Mechanisms of Ageing and Development 160 (2016) 54–68

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Original article

With mouse age comes wisdom: A review and suggestions of relevant mouse models for age-related conditions

Susanne Drechsler[a], Marina A Lynch[b], Susana Novella[c,d], Herminia González-Navarro[d,e], Silva Hecimovic[f], Erica Barini[g], Valter Tucci[g], Rui E Castro[e], Roosmarijn E. Vandenbroucke[h,i], Marcin Osuchowski[a], Paul K. Potter[j,*]

[a] *Ludwig Botlzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria*
[b] *Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland*
[c] *Department of Physiology, Universitat de València, València, Spain*
[d] *Institute of Health Research-INCLIVA, 46010 València, Spain*
[e] *The Research Institute for Medicines (iMed.ULisboa) and Faculty of Pharmacy, University of Lisbon, 1649-003 Lisbon, Portugal*
[f] *Laboratory of Molecular Neuropharmacology, Division of Molecular Medicine, Rudjer Boskovic Institute, Croatia*
[g] *Neurobehavioural Genetics Group, NBT – IIT, Genova, Italy*
[h] *Inflammation Research Center, VIB, Ghent, Belgium*
[i] *Department of Biomedical Molecular Biology, Ghent University, Ghent, Belgium*
[j] *Mammalian Genetics Unit, MRC Harwell, Oxfordshire, UK*

ARTICLE INFO

Article history:
Received 29 February 2016
Received in revised form 7 July 2016
Accepted 15 July 2016
Available online 21 July 2016

Keywords:
Mouse models
Ageing
Phenotyping

ABSTRACT

Ageing is a complex multifactorial process that results in many changes in physiological changes processes that ultimately increase susceptibility to a wide range of diseases. As such an ageing population is resulting in a pressing need for more and improved treatments across an assortment of diseases. Such treatments can come from a better understanding of the pathogenic pathways which, in turn, can be derived from models of disease. Therefore the more closely the model resembles the disease situation the more likely relevant the data will be that is generated from them. Here we review the state of knowledge of mouse models of a range of diseases and aspects of an ageing physiology that are all germane to ageing. We also give recommendations on the most common mouse models on their relevance to the clinical situations occurring in aged patients and look forward as to how research in ageing models can be carried out. As we continue to elucidate the pathophysiology of disease, often through mouse models, we also learn what is needed to refine these models. Such factors can include better models, reflecting the ageing patient population, or a better phenotypic understanding of existing models.

Contents

1. Introduction 55
2. Acute trauma and sepsis 55
   2.1. Neuroinflammation 56
   2.2. Alzheimer's disease 58
   2.3. Cardiovascular diseases 59
   2.4. Metabolic dysfunction 60
   2.5. Sleep and ageing 62
3. Looking to the future 64
   Acknowledgments 64
   References 64

* Corresponding author.
E-mail address: p.potter@har.mrc.ac.uk (P.K. Potter).

http://dx.doi.org/10.1016/j.mad.2016.07.005

1. Introduction

The utility of the mouse in aiding our understanding of disease is clear; the ability to manipulate its genome, a short breeding cycle, defined genetic backgrounds, and the array of phenotypic interrogations available for the mammalian physiology have all helped elucidate the pathogenesis of disease. Whilst ageing is a risk factor for a range of diseases (Niccoli and Partridge, 2012) and there are many efforts to understand the effect of ageing through the modulation of ageing itself (Fontana et al., 2010; Guarente, 2014) it is also clear many diseases have a significant genetic component. This genetic susceptibility may be exacerbated in the context of an ageing physiology, thereby resulting in the observed increased disease risk with age. Thus, the study of individual disease pathways through specific mouse models could aid our understanding of not only disease but also the increased risk associated with ageing. Studies in young mice are often fruitful, but to understand disease, model it accurately, and subsequently test interventions it is only logical that if one is studying a chronic or age-related disease the best models will be chronic or have an ageing component. The disease burden faced by the aged is wide-ranging and varies from individual to individual but there are diseases that are common among aged patients. It is therefore a challenge in many disease areas to include the role of ageing, which may add additional complications or comorbidities that compound the underlying condition (Fabbri et al., 2015). Here we highlight a subset of relevant illnesses and how mice, young, old, and indeed with accelerated ageing, have been used to study them. In this review we highlight the potential impacts of ageing on disease susceptibility in a range of disease areas to emphasise the relevance of current models, and make suggestions for refinements and new developments.

