Neuroimmunology – the past, present and future

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Summary

Neuroimmunology as a separate discipline has its roots in the fields of neurology, neuroscience and immunology. Early studies of the brain by Golgi and Cajal, the detailed clinical and neuropathology studies of Charcot and Thompson's seminal paper on graft acceptance in the central nervous system, kindled a now rapidly expanding research area, with the aim of understanding pathological mechanisms of inflammatory components of neurological disorders. While neuroimmunologists originally focused on classical neuro-inflammatory disorders, such as multiple sclerosis and infections, there is strong evidence to suggest that the immune response contributes to genetic white matter disorders, epilepsy, neurodegenerative diseases, neuropsychiatric disorders, peripheral nervous system and neuro-oncological conditions, as well as ageing. Technological advances have greatly aided our knowledge of how the immune system influences the nervous system during development and ageing, and how such responses contribute to disease as well as regeneration and repair. Here, we highlight historical aspects and milestones in the field of neuroimmunology and discuss the paradigm shifts that have helped provide novel insights into disease mechanisms. We propose future perspectives including molecular biological studies and experimental models that may have the potential to push many areas of neuroimmunology. Such an understanding of neuroimmunology will open up new avenues for therapeutic approaches to manipulate neuroinflammation.

Keywords: central nervous system, inflammation, neurodegeneration, neuroimmunology, neuroinflammation

Introduction

Neuroimmunology encompasses fundamental and applied biology, immunology, chemistry, neurology, pathology, psychiatry and virology of the central nervous system (CNS). Scientists in the field study the interactions of the immune and nervous system during development, homeostasis and response to injuries with the major aim of developing approaches to treat or prevent neuroimmunological diseases.

The immune system has been generally regarded as autonomous and the brain protected by the blood–brain barrier, (BBB) and in the words of Rudyard Kipling (*Barrack-room ballads*, 1892), 'never the twain shall meet'. In the past decades these dogmas have been strongly challenged and dispelled with the wealth of evidence showing that not only does the nervous system receive messages from the immune system, but that signals from the brain regulate immune functions that subsequently control inflammation in other tissues [1]. Communication between the immune system and the CNS is exemplified by the finding that many molecules associated with the immune system are widely expressed and functional in the nervous system and vice versa. Cross-talk between microglia and neurones is known to be essential for maintaining homeostasis, yet such cross-talk also occurs between oligodendrocytes and microglia [2]. Disturbance in this communication due to peripheral infections in mice are known to trigger microglia activation and augment neurodegeneration [3]. Similarly, recent experimental studies show that maternal infections lead to long-term changes in microglia and abnormal brain development in the offspring [4,5].
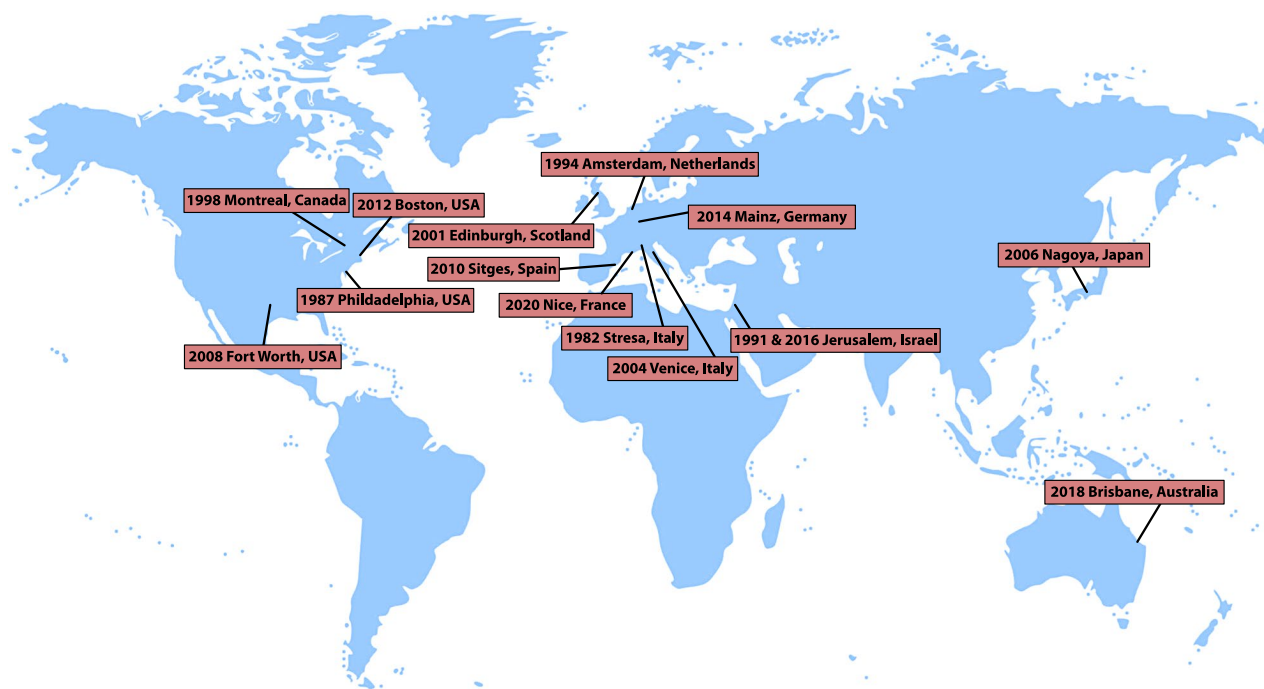
Fig. 1. World map showing location of International School of Neuroimmunology (ISNI) meetings.

Despite this evidence, it is surprising that the term 'neuroimmunology' was only first used on PubMed in 1982, coinciding with the first Neuroimmunology Congress in Stresa, Italy (Fig. 1) and following the launch of the *Journal of Neuroimmunology* in 1981. Although neuroimmunology research has focused on multiple sclerosis (MS; using the search term 'neuroimmunology', 43% of papers on PubMed in 2018 were on MS), immune responses are also observed in Guillain–Barré syndrome (GBS), white matter diseases, psychiatric disorders, infections, trauma and neurodegenerative diseases traditionally considered to be 'cell autonomous' (Table 1).

One of the greatest misconceptions that impeded progress in neuroimmunology was the idea that the blood–brain barrier (BBB) and the perceived immunological privilege of the brain prevent cross-talk between the CNS and immune systems. This long-standing dogma has been challenged by recent studies and the discovery of glymphatics and meningeal lymphatic vessels [43]. Although this paradigm shift is a recent advancement in thinking of nervous-immune system cross-talk, such changes in the field, beginning over 150 years earlier, have been generally linked to technological advances, some of which have yielded Nobel Prizes in neuroimmunology (Table 2), including the development of mutant and transgenic mice to examine disease mechanisms, stem cell technologies and the novel CRISPR/cas9 system, that allows gene editing enabling personalized treatments.

