick, T. J. 2000, "Treatment of experimental autoimmune encephalomyelitis with antisense oligonucleotides against the low affinity neurotrophin receptor", Journal of Neuroscience Research.59(6)()(pp 712-721), 2000.Date of Publication: 15 Mar 2000. no. 6, pp. 712-721.

Sommer, N., Loschmann, P. A., Northoff, G. H., Weller, M., Steinbrecher, A., Steinbach, J. P., Lichtenfels, R., Meyermann, R., Riethmuller, A., Fontana, A., & . 1995, "The antidepressant rolipram suppresses cytokine production and prevents autoimmune encephalomyelitis", Nat.Med., vol. 1, no. 3, pp. 244-248.

Sommer, N., Martin, R., McFarland, H. F., Quigley, L., Cannella, B., Raine, C. S., Scott, D. E., Loschmann, P. A., & Racke, M. K. 1997, "Therapeutic potential of phosphodiesterase type 4 inhibition in chronic autoimmune demyelinating disease", J.Neuroimmunol., vol. 79, no. 1, pp. 54-61.

Soos, J. M., Mujtaba, M. G., Subramaniam, P. S., Streit, W. J., & Johnson, H. M. 1997, "Oral feeding of interferon tau can prevent the acute and chronic relapsing forms of experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 75, no. 1-2, pp. 43-50.

Soos, J. M., Schiffenbauer, J., & Johnson, H. M. 1993, "Treatment of PL/J mice with the superantigen, staphylococcal enterotoxin B, prevents development of experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 43, no. 1-2, pp. 39-43.

Soos, J. M., Stuve, O., Youssef, S., Bravo, M., Johnson, H. M., Weiner, H. L., & Zamvil, S. S. 2002, "Cutting edge: oral type I IFN-tau promotes a Th2 bias and enhances suppression of autoimmune encephalomyelitis by oral glatiramer acetate", J.Immunol., vol. 169, no. 5, pp. 2231-2235.

Soos, J. M., Subramaniam, P. S., Hobeika, A. C., Schiffenbauer, J., & Johnson, H. M. 1995, "The IFN pregnancy recognition hormone IFN-tau blocks both development and superantigen reactivation of experimental allergic encephalomyelitis without associated toxicity", J.Immunol., vol. 155, no. 5, pp. 2747-2753.

Spach, K. M. & Hayes, C. E. 2005, "Vitamin D3 confers protection from autoimmune encephalomyelitis only in female mice", J.Immunol., vol. 175, no. 6, pp. 4119-4126.

Spach, K. M., Nashold, F. E., Dittel, B. N., & Hayes, C. E. 2006, "IL-10 signaling is essential for 1,25-dihydroxyvitamin D3-mediated inhibition of experimental autoimmune encephalomyelitis", J.Immunol., vol. 177, no. 9, pp. 6030-6037.

Spitsin, S. V., Scott, G. S., Mikheeva, T., Zborek, A., Kean, R. B., Brimer, C. M., Koprowski, H., & Hooper, D. C. 2002, "Comparison of uric acid and ascorbic acid in protection against EAE", Free Radic.Biol.Med., vol. 33, no. 10, pp. 1363-1371.

Srinivasan, M., Gienapp, I. E., Stuckman, S. S., Rogers, C. J., Jewell, S. D., Kaumaya, P. T., & Whitacre, C. C. 2002, "Suppression of experimental autoimmune encephalomyelitis using peptide mimics of CD28", J.Immunol., vol. 169, no. 4, pp. 2180-2188.

Sriram, S., Bright, J., & Rodriguez, M. 1996, "In vivo therapy with anti-IL-12 antibody prevents EAE but does not alter the course of TMEV-induced CNS demyelination", Neurology, vol. 46, no. 2 SUPPL..

Sriram, S. & Carroll, L. 1988, "In vivo depletion of Lyt-2 cells fails to alter acute and relapsing EAE", J Neuroimmunol, vol. 17, no. 2, pp. 147-157.

Sriram, S. & Carroll, L. 1991, "Haplotype-specific inhibition of homing of radiolabeled lymphocytes in experimental allergic encephalomyelitis following treatment with anti-IA antibodies", Cell Immunol., vol. 135, no. 1, pp. 222-231.

Sriram, S., Carroll, L., Fortin, S., Cooper, S., & Ranges, G. 1988, "In vivo immunomodulation by monoclonal anti-CD4 antibody. II. Effect on T cell response to myelin basic protein and experimental allergic encephalomyelitis", J.Immunol., vol. 141, no. 2, pp. 464-468.

Sriram, S. & Roberts, C. A. 1986, "Treatment of established chronic relapsing experimental allergic encephalomyelitis with anti-L3T4 antibodies", J.Immunol., vol. 136, no. 12, pp. 4464-4469.

Sriram, S., Schwartz, G., & Steinman, L. 1983, "Administration of myelin basic protein-coupled spleen cells prevents experimental allergic encephalitis", Cell Immunol., vol. 75, no. 2, pp. 378-382.

Sriram, S. & Steinman, L. 1983, "Anti I-A antibody suppresses active encephalomyelitis: treatment model for diseases linked to IR genes", J.Exp.Med., vol. 158, no. 4, pp. 1362-1367.

Sriram, S., Topham, D. J., & Carroll, L. 1987, "Haplotype-specific suppression of experimental allergic encephalomyelitis with anti-IA antibodies", J.Immunol., vol. 139, no. 5, pp. 1485-1489.

St Louis, J., Gilbert, J. J., Moscarello, M. A., & Strejan, G. H. 1989, "Chronic-relapsing experimental allergic encephalomyelitis in strain-13 guinea pigs: cell-mediated immunity and IgG isoelectric focusing in myelin basic protein-liposome-treated and untreated animals", J Neuroimmunol, vol. 21, no. 2-3, pp. 137-147.

St, L. J., Chan, E. L., Singh, B., & Strejan, G. H. 1997, "Suppression of experimental allergic encephalomyelitis in the Lewis rat, by administration of an acylated synthetic peptide of myelin basic protein", J.Neuroimmunol., vol. 73, no. 1-2, pp. 90-100.

St, L. J., Uniyal, S., Xu, L., Chan, E., Singh, B., Chan, B. M., & Strejan, G. H. 2001, "Tolerance induction by acylated peptides: suppression of EAE in the mouse with palmitoylated PLP peptides", J.Neuroimmunol., vol. 115, no. 1-2, pp. 79-90.

Stanislaus, R., Singh, A. K., & Singh, I. 2001, "Lovastatin treatment decreases mononuclear cell infiltration into the CNS of Lewis rats with experimental allergic encephalomyelitis", J.Neurosci.Res., vol. 66, no. 2, pp. 155-162.

Stanley, N. C., Jackson, F. L., & Orr, E. L. 1990, "Attenuation of experimental autoimmune encephalomyelitis by Compound 48/80 in Lewis rats", J.Neuroimmunol., vol. 29, no. 1-3, pp. 223-228.

Staykova, M., Goranov, I., & Nikolov, T. 1978, "[Influence of cyclophosphamide on the production of experimentale autoimmune encephalomyelitis (author's transl)]", Ann Immunol (Paris), vol. 129, no. 2-3, pp. 415-427.

Staykova, M., Kozovska, M., Kirazian, N., & Goranov, I. 1988, "Aggravation of experimental allergic encephalomyelitis by cimetidine", Ann.Inst.Pasteur Immunol., vol. 139, no. 5, pp. 501-505.

Staykova, M., Kozovska, M., Kirazjan, N., & Goranov, I. 1989, "Induction of resistance to experimental allergic encephalomyelitis in newborn guinea pigs", Neurol.Psychiatr.(Bucur.), vol. 27, no. 3, pp. 225-229.

Staykova, M. A., Simmons, R. D., & Willenborg, D. O. 1997, "Infusion of soluble myelin basic protein protects long-term against induction of experimental autoimmune encephalomyelitis", Immunol.Cell Biol., vol. 75, no. 1, pp. 54-64.

Stedra, J., Holan, V., & Lodin, Z. 1986, "Suppression of experimental allergic encephalomyelitis in rats by suppressor factor from a permanent T cell line", Folia Biol.(Praha), vol. 32, no. 3, pp. 212-217.

Stein, C. S., St, L. J., Gilbert, J. J., & Strejan, G. H. 1990, "Treatment of spinal cord-induced experimental allergic encephalomyelitis in the Lewis rat with liposomes presenting central nervous system antigens", J.Neuroimmunol., vol. 28, no. 2, pp. 119-130.

Steinbrecher, A., Reinhold, D., Quigley, L., Gado, A., Tresser, N., Izikson, L., Born, I., Faust, J., Neubert, K., Martin, R., Ansorge, S., & Brocke, S. 2001, "Targeting dipeptidyl peptidase IV (CD26) suppresses autoimmune encephalomyelitis and up-regulates TGF-beta 1 secretion in vivo", J.Immunol., vol. 166, no. 3, pp. 2041-2048.

Steiner, I., Brenner, T., Mizrachi-Kol, R., & Abramsky, O. 1991, "Development of experimental allergic encephalomyelitis during steroid administration. Outcome of neurological immune-mediated disorders under immunosuppressive therapy", Isr.J.Med.Sci., vol. 27, no. 7, pp. 365-368.

Steinman, L., Solomon, D., Lim, M., Zamvil, S., & Sriram, S. 1983, "Prevention of experimental allergic encephalitis with in vivo administration of anti I-A antibody. Decreased accumulation of radiolabelled lymph node cells in the central nervous system", J.Neuroimmunol., vol. 5, no. 1, pp. 91-97.

Stern, J. N., Illes, Z., Reddy, J., Keskin, D. B., Fridkis-Hareli, M., Kuchroo, V. K., & Strominger, J. L. 2005, "Peptide 15-mers of defined sequence that substitute for random amino acid copolymers in amelioration of experimental autoimmune encephalomyelitis", Proc.Natl.Acad.Sci.U.S.A, vol. 102, no. 5, pp. 1620-1625.

Stern, J. N., Illes, Z., Reddy, J., Keskin, D. B., Sheu, E., Fridkis-Hareli, M., Nishimura, H., Brosnan, C. F., Santambrogio, L., Kuchroo, V. K., & Strominger, J. L. 2004, "Amelioration of proteolipid protein 139-151-induced encephalomyelitis in SJL mice by modified amino acid copolymers and their mechanisms", Proc.Natl.Acad.Sci.U.S.A, vol. 101, no. 32, pp. 11743-11748.

Stern, P. 1975, "The effect of specific brain phospholipid on the rat's allergic encephalomyelitis", Arzneimittelforschung., vol. 25, no. 5, pp. 753-755.

Stevens, D. B., Karpus, W. J., Gould, K. E., & Swanborg, R. H. 1992, "Studies of V beta 8 T cell receptor peptide treatment in experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 37, no. 1-2, pp. 123-129.

Stojkov, D., Lavrnja, I., Pekovic, S., Dacic, S., Bjelobaba, I., Mostarica-Stojkovic, M., Stosic-Grujicic, S., Jovanovic, S., Nedeljkovic, N., Rakic, L., & Stojiljkovic, M. 2008, "Therapeutic effects of combined treatment with ribavirin and tiazofurin on experimental autoimmune encephalomyelitis development: clinical and histopathological evaluation", J Neurol Sci, vol. 267, no. 1-2.

Storch, M., Rausch, M., Hiestand, P., Balatoni, B., & Foster, C. A. 2005, "FTY720 not only prevents EAE onsetm, as assessed by MRI, but also reverses established neurological deficits and extensive demyelination", Multiple Sclerosis, vol. 11, no. S1, p. 64.

Stosic-Grujicic, S., Savic-Radojevic, A., Maksimovic-Ivanic, D., Markovic, M., Bumbasirevic, V., Ramic, Z., & Mostarica-Stojkovic, M. 2002, "Down-regulation of experimental allergic encephalomyelitis in DA rats by tiazofurin", J.Neuroimmunol., vol. 130, no. 1-2, pp. 66-77.

Strejan, G. H., Gilbert, J. J., & St, L. J. 1984a, "Suppression of chronic-relapsing EAE by basic protein-liposome complexes", Prog.Clin.Biol.Res., vol. 146, pp. 429-434.

Strejan, G. H., Gilbert, J. J., & St, L. J. 1984b, "Suppression of chronic-relapsing experimental allergic encephalomyelitis in strain-13 guinea pigs by administration of liposome-associated myelin basic protein", J.Neuroimmunol., vol. 7, no. 1, pp. 27-41.

Strejan, G. H., Gilbert, J. J., & St, L. J. 1988, "Effect of treatment with glutaraldehyde-fixed myelin basic protein-liposomes on active induction and passive transfer of experimental allergic encephalomyelitis in Lewis rats", Cell Immunol., vol. 116, no. 1, pp. 250-256.

Strejan, G. H., Percy, D. H., & St, L. J. 1984, "Suppression of experimental allergic encephalomyelitis in Lewis rats treated with myelin basic protein-liposome complexes: clinical, histopathological, and cell-mediated immunity correlates", Cell Immunol., vol. 84, no. 1, pp. 171-184.

Strejan, G. H., Percy, D. H., St, L. J., Surlan, D., & Paty, D. W. 1981, "Suppression of experimental allergic encephalomyelitis in guinea/pigs by liposome-associated human myelin basic protein", J.Immunol., vol. 127, no. 5, pp. 2064-2069.

Strejan, G. H. & St Louis, J. 1990, "Suppression of experimental allergic encephalomyelitis by MBP-coupled lymphoid cells and by MBP-liposomes: a comparison", Cell Immunol, vol. 127, no. 2, pp. 284-298.

Stuve, O., Youssef, S., Weber, M. S., Nessler, S., von Budingen, H. C., Hemmer, B., Prod'homme, T., Sobel, R. A., Steinman, L., & Zamvil, S. S. 2006, "Immunomodulatory synergy by combination of atorvastatin and glatiramer acetate in treatment of CNS autoimmunity", J Clin Invest, vol. 116, no. 4, pp. 1037-1044.

Su, X. M. & Sriram, S. 1991, "Treatment of chronic relapsing experimental allergic encephalomyelitis with the intravenous administration of splenocytes coupled to encephalitogenic peptide 91-103 of myelin basic protein", J.Neuroimmunol., vol. 34, no. 2-3, pp. 181-190.

Subramanian, S., Matejuk, A., Zamora, A., Vandenbark, A. A., & Offner, H. 2003, "Oral feeding with ethinyl estradiol suppresses and treats experimental autoimmune encephalomyelitis in SJL mice and inhibits the recruitment of inflammatory cells into the central nervous system", J.Immunol., vol. 170, no. 3, pp. 1548-1555.

Suckling, A. J., Baron, P. W., & Reiber, H. 1986, "Chronic relapsing experimental allergic encephalomyelitis: cyclosporin-A treatment of relapsing and remitting disease", J.Clin.Lab Immunol., vol. 21, no. 4, pp. 173-176.

Sun, D. 1992, "Synthetic peptides representing sequence 39 to 59 of rat V beta 8 TCR fail to elicit regulatory T cells reactive with V beta 8 TCR on rat encephalitogenic T cells", Cell Immunol, vol. 141, no. 1, pp. 200-210.

Sun, D., Ben-Nun, A., & Wekerle, H. 1988, "Regulatory circuits in autoimmunity: recruitment of counter-regulatory CD8+ T cells by encephalitogenic CD4+ T line cells", Eur.J.Immunol., vol. 18, no. 12, pp. 1993-1999.

Sun, D., Branum, K., & Sun, Q. 1992, "Prevention of experimental autoimmune encephalomyelitis in Lewis rats by treatment with an anti-rat CD5 antibody (OX19)", Cell Immunol, vol. 145, no. 2, pp. 263-271.

Sun, J. B., Xiao, B. G., Lindblad, M., Li, B. L., Link, H., Czerkinsky, C., & Holmgren, J. 2000, "Oral administration of cholera toxin B subunit conjugated to myelin basic protein protects against experimental autoimmune encephalomyelitis by inducing transforming growth factor-beta-secreting cells and suppressing chemokine expression", Int.Immunol., vol. 12, no. 10, pp. 1449-1457.

Sun, X., Minohara, M., Kikuchi, H., Ishizu, T., Tanaka, M., Piao, H., Osoegawa, M., Ohyagi, Y., Shimokawa, H., & Kira, J. i. 2006, "The selective Rho-kinase inhibitor Fasudil is protective and therapeutic in experimental autoimmune encephalomyelitis", J Neuroimmunol, vol. 180, no. 1-2.

Sun, Y., Lin, X., Chen, H. M., Wu, Q., Subudhi, S. K., Chen, L., & Fu, Y. X. 2002, "Administration of agonistic anti-4-1BB monoclonal antibody leads to the amelioration of experimental autoimmune encephalomyelitis", J.Immunol., vol. 168, no. 3, pp. 1457-1465.

Suzuki, M., Cheng, K. C., Krug, M. S., & Yoo, T. J. 1998, "Successful prevention of retrocochlear hearing loss in murine experimental allergic encephalomyelitis with T cell receptor Vbeta8-specific antibody", Ann.Otol.Rhinol.Laryngol., vol. 107, no. 11 Pt 1, pp. 917-927.

Swanborg, R. H. 1972, "Antigen-induced inhibition of experimental allergic encephalomyelitis. I. Inhibition in guinea pigs injected with non-encephalitogenic modified myelin basic protein", J.Immunol., vol. 109, no. 3, pp. 540-546.

Swanborg, R. H. 1973, "Antigen-induced inhibition of experimental allergic encephalomyelitis. II. Studies in guinea pigs with the small rat myelin basic protein", J.Immunol., vol. 111, no. 4, pp. 1067-1070.

Swanborg, R. H. 1975a, "Antigen-induced inhibition of experimental allergic encephalomyelitis. III. Localization of an inhibitory site distinct from the major encephalitogenic determinant of myelin basic protein", J.Immunol., vol. 114, no. 1 Pt 1, pp. 191-194.

Swanborg, R. H. 1975b, "Antigen-induced inhibition of experimental allergic encephalomyelitis. IV. Studies of the C-terminal end of the myelin basic protein molecule (1)", Immunol Commun., vol. 4, no. 4, pp. 387-397.

Swierkosz, J. E. & Swanborg, R. H. 1975, "Suppressor cell control of unresponsiveness to experimental allergic encephalomyelitis", J.Immunol., vol. 115, no. 3, pp. 631-633.

Szczepanik, M., Tutaj, M., Bryniarski, K., & Dittel, B. N. 2005, "Epicutaneously induced TGF-beta-dependent tolerance inhibits experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 164, no. 1-2, pp. 105-114.

Tadokoro, C. E., Vallochi, A. L., Rios, L. S., Martins, G. A., Schlesinger, D., Mosca, T., Kuchroo, V. K., Rizzo, L. V., & Abrahamsohn, I. A. 2004, "Experimental autoimmune encephalomyelitis can be prevented and cured by infection with Trypanosoma cruzi", J.Autoimmun., vol. 23, no. 2, pp. 103-115.

Tafreshi, A. P. 2006, "Nerve growth factor prevents demyelination, cell death and progression of the disease in experimental allergic encephalomyelitis", Iranian Journal of Allergy, Asthma and Immunology.5(4)()(pp 177-181), 2006.Date of Publication: Dec 2006. no. 4, pp. 177-181.

Takahashi, K., Prinz, M., Stagi, M., Chechneva, O., & Neumann, H. 2007, "TREM2-transduced myeloid precursors mediate nervous tissue debris clearance and facilitate recovery in an animal model of multiple sclerosis", PLoS.Med., vol. 4, no. 4, p. e124.

Takenaka, A., Nakamura, T., Mori, R., Shibasaki, H., Kondo, S., & Hisatsune, K. 1982, "Further studies on bacterial lipopolysaccharide-induced protection against experimental allergic encephalomyelitis in guinea pigs. Effects of chemical modifications", J.Neurol.Sci., vol. 55, no. 2, pp. 165-174.

Tan, L. J., Kennedy, M. K., Dal Canto, M. C., & Miller, S. D. 1991, "Successful treatment of paralytic relapses in adoptive experimental autoimmune encephalomyelitis via neuroantigen-specific tolerance", J.Immunol., vol. 147, no. 6, pp. 1797-1802.

Tang, X., Maricic, I., & Kumar, V. 2007, "Anti-TCR antibody treatment activates a novel population of nonintestinal CD8 alpha alpha+ TCR alpha beta+ regulatory T cells and prevents experimental autoimmune encephalomyelitis", J.Immunol., vol. 178, no. 10, pp. 6043-6050.

Tanuma, N., Abe, S., Shin, T., Kojima, T., Ishihara, Y., Arai, Y., Toyoshima, S., & Matsumoto, Y. 1996, "Pretreatment with T cell receptor peptides using a conventional immunization protocol does not induce effective protection against autoimmune encephalomyelitis", Cell Immunol., vol. 168, no. 1, pp. 85-90.

Targoni, O. S., Tary-Lehmann, M., & Lehmann, P. V. 1999, "Prevention of murine EAE by oral hydrolytic enzyme treatment", J.Autoimmun., vol. 12, no. 3, pp. 191-198.

Teitelbaum, D., Aharoni, R., Klinger, E., Kreitman, R., Raymond, E., Malley, A., Shofti, R., Sela, M., & Arnon, R. 2004, "Oral glatiramer acetate in experimental autoimmune encephalomyelitis: clinical and immunological studies", Ann.N.Y.Acad.Sci., vol. 1029, pp. 239-249.

Teitelbaum, D., Arnon, R., & Sela, M. 1999, "Immunomodulation of experimental autoimmune encephalomyelitis by oral administration of copolymer 1", Proc.Natl.Acad.Sci.U.S.A, vol. 96, no. 7, pp. 3842-3847.

Teitelbaum, D., Meshorer, A., Hirshfeld, T., Arnon, R., & Sela, M. 1971, "Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide", Eur.J.Immunol., vol. 1, no. 4, pp. 242-248.

Teitelbaum, D., Webb, C., Bree, M., Meshorer, A., Arnon, R., & Sela, M. 1974, "Suppression of experimental allergic encephalomyelitis in Rhesus monkeys by a synthetic basic copolymer", Clin.Immunol.Immunopathol., vol. 3, no. 2, pp. 256-262.

Teitelbaum, D., Webb, C., Meshorer, A., Arnon, R., & Sela, M. 1972, "Protection against experimental allergic encephalomyelitis", Nature, vol. 240, no. 5383, pp. 564-566.

Teuscher, C., Hickey, W. F., & Korngold, R. 1990, "An analysis of the role of tumor necrosis factor in the phenotypic expression of actively induced experimental allergic orchitis and experimental allergic encephalomyelitis", Clin.Immunol.Immunopathol., vol. 54, no. 3, pp. 442-453.

thanasas-Platsis, S., Zhang, B., Hillyard, N. C., Cavanagh, A. C., Csurhes, P. A., Morton, H., & McCombe, P. A. 2003, "Early pregnancy factor suppresses the infiltration of lymphocytes and macrophages in the spinal cord of rats during experimental autoimmune encephalomyelitis but has no effect on apoptosis", J.Neurol.Sci., vol. 214, no. 1-2, pp. 27-36.

Theien, B. E., Vanderlugt, C. L., Eagar, T. N., Nickerson-Nutter, C., Nazareno, R., Kuchroo, V. K., & Miller, S. D. 2001, "Discordant effects of anti-VLA-4 treatment before and after onset of relapsing experimental autoimmune encephalomyelitis", J.Clin.Invest, vol. 107, no. 8, pp. 995-1006.

Theien, B. E., Vanderlugt, C. L., Nickerson-Nutter, C., Cornebise, M., Scott, D. M., Perper, S. J., Whalley, E. T., & Miller, S. D. 2003, "Differential effects of treatment with a small-molecule VLA-4 antagonist before and after onset of relapsing EAE", Blood, vol. 102, no. 13, pp. 4464-4471.

Tiwari-Woodruff, S., Morales, L., Softoniew, M., & Voskuhl, R. 2007, "Reactive astrocytes restrict inflammation and inhibit axonal degeneration in experimental autoimmune encephalomyelitis", Multiple Sclerosis, vol. 13, p. S248.

Todorov, D. M., Michailov, W. G., & Drumtcheva, M. A. 1982, "Influence of tetramisole on the induction of experimental allergic encephalomyelitis (EAE)", Allerg.Immunol.(Leipz.), vol. 28, no. 3, pp. 192-196.

Topham, D. J., Nag, B., Arimilli, S., & Sriram, S. 1994, "A synthetic peptide from the third hypervariable region of major histocompatibility complex class II beta chain as a vaccine for treatment of experimental autoimmune encephalomyelitis", Proc.Natl.Acad.Sci.U.S.A, vol. 91, no. 17, pp. 8005-8009.

Touil, T., Ciric, B., Ventura, E., Shindler, K. S., Gran, B., & Rostami, A. 2008, "Bowman-Birk inhibitor suppresses autoimmune inflammation and neuronal loss in a mouse model of multiple sclerosis", Journal of the Neurological Sciences.271(1-2)()(pp 191-202), 2008.Date of Publication: 15 Aug 2008. no. 1-2, pp. 191-202.

Touil, T., Fitzgerald, D., Zhang, G.-X., Rostami, A., & Gran, B. 2006, "Cutting edge: TLR3 stimulation suppresses experimental autoimmune encephalomyelitis by inducing endogenous IFN-beta", Journal of Immunology.177(11)()(pp 7505-7509), 2006.Date of Publication: 01 Dec 2006. no. 11, pp. 7505-7509.

Tran, E. H., Hoekstra, K., van Rooijen, N., Dijkstra, C. D., & Owens, T. 1998, "Immune invasion of the central nervous system parenchyma and experimental allergic encephalomyelitis, but not leukocyte extravasation from blood, are prevented in macrophage-depleted mice", Journal of Immunology.161(7)()(pp 3767-3775), 1998.Date of Publication: 01 Oct 1998. no. 7, pp. 3767-3775.

Tran, G. T., Carter, N., He, X. Y., Spicer, T. S., Plain, K. M., Nicolls, M., Hall, B. M., & Hodgkinson, S. J. 2001, "Reversal of experimental allergic encephalomyelitis with non-mitogenic, non-depleting anti-CD3 mAb therapy with a preferential effect on T(h)1 cells that is augmented by IL-4", Int.Immunol., vol. 13, no. 9, pp. 1109-1120.

Tran, G. T., Carter, N., & Hodgkinson, S. J. 2001, "Mycophenolate mofetil treatment accelerates recovery from experimental allergic encephalomyelitis", Int.Immunopharmacol., vol. 1, no. 9-10, pp. 1709-1723.

Traugott, U., Stone, S. H., & Raine, C. S. 1979, "Chronic relapsing experimental allergic encephalomyelitis. Correlation of circulating lymphocyte fluctuations with disease activity in suppressed and unsuppressed animals", J.Neurol.Sci., vol. 41, no. 1, pp. 17-29.

Traugott, U., Stone, S. H., & Raine, C. S. 1982, "Chronic relapsing experimental autoimmune encephalomyelitis. treatment with combinations of myelin components promotes clinical and structural recovery", J.Neurol.Sci., vol. 56, no. 1, pp. 65-73.

Triaca, V., Tirassa, P., & Aloe, L. 2005, "Presence of nerve growth factor and TrkA expression in the SVZ of EAE rats: Evidence for a possible functional significance", Experimental Neurology.191(1)()(pp 53-64), 2005.Date of Publication: Jan 2005. no. 1, pp. 53-64.

Trooster, W. J., Teelken, A. W., Kampinga, J., Loof, J. G., Nieuwenhuis, P., & Minderhoud, J. M. 1993, "Suppression of acute experimental allergic encephalomyelitis by the synthetic sex hormone 17-alpha-ethinylestradiol: an immunological study in the Lewis rat", Int.Arch.Allergy Immunol., vol. 102, no. 2, pp. 133-140.

Tselios, T., Apostolopoulos, V., Daliani, I., Deraos, S., Grdadolnik, S., Mavromoustakos, T., Melachrinou, M., Thymianou, S., Probert, L., Mouzaki, A., & Matsoukas, J. 2002, "Antagonistic effects of human cyclic MBP(87-99) altered peptide ligands in experimental allergic encephalomyelitis and human T-cell proliferation", J.Med.Chem., vol. 45, no. 2, pp. 275-283.

Tselios, T., Daliani, I., Deraos, S., Thymianou, S., Matsoukas, E., Troganis, A., Gerothanassis, I., Mouzaki, A., Mavromoustakos, T., Probert, L., & Matsoukas, J. 2000a, "Treatment of experimental allergic encephalomyelitis (EAE) by a rationally designed cyclic analogue of myelin basic protein (MBP) epitope 72-85", Bioorg.Med.Chem.Lett., vol. 10, no. 24, pp. 2713-2717.

Tselios, T., Daliani, I., Probert, L., Deraos, S., Matsoukas, E., Roy, S., Pires, J., Moore, G., & Matsoukas, J. 2000b, "Treatment of experimental allergic encephalomyelitis (EAE) induced by guinea pig myelin basic protein epitope 72-85 with a human MBP(87-99) analogue and effects of cyclic peptides", Bioorg.Med.Chem., vol. 8, no. 8, pp. 1903-1909.

Tsukimoto, M., Nakatsukasa, H., Sugawara, K., Yamashita, K., & Kojima, S. 2008, "Repeated 0.5-Gy gamma irradiation attenuates experimental autoimmune encephalomyelitis with up-regulation of regulatory T cells and suppression of IL17 production", Radiat.Res, vol. 170, no. 4, pp. 429-436.

Tsumita, T., Saito, M., & Nagai, Y. 1972, "Effect of myo-inositol on the induction of experimental allergic encephalomyelitis in guinea pigs", Jpn.J.Exp.Med., vol. 42, no. 6, pp. 587-588.

Tsunoda, I., Terry, E. J., Marble, B. J., Lazarides, E., Woods, C., & Fujinami, R. S. 2007, "Modulation of experimental autoimmune encephalomyelitis by VLA-2 blockade", Brain Pathol, vol. 17, no. 1, pp. 45-55.