2. Acute trauma and sepsis

Although traumatic injuries are not the main cause of death in people aged ≥60 years, traumas like falls or motor vehicle collisions are associated with an increased mortality risk in elderly patients (Sampalis et al., 2009; Schoeneberg et al., 2014). Often, the trauma itself is not the actual killer; most frequently, the main cause of the ensuing morbidity/mortality in those patients are secondary infections rapidly progressing to sepsis and/or multiple organ dysfunction syndrome (MODS) (Angus, 2001; Frohlich et al., 2014). Susceptibility and mortality from systemic infections increase with patient's age, and sepsis is among the leading causes of death in ageing patients worldwide (Angus, 2001; Wafaisade et al., 2011). To study the above mentioned critical care conditions, the availability of effective age modeling approaches is essential.

Regardless whether trauma or infection occurs, similar immuno-inflammatory reactions are triggered via either DAMPS (danger associated molecular patterns) or PAMPS (pathogen associated molecular patterns) (Lord et al., 2014; Boomer et al., 2014). With advanced age, the host's capability to mount an adequate immune response against inflammatory stimuli declines. This phenomenon is apparent in humans and laboratory animals, including mice (Frasca and Blomberg, 2015). For example, while the number of B-cells and naïve T-lymphocytes decreases, T_2-helper cells (producing the anti-inflammatory interleukins (IL) 4 and 10) accumulate (Linton et al., 1996; Miller, 1996; Weksler et al., 2002). Simultaneously, ageing is associated with a persistent low-grade increase of various pro-inflammatory and acute phase proteins, many of which are independent predictors of mortality/morbidity in patients (Bruunsgaard et al., 2003; Giovannini et al., 2011; Harris, 1999). All those immunologic changes are part of an age-related decline of physiologic functions termed frailty, which occurs in both humans and mice (Mohler et al., 2014). Thus, those similar immuno-inflammatory characteristics justify the age-oriented investigative utility of the mouse in critical care conditions.

Despite the critical need for such translational studies, preclinical research addressing the mechanisms and impact of age on immuno-inflammatory endpoints is infrequent. The main reason is undoubtedly the financial burden: aged mice must be either purchased (e.g. €156 for an 18-month old female CD-1 mouse) or "matured" from a young age for 18–24 months. The latter option, although seemingly attractive, poses many underappreciated risks that may eventually surpass the costs of "ready-to-use" mice (Miller and Nadon, 2000). Despite those hurdles and recently voiced translational doubts (Seok et al., 2013), many important and findings stem from mouse studies in critical care (Osuchowski et al., 2014). In trauma, the majority of existing studies concentrate not on the age itself but rather on the interplay between the age and gender (Kahlke et al., 2000; Mees et al., 2007, 2008), given that sex hormones influence the immune response and their production is age-dependent. For example, estrogens have demonstrated strong protective effects in sexually mature mice when subjected to sepsis after traumatic insults (Choudhry, 2005) and to burn injuries alone (Kovacs, 2005). A frequently used model combining laparotomy and hemorrhagic shock (Kahlke et al., 2000; Schneider et al., 2007) showed that, similarly to human patients (Livingston et al., 2003), trauma affects the amount of circulating bone marrow-associated cells in mice (Schneider et al., 2007). Moreover, the same model demonstrated the (clinically valid) phenomenon of compartmentalisation of immune responses in aged mice, resulting in different responses in distinct tissues. For example an enhanced inflammation in the spleen and inflammatory depression in peripheral blood mononuclear cells (PBMC) can occur conincidently (Kahlke, 2000; Schneider et al., 2006).