Here, we review the developments in neuroimmunology since its roots in the first descriptions of immunological processes and neurological diseases, as well as the development of technologies and clinical trials for such diseases. Important events are given in major timelines or eras, along with the Nobel Prizes considered relevant by their impact on the field of neuroimmunology. The review also includes a perspective on the future of neuroimmunology that should herald prospective approaches to understanding these diseases, and we address several outstanding questions in the field. The long-term goal of this rapidly developing field of neuroimmunology is to further the understanding of how immune responses shape the nervous system during development and ageing, how such responses lead to neurological diseases, and ultimately to develop new pharmacological treatments. These aspects are thus the major topics of the International Society of Neuroimmunology meetings (ISNI) (Fig. 1) and the educational topics of the global schools in neuroimmunology.

Historical beginnings

The first descriptions of many neuroinflammatory disorders come from personal notes, early authors and diarists. The earliest report purported to be MS was in an Icelandic woman (in approximately 1200) and Saint Lidwina of Schiedam (1380–1433), while the detailed personal diaries of Sir Augustus d'Esté, born in 1794 (grandson of King

Table 1. Neuroimmune diseases

Disease	Clinical characteristics	Immune involvement	Ref
ADEM	Lethargy, visual problems, paralysis associated with viral infection or vaccination	Demyelination, inflammation, axonal loss, hypertrophic astrocytes, activated microglia	[6]
ALS motor neurone disease	Fatal motor neurone disease affecting the motor neurones leading to weakness of voluntary muscles	Systemic immune activation, microglia activation and hypertrophic astrocytes. Complement deposition	[7–9]
AD	Progressive cognitive decline. Amyloid plaques, synaptic loss and neurofibrillary tangles. Anti-inflammatory drugs associated with reduced risk	Microglia, astrocytes, complement and cytokines in plaques. Aβ binds and activates microglia. Aβ reactive T cells in blood, immunoglobulin in CSF	[10,11]
Autoimmune encephalitis	Psychiatric symptoms may predominate	Autoantibodies directed against neuronal surface proteins including adhesion molecules, ion channels and receptors used as biomarkers of disease	[12,13]
CFS	Chronic dysfunction including fatigue, headaches and cognitive impairment	PET imaging shows microglia activation. Immune dysregulation in cytokine profiles and T and B cells, immunoglobulin and natural killer cell cytotoxicity	[14]
CNS vasculitis	Fatigue, impaired cognition, speech problems, seizures, paralysis	Inflammation of blood vessels in the CNS	[15]
Depression	Anxiety, cognitive impairment, panic attacks. Changes in serotonergic or glutamatergic transmission	Increased T cells and cytokines. Injection of inflammatory mediators, e.g. interleukin-2 and interferon gamma induce symptoms of depression	[16,17]
Epilepsy	Seizures associated with cognitive and psycho-logical sequelae	Innate and adaptive immune responses. Antibodies deposits on BBB. Anti-inflammatory agents control forms of epilepsy	[18,19]
GBS	Acute paralytic neuropathy. High cerebrospinal fluid protein levels Disease seen following Zika virus infection	Pathogenic antibodies to gangliosides arise due to molecular mimicry in *Campylobacter jejuni* lipo-oligosaccharide infection	[20,21]
HD and other polyQ diseases	Mutant huntingtin protein (or other polyQ) aggregates. Neostriatal atrophy and neuronal loss in putamen and caudate nucleus	Microglia express mutant huntingtin (and other polyQ) protein are dysfunctional. Expression of complement components in associated with severe atrophy	[22]
Infections	Encephalitis, encephalomyelitis, meningitis, polyradiculitis or polyneuritis	Immune responses to infectious agent Some viruses induce immunosuppression (e.g. HIV, EBV, Herpes simplex virus)	[23]
Leucodystrophies	e.g. X-ALD: progressive cognitive and motor function impairment and eventually total disability. Accumulated levels of very long chain fatty acids (VLCFA)	X-ALD: severe lymphocytic response. VLCFA impair monocytes. Activated microglia and astrocytes become dystrophic	[24,25]
MS	Relapsing remitting or progressive neurological dysfunction. Oligoclonal cerebrospinal fluid bands	Demyelination and axonal loss in CNS associated with innate and adaptive immune cell activation	[26]
MG and other channel-opathies	Clinical features depend on antibody e.g. synaptic dysfunction, neuronal excitability due to inhibition of ion channel function	Antibody-mediated disorders of the neuromuscular junction, e.g. antibodies to AChR in MG	[27,28]
Neuromyelitis optica	(Devic's disease) Inflammatory disorder affecting optic nerves and spinal cord	Presence of antibodies to aquaporin 4 in 80% cases damage astrocytes	[29]
Paraneoplastic disorders	Immune mediated disorders triggered by tumour expressing neuronal antigens. Clinical manifestations depend on target of antibody	Disease associated with antibody deposits on neuromuscular junction, Purkinje cell or peripheral nerves. T cells and immunoglobulin in cerebrospinal fluid	[30]

(Continues)

Table 1. (Continued)

Disease	Clinical characteristics	Immune involvement	Ref
Parkinson's disease	Progressive movement disorder associated with loss of dopaminergic neurones	Microglia and astrocyte activation associated with neuronal loss. IL-1b gene polymorphisms associated with early onset. CD4+ and CD8 T cells in animal models	[31]
SLE, PSS, diabetes, gluten ataxia	SLE: cognitive decline, depression, seizures, chorea. PSS: optic neuritis, vasculitis, results neurological syndrome. Gluten ataxia: cerebellar ataxia and atrophy	SLE: vasculitis, autoantibodies, immune complexes. PSS: inflammation mimicking MS. Gluten ataxia: loss of Purkinje cells associated with immune activation	[30]
Stroke	Blockage of blood vessel or haemorrhage deprives CNS of oxygen resulting in various levels of unconsciousness	Systemic and local inflammation triggered to clear debris	[32]
Traumatic spinal injury	Contusions and bruising due to fracture or dislocation leading to paralysis, or degrees of dysfunction below level of injury	Injury triggers inflammation that may contribute to secondary tissue damage	[33]
Neuroinfections			
Virus	Clinical characteristics	Neuroimmune involvement	Ref
HIV dementia	Cognitive changes	HIV-infected monocytes and T cells produce chemokines and cytokines	[34]
Arbovirus	Depends on infection	Virus infects neurones, local immune response, microglia and macrophages present viral antigens to T cells. Antibodies may control spread	[35,36]
TBE, e.g. Zika	Depends on infection, e.g. Zika virus: microcephaly, GBS and CNS disorders	Role of myeloid cells in facilitating viral spread and pathology	[37]
Rabies	Encephalitis	Immune responses crucial to clear neurotrophic virus	[38]
HSV	Fever can induce anti-NMDAR encephalitis	Innate and adaptive immune responses control infection. Virus evades CD8+ T cells. TLR-3 polymorphisms associated with susceptibility	[39]
EBV	Febrile illness, meningeal signs, epileptic insults, depression polyradiculomyelitis, cognitive disorders, encephalitis	EBV-related lymphomas in CNS. Increased mononuclear leucocytes. Evidence that EBV infection is linked to MS and CFS	[40,41]
SSPE	Fatal complication of measles infection. Latency period of 4–10 years leading to coma	Immaturity of immune response leads to widespread infection	[42]

CFS = chronic fatigue syndrome; HSV = herpes simplex virus; NMDAR = N-methyl-D-aspartate receptor; PSS = primary Sjögren's syndrome; SSPE = subacute sclerosing panencephalitis; TBE = tick-borne encephalitis virus; AChR = acetylcholine receptor; AD = Alzheimer's disease; ADEM = acute demyelinating encephalomyelitis virus; ALS = amyotrophic lateral sclerosis; CNS = central nervous system; CSF = cerebrospinal fluid; EBV = Epstein–Barr virus; GBS = Guillain–Barré syndrome; HD = Huntington's disease; MS = multiple sclerosis; MG = myasthenia gravis; SLE = systemic lupus erythematosus; TLR = Toll-like receptor.