Tsutsui, S., Vergote, D., Shariat, N., Warren, K., Ferguson, S. S., & Power, C. 2008, "Glucocorticoids regulate innate immunity in a model of multiple sclerosis: reciprocal interactions between the A1 adenosine receptor and beta-arrestin-1 in monocytoid cells", FASEB J., vol. 22, no. 3, pp. 786-796.

Tsutsui, S., Schnermann, J., & Power, C. 2003, "Adenosine A1 receptor regulates inflammation at the severity of a murine model of multiple sclerosis", Faseb Journal, vol. 17, no. 4-5.

Turley, D. M. & Miller, S. D. 2007, "Peripheral tolerance induction using ethylenecarbodiimide-fixed APCs uses both direct and indirect mechanisms of antigen presentation for prevention of experimental autoimmune encephalomyelitis", J.Immunol., vol. 178, no. 4, pp. 2212-2220.

Tutaj, M. & Szczepanik, M. 2007, "Epicutaneous (EC) immunization with myelin basic protein (MBP) induces TCRalphabeta+ CD4+ CD8+ double positive suppressor cells that protect from experimental autoimmune encephalomyelitis (EAE)", J.Autoimmun., vol. 28, no. 4, pp. 208-215.

Uccelli, A., Morini, M., Pedemonte, E., Roccatagliata, L., Dell'Eva, R., Marchese, M., Pfeffer, U., Furlan, R., Noonan, D., Giunti, D., Albini, A., & Mancardi, G. 2003, "Lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis", European Journal of Neurology, vol. 10, no. Supplement 1.

Uemura, Y., Ohno, H., Ohzeki, Y., Takanashi, H., Murooka, H., Kubo, K., & Serizawa, I. 2008, "The selective M-CSF receptor tyrosine kinase inhibitor Ki20227 suppresses experimental autoimmune encephalomyelitis", J Neuroimmunol, vol. 195, no. 1-2, pp. 73-80.

Uitdehaag, B. M., Polman, C. H., De Groot, C. J., & Dijkstra, C. D. 1994, "Effect of K+ channel blockers on the clinical course and histological features of experimental allergic encephalomyelitis", Acta Neurol.Scand., vol. 90, no. 4, pp. 299-301.

Urban, J. L., Horvath, S. J., & Hood, L. 1989, "Autoimmune T cells: immune recognition of normal and variant peptide epitopes and peptide-based therapy", Cell, vol. 59, no. 2, pp. 257-271.

Uyttenhove, C., Arendse, B., Stroobant, V., Brombacher, F., & Van, S. J. 2004, "Development of an anti-IL-12 p40 auto-vaccine: protection in experimental autoimmune encephalomyelitis at the expense of increased sensitivity to infection", Eur.J.Immunol., vol. 34, no. 12, pp. 3572-3581.

Uyttenhove, C., Sommereyns, C., Theate, I., Michiels, T., & Van Snick, J. 2007, "Anti-IL-17A autovaccination prevents clinical and histological manifestations of experimental autoimmune encephalomyelitis", Ann.N.Y.Acad.Sci., vol. 1110, pp. 330-336.

van Bekkum, D. W., Van Gelder, M., & Kinwel-Bohre, E. P. M. 1992, "Treatment of Eae with Bone Marrow Transplantation", Journal of Cellular Biochemistry Supplement no. 16 PART A.

van der Laan, L. J., van der, G. A., Wauben, M. H., Ruuls, S. R., Dopp, E. A., De Groot, C. J., Kuijpers, T. W., Elices, M. J., & Dijkstra, C. D. 2002, "Beneficial effect of modified peptide inhibitor of alpha4 integrins on experimental allergic encephalomyelitis in Lewis rats", J.Neurosci.Res., vol. 67, no. 2, pp. 191-199.

van der Meide, P. H., de Labie, M. C., Ruuls, S. R., Groenestein, R. J., Botman, C. A., Olsson, T., & Dijkstra, C. D. 1998, "Discontinuation of treatment with IFN-beta leads to exacerbation of experimental autoimmune encephalomyelitis in Lewis rats. Rapid reversal of the antiproliferative activity of IFN-beta and excessive expansion of autoreactive T cells as disease promoting mechanisms", J.Neuroimmunol., vol. 84, no. 1, pp. 14-23.

van Etten, E., Gysemans, C., Branisteanu, D. D., Verstuyf, A., Bouillon, R., Overbergh, L., & Mathieu, C. 2007, "Novel insights in the immune function of the vitamin D system: synergism with interferon-beta", J.Steroid Biochem.Mol.Biol., vol. 103, no. 3-5, pp. 546-551.

Van Wijmeersch, B., Sprangers, B., Rutgeerts, O., Lenaerts, C., Landuyt, W., Waer, M., Billiau, A. D., & Dubois, B. 2007, "Allogeneic bone marrow transplantation in models of experimental autoimmune

encephalomyelitis: evidence for a graft-versus-autoimmunity effect", Biol.Blood Marrow Transplant., vol. 13, no. 6, pp. 627-637.

van, d., V, Asghar, S. S., Uitdehaag, B. M., van der Helm, H. J., & Hommes, O. R. 1985, "Suppression of the development of experimental allergic encephalomyelitis by suramin", Neuropharmacology, vol. 24, no. 11, pp. 1139-1142.

Van, E. E., Branisteanu, D. D., Overbergh, L., Bouillon, R., Verstuyf, A., & Mathieu, C. 2003, "Combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents experimental autoimmune encephalomyelitis and preserves bone", Bone, vol. 32, no. 4, pp. 397-404.

van, G. M. & van Bekkum, D. W. 1995, "Treatment of relapsing experimental autoimmune encephalomyelitis in rats with allogeneic bone marrow transplantation from a resistant strain", Bone Marrow Transplant., vol. 16, no. 3, pp. 343-351.

van, L. R. & Jonker, M. 1987, "Experimental allergic encephalomyelitis in rhesus monkeys: II. Treatment of EAE with anti-T lymphocyte subset monoclonal antibodies", Clin.Exp.Immunol., vol. 68, no. 2, pp. 305-312.

Vandenbark, A. A., Celnik, B., Vainiene, M., Miller, S. D., & Offner, H. 1995, "Myelin antigen-coupled splenocytes suppress experimental autoimmune encephalomyelitis in Lewis rats through a partially reversible anergy mechanism", J.Immunol., vol. 155, no. 12, pp. 5861-5867.

Vandenbark, A. A., Hashim, G., & Offner, H. 1989, "Immunization with a synthetic T-cell receptor V-region peptide protects against experimental autoimmune encephalomyelitis", Nature, vol. 341, no. 6242, pp. 541-544.

Vandenbark, A. A., Vainiene, M., Ariail, K., Miller, S. D., & Offner, H. 1996, "Prevention and treatment of relapsing autoimmune encephalomyelitis with myelin peptide-coupled splenocytes", J.Neurosci.Res., vol. 45, no. 4, pp. 430-438.

Vanderlugt, C. L., Karandikar, N. J., Lenschow, D. J., Dal Canto, M. C., Bluestone, J. A., & Miller, S. D. 1997, "Treatment with intact anti-B7-1 mAb during disease remission enhances epitope spreading and exacerbates relapses in R-EAE", J.Neuroimmunol., vol. 79, no. 2, pp. 113-118.

Vanderlugt, C. L., Rahbe, S. M., Elliott, P. J., Dal Canto, M. C., & Miller, S. D. 2000, "Treatment of established relapsing experimental autoimmune encephalomyelitis with the proteasome inhibitor PS-519", J.Autoimmun., vol. 14, no. 3, pp. 205-211.

Vansant, G., Trauger, R. J., Cameron, A., Vendemelio, M., Kreitschitz, S., Carlo, A. T., Banaszczyk, M. G., Carlo, D. J., Hendler, S., & Ill, C. R. 2007, "Propofol hemisuccinate suppression of experimental autoimmune encephalomyelitis", Autoimmunity, vol. 40, no. 3, pp. 180-186.

Varriale, S., Beraud, E., Barbaria, J., Galibert, R., & Bernard, D. 1994, "Regulation of experimental autoimmune encephalomyelitis: inhibition of adoptive experimental autoimmune encephalomyelitis by 'recovery-associated suppressor cells'", J.Neuroimmunol., vol. 53, no. 2, pp. 123-131.

Vecchi, A., Tagliabue, A., Mantovani, A., Anaclerio, A., Barale, C., & Spreafico, F. 1976, "Steroid contraceptive agents and immunological reactivity in experimental animals", Biomedicine., vol. 24, no. 4, pp. 231-237.

Veljic, J., Maric, D., & Jankovic, B. D. 1991, "Changes of experimental allergic encephalomyelitis by methionine-enkephalin injected into lateral ventricles of the rat brain", Int.J.Neurosci., vol. 59, no. 1-3, pp. 81-89.

Verbeek, R., van Tol, E. A., & van Noort, J. M. 2005, "Oral flavonoids delay recovery from experimental autoimmune encephalomyelitis in SJL mice", Biochem.Pharmacol., vol. 70, no. 2, pp. 220-228.

Verda, L., Luo, K., Kim, D.-A., Bronesky, D., Kohm, A. P., Miller, S. D., Statkute, L., Oyama, Y., & Burt, R. K. 2006, "Effect of hematopoietic growth factors on severity of experimental autoimmune encephalomyelitis", Bone Marrow Transplantation.38(6)()(pp 453-460), 2006.Date of Publication: Sep 2006. no. 6, pp. 453-460.

Vescovi, A., Pluchino, S., Gritti, A., Galli, R., Brambilla, E., Salani, G., Dina, G., del Carro, U., Amadio, S., Bergami, A., Furlan, R., Comi, G., & Martino, G. 2003, "Intravenous and intracerebroventricular injection of adult neural stem cells induce clinical recovery in a chronic model of multiple sclerosis", Society for Neuroscience Abstract Viewer and Itinerary Planner, vol. 2003.

Villoslada, P., Hauser, S. L., Bartke, I., Unger, J., Heald, N., Rosenberg, D., Cheung, S. W., Mobley, W. C., Fisher, S., & Genain, C. P. 2000, "Human nerve growth factor protects common marmosets against autoimmune encephalomyelitis by switching the balance of T helper cell type 1 and 2 cytokines within the central nervous system", J.Exp.Med., vol. 191, no. 10, pp. 1799-1806.

Vladutiu, A. & Cringulescu, N. 1968, "Suppression of experimental allergic encephalomyelitis by vitamin A", Experientia, vol. 24, no. 7, pp. 718-719.

Vlajkovic, S. & Jankovic, B. D. 1990, "Experimental epilepsy: electrically and chemically induced convulsions modulate experimental allergic encephalomyelitis and other immune inflammatory reactions in the rat", Int.J.Neurosci., vol. 54, no. 1-2, pp. 165-172.

Voda, J., Bourdette, D. N., & Gold, B. G. 2002, "A nonimmunosuppressant FK506 derivative reduces axonal and myelin damage in autoimmune encephalomyelitis (EAE) mice", Journal of Neuropathology and Experimental Neurology, vol. 61, no. 5, p. 7.

Voda, J., McKeon, G., Bourdette, D., & Gold, B. 2002, "Fk506 and A Nonimmunosuppressant Derivative Reduce Axonal and Myelin Damage in Autoimmune Encephalomyelitis (Eae) Mice", Society for Neuroscience Abstract Viewer and Itinerary Planner, vol. 2002.

Vogel, C., Paty, D. W., & Kibler, R. F. 1972, "Treatment of experimental allergic encephalomyelitis in the rabbit", Arch.Neurol., vol. 26, no. 4, pp. 366-373.

Vogel, C. L. & Calabresi, P. 1969, "Enhanced suppression of experimental allergic encephalomyelitis by combination chemotherapy with duazomycin-A and 6-mercaptopurine", Proc.Soc.Exp.Biol.Med., vol. 131, no. 1, pp. 251-256.

Vogel, C. L., De, V., V, Lisak, R. P., & Kies, M. W. 1969, "Suppression of experimental allergic encephalomyelitis by NSC 82196, a new imidazole carboxamide derivative", Cancer Res., vol. 29, no. 12, pp. 2249-2253.

Vohl, M. L., Westarp, M. E., Wekerle, H., Gerlach, M., Jutzi, P., & Przuntek, H. 1990, "[Mercaptopurine and silylated mercaptopurine the treatment of experimental allergic encephalomyelitis]", Arzneimittelforschung., vol. 40, no. 1, pp. 80-84.

Vollmar, P., Nessler, S., Kalluri, S. R., Hartung, H. P., & Hemmer, B. 2009, "The antidepressant venlafaxine ameliorates murine experimental autoimmune encephalomyelitis by suppression of pro-inflammatory cytokines", Int J Neuropsychopharmacol, vol. 12, no. 4.

Vollmer, T. L., Liu, R., Price, M., Rhodes, S., La Cava, A., & Shi, F. D. 2005, "Differential effects of IL-21 during initiation and progression of autoimmunity against neuroantigen", J Immunol, vol. 174, no. 5, pp. 2696-2701.

Voorthuis, J. A., Uitdehaag, B. M., De Groot, C. J., Goede, P. H., van der Meide, P. H., & Dijkstra, C. D. 1990, "Suppression of experimental allergic encephalomyelitis by intraventricular administration of interferon-gamma in Lewis rats", Clin.Exp.Immunol., vol. 81, no. 2, pp. 183-188.

Vroegop, S. M., Chapman, D. L., Decker, D. E., Galinet, L. A., Brideau, R. J., Ready, K. A., Dunn, C. J., & Buxser, S. E. 1999a, "Pharmacokinetic properties, induction of interferon, and efficacy of selected 5-halo-6-phenyl pyrimidinones, bropirimine analogues, in a model of severe experimental autoimmune encephalomyelitis", Int.J.Immunopharmacol., vol. 21, no. 10, pp. 647-662.

Vroegop, S. M., Chapman, D. L., Galinet, L. A., Decker, D. E., Ready, K. A., Brideau, R. J., Dunn, C. J., & Buxser, S. E. 1999b, "Pharmacology of the biological response modifier bropirimine (PNU-54461) on experimental autoimmune encephalomyelitis (EAE) in mice", Int.J.Immunopharmacol., vol. 21, no. 6, pp. 391-409.

Vymazal, J., Krasenska-Dlabacova, J., Miler, I., & Malbohan, I. 1974, "[Effect of carrageenan on the course of experimental allergic encephalomyelitis in the rat]", Cesk.Neurol.Neurochir., vol. 37, no. 6, pp. 345-348.

Waisman, A., Ruiz, P. J., Hirschberg, D. L., Gelman, A., Oksenberg, J. R., Brocke, S., Mor, F., Cohen, I. R., & Steinman, L. 1996, "Suppressive vaccination with DNA encoding a variable region gene of the T-cell receptor prevents autoimmune encephalomyelitis and activates Th2 immunity", Nat.Med., vol. 2, no. 8, pp. 899-905.

Walczak, A., Szymanska, B., & Selmaj, K. 2004, "Differential prevention of experimental autoimmune encephalomyelitis with antigen-specific DNA vaccination", Clin.Neurol.Neurosurg., vol. 106, no. 3, pp. 241-245.

Waldor, M. K., Mitchell, D., Kipps, T. J., Herzenberg, L. A., & Steinman, L. 1987, "Importance of immunoglobulin isotype in therapy of experimental autoimmune encephalomyelitis with monoclonal anti-CD4 antibody", J.Immunol., vol. 139, no. 11, pp. 3660-3664.

Waldor, M. K., Sriram, S., Hardy, R., Herzenberg, L. A., Herzenberg, L. A., Lanier, L., Lim, M., & Steinman, L. 1985, "Reversal of experimental allergic encephalomyelitis with monoclonal antibody to a T-cell subset marker", Science, vol. 227, no. 4685, pp. 415-417.

Wallberg, M., Wefer, J., & Harris, R. A. 2003, "Vaccination with myelin oligodendrocyte glycoprotein adsorbed to alum effectively protects DBA/1 mice from experimental autoimmune encephalomyelitis", Eur.J.Immunol., vol. 33, no. 6, pp. 1539-1547.

Walter, S., Fassbender, K., Gulbins, E., Liu, Y., Rieschel, M., Herten, M., Bertsch, T., & Engelhardt, B. 2002, "Glycosylation processing inhibition by castanospermine prevents experimental autoimmune encephalomyelitis by interference with IL-2 receptor signal transduction", J Neuroimmunol, vol. 132, no. 1-2, pp. 1-10.

Wang, C., Gold, B. G., Kaler, L. J., Yu, X., Afentoulis, M. E., Burrows, G. G., Vandenbark, A. A., Bourdette, D. N., & Offner, H. 2006a, "Antigen-specific therapy promotes repair of myelin and axonal damage in established EAE", J.Neurochem., vol. 98, no. 6, pp. 1817-1827.

Wang, E. Y., Gao, H., Salter-Cid, L., Zhang, J., Huang, L., Podar, E. M., Miller, A., Zhao, J., O'rourke, A., & Linnik, M. D. 2006b, "Design, synthesis, and biological evaluation of semicarbazide-sensitive amine oxidase (SSAO) inhibitors with anti-inflammatory activity", J.Med.Chem., vol. 49, no. 7, pp. 2166-2173.

Wang, G. Y., Sun, B., Kong, Q. F., Zhang, Y., Li, R., Wang, J. H., Wang, D. D., Lv, G. X., & Li, H. L. 2008a, "IL-17 eliminates the therapeutic effects of myelin basic protein-induced nasal tolerance in experimental autoimmune encephalomyelitis by activating IL-6", Scand J Immunol, vol. 68, no. 6, pp. 589-597.

Wang, G.-J., Li, S.-Y., & Xu, J. 1992, "Effect of A Poriatin on the Induction of Experimental Autoimmune Encephalomyelitis in Wistar Rats", Zhongguo Kangshengsu Zazhi, vol. 17, no. 1, pp. 38-41.

Wang, J., Takeuchi, H., Sonobe, Y., Jin, S., Mizuno, T., Miyakawa, S., Fujiwara, M., Nakamura, Y., Kato, T., Muramatsu, H., Muramatsu, T., & Suzumura, A. 2008b, "Inhibition of midkine alleviates experimental autoimmune encephalomyelitis through the expansion of regulatory T cell population", Proc.Natl.Acad.Sci.U.S.A, vol. 105, no. 10, pp. 3915-3920.

Wang, J., Wang, G., Sun, B., Li, H., Mu, L., Wang, Q., Li, G., Shi, L., Jin, L., & Kostulas, N. 2008c, "Interleukin-27 suppresses experimental autoimmune encephalomyelitis during bone marrow stromal cell treatment", J Autoimmun, vol. 30, no. 4, pp. 222-229.

Wang, T., Nagai, H., Bouda, K., Matsuura, S., Takaoka, Y., Niwa, S., Homma, T., Tanaka, H., & Shudo, K. 2000a, "Effect of selective IL-6 inhibitor Am-80 on experimental autoimmune encephalomyelitis in DA rats", Acta Pharmacol Sin., vol. 21, no. 11, pp. 967-976.

Wang, T., Niwa, S., Bouda, K., Matsuura, S., Homma, T., Shudo, K., & Nagai, H. 2000b, "The effect of Am-80, one of retinoids derivatives on experimental allergic encephalomyelitis in rats", Life Sci., vol. 67, no. 15, pp. 1869-1879.

Wang, X. S., Chen, Y. Y., Shang, X. F., Zhu, Z. G., Chen, G. Q., Han, Z., Shao, B., Yang, H. M., Xu, H. Q., Chen, J. F., & Zheng, R. Y. 2009, "Idazoxan attenuates spinal cord injury by enhanced astrocytic activation and reduced microglial activation in rat experimental autoimmune encephalomyelitis", Brain Res, vol. 1253, pp. 198-209.

Wang, Y., Mei, Y., Feng, D., & Xu, L. 2008d, "Triptolide modulates T-cell inflammatory responses and ameliorates experimental autoimmune encephalomyelitis", Journal of Neuroscience Research.86(11)()(pp 2441-2449), 2008.Date of Publication: 15 Aug 2008. no. 11, pp. 2441-2449.

Wang, Z., Qiu, J., Guo, T. B., Liu, A., Wang, Y., Li, Y., & Zhang, J. Z. 2007, "Anti-inflammatory properties and regulatory mechanism of a novel derivative of artemisinin in experimental autoimmune encephalomyelitis", J.Immunol., vol. 179, no. 9, pp. 5958-5965.

Wang, Z. Y., He, B., Qiao, J., & Link, H. 1995, "Suppression of experimental autoimmune myasthenia gravis and experimental allergic encephalomyelitis by oral administration of acetylcholine receptor and myelin basic protein: double tolerance", J.Neuroimmunol., vol. 63, no. 1, pp. 79-86.

Warren, J., Sacksteder, M. R., & Thuning, C. A. 1978, "Oxygen immunosuppression: modification of experimental allergic encephalomyelitis in rodents", J.Immunol., vol. 121, no. 1, pp. 315-320.

Watnick, A. S. & Sabin, C. 1972, "The effect of clonixin and betamethasone on adjuvant-induced arthritis and experimental allergic encephalomyelitis in rats", Jpn.J.Pharmacol., vol. 22, no. 6, pp. 741-748.

Wauben, M. H., Boog, C. J., van der, Z. R., Joosten, I., Schlief, A., & van, E. W. 1992, "Disease inhibition by major histocompatibility complex binding peptide analogues of disease-associated epitopes: more than blocking alone", J.Exp.Med., vol. 176, no. 3, pp. 667-677.

Webb, C., Teitelbaum, D., Herz, A., Arnon, R., & Sela, M. 1976, "Molecular requirements involved in suppression of EAE by synthetic basic copolymers of amino acids", Immunochemistry., vol. 13, no. 4, pp. 333-337.

Webb, M., Tham, C. S., Lin, F. F., Lariosa-Willingham, K., Yu, N., Hale, J., Mandala, S., Chun, J., & Rao, T. S. 2004, "Sphingosine 1-phosphate receptor agonists attenuate relapsing-remitting experimental autoimmune encephalitis in SJL mice", J.Neuroimmunol., vol. 153, no. 1-2, pp. 108-121.

Weber, F. & Hempel, K. 1987, "Protection against experimental allergic encephalomyelitis with complete Freund's adjuvant is unaffected by ionizing irradiation", Int.Arch.Allergy Appl.Immunol., vol. 83, no. 2, pp. 174-177.

Weber, F. & Hempel, K. 1989, "Protection against experimental allergic encephalomyelitis with complete Freund's adjuvant is unaffected by prostaglandin synthesis inhibition", Int.Arch.Allergy Appl.Immunol., vol. 89, no. 2-3, pp. 242-245.

Weber, F., Meyermann, R., & Hempel, K. 1991, "Experimental allergic encephalomyelitis-prophylactic and therapeutic treatment with the cyclooxygenase inhibitor piroxicam (Feldene)", Int.Arch.Allergy Appl.Immunol., vol. 95, no. 2-3, pp. 136-141.

Weber, M. S., Prod'homme, T., Youssef, S., Dunn, S. E., Rundle, C. D., Lee, L., Patarroyo, J. C., Stuve, O., Sobel, R. A., Steinman, L., & Zamvil, S. S. 2007, "Type II monocytes modulate T cell-mediated central nervous system autoimmune disease", Nat.Med., vol. 13, no. 8, pp. 935-943.

Wegmann, K. W., Wagner, C. R., Whitham, R. H., & Hinrichs, D. J. 2008, "Synthetic Peptide dendrimers block the development and expression of experimental allergic encephalomyelitis", J Immunol, vol. 181, no. 5, pp. 3301-3309.

Wegner, C., Stadelmann, C., Kaye, J., Fine, T., Mayk, A., Raymond, E., & Bruck, W. 2008, "Laquinimod given before and after disease onset reduces inflammatory cell infiltration and demyelination in experimental autoimmune encephalomyelitis", Multiple Sclerosis, vol. 14, p. S276.

Wegner, C., Stadeltmann, C., Kaye, J., Fine, T., Mayk, A., Raymond, E., & Bruck, W. 2007, "Laquinimod reduces inflammation, demyelination and axonal damage in experimental autoimmune encephalomyelitis", Multiple Sclerosis, vol. 13, p. S254.

Weilbach, F. X., Chan, A., Toyka, K. V., & Gold, R. 2004, "The cardioprotector dexrazoxane augments therapeutic efficacy of mitoxantrone in experimental autoimmune encephalomyelitis", Clin.Exp.Immunol., vol. 135, no. 1, pp. 49-55.

Weinberg, A. D., Bourdette, D. N., Sullivan, T. J., Lemon, M., Wallin, J. J., Maziarz, R., Davey, M., Palida, F., Godfrey, W., Engleman, E., Fulton, R. J., Offner, H., & Vandenbark, A. A. 1996, "Selective depletion of myelin-reactive T cells with the anti-OX-40 antibody ameliorates autoimmune encephalomyelitis", Nat.Med., vol. 2, no. 2, pp. 183-189.

Weinberg, A. D., Celnik, B., Vainiene, M., Buenafe, A. C., Vandenbark, A. A., & Offner, H. 1994, "The effect of TCR V beta 8 peptide protection and therapy on T cell populations isolated from the spinal cords of Lewis rats with experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 49, no. 1-2, pp. 161-170.

Weishaupt, A., Jander, S., Bruck, W., Kuhlmann, T., Stienekemeier, M., Hartung, T., Toyka, K. V., Stoll, G., & Gold, R. 2000, "Molecular mechanisms of high-dose antigen therapy in experimental autoimmune encephalomyelitis: rapid induction of Th1-type cytokines and inducible nitric oxide synthase", J Immunol, vol. 165, no. 12, pp. 7157-7163.

Weishaupt, A., Kreiss, M., Gold, R., & Herrmann, T. 2004, "Modulation of experimental autoimmune encephalomyelitis by administration of cells expressing antigenic peptide covalently linked to MHC class II", J Neuroimmunol, vol. 152, no. 1-2, pp. 11-19.

Weishaupt, A., Kuhlmann, T., Schonrock, L. M., Toyka, K. V., Bruck, W., & Gold, R. 2002, "Effects of intravenous immunoglobulins on T cell and oligodendrocyte apoptosis in high-dose antigen therapy in

experimental autoimmune encephalomyelitis", Acta Neuropathologica.104(4)()(pp 385-390), 2002.Date of Publication: 2002. no. 4, pp. 385-390.

Weissert, R., Wiendl, H., Pfrommer, H., Storch, M. K., Schreiner, B., Barth, S., Seifert, T., Melms, A., Dichgans, J., & Weller, M. 2003, "Action of treosulfan in myelin-oligodendrocyte-glycoprotein-induced experimental autoimmune encephalomyelitis and human lymphocytes", J.Neuroimmunol., vol. 144, no. 1-2, pp. 28-37.

Wekerle, H. 1984, "Immunospecific therapy of central nervous system autoaggression with an antigen-specific T cell line", Prog.Clin.Biol.Res., vol. 146, pp. 435-441.

Welch, A. M., Holda, J. H., & Swanborg, R. H. 1980, "Regulation of Experimental Allergic Encephalo Myelitis 2. Appearance of Suppressor Cells During the Remission Phase of the Disease", Journal of Immunology, vol. 125, no. 1, pp. 186-189.

Welsh, C. T., Rose, J. W., Hill, K. E., & Townsend, J. J. 1993, "Augmentation of adoptively transferred experimental allergic encephalomyelitis by administration of a monoclonal antibody specific for LFA-1alpha", Journal of Neuroimmunology.43(1-2)()(pp 161-168), 1993.Date of Publication: 1993. no. 1-2, pp. 161-168.

Wender, M., Michalak, S., & Wygladalska-Jernas, H. 2001, "The effect of short-term treatment with interferon beta 1a on acute experimental allergic encephalomyelitis", Folia Neuropathol., vol. 39, no. 2, pp. 91-93.

Werner, P., Pitt, D., & Raine, C. S. 2000, "Glutamate excitotoxicity--a mechanism for axonal damage and oligodendrocyte death in Multiple Sclerosis?", J Neural Transm Suppl no. 60, pp. 375-385.

Werner, P., Brand-Schieber, E., & Di Rocco, A. 2003, "Blockers of L-type Ca2+ channels ameliorate disease in a mouse model of inflammatory demyelination", Neurology, vol. 60, no. 5 Supplement 1.

Westarp, M. E., Wekerle, H., Ben-Nun, A., Cohen, I. R., Vohl, M. L., & Przuntek, H. 1987, "T lymphocyte line-mediated experimental allergic encephalomyelitis--a pharmacologic model for testing of immunosuppressive agents for the treatment of autoimmune central nervous system disease", J.Pharmacol.Exp.Ther., vol. 242, no. 2, pp. 614-620.

Weston, P. G. & Johnston, P. V. 1978, "Incidence and severity of experimental allergic encephalomyelitis and cerebral prostaglandin synthesis in essential fatty acid deficient and aspirin-treated rats", Lipids, vol. 13, no. 12, pp. 867-872.

Whitacre, C., Apseloff, G., Cox, K., Matkovic, V., Jewell, S., & Gerber, N. 1992, "Suppression of experimental autoimmune encephalomyelitis by gallium nitrate", J.Neuroimmunol., vol. 39, no. 1-2, pp. 175-181.

Whitacre, C. C., Gienapp, I. E., Orosz, C. G., & Bitar, D. M. 1991, "Oral tolerance in experimental autoimmune encephalomyelitis. III. Evidence for clonal anergy", J.Immunol., vol. 147, no. 7, pp. 2155-2163.

White, S. R., Black, P. C., Samathanam, G. K., & Paros, K. C. 1992, "Prazosin suppresses development of axonal damage in rats inoculated for experimental allergic encephalomyelitis", J.Neuroimmunol., vol. 39, no. 3, pp. 211-218.

White, S. R., Samathanam, G., Black, P., & Owada, K. 1990, "Prazosin Treatment Attenuates Monoaminergic Axonal Damage During Development of Eae in Rats", Society for Neuroscience Abstracts, vol. 16, no. 2.

Whitham, R. H., Kotzin, B. L., Buenafe, A. C., Weinberg, A. D., Jones, R. E., Hashim, G. A., Hoy, C. M., Vandenbark, A. A., & Offner, H. 1993, "Treatment of relapsing experimental autoimmune encephalomyelitis with T cell receptor peptides", J.Neurosci.Res., vol. 35, no. 2, pp. 115-128.