Recently, more sophisticated polytrauma models combining hemorrhage with bone fractures (Kleber et al., 2015; Wichmann et al., 1998; Wichmann, 1996), chest trauma (Seitz et al., 2011) or cecotomy (Gentile et al., 2013) have been introduced. Their main strength is that they more closely recapitulate the immuno-inflammatory deregulations occurring in trauma patients. These include a reduced cytokine release capacity by splenocytes, peritoneal macrophages (Wichmann et al., 1998; Wichmann, 1996) and PBMCs (Seitz et al., 2011) and a loss of major histocompatibility complex class II and CD4+ cells (Gentile et al., 2013). Similar immuno-inflammatory deficits were shown to be induced in aged mouse burn models (Kovacs et al., 2002, 2004; Plackett et al., 2003; Nomellini et al., 2008; Plotnikov et al., 2013). Although traumatic brain injuries (TBI) typically occurs in very young or old humans (Langlois et al., 2006), experimental mouse studies are primarily performed in young subjects. The only three existing TBI studies comparing young and aged mice demonstrated higher mortality, stronger neurological function deficits and increased inflammatory markers (Kumar et al., 2013; Onyszchuk et al., 2008; Timaru-Kast et al., 2012) in the latter. The most sophisticated, and clinically relevant, approach are so called two-hit models combining these trauma-induced immuno-inflammatory deregulations (e.g. after first-hit hemorrhage, laparotomy, and/or bone fracture insult) and infections/sepsis as a delayed second hit (see below) (Seitz et al., 2011; Gentile et al., 2013; Kovacs et al., 2002, 2004). The most commonly used trauma models and their application in aged animals are listed in Table 1.

Sepsis can originate from many sites in the body, most frequently the lungs, abdomen, urogenital tract and iatrogenic sources (e.g. indwelling catheters) (Angus, 2001; Vincent, 2006) and the elderly (and neonates) are most at risk. As our understanding of sepsis pathophysiology and epidemiology has grown, the murine modeling has been gradually evolving in an attempt to match the complex clinical reality but this evolution is too slow regarding the age component. Currently, the live bacteria pneumonias and

Table 1
The most commonly used mouse models of trauma categorized by their clinical relevance and frequency in aged-oriented research use.

Trauma model[a]	Clinical Relevance[b]	Tested in Aged Mice[c]	Relevant References[d]
Hemorrhagic shock Barrientos (2006)	low/medium	yes	Seok et al. (2013),Osuchowski et al. (2014)
Hemorrhage + laparotomy	medium	yes	Mohler et al. (2014),Miller and Nadon (2000),Mees et al. (2007),Mees et al. (2008)
Hemorrhage + chest trauma Schneider et al. (2006)	high	no	–
Traumatic brain injury Frank et al. (2009)	high	yes	Plackett et al. (2003),Nomellini et al. (2008),Plotnikov et al. (2013),Cowley et al. (2012),Kohama et al. (1995)
Chest trauma Mawhinney et al. (2011)	high	no	–
Burn Li et al. (2009)	High/very high	yes	Wichmann et al. (1998),Wichmann (1996),Seitz et al. (2011),Gentile et al. (2013)
Polytrauma Kleber et al. (2015),Cowley et al. (2012)	very high	no	Gentile et al. (2014),Lyons et al. (2009)

[a] Most common experimental setups are listed; listed references include selected relevant model development publications and/or review papers.
[b] Relevance of each listed model applies to a corresponding human condition.
[c] Mice ≥ 18 months of age.
[d] Maximum of 5 relevant references listed.