George III of England) and the British writer W. N. P. Barbellion (1889–1919) reveal their daily struggle with symptoms of MS [44,45]. Examples of early reports of other neuroinflammatory diseases include Sir Thomas Willis, credited with the first description of myasthenia gravis (MG) in 1672 [46] (Fig. 2), as well as in early medical documents and diaries descriptions of encephalitis. Neuroinflammatory disorders were also documented in (albeit) fictional characters in novels such as those by Charles Dickens [47,48].

Early detailed descriptions of many neurological diseases expanded in the early 1800s (Fig. 2), due in part to

Jean-Martin Charcot (1825–1893), who systematically identified many neurological diseases including Charcot–Marie–Tooth, MS, Parkinson's disease (PD; only later in 1872 was Parkinson credited for his earlier description, Fig. 2) and amyotrophic lateral sclerosis (ALS), by linking the clinical disease in patients with detailed studies of the anatomy and microscopy of diseased tissues [49]. The link between neurology and immunology gained momentum with the refinement of the microscope and development of staining techniques to allow detailed studies of tissue. For example, the identification of different types of glial cells in the CNS and peripheral nervous system

Table 2. Nobel prizes relevant to the field of neuroimmunology

Year	Recipient	Topic	Influence on neuroimmunology field
1901	Emile A. Behring	Serum therapy	Opened a new road in medical science for treating diseases
1906	Camillo Golgi and Santiago Ramón y Cajal	Structure of the nervous system	Impregnation method allowed microscopy of neuroglia
1908	Ilya I. Metchnikoff and Paul Ehrlich	Recognition of work on immunity. Metchnikoff discovered types and functions of phagocytes. Ehrlich identified types of blood leucocytes	Formulating the concept of antibody: antigens complexes. Antibodies are the foundation for immunohistochemistry and for some therapies
1919	Jules Bordet	Discoveries relating to immunity	Interaction of antibodies and complement. Of diagnostic importance and understanding mechanisms of cell death
1927	Julius Wager-Jauregg	Therapeutic value of malaria inoculation in the treatment of dementia paralytica	The link between infection, inflammation and neurological diseases
1945	Alexander Fleming, Ernst B. Chain and Howard W. Florey	Discovery of penicillin and treatment for various infectious diseases	Key approach to managing bacterial infections including central nervous system (CNS) diseases, e.g. brain abscesses
1951	Max Theiler	Yellow fever and how to combat it	Controlling arboviruses using live attenuated viruses. Paved the way for controlling neurotrophic viruses
1953	Watson and Crick	Structure of DNA	Understanding genetic disorders and potential of gene therapy
1954	John F. Enders, Thomas H. Weller and Frederick C. Robbins	Ability of poliomyelitis viruses to grow in cultures of various types of tissue	*In-vitro* testing of vaccines, neutralizing antibodies, typing infectious agents and cytopathic effects
1960	Frank Macfarlane Burnet and Peter B. Medawar	Acquired immunological tolerance	Self/non-self-discrimination led to approaches to induce tolerance to self-antigens in neuroinflammatory diseases
1972	Gerald M. Edelman and Rodney R. Porter	Discoveries concerning the chemical structure of antibodies	Role of antibodies in disease, use in technologies, e.g. vaccine development, enzyme-linked immunosorbent assay
1976	Baruch S. Blumberg and D. Carleton Gajdusek	New mechanisms for the origin and dissemination of infectious diseases	Idea of persistent infections and slow viruses (spongiform encephalopathies)
1980	Baruj Benacerraf, Jean Dausset and George D. Snell	Genetically determined structures on the cell surface regulating immunological reactions	Relevance of major histocompatibility complex (MHC) to developing neuroinflammatory disorders, e.g. DR2 in multiple sclerosis
1984	Niels K. Jerne, Georges J.F. Köhler and César Milstein	Specificity in development and control of the immune system. Principle for production of monoclonal antibodies	Development of monoclonal antibody (mAb) for therapies in neuroinflammatory diseases. mAb for characterizing immune molecules and role in diseases using immunohistochemistry
1987	Susumu Tonegawa	Genetic principle for generation of antibody diversity	Autoantibodies to peripheral nervous system (PNS) and CNS surface proteins, e.g. ion channels, receptors, myelin, axons

(Continues)

Table 2. (Continued)

Year	Recipient	Topic	Influence on neuroimmunology field
1996	Peter C. Doherty and Rolf M. Zinkernagel	specificity of the cell mediated immune defence	MHC class I and II restricted immune response applicable to infections and autoimmunity
1997	Stanley B. Prusiner	Prions: a new biological principle of infection	Modes of action may be applicable to neurodegenerative diseases
2002	Sydney Brenner, H. Robert Horvitz and John E. Sulston	Genetic regulation of organ development and programmed cell death	Cell death mechanism key to regulating neuronal development, neurodegeneration and control of immune responses
2003	Paul C. Lauterbur and Sir Peter Mansfield	Magnetic resonance imaging	Imaging neuroinflammatory diseases and response to therapy
2006	Andrew Z. Fire and Craig C. Mello	RNA interference: gene silencing by double-stranded RNA	Therapeutic approaches targeting aberrant gene associated with neurological disorders
2007	Mario R. Capecchi, Martin J. Evans and Oliver Smithies	Principles for introducing gene modifications in mice using embryonic stem cells	The approach allows the study specific gene function and to create animal models for, e.g. neuroinflammatory diseases
2011	Bruce A. Beutler, Jules A. Hoffmann and Ralph M. Steinman	Discoveries concerning activation of innate immunity (B.A.B., J.A.H.). Role of dendritic cells in adaptive immunity (R.M.S.)	How innate and adaptive immune responses are activated are key to understanding and manipulation of immune responses to control diseases
2012	John B. Gurdon and Shinya Yamanaka	Mature cells can be reprogrammed to become pluripotent	Stem cells will facilitate regeneration within the nervous system to replace damaged cells and tissues

(PNS) was aided by the use of chemicals to enhance the microscopic visibility of nerve cells [50,51], approaches for which Camillo Golgi and Santiago Ramon y Cajal received the Nobel Prize for Medicine in 1906 (Table 2). It was also with these new staining techniques that Alois Alzheimer identified the pathology underlying dementia that later became known as Alzheimer's disease (AD) (1906) [52], and allowed Dawson to perform detailed microscopic examinations of MS (1916) [53] showing inflammation around blood vessels in CNS lesions.