Whitham, R. H., Wingett, D., Wineman, J., Mass, M., Wegmann, K., Vandenbark, A., & Offner, H. 1996, "Treatment of relapsing autoimmune encephalomyelitis with T cell receptor V beta-specific antibodies when proteolipid protein is the autoantigen", J.Neurosci.Res., vol. 45, no. 2, pp. 104-116.

Wiegmann, K., Muthyala, S., Kim, D. H., Arnason, B. G., & Chelmicka-Schorr, E. 1995, "Beta-adrenergic agonists suppress chronic/relapsing experimental allergic encephalomyelitis (CREAE) in Lewis rats", J.Neuroimmunol., vol. 56, no. 2, pp. 201-206.

Wiemann, B., Van, G. Y., Danilenko, D. M., Yan, Q., Matheson, C., Munyakazi, L., Ogenstad, S., & Starnes, C. O. 1998, "Combined treatment of acute EAE in Lewis rats with TNF-binding protein and interleukin-1 receptor antagonist", Exp.Neurol., vol. 149, no. 2, pp. 455-463.

Wildbaum, G. & Karin, N. 1999, "Augmentation of natural immunity to a pro-inflammatory cytokine (TNF-alpha) by targeted DNA vaccine confers long-lasting resistance to experimental autoimmune encephalomyelitis", Gene Ther., vol. 6, no. 6, pp. 1128-1138.

Wildbaum, G., Netzer, N., & Karin, N. 2002, "Plasmid DNA encoding IFN-gamma-inducible protein 10 redirects antigen-specific T cell polarization and suppresses experimental autoimmune encephalomyelitis", J.Immunol., vol. 168, no. 11, pp. 5885-5892.

Wildbaum, G., Westermann, J., Maor, G., & Karin, N. 2000, "A targeted DNA vaccine encoding fas ligand defines its dual role in the regulation of experimental autoimmune encephalomyelitis", J Clin Invest, vol. 106, no. 5, pp. 671-679.

Wildfeuer, A., Neu, I. S., Safayhi, H., Metzger, G., Wehrmann, M., Vogel, U., & Ammon, H. P. 1998, "Effects of boswellic acids extracted from a herbal medicine on the biosynthesis of leukotrienes and the course of experimental autoimmune encephalomyelitis", Arzneimittelforschung., vol. 48, no. 6, pp. 668-674.

Willenborg, D. O. 1987, "Protection against allergic encephalomyelitis by recruitment of myelin basic protein reactive lymphocytes into a single lymph node", J.Neurol.Sci., vol. 77, no. 2-3, pp. 193-201.

Willenborg, D. O., Bowern, N. A., Danta, G., & Doherty, P. C. 1988, "Inhibition of allergic encephalomyelitis by the iron chelating agent desferrioxamine: differential effect depending on type of sensitizing encephalitogen", J.Neuroimmunol., vol. 17, no. 2, pp. 127-135.

Willenborg, D. O., Fordham, S. A., Cowden, W. B., & Ramshaw, I. A. 1995, "Cytokines and murine autoimmune encephalomyelitis: inhibition or enhancement of disease with antibodies to select cytokines, or by delivery of exogenous cytokines using a recombinant vaccinia virus system", Scand.J.Immunol., vol. 41, no. 1, pp. 31-41.

Willenborg, D. O. & Higgins, T. J. 1981, "Liposomes containing myelin basic protein (BP) suppress but do not induce allergic encephalomyelitis in Lewis rats", Aust.J Exp Biol Med Sci, vol. 59, no. Pt 2, pp. 135-141.

Willenborg, D. O. & Parish, C. R. 1988, "Inhibition of allergic encephalomyelitis in rats by treatment with sulfated polysaccharides", J.Immunol., vol. 140, no. 10, pp. 3401-3405.

Willenborg, D. O., Parish, C. R., & Cowden, W. B. 1989a, "Inhibition of experimental allergic encephalomyelitis by the alpha-glucosidase inhibitor castanospermine", J.Neurol.Sci., vol. 90, no. 1, pp. 77-85.

Willenborg, D. O., Parish, C. R., & Cowden, W. B. 1989b, "Phosphosugars are potent inhibitors of central nervous system inflammation", FASEB J., vol. 3, no. 8, pp. 1968-1971.

Willenborg, D. O., Simmons, R. D., Tamatani, T., & Miyasaka, M. 1993, "ICAM-1-dependent pathway is not critically involved in the inflammatory process of autoimmune encephalomyelitis or in cytokine-induced inflammation of the central nervous system", J Neuroimmunol, vol. 45, no. 1-2, pp. 147-154.

Willenborg, D. O., Sjollema, P., & Danta, G. 1986, "Immunoglobulin deficient rats as donors and recipients of effector cells of allergic encephalomyelitis", J.Neuroimmunol., vol. 11, no. 2, pp. 93-103.

Willenborg, D. O., Staykova, M. A., & Miyasaka, M. 1996, "Short term treatment with soluble neuroantigen and anti-CD11a (LFA-1) protects rats against autoimmune encephalomyelitis: treatment abrogates autoimmune disease but not autoimmunity", J.Immunol., vol. 157, no. 5, pp. 1973-1980.

Williams, K. C., Zhao, W., Politopoulou, G., Male, D., & Hickey, W. F. 2000, "Inhibition of experimental allergic encephalomyelitis with an antibody that recognizes a novel antigen expressed on lymphocytes, endothelial cells, and microglia", Lab Invest, vol. 80, no. 3, pp. 313-326.

Wong, C. W., Seow, W. K., & Thong, Y. H. 1992, "Comparative effects of tetrandrine and berbamine on acute and relapsing experimental allergic encephalitis in Lewis rats", Int.Arch.Allergy Immunol., vol. 97, no. 1, pp. 31-36.

Worku, H. G., Feliberti, J., Kesner, L., Stracher, A., & Mokhtarian, F. 2008, "Prevention of axonal injury using calpain inhibitor in chronic progressive experimental autoimmune encephalomyelitis", Brain Research.1236(C)()(pp 206-215), 2008.Date of Publication: 21 Oct 2008. no. C, pp. 206-215.

Woyciechowska, J., Goldstein, A. L., & Driscoll, B. 1985, "Experimental allergic encephalomyelitis in guinea pigs. Influence of thymosin fraction V on the disease", J.Neuroimmunol., vol. 7, no. 4, pp. 215-219.

Wraith, D. C., Smilek, D. E., Mitchell, D. J., Steinman, L., & McDevitt, H. O. 1989, "Antigen recognition in autoimmune encephalomyelitis and the potential for peptide-mediated immunotherapy", Cell, vol. 59, no. 2, pp. 247-255.

Xian, C. J., Simmons, R. D., Willenborg, D. O., Vandenbark, A. A., Hashim, G. A., & Carnegie, P. R. 1995, "Studies on T-cell receptors involved in experimental autoimmune encephalomyelitis using the complementary peptide recognition approach", J.Neurosci.Res., vol. 41, no. 5, pp. 620-627.

Xiao, B. G., Bai, X. F., Zhang, G. X., & Link, H. 1998, "Suppression of acute and protracted-relapsing experimental allergic encephalomyelitis by nasal administration of low-dose IL-10 in rats", J.Neuroimmunol., vol. 84, no. 2, pp. 230-237.

Xiao, B. G., Huang, Y. M., Yang, J. S., Xu, L. Y., & Link, H. 2001, "Bone marrow-derived dendritic cells from experimental allergic encephalomyelitis induce immune tolerance to EAE in Lewis rats", Clin.Exp.Immunol., vol. 125, no. 2, pp. 300-309.

Xiao, B. G., Wu, X. C., Yang, J. S., Xu, L. Y., Liu, X., Huang, Y. M., Bjelke, B., & Link, H. 2004, "Therapeutic potential of IFN-gamma-modified dendritic cells in acute and chronic experimental allergic encephalomyelitis", Int.Immunol., vol. 16, no. 1, pp. 13-22.

Xie, C., Alcaide, P., Geisbrecht, B. V., Schneider, D., Herrmann, M., Preissner, K. T., Luscinskas, F. W., & Chavakis, T. 2006, "Suppression of experimental autoimmune encephalomyelitis by extracellular adherence protein of Staphylococcus aureus", J.Exp.Med., vol. 203, no. 4, pp. 985-994.

Xu, B., Haviernik, P., Wolfraim, L. A., Bunting, K. D., & Scott, D. W. 2006, "Bone marrow transplantation combined with gene therapy to induce antigen-specific tolerance and ameliorate EAE", Mol.Ther., vol. 13, no. 1, pp. 42-48.

Xu, B. & Scott, D. W. 2004, "A novel retroviral gene therapy approach to inhibit specific antibody production and suppress experimental autoimmune encephalomyelitis induced by MOG and MBP", Clin.Immunol., vol. 111, no. 1, pp. 47-52.

Xu, L., Huang, Y., Yang, J., van der Meide, P. H., Levi, M., Wahren, B., Link, H., & Xiao, B. 1999, "Dendritic cell-derived nitric oxide is involved in IL-4-induced suppression of experimental allergic encephalomyelitis (EAE) in Lewis rats", Clin Exp Immunol, vol. 118, no. 1, pp. 115-121.

Xu, L. Y., Huang, Y. M., Yang, J. S., van der Meide, P. H., Link, H., & Xiao, B. G. 2000a, "Suppression of ongoing experimental allergic encephalomyelitis (EAE) in Lewis rats: synergistic effects of myelin basic protein (MBP) peptide 68-86 and IL-4", Clin.Exp.Immunol., vol. 120, no. 3, pp. 526-531.

Xu, L. Y., Ishikawa, M., Huang, Y. M., Levi, M., van der Meide, P. H., Wahren, B., Link, H., & Xiao, B. G. 2000b, "The complexicity of cytokine treatment in ongoing EAE induced with MBP peptide 68-86 in Lewis rats", Clin.Immunol., vol. 95, no. 1 Pt 1, pp. 70-78.

Xu, L. Y., Yang, J. S., Huang, Y. M., Levi, M., Link, H., & Xiao, B. G. 2000c, "Combined nasal administration of encephalitogenic myelin basic protein peptide 68-86 and IL-10 suppressed incipient experimental allergic encephalomyelitis in Lewis rats", Clin.Immunol., vol. 96, no. 3, pp. 205-211.

Xu, L. Y., Yang, J. S., Link, H., & Xiao, B. G. 2001, "SIN-1, a nitric oxide donor, ameliorates experimental allergic encephalomyelitis in Lewis rats in the incipient phase: the importance of the time window", J.Immunol., vol. 166, no. 9, pp. 5810-5816.

Xu, S., Jordan, E. K., Li, W., Yang, Y., Chesnick, S. A., Webster, H. D., Brocke, S., Quigley, L., McFarland, H. F., & Frank, J. A. 1998, "In vivo three-dimensional MR microscopy of mice with chronic relapsing experimental autoimmune encephalomyelitis after treatment with insulin-like growth factor-I", AJNR Am.J.Neuroradiol., vol. 19, no. 4, pp. 653-658.

Yamamura, T., Da-Lin, Y., Satoh, J., & Tabira, T. 1987, "Suppression of experimental allergic encephalomyelitis by 15-deoxyspergualin", J.Neurol.Sci., vol. 82, no. 1-3, pp. 101-110.

Yan, S. S., Wu, Z. Y., Zhang, H. P., Furtado, G., Chen, X., Yan, S. F., Schmidt, A. M., Brown, C., Stern, A., LaFaille, J., Chess, L., Stern, D. M., & Jiang, H. 2003, "Suppression of experimental autoimmune encephalomyelitis by selective blockade of encephalitogenic T-cell infiltration of the central nervous system", Nat.Med., vol. 9, no. 3, pp. 287-293.

Yang, J. S., Xu, L. Y., Xiao, B. G., Hedlund, G., & Link, H. 2004, "Laquinimod (ABR-215062) suppresses the development of experimental autoimmune encephalomyelitis, modulates the Th1/Th2 balance and induces the Th3 cytokine TGF-beta in Lewis rats", J.Neuroimmunol., vol. 156, no. 1-2, pp. 3-9.

Yao, D., Liu, X., Hudson, L., & Webster, H. 1995a, "IGF-I treatment of EAE reduces demyelination and upregulates oligodendroglial gene expression of myelin-related proteins", Journal of Neurochemistry, vol. 64, no. SUPPL. 1.

Yao, D. L., Liu, X., Hudson, L. D., & Webster, H. D. 1995b, "Insulin-like growth factor I treatment reduces demyelination and up-regulates gene expression of myelin-related proteins in experimental autoimmune encephalomyelitis", Proc.Natl.Acad.Sci.U.S.A, vol. 92, no. 13, pp. 6190-6194.

Yasuda, C. L., Al Sabbagh, A., Oliveira, E. C., Diaz-Bardales, B. M., Garcia, A. A., & Santos, L. M. 1999, "Interferon beta modulates experimental autoimmune encephalomyelitis by altering the pattern of cytokine secretion", Immunol Invest, vol. 28, no. 2-3, pp. 115-126.

Yednock, T. A., Cannon, C., Fritz, L. C., Sanchez-Madrid, F., Steinman, L., & Karin, N. 1992, "Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha 4 beta 1 integrin", Nature, vol. 356, no. 6364.

Yehuda, S., Rabinovitz, S., Mostofsky, D. I., Huberman, M., & Sredni, B. 1997, "Essential fatty acid preparation improves biochemical and cognitive functions in experimental allergic encephalomyelitis rats", Eur.J.Pharmacol., vol. 328, no. 1, pp. 23-29.

Yin, P., Luby, T. M., Chen, H., Etemad-Moghadam, B., Lee, D., Aziz, N., Ramstedt, U., & Hedley, M. L. 2003, "Generation of expression constructs that secrete bioactive alphaMSH and their use in the treatment of experimental autoimmune encephalomyelitis", Gene Ther., vol. 10, no. 4, pp. 348-355.

Youssef, S., Wildbaum, G., & Karin, N. 1999, "Prevention of experimental autoimmune encephalomyelitis by MIP-1alpha and MCP-1 naked DNA vaccines", J Autoimmun, vol. 13, no. 1, pp. 21-29.

Youssef, S., Wildbaum, G., Maor, G., Lanir, N., Gour-Lavie, A., Grabie, N., & Karin, N. 1998, "Long-lasting protective immunity to experimental autoimmune encephalomyelitis following vaccination with naked DNA encoding C-C chemokines", J Immunol, vol. 161, no. 8, pp. 3870-3879.

Yu, C.-Y., Zheng, H.-Z., & Fan, R.-M. 2006, "Alterations of CD4⁺ and CD8⁺ in experimental allergic encephalomyelitis and its significance in rats. [Chinese]", Chinese Journal of Clinical Rehabilitation.10(34)()(pp 76-78), 2006.Date of Publication: 15 Sep 2006. no. 34, pp. 76-78.

Yu, M., Nishiyama, A., Trapp, B. D., & Tuohy, V. K. 1996, "Interferon-beta inhibits progression of relapsing-remitting experimental autoimmune encephalomyelitis", J.Neuroimmunol., vol. 64, no. 1, pp. 91-100.

Yu, R. K., Kusunoki, S., & Kim, J. H. 1987, "Augmentation of Demyelination by Asialo-Gm1 in Experimental Autoimmune Encephalomyelitis", Journal of Neuroimmunology, vol. 16, no. 1.

Yura, M., Takahashi, I., Terawaki, S., Hiroi, T., Kweon, M. N., Yuki, Y., & Kiyono, H. 2001, "Nasal administration of cholera toxin (CT) suppresses clinical signs of experimental autoimmune encephalomyelitis (EAE)", Vaccine, vol. 20, no. 1-2, pp. 134-139.

Zamora, A., Matejuk, A., Silverman, M., Vandenbark, A. A., & Offner, H. 2002, "Inhibitory effects of incomplete Freund's adjuvant on experimental autoimmune encephalomyelitis", Autoimmunity, vol. 35, no. 1, pp. 21-28.

Zappia, E., Casazza, S., Pedemonte, E., Benvenuto, F., Bonanni, I., Gerdoni, E., Giunti, D., Ceravolo, A., Cazzanti, F., Frassoni, F., Mancardi, G., & Uccelli, A. 2005, "Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy", Blood.106(5)()(pp 1755-1761), 2005.Date of Publication: 01 Sep 2005. no. 5, pp. 1755-1761.

Zargari, M. & Allameh, A. 2008, "Protective effects of uric acid against experimental allergic encephalomyelitis-induced oxidative stress", Febs Journal, vol. 275, no. Suppl. 1.

Zargarova, T., Kulakova, O., Prassolov, V., Zharmukhamedova, T., Tsyganova, V., Turobov, V., Ivanov, D., Parfenov, M., Sudomoina, M., Chernajovsky, Y., & Favorova, O. 2004, "Prevention of experimental autoimmune encephalomyelitis in DA rats by grafting primary skin fibroblasts engineered to express transforming growth factor-beta1", Clin.Exp.Immunol., vol. 137, no. 2, pp. 313-319.

Zavala, F., Abad, S., Ezine, S., Taupin, V., Masson, A., & Bach, J. F. 2002, "G-CSF therapy of ongoing experimental allergic encephalomyelitis via chemokine- and cytokine-based immune deviation", J.Immunol., vol. 168, no. 4, pp. 2011-2019.

Zehntner, S. P., Bourbonniere, L., Moore, C. S., Morris, S. J., Methot, D., St Jean, M., Lacasse, E., Hebb, A. L., Robertson, G. S., Durkin, J., Gillard, J. W., & Owens, T. 2007, "X-linked inhibitor of apoptosis regulates T cell effector function", J.Immunol., vol. 179, no. 11, pp. 7553-7560.

Zeng, Y., Gu, B., Ji, X., Ding, X., Song, C., & Wu, F. 2007a, "Sinomenine, an antirheumatic alkaloid, ameliorates clinical signs of disease in the Lewis rat model of acute experimental autoimmune encephalolmyelitis", Biol.Pharm.Bull., vol. 30, no. 8, pp. 1438-1444.

Zeng, Y., Song, C., Ding, X., Ji, X., Yi, L., & Zhu, K. 2007b, "Baicalin reduces the severity of experimental autoimmune encephalomyelitis", Braz.J Med Biol.Res, vol. 40, no. 7, pp. 1003-1010.

Zhang, B., Harness, J., Somodevilla-Torres, M. J., Hillyard, N. C., Mould, A. W., Alewood, D., Love, S. G., Alewood, P. F., Greer, J. M., Cavanagh, A. C., McCombe, P. A., & Morton, H. 2000, "Early pregnancy factor suppresses experimental autoimmune encephalomyelitis induced in Lewis rats with myelin basic protein and in SJL/J mice with myelin proteolipid protein peptide 139-151", J.Neurol.Sci., vol. 182, no. 1, pp. 5-15.

Zhang, B., Walsh, M. D., Nguyen, K. B., Hillyard, N. C., Cavanagh, A. C., McCombe, P. A., & Morton, H. 2003, "Early pregnancy factor treatment suppresses the inflammatory response and adhesion molecule expression in the spinal cord of SJL/J mice with experimental autoimmune encephalomyelitis and the delayed-type hypersensitivity reaction to trinitrochlorobenzene in normal BALB/c mice", J.Neurol.Sci., vol. 212, no. 1-2, pp. 37-46.

Zhang, G. X., Xu, H., Kishi, M., Calida, D., & Rostami, A. 2002a, "The role of IL-12 in the induction of intravenous tolerance in experimental autoimmune encephalomyelitis", J Immunol, vol. 168, no. 5, pp. 2501-2507.

Zhang, G. X., Yu, S., Gran, B., & Rostami, A. 2005a, "Glucosamine abrogates the acute phase of experimental autoimmune encephalomyelitis by induction of Th2 response", J.Immunol., vol. 175, no. 11, pp. 7202-7208.

Zhang, G.-X., Kishi, M., Xu, H., & Rostami, A. 2002b, "Mature bone marrow-derived dendritic cells polarize Th2 response and suppress experimental autoimmune encephalomyelitis", Multiple Sclerosis.8(6)()(pp 463-468), 2002.Date of Publication: Dec 2002. no. 6, pp. 463-468.

Zhang, J., Brodie, C., Li, Y., Zheng, X., Roberts, C., Lu, M., Gao, Q., Borneman, J., Savant-Bhonsale, S., Elias, S. B., & Chopp, M. 2009, "Bone marrow stromal cell therapy reduces proNGF and p75 expression in mice with experimental autoimmune encephalomyelitis", Journal of the Neurological Sciences.279(1-2)()(pp 30-38), 2009.Date of Publication: 15 Apr 2009. no. 1-2, pp. 30-38.

Zhang, J., Chen, J. L., Li, Y., Cui, X., Zheng, X. G., Roberts, C., Lu, M., Elias, S. B., & Chopp, M. 2008, "Niaspan treatment improves neurological functional recovery in experimental autoimmune encephalomyelitis mice", Neurobiology of Disease, vol. 32, no. 2, pp. 273-280.

Zhang, J., Li, Y., Chen, J., Cui, Y., Lu, M., Elias, S. B., Mitchell, J. B., Hammill, L., Vanguri, P., & Chopp, M. 2005b, "Human bone marrow stromal cell treatment improves neurological functional recovery in EAE mice", Exp.Neurol., vol. 195, no. 1, pp. 16-26.

Zhang, J., Li, Y., Cui, Y., Chen, J., Lu, M., Elias, S. B., & Chopp, M. 2005c, "Erythropoietin treatment improves neurological functional recovery in EAE mice", Brain Res., vol. 1034, no. 1-2, pp. 34-39.

Zhang, J., Li, Y., Lu, M., Cui, Y., Chen, J., Noffsinger, L., Elias, S. B., & Chopp, M. 2006, "Bone marrow stromal cells reduce axonal loss in experimental autoimmune encephalomyelitis mice", J.Neurosci.Res., vol. 84, no. 3, pp. 587-595.

Zhang, J. F., Huang, R., Xu, J., Jin, S. J., & Yang, Y. J. 2007, "[Protective effects of heat shock preconditioning on the experimental autoimmune encephalomyelitis rats]", Zhongguo Dang.Dai Er.Ke.Za Zhi., vol. 9, no. 6, pp. 563-566.

Zhang, Q. H., Link, H., & Xiao, B. G. 2004, "Efficacy of peripheral tolerance induced by dendritic cells is dependent on route of delivery", J Autoimmun, vol. 23, no. 1, pp. 37-43.

Zheng, X., Hu, X., Zhou, G., Lu, Z., Qiu, W., Bao, J., & Dai, Y. 2008, "Soluble egg antigen from Schistosoma japonicum modulates the progression of chronic progressive experimental autoimmune encephalomyelitis via Th2-shift response", Journal of Neuroimmunology.194(1-2)()(pp 107-114), 2008.Date of Publication: Feb 2008. no. 1-2, pp. 107-114.

Zhitnukhin, I. & Baikovskaia, M. N. 1976, "[Influence of antilymphocyte sera on the development of experimental allergic encephalomyelitis]", Biull.Eksp.Biol.Med., vol. 82, no. 7, pp. 844-847.

Zhitnukhin, I., Karasik, O. A., & Sofronov, B. N. 1978, "[Suppressant effect of unrelated antigens on the development of allergic encephalomyelitis]", Patol.Fiziol.Eksp.Ter. no. 4, pp. 58-61.

Zhitnukhin, I., Litvinenko, I. V., Bisaga, G. N., & Odinak, M. M. 1997, "[Changes in clinico-immunological indices of experimental allergic encephalomyelitis after treatment with perftoran]", Biull.Eksp.Biol.Med., vol. 123, no. 3, pp. 315-318.

Zhitnukhin, I., Sofronov, B. N., Beme, D. K., & Baikovskaia, M. N. 1978, "[Prevention of development of experimental allergic encephalomyelitis by encephalitogenic protein]", Patol.Fiziol.Eksp.Ter. no. 5, pp. 55-60.

Zhitnukhin, I., Zatepiakin, I., & Karasik, O. A. 1980, "[Prevention of experimental allergic encephalomyelitis in guinea pigs by treatment with magnetophores]", Biull.Eksp.Biol.Med., vol. 90, no. 12, pp. 713-715.

Zhou, S. R. & Whitaker, J. N. 1993, "Specific modulation of T cells and murine experimental allergic encephalomyelitis by monoclonal anti-idiotypic antibodies", J.Immunol., vol. 150, no. 4, pp. 1629-1642.

Zhu, B., Guleria, I., Khosroshahi, A., Chitnis, T., Imitola, J., Azuma, M., Yagita, H., Sayegh, M. H., & Khoury, S. J. 2006a, "Differential role of programmed death-ligand 1 [corrected] and programmed death-ligand 2 [corrected] in regulating the susceptibility and chronic progression of experimental autoimmune encephalomyelitis", J Immunol, vol. 176, no. 6, pp. 3480-3489.

Zhu, B., Luo, L., Chen, Y., Chung, S., Moore, G., Paty, D., & Cynader, M. 2000, "Intrathecal infusion of soluble Fas ligand dose-dependently reduces symptoms and maintains CNS immune privilege in a rat model of multiple sclerosis", Society for Neuroscience Abstracts, vol. 26, no. 1-2, p. Abstract-516.

Zhu, B., Luo, L., Chen, Y., Paty, D. W., & Cynader, M. S. 2002, "Intrathecal Fas ligand infusion strengthens immunoprivilege of central nervous system and suppresses experimental autoimmune encephalomyelitis", J.Immunol., vol. 169, no. 3, pp. 1561-1569.

Zhu, C. S., Hu, X. Q., Xiong, Z. J., Lu, Z. Q., Zhou, G. Y., & Wang, D. J. 2008, "Adenoviral delivery of soluble VEGF receptor 1 (sFlt-1) inhibits experimental autoimmune encephalomyelitis in dark Agouti (DA) rats", Life Sci, vol. 83, no. 11-12, pp. 404-412.

Zhu, J., Diab, A., Mustafa, M., Levi, M., Wahren, B., Bjork, J., & Hedlund, G. 1998, "Linomide suppresses chronic-relapsing experimental autoimmune encephalomyelitis in DA rats", J.Neurol.Sci., vol. 160, no. 2, pp. 113-120.

Zhu, Y.-N., Zhong, X.-G., Feng, J.-Q., Yang, Y.-F., Fu, Y.-F., Ni, J., Liu, Q.-F., Tang, W., Zhao, W.-M., & Zuo, J.-P. 2006b, "Periplocoside E inhibits experimental allergic encephalomyelitis by suppressing interleukin 12-dependent CCR5 expression and interferon-gamma- dependent CXCR3 expression in T lymphocytes", Journal of Pharmacology and Experimental Therapeutics.318(3)()(pp 1153-1162), 2006.Date of Publication: 2006. no. 3, pp. 1153-1162.

Zinn, K. H., Huber, H., Mach, W., & Stickl, H. 1975, "[Anti-inflammatory activity of a new quinoid polyradical (FL-70)]", Arzneimittelforschung., vol. 25, no. 1, pp. 71-77.

Zinser, E., Lechmann, M., Golka, A., Lutz, M. B., & Steinkasserer, A. 2004, "Prevention and treatment of experimental autoimmune encephalomyelitis by soluble CD83", J.Exp.Med., vol. 200, no. 3, pp. 345-351.

Zinser, E., Turza, N., & Steinkasserer, A. 2004, "CNI-1493 mediated suppression of dendritic cell activation in vitro and in vivo", Immunobiology, vol. 209, no. 1-2, pp. 89-97.

Zozulya, A. L., Ortler, S., Lee, J., Weidenfeller, C., Sandor, M., Wiendl, H., & Fabry, Z. 2009, "Intracerebral dendritic cells critically modulate encephalitogenic versus regulatory immune responses in the CNS", J Neurosci, vol. 29, no. 1, pp. 140-152.