the cecal ligation and puncture (CLP) peritonitis are considered by many as the most clinically relevant model systems. Both closely mimic the protracted pathophysiologic processes (e.g. concurrent release of pro- and anti-inflammatory mediators, impaired coagulation/fibrinolysis, and organ dysfunction) which typically occur in sepsis patients (Saito et al., 2003; Remick et al., 2000; Esposito and Pennington, 1983; Angus and van der Poll, 2013; Dejager et al., 2011). Pneumonia is produced via intranasal/tracheal instillation of various pathogens (i.e. *Pseudomonas, Klebsiella, Streptococcus pneumonia*, *Influenza virus*) (Starr and Saito, 2014; McConnell et al., 2011; Mares et al., 2010; Shivshankar et al., 2011), while CLP and colon ascendens stent peritonitis (CASP) induce polymicrobial abdominal peritonitis via leakage of feces from the gut (Hubbard, 2005; Zantl, 1998). Furthermore, instillation of single or double strains of bacteria into the murine bladder produces urosepsis and revealed the role of bacterial adhesins for retention of bacteria in the urinary tract (Hagberg, 1983a,b). However, this model has not yet been tested in aged mice. Less relevant peritonitis models include intraperitoneal fecal pellets, fibrin clots containing fecal bacteria (Ahrenholz and Simmons, 1980; Starr et al., 2014; Gentile et al., 2014; Nulsen et al., 1983), and injection of live/inactivated bacteria (Hyde and McCallum, 1992). Historically, the administration of a bacterial lipopolysaccharide (LPS) has been the most frequently used experimental setup aiming to produce sepsis-like symptoms. The current consensus is that LPS does not recapitulate the protracted immuno-inflammatory responses of human sepsis (Osuchowski et al., 2014; Remick et al., 2000).

Sepsis models can be successfully used to mimic secondary complications after trauma (i.e. two-hit models) (Drechsler et al., 2012; Nacionales et al., 2015). Importantly, the clinical relevance of those models critically depends on the severity and mode of action of each hit. For example the more severe the initial trauma, the more likely patients will develop secondary complications (due to dysfunctional/suppressed inflammatory responses). Thus, when combined with a subsequent (two-hit) infectious insult, the relatively low-severity first trauma hits (e.g. hemorrhage only) appear as an inferior choice. Given that mice possess an innate high resistance to trauma (and inflammation) even severe mouse trauma models cannot recapitulate a full pallet of the most severe responses that occur in patients. It is equally crucial to choose an appropriate sepsis model match (e.g. CLP for abdominal sepsis) and a suitable level of its severity ensuring a clinically-realistic outcome proportion (e.g. approx. 30–40% mortality post-CLP). Finally, different types of sepsis frequently occur simultaneously in immunocompromised (e.g. posttraumatic) patients, thus, combination of different sepsis models is theoretically possible. Yet, such setups appear very burdensome (and ethically problematic) to be tested in aged mice (especially 2-hit scenarios) (Muenzer et al., 2006; Davis et al., 2011). Most common available sepsis models and their application in aged animals are listed in Table 2.

In summary, the similar responses and age-adjusted survival patterns (Turnbull, 2003) further emphasise the utility of well-designed mouse modeling. The great advantage in mouse modeling of age-related critical care disorders is that it does not require development of new sophisticated modeling platforms solely devoted to this purpose. Thus, the dire demand for age research in trauma/sepsis can be met relatively quickly: it merely requires a thoughtful selection of the most hypothesis-fitting and clinically relevant models (from the myriad of existing variations) and their application in aged mice, typically around 18–24 months of age. The relatively short life time-span of the mouse (compared to larger mammals) allows for multiple repetitions and solid verification of the generated data – a key component of the effective extrapolation to human medicine.

2.1. Neuroinflammation

Systemic inflammation occurs with ageing (Frasca and Blomberg, 2015; Franceschi and Campisi, 2014; Ostan et al., 2008) and it is generally agreed inflammatory changes are characteristic of the aged brain and are a prominent feature of most, if not all, neurodegenerative conditions. Neuroinflammation is characterized by increased expression of inflammatory cytokines including interleukin 1 beta (IL-1β), tumour necrosis factor (TNF)-α, and interleukin 6 (IL-6), and it has been known for more than two decades that the expression of these cytokines is increased in an age-related manner (Lynch, 2010; Godbout et al., 2005).