Purkinje is credited for the first descriptions of neurones in 1837 [54], and only later did Golgi describe glial cells (1871), although Virchow had introduced the name 'neuroglia' and created the concept that nerve cells are held together by 'glia' (meaning glue) in 1856 [55]. Alongside the descriptions of neurological disease, various aspects of immunology were also investigated (Fig. 2). Metchnikoff revealed the rudimentary immune cells in freshwater starfish (1880) [56], and used the term 'phagocytosis', which became the basis of his research for which he was awarded the Nobel Prize in 1908 with Paul Ehrlich for discovery of blood leucocytes (Table 2). Later, Rio-Hortega showed that cells in the brain (microglia) were able to phagocytose (1919) [57]. In the same year, Jules Bordet was awarded the Nobel

Prize for identifying factors (antibodies) in blood arising after vaccination [58], although it was not until 70 years ago that B cells were found to be important producers of antibodies in 1948 [59].

Immunology at the time was focused on the vaccine development for infectious diseases after the published work on the first vaccine for smallpox by British physician Edward Jenner in 1796 [60]. More relevant for the neuroimmunological field was the discovery of the vaccine for the neurotrophic rabies virus by Louis Pasteur (1885) [61] and the vaccine for polio by Jonas Edward Salk (1953) [62]. Importantly, Pasteur used dried virus-infected rabbit spinal cord for immunization which occasionally induced a post-vaccine encephalomyelitis in humans. That the disease did not reflect rabies indicated that brain components in the vaccine were antigenic. In the 1940s adjuvants were developed to potentiate vaccines, and several vaccines as well as infections have been linked to neuroinflammatory diseases such as, for example, e.g. MS and acute disseminated encephalomyelitis (ADEM) (Table 1). The serendipitous finding of post-rabies vaccination encephalitis was later exploited for immunization strategies to deliberately induce experimental autoimmune diseases (Fig. 2). Of relevance to the immune privilege nature of the CNS, in 1890 Gilman Thomson showed that brain cells can be transplanted without being rejected,
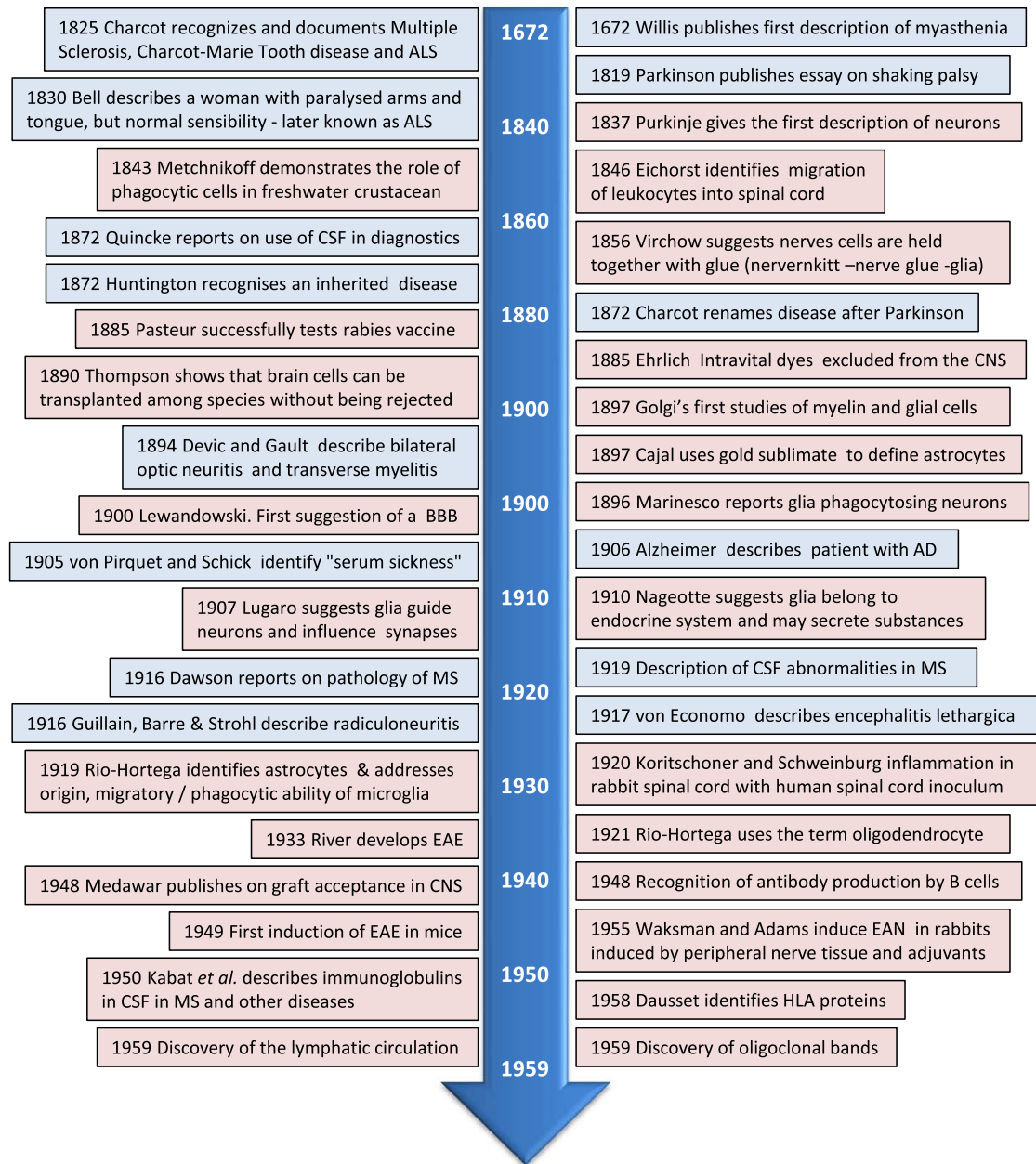
Fig. 2. Neuroimmunology timeline 1672–1959 clinical studies = blue box; research = pink box. AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; BBB = blood–brain barrier; CNS = central nervous system; CSF = cerebrospinal fluid; EAE = experimental autoimmune encephalomyelitis; EAN = experimental autoimmune neuritis; HLA = human leucocyte antigen; MS = multiple sclerosis.

many years before Sir Frank Macfarlane Burnet and Peter B. Medawar's seminal studies, for which they received the Nobel prize in 1960 (Table 2).

1960–1980

Further to the identification and description of diseases, this era prompted the development of precise criteria for diagnosis of neuroinflammatory diseases, as well as examining the pathological mechanisms underlying disease and testing therapeutic approaches (Fig. 3). Technically, the development of computed tomography scans, positron emission spectroscopy (PET) and magnetic resonance imaging (MRI) allowed the first images of living brain, revolutionizing the diagnosis of neuro-inflammatory diseases and allowing non-invasive monitoring of disease progression as well as response to therapy.