Appendix 2. Quality of preclinical EAE studies

(1) Peer reviewed publication
(2) Random allocation to group
(3) Blinded assessment of outcome
(4) Sample size calculation
(5) Compliance with animal welfare regulations
(6) Statement of a potential conflict of interest

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Abdarasulova,I	2007	+				+		2
Abramsky,O	1982	+						1
Abramsky,O	1987	+						1
Abramsky,O	1994	+						1
Abreu,S	1982	+						1
Abreu,S	1986	+						1
Achiron,A	1994	+						1
Achiron,A	1994	+		+				2
Achiron,A	2000	+						1
Achiron,A	2000	+						1
Adams,R	2007						+	1
Adamus,G	2001	+				+		2
Adda,D	1977	+						1
Agnello,D	2000	+				+		2
Agnello,D	2002	+		+		+		3
Aharoni,R	1993	+						1
Aharoni,R	2005	+				+	+	3
Aharoni,R	2005	+						1
Aharoni,R	2008	+		+		+	+	4
Aharonowiz,M	2008	+		+				2
Ahmed,Z	2001	+						1
Aikawa,Y	1998	+		+				2
Akabane,H	2004	+				+		2
Akiyama,K	1981	+						1
Aktas,O	2002							0
Aktas,O	2003	+	+	+		+		4
Aktas,O	2004	+	+	+		+		4
Aktas,O	2005							0
Aktas,O	2005	+		+				2
Al-Sabbagh,A	1994	+				+		2
Al-Sabbagh,A	1996	+		+		+	+	4
Al-Sabbagh,A	1996	+						1
Alvord,E	1979	+	+	+				3
Anane,R	2003	+				+		2
Anderton,S	1998	+	+					2
Anghelescu,N	1979	+						1
Aoyagi,T	1984	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Archelos,J	1993	+		+		+		3
Archelos,J	1998	+				+		2
Arima,T	1996	+		+		+		3
Arnason,B	1969	+		+				2
Aroeira,L	2006	+				+		2
Arredondo,L	2001	+		+		+		3
Athanasas-Platsis,S	2003	+				+		2
Auci,D	2005	+				+		2
Avrilionis,k	1991	+						1
Babington,R	1971	+						1
Badger,A	1989	+						1
Badmaev,V	1999	+		+				2
Badovinac,V	1998	+						1
Bai,X	1997	+		+				2
Bai,X	1998	+		+				2
Baker,D	1991	+						1
Baker,D	1992	+						1
Baker,D	1994	+						1
Baker,D	2000	+						1
Baker,A	2008	+						1
Bakker,J	2000	+	+	+				3
Balatoni,B	2007	+		+		+		3
Barnard,A	2009	+		+		+	+	4
Basso,A	2002						+	1
Basso,A	2007							0
Basso,A	2008	+				+	+	3
Bauer,J	1995	+						1
Bebo,B	1999	+				+		2
Bebo,B	2001	+		+		+		3
Bebo,B	2009	+				+		2
Bechtold,D	2002							0
Bechtold,D	2004	+	+	+		+		4
Bechtold,D	2006	+	+	+		+		4
Beck,F	1975	+						1
Becklund,B	2009	+				+		2
Bedoui,S	2003	+						1
Beeton,C	2001	+						1
Beeton,C	2001	+						1
Belik,I	1978	+						1
Bell,J	2008	+				+	+	3
Ben-Nun,A	1981	+						1
Ben-Nun,A	1981	+						1
Ben-Nun,A	1990	+						1
Ben-Nun,A	1993	+						1
Ben-Nun,A	1995	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Benou,C	2005	+				+	+	3
Benson,J	1999	+						1
Beraud,E	1980	+						1
Beraud,E	1982	+						1
Beraud,E	1991	+						1
Beraud,E	2006	+				+		2
Bergstrand,H	1976	+						1
Berman,Z	1977	+						1
Bernard,C	1976	+		+				2
Bernard,C	1976	+						1
Bernard,C	1977	+						1
Bernard,C	1977	+						1
Besong,G	2002	+		+				2
Beyersdorf,N	2005	+	+			+	+	4
Bhasin,M	2007	+		+		+		3
Biasi,G	1997	+		+				2
Birnbaum,G	1996	+						1
Bitar,D	1988	+						1
Blaber,S	2004	+				+		2
Black,J	2006	+				+		2
Black,J	2007	+				+		2
Blaszczyk,B	1978	+						1
Boehme,D	1978	+						1
Bolton,C	1982	+						1
Bolton,C	1982	+						1
Bolton,C	1997	+		+				2
Bolton,C	2008	+		+		+		3
Boon,L	2001	+	+	+		+		4
Borel,J	1976	+						1
Bouerat,L	2005	+						1
Bourquin,C	2000	+						1
Bourrie,B	1999	+				+		2
Bowern,N	1984	+						1
Brahmachari,S	2007	+		+		+	+	4
Brand-Schieber,E	2004	+		+		+		3
Brandt,A	1993	+						1
Branisteanu,D	1997	+	+	+				3
Brenner,T	1985	+						1
Brenner,T	1997	+		+		+		3
Brenner,T	1998	+		+		+		3
Brenner,T	1999	+		+		+		3
Bright,J	1998	+						1
Bright,J	1999	+						1
Brini,E	2008			+				1
Brini,E	2009	+	+			+		3

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Brinkman,C	1985	+						1
Broberg,E	2001	+				+		2
Brocke,S	1999	+				+		2
Brod,S	1991	+	+	+		+		4
Brod,S	1994	+		+				2
Brod,S	1995	+		+		+		3
Brod,S	1995	+		+		+		3
Brod,S	1999	+						1
Brod,S	1999	+		+	+			3
Brod,S	2007	+		+				2
Brod,S	2008	+		+				2
Brodmerkel,C	2005	+				+	+	3
Brok,H	2002	+	+	+		+		4
Brooks,J	2002	+						1
Brosnan,C	1980	+						1
Brosnan,C	1985	+						1
Brosnan,C	1986	+		+				2
Brostoff,S	1984	+		+				2
Brostoff,S	1986	+		+				2
Brostoff,S	1986	+		+				2
Brostoff,S	1988	+		+				2
Brucchieri,A	1966	+						1
Bruck,W	2007							0
Brundula,V	2002	+				+		2
Brunmark,C	2002	+						1
Bucher,A	1996	+						1
Buenafe,A	1995	+						1
Buenafe,A	2007	+				+		2
Burrows,G	1998	+				+		2
Burrows,G	2000	+				+		2
Burt,R	1995	+						1
Burt,R	1996							0
Burt,R	1997							0
Burt,R	1998	+		+				2
Butovsky,O	2006	+		+		+	+	4
Butzkueven,H	2002	+				+	+	3
Butzkueven,H	2006	+	+	+				3
Bynoe,M	2003	+						1
Byrne,F	2009	+				+	+	3
Cabranes,A	2005	+				+		2
Cabrelle,A	2008	+						1
Camelo,S	2005	+		+				2
Cammisuli,S	1984	+						1
Cannella,B	1993	+		+		+		3
Cannella,B	1996	+	+	+		+		4

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Cannella,B	1998	+		+		+		3
Cannella,B	2000	+		+				2
Cannella,B	2003	+		+		+		3
Canonico,P	1993	+						1
Cantorna,M	1996	+				+		2
Cantorna,M	1999	+						1
Cantorna,M	2000	+		+				2
Cao,L	2000	+		+				2
Caputo,D	1978	+						1
Carlson,R	1986	+						1
Cash,E	1994	+						1
Caspary,E	1977	+						1
Cassiani-Ingoni,R	2007	+				+		2
Castedo,M	1993	+						1
Cavaletti,G	2001	+		+		+		3
Cavaletti,G	2004	+	+	+		+		4
Cavaletti,G	2004	+	+			+		3
Ceroni,M	1988	+	+					2
Chabannes,D	1992	+						1
Chabannes,D	2002	+						1
Chakravarti,S	2005	+				+	+	3
Chan,J	2008	+				+	+	3
Chan,J	2008	+		+		+	+	4
Chaudhary,P	2006	+	+	+		+		4
Chelmicka-Schorr,E	1988	+		+				2
Chelmicka-Schorr,E	1989	+						1
Chelmicka-Schorr,E	1998	+		+				2
Chelmicka-Szorc,E	1972	+						1
Chelmicka-Szorc,E	1975	+		+				2
Chen,Y	1994	+						1
Chen,C	2001	+						1
Chen,C	2004	+						1
Chen,X	2006	+		+		+	+	4
Chen,Y	2006	+					+	2
Chen,W	2007	+						1
Chen,X	2009	+	+	+		+		4
Cheng,X	2007	+		+		+		3
Chiarugi,A	2002	+				+		2
Chora,A	2007	+	+			+	+	4
Chorny,A	2006	+						1
Chou,F	1979	+						1
Chow,L	1988	+						1
Chung,D	2007	+				+		2
Ciusani,E	2001	+		+		+		3
Claudio,L	1992	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Clayton,J	1989	+						1
Clements,J	1997	+						1
Coates,A	1974	+						1
Columba-Cabezas,S	2006	+				+		2
Constantin,G	1998	+						1
Constantin,G	1999	+	+					2
Constantinescu,C	1995	+						1
Constantinescu,C	1995							0
Constantinescu,C	1997	+		+				2
Constantinescu,C	1998	+		+				2
Constantinescu,C	2001	+						1
Correale,J	1991	+						1
Cowing,C	1974	+						1
Craner,M	2005	+		+		+		3
Cretney,E	2005	+		+		+		3
Crisi,G	1995	+						1
Critchfield,J	1994	+				+		2
Cross,A	1994	+		+		+		3
Cross,A	1995	+		+		+		3
Cross,A	1998							0
Cross,A	1999	+	+	+		+		4
Cross,A	2000	+		+				2
Croxford,J	1998	+						1
Croxford,J	2000	+				+		2
Croxford,J	2001	+						1
Croxford,J	2008	+				+		2
Cua,D	2001	+	+					2
Dahlen,E	2000	+				+		2
Dai,L	1982	+						1
Dal Canto,R	1998	+						1
Danilov,A	2005	+				+		2
Danusevich,I	1975	+						1
Dasgupta,S	2003	+		+		+		3
Dasgupta,S	2007	+		+		+		3
de Brito,F	1984	+						1
de Graaf,K	2004	+				+		2
de Lago,E	2004	+				+		2
de Lago,E	2006	+				+		2
De Rosa,V	2006	+		+		+	+	4
De Sarno,P	2008	+				+	+	3
De Vries,J	2004							0
Degano,A	1998	+						1
Degano,A	2004	+				+		2
Deguchi,K	1990	+						1
Deguchi,K	1991	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Deloire,M	2004	+	+			+		3
Denkinger,C	2003	+	+	+		+		4
Desai,S	1989	+						1
Desplat-Jego,S	2005	+		+				2
Devaux,B	1997	+						1
Devaux,J	2004	+						1
DeVry,C	2004	+		+		+		3
Di Marco,R	2001	+		+				2
Di Marco,R	2001	+	+	+				3
Diab,A	1998	+						1
Diab,A	2001	+				+		2
Diab,A	2002	+				+		2
Diaz-Bardales,M	2001	+						1
Diem,R	2003	+		+		+		3
Diem,R	2005	+	+	+		+		4
Dietsch,G	1989	+				+		2
Dijkstra,C	1988	+						1
Dijkstra,C	1994	+						1
Dijkstra,S	2008	+		+		+		3
DiMartino,M	1988	+						1
Dimitrijevic,M	2007	+	+		+	+		4
Ding,M	1998	+		+		+		3
Driscoll,B	1974	+	+	+				3
Driscoll,B	1976	+						1
Driscoll,B	1982	+		+				2
Du,C	2000	+	+					2
Du,C	2001	+						1
Duckers,H	1996	+	+					2
Duckers,H	1997	+	+	+				3
Duckers,H	1998	+		+				2
Duong,T	1992	+		+				2
Duong,T	1994	+		+				2
Duplan,V	2002	+				+		2
Duplan,V	2003	+				+		2
Duplan,V	2006	+				+	+	3
Dussault,N	2001							0
Edling,A	2001	+		+				2
Edling,A	2002	+	+	+		+		4
Einstein,E	1972	+						1
Einstein,O	2003	+		+		+		3
Einstein,O	2005	+		+		+		3
Einstein,O	2006	+				+		2
El-Gouhary,I	2005	+	+	+				3
Elkin,R	1987							0
Elliott,G	1973	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Elliott,G	1973	+		+				2
Elliott,E	1996	+				+		2
Elliott,E	1997	+		+		+		3
Elliott,E	1997	+		+		+		3
Ellison,G	1970	+	+					2
Elyaman,W	2007	+				+	+	3
Emerson,M	2001	+	+			+		3
Emerson,M	2002	+		+		+		3
Endoh,M	1990	+						1
Engelhardt,B	1989	+						1
Englert,D	1981	+						1
Ephrem,A	2008	+				+	+	3
Eralinna,J	1997							0
Eralinna,J	1998	+						1
Esquifino,A	2007	+				+		2
Eylar,E	1972	+						1
Eylar,E	1979	+						1
Ezendam,J	2008	+	+		+	+		4
Falk,G	1969	+		+				2
Falk,K	2000	+		+		+		3
Faunce,D	2004	+				+		2
Feinstein,D	2002	+		+				2
Fernandez,M	2004	+	+			+		3
Feurer,C	1988	+						1
Field,E	1967	+						1
Field,E	1969	+						1
Fife,B	2001	+				+		2
Filipp,G	1981	+						1
Fischer,W	1970	+						1
Flanagan,E	1995	+				+		2
Floris,S	2002	+				+		2
Floris,S	2004	+				+		2
Folcik,V	1999	+						1
Foster,C	2007	+				+		2
Foster,C	2008							0
Foster,C	2009	+	+	+			+	4
Franco,A	1994	+						1
Fredane,L	1983	+						1
Freire-Garabal,M	2003	+		+		+		3
Frenkel,D	2007						+	1
Fretland,D	1991	+						1
Friese,M	2007	+				+		2
Frost,H	1980	+						1
Fu,Y	2006	+		+		+		3
Fu,Y	2006	+		+		+		3

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Fujino,M	2003	+		+		+		3
Fukumoto,N	2004	+						1
Fuller,K	1990	+		+				2
Furlan,R	1998	+						1
Furlan,R	1999	+				+		2
Furlan,R	2001	+	+			+		3
Furlan,R	2001	+	+			+		3
Furlan,R	2003	+						1
Furlan,R	2004	+				+		2
Furlan,R	2007	+						1
Galazka,G	2001	+						1
Galazka,G	2006	+		+			+	3
Galazka,G	2007	+				+	+	3
Galle,P	2007	+	+			+		3
Garay,L	2007	+				+		2
Garcion,E	2003	+						1
Garin,T	2007	+	+	+		+		4
Garren,H	2001	+	+		+			3
Gaur,A	1992	+						1
Gaur,A	1993	+						1
Gaur,A	1997	+				+		2
Gautam,A	1990	+						1
Gautam,A	1992	+						1
Gautam,A	1995	+						1
Gelder,E	1992							0
Genain,C	1997	+		+		+		3
Genoud,S	2005	+						1
Gerber,R	1972	+						1
Gerdoni,E	2006	+		+		+		3
Gerdoni,E	2006							0
Gerdoni,E	2006							0
Gienapp,I	1996	+						1
Gijbels,K	1994	+	+					2
Gijbels,K	1995	+		+				2
Gilgun-Sherki,Y	2002						+	1
Gilgun-Sherki,Y	2003	+		+		+		3
Gilgun-Sherki,Y	2003	+		+		+		3
Gilgun-Sherki,Y	2005	+				+		2
Gilman,S	1981	+	+					2
Giuliani,F	2005	+		+				2
Giuliani,F	2005	+		+				2
Glabinski,A	2004	+				+		2
Gladue,R	1991	+						1
Glenn,E	1971	+						1
Gocke,A	2007	+					+	2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Goihman-Yahr,M	1974	+						1
Gold,B	2004	+	+	+		+		4
Goldberg,R	2004	+		+				2
Goldenberg,M	1980	+	+					2
Goldmuntz,E	1986	+						1
Goldowitz,D	1987	+						1
Gonzalez-Rey,E	2005	+		+				2
Goss,J	1994	+		+		+		3
Gozez,I	2003						+	1
Graham,D	1974	+		+		+		3
Gran,B	2004	+		+				2
Gran,B	2006	+		+		+		3
Grant,S	2003	+		+		+		3
Grassin,M	1998	+	+	+				3
Greenwood,J	2003	+						1
Greig,M	1969	+						1
Griffiths,M	2009	+	+	+		+		4
Gruenewald,R	1977	+						1
Guo,S	2006	+	+			+		3
Guo,X	2007	+				+		2
Guy,J	1989	+				+		2
Guy,J	1994	+				+		2
Guy,J	1998	+				+		2
Guyton,M	2005			+			+	2
Guyton,M	2006							0
Hallal,D	2003	+				+		2
Han,D	2007	+				+		2
Harbige,L	1997							0
Harbige,L	2000	+						1
Harling-Berg,C	1991	+						1
Harness,J	2003	+				+		2
Hashim,G	1973	+						1
Hashim,G	1975	+						1
Hashim,G	1976	+		+				2
Hashim,G	1980	+						1
Hashim,G	1981	+						1
Hashim,G	1981	+		+				2
Hashim,G	1990	+						1
Hassen,G	2006	+	+					2
Hassen,G	2008	+	+					2
Hauser,S	1984	+						1
Hayashi,T	2009	+				+	+	3
Hayosh,N	1987	+						1
Held,K	2008	+						1
Hempel,K	1984	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Hempel,K	1985	+						1
Hendriks,J	2004	+				+	+	3
Heneka,M	2001	+		+		+		3
Henson,E	1969	+						1
Herrmann,I	2006	+				+		2
Herrmann,M	2008	+				+		2
Hewson,A	1995	+						1
Hiestand,P	1992	+						1
Higgins,P	1988	+		+				2
Hilliard,B	1999	+		+		+		3
Hilliard,B	2001	+						1
Hindinger,C	2006	+				+		2
Hinrichs,D	1983	+						1
Hirata,S	2005	+				+		2
Hirata,S	2007	+				+	+	3
Ho,P	2005	+	+			+	+	4
Ho,S	2006	+		+				2
Holoshitz,J	1983	+						1
Hooper,D	1998	+						1
Hooper,D	2000	+						1
Horie,T	2002	+				+		2
Hosseini,H	2001	+						1
Hou,G	2008	+		+		+		3
Howard,L	1999	+		+				2
Howard,L	2002	+				+		2
Howard,L	2002	+		+				2
Howat,D	1989	+						1
Howell,M	1989	+						1
Hu,H	1997	+	+			+		3
Huan,J	2004	+				+		2
Hudson,R	1983	+						1
Hugh,A	1989	+						1
Hughes,R	1974	+		+				2
Hughes,D	1980	+		+				2
Huitinga,I	1990	+						1
Huitinga,I	1993	+						1
Huitinga,I	1995	+				+		2
Huitinga,I	1998	+						1
Huitinga,I	2000	+				+		2
Hultqvist,M	2009	+				+		2
Hunter,N	1991	+						1
Huntington,N	2006	+		+		+		3
Ichikawa,M	2000	+				+		2
Ilhan,A	2004	+				+		2
Imrich,H	1995	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Inaba,Y	1999	+		+		+		3
Inada,T	1986	+						1
Inobe,J	1996	+						1
Inobe,J	1998	+						1
Inoue,A	1996	+				+		2
Inuzuka,T	1988	+						1
Irony-Tur-Sinai,M	2003	+	+			+		3
Irony-Tur-Sinai,M	2006	+		+		+		3
Iruretagoyena,M	2005	+				+		2
Iruretagoyena,M	2006	+				+		2
Isetta,A	1991	+						1
Ishigami,T	1998	+		+				2
Ishikawa,M	1999	+		+				2
Issekutz,T	2005							0
Ito,A	2001	+				+		2
Ito,A	2003	+				+		2
Jackson,S	2008							0
Jacobs,C	1991	+	+	+				3
Jaini,R	2006	+	+	+		+		4
Jameson,B	1994	+						1
Jankovik,B	1987	+						1
Jansson,L	1994	+						1
Javed,N	1995	+						1
Jee,Y	2006	+						1
Jee,Y	2007	+						1
Jerusalmi,A	2003	+						1
Jia,Y	2006	+						1
Jia,Y	2007	+	+					2
Jia,J	2008	+				+		2
Jiang,Z	2009	+				+	+	3
Jiao,Z	2008	+	+	+		+		4
Johns,L	1991	+		+				2
Jolivalt,C	2003	+				+		2
Jonker,M	1988	+						1
Jonsson,S	2004	+						1
Jorgensen,S	2005	+		+		+		3
Jun,S	2005							0
Jun,S	2005	+				+	+	3
Jung,S	1993	+						1
Jung,S	1995	+						1
Jung,S	1997	+		+		+		3
Jurynczyk,M	2005	+		+		+	+	4
Jurynczyk,M	2008	+		+		+		3
Jurynczyk,M	2008	+		+		+	+	4
Jyothi,M	2002	+					+	2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Kahl,K	2003	+				+		2
Kallen,B	1986	+						1
Kalyvas,A	2004	+	+	+		+		4
Kalyvas,A	2009	+	+	+				3
Kanchurin,A	1972	+						1
Kaneko,H	1995	+						1
Kaneko,S	2006	+		+				2
Kang,J	2001	+						1
Kang,S	2008	+				+		2
Kanwar,J	2000	+				+		2
Kanwar,J	2000	+				+		2
Kanwar,J	2004	+		+		+		3
Kanwar,J	2005							0
Kardys,E	1981	+						1
Karlik,S	1991							0
Karlik,S	1995			+				1
Karlik,S	1996	+						1
Karlik,S	1998	+				+		2
Karpus,W	1988	+						1
Karpus,W	1991	+						1
Karpus,W	1995	+				+		2
Karpus,W	1996	+				+		2
Karussis,D	1991							0
Karussis,D	1991							0
Karussis,D	1992	+						1
Karussis,D	1992	+						1
Karussis,D	1993	+		+				2
Karussis,D	1993	+						1
Karussis,D	1993	+		+				2
Karussis,D	1999	+						1
Karussis,D	2001	+						1
Kasckow,J	1981	+						1
Kassabova,T	1990	+						1
Kassis,I	2008	+		+		+		3
Kataoka,H	2005	+						1
Kataoka,H	2006							0
Kato,S	1988	+						1
kato,S	1991	+						1
Kato,H	2004	+						1
Kaushansky,N	2007	+						1
Kawaguchi,Y	1999	+						1
Kawai,K	1996	+		+				2
Kayhan,B	2003	+						1
Keith,A	1979	+						1
Kelemen,J	1970	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Kelly,K	1996	+		+		+		3
Kennedy,M	1988	+		+				2
Kennedy,M	1990	+		+				2
Kennedy,M	1990	+	+	+				3
Kennedy,K	1997	+				+		2
Kent,S	1995	+						1
Kerfoot,S	2006	+				+	+	3
Keszthelyi,E	1996	+		+				2
Khan,A	1970	+						1
Khan,A	1974	+		+				2
Khoury,S	1990	+						1
Khoury,S	1993	+						1
Khoury,S	1995	+						1
Khoury,S	1996	+						1
Kikukawa,A	1988	+						1
Kim,S	1999	+						1
Kinoshameg,S	2004	+						1
Kipper-Galperin,M	1999	+	+					2
Klein-Franke,A	1992	+						1
Klemann,C	2009	+				+		2
Klinkert,W	1997	+						1
Kobayashi,N	2007	+		+		+		3
Koh,C	1987	+	+					2
Kohm,A	2002	+		+				2
Kohm,A	2005	+		+			+	3
Komarek,A	1971	+						1
Konkol,R	1990	+						1
Korn,T	2004	+				+		2
Korner,H	1997	+				+		2
Kovarik,J	1995	+						1
kryzhanovskii,G	1985	+						1
Kuchroo,V	1994							0
Kuchroo,V	1994	+				+		2
Kuchroo,V	1995	+				+		2
Kuhlmann,T	2006	+				+		2
Kuhns,M	2000	+		+		+		3
Kumar,V	1997	+						1
Kumar,V	2001	+						1
Kupfer,M	1969	+						1
Kuroda,Y	1979	+						1
Kuroda,Y	1980	+						1
Kuruvilla,A	1991	+						1
Kwak,H	2003	+		+		+		3
Kwiatkowska-Petzer,B	2004	+						1
Kwidzinski,E	2003	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Kwidzinski,E	2005	+	+	+		+		4
Kwon,S	2005	+						1
La Flamme,A	2006	+				+		2
Laman,J	1998	+				+		2
Laman,J	2002	+	+			+		3
Lamont,A	1990	+						1
Land,W	1968	+						1
Lando,Z	1979	+						1
Lando,Z	1979	+						1
Lando,Z	1981	+						1
Lange,F	2004	+		+		+		3
Lassmann,H	1988	+						1
Lavasani,S	2007	+	+	+		+		4
Lavrnja,I	2005	+						1
Lawson,B	2007	+				+		2
Leadbetter,E	1998	+						1
Lee,Y	2008	+				+	+	3
Leech,M	2007	+					+	2
Leger,O	1997	+	+					2
Legge,k	2000	+						1
Lehmann,D	1991							0
Lehmann,D	1992	+						1
Lehmann,D	1994	+						1
Lehmann,D	1997	+						1
Leibowitz,S	1968	+						1
Leibowitz,S	1968	+						1
Lemire,J	1991	+						1
Lemire,J	1994	+						1
Leonard,J	1995	+						1
Leone,D	2003	+				+		2
Leong,S	1996	+				+		2
Levine,S	1969	+						1
Levine,S	1970	+		+				2
Levine,S	1971	+						1
Levine,S	1971	+		+				2
Levine,S	1976	+						1
Levine,S	1977	+						1
Levine,S	1977	+						1
Levine,S	1977	+						1
Levine,S	1978	+						1
Levine,S	1979	+						1
Levine,S	1979	+	+					2
Levine,S	1983	+						1
Levine,S	1986	+	+					2
Levine,S	1989	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Levine,S	1991	+						1
Levi-Schaffer,F	1991	+						1
Li,C	1989	+	+					2
Li,H	1998	+		+				2
Li,W	1998	+	+	+		+		4
Li,W	2004	+		+				2
Li,H	2006	+				+		2
Li,F	2006	+	+	+		+		4
Li,X	2006	+	+					2
Li,X	2008	+				+		2
Li,H	2008	+		+		+	+	4
Liang,M	2000	+						1
Lichtenegger,F	2007	+				+	+	3
Lider,O	1986	+						1
Lider,O	1988	+						1
Lider,O	1989	+						1
Liedtke,W	1998	+		+				2
Linington,C	1988	+						1
Linington,C	1989	+						1
Linker,R	2008	+		+				2
Linker,R	2008	+		+		+		3
Lisak,R	1968	+						1
Lisak,R	1970	+						1
Lisak,R	1974	+						1
Lisak,R	1980	+						1
Lisak,R	1983	+						1
Liu,G	1994	+						1
Liu,X	1995	+		+		+		3
Liu,X	1997	+				+		2
Liu,J	1998	+						1
Liu,Y	2003	+		+		+		3
Liu,Y	2006	+		+		+		3
Liu,X	2007	+	+					2
Livine,S	1967	+						1
Lo,A	2002	+				+		2
Lo,A	2003	+				+		2
Lobell,A	1998	+						1
Lobell,A	1999	+						1
Lobell,A	2003	+						1
Lohse,A	1989	+						1
Loria,F	2007							0
Louie,K	2005	+		+				2
Love,S	1987	+						1
Lovett-Racke,A	1998	+		+		+		3
Lovett-Racke,A	2004	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Lowe,V	1993	+		+				2
Lu,P	2003	+				+		2
Lublin,F	1984	+						1
Lublin,F	1987	+						1
Lublin,F	1993	+		+				2
Luca,M	1999	+						1
Luccarini,I	2008	+		+		+		3
Lyman,W	1989	+						1
Lyons,M	1986	+						1
Maassen,C	2003	+				+		2
Maccio,D	2005	+	+	+		+		4
Maccioni,M	1999	+						1
Mackenzie,A	1979	+						1
MacPhee,I	1988	+						1
MacPhee,I	1990	+						1
MacPhee,I	2001	+				+		2
Macpherson,C	1973	+						1
Macpherson,C	1977	+						1
Macpherson,C	1977	+						1
Macpherson,C	1980	+						1
Maier,K	2004	+		+		+		3
Maier,K	2006	+	+	+		+		4
Maier,K	2007	+		+		+		3
Makar,T	2008	+	+	+				3
Makar,T	2008							0
Makar,T	2008	+		+		+	+	4
Makar,T	2009	+				+		2
Malfitano,A	2006	+		+				2
Malfroy,B	1997	+						1
Malotky,M	1994	+						1
Mana,P	2004	+				+		2
Mannie,M	2007	+				+	+	3
Marchionni,M	1999	+						1
Margot,C	2005	+				+	+	3
Maricic,I	2005							0
Marini,J	1996	+						1
Marino,M	1999	+						1
Marino,M	2000	+						1
Marques,K	2009	+				+		2
Marracci,G	2002	+	+			+		3
Martel,R	1977	+						1
Martin,D	1995	+		+				2
Martiney,J	1998	+		+		+		3
Martinez,I	1999	+						1
Martin-Saavedra,F	2007	+				+		2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Marusic,S	2008	+	+	+		+	+	5
Massacesi,L	1987	+		+				2
Massacesi,L	1987	+		+				2
Massacesi,L	1991	+						1
Mastronardi,F	2004	+		+		+		3
Mastronardi,F	2007	+				+		2
Matarese,G	2001	+		+		+		3
Matarese,G	2005	+		+		+		3
Matejuk,A	2004	+				+		2
Matejuk,A	2005	+					+	2
Mathey,E	2007	+				+	+	3
Mathisen,P	1997	+		+				2
Mathisen,P	1997							0
Matous-Malbohan,I	1976	+						1
Matsui,M	2002	+		+				2
Matsumo,Y	2005	+						1
Matsumoto,Y	1994	+						1
Matsumoto,Y	1994	+						1
Matsumoto,Y	2001	+						1
Matsuo,H	1997	+						1
Matsushima,S	1990	+						1
Matsushima,S	1990	+						1
Mattner,F	2000	+						1
Matute,C	2007	+						1
McCandless,E	2006	+						1
McCombe,P	1996	+						1
McCombe,P	1998	+						1
McCreary,P	1966	+						1
McDermott,J	1979	+						1
McFarland,H	2001	+	+	+		+		4
McIlhenny,H	1978	+						1
McKenna,R	1983	+						1
McKenna,R	1984	+						1
McRae,B	1995	+						1
Meade,C	1977							0
Meade,C	1978	+		+				2
Meehan,T	2002	+						1
Megel,H	1977	+						1
Meiron,M	2008	+		+		+	+	4
Mekala,D	2005	+						1
Mekala,D	2005	+					+	2
Mel'nyk,V	2005	+						1
Merendino,A	1987	+		+				2
Merrill,J	2009	+	+	+			+	4
Mertin,J	1976	+	+					2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Mertin,J	1978	+		+				2
Metzler,B	1993	+						1
Metzler,B	1996	+						1
Meuth,S	2008	+		+		+		3
Meyer,A	1996	+						1
Mi,S	2007	+				+		2
Milford,C	1995	+	+			+		3
Milicevic,I	2003	+						1
Miller,S	1991	+						1
Miller,A	1991	+		+		+		3
Miller,A	1992	+						1
Miller,A	1992	+		+				2
Miller,A	1993	+		+		+		3
Miller,A	1993	+		+		+	+	4
Miller,A	1994	+		+				2
Miller,D	1997	+	+	+				3
Min,B	1998	+				+		2
Min,B	2000	+				+		2
Min,K	2007	+						1
Minagawa,H	1987	+						1
Minter,L	2005	+				+	+	3
Mirshafiey,A	2005	+	+			+		3
Mirshafiey,A	2005	+	+	+				3
Misiewiez,B	1996							0
Miskolczy,D	1965	+						1
Mitchell,K	2007	+	+	+		+		4
Mitsuzawa,E	1984	+		+				2
Miyagawa,N	2003	+				+		2
Miyake,M	2006	+					+	2
Miyamoto,K	2001	+						1
Miyamoto,K	2005	+		+		+	+	4
Miyamoto,K	2006	+						1
Mizobuchi,M	1997	+						1
Mohamed,A	2002	+		+				2
Mohamed,A	2003	+	+	+				3
Mohamed,A	2005	+						1
Mohamed,A	2006	+		+				2
Mohamed,A	2009	+		+				2
Mokhtarian,F	1988	+						1
Mokhtarian,F	1996	+						1
Monastra,G	1991							0
Monastra,G	1993	+		+				2
Mondal,S	2009	+		+		+	+	4
Montero,E	2007	+						1
Montgomery,I	1980	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Moon,C	2004	+						1
Moon,C	2005	+				+		2
Moore,M	1974	+		+				2
Moore,C	2006	+		+		+		3
Morariu,M	1978	+						1
Moreno,B	2006	+	+	+		+		4
Morgan,B	2004	+	+	+		+		4
Morini,M	2004	+				+		2
Moriya,M	2005	+		+		+		3
Morris,M	1996							0
Morris,M	1997							0
Morrissey,S	1996	+		+		+		3
Mosayebi,G	2007	+				+		2
Mostarica-Stojkovic,M	1982	+						1
Mostarica-Stojkovic,M	1988	+						1
Moulias,R	1968	+						1
Mueller,A	2005	+		+		+		3
Muhvic,D	1992	+						1
Mujtaba,M	1998	+						1
Mujtaba,M	2005	+				+	+	3
Mullin,B	1984	+		+				2
Mullin,B	1986	+		+				2
Murphy,P	2002	+		+				2
Mustafa,M	1993	+						1
Muthian,G	2004	+		+				2
Nagai,Y	1982	+						1
Nagasawa,K	1976	+						1
Nagasawa,K	1976	+						1
Nagasawa,K	1977	+						1
Nagasawa,K	1979	+						1
Nagelkerken,L	1997	+						1
Nagelkerken,L	2004	+				+		2
Naiki,M	1991	+						1
Nakajima,A	2000	+				+		2
Nakane,S	2003	+				+		2
Namer,I	1994	+						1
Narumi,S	2002	+				+		2
Nashold,F	2000	+	+	+				3
Nashold,F	2001	+				+		2
Nataf,S	1993	+	+					2
Nataf,S	1996	+	+					2
Natarajan,C	2002	+						1
Natarajan,C	2002	+						1
Nath,N	2004	+		+				2
Nath,N	2005	+		+		+	+	4