Microglia are the primary source of inflammatory cytokines and numerous studies have reported that the increase in inflammatory cytokines is accompanied by an age-related increase in microglial activation. Consistent with this, microarray analysis has revealed an upregulation of genes associated with inflammation, including genes that are indicative of microglial activation like major histocompatibility complex class II (MHCII) (Lee et al., 2000; Godbout et al., 2005). Further analyses confirmed the age-related increase in MHCII and also reported increased expression of other markers of microglial activation including CD68, CD80 and CD86. These changes have also been confirmed by immunohistochemistry and flow cytometry, which demonstrated an age-related increase in $CD11b^{+}MHCII^{+}$ cells in the brain (Lynch, 2010, 2014; Barrett et al., 2015). More recently, microarray data obtained from analysing human post-mortem brain tissue identified age-related changes in expression of several immune/inflammation genes, especially in the hippocampus, including IL-1β, IL-6 and TNFα as well as MHCII, especially in the hippocampus, an area that plays an important role in memory. In the choroid plexus, an interface

Table 2
The most commonly used mouse models of sepsis categorized by their clinical relevance and frequency in aged-oriented research use.

Infection/Sepsis model[a]	Model Complexity	Clinical Relevance[b]	Tested in Aged Mice[c]	Relevant References [d]
Endotoxemia[e] Drechsler et al. (2012),Nacionales et al. (2015) (LPS bolus)	1 hit	very low[f]	yes	Kumar et al. (2013),Davis et al. (2011),Turnbull (2003),Franceschi and Campisi (2014),Ostan et al. (2008)
Live/inactivated bacteria[g] (iv/ip administation)	1 hit; monobacterial	low/medium[h]	yes	Ahrenholz and Simmons (1980)
Intra-abdominal Ostan et al. (2008)	1 hit			
a) Feces Hagberg (1983a)	polybacterial	medium	yes	Zantl (1998),Hagberg (1983a)
b) Fibrin clot Shivshankar et al. (2011)	mono/polybacterial	medium	no	–
c) CASP Starr and Saito (2014)	polybacterial	medium	no	–
d) CLP Dejager et al. (2011),Lynch (2010)	polybacterial	high	yes	Kumar et al. (2013),Drechsler et al. (2012),Lee et al. (2000),Lynch (2014),Barrett et al. (2015)
Urosepsis McConnell et al. (2011),Mares et al. (2010)	1 hit; mono /polybacterial[i]	high	no	–
Pneumonia[j] Timaru-Kast et al. (2012),Barrett et al. (2015)	1 hit; monobacterial	high	yes	Timaru-Kast et al. (2012),Baruch et al. (2013),Baruch et al. (2014),Maher et al. (2006),Maher et al. (2005)
Trauma/CLP or pneumonia[k] Starr et al. (2014),Maher et al. (2005),Nolan (2005)	2 hit	medium/very high[l]	yes	Starr et al. (2014),Gentile et al. (2014)
CLP/Pneumonia or fungemia Gentile et al. (2014),Nulsen et al. (1983)	2 hit	very high	no	–

LPS: lipolysaccharide; iv: intravenous; ip: intraperitoneal; CASP: colon ascendens stent peritonitis; CLP: cecal ligation and puncture.
[m]Combination of models simulating the two most commonly occurring types of sepsis syndromes in patients; systemic candidiasis (by *Candida albicans*) is one of the most common nosocomial infections in immuno-compromised sepsis patients.
[a] Most common experimental setups are listed; listed references include selected relevant model development publications and/or review papers.
[b] Relevance of each listed model applies only to a corresponding human condition (e.g. CLP to human ruptured diverticulitis/appendicitis), not across all existing sepsis syndromes.
[c] Mice ≥ 18 months of age.
[d] Maximum of 5 relevant references listed.
[e] Irrespective of the administration route.
[f] Resemblance to fulminant meningococcemia only; not a true infection.
[g] Other administration routes of live bacteria are included in specific organ compartments as more clinically relevant model designs (e.g. intratracheal administration of *S. pneumoniae*).
[h] Relevance depends on the model design-to-hypothesis match; e.g., low relevance of an inactivated *E. coli* ip bolus injection to simulate peritonitis, medium relevance of protracted iv infusion of live *E. coli* to simulate septic shock.
[i] Simultaneous administration (into the urinary bladder) of maximum 2 bacterial strains; to date, a wide-range polybacterial inoculus (e.g. feces) used in rats (Kovacs et al., 2002) but not mice.
[j] High relevance does not apply to iv/ip administration of typical lung pathogens (e.g. S. pneumoniae).
[k] Various trauma hits are utilised (e.g. hemorrhage (H), laparotomy (L), bone fracture (BF), acute lung injury (ALI); any order of hits is possible (e.g. H-BF/CLP; CLP/ALI).
[l] Relevance depends on the proper severity match in both hits.