Left (research/clinical)	Year	Right (research/clinical)
1960 Transfer EAE with lymph node cells	1960	1960 possible link between MG and antibodies to an "endplate" protein?
1962 Discovery of antibody structure		1962 Passive transfer of EAN with lymphoid cells
1962 Finding that thymus is involved in cellular immune reactions	1962	
1965 Diagnostic criteria for MS		1965 Identification of secretory immunoglobulins
1967 Diphtheria toxin's mode of action reported	1966	1967 Identify BBB tight junctions
1967 First specific gene transfer		1968 Steroid ACTH for treatment of MS
1968 Isolatation of MSC	1968	1969 Pathology of inflammatory lesion in idiopathic polyneuritis
1970 Antibodies to neurons found in SLE, cerebral palsy, and epilepsy	1970	1973 MG induced in rabbits with acetylcholine receptor
1974 First report on MHC-T-cell restriction		1973 Identification of dendritic cells
1975 Use of the term "psychoneuroimmunology"	1972	1974 Neurofibrillary tangles isolated from AD brain
1976 Link between antibodies to AChR and MG		1976 Transplanted brain cells functionally integrate within the brain parenchyma
1976 Plasma exchange used in MG	1976	1976-1977 Report on GBS following vaccination in USA vaccination programme
1977 Induction of EAN with P2 basic protein peptide		
1978 Antibodies from MG patients accelerates degeneration	1978	1978 FDA approve ACTH for MS
1979 Antibodies to galactocerebroside damage myelin in vitro		1979 Identification of a neuritogen for EAN
	1980	1979 FDA approve i.v. methylprednisolone for MS
1981 EAE transferred by T cells		1980 1st large trial for use of IFN alpha in MS
1983 First report of impaired immune response in depression	1984	1984 T cells induce chronic relapsing demyelinating disease in mice
1987 Brain cells produce complement	1988	1988 Pathogenic role of antibodies in EAE
1989 Role of TCR in EAE		1991 Role of inflammation in AD
1992 mAb to VLA-4 prevents EAE	1990	1992 Removal of anti-AChR antibodies in MG
1992 Kinetics of T cells trafficking BBB		1992 HSCs protect from EAE
1992 Trial comparing IVIg and plasma-exchange in GBS	1992	1993 Use of TCR MBP transgenic mice in EAE
1993 Serum GQ1b IgG associated with MFS and GBS		1993 Interferon beta approved for relapsing MS
1994 MOG EAE first reported	1994	1995 Link between *Campylobacter-jejuni* and GBS
1996 Copaxone approved for use in MS		1996 Use of APLs to modulate EAE
1999 HLA-DR2 humanised mouse model of MS	1998	1998 Human NSC can replace neurons
1999 Glia limitans expresses FasL		1999 Alemtuzumab suppresses MS inflammation
1999 Immunization with Aβ attenuates AD in mice	1999	1999 Use of GFP T cells in CNS disease

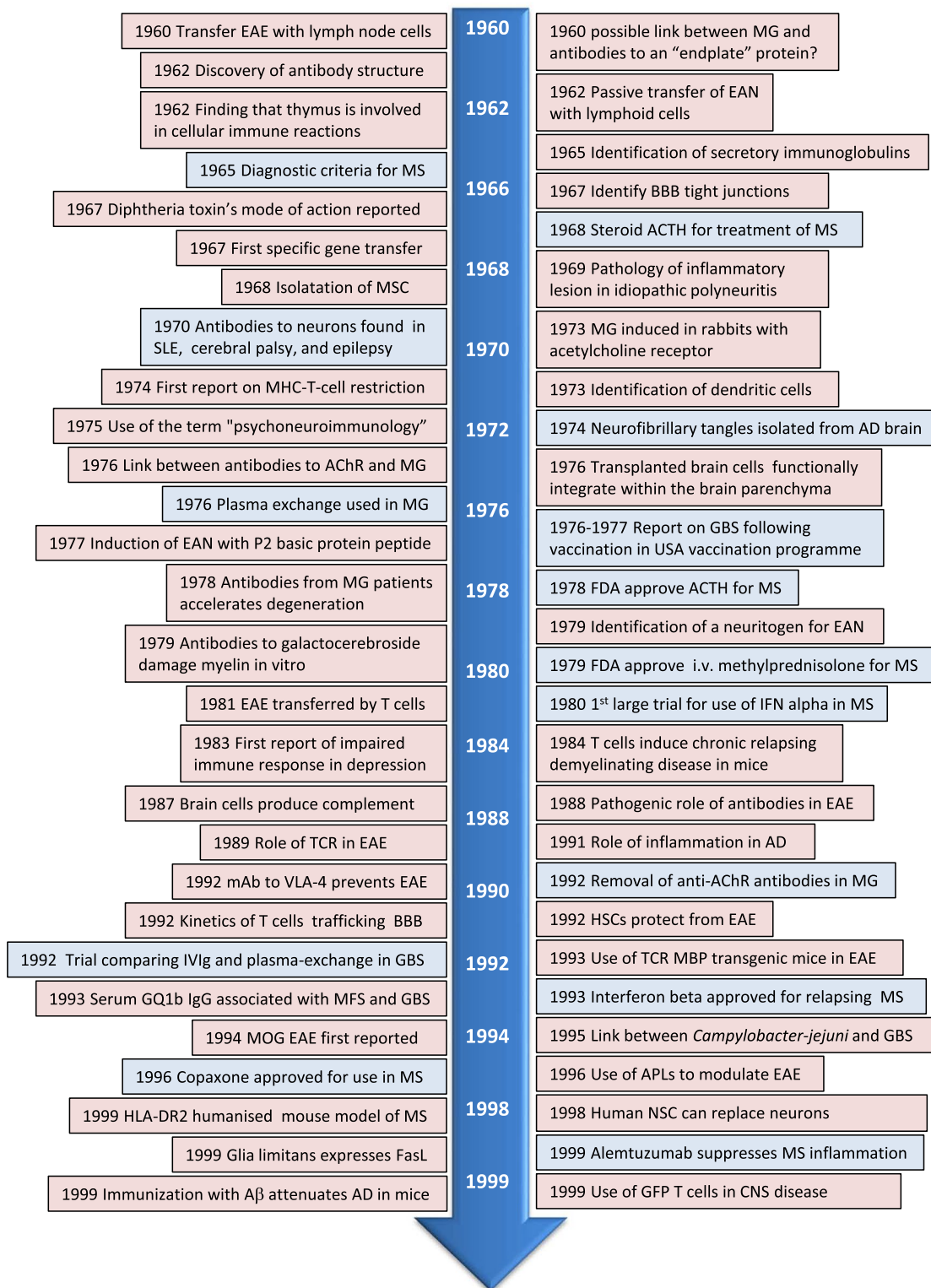**Fig. 3.** Neuroimmunology timeline 1960–1999 clinical studies = blue box; research = pink box. Aβ = A beta; AChR = acetyl choline receptor; ACTH = adrenocorticotrophic hormone; AD = Alzheimer's disease; BBB = blood–brain barrier; CNS = central nervous system; EAE = experimental autoimmune encephalomyelitis, EAN = experimental autoimmune neuritis; FDA = US Food and Drug Administration; GBS = Guillain–Barré syndrome; GFP = green fluorescent protein; HLA = human leucocyte antigen; HSC = haematopoietic stem cells; IFN = interferon; MG = myasthenia gravis; MHC = major histocompatibility antigen; MOG = myelin associated glycoprotein; MS = multiple sclerosis; MSC = mesenchymal stem cells; NSC = neuronal stem cells; TCR = T cell receptor.