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Nath,N	2009	+		+		+	+	4
Nelson,P	1996	+		+		+		3
Nelson,P	1996							0
Nemoto,K	1987	+						1
Nessler,S	2006	+		+		+		3
Neu,I	1992	+						1
Nguyen,K	1997	+		+				2
Ni,X	2002							0
Ni,X	2004	+		+		+		3
Ni,J	2007	+				+		2
Nicholson,L	1995	+				+		2
Niedieck,B	1966	+						1
Niino,M	2001	+				+		2
Nikodemova,M	2007	+				+		2
Nikolajeva,V	2000	+		+		+		3
Nizri,E	2005	+				+		2
Nizri,E	2005	+				+		2
Nizri,E	2007	+						1
Nizri,E	2008	+				+		2
Norga,K	1995	+	+			+		3
Nunez,M	2007	+		+		+		3
O'Brien,N	1999	+				+		2
Ochi,H	2006	+	+	+		+	+	5
Ochoa-Reparaz,J	2007	+				+	+	3
Odoardi,F	2007	+				+	+	3
Offen,D	2004	+	+	+		+		4
Offner,H	1988	+						1
Offner,H	1989	+		+				2
Offner,H	1990	+				+		2
Offner,H	1991	+						1
Offner,H	1991	+				+		2
Offner,H	1994	+				+		2
Offner,H	1995	+				+		2
Offner,H	2002	+				+		2
Offner,H	2005	+				+	+	3
Ofosui-Appiah,W	1991	+						1
Ohta,Y	1997	+		+				2
Okuda,Y	1996	+						1
Okuda,Y	1998	+		+				2
Okuda,Y	2000	+		+				2
Olive,C	1997	+						1
O'Neill,M	1992	+						1
O'Neill,J	1992	+						1
O'Neill,J	1993	+						1
O'Neill,E	2006	+		+		+		3

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
O'Rourke,A	2007	+						1
Osanai,T	1984	+						1
Otero,D	1998							0
Ousman,S	2007	+		+		+	+	4
Ovadia,H	1982	+						1
Ovadia,H	1994							0
Pabst,H	1971	+						1
Paintlia,A	2004	+		+		+		3
Paintlia,A	2005	+		+		+		3
Paintlia,A	2006							0
Paintlia,A	2006	+		+		+		3
Paintlia,A	2008	+		+		+		3
Paintlia,A	2008	+		+		+		3
Paintlia,A	2009	+		+		+		3
Pal,E	2001	+				+		2
Palaszynski,K	2004	+				+		2
Papenfuss,T	2007	+						1
Park,I	2008	+						1
Pashov,A	1997	+						1
Pashov,A	1998	+				+		2
Paterson,P	1969	+						1
Paterson,P	1969	+						1
Paterson,P	1969	+	+					2
Paterson,P	1971	+	+	+				3
Paterson,P	1977	+						1
Paul,C	2002	+		+		+		3
Pedchenko,T	1998	+		+				2
Pedemonte,E	2007	+						1
Pedotti,R	2003	+						1
Peers,S	1995	+		+				2
Peiris,M	2007	+		+		+		3
Pekarski,O	1998	+						1
Pellet,H	1968	+						1
Pelletier,L	1988	+						1
Pender,M	1990	+						1
Penkowa,M	2001	+		+		+		3
Penkowa,M	2003	+	+	+		+		4
Pepinksy,R	2005	+				+		2
Perper,S	1999						+	1
Perrin,P	1995							0
Perrin,P	1999	+				+		2
Persinger,M	2000	+		+		+		3
Peruche,S	2008	+				+	+	3
Pesoa,S	1984	+						1
Peterson,L	2008	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Petterson,A	2004	+		+				2
Pettersson,A	2004	+		+				2
Phillips,S	2007	+		+				2
Piao,W	2007	+	+			+	+	4
Piao,W	2007	+				+	+	3
Piccio,L	2007	+		+				2
Piccio,L	2008	+	+	+		+		4
Piccirillo,C	1999	+		+				2
Piddlesden,S	1991	+						1
Piddlesden,S	1994	+						1
Pietropaolo,M	2000	+						1
Pinto,F	2003	+				+		2
Piraino,P	2002	+		+				2
Piraino,P	2005	+				+		2
Piraino,P	2005	+		+				2
Pitt,D	1999							0
Pitt,D	2000	+		+		+		3
Platten,M	2005	+		+			+	3
Pluchino,S	2003	+				+	+	3
Podojil,J	2006	+		+			+	3
Polak,P	2005	+				+		2
Poliani,P	2001	+						1
Pollak,Y	2003	+						1
Pope,L	1992	+						1
Popovic,N	2001	+				+		2
Popovich,P	1997	+	+					2
Pozza,M	2000	+				+		2
Prasad,D	2004	+						1
Prasad,R	2006	+				+		2
Prockop,L	1978	+	+					2
Prosiegel,M	1989	+	+	+				3
Prosiegel,M	1990	+	+	+				3
Pryce,G	2005	+		+		+		3
Przuntek,H	1987	+						1
Puerta,C	2000	+				+		2
Qi,X	2007	+				+	+	3
Qin,Y	1989	+						1
Quinn,K	2008	+		+		+		3
Rabin,B	1983	+						1
Racke,M	1961	+		+		+		3
Racke,M	1991	+		+				2
Racke,M	1992	+		+				2
Racke,M	1993	+		+		+		3
Racke,M	1994	+		+		+		3
Racke,M	1995	+		+		+		3

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Racke,M	1996	+		+		+		3
Racke,M	2003						+	1
Raikwar,H	2005	+		+		+		3
Raikwar,H	2006	+		+		+		3
Raine,C	1977	+						1
Raine,C	1978	+						1
Raine,C	1978	+						1
Raine,C	1983	+						1
Rajan,A	1996	+		+				2
Rajan,A	1998	+				+		2
Rauch,H	1968	+						1
Rauch,H	1974	+						1
Rauch,H	1979	+						1
Rauch,H	1980	+						1
Rauch,H	1981	+						1
Rausch,M	2004	+	+					2
Rausch,M	2005							0
Ravkina,L	1978	+						1
Raziuddin,S	1981	+						1
Raziuddin,S	1982	+						1
Razmara,M	2009	+				+		2
Reber,N	1972	+						1
Reber,N	1973	+						1
Reder,A	1994	+				+		2
Reiber,H	1986	+						1
Reichert,F	1999	+				+		2
Reinke,E	2006	+				+		2
Reinke,E	2007	+		+		+		3
Reiseter,B	1998	+	+	+				3
Richert,J	1982	+						1
Ridge,S	1985	+						1
Riskind,P	1991	+		+		+		3
Rivero,V	1997	+						1
Rolls,A	2006	+						1
Root-Bernstein,R	1986	+						1
Roscoe,W	2007	+		+		+		3
Rose,L	1987	+	+	+		+		4
Rose,L	1988	+						1
Rose,J	1991							0
Rose,J	1991	+		+				2
Rose,L	1997	+	+	+		+		4
Rosenthale,M	1967	+	+					2
Rosenthale,M	1969	+						1
Rosenthale,M	1969	+	+					2
Rosenthale,M	1972	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Roth,G	1982	+						1
Rott,O	1993	+						1
Rott,O	1994	+						1
Rottman,J	2001	+						1
Ruddle,N	1990	+		+				2
Ruffini,F	2001	+	+					2
Ruiz,P	1999	+						1
Ruocco,H	2004	+				+		2
Russo,C	2006	+		+				2
Ruuls,S	1995	+						1
Ruuls,S	1996	+		+				2
Ryffel,B	1982	+						1
Ryskova,O	1988	+						1
Sacks,H	1987	+						1
Sakai,k	1989	+						1
Sakurai,K	2002	+		+		+		3
Samoilova,E	1997	+						1
Samson,M	1995	+		+			+	3
Sanchez,A	2006	+				+		2
Santambrogio,L	1993	+						1
Santambrogio,L	1993	+						1
Santambrogio,L	1995	+						1
Santos,L	1994	+						1
Saoudi,A	1995	+						1
Satoh,J	1988	+	+					2
Sattler,M	2005	+		+		+		3
Sattler,M	2006	+		+		+		3
Sattler,M	2008	+	+	+		+		4
Savino,C	2006	+		+		+		3
Scelsi,R	1983	+						1
Scelsi,R	1989	+						1
Schaefer,C	2006	+				+		2
Schaub,M	1999	+						1
Scheinberg,L	1967	+						1
Scherer,R	1980	+		+				2
Schiffenbauer,J	1998	+						1
Schiffer,R	1990	+	+					2
Schif-Zuck,S	2006	+		+			+	3
Schilling,S	2006	+		+		+		3
Schluesener,H	1986	+						1
Schluesener,H	1987	+						1
Schluesener,H	1988	+		+				2
Schluesener,H	1989	+	+					2
Schluesener,H	1999	+	+					2
Schmidt,J	2003	+		+		+		3

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Schmidt,J	2003	+		+				2
Schmitz,D	2003	+				+		2
Schnermann,J	2003							0
Schorlemmer,H	1989	+						1
Schorlemmer,H	1990							0
Schorlemmer,H	1991	+						1
Schorlemmer,H	1991	+						1
Schorlemmer,H	1991	+						1
Schorlemmer,H	1997	+						1
Schorlemmer,H	1997	+						1
Schreibelt,G	2006	+				+	+	3
Schubart,A	2008							0
Schuller-Levis,G	1986	+		+				2
Scott,C	1982	+						1
Scott,C	1982	+						1
Scott,G	1996	+				+		2
Scott,G	2000	+		+		+		3
Scott,G	2001	+				+		2
Scott,G	2002	+	+					2
Scott,G	2004	+				+		2
Sedgwick,J	1986	+						1
Seki,N	2006							0
Sekiguchi,Y	2001	+		+		+		3
Selivonchick,D	1975	+						1
Selmaj,K	1991	+		+		+		3
Selmaj,K	1991							0
Selmaj,K	1995	+		+				2
Selmaj,K	1998	+		+				2
Selmaj,K	2000	+		+				2
Sewell,D	2000							0
Sewell,D	2002	+				+		2
Sewell,D	2003	+		+				2
Shankaran,M	2007	+				+		2
Sharma,S	1991	+				+		2
Shaw,M	1997	+				+		2
Shi,F	1998	+		+				2
Shijie,J	2009	+				+		2
Shimada,K	1994	+	+					2
Shin,T	2000	+						1
Shin,T	2001	+						1
Shin,T	2001	+						1
Shindler,K	2007	+	+			+	+	4
Sibley,W	1978	+						1
Simmons,R	1989	+						1
Simmons,R	1991	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Simon,J	1978	+						1
Simon,J	1979	+						1
Singh,N	2007	+				+		2
Singh,M	2009	+		+				2
Sinha,S	2007	+				+	+	3
Sinha,S	2009	+				+	+	3
Skundric,D	2005							0
Skundric,D	2005	+		+				2
Slavin,A	2001	+				+		2
Sloane,E	2009	+		+		+		3
Smilek,D	1991	+				+		2
Smith,M	1982	+						1
Smith,S	1987	+						1
Smith,S	1993	+						1
Smith,R	1994	+						1
Smith,T	2000	+		+				2
Smith,T	2002							0
Smith,S	2002							0
Smith,C	2006	+				+		2
Snyder,A	1980	+						1
Sobel,R	1987	+		+				2
Soilu-Hanninen,M	2000	+				+		2
Sommer,N	1995	+		+				2
Sommer,N	1997	+	+	+		+		4
Soos,J	1993	+						1
Soos,J	1995	+						1
Soos,J	1997	+						1
Soos,J	2002	+				+		2
Spach,K	2005	+		+		+	+	4
Spach,K	2006	+				+		2
Spitsin,S	2002	+						1
Srinivasan,M	2002	+	+					2
Sriram,S	1983	+		+				2
Sriram,S	1983	+	+					2
Sriram,S	1986	+	+	+				3
Sriram,S	1987	+		+				2
Sriram,S	1988	+		+				2
Sriram,S	1988	+	+					2
Sriram,S	1991	+	+	+				3
Sriram,S	1996							0
St Louis,J	1989	+		+				2
St Louis,J	1997	+		+				2
Stanislaus,R	2001	+		+		+		3
Stanley,N	1990	+				+		2
Staykova,M	1977	+	+					2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Staykova,M	1988	+						1
Staykova,M	1989	+						1
Staykova,M	1997	+				+		2
Stedra,J	1985	+						1
Stein,C	1990	+						1
Steinbrecher,A	2001	+		+		+		3
Steiner,I	1991	+		+				2
Steinman,L	1983	+						1
Stern,P	1975	+						1
Stern,J	2004	+						1
Stern,J	2004	+		+		+	+	4
Stevens,D	1992	+						1
St-Louis,J	2001	+		+		+		3
Stojkov,D	2008	+				+		2
Storch,M	2005							0
Stosic-Grujicic,S	2002	+		+				2
Strejan,G	1981	+						1
Strejan,G	1984	+		+				2
Strejan,G	1984	+						1
Strejan,G	1984	+		+				2
Strejan,G	1988	+						1
Strejan,G	1990	+						1
Stuve,O	2006	+	+	+		+	+	5
Su,X	1991	+	+	+				3
Subramanian,S	2003	+				+		2
Suckling,A	1986	+						1
Sun,D	1988	+						1
Sun,D	1992	+						1
Sun,D	1992	+						1
Sun,J	2000	+		+				2
Sun,Y	2002	+						1
Sun,X	2006	+				+		2
Suzuki,M	1998	+				+		2
Swanborg,R	1972	+		+				2
Swanborg,R	1973	+		+				2
Swanborg,R	1975	+						1
Swanborg,R	1975	+						1
Swierkosz,J	1975	+						1
Szczepanik,M	2005	+						1
't Hart,B	2005	+				+		2
't Hart,B	2005	+	+			+	+	4
Tadokoro,C	2004	+				+		2
Tafreshi,A	2006	+						1
Takahashi,K	2007	+		+			+	3
Takenaka,A	1982	+		+				2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Tan,L	1991	+		+				2
Tang,X	2007	+				+	+	3
Tanuma,N	1996	+						1
Targoni,O	1999	+						1
Teitelbaum,D	1971	+		+				2
Teitelbaum,D	1972	+						1
Teitelbaum,D	1974	+		+				2
Teitelbaum,D	1999	+						1
Teitelbaum,D	2004	+						1
Teuscher,C	1990	+		+				2
Theien,B	2001	+						1
Theien,B	2003	+				+		2
Tiwari-Woodruff,S	2007			+				1
Todorov,D	1982	+						1
Topham,D	1994	+	+					2
Touil,T	2006	+					+	2
Touil,T	2008	+		+				2
Tran,E	1998	+				+		2
Tran,G	2001	+				+		2
Tran,G	2001	+				+		2
Traugott,U	1979	+						1
Traugott,U	1982	+						1
Triaca,V	2005	+				+		2
Trooster,W	1993	+	+	+				3
Tselios,T	2000	+						1
Tselios,T	2000	+						1
Tselios,T	2002	+						1
Tsukimoto,M	2008	+						1
Tsumita,T	1972	+						1
Tsunoda,I	2007	+	+			+		3
Tsutsui,S	2008	+				+	+	3
Turley,D	2007	+		+		+	+	4
Tutaj,M	2007	+				+		2
Uccelli,A	2003							0
Uemura,Y	2008	+				+		2
Uitdehaag,B	1994	+						1
Urban,J	1989	+						1
Uyttenhove,C	2004	+				+		2
Uyttenhove,C	2007	+						1
van den Elzen,P	2001							0
van der Laan,L	2002	+						1
van der Meide,P	1998	+						1
van der Veen,R	1985	+						1
van Etten,E	2003	+	+	+				3
van Etten,E	2007	+	+					2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
van Gelder,M	1995	+						1
van Lambalgen,R	1987	+						1
Van Wijmeersch,B	2007	+						1
Vandenbark,A	1989	+						1
Vandenbark,A	1995	+						1
Vandenbark,A	1996	+	+					2
Vanderlugt,C	1997	+		+				2
Vanderlugt,C	2000	+		+				2
Vansant,G	2007	+						1
Varriale,S	1994	+						1
Vecchi,A	1976	+		+				2
Veljic,J	1991	+	+					2
Verbeek,R	2005	+						1
Verda,L	2006	+		+		+		3
Vescovi,A	2003							0
Villoslada,P	2000	+	+	+		+		4
Vladutiu,A	1968	+						1
Vlajkovic,S	1990	+						1
Voda,J	2002							0
Voda,J	2002							0
Vogel,C	1969	+						1
Vogel,C	1969	+						1
Vogel,C	1972	+	+	+				3
Vohl,M	1990	+						1
Vollmer,T	2005	+					+	2
Volmar,C	2008	+				+		2
Voorthuis,J	1990	+		+				2
Vroegop,S	1999	+		+		+		3
Vroegop,S	1999	+				+		2
Vymazal,J	1974	+						1
Waisman,A	1996	+						1
Walczak,A	2004	+		+				2
Waldor,M	1985	+	+	+				3
Waldor,M	1987	+		+				2
Wallberg,M	2003	+				+		2
Walter,S	2002	+						1
Wang,Y	1992	+						1
Wang,C	1995	+						1
Wang,T	2000	+				+		2
Wang,T	2000	+				+		2
Wang,E	2006	+						1
Wang,C	2006	+		+		+		3
Wang,Z	2007	+				+	+	3
Wang,G	2008	+	+			+		3
Wang,J	2008	+				+	+	3

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Wang,J	2008	+				+		2
Wang,Y	2008	+		+		+		3
Wang,X	2009	+	+					2
Warren,J	1978	+		+				2
Watnick,A	1972	+						1
Wauben,M	1992	+						1
Webb,C	1976	+						1
Webb,M	2004	+				+		2
Weber,F	1987	+						1
Weber,F	1989	+						1
Weber,F	1991	+						1
Weber,M	2007	+	+				+	3
Wegmann,K	2008	+				+		2
Wegner,C	2007							0
Wegner,C	2008							0
Weilbach,F	2004	+		+		+		3
Weinberg,A	1994	+				+		2
Weinberg,A	1996	+				+		2
Weishaupt,A	2000	+		+		+		3
Weishaupt,A	2002	+		+				2
Weishaupt,A	2004	+		+		+		3
Weissert,R	2003	+				+		2
Wekerle,H	1984	+						1
Welch,A	1980	+						1
Welsh,C	1993	+		+		+		3
Wender,M	2001	+						1
Wenjie,C	2007	+	+					2
Werner,P	2000	+						1
Werner,P	2003						+	1
Westarp,M	1987	+						1
Weston,P	1978	+						1
Whitacre,C	1991	+						1
Whitacre,C	1992	+	+					2
White,S	1990							0
White,S	1992	+						1
Whitham,R	1993	+				+		2
Whitham,R	1996	+		+		+		3
Wiegmann,K	1995	+						1
Wiemann,B	1998	+		+				2
Wildbaum,G	1999	+		+				2
Wildbaum,G	2000	+		+				2
Wildbaum,G	2002	+		+				2
Wildfeuer,A	1998	+				+		2
Willenborg,D	1968	+						1
Willenborg,D	1981	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Willenborg,D	1986	+						1
Willenborg,D	1987	+						1
Willenborg,D	1988	+						1
Willenborg,D	1988	+						1
Willenborg,D	1989	+						1
Willenborg,D	1993	+						1
Willenborg,D	1995	+						1
Willenborg,D	1996	+						1
Williams,K	2000	+		+		+		3
Wong,C	1992	+						1
Woyciechowska,J	1985	+						1
Wraith,D	1989	+		+				2
Xian,C	1995	+						1
Xiao,B	1998	+		+				2
Xiao,B	2001	+		+				2
Xiao,B	2004	+		+				2
Xie,C	2006	+		+		+		3
Xu,S	1998	+				+		2
Xu,L	1999	+		+				2
Xu,L	2000	+		+				2
Xu,L	2000	+		+				2
Xu,L	2000	+		+				2
Xu,L	2001	+		+				2
Xu,B	2004	+						1
Xu,B	2006	+	+					2
Yamamura,T	1987	+						1
Yan,S	2003	+				+	+	3
Yang,J	2004	+		+				2
Yao,D	1995							0
Yao,D	1995	+						1
Yasuda,C	1999	+						1
Yednock,T	1992	+						1
Yehuda,S	1997	+		+		+		3
Yin,P	2003	+				+		2
Youssef,S	1998	+		+				2
Youssef,S	1999	+		+				2
Yu,R	1987							0
Yu,M	1996	+		+		+		3
Yu,C	2006	+	+	+				3
Yura,M	2002	+						1
Zamora,A	2002	+				+		2
Zappia,E	2005	+				+		2
Zargari,M	2008							0
Zargarova,T	2004	+				+		2
Zavala,F	2002	+						1

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Zehntner,S	2007	+				+	+	3
Zeng,Y	2007	+				+		2
Zeng,Y	2007	+		+		+		3
Zhang,B	2000	+				+		2
Zhang,G	2002	+		+		+		3
Zhang,G	2002	+	+	+		+		4
Zhang,B	2003	+				+		2
Zhang,Q	2004	+		+				2
Zhang,J	2005	+	+	+		+		4
Zhang,G	2005	+		+		+	+	4
Zhang,J	2005	+	+	+		+		4
Zhang,J	2006	+	+	+		+		4
Zhang,J	2007	+	+	+				3
Zhang,J	2008	+	+	+			+	4
Zhang,J	2009	+	+	+		+		4
Zheng,X	2008	+		+				2
Zhitnukhin,I	1976	+						1
Zhitnukhin,I	1978	+						1
Zhitnukhin,I	1978	+						1
Zhitnukhin,I	1981	+						1
Zhitnukhin,Y	1997	+						1
Zhou,S	1993	+						1
Zhu,J	1998	+						1
Zhu,B	2000							0
Zhu,B	2002	+				+		2
Zhu,Y	2006	+				+		2
Zhu,B	2006	+		+		+	+	4
Zhu,C	2008	+		+				2
Zinn,K	1975	+						1
Zinser,E	2004	+						1
Zinser,E	2004	+					+	2
Zozulya,A	2009	+		+		+		3

Appendix 3. References used in the systematic review and meta-analysis of dopamine agonists tested in preclinical studies of Parkinson's disease

Abuirmeileh, A., Harkavyi, A., Kingsbury, A., Lever, R., & Whitton, P. S. 2008, "The CRF-like peptide urocortin produces a long-lasting recovery in rats made hemiparkinsonian by 6-hydroxydopamine or lipopolysaccharide", *J Neurol Sci*, vol. 271, no. 1-2, pp. 131-136.

Abuirmeileh, A., Harkavyi, A., Lever, R., Biggs, C. S., & Whitton, P. S. 2007, "Urocortin, a CRF-like peptide, restores key indicators of damage in the substantia nigra in a neuroinflammatory model of Parkinson's disease", *J Neuroinflammation*, vol. 4, p. 19.

Aguiar, L. M., Macedo, D. S., Vasconcelos, S. M., Oliveira, A. A., de Sousa, F. C., & Viana, G. S. 2008, "CSC, an adenosine A(2A) receptor antagonist and MAO B inhibitor, reverses behavior, monoamine neurotransmission, and amino acid alterations in the 6-OHDA-lesioned rats", *Brain Res*, vol. 1191, pp. 192-199.

Ahmed, M. R., Bychkov, E., Gurevich, V. V., Benovic, J. L., & Gurevich, E. V. 2008a, "Altered expression and subcellular distribution of GRK subtypes in the dopamine-depleted rat basal ganglia is not normalized by l-DOPA treatment", *J Neurochem*, vol. 104, no. 6, pp. 1622-1636.

Ahmed, R., Nim, S., Mostafavi, S., Jain, A. K., & Krishana, B. 2008b, "Neuroprotective effects of 1, 25-dihydroxycholecalciferol against 6-hydroxydopamine-induced neurotoxicity in rats", *Biomedicine.28(1)()(pp 24-28), 2008.Date of Publication: Jan 2008.* no. 1, pp. 24-28.

Akai, T., Ozawa, M., Yamaguchi, M., Mizuta, E., & Kuno, S. 1995, "Combination treatment of the partial D2 agonist terguride with the D1 agonist SKF 82958 in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian cynomolgus monkeys", *J.Pharmacol.Exp.Ther.*, vol. 273, no. 1, pp. 309-314.

Akai, T., Yamaguchi, M., Mizuta, E., & Kuno, S. 1993, "Effects of terguride, a partial D2 agonist, on MPTP-lesioned parkinsonian cynomolgus monkeys", *Ann.Neurol.*, vol. 33, no. 5, pp. 507-511.

Alexander, G. M., Brainard, D. L., Gordon, S. W., Hichens, M., Grothusen, J. R., & Schwartzman, R. J. 1991, "Dopamine receptor changes in untreated and (+)-PHNO-treated MPTP parkinsonian primates", *Brain Research*, vol. . 547, no. 2, pp. 181-189.

Anderson, J. J., Chase, T. N., & Engber, T. M. 1992, "Differential effect of subthalamic nucleus ablation on dopamine-D1 and dopamine-D2 agonist induced rotation in 6-hydroxydopamine-lesioned rats", *Brain Research*, vol. 588, no. 2, pp. 307-310.

Anderson, J. J. E. 1991, "Differential effect of subthalamic nucleus lesion on D1 and D2 agonist-induced rotation in 6 hydroxydopamine lesioned rats", *Society for Neuroscience Abstracts*, vol. 17, no. 1-2, p. 1220.

Andringa, G., Lubbers, L., Drukarch, B., Stoof, J. C., & Cools, A. R. 1999a, "The predictive validity of the drug-naive bilaterally MPTP-treated monkey as a model of Parkinson's disease: Effects of L-DOPA and the D1 agonist SKF 82958", *Behavioural Pharmacology*, vol. . 10, no. 2, pp. 175-182.

Andringa, G., Stoof, J. C., & Cools, A. R. 1999, "Sub-chronic administration of the dopamine D1 antagonist SKF 83959 in bilaterally MPTP-treated rhesus monkeys: Stable therapeutic effects and wearing-off dyskinesia", *Psychopharmacology*, vol. . 146, no. 3, pp. 328-334.

Andringa, G., Vermeulen, R. J., Drukarch, B., Renier, W. O., Stoof, J. C., & Cools, A. R. 1999b, "The validity of the pretreated, unilaterally MPTP-treated monkey as a model of Parkinson's disease: A detailed behavioural analysis of the therapeutic and undesired effects of the D2 agonist quinpirole and the D1 agonist SKF 81297", *Behavioural Pharmacology*, vol. . 10, no. 2, pp. 163-173.

Aquiar, L. M., Macedo, D. S., Vasconcelos, S. M. M., Oliveira, A. A., Clea, F., de Sousa, F., & Viana, G. S. B. 2008, "CSC, an adenosine A(2A) receptor antagonist and MAO B inhibitor, reverses behavior,

monoamine neurotransmission, and amino acid alteration in the 6-OHDA-lesioned rats", *Brain Research*, vol. 1191, pp. 192-199.

Arai, N., Isaji, M., Kojima, M., Mizuta, E., & Kuno, S. 1996, "Combined effects of cabergoline and L-dopa on parkinsonism in MPTP-treated cynomolgus monkeys", *J.Neural Transm.*, vol. 103, no. 11, pp. 1307-1316.

Asin, K. E., Domino, E. F., Nikkel, A., & Shiosaki, K. 1997, "The selective dopamine D1 receptor agonist A-86929 maintains efficacy with repeated treatment in rodent and primate models of Parkinson's disease", *Journal of Pharmacology & Experimental Therapeutics*, vol. . 281, no. 1, pp. 454-459.

Atsumi, M., Kawakami, J., Sugiyama, E., Kotaki, H., Sawada, Y., Sato, H., Yamada, Y., & Iga, T. 2003, "Pharmacokinetic and pharmacodynamic analyses, based on dopamine D2-receptor occupancy of bromocriptine, of bromocriptine-induced contralateral rotations in unilaterally 6-OHDA-lesioned rats", *Synapse.*, vol. 50, no. 2, pp. 110-116.