between the brain and the circulation and an important gateway for leukocyte infiltration into the brain (Demeestere et al., 2015), the anti-inflammatory cytokine IL-4 was elevated, whereas the pro-inflammatory cytokine, interferon gamma (IFN-γ)was decreased in the aged mouse. This is indicative of a shift toward a pro-inflammatory state (Baruch et al., 2013). Additionally, a chronic ageing-induced type I interferon signature was observed at the brain's choroid plexus, which negatively influences brain function (Baruch et al., 2014).

Microglia share many properties of macrophages, including their ability to respond to numerous stimuli, reflecting the huge array of receptors expressed on their cell surface. In the past few years, it has become clear that microglia, like macrophages, adopt different activation states (at least *in vitro*) with evidence of polarization to a 'classical' M1 phenotype in response to interferon IFNγ and an 'alternative' M2 phenotype in response to IL-4 and other anti-inflammatory cytokines. Translation of these phenotypes into the *in vivo* situation is fraught with difficulties but the evidence suggests that IFNγ concentration increases with age, in contrast to the decrease in IL-4 (Maher et al., 2006, 2005; Nolan, 2005) suggesting an age-related bias towards the inflammatory M1 phenotype. This is also consistent with the proposal that microglia become primed with age, making them more susceptible to subsequent inflammatory stimuli. Thus treatment of aged mice with LPS exerted a more profound effect on sickness behaviour and induced a greater production inflammatory cytokines than in young mice (Godbout et al., 2005). LPS also induced a greater degree of microglial activation and a more profound depressive behaviour (Godbout et al., 2005) in aged mice (compared with young). Similarly an age-related sensitization to *E. Coli* has been reported with evidence of exaggerated and persistent behavioral effects (Barrientos, 2006), which were attributed to IL-1β (Frank et al., 2009). An increase in responsiveness to amyloid- (Aβ), the principal constituent of the plaques in Alzheimer's disease (AD), has also been reported in aged animals whereby central injection of a sub-threshold concentration of $A\beta_{1-42}$ in young animals induced a significant effect on IL-1β concentration in hippocampus of aged animals (Minogue et al., 2007).

Interestingly, the evidence indicates that there is an age-related upregulation of genes relating to activation of the inflammasome (Cribbs et al., 2012); this cytosolic multiprotein complex is necessary to activate caspase 1 and therefore to process IL-1β to its active form. Consistent with this, there is an increase in the expression of cleaved caspase 1 and pannexin 1 in the hippocampus, which is indicative of increased inflammasome activation (Mawhinney et al., 2011). It is important to note that whereas microglia may be the primary source of inflammatory cytokines, astrocytes are also capable of producing IL-6, IL-1β and TNFα, albeit to a lesser extent than microglia (Li et al., 2009) and there is clear evidence of an increased astrocytic activation with age. Several studies have reported increases in the archetypal marker of astrocytic activation, glial fibrillary acidic protein (GFAP) (Godbout et al., 2005; Lee et al., 2000; Cowley et al., 2012; Kohama et al., 1995; Hayakawa et al., 2007).

When the brain is not challenged, the primary function of microglia is surveillance; microglial processes sample their

microenvironment every few hours (Nimmerjahn et al., 2005) and this surveillance state is somewhat misleadingly called the resting state. Under these conditions microglia are kept in check by ligand-receptor interactions like the interaction between CD200 and CX3CL1 and their respective receptors that are expressed on microglia (Lyons et al., 2007, 2009) but also by a variety of soluble factors (Ransohoff and Perry, 2009). A decrease in the repressive tone might contribute to microglial activation and it has been shown that both CD200 and CXCL1 are decreased in the hippocampus with age and coupled with evidence of microglial activation. It is also worth noting that IL-4 concentration, albeit low under resting circumstances, is decreased in the hippocampus with age and IL-4-induced phosphorylation of JAK1 (janus kinase 1) and STAT6 (signal transducer and activator of transcription 6, interleukin-4 induced) is similarly decreased (Maher et al., 2005; Nolan, 2005), whereas IL-1β-associated signalling through JNK (Jun amino-terminal kinases) is increased (Nolan, 2005). These signalling pathways were confirmed as being protective as addition of IL-4 to aged animals prevented the age related impairment of long term potentiation (Nolan, 2005).