There was a surge in discoveries related to antibodies after the antibody structure was discovered (1959) [63]. In this era associations were made linking antibodies to diseases such as MG and other neuroinflammatory diseases [64]. For some diseases the target of the antibodies were identified [65], and the impact of pathogenic antibodies shown *in vitro* [66]. A key development in the immunology field was the generation of monoclonal antibodies (mAb) [67]. Not only were mAb key to the development of assays such as enzyme-linked immunosorbent assay and other techniques key to linking immune cells to neurological diseases [68], this advancement also allowed development of specific therapeutic approaches in which mAb were designed to block or deplete specific cells of the immune system.

The involvement of immune responses in neurological diseases prompted new approaches to treat disease and development of animal models of human diseases. While adjuvants developed in the 1940s were essential for inducing clinical disease in the case of experimental autoimmune encephalitis (EAE) [69] and experimental autoimmune neuritis (EAN), injection of antibodies to acetylcholine receptor (AchR) and from patients with myasthenia gravis (MG) induced experimental disease in rabbits. The therapy used for antibody-mediated diseases included plasma exchange [70], while broad immunosuppressive approaches, e.g. adrenocorticotrophic hormone, were implemented for MS [Food and Drug Administration (FDA)-approved in 1978].

Study of the immune system differentiated between cellular and humoral immunity and recognized T and B cell interactions, as well as the discovery of the first interleukins. Key to further developments in immune-mediated diseases was Zinkernagel and Doherty's finding (1974) that elimination of virus-infected cells killer T cells required not only to recognize the virus but also the major histocompatibility complex (MHC) molecule of the host [71]. Around this time the realization grew that cells later named as dendritic cells, due to their morphology, were intricately linked with adaptive immune responses, a notion that would later earn Steinman the Nobel Prize [72]. Studies in this era supporting Cajal's idea, that glia assist neurones, were aided by the development of the electron microscope and electrophysiological studies, although how this impacted on neuroinflammatory disease was as yet unknown.

1981–2000

This era saw major steps in putting neuroimmunology on the map as a new field with the launch of the *Journal of Neuroimmunology* by Cedric Raine and colleagues (1981), the first PubMed term of neuroimmunology (1981), the initiation of Neuroimmunology Congresses in Stresa, Italy (1982), the foundation of the ISNI (1987) and the launch of the *Journal of Clinical and Experimental Neuroimmunology* in 1988.

If the previous era was dedicated to the role of antibodies in disease for which Tonegawa received the Nobel Prize in 1987 (Table 2) [73], this era was that of T cells in neuroimmunology and the recognition of the importance of innate immunity (Fig. 3). Following Doherty and Zinkernagel's discovery in 1974, for which they were awarded the Nobel Prize in 1996, major steps were made in identifying the T cell receptor (1983–1987) [74,75] (Table 2), classification of T cells (1986) [76], the role of MHC peptide complex in triggering T cell responses (1991) [77] and how T cells are regulated (1995) [78] or modified using altered peptide ligands (1998) [79]. Models also made use of the emerging field of transgenic mice designed to express human proteins such as human leucocyte antigens (HLA), T cells expressing specific T cell receptors (TCRs), markers such as green fluorescent protein (GFP) to allow tracking of cells or generated to lack specific molecules (knock-out or deficient mice). Many of the studies examining the pathogenic role of T cells focused on the EAE model of MS (1981–1984) [80–82] although inflammation was also reported in depression (1983) [83] and neurodegenerative diseases, e.g. AD, which up to that point had been widely assumed to be due to neuronal degeneration. While many studies focused on immune-mediated damage, studies also revealed the importance of the immune response in shaping neuronal development. For example, while microglia were reported to be crucial for synaptic pruning, new studies from the Shatz laboratory revealed that neuronal expression of MHC class I was key to long-term structural and synaptic modifications [84].

The focus on pathogenic T cells in EAE models of MS increased and experiments using antibodies to block TCRs were performed [85,86]. Further studies highlighted the importance of other myelin antigens as targets for the demyelinating response and induction of chronic relapsing clinical disease to model the disease course in MS more clearly [87].

Although T cells were at the forefront of many studies, therapeutic approaches targeting pathogenic antibodies such as trials using intravenous immunoglobulin (IVIg) in GBS, or use of therapeutic mAB to block adhesion molecules on immune cells, revealed the importance of cell trafficking across the BBB [88]. Although such approaches were effective in animal models, blocking immune cell entry in the CNS in humans had serious side effects. Other strategies focused on repairing damage in the nervous systems were examined. These strategies included transplanting oligodendrocyte progenitor cells for remyelination [89] and stem cells that, although originally designed to replace damaged cells, they were later recognized to be neuroprotective via the release of growth factors and immune modulatory molecules (i.e. therapeutic plasticity) [90].

This era saw the emergence of the human immunodeficiency virus (HIV), the isolation of HTLV-1-like retrovirus from tropical spastic paraparesis cases, the link between *Campylobacter jejuni* infection and GBS and the Nobel Prize to Prusiner for his studies on prions as new infectious particles promoting neurological disease (Table 2). These findings clearly highlighted the role of infectious agents in triggering neuroinflammatory disorders, although it was unclear how the different infections triggered disease. One innovative concept at the time was proposed by Janeway (1989) [91], suggesting that microbes act via receptors on innate immune cells. Only later was this concept validated by the discovery of Toll-like receptors (TLR) and other innate receptors, as well as dendritic cells (Nobel Prize: Beutler, Hoffman, Steinman 2011). Further revelations were made in 1994, when Matzinger proposed the 'danger model' (1994) to include the concept that changes in the host's tissues due to 'dangerous' situations, i.e. trauma or disease, could also activate innate immunity [92].

Another technological leap during this era was the use of genetic engineering that enabled the generation of mice expressing antigen-specific TCR, such as against the myelin basic protein, and humanized mice expressing certain HLA haplotypes in an attempt to understand how human genes contributed to neuroinflammmatory diseases.

2001–2018

Accumulating evidence during the last two decades shows that immune senescence is associated with late-onset neurodegenerative diseases such as AD, PD, spinal cerebellar ataxia, ALS and Huntington's disease, thus broadening the range of diseases falling within the neuroimmunology field (Table 1). Further evidence that the immune response is also key to neuronal development was highlighted by the finding that the complement component C1q is expressed by synapses of postnatal but not adult neurones [93] (Fig. 4). Studies in this era have also expanded ideas of how microbes, such as the newly emerging Zika virus, the re-emergence of Ebola and the gut microbiome, influence susceptibility to neuroinflammatory disease. In line with this, clinical trials have highlighted the need to develop more specific approaches in neuroimmune diseases other than broad immunosuppression or blocking cells from entering into the CNS, in order to avoid the emergence of opportunistic infections. Thus, specific approaches such as cell depletion therapies (e.g. of B cells in MS), tolerance-inducing strategies and the use of stem cells have been a major focus in MS, while gene therapy approaches have been initiated in an attempt to correct genetic mutations in ALS [94] (Fig. 4).

Probing neuroinflammatory diseases has been aided with improved higher-resolution MRI, single photon emission computed tomography and PET ligands [95,96], and optical coherence tomography to visualize the progression of disease in patients and for some modes the contribution of inflammation. Similarly, *in-vivo* optical imaging, for example of GFP-labelled T cells, glia or transplanted human induced pluripotent stem cells (iPSC), in experimental models has greatly influenced our knowledge of the cross-talk between the immune and nervous systems [97].