Belluzzi, J. D., Domino, E. F., May, J. M., Bankiewicz, K. S., & McAfee, D. A. 1994, "N-0923, a selective dopamine D2 receptor agonist, is efficacious in rat and monkey models of Parkinson's disease", *Movement Disorders*, vol. . 9, no. 2, pp. 147-154.

Bibbiani, F. C. L. P. R. C. T. 2003, "Continuous apomorphine administration with novel EVA implants reduces the risk of motor complications compared to pulsatile apomorphine in L-DOPA-Naive, MPTP-lesioned primates", *Neurology*, vol. 60, no. 5, p. A330.

Blanchet, P. J., Konitsiotis, S., & Chase, T. N. 1997, "Motor response to a dopamine D3 receptor preferring agonist compared to apomorphine in levodopa-primed 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys", *J.Pharmacol.Exp.Ther.*, vol. 283, no. 2, pp. 794-799.

Blanco, L. L., Alvarez, P., Pavon, N., Macias, R., Castellanos, O., Torres, A., de la, C. K., Moreno, H., & Sanz, V. 1995, "Effect of apomorphine in hemiparkinsonian monkeys assessed with a clinical scale. Preliminary study of dyskinesias", *Revista Neurologica Argentina*, vol. . 20, no. 3, pp. 80-86.

Boldry, R. C., Chase, T. N., & Engber, T. M. 1993, "Influence of previous exposure to levodopa on the interaction between dizocilpine and dopamine D1 and D2 agonists in rats with 6-hydroxydopamine- induced lesions", *Journal of Pharmacology & Experimental Therapeutics*, vol. . 267, no. 3, pp. 1454-1459.

Bruke, T., Bankiewicz, K., Harvey-White, J., & Kopin, I. 1988, "The partial dopamine receptor agonist terguride in the MPTP- induced hemiparkinsonian monkey model", *European Journal of Pharmacology*, vol. 148, no. 3, pp. 445-448.

Buck, K. & Ferger, B. 2008, "Intrastriatal inhibition of aromatic amino acid decarboxylase prevents L-DOPA-induced dyskinesia: A bilateral reverse in vivo microdialysis study in 6-hydroxydopamine lesioned rats", *Neurobiology of Disease*, vol. 29, no. 2, pp. 210-220.

Burke, W. J., Panneton, M. W., Galvin, J. E., & Kumar, V. B. 2009, "DOPAL Treated Rat: A New Behavioral Model for Parkinson's Disease", *Neurology*, vol. 72, no. 11, p. A342.

Burunat, E., Castro, R., Diaz-Palarea, M. D., & Rodriguez, M. 1987, "Conditioned response to apomorphine in nigro-striatal system-lesioned rats: the origin of undrugged rotational response", *Life Sci.*, vol. 41, no. 15, pp. 1861-1866.

Bychkov, E., Ahmed, M. R., Dalby, K. N., & Gurevich, E. V. 2007, "Dopamine depletion and subsequent treatment with L-DOPA, but not the long-lived dopamine agonist pergolide, enhances activity of the Akt pathway in the rat striatum", *Journal of Neurochemistry*, vol. 102, no. 3, pp. 699-711.

Cannon, J. R., Tapias, V., Na, H. M., Honick, A. S., Drolet, R. E., & Greenamyre, J. T. 2009, "A highly reproducible rotenone model of Parkinson's disease", *Neurobiol Dis*, vol. 34, no. 2, pp. 279-290.

Carta, A. R., Lucia, F., Annalisa, P., Silvia, P., Nicola, S., Nicoletta, S., & Micaela, M. 2008a, "Behavioral and biochemical correlates of the dyskinetic potential of dopaminergic agonists in the 6-OHDA lesioned rat", *Synapse*, vol. 62, no. 7, pp. 524-533.

Carta, A. R., Frau, L., Pontis, S., Pinna, A., & Morelli, M. 2008b, "Direct and indirect striatal efferent pathways are differentially influenced by low and high dyskinetic drugs: behavioural and biochemical evidence", *Parkinsonism Relat Disord*, vol. 14 Suppl 2, p. S165-S168.

Casas, M., Prat, G., Rubio, A., Barbanoj, M., & Jane, F. 2000, "Lack of synergism between caffeine and SKF 38393 on rotational behavior in 6-hydroxydopamine-denervated rats", *Eur.J.Pharmacol.*, vol. %19;396, no. 2-3, pp. 93-99.

Castellano, J. M., Batrynchuk, J., Dolbeare, K., Verma, V., Mann, A., Skoblenick, K. J., Johnson, R. L., & Mishra, R. K. 2007, "MIF-1 and its peptidomimetic analogs attenuate haloperidol-induced vacuous chewing movements and modulate apomorphine-induced rotational behavior in 6-hydroxydopamine-lesioned rats", *Peptides*, vol. 28, pp. 2009-2015.

Chang, J. W., Chung, S. S., & Park, Y. G. 1994, "The study of apomorphine-induced rotational behavior in partial lesioned rat parkinsonian models with 6-hydroxydopamine", *Society for Neuroscience Abstracts*, vol. 20, no. 1-2, p. 1328.

Chen, X., Li, J., Qi, W. Q., & Shen, S. H. 2007, "Experimental change on dopaminergic neurons in striatum of Parkinson disease rats", *Histology and Histopathology*, vol. 22, no. 10-12, pp. 1085-1090.

Close, S. P., Elliott, P. J., Hayes, A. G., & Marriott, A. S. 1990, "Effects of classical and novel agents in a MPTP-induced reversible model of Parkinson's disease", *Psychopharmacology (Berl).*, vol. 102, no. 3, pp. 295-300.

Close, S. P., Marriott, A. S., & Pay, S. 1985, "Failure of SKF 38393-A to relieve parkinsonian symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the marmoset", *British Journal of Pharmacology*, vol. . 85, no. 2, pp. 320-322.

Cools, A., R, Verheij, M., M, M, Paans, N., Hooimans, C., Gielen, K., DaCostaGomez, D., Schennink, A., & Oosterhout, F. 2003, "SKF83959, a unique antiparkinson agent in animal models, stimulates dopamine D1 receptors that are coupled to phospholipase C, in denervated striatum and intact nucleus accumbens of freely moving rats", *Society for Neuroscience Abstract Viewer and Itinerary Planner*.

Coppi, G. 1995, "Neuroprotective activity of alpha-dihydroergocryptine in animal models", *Journal of Neural Transmission Supplement*, vol. 45, no. Supplement, pp. 307-318.

Costall, B. & Naylor, R. J. 1975, "Neuropharmacological studies on D145 (1,3-dimethyl-5-aminoadamantan)", *Psychopharmacologia.*, vol. 43, no. 1, pp. 53-61.

Crossman, A., R, Hill, M., P, McGuire, S., G, Millan, M., J, Rochat, C., Brotchie, J., & M 2001, "S32504, a preferential dopamine D3 versus D2 receptor agonist displays rapid anti-parkinsonian properties in a MPTP-lesioned primate model", *Society for Neuroscience Abstracts*, vol. 27, no. 1, p. 530.

Curzon, P., Kebabian, J. W., & Britton, D. R. 1990, "A-68930 and L Dopa rapidly diminish the rotation response to D1 agonists in 6 OHDA lesioned rats", *Society for Neuroscience Abstracts*, vol. 16, no. 1, p. 131.

DaSilva, J., N, Schwartz, R., A, Fletcher, P., J, & Houle, S. 2000, "Studying D1 receptor supersensitivity in vivo in unilateral 6-hydroxydopamine treated rats with (11C)SCH 23390 and D1 agonist R-(11C)SKF 82957", *Society for Neuroscience Abstracts*, vol. 26, no. 1-2, p. 478.5.

Delfino, M., Kalisch, R., Czisch, M., Larramendy, C., Ricatti, J., Taravini, I. R., Trenkwalder, C., Murer, M. G., Auer, D. P., & Gershanik, O. S. 2007, "Mapping the effects of three dopamine agonists with different dyskinetogenic potential and receptor selectivity using pharmacological functional magnetic resonance imaging", *Neuropsychopharmacology*, vol. 32, no. 9, pp. 1911-1921.

Doan, V. D., Grondin, R., Tahar, A. H., Gregoire, L., & Bedard, P. J. 1999, "Effect of the selective D1 antagonists SCH 23390 and NNC 01-0112 on the delay, duration, and improvement of behavioral responses to dopaminergic agents in MPTP-treated monkeys", *Clinical Neuropharmacology*, vol. . 22, no. 5, pp. 281-287.

Domino, E. F. & Ni, L. Z. H. K. Y. S. M. 1997, "Talipexole or pramipexole combinations with chloro-APB (SKF 82958) in MPTP-induced hemiparkinsonian monkeys", *European Journal of Pharmacology*, vol. 325, no. 2-3, pp. 137-144.

Drukarch, B., Vermeulen, R., J, Schoffelmeer, A., N, M, Wolters, E., C, Goosen, C., Stoof, J., & C 1993, "Naltrexone decreases dopamine D-2 but not D-1 receptor mediated rotational behaviour in unilaterally MPTP-lesioned monkeys", *Society for Neuroscience Abstracts*, vol. 19, no. 1-3, p. 1051.

Dupre, K. B., Eskow, K. L., Barnum, C. J., & Bishop, C. 2008, "Striatal 5-HT1A receptor stimulation reduces D1 receptor-induced dyskinesia and improves movement in the hemiparkinsonian rat", *Neuropharmacology*, vol. 55, no. 8, pp. 1321-1328.

Dupre, K. B., Eskow, K. L., Negron, G., & Bishop, C. 2007, "The differential effects of 5-HT1A receptor stimulation on dopamine receptor-mediated abnormal involuntary movements and rotations in the primed herniparkinsonian rat", *Brain Research*, vol. 1158, pp. 135-143.

Duty, S. & Brotchie, J. M. 1997, "Enhancement of the behavioral response to apomorphine administration following repeated treatment in the 6-hydroxydopamine-lesioned rat is temporally correlated with a rise in striatal preproenkephalin-B, but not preproenkephalin-A, gene expression", *Exp.Neurol.*, vol. 144, no. 2, pp. 423-432.

Duvoisin, R. C., Heikkila, R. E., & Manzino, L. 1982, "Pergolide-induced circling in rats with 6-hydroxydopamine lesions in the nigrostriatal pathway", *Neurology*, vol. . 32, no. 12, pp. 1387-1391.

Eden, R. J., Costall, B., Domeney, A. M., Gerrard, P. A., Harvey, C. A., Kelly, M. E., Naylor, R. J., Owen, D. A. A., & Wright, A. 1991, "Preclinical pharmacology of ropinirole (SK and F 101468-A) a novel dopamine D2 agonist", *Pharmacology, Biochemistry & Behavior*, vol. . 38, no. 1, pp. 147-154.

Ekesbo, A., Andren, P. E., Gunne, L. M., Sonesson, C., & Tedroff, J. 2000, "Motor effects of (-)-OSU6162 in primates with unilateral 6-hydroxydopamine lesions", *Eur.J.Pharmacol.*, vol. 389, no. 2-3, pp. 193-199.

Esposito, E., Fantin, M., Marti, M., Drechsler, M., Paccamiccio, L., Mariani, P., Sivieri, E., Lain, F., Menegatti, E., Morari, M., & Cortesi, R. 2008, "Solid lipid nanoparticles as delivery systems for bromocriptine", *Pharmaceutical Research*, vol. 25, no. 7, pp. 1521-1530.

Evans, M. C., Pradhan, A., Venkatraman, S., Ojala, W. H., Gleason, W. B., Mishra, R. K., & Johnson, R. L. 1999, "Synthesis and dopamine receptor modulating activity of novel peptidomimetics of L-prolyl-L-leucyl-glycinamide featuring alpha,alpha- disubstituted amino acids", *Journal of Medicinal Chemistry*, vol. . 42, no. 8, pp. 1441-1447.

Feng, D.-Q. & Chen, X.-R. 2005, "Apomorphine induced c-fos expression in the striatum of 6-OHDA-lesioned rats", *Chinese Pharmacological Bulletin*, vol. . 21, no. 9, pp. 1119-1122.

Filion, M., Tremblay, L., & Bedard, P. J. 1991, "Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism", *Brain Research*, vol. . 547, no. 1, pp. 152-161.

Fleming, S., M, Salcedo, J., Hutson, C., B, Rockenstein, E., Masliah, E., Levine, M., S, Chesselet, M., -F, (Mchesselet@mednet, ucla, & edu) "Behavioral effects of dopaminergic agonists in transgenic mice overexpressing human wildtype alpha-synuclein", *Neuroscience*.

Fornaguera, J., Huston, J. P., CAREY, R. J., & Schwarting, R. K. 1995, "Stimulation of D1- or D2-receptors in drug-naive rats with different degrees of unilateral nigro-striatal dopamine lesions", *Psychopharmacology (Berl).*, vol. 119, no. 2, pp. 145-154.

Fox, S. & Brotchie, J. 1996, "Normethylclozapine potentiates the action of quinpirole in the 6-hydroxydopamine lesioned rat", *Eur.J.Pharmacol.*, vol. 301, no. 1-3, pp. 27-30.

Fox, S. H. & Brotchie, J. M. 2000, "5-HT2C receptor antagonists enhance the behavioural response to dopamine D1 receptor agonists in the 6-hydroxydopamine-lesioned rat", *European Journal of Pharmacology*, vol. 398, no. 1, pp. 59-64.

Fukuzaki, K., Kamenosono, T., Kitazumi, K., & Nagata, R. 2000, "Effects of ropinirole on motor behavior in MPTP-treated common marmosets", *Pharmacol.Biochem.Behav.*, vol. 67, no. 1, pp. 121-129.

Fukuzaki, K., Kamenosono, T., & Nagata, R. 2000, "Effects of ropinirole on various parkinsonian models in mice, rats, and cynomolgus monkeys", *Pharmacol.Biochem.Behav.*, vol. 65, no. 3, pp. 503-508.

Gagnon, C., Gomezmancilla, B., Markstein, R., Bedard, P. J., & Dipaolo, T. 1995, "Effect of adding the D-1 agonist CY 208-243 to chronic bromocriptine treatment of MPTP-monkeys: Regional changes of brain dopamine receptors", *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 119, no. 4, pp. 667-676.

Gancher, S., Crabbe, J., Garland, A., Lea, E., & Woodward, W. 1995, "Dose- and duration-dependent tolerance to rotational effects of apomorphine in a rat model of Parkinsonism", *J.Pharmacol.Exp.Ther.*, vol. 272, no. 1, pp. 275-281.

Gancher, S. & Mayer, A. 1995, "Sensitization to apomorphine-induced rotational behavior in 6-OHDA-lesioned rat: Effects of NMDA antagonists on drug response", *Brain Research*, vol. 682, no. 1-2, pp. 63-68.

Garcia, d. Y., Fahn, S., Mena, M. A., Pardo, B., & Casarejos, M. J. 1988, "Intracerebroventricular infusion of dopamine and its agonists in rodents and primates. An experimental approach to the treatment of Parkinson's disease", *ASAIO Transactions*, vol. . 34, no. 4, pp. 951-957.

Giardina, W., J, Williams, M., Roux, S., & Porsolt, R. 2000, "ABT-431, a prodrug of the dopamine D1 receptor agonist A-86929, is inactive in conditioned place preference and self-administration tests of abuse liability", *Society for Neuroscience Abstracts*, vol. 26, no. 1-2, p. 278.11.

Gnanalingham, K. K., Hunter, A. J., Jenner, P., & Marsden, C. D. 1995a, "Selective dopamine antagonist pretreatment on the antiparkinsonian effects of benzazepine D1 dopamine agonists in rodent and primate models of Parkinson's disease - the differential effects of D1 dopamine antagonists in the primate", *Psychopharmacology*, vol. . 117, no. 4, pp. 403-412.

Gnanalingham, K. K., Hunter, A. J., Jenner, P., & Marsden, C. D. 1995b, "The differential behavioural effects of benzazepine D1 dopamine agonists with varying efficacies, co-administered with quinpirole in primate and rodent models of Parkinson's disease", *Psychopharmacology*, vol. . 117, no. 3, pp. 287-297.

Gold, S. J., Hoang, C. V., Potts, B. W., Porras, G., Pioli, E., Kim, K. W., Nadjar, A., Qin, C., LaHoste, G. J., Li, Q., Bioulac, B. H., Waugh, J. L., Gurevich, E., Neve, R. L., & Bezard, E. 2007, "RGS9-2 negatively modulates L-3,4-dihydroxyphenylalanine-induced dyskinesia in experimental Parkinson's disease", *J Neurosci*, vol. 27, no. 52, pp. 14338-14348.

Gomez-Manicilla, B. & Bedard, P. J. 1992, "Effect of chronic treatment with (+)-PHNO, a D2 agonist in MPTP-treated monkeys", *Experimental Neurology*.

Gossel, M., Schmidt, W. J., Loscher, W., Zajaczkowski, W., & Danysz, W. 1995, "Effect of coadministration of glutamate receptor antagonists and dopaminergic agonists on locomotion in monoamine-depleted rats", *J.Neural Transm.Park Dis.Dement.Sect.*, vol. 10, no. 1, pp. 27-39.

Goulet, M., Morissette, M., Blanchet, P., J, Bedard, P., J, & Di Paolo, T. 1995, "In situ hybridization of D1 and D2 dopamine receptor mRNAs in the caudate-putamen of MPTP monkeys: Effect of chronic treatment with the D2 agonist U91356A", *Society for Neuroscience Abstracts*, vol. 21, no. 1-3, p. 1254.

Goulet, M. M. "D1 dopamine receptor agonists are more effective in alleviating advanced than mild parkinsonism in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys", *Journal of Pharmacology and Experimental Therapeutics*.

Gramsbergen, J. B., Christensen, L. P., & Petersen, K. K. 2009, "Therapeutic and adverse effects of chronic adminstration of Mucuna pruriens extract as compared with L-DOPA in 6-hydroxydopamine lesioned rats", *Journal of Neurochemistry*, vol. 110, p. 127.

Gray, B. C., McNeish, C. S., Mandel, R. J., & Strecker, R. E. 1991, "Efficacy of antiparkinsonian drugs on the spontaneous paw reaching and sensorimotor deficits caused by complete unilateral dopamine depletion of the rat forebrain", *Society for Neuroscience Abstracts*, vol. 17, no. 1-2, p. 501.

Gregoire, L., Samadi, P., Graham, J., Bedard, P. J., Bartoszyk, G. D., & Di Paolo, T. 2009, "Low doses of sarizotan reduce dyskinesias and maintain antiparkinsonian efficacy of L-Dopa in parkinsonian monkeys", *Parkinsonism Relat Disord*, vol. 15, no. 6, pp. 445-452.

Grondin, R., Bedard, P. J., Britton, D. R., & Shiosaki, K. 1997, "Potential therapeutic use of the selective dopamine D1 receptor agonist, A-86929: An acute study in parkinsonian levodopa-primed monkeys", *Neurology*, vol. . 49, no. 2, pp. 421-426.

Grondin, R., Blanchet, P., J, Bedard, P., J, Britton, D., R, Shiosaki, K., Kebabian, J., & W 1994, "Dramatic desensitization of the behavioral response to a long-acting D1 but not D2 agonist in MPTP monkeys", *Society for Neuroscience Abstracts*, vol. 20, no. 1-2, p. 1645.

Gu, S., Huang, H., Bi, J., Yao, Y., & Wen, T. 2009, "Combined treatment of neurotrophin-3 gene and neural stem cells is ameliorative to behavior recovery of Parkinson's disease rat model", *Brain Res*, vol. 1257, pp. 1-9.

Guilloux, J. P., Massart, R., Mignon, V., Diaz, J., & Arrang, J. M. 2008, "Could nicotine potentiate the beneficial effects of levodopa in the 6-OHDA rat model? A behavioural study", *European Neuropsychopharmacology*, vol. 18, p. S52-S53.

Gulwadi, A. G., Korpinen, C. D., Mailman, R. B., Nichols, D. E., Sit, S. Y., & Taber, M. T. 2001, "Dinapsoline: characterization of a D1 dopamine receptor agonist in a rat model of Parkinson's disease", *J.Pharmacol.Exp.Ther.*, vol. 296, no. 2, pp. 338-344.

Gunzler, S. A., Shakil, S., Carlson, N. E., Nutt, J. G., & Meshul, C. K. 2007, "Low doses of apomorphine transiently reduce locomotor activity in MPTP-treated mice", *Neuroscience Letters*, vol. 428, no. 2-3, pp. 64-67.

Hara, K., Ikoma, Y., Nakada, Y., & Oshino, N. 1989, "Effects of an ergot derivative, lisuride, on the function of dopaminergic neurons in the central nervous system of rats", *Japanese Pharmacology & Therapeutics*, vol. . 17, no. 10, pp. 335-364.

Harkavyi, A., Abuirmeileh, A., Lever, R., Kingsbury, A. E., Biggs, C. S., & Whitton, P. S. 2008, "Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease", *J Neuroinflammation*, vol. 5, p. 19.

Hashizume, Y., Ohgoh, M., Ueno, M., Hanada, T., & Nishizawa, Y. 2008, "Effects of Perampanel, a selective amPA Receptor Antagonist, on L-DOPA-Induced Rotational Behaviour in L-DOPA Primed 6-OHDA Hemiparkinsoian Rats", *Neurology*, vol. 70, no. Supplement 1, p. A323.

Hassan, M. N., Higgins, D., Traub, M., & Fahn, S. 1986, "Chronic treatment with bromocriptine induces behavioral supersensitivity in rats", *Life Sci.*, vol. 39, no. 6, pp. 513-518.

Hayakawa, T., Sugimoto, Y., Chen, Z., Fujii, Y., & Kamei, C. 1999, "Effects of anti-Parkinsonian drugs on neurobehavioural changes induced by bilateral 6-hydroxydopamine lesions in rats", *Clin.Exp.Pharmacol.Physiol.*, vol. 26, no. 5-6, pp. 421-425.

Hayakawa, T. K. 1998, "Effects of certain drugs for Parkinson's disease on neurobehavioral changes induced by bilateral 6-hydroxydopamine lesions in rats", *Methods and Findings in Experimental and Clinical Pharmacology*, vol. 20, no. 7, p. 635.

Hazelhoff, B., De Vries, J. B., & Dijkstra, D. 1986, "Neuropharmacological profile of a new series of dopamine agonists: N-n-propyl-hexahydronaphthoxazines", *European Journal of Pharmacology*, vol. . 124, no. 1-2, pp. 93-106.

Heinrich, J. N., Brennan, J., Lai, M. H., Sullivan, K., Hornby, G., Popiolek, M., Jiang, L. X., Pausch, M. H., Stack, G., Marquis, K. L., & Andree, T. H. 2006, "Aplindore (DAB-452), a high affinity selective dopamine D2 receptor partial agonist", *Eur.J.Pharmacol.*, vol. 552, no. 1-3, pp. 36-45.

Henry, B., Crossman, A. R., & Brotchie, J. M. 1999, "Effect of repeated L-DOPA, bromocriptine, or lisuride administration on preproenkephalin-A and preproenkephalin-B mRNA levels in the striatum of the 6-hydroxydopamine-lesioned rat", *Exp.Neurol.*, vol. 155, no. 2, pp. 204-220.

Hill, M. P., Ravenscroft, P., McGuire, S. G., Brotchie, J. M., Crossman, A. R., Rochat, C., & Millan, M. J. 2006, "Antiparkinsonian effects of the novel D3/D2 dopamine receptor agonist, S32504, in MPTP-lesioned marmosets: Mediation by D2, not D3, dopamine receptors", *Mov Disord.*, vol. 21, no. 12, pp. 2090-2095.

Hinzen, D., Hornykiewicz, O., & Kobinger, W. 1986, "The dopamine autoreceptor agonist B-HT 920 stimulates denervated postsynaptic brain dopamine receptors in rodent and primate models of Parkinson's disease: A novel approach to treatment", *European Journal of Pharmacology*, vol. . 131, no. 1, pp. 75-86.

Hironaka, N., Kohno, Y., & Yanagita, T. 1998, "Comparative studies on antiparkinsonian agents, talipexole and bromocriptine, evaluated by contralateral rotational behavior in unilaterally nigral-lesioned rats", *Folia Pharmacologica Japonica*, vol. . 112, no. 4, pp. 257-266.

Honkanen, A., Ingman, K., Korpi, E., R, Savola, J., & -M 1999, "JP 1730, a novel alpha2-adrenoceptor antagonist, enhances apomorphine- and L-dopa-induced circling behavior in the rat", *Society for Neuroscience Abstracts*, vol. 25, no. 1-2, p. 1344.

Hsu, A., Togasaki, D. M., Bezard, E., Sokoloff, P., Langsten, J. W., Di Monte, D. A., & Quik, M. 2004, "Effect of the D3 dopamine receptor partial agonist BP897 [N-[4-(4-(2-methoxyphenyl)piperazinyl)butyl]-2-naphthamide] on L-3,4-dihydroxyphenylalanine-induced dyskinesias and parkinsonism in squirrel monkeys", *Journal of Pharmacology & Experimental Therapeutics*, vol. . 311, no. 2, pp. 770-777.

Hubbard, C. A. & Trugman, J. M. 1993, "Reversal of reserpine-induced catalepsy by selective D1 and D2 dopamine agonists", *Mov Disord.*, vol. 8, no. 4, pp. 473-478.

Hudson, J. L., Van Horne, C. G., & Stromberg, I. 1991, "Correlation of apomorphine and amphetamine-induced turning behaviour with nigrostriatal dopamine depletion", *Society for Neuroscience Abstracts*, vol. 17, no. 1-2, p. 1245.

Hudson, J. L., Fong, C.-S., BOYSON, S. J., & Hoffer, B. J. 1994, "Conditioned apomorphine-induced turning in 6-OHDA-lesioned rats", *Pharmacology, Biochemistry & Behavior*, vol. . 49, no. 1, pp. 147-154.

Hudson, J. L., van Horne, C. G., Stromberg, I., Brock, S., Clayton, J., Masserano, J., Hoffer, B. J., & Gerhardt, G. A. 1993, "Correlation of apomorphine- and amphetamine-induced turning with nigrostriatal dopamine content in unilateral 6-hydroxydopamine lesioned rats", *Brain Res.*, vol. 626, no. 1-2, pp. 167-174.

Huynh, T., Mehta, A., & Chesselet, MF. 2002, "Pramipexole differentially affects behaviors induced in rodent models of early and late Parkinson's disease", *Journal of Investigative Medicine*, vol. 50, no. 5, p. 58A.

Iarkov, A., V, Hanger, D., Reploge, M., Joyce, J., & N 2003, "Behavioral effects of dopamine agonists and antagonist in MPTP lesioned D3 receptor knockout mice", *Pharmacology, Biochemisty and Behaviour*, vol. 76, no. 3-4, pp. 551-562.

Ichikawa, K. & Kojima, M. 2001, "Pharmacological effects of cabergoline against parkinsonism", *Folia Pharmacologica Japonica*, vol. 117, no. 6, pp. 395-400.

Irifune, M., Nomoto, M., & Fukuda, T. 1993, "Effects of talipexole on motor behavior in normal and MPTP-treated common marmosets", *Eur.J.Pharmacol.*, vol. %20;238, no. 2-3, pp. 235-240.

Irifune, M., Nomoto, M., & Fukuka, T. 1994, "Antiparkinsonian activity of talipexole in MPTP-treated monkeys: In combination with L-DOPA and as chronic treatment", *European Journal of Pharmacology*, vol. 264, no. 2, pp. 117-123.

Ismayilova, N., Crossman, A., Verkhratsky, A., & Brotchie, J. 2004, "Effects of adenosine A1, dopamine D1 and metabotropic glutamate 5 receptors-modulating agents on locomotion of the reserpinised rats", *Eur.J.Pharmacol.*, vol. 497, no. 2, pp. 187-195.

Jadavji, N. M. & Metz, G. A. 2009, "Both pre- and post-lesion experiential therapy is beneficial in 6-hydroxydopamine dopamine-depleted female rats", *Neuroscience.158(2)()(pp 373-386), 2009.Date of Publication: 23 Jan 2009.* no. 2, pp. 373-386.

Jenkins, O. F. & Jackson, D. M. 1985, "Bromocriptine potentiates the behavioral-effects of directly and indirectly acting dopamine receptor agonists in mice", *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 331, no. 1, pp. 7-11.

Jenner, P., Marsden, C. D., & Nomoto, M. 1986, "Antiparkinsonian activity of dextro 4 propyl-9-hydroxynapthoxazine in the 1 methyl-4-phenyl-1 2 3 6-tetrahydropyridine-treated marmoset following subcutaneous infusion or skin application", *British Journal of Pharmacology*, vol. 89, no. Supplement, p. 626P.

Jenner, P. 1992, "Parkinson's disease: Pathological mechanisms and actions of piribedil", *Journal of Neurology, Supplement*, vol. . 239, no. 1, p. S2-S8.

Jeon, M. Y., Lee, W. Y., Kang, H. Y., & Chung, E. J. 2007, "The effects of L-3,4-dihydroxyphenylalanine and dopamine agonists on dopamine neurons in the progressive hemiparkinsonian rat models", *Neurological Research*, vol. 29, no. 3, pp. 289-295.

Jiang, H., Jackson-Lewis, V., Muthane, U., Dollison, A., Ferreira, M., Espinosa, A., Parsons, B., & Przedborski, S. 1993a, "Adenosine receptor antagonists potentiate dopamine receptor agonist-induced rotational behavior in 6-hydroxydopamine-lesioned rats", *Brain Res.*, vol. 613, no. 2, pp. 347-351.

Jiang, H., Jackson-Lewis, V., Muthane, U., Parson, B., Fahn, S., & Przedborski, S. 1993b, "Potentiation of antiparkinsonian effects of dopamine agonists by adenosine antagonists in 6-hydroxydopamine-lesioned rats", *Neurology*, vol. 43, no. 4 Suppl.2, p. A154.