The age-related glial activation and increased hippocampal expression of inflammatory cytokines negatively impacts spatial learning and synaptic plasticity. IL-1β profoundly affects several behaviours (Goshen and Yirmiya, 2009). The first report of its ability to inhibit hippocampal-dependent learning (Oitzl et al., 1993) was confirmed by several other groups (Gibertini et al., 1995; Barrientos et al., 2002) identifying IL-1β as key to the inhibitory effect of LPS on hippocampal function. It has also been shown that persistent overexpression of IL-1β in the hippocampus results in poor performance in hippocampal-dependent tasks (Hein et al., 2009) and is, predictably, associated with microglial activation (Moore et al., 2009). Chronic upregulation of IL-6 has also been demonstrated to be associated with deficits in learning and microglial activation (Heyser et al., 1997; Sparkman, 2006) although at least one recent study does not entirely concur with this (Donegan et al., 2014).

In addition to age-related increased hippocampal concentrations of IL-1β, IL-6 and TNFα, increases in IFNγ and IL-18 have also been reported (Griffin, 2006). These cytokines were shown to exert an inhibitory effect on long-term potentiation (LTP), the most-commonly studied form of synaptic plasticity (the ability of synapses to respond to changes in their activity) (Lynch, 2014; Maher et al., 2006; Curran and O'Connor, 2001; Kelly et al., 2013). Interestingly, when the age-related microglial activation (which accompanies the increased expression of these cytokines) is decreased by acute administration of minocycline (Griffin, 2006) or IL-4 (Nolan, 2005), long term potentiation was partially restored. Similarly, longer-term treatments of aged animals with atorvastatin, rosiglitazone or the polyunsaturated fatty acid, eicosapentaenoic acid (EPA), decreased microglial activation and improved the ability of aged animals to sustain synaptic plasticity (Clarke, 2008; Loane, 2009; Lynch et al., 2007), pointing to a causal relationship between microglial activation and loss of synaptic function. The findings suggest that strategies which reduce neuroinflammation will improve the age-dependent deterioration of the CNS function.

2.2. Alzheimer's disease

Age is the most significant risk factor for developing AD (AD), the most common neurodegenerative disorder and the most common cause of dementia. The prevalence of this still untreatable disorder is rising, due to and the increase in the ageing population. It is the estimated that there will be 106 million AD patients by the year 2050 (Brookmeyer et al., 2007). Consequently, there is an urgent need for the development and characterisation of relevant animal models to facilitate preclinical drug development and translation research through to human clinical trials.

The most widely used animal models of AD are models of a rare form of autosomal dominant familial AD (FAD) which comprises less than 1% of AD cases (see the currently available genetic models at http://www.alzforum.org/research-models). The major advantage of using such models is that genetic causes of FAD are known, while the cause(s) of the most common sporadic AD (SAD) are still unknown and are likely comprise multiple genetic and environmental risk factors. Importantly, although the etiology of sporadic and familial AD is different, both forms of AD develop indistinguishable clinical and neuropathological phenotype. This includes the accumulation of the amyloid plaques, comprised of the aggregated Aβ peptides and hyperphosphorylated protein tau in neurofibrillary tangles (NFTs).