Although mainly limited to *in-vitro* and animal studies, genetic modification has proved to be an indispensable tool to study gene function in normal development and disease and has yielded several Nobel Prizes in this area (2006, Fire and Mello; 2007, Capecchi, Evans, Smithies). Breakthroughs in this era include the generation of human iPSCs for which Gurdon and Yamanaka received the Nobel Prize in 2012; gene-targeting approaches and genome-editing tools, the most effective for interrogation of neuroimmune disease being the CRISPR/Cas9 system (derived from clustered regularly interspaced short palindromic repeats) originating from early discoveries in bacteria [98]. While yet to prove applicable to human disorders, such gene editing has allowed genetic manipulation of iPSC from humans, ALS models and elimination of viral infections by targeting viral genomes.

Future perspectives

While current therapies aim to modulate neuroinflammation arising during the disease, future approaches should aim at disease prevention. For some diseases, the aetiological agents are known, and thus vaccination strategies are key for disease prevention. In other cases, the specific genes or environmental agents triggering disease require clarification. Prophylactic approaches for genetic disorders could exploit genetic modification during development, while cell therapy strategies may aid regeneration of the damaged nervous system. Exploitation of infections agents may also be beneficial, as demonstrated by the recent clinical trial using a non-pathogenic poliovirus for treating glioblastomas [99].

For disease prevention, rapid and specific diagnosis as well as adequate ways to monitor the disease course and response to therapy are crucial. Thus, advancements in biomarker research will be key to faster diagnosis and more efficient monitoring in clinical trials, speeding up drug development and reducing costs. Biomarkers of neuroimmunological diseases may include markers of BBB disruption, demyelination, oxidative stress and excitotoxicity, axonal/neuronal damage, gliosis, remyelination and repair, but should also focus on markers of altered immune function such as cytokines, chemokines, antibodies, adhesion molecules, antigen presentation and changes in cellular subpopulations
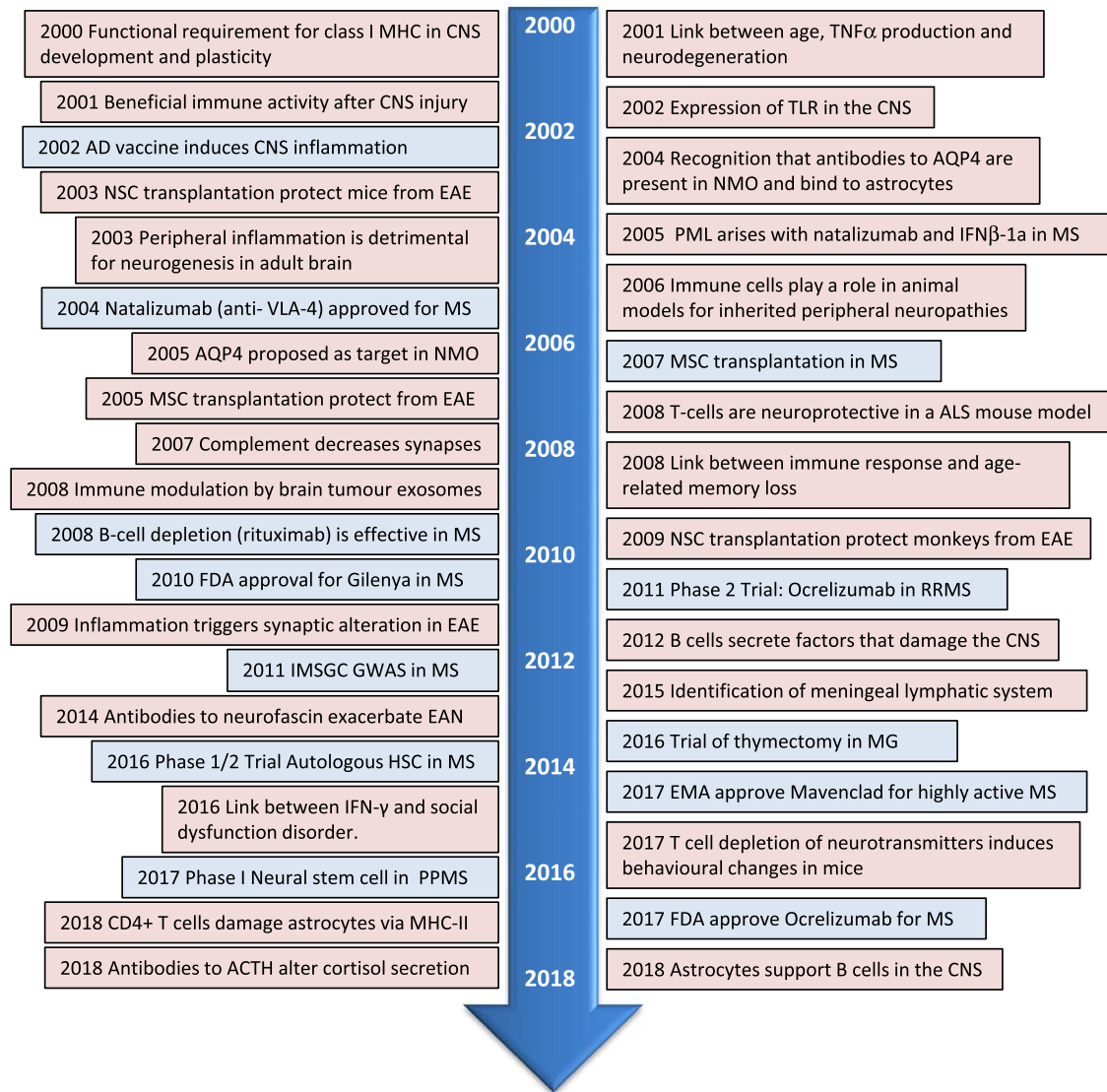
2000