Jin, F., Wu, Q., Lu, Y. F., Gong, Q. H., & Shi, J. S. 2008, "Neuroprotective effect of resveratrol on 6-OHDA-induced Parkinson's disease in rats", *European Journal of Pharmacology*, vol. 600, no. 1-3, pp. 78-82.

Johnson, B. J., Peacock, V., & SCHNEIDER, J. S. 1995, "Dihydrexidine, a full D1 dopamine receptor agonist, induces rotational asymmetry in hemiparkinsonian monkeys", *Pharmacol.Biochem.Behav.*, vol. 51, no. 4, pp. 617-622.

Johnston, L., C, McCreary, A., C, Rose, S., Smith, L., Jackson, M., & Jenner, P. 2003, "Association between intrinsic activity and the antiparkinsonian effects of a novel dopamine D2 agonist series in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treated primate model of Parkinson's disease", *European Journal of Neurology*, vol. 20, no. Supplement 1, pp. 169-170.

Johnston, L., C, Smith, L., McCreary, A., C, Jenner, P., & Ronken, E. 2001a, "SLV308: Antiparkinsonian effects in the MPTP-treated common marmoset (Callithrix jacchus)", *Society for Neuroscience Abstracts*, vol. 27, no. 1, p. 531.

Johnston, L., C, Smith, L., Rose, S., & Jenner, P. 2001b, "The novel dopamine D2 receptor partial agonist, SLV-308, reverses motor disability in MPTP-lesioned common marmosets (Callithrix jacchus)", *British Journal of Pharmacology*, vol. 133, p. 134P.

Johnston, L. C., Su, X., Maguire-Zeiss, K., Horovitz, K., Ankoudinova, I., Guschin, D., Hadaczek, P., Federoff, H. J., Bankiewicz, K., & Forsayeth, J. R. 2008, "Human interleukin-10 gene transfer is protective in a rat model of parkinson's disease", *Molecular Therapy*, vol. 16, no. 8, pp. 1392-1399.

Kaariainen, T. M., Piltonen, M., Ossola, B., Kekki, H., Lehtonen, S., Nenonen, T., Lecklin, A., Raasmaja, A., & Mannisto, P. T. 2008, "Lack of robust protective effect of quercetin in two types of 6-

hydroxydopamine-induced parkinsonian models in rats and dopaminergic cell cultures", *Brain Res*, vol. 1203, pp. 149-159.

Kalda, A., Herm, L., Rinken, A., Zharkovsky, A., & Chen, J. F. 2009, "Co-administration of the partial dopamine D2 agonist terguride with L-dopa attenuates L-dopa-induced locomotor sensitization in hemiparkinsonian mice", *Behavioural Brain Research*, vol. 202, no. 2, pp. 232-237.

Kashihara, K., Akiyama, K., Ishihara, T., Shiro, Y., & Shohmori, T. 1996, "Levodopa but not bromocriptine induces AP-1 and CREB DNA-binding activity in the dopamine-depleted striatum of the rat", *Life Sciences*, vol. . 58, no. 10, p. L159-L170.

Kashihara, K., Manabe, Y., Murakami, T., & Abe, K. 2002, "Effects of short- and long-acting dopamine agonists on sensitized dopaminergic neurotransmission in rats with unilateral 6-OHDA lesions", *Life Sci.*, vol. 70, no. 9, pp. 1095-1100.

Kaur, S., Starr, M. S., & Starr, B. S. 1994, "Role of D1 receptor mechanisms in the potentiation of motor responses to L-DOPA and apomorphine by MK 801 in the reserpine-treated mouse", *Journal of Neural Transmission - Parkinsons Disease & Dementia Section*, vol. . 8, no. 1-2, pp. 107-116.

Kenny, A. M., Schneider, M. B., Baden, D. R., Pfeiffer, R. F., & Murrin, L. C. 1986, "Bromocriptine holiday: effects on dopamine receptors and turning behavior in rats", *Neurology.*, vol. 36, no. 3, pp. 400-404.

Koller, W., Herbster, G., & Gordon, J. 1987, "PHNO, a novel dopamine agonist, in animal models of parkinsonism", *Mov Disord.*, vol. 2, no. 3, pp. 193-199.

Koller, W. C., Fields, J. Z., Gordon, J. H., & Perlow, M. J. 1986, "Evaluation of ciladopa hydrochloride as a potential anti-Parkinson drug", *Neuropharmacology.*, vol. 25, no. 9, pp. 973-979.

Koller, W. C., Weiner, W. J., & Diamond, B. I. 1980, "The pharmacological evaluation of pergolide mesylate as a potential anti-Parkinson agent", *Neuropharmacology*, vol. . 19, no. 9, pp. 831-837.

Kreisler, A., Duhamel, A., Destee, A., & Bordet, R. 2008, "Fenofibrate has a disease modifier effect in the MPTP mouse model of Parkinson's disease", *Neurology*, vol. 70, no. 11, p. A283.

Kuno, S. 1997, "Differential therapeutic effects of dopamine D1 and D2 agonists in MPTP-induced parkinsonian monkeys: clinical implications", *Eur.Neurol.*, vol. 38 Suppl 1:18-22., pp. 18-22.

Kuno, S., Akai, T., Ozawa, M., Yamaguchi, M., & Mizuta, E. 1996, "Ameliorative and adverse effects produced by coactivation of D-1 and D-2 receptors in MPTP-induced Parkinsonian monkeys", *Society for Neuroscience Abstracts*, vol. 22, no. 1-3, p. 225.

Kuno, S., Mizuta, E., Sakamoto, H., Ichihara, K., & Nagasaka, M. 1998, "Antiparkinsonian effects of BAM-1110, a novel ergoline derivative, in MPTP-treated cynomolgus monkeys", *Clinical Neuropharmacology*, vol. . 21, no. 1, pp. 35-40.

LaHoste, G. J. & Marshall, J. F. 1990, "Nigral D1 and striatal D2 receptors mediate the behavioral effects of dopamine agonist", *Behavioural Brain Research*, vol. . 38, no. 3, pp. 233-242.

Laloux, C., Derambure, P., Jacquesson, J. M., Erambure, R., Destee, A., & Monaca, C. 2008, "Effect of dopaminergic substances on sleep/wakefulness in saline- and MPTP-treated mice", *Journal of Sleep Research*, vol. 17, no. 1, pp. 101-110.

Larramendy, C., Taravini, I. R. E., Saborido, M. D., Ferrario, J. E., Murer, M. G., & Gershanik, O. S. 2008, "Cabergoline and pramipexole fail to modify already established dyskinesias in an animal model of parkinsonism", *Behavioural Brain Research*, vol. 194, no. 1, pp. 44-51.

Lee, J. I., Shin, H. J., Nam, D. H., Kim, J. S., Hong, S. C., Shin, H. J., Park, K., Eoh, W., Kim, J. H., & Lee, W. Y. 2001, "Increased burst firing in substantia nigra pars reticulata neurons and enhanced response to selective D2 agonist in hemiparkinsonian rats after repeated administration of apomorphine", *J.Korean Med.Sci.*, vol. 16, no. 5, pp. 636-642.

Levesque, D., D'Antoni, T., Greenamyre, J., & T 1999, "Remacemide, an NMDA antagonist, potentiates a D2 dopamine receptor agonist in MPTP-treated monkeys", *Society for Neuroscience Abstracts*, vol. 25, no. 1-2, p. 1600.

Lindgren, H. S., Rylander, D., Ohlin, K. E., Lundblad, M., & Cenci, M. A. 2007, "The "motor complication syndrome" in rats with 6-OHDA lesions treated chronically with L-DOPA: Relation to dose and route of administration", *Behavioural Brain Research*, vol. 177, no. 1, pp. 150-159.

Liu, W. G., Lu, G. Q., Li, B., & Chen, S. D. 2007, "Dopaminergic neuroprotection by neurturin-expressing c17.2 neural stem cells in a rat model of Parkinson's disease", *Parkinsonism Relat Disord*, vol. 13, no. 2, pp. 77-88.

Lorenc-Koci, E. & Wolfarth, S. 1999, "Efficacy of pramipexole, a new dopamine receptor agonist, to relieve the parkinsonian-like muscle rigidity in rats", *Eur.J.Pharmacol.*, vol. 385, no. 1, pp. 39-46.

Loschmann, P.-A., Smith, L. A., LANGE, K. W., Jahnig, P., Jenner, P., & Marsden, C. D. 1992, "Motor activity following the administration of selective D-1 and D-2 dopaminergic drugs to MPTP-treated common marmosets", *Psychopharmacology*, vol. . 109, no. 1-2, pp. 49-56.

Loschmann, P.-A., Wullner, U., Heneka, M. T., Schulz, J. B., Kunow, M., Wachtel, H., & Klockgether, T. 1997, "Differential interaction of competitive NMDA and AMPA antagonists with selective dopamine D-1 and D-2 agonists in a rat model of Parkinson's disease", *Synapse*, vol. . 26, no. 4, pp. 381-391.

Luan, L. M., Ding, F., Ai, Y., Andersen, A., Hardy, P., Forman, E., Gerhardt, G. A., Gash, D. M., Grondin, R., & Zhang, Z. M. 2008, "Pharmacological MRI (phMRI) monitoring of treatment in hemiparkinsonian rhesus monkeys", *Cell Transplantation*, vol. 17, no. 4, pp. 417-425.

Luquin, M. R., Laguna, J., Trinidad, H. M., & Obeso, J. A. 1993, "Behavioral tolerance to repeated apomorphine administration in parkinsonian monkeys", *Journal of the Neurological Sciences*, vol. . 114, no. 1, pp. 40-44.

Maneuf, Y., P, Ivanov, T., R, Brotchie, J., & M 1997, "Cannabinoids decreased D-2 receptor-mediated alleviation of akinesia in the reserpine-treated rat model of Parkinson's disease", *Society for Neuroscience Abstracts*, vol. 23, no. 1-2, p. 467.

Maneuf, Y. P., Crossman, A. R., & Brotchie, J. M. 1997, "The cannabinoid receptor agonist WIN 55,212-2 reduces D2, but not D1, dopamine receptor-mediated alleviation of akinesia in the reserpine-treated rat model of Parkinson's disease", *Exp.Neurol.*, vol. 148, no. 1, pp. 265-270.

Maratos, E., Smith, L., Jackson, M., Pearce, R., Jenner, P., & Marsden, C. Effects of repeated treatment with combinations of L-Dopa and ropinarole on dyskinesia induction in MPTP-treated marmosets. British Journal of Pharmacology 123, 252P. 1998.
Ref Type: Abstract

Marin, C., Aguilar, E., Mengod, G., Cortes, R., Rodriguez-Oroz, M. C., & Obeso, J. A. 2008, "Entacapone potentiates the long-duration response but does not normalize levodopa-induced molecular changes", *Neurobiology of Disease*, vol. 32, no. 3, pp. 340-348.

Marin, C., Aguilar, E., Rodriguez-Oroz, M. C., Bartoszyk, G. D., & Obeso, J. A. 2009, "Local administration of sarizotan into the subthalamic nucleus attenuates levodopa-induced dyskinesias in 6-OHDA-lesioned rats", *Psychopharmacology.204(2)()(pp 241-250), 2009.Date of Publication: June 2009.* no. 2, pp. 241-250.

Maurin, B., Puma, C., Baunez, C., Bonhomme, C., Chezaubernard, C., Nieoullon, A., & Amalric, M. 2001, "The D2/D3 dopamine agonist piribedil improves time estimation in a rat model of Parkinson's disease", *Society for Neuroscience Abstracts*, vol. 27, no. 1, p. 532.

May, C. H., Guilarte, T. R., Wagner, Henry, N., , J., & Vogel, S. 1994, "Intrastriatal infusion of lisuride-A potential treatment for Parkinson's Disease? Behavioral and autoradiographic studies in 6-OHDA lesioned rats", *Neurodegeneration*, vol. 3, no. 4, pp. 305-313.

McCall, R. B., Lookingland, K. J., Bedard, P. J., & Huff, R. M. 2005, "Sumanirole, a highly dopamine D2-selective receptor agonist: in vitro and in vivo pharmacological characterization and efficacy in animal models of Parkinson's disease", *J.Pharmacol.Exp.Ther.*, vol. 314, no. 3, pp. 1248-1256.

McElroy, J. F. & Ward, K. A. 1995, "7-OH-DPAT, a Dopamine D-3-selective receptor agonist, produces contralateral rotation in 6-hydroxydopamine-lesioned rats", *Drug Development Research*, vol. 34, no. 4, pp. 329-335.

Meloni, E. G. & Davis, M. 2000, "Enhancement of the acoustic startle response by dopamine agonists after 6-hydroxydopamine lesions of the substantia nigra pars compacta: corresponding changes in c-Fos expression in the caudate-putamen", *Brain Res.*, vol. 879, no. 1-2, pp. 93-104.

Menon, M. K., Clark, W. G., & Cannon, J. G. 1976, "Comparison of dopaminergic effects of N-Substituted aporphines", *Journal of Pharmacy and Pharmacology*, vol. 28, no. 10, pp. 778-781.

Mera, T. O., Johnson, M. D., Rothe, D., Zhang, J., Xu, W., Ghosh, D., Vitek, J., & Alberts, J. L. 2009, "Objective quantification of arm rigidity in MPTP-treated primates", *J Neurosci Methods*, vol. 177, no. 1, pp. 20-29.

Metz, G., A, Whishaw, I., & Q 2000, "The effects of drug treatments on motor function in a rat model of Parkinson's disease", *Society for Neuroscience Abstracts*, vol. 26, no. 1-2, p. 666.

Michaelides, M. R., Hong, Y., DiDomenico S Jr, Bayburt, E. K., Asin, K. E., Britton, D. R., Chun, W. L., & Shiosaki, K. 1997, "Substituted hexahydrobenzo[f]thieno[c]quinolines as dopamine D1- selective agonists: Synthesis and biological evaluation in vitro and in vivo", *Journal of Medicinal Chemistry*, vol. . 40, no. 11, pp. 1585-1599.

Mierau, J. & Schingnitz, G. 1992, "Biochemical and pharmacological studies on pramipexole, a potent and selective dopamine D2 receptor agonist", *Eur.J.Pharmacol.*, vol. 215, no. 2-3, pp. 161-170.

Mignon, L. & Wolf, W. A. 2007, "Postsynaptic 5-HT1A receptor stimulation increases motor activity in the 6-hydroxydopamine-lesioned rat: implications for treating Parkinson's disease", *Psychopharmacology*, vol. 192, no. 1, pp. 49-59.

Mihara, T., Iwashita, A., & Matsuoka, N. 2008, "A novel adenosine A(1) and A(2A) receptor antagonist ASP5854 ameliorates motor impairment in MPTP-treated marmosets: Comparison with existing anti-Parkinson's disease drugs", *Behavioural Brain Research*, vol. 194, no. 2, pp. 152-161.

Milioli, E. M., Cologni, P., Santos, C. C., Marcos, T. D., Yunes, V. M., Fernandes, M. S., Schoenfelder, T., & Costa-Campos, L. 2007, "Effect of acute administration of hydroalcohol extract of Ilex paraguariensis St Hilaire (Aquifoliaceae) in animal models of Parkinson's disease", *Phytotherapy Research*, vol. 21, no. 8, pp. 771-776.

Millan, M. J., (mark, millan@fr, netgrs, com) Di Cara, B. H. M. J. M. J. J., & Brotchie, J. M. S. C. A. S. L. J. P. G. A. P. J.-L. B. M. 2004, "S32504, a novel naphtoxazine agonist at dopamine D3/D2 receptors: II", *Journal of Pharmacology and Experimental Therapeutics*, vol. 309, no. 921, p. 935.

Ming, M., Li, X. P., Fan, X. L., Yang, D. H., Li, L., Chen, S., Gu, Q., & Le, W. D. 2009, "Retinal pigment epithelial cells secrete neurotrophic factors and synthesize dopamine: possible contribution to therapeutic effects of RPE cell transplantation in Parkinson's disease", *Journal of Translational Medicine*, vol. 7, no. 53.

Miyagi, M., Arai, N., Taya, F., Itoh, F., Komatsu, Y., Kojima, M., & Isaji, M. 1996, "Effect of cabergoline, a long-acting dopamine D2 agonist, on reserpine-treated rodents", *Biol.Pharm.Bull.*, vol. 19, no. 11, pp. 1499-1502.

Mohanasundari, M., Srinivasan, M. S., Sethupathy, S., & Sabesan, M. 2006, "Enhanced neuroprotective effect by combination of bromocriptine and Hypericum perforatum extract against MPTP-induced neurotoxicity in mice", *Journal of the Neurological Sciences*, vol. . 249, no. 2, pp. 140-144.

Monty Silverdale 2003, *The pathophysiology of levodopa-induced dyskinesia in animal models of Parkinson's disease*.

Morelli, M., Fenu, S., Cozzolino, A., & Di Chiara, G. 1991, "Positive and negative interactions in the behavioural expression of D1 and D2 receptor stimulation in a model of Parkinsonism: role of priming", *Neuroscience.*, vol. 42, no. 1, pp. 41-48.

Nakagawa, M., Ohgoh, M., Nishizawa, Y., & Ogura, H. 2004, "Dopaminergic agonists and muscarinic antagonists improve lateralization in hemiparkinsonian rats in a novel exploratory Y-maze", *J.Pharmacol.Exp.Ther.*, vol. 309, no. 2, pp. 737-744.

Neisewander, J. L., Lucki, I., & McGonigle, P. 1991, "Behavioral and neurochemical effects of chronic administration of reserpine and SKF-38393 in rats", *Journal of Pharmacology & Experimental Therapeutics*, vol. . 257, no. 2, pp. 850-860.

Nomoto, M., Iwata, S.-I., Irifune, M., Kaseda, S., Osame, M., & Fukuda, T. 1998a, "Dermal application of lisuride on parkinsonism induced by 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset and on cases with Parkinson's disease", *Nihon Shinkei Seishin Yakurigaku Zasshi*, vol. . 18, no. 3, pp. 81-87.

Nomoto, M., Jenner, P., & Marsden, C. D. 1988, "The D1 agonist SKF 38393 inhibits the antiparkinsonian activity of the D2 agonist LY 171555 in the MPTP-treated marmoset", *Neuroscience Letters*, vol. . 93, no. 2-3, pp. 275-280.

Nomoto, M., Kita, S., Iwata, S. I., Kaseda, S., & Fukuda, T. 1998b, "Effects of acute or prolonged administration of cabergoline on parkinsonism induced by MPTP in common marmosets", *Pharmacol.Biochem.Behav.*, vol. 59, no. 3, pp. 717-721.

Nomoto, M., Stahl, S., Jenner, P., & Marsden, C. D. 1987, "Antiparkinsonian activity of (+)-PHNO in the MPTP-treated common marmoset", *Mov Disord.*, vol. 2, no. 1, pp. 37-45.

Nomoto, M. F. 1993, "The effects of D-1 and D-2 dopamine receptor agonist and antagonist on Parkinsonism in chronic MPTP-treated monkeys", *Advances in Neurology; Parkinson's Disease: From basic research to treatment*, vol. 60, pp. 119-122.

Norton, D., Schallert, T., Jones, T., & A 1992, "Akinesia during dopamine agonist induced circling behavior after severe unilateral neostriatal dopamine depletion in rats", *Society for Neuroscience Abstracts*, vol. 18, no. 1-2, p. 1080.

Nowak, P., Szkilnik, R., Korossy, E., Noras, L., Kostrzewa, R. M., & Brus, R. 2008, "Effect of histamine receptor antagonists on oral activity and stereotyped behaviors in neonatally 6-OHDA-lesioned rats (rodent model of Parkinson's disease)", *Pharmacological Reports*, vol. 60, no. 2, pp. 288-289.

Obeso, J., A, Rodriguez, M., Rodriguez-Oroz, M., & C 2001, "Direct apomorphine infusion into the subthalamic nucleus improves MPTP-induced parkinsonism", *Society for Neuroscience Abstracts*, vol. 27, no. 1, p. 174.

Olsson, M., Nikkhah, G., Bentlage, C., & Bjorklund, A. 1995, "Forelimb akinesia in the rat Parkinson model: differential effects of dopamine agonists and nigral transplants as assessed by a new stepping test", *J.Neurosci.*, vol. 15, no. 5 Pt 2, pp. 3863-3875.

Paterna, J.-C., Leng, A., Weber, E., Feldon, J., & Bueler, H. 2007, "DJ-1 and parkin modulate dopamine-dependent behavior and inhibit MPTP-induced nigral dopamine neuron loss in mice", *Molecular Therapy*, vol. 15, no. 4, pp. 698-704.

Pearce, P. K. B., Jackson, M., Britton, D. R., Shiosaki, K., Jenner, P., & Marsden, C. D. 1999, "Actions of the D1 agonists A-77636 and A-86929 on locomotion and dyskinesia in MPTP-treated L-dopa-primed common marmosets", *Psychopharmacology*, vol. . 142, no. 1, pp. 51-60.

Piercey, M., Moon, M., Hoffmann, W., Walters, R., Blanchette, P., & Bedard, P. U-91356A, a potent, effective, orally active D2 agonist potentially useful in treating parkinson's disease. Society for Neuroscience Abstracts 18[1081]. 1992.
Ref Type: Abstract

Pollack, A. E. & Haisley, E. C. 2001, "NMDA glutamate receptor stimulation is required for the expression of D2 dopamine mediated responses in apomorphine primed 6-hydroxydopamine lesioned rats", *Brain Res.*, vol. 897, no. 1-2, pp. 213-216.

Pollack, A. E., Turgeon, S. M., & Fink, J. S. 1997, "Apomorphine priming alters the response of striatal outflow pathways to D2 agonist stimulation in 6-hydroxydopamine-lesioned rats", *Neuroscience.*, vol. 79, no. 1, pp. 79-93.

Popoli, P., Reggio, R., & Pezzola, A. 2000, "Effects of SCH 58261, an adenosine A(2A) receptor antagonist, on quinpirole-induced turning in 6-hydroxydopamine-lesioned rats. Lack of tolerance after chronic caffeine intake", *Neuropsychopharmacology.*, vol. 22, no. 5, pp. 522-529.

Prat, G., Robledo, P., Rubio, A., Barbanoj, M., Jane, F., & Casas, M. 2000, "Effects of sub-chronic combined treatment with pergolide and caffeine on contralateral rotational behavior in unilateral 6-hydroxydopamine-denervated rats", *Brain Res.*, vol. 868, no. 2, pp. 376-379.

Prikhojan, A., Brannan, T., & Yahr, M. D. 2000, "Comparative effects of repeated administration of dopamine agonists on circling behavior in rats", *Journal of Neural Transmission*, vol. . 107, no. 10, pp. 1159-1164.

Ravenscroft, P., Brotchie, J., M, Crossman, A., & R 2001, "The ability of ropinirole to alleviate parkinsonism without eliciting dyskinesia may be due to its reduced propensity to elevate opioid peptide expression", *Society for Neuroscience Abstracts*, vol. 27, no. 1, p. 771.

Reavill, C., Boyfield, I., Coldwell, M., & Nelson, P. 2000, "Comparative pharmacological study of ropinirole (SKF-101468) and its metabolites in rats", *J.Pharm.Pharmacol.*, vol. 52, no. 9, pp. 1129-1135.

Robertson, H. A., Peterson, M. R., & Worth, G. G. 1992, "Synergistic and persistent interaction between the D2 agonist, bromocriptine, and the D1 selective agonist, CY 208-243", *Brain Research*, vol. . 593, no. 2, pp. 332-334.

Rose, S., Scheller, D. K. A., Breidenbach, A., Smith, L., Jackson, M., Stockwell, K., & Jenner, P. 2007, "Plasma levels of rotigotine and the reversal of motor deficits in MPTP-treated primates", *Behavioural Pharmacology*, vol. 18, no. 2, pp. 155-160.

Rouillard, C., Bedard, P. J., & Dipaolo, T. 1990, "Effects of chronic treatment of MPTP monkeys with bromocriptine alone or in combination with SKF 38393", *European Journal of Pharmacology*, vol. 185, no. 2-3, pp. 209-215.

Rupniak, N. M., Tye, S. J., Jennings, C. A., Loper, A. E., Bondi, J. V., Hichens, M., Hand, E., Iversen, S. D., & Stahl, S. M. 1989, "Antiparkinsonian efficacy of a novel transdermal delivery system for (+)-PHNO in MPTP-treated squirrel monkeys", *Neurology.*, vol. 39, no. 3, pp. 329-335.

Rupniak, N. M. J., Boyce, S., Steventon, M. J., & Iversen, S. D. 1990, "(+)-PHNO: A new anti-Parkinsonian agent which does not induce chorea in MPTP-treated squirrel monkeys", *Journal of Neurology, Neurosurgery & Psychiatry*, vol. . 53, no. 7, pp. 622-623.

Samadi, P., Gregoire, L., Morissette, M., Calon, F., Hadj, T. A., Belanger, N., Dridi, M., Bedard, P. J., & Di Paolo, T. 2008a, "Basal ganglia group II metabotropic glutamate receptors specific binding in non-human primate model of L-Dopa-induced dyskinesias", *Neuropharmacology*, vol. 54, no. 2, pp. 258-268.

Samadi, P., Morissette, M., Calon, F., Hadj, T. A., Dridi, M., Belanger, N., Meltzer, L. T., Bedard, P. J., & Di Paolo, T. 2008b, "Normalization of GABAA receptor specific binding in the substantia nigra reticulata and the prevention of L-dopa-induced dyskinesias in MPTP parkinsonian monkeys", *Synapse*, vol. 62, no. 2, pp. 101-109.

Scheller, D., Chan, P., Li, Q., Wu, T., Zhang, R., Guan, L., Ravenscroft, P., Guigoni, C., Crossman, A. R., Hill, M., & Bezard, E. 2007, "Rotigotine treatment partially protects from MPTP toxicity in a progressive macaque model of Parkinson's disease", *Exp.Neurol.*, vol. 203, no. 2, pp. 415-422.

Schmidt, W. J., Lebsanft, H., Heindl, M., Gerlach, M., Gruenblatt, E., Riederer, P., Mayerhofer, A., & Scheller, D. K. A. 2008, "Continuous versus pulsatile administration of rotigotine in 6-OHDA-lesioned

rats: contralateral rotations and abnormal involuntary movements", *Journal of Neural Transmission*, vol. 115, no. 10, pp. 1385-1392.

Schneider, J. S., Sun, Z. Q., & Roeltgen, D. P. 1994a, "Effects of dopamine agonists on delayed response performance in chronic low-dose MPTP-treated monkeys", *Pharmacol.Biochem.Behav.*, vol. 48, no. 1, pp. 235-240.

Schneider, J. S., Sun, Z. Q., & Roeltgen, D. P. 1994b, "Effects of dihydrexidine, a full dopamine D-1 receptor agonist, on delayed response performance in chronic low-dose MPTP-treated monkeys", *Brain Research*, vol. . 663, no. 1, pp. 140-144.

Schneider, J. & roeltgen, D. Recovery of volitional motor function but not rotational asymmetry in hemi-parkinsonian monkeys. Society for Neuroscience Abstracts 18, 1081. 1992.
Ref Type: Abstract

Senthilkumar, K. S., Saravanan, K. S., Chandra, G., Sindhu, K. M., Jayakrishnan, A., & Mohanakumar, K. P. 2007, "Unilateral implantation of dopamine-loaded biodegradable hydrogel in the striatum attenuates motor abnormalities in the 6-hydroxydopamine model of hemi-parkinsonism", *Behavioural Brain Research*, vol. 184, no. 1, pp. 11-18.

Serpa, K., A, Meltzer, L., & T 1997, "Does nitric oxide synthetase inhibition potentiate dopamine agonist induced rotation in 6-OHDA lesioned rats?", *Society for Neuroscience Abstracts*, vol. 23, no. 1-2, p. 1903.

Shiosaki, K., Jenner, P., Asin, K. E., Britton, D. R., Lin, C. W., Michaelides, M., Smith, L., Bianchi, B., Didomenico, S., Hodges, L., Hong, Y., Mahan, L., Mikusa, J., Miller, T., Nikkel, A., Stashko, M., Witte, D., & Williams, M. 1996, "ABT-431: the diacetyl prodrug of A-86929, a potent and selective dopamine D1 receptor agonist: in vitro characterization and effects in animal models of Parkinson's disease", *J.Pharmacol.Exp.Ther.*, vol. 276, no. 1, pp. 150-160.

Shropshire, A., T, Marquis, K., & L 1995, "CPP and NBQX fail to potentiate dopamine D1 and D2 agonist-induced responses in the 6-OHDA model of Parkinson's disease", *Society for Neuroscience Abstracts*, vol. 21, no. 1-3, p. 2108.

Silverdale, M., A, Nicholson, S., L, Ravenscroft, P., Crossman, A., R, Millan, M., J, Brotchie, J., M, (brotchie@uhnres, utoronto, & ca) "Selective blockade of D3 dopamine receptors enhances the antiparkinsonian properties of ropinirole and levodopa in the MPTP-lesioned primate", *Experimental Neurology*.

Silverdale, M. A., Millan, M. J., Crossman, A. R., & Brotchie, J. M. 2002, "Dopamine D3 receptor blockade, and not stimulation, is associated with anit-parkinsonian activity in the MPTP-lesioned, nonhuman primate model of Parkinson disease", *Neurology*, vol. 58, no. 7 Suppl.3, p. A493.

Silvestrin, R. B., de Oliveira, L. F., Batassini, C., Oliveira, A., & Souza, T. M. 2009, "The footfault test as a screening tool in the 6-hydroxydopamine rat model of Parkinson's disease", *J Neurosci Methods*, vol. 177, no. 2, pp. 317-321.

Simola, N., Fenu, S., Baraldi, P. G., Tabrizi, M. A., & Morelli, M. 2008, "Blockade of globus pallidus adenosine A(2A) receptors displays antiparkinsonian activity in 6-hydroxydopamine-lesioned rats treated with D-1 or D-2 dopamine receptor agonists", *Synapse*, vol. 62, no. 5, pp. 345-351.