The currently available single transgenic or multiple transgenic FAD mice that express human mutated *APP* and/or *PS1/2* genes do not completely recapitulate AD pathology (reviewed in LaFerla et al. (LaFerla and Green, 2012)). Although these FAD models show early learning disability and cognitive impairment followed by the accumulation of Aβ and senile plaque formation they do not develop NFTs in their brains (although some show hyperphosphorylation of tau). More importantly, none of the models show profound neuronal loss – a characteristic feature of human AD (reviewed in Gotz (Gotz et al., 2007)). The amyloid cascade hypothesis predicts that accumulation of Aβ peptides precedes hyperphosphorylation of tau and NFT formation, thus initiating the cascade of events leading to synaptic loss and neurodegeneration. To better model this, transgenic murine models have been developed that express mutated human tau (i.e. *MAPT* mutation which causes frontotemporal dementia and does not cause AD) together with human mutated *APP* and/or *PS1/2* genes (Lewis et al., 2001; Oddo et al., 2003; Oddo, 2003). Indeed, these mice show a characteristic senile plaque formation which precedes formation of NFTs and are valuable models to monitor the interrelationship between Aβ and tau accumulation. Over the past two decades, these transgenic murine models of familial AD have significantly contributed to our understanding of the molecular mechanism(s) of the disease, drug development and preclinical testing. However, numerous reported failures of new treatments for AD in clinical trials indicate that the use of genetic models of familial AD does not represent the complete picture of AD in humans. Consequently, there is a pressing need to develop other animal models relevant to the sporadic form (SAD), which represents 99% of AD cases.

Although both forms of AD are highly influenced by ageing, FAD is more aggressive in its progression and manifests at younger age. Understanding the differences between SAD and FAD, and the causes of the build-up in pathologies, may be important in developing models for evaluating interventions against the more common SAD. Furthermore, we should consider incorporating the use of animal models that deal with the issue of extensive neuronal loss (already present in patients with mild-moderate AD and causing cognitive impairment), with the current AD mouse models that primarily model AD pathologies. Such models will enable identification of treatments that target both cognition, due to neuronal loss, and clearance of Aβ and/or tau pathologies, and these are predicted to be more successful than treatments that target the pathology alone. As ageing is the major risk factor of sporadic AD, any models must reflect pathology that develops with age rather than genetic manipulation alone, such as occurs in current FAD models. These models will be important in identification of critical component(s) of the ageing process that drive AD pathology and target them for the treatment/prevention (Table 3).

Animal models of the apolipoprotein E (apoE), in particular of the apoE4 isoform which is the major genetic risk factor of SAD, are of particular interest both for understanding the role of apoE4

Table 3
The most widely used genetic mouse models of Alzheimer's disease categorized by their clinical relevance and frequency in aged-oriented research use.

AD model[a]	Genetic modification	Clinical Relevance[b]	Tested in Aged Mice[c]	Relevant References[d]
PDAPP	A PDGF-driven human APP minigene with the V717F (Indiana) mutation.	Amyloid plaques in the hippocampus, cerebral cortex. Gliosis. Dystrophic neurites. Decreased synaptic and dendritic density in the hippocampus. Memory deficits.	Yes	Sterniczuk et al. (2010a),Sterniczuk et al. (2010b),Jyoti et al. (2010)
Tg2576	The human APP gene (isoform 695) containing the double mutation K670N, M671L (Swedish mutation) under the control of the hamster prion protein.	Amyloid plaques with some vascular amyloid. Astrogliosis and microgliosis. No tangles or neuronal loss. Impaired spatial learning, working memory, and contextual fear conditioning.	Yes	Schrempf et al. (2014),Lima et al. (2008),Dzirasa et al. (2006)
APP23	Transgene containing human APP (isoform 751) containing the Swedish (KM670/671NL) mutation under the murine Thy1 promoter.	Amyloid plaques. Astrogliosis and microgliosis. Dystrophic neurites containing hyperphosphorylated tau (no neurofibrillary tangles). Neuronal loss in the CA1 region of the hippocampus. Memory defects, anxiety, agression, aletred circadian rhythm.	Yes	Maloney et al. (2002),Gossan et al. (2013),Ayadi et al. (2012)
APP/PS1	Human transgenes APP KM670/671NL and PSEN1 L166P, both under the control of the Thy1 promoter.	Amyloid plaques. Phosphorylated tau-positive neuritic processes, but no neurofibrillary tangles. Microgliosis. Cognitive deficits in