2000 Functional requirement for class I MHC in CNS development and plasticity

2001 Beneficial immune activity after CNS injury

2002 AD vaccine induces CNS inflammation

2003 NSC transplantation protect mice from EAE

2003 Peripheral inflammation is detrimental for neurogenesis in adult brain

2004 Natalizumab (anti- VLA-4) approved for MS

2005 AQP4 proposed as target in NMO

2005 MSC transplantation protect from EAE

2007 Complement decreases synapses

2008 Immune modulation by brain tumour exosomes

2008 B-cell depletion (rituximab) is effective in MS

2010 FDA approval for Gilenya in MS

2009 Inflammation triggers synaptic alteration in EAE

2011 IMSGC GWAS in MS

2014 Antibodies to neurofascin exacerbate EAN

2016 Phase 1/2 Trial Autologous HSC in MS

2016 Link between IFN-γ and social dysfunction disorder.

2017 Phase I Neural stem cell in PPMS

2018 CD4+ T cells damage astrocytes via MHC-II

2018 Antibodies to ACTH alter cortisol secretion

2002

2004

2006

2008

2010

2012

2014

2016

2018

2001 Link between age, TNFα production and neurodegeneration

2002 Expression of TLR in the CNS

2004 Recognition that antibodies to AQP4 are present in NMO and bind to astrocytes

2005 PML arises with natalizumab and IFNβ-1a in MS

2006 Immune cells play a role in animal models for inherited peripheral neuropathies

2007 MSC transplantation in MS

2008 T-cells are neuroprotective in a ALS mouse model

2008 Link between immune response and age-related memory loss

2009 NSC transplantation protect monkeys from EAE

2011 Phase 2 Trial: Ocrelizumab in RRMS

2012 B cells secrete factors that damage the CNS

2015 Identification of meningeal lymphatic system

2016 Trial of thymectomy in MG

2017 EMA approve Mavenclad for highly active MS

2017 T cell depletion of neurotransmitters induces behavioural changes in mice

2017 FDA approve Ocrelizumab for MS

2018 Astrocytes support B cells in the CNS

Fig. 4. Neuroimmunology timeline 2001–2018. Clinical studies = blue box; research = pink box. ACTH = adrenocorticotrophic hormone; ALS = amyotrophic lateral sclerosis; AQP4 = aquaporin 4; CNS = central nervous system; EAE = experimental autoimmune encephalomyelitis; EAN = experimental autoimmune neuritis; EMA = European medical agency; FDA = US Food and Drug Administration; GWAS = genomewide association study; IFN = interferon; IMSGC = International Multiple Sclerosis Genetics Consortium (IMSGC); MHC = major histocompatibility antigen; MG = myasthenia gravis; MS = multiple sclerosis; MSC = mesenchymal stem cells; NMO = neuromyelitis optica; NSC ; neuronal stem cells; PML = progressive multifocal leucoencephalopathy; PPMS = primary progressive multiple sclerosis; RRMS = relapsing–remitting multiple sclerosis; VLA-4 = integrin α4β1 (very late antigen-4); TLR = Toll-like receptors; TNF = tumour necrosis factor.

[100]. Ideally, detection and collection of new biomarkers will be minimally invasive, specific for the disease and reflect response to therapy Additionally, well-characterized tissue biobanks will be crucial to these advancements in biomarkers.

Another important aspect of future neuroimmunology research and developments will be in disease modelling. The highly effective CRISPR/cas9 system will allow precision engineering of the genome, and has the potential to speed up the generation of transgenic animal models, generating single-gene mutations in adult animals. Model systems making use of iPSCs from patients will also allow better translation of fundamental research data to the clinic. Further advances in CRISPR/cas9 or similar systems to increase transgene efficiency or to regulate gene expression using inducible expression systems will allow genes to be regulated once gene editing is completed. Such approaches will herald better treatments in the form of personalized medicine, gene editing (taking into account the ethical issues) and improved clinical trial design.

The increase in data generated by next-generation sequencing is expected to aid identification of genetic variants in neuroimmunological diseases. Such data are already contributing to designing algorithms, development of pharmacogenomics and personalized medicine. These approaches will be fundamental in reducing risks in drug development by avoiding adverse drug reactions, and minimizing cost by limiting drug administration solely to those patients who will benefit [101]. While drug discovery is increasingly costly and prolonged, artificial intelligence (AI) may be key to reversing this trend. AI will use previously collected data and molecular dynamic predictions to reduce the number of compounds to be screened, repurpose compounds, predict interactions between compounds and their target and refine clinical trial populations [102]. Advancements in targeted drug delivery will also reduce side-effect profiles of compounds and aid in those compounds that will readily cross the BBB [103]. Both Big Pharma and academia have the potential to increase drug discovery efficiency by embracing AI, pharmacogenomics, personalized medicine and targeted drug delivery to provide future treatments of neuroimmunological diseases.

Conclusions

The field of neuroimmunology has evolved from early studies recognizing that immune responses are present in the CNS and PNS during disease, to sophisticated approaches for manipulation of the immune system. The list of neuroimmune diseases has expanded from the prototypical cases of MS, GBS and MG to incorporate diseases considered to be purely neurological such as AD, PD, ALS as well as behavioural and mood disorders. Neuroimmunology has evolved to encompassed less disease-orientated fields by addressing how the immune system impacts upon the developing nervous systems during pregnancy, how neural stem cells play an immune regulatory role, the contribution of immune-senescence to ageing, how microbiota influence the immune system, and how this impacts upon development and susceptibility to neurological diseases.

Understanding the delicate balance between the beneficial and pathological effects of the immune system with neuronal development and diseases has already allowed the development of rational approaches for treating neuroimmune disorders. Further advances are expected to address the following points.

How pathogenic (auto)antibodies arise and how they contribute to immune-mediated neurological disorders

While the source of pathogenic antibodies in paraneoplastic neurological syndrome (PNS) are well described, a significant number of neurological diseases in which pathogenic antibodies directed to neuronal structures are not related to cancer. Uncovering how these antibodies arise, how they enter the nervous systems and approaches to inhibit antibody formation will be key to developing effective therapeutic approaches.

The role of memory B cells in autoimmune diseases

For several autoimmune disorders, e.g. MS, rheumatoid arthritis and Graves' disease, among others, an association has been made between Epstein–Barr virus (EBV) and development of disease. The recent awareness that effective therapies target memory B cells makes the hypothesis that EBV triggers autoreactive B cells and/or antibodies is very compelling. Exactly how EBV triggers autoimmune neurological diseases will be an important step in understanding neuroimmunological diseases such as MS.

Inflammaging and neurological diseases

The term 'inflammaging' has been used to describe the chronic, low-grade inflammation associated with ageing. Senescence in the immune and nervous systems covers a multitude of factors, including lowered response to vaccination, decline in effective autophagy and increased susceptibility to cancer and autoimmune diseases. Why such changes occur will be aided by studying healthy aged cohorts of different backgrounds and races and highlight how environmental factors such as diet, gut microbiota or genes and lifestyle contribute to the immune imbalance associated with 'inflammaging'. A key question will thus be: 'Can we manipulate the immune response to combat the effects of ageing?'.

Neuroimmunology of pregnancy and development

Maternal stress or infections during pregnancy have been linked to impaired cognitive development and psychiatric disorders in the offspring. The recent emergence of Zika virus has underscored not only how the brain may be shaped by infections during development, but that such infections may predispose to autoimmune diseases later in life. A future challenge will thus be to understand how maternal immune factors, including immune cells and cytokines, influence brain development *in utero* and modulate the beneficial factors to enhance brain development to prevent and limit the detrimental effects of the immune system that may contribute to behavioural and mood disorders.

Human stem cell technology and personalized medicine

The advances in reprogramming somatic cells into iPSCs has allowed the culture of patient-specific stem cells, e.g. neuronal stem cells (NSC), to study the disease specific pathways. This technology will allow the development of

human *in-vitro* models to study disease and patient-specific pathways. More importantly, these models should also allow approaches to modulate disease-specific factors aiding personalized medicine. For some neuroimmunological diseases the use of NSC has already proved effective in experimental settings to not only repair the nervous system but examine an unexpected trait by which NSC modulate immune responses. While in its infancy, gene-editing approaches are expected to develop to the point that genetic neurological diseases may be treatable and modulate the immune and nervous systems to combat neuroimmunological disease, and in the meantime allow standardization of iPSC cells.

Acknowledgements

Disclosures

None.

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