Sit, S.-Y., Xie, K., Jacutin-Porte, S., Taber, M. T., Gulwadi, A. G., Korpinen, C. D., Burris, K. D., Molski, T. F., Ryan, E., Xu, C., Wong, H., Zhu, J., Krishnananthan, S., Gao, Q., Verdoorn, T., & Johnson, G. 2002, "(+)-Dinapsoline: An efficient synthesis and pharmacological profile of a novel dopamine agonist", *Journal of Medicinal Chemistry*, vol. . 45, no. 17, pp. 3660-3668.

Smith, L., A, Kebabian, J., Britton, D., Williams, M., De Ninno, M., Jenner, P., Marsden, C., & D 1992, "A77636, a full D-1 dopamine agonist, reverses MPTP-induced motor deficits in common marmosets", *British Journal of Pharmacology*, vol. 107, no. Supplement, p. 66P.

Smith, L., De Salvia, M., Jenner, P., & Marsden, C. D. 1996, "An appraisal of the antiparkinsonian activity of piribedil in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine common marmosets", *Movement Disorders*, vol. . 11, no. 2, pp. 125-135.

Smith, L. A., Jackson, M. G., Bonhomme, C., Chezaubernard, C., Pearce, R. K. B., & Jenner, P. 2000, "Transdermal administration of piribedil reverses MPTP-induced motor deficits in the common marmoset", *Clinical Neuropharmacology*, vol. . 23, no. 3, pp. 133-142.

Smith, L. A., Jackson, M. J., Al Barghouthy, G., & Jenner, P. 2002a, "The actions of a D-1 agonist in MPTP treated primates show dependence on both D-1 and D-2 receptor function and tolerance on repeated administration", *Journal of Neural Transmission*, vol. . 109, no. 2, pp. 123-140.

Smith, L. A., Jackson, M. J., Johnston, L., Kuoppamaki, M., Rose, S., Al Barghouthy, G., Del Signore, S., & Jenner, P. 2006, "Switching from levodopa to the long-acting dopamine D2/D3 agonist piribedil reduces the expression of dyskinesia while maintaining effective motor activity in MPTP-treated primates", *Clinical Neuropharmacology*, vol. . 29, no. 3, pp. 112-125.

Smith, L. A., Tel, B. C., Jackson, M. J., Hansard, M. J., Braceras, R., Bonhomme, C., Chezaubernard, C., Del Signore, S., Rose, S., & Jenner, P. 2002b, "Repeated administration of piribedil induces less dyskinesia than L-dopa in MPTP-treated common marmosets: a behavioural and biochemical investigation", *Mov Disord.*, vol. 17, no. 5, pp. 887-901.

Smith, L. A. J. 1992, "Reversal of MPTP-Induced motor deficits in common marmosets following oral or transdermal administration of piribidel", *British Journal of Pharmacology*, vol. 105, p. 153p.

Spooren, W. P. J., Waldmeier, P., & Gentsch, C. 1999, "The effect of a subchronic post-lesion treatment with (-)-deprenyl on the sensitivity of 6-OHDA-lesioned rats to apomorphine and d-amphetamine", *Journal of Neural Transmission*, vol. . 106, no. 9-10, pp. 825-833.

Starr, M., S, Starr, B., & S 1994, "Comparison of the effects of NMDA and AMPA antagonists on the locomotor activity induced by selective D-1 and D-2 dopamine agonists in reserpine-treated mice", *Psychopharmacology*, vol. 114, no. 3, pp. 469-476.

Starr, M. S. & Starr, B. S. 1994, "Potentiation of dopamine-dependent locomotion by clonidine in reserpine-treated mice is restricted to D2 agonists", *Journal of Neural Transmission - Parkinsons Disease & Dementia Section*, vol. . 7, no. 2, pp. 133-142.

Stephenson, D. T., Meglasson, M. D., Connell, M. A., Childs, M. A., Hajos-Korcsok, E., & Emborg, M. E. 2005, "The effects of a selective dopamine D2 receptor agonist on behavioral and pathological outcome in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated squirrel monkeys", *J.Pharmacol.Exp.Ther.*, vol. 314, no. 3, pp. 1257-1266.

Stockwell, K. A., Scheller, D., Rose, S., Jackson, M. J., Tayarani-Binazir, K., Iravani, M. M., Smith, L. A., Olanow, C. W., & Jenner, P. 2009, "Continuous administration of rotigotine to MPTP-treated common marmosets enhances anti-parkinsonian activity and reduces dyskinesia induction", *Exp Neurol*, vol. 219, no. 2, pp. 533-542.

Stockwell, K. A., Virley, D. J., Perren, M., Iravani, M. M., Jackson, M. J., Rose, S., & Jenner, P. 2008, "Continuous delivery of ropinirole reverses motor deficits without dyskinesia induction in MPTP-treated common marmosets", *Experimental Neurology*, vol. 211, no. 1, pp. 172-179.

Sun, J., Gao, Y., Yang, L., Li, Z., Lu, G., & Yew, D. 2007, "Neural-tube-derived neuroepithelial stem cells: a new transplant resource for Parkinson's disease", *Neuroreport*, vol. 18, no. 6, pp. 543-547.

Sun, Z., -Q, Johnson, B., J, Schneider, J., & S 1994, "Effects of the full dopamine D-1 receptor agonist dihydrexidine on cognitive function and motor activity in MPTP-treated monkeys", *Society for Neuroscience Abstracts*, vol. 20, no. 1-2, p. 1645.

Tanaka, K., Asanuma, M., & Ogawa, N. "Neuroprotective effects of four dopamine agonists on 6-hydroxydopamine-induced endoplasmic reticulum stress in the mouse brain", *International Journal of Neuropsychopharmacology*.

Temlett, J. A., Quinn, N. P., Jenner Marsden, P. G. C. D., Pourcher, E., Bonnet, A.-M., Agid, Y., Markstein, R., & Lataste, X. 1989, "Antiparkinsonian activity of CY 208-243, a partial D-1 dopamine receptor agonist, in MPTP-treated marmosets and patients with Parkinson's disease", *Movement Disorders*, vol. . 4, no. 3, pp. 261-265.

Toriumi, H., Yoshikawa, M., Matsuda, R., Nishimura, F., Yamada, S. I., Hirabayashi, H., Nakase, H., Nonaka, J. I., Ouji, Y., Ishizaka, S., & Sakaki, T. 2009, "Treatment of Parkinson's disease model mice with allogeneic embryonic stem cells: necessity of immunosuppressive treatment for sustained improvement", *Neurological Research*, vol. 31, no. 3, pp. 220-227.

Treseder, S., A, Smith, L., Jackson, M., Jenner, P., Marsden, C., & D 1998, "The actions of L-DOPA and dopamine agonists following dopamine depletion in MPTP-treated common marmosets", *British Journal of Pharmacology*, vol. 123, no. Supplement, p. 251P.

Turle-Lorenzo, N., Maurin, B., Puma, C., Chezaubernard, C., Morain, P., Baunez, C., Nieoullon, A., & Amalric, M. 2006, "The dopamine agonist Piribedil with L-DOPA improves attentional dysfunction: Relevance for Parkinson's disease", *Journal of Pharmacology and Experimental Therapeutics*, vol. 319, no. 2, pp. 914-923.

Van Kampen, J. M. & Eckman, C. B. 2006, "Dopamine D3 receptor agonist delivery to a model of Parkinson's disease restores the nigrostriatal pathway and improves locomotor behavior", *J.Neurosci.*, vol. 26, no. 27, pp. 7272-7280.

Vermeulen, R. J., Drukarch, B., Sahadat, M. C. R., Goosen, C., Wolters, E. C., & Stoof, J. C. 1993, "The selective dopamine D1 receptor agonist, SKF 81297, stimulates motor behaviour of MPTP-lesioned monkeys", *European Journal of Pharmacology*, vol. . 235, no. 1, pp. 143-147.

Vermeulen, R. J., Drukarch, B., Sahadat, M. C. R., Goosen, C., Wolters, E. C., & Stoof, J. C. 1994a, "The dopamine D1 agonist SKF 81297 and the dopamine D2 agonist LY 171555 act synergistically to stimulate motor behavior of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian rhesus monkeys", *Movement Disorders*, vol. . 9, no. 6, pp. 664-672.

Vermeulen, R. J., Drukarch, B., Verhoeff, N. P., Goosen, C., Sahadat, M. C., Wolters, E. C., van Royen, E. A., & Stoof, J. C. 1994b, "No direct correlation between behaviorally active doses of the dopamine D2 agonist LY 171555 and displacement of [123I]IBZM as measured with SPECT in MPTP monkeys", *Synapse.*, vol. 17, no. 2, pp. 115-124.

Voith, K. 1984, "The behavioral pharmacology of AY-27,110, a novel nonergot dopaminergic agonist", *Drug Development Research*, vol. . 4, no. 4, pp. 391-404.

Wachtel, H., Kunow, M., & Loschmann, P. A. 1992, "NBQX (6-nitro-sulfamoyl-benzo-quinoxaline-dione) and CPP (3-carboxy-piperazin-propyl phosphonic acid) potentiate dopamine agonist induced rotations in substantia nigra lesioned rats", *Neurosci.Lett.*, vol. 142, no. 2, pp. 179-182.

Waddington, J. L. & Crow, T. J. 1979, "Rotational responses to serotonergic and dopaminergic agonists after unilateral dihydroxytryptamine lesions of the medial forebrain bundle: Co-operative interactions of serotonin and dopamine in neostriatum", *Life Sciences*, vol. . 25, no. 15, pp. 1307-1314.

Wakamatsu, M., Iwata, S., Funakoshi, T., & Yoshimoto, M. 2008, "Dopamine receptor agonists reverse behavioral abnormalities of alpha-synuclein transgenic mouse, a new model of Parkinson's disease", *Journal of Neuroscience Research*, vol. 86, no. 3, pp. 640-646.

Wang, J., Jiang, H., & Xie, J. X. 2007, "Ferroportin1 and hephaestin are involved in the nigral iron accumulation of 6-OHDA-lesioned rats", *Eur J Neurosci*, vol. 25, no. 9, pp. 2766-2772.

Wang, J., Peng, G.-G., Zheng, M., & Luo, H.-Y. 2004, "Protective effect of pergolide on parkinsonian model rats", *Chinese Pharmacological Bulletin*, vol. . 20, no. 11, pp. 1273-1276.

Warraich, S. T., Allbutt, H. N., Billing, R., Radford, J., Coster, M. J., Kassiou, M., & Henderson, J. M. 2009, "Evaluation of behavioural effects of a selective NMDA NR1A/2B receptor antagonist in the unilateral 6-OHDA lesion rat model", *Brain Res Bull*, vol. 78, no. 2-3, pp. 85-90.

Wei, P., Liu, J., Zhou, H. L., Han, Z. T., Wu, Q. Y., Pang, J. X., Liu, S., & Wang, T. H. 2007, "Effects of engrafted neural stem cells derived from GFP transgenic mice in Parkinson's diseases rats", *Neurosci Lett*, vol. 419, no. 1, pp. 49-54.

Woiciechowsky, C., Guilarte, T. R., May, C. H., Vesper, J., Wagner, H. N., Jr., & Vogel, S. 1995, "Intrastriatal dopamine infusion reverses compensatory increases in D2-dopamine receptors in the 6-OHDA lesioned rat", *Neurodegeneration.*, vol. 4, no. 2, pp. 161-169.

Wu, T., H, Locke, K., W, Loar, S., B, Maher, T., & J 1997, "Behavioral effects of intranasal dopaminergic agonists in 6-hydroxydopamine (6-OHDA)-lesioned rats", *Society for Neuroscience Abstracts*, vol. 23, no. 1-2, p. 414.

Xinliang, T., Xingzhi, G., & Bin, L. 1997, "Effects of ganglioside on apomorphine-induced rotational behavior, dopamine content of striatum and pathological changes of substantia nigra in the rat models of Parkinson disease", *Chinese Journal of Neurology*, vol. . 30, no. 4, pp. 208-210.

Xu, L., Liu, L. X., & Chen, W. F. 2008, "[Effect and mechanism on dopamine contents of striatum in rat model of Parkinson's disease ginsenoside Rg1]", *Zhongguo Zhong Yao Za Zhi*, vol. 33, no. 15, pp. 1856-1859.

Yoon, M.-C., Shin, M.-S., Kim, T.-S., Kim, B.-K., Ko, I.-G., Sung, Y.-H., Kim, S.-E., Lee, H.-H., Kim, Y.-P., & Kim, C.-J. 2007, "Treadmill exercise suppresses nigrostriatal dopaminergic neuronal loss in 6-hydroxydopamine-induced Parkinson's rats", *Neuroscience Letters.423(1)()(pp 12-17), 2007.Date of Publication: 09 Aug 2007.* no. 1, pp. 12-17.

Yuan, C.-X., Ye, Q., Wang, J., Zhang, Y., & Yuan, C.-G. 2008, "Effects of traditional Chinese herbal medicine on the neurobehavioral manifestations and the activity of dopamine D2 receptor in corpora striatum of rats with levodopa-induced dyskinesias.", *Journal of Chinese Integrative Medicine*, vol. 6, no. 10, pp. 1024-1028.

Yuan, H., Sarre, S., Ebinger, G., & Michotte, Y. 2004, "Neuroprotective and neurotrophic effect of apomorphine in the striatal 6-OHDA-lesion rat model of Parkinson's disease", *Brain Research*, vol. . 1026, no. 1, pp. 95-107.

Zhang, H., Ma, L. Q., Wang, F., Chen, J. G., & Zhen, X. C. 2007, "Chronic SKF83959 induced less severe dyskinesia and attenuated L-DOPA-induced dyskinesia in 6-OHDA-lesioned rat model of Parkinson's disease", *Neuropharmacology*, vol. 53, no. 1, pp. 125-133.

Zhao, X., Cao, Y., Liu, H., Li, F., You, B., & Zhou, X. 2009, "Long term high frequency stimulation of STN increases dopamine in the corpus striatum of hemiparkinsonian rhesus monkey", *Brain Research.1286()(pp 230-238), 2009.Date of Publication: 25 Aug 2009.* pp. 230-238.

Zivin, M., Sprah, L., & Sket, D. 1998, "Antiparkinsonian potential of interaction of LEK-8829 with bromocriptine", *European Journal of Pharmacology*, vol. 349, no. 2-3, pp. 151-157.

Appendix 4. Quality of preclinical Parkinson's disease studies

(1) Peer reviewed publication
(2) Random allocation to group
(3) Blinded assessment of outcome
(4) Sample size calculation
(5) Compliance with animal welfare regulations
(6) Statement of a potential conflict of interest

Name & Initial 2	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Abuirmeileh,A	2007	+				+	+	3
Abuirmeileh,A	2008	+				+		2
Aguiar,L	2008	+				+		2
Aguiar,L	2008	+				+		2
Ahmed,M	2008	+	+			+		3
Ahmed,R	2008	+				+		2
Akai,T	1993	+		+				2
Akai,T	1995	+		+				2
Alexander,G	1991	+		+				2
Anderson,J	1991							0
Anderson,J	1992	+						1
Andringa,G	1999	+				+		2
Andringa,G	1999	+				+		2
Andringa,G	1999	+				+		2
Arai,N	1996	+		+				2
Asin,K	1997	+				+		2
Atsumi,M	2003	+				+		2
Belluzzi,J	1994	+				+		2
Bibbiani,F	2003						+	1
Blanchet,P	1997	+				+		2
Blanco,L	1995	+						1
Boldry,R	1993	+						1
Brucke,t	1988	+						1
Buck,K	2008	+				+		2
Burke,W	2009						+	1
Burunat,E	1987	+						1
Bychkov,E	2007	+	+			+		3
Cannon,J	2009	+		+		+		3
Carta,A	2008	+				+		2
Carta,A	2008	+				+		2
Casas,M	2000	+	+			+		3
Castren,E	2007	+				+		2
Chang,J	1994							0
Chen,X	2007	+	+			+		3

Name & Initial 2	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Close,S	1985	+		+				2
Close,S	1990	+	+	+				3
Cools,A	2003							0
Coppi,G	1995	+	+					2
Costall,B	1975	+						1
Crossman,A	2001							0
Curzon,P	1990							0
DaSilva,K	2000							0
de Yebenes,J	1988	+						1
Delfino,M	2007	+	+					2
Doan,V	1999	+						1
Domino,E	1997	+		+		+		3
Drukarch,B	1993							0
Dupre,K	2007	+				+		2
Dupre,K	2008	+		+		+		3
Duty,S	1997	+		+				2
Duvoisin,R	1982	+						1
Eden,R	1991	+						1
Ekesbo,A	2000	+	+			+		3
Esposito,E	2008	+				+		2
Evans,M	1999	+						1
Feng,D	2005	+	+					2
Filion,M	1991	+						1
Fleming,S	2006	+		+		+		3
Fornaguera,J	1995	+	+	+		+		4
Fox,S	1996	+						1
Fox,S	2000	+	+					2
Fukuzaki,K	2000	+				+		2
Fukuzaki,K	2000	+				+		2
Gagnon,c	1995	+						1
Gancher,S	1994	+						1
Gancher,S	1994	+						1
Giardina,W	2000							0
Gnanalingham,K	1995	+				+		2
Gnanalingham,K	1995	+	+			+		3
Gold,S	2007	+				+		2
Gomez-Mancilla,B	1992	+						1
Gossel,M	1995	+						1
Goulet,M	1995							0
Goulet,M	2000	+		+		+		3
Gramsbergen,J	2009							0
Gray,B	1991							0
Gregoire,L	2009	+				+		2
Grondin,R	1994							0
Grondin,R	1997	+						1

Name & Initial 2	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Gu,S	2009	+						1
Guilloux,J	2008							0
Gulwadi,A	2001	+				+		2
Gunzler,S	2007	+	+			+		3
Hara,K	1989	+						1
Harkavyi,A	2008	+				+		2
Hashizume,H	2008							0
Hassan,M	1986	+						1
Hayakawa,T	1998							0
Hayakawa,T	1999	+						1
Hazelhoff,B	1986	+						1
Heinrich,J	2006	+	+					2
Henry,B	1999	+		+				2
Hill,M	2006	+						1
Hinzen,D	1986	+						1
Hironaka,N	1998	+						1
Honkanen,A	1999							0
Hsu,A	2004	+		+		+		3
Hubbard,C	1993	+						1
Hudson,J	1991							0
Hudson,J	1993	+						1
Hudson,J	1994	+	+					2
Huynh,T	2002							0
Ichikawa,K	2001	+						1
Irifune,M	1993	+						1
Irifune,M	1994	+						1
Ismayilova,N	2004	+				+		2
Jadavji,N	2009	+				+		2
Jenkins,O	1985	+						1
Jenner,P	1986							0
Jenner,P	1992	+						1
Jeon,M	2007	+				+		2
Jiang,H	1993							0
Jiang,H	1993	+						1
Jin,F	2008	+				+		2
Johnson,B	1994							0
Johnson,B	1995	+	+					2
Johnston,L	2001							0
Johnston,L	2008	+		+		+		3
Johnston,M	2001							0
Johnston,M	2003							0
Kaariainen,T	2008	+				+		2
Kalda,A	2009	+	+			+		3
Kashihara,K	1996	+	+					2
Kashihara,K	2002	+	+			+		3

Name & Initial 2	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Kaur,S	1994	+						1
Kenny,A	1986	+						1
Koller,W	1980	+		+				2
Koller,W	1986	+						1
Koller,W	1987	+						1
Kreisler,A	2008						+	1
Kuno,S	1996							0
Kuno,S	1997	+						1
Kuno,S	1998	+						1
LaHoste,G	1990	+						1
Laloux,C	2008	+				+		2
Larramendy,C	2008	+	+			+		3
Lee,J	2001	+						1
Levesque,D	1999			+				1
Lindgren,H	2007	+				+		2
Liu,W	2007	+				+		2
Lorenc-Koci,E	1999	+				+		2
Loschmann,P	1992	+	+					2
Loschmann,P	1997	+	+					2
Luan,L	2008	+				+		2
Luquin,M	1993	+				+		2
Maneuf,Y	1997							0
Maneuf,Y	1997	+						1
Maratos,E	1998	+						1
Marin,C	2009	+				+		2
Marin,R	2008	+				+		2
Maurin,B	2001							0
May,C	1994	+						1
McCall,R	2005	+				+		2
McElroy,J	1995	+						1
McLaughlin,W	1992							0
Meloni,E	2000	+						1
Menon,M	1976	+						1
Mera,T	2009	+				+		2
Metz,G	2000							0
Michaelides,M	1997	+						1
Mierau,J	1992	+						1
Mignon,L	2007	+				+		2
Mihara,K	2008	+		+		+		3
Milioli,E	2007	+						1
Millan,M	2004	+		+		+		3
Ming,M	2009	+					+	2
Miyagi,M	1996	+						1
Mohanasundari,M	2006	+				+		2
Morelli,M	1991	+						1

Name & Initial 2	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Nakagawa,M	2004	+						1
Neisewander,J	1991	+	+					2
Nomoto,M	1987	+						1
Nomoto,M	1988	+	+					2
Nomoto,M	1993	+						1
Nomoto,M	1998	+		+		+		3
Nomoto,M	1998	+						1
Norton,D	1992							0
Nowak,P	2008							0
Obeso,J	2001							0
Olsson,M	1995	+						1
paterna,J	2007	+						1
Pearce,R	1999	+				+		2
Piercey,M	1992							0
Pollack,A	1997	+				+		2
Pollack,A	2001	+				+		2
Popoli,P	2000	+		+		+		3
Prat,G	2000	+				+		2
Prikhojan,A	2000	+						1
Ravensoft,P	2001							0
Reavill,C	2000	+				+		2
Robertson,H	1992	+						1
Rose,S	2007	+		+		+		3
Rouillard,C	1990	+						1
Rupniak,N	1989	+						1
Rupniak,N	1990	+						1
Samadi,P	2008	+				+		2
Samadi,P	2008	+				+		2
Scheller,D	2007	+	+	+		+		4
Schmidt,W	2008	+	+			+		3
Schneider,A	1994	+						1
Schneider,J	1994	+						1
Senthilkumar,K	2007	+				+		2
Serpa,K	1997							0
Shiosaki,K	1996	+						1
Shropshire,A	1995							0
Silverdale,M	2002			+				1
Silverdale,M	2003			+		+		2
Silverdale,M	2004	+		+		+		3
Silverstrin,R	2009	+				+		2
Simola,N	2008	+				+		2
Sit,S	2002	+						1
Smith,L	1992							0
Smith,L	1992							0
Smith,L	1996	+		+				2

Name & Initial 2	Year	(1)	(2)	(3)	(4)	(5)	(6)	Quality Score
Smith,L	2000	+				+		2
Smith,L	2002	+	+			+		3
Smith,L	2002	+				+		2
Smith,L	2006	+		+		+		3
Spooren,W	1999	+	+					2
Starr,M	1994	+						1
Starr,M	1994	+						1
Stephenson,D	2005	+	+	+		+		4
Stockwell,K	2008	+		+		+		3
Stockwell,K	2009	+		+		+		3
Sun,J	2006	+				+		2
Tanaka,K	2006							0
Temlett,J	1989	+						1
Toriumi,H	2009	+				+		2
Treseder,S	1998		+	+				2
TurleLorenzo,N	2006	+			+	+		3
Van Kampen,J	2006	+				+		2
Vermeulen,R	1993	+	+	+				3
Vermeulen,R	1994	+	+	+				3
Vermeulen,R	1994	+	+	+				3
Voith,K	1984	+						1
Wachtel,H	1992	+						1
Waddington,J	1979	+						1
Wakamatsu,M	2008	+		+		+		3
Wang,J	2004	+	+					2
Wang,J	2007	+				+		2
Warraich,S	2009	+	+	+		+		4
Wei,P	2007	+						1
woiciechowsky,C	1995	+						1
Wu,T	1997							0
Xinglian,T	1997	+	+					2
Xu,L	2008	+	+			+		3
Yarkov,A	2003	+				+		2
Yoon,E	2007	+	+			+		3
Yuan,C	2008	+				+		2
Yuan,H	2004	+				+		2
Zhang,H	2007	+	+			+		3
Zhao,X	2009	+					+	2
Zivin,J	1998	+	+					2

Appendix 5. Summary of dopamine agonists tested in animal models of Parkinson's disease

Highlighted interventions are those in clinical use.

[1]See appendix 3 for references.

[2]Where available summary estimates of efficacy were calculated.

Intervention	Number of Publications[1]	First Tested In	Average Quality	Number of Experiments	Effect Size	Lower 95% CI	Upper 95% CI
(-)3PPP	1	1990	1	n/a	n/a	n/a	n/a
(+)3PPP	1	1990	1	n/a	n/a	n/a	n/a
(+)Dinapsoline	1	2002	0	n/a	n/a	n/a	n/a
(+-)Dinapsoline	1	2002	0	n/a	n/a	n/a	n/a
(+)-PHNO	11	1986	0.4	38	1.23	0.88	1.59
18Dinapsoline	1	2002	0	n/a	n/a	n/a	n/a
5-OH-DPAT	1	1997	0	n/a	n/a	n/a	n/a
7-OH-DPAT	2	1995	0.5	5	1.26	0.71	1.82
A68930	1	1997	1	5	0.54	0.16	0.92
A77636	5	1992	0.6	16	1.5	0.95	2.05
A86929	5	1996	0.4	10	1.55	0.76	2.34
ABT-431	2	1996	0	8	0.9	-0.14	1.95
Alpha-DHEC	1	1995	1	n/a	n/a	n/a	n/a
Amantadine	1	2008	1	4	-1.35	-2.49	-0.21
Aplindore	1	2006	1	6	1.86	1.18	2.54
Apomorphine	123	1975	0.6	89	1.54	1.19	1.9
AY27110	2	1984	0	8	-0.37	-1.36	0.62
BAM-1110	1	1998	0	3	6.57	0.75	12.4
BP897	1	2004	1	n/a	n/a	n/a	n/a
Bromocriptine	32	1982	0.4	58	0.96	0.73	1.19
C1-APB	2	1997	0	1	1.49	0.58	2.41
Cabergoline	11	1994	0.6	13	0.73	-0.24	1.7
CY208-243	3	1989	0	4	1.29	0.43	2.15
D145	1	1975	0	n/a	n/a	n/a	n/a
Dihydrexidine	5	1994	0.4	15	0.55	-0.06	1.17

Intervention	Number of Publications[1]	First Tested In	Average Quality	Number of Experiments	Effect Size	Lower 95% CI	Upper 95% CI
Dinapsoline	1	2001	1	9	2.37	1.34	3.41
Dopamine	4	1988	0.5	3	1.3	-0.23	2.82
DPPP	1	1986	0	1	0.32	-0.67	1.31
DU127090	1	2003	0	n/a	n/a	n/a	n/a
Hexahydrothieno[c]benzo[f]quinoline[f]quinolines	1	1997	0	n/a	n/a	n/a	n/a
Lergotrile	1	1982	0	n/a	n/a	n/a	n/a
Lisuride	8	1984	0.1	10	1.5	0.98	2.03
LY-171555	10	1988	0.7	19	0.48	-0.05	1.01
N-0498	1	1986	0	n/a	n/a	n/a	n/a
N-0499	1	1986	0	n/a	n/a	n/a	n/a
N-0500	1	1986	0	n/a	n/a	n/a	n/a
N-0923	2	1992	0.5	n/a	n/a	n/a	n/a
N-0924	1	1994	1	n/a	n/a	n/a	n/a
N-Ethylnorapomorphine	1	1976	0	n/a	n/a	n/a	n/a
N-Methylcyclopropylnorapomorphine	1	1976	0	n/a	n/a	n/a	n/a
NNDipropylA56DTN	1	1990	1	n/a	n/a	n/a	n/a
N-n-Proplynorapomorphine	1	1976	0	n/a	n/a	n/a	n/a
Norapomorphine	1	1976	0	n/a	n/a	n/a	n/a
PD128,907	1	1997	1	n/a	n/a	n/a	n/a
Pergolide	13	1980	0.5	14	1.01	0.26	1.76
Piribedil	8	1992	0.8	26	1.07	0.48	1.66
Pramipexole	7	1992	0.6	14	1.31	0.67	1.96
Quinelorane	2	2000	1	5	1.22	-0.43	2.86
Quinpirole	33	1990	0.6	30	1.25	0.8	1.7
Ropinirole	16	1991	0.7	23	1.85	1.39	2.32
Rotigotine	4	2007	1.5	10	1.8	1.1	2.51
RU24213	2	1994	0	6	0.82	0.17	1.48
RU29717	1	1986	0	n/a	n/a	n/a	n/a
S31411	1	2004	1	3	0.99	-0.13	2.11
S32504	4	2001	0.5	23	1	0.33	1.67
S32601	1	2004	1	2	0.13	-0.95	1.21
S33084	2	2002	0.5	1	0.72	-0.13	1.57
Sarizotan	1	2009	1	6	-0.13	-0.66	0.4

Intervention	Number of Publications[1]	First Tested In	Average Quality	Number of Experiments	Effect Size	Lower 95% CI	Upper 95% CI
SFK 83959	5	1995	1.2	2	1.3	-0.32	2.93
SKF 104557	1	2000	1	2	0.1	-2.73	2.93
SKF 38393	32	1985	0.6	27	0.3	-0.26	0.86
SKF 75670	1	1995	2	n/a	n/a	n/a	n/a
SKF 80723	2	1995	1.5	1	3.04	1.42	4.67
SKF 81297	9	1993	1	17	0.55	0.2	0.9
SKF 82958	12	1993	0.5	7	1.79	0.87	2.71
SKF 89124	1	2000	1	4	0.68	-2.54	3.9
SKF 96990	1	2000	1	3	-0.02	-1.81	1.77
SKF 97930	1	2000	1	2	0.09	-2.33	2.51
SLV308	3	2001	0	5	1.14	0.04	2.25
SLV318	1	2003	0	n/a	n/a	n/a	n/a
Sumanirole	2	2005	1.5	8	1.7	0.15	3.25
Talipexole	7	1993	0.4	28	0.86	0.51	1.21
Terguride	4	1988	0.5	7	0.8	0.22	1.37
U91356A	2	1992	0	n/a	n/a	n/a	n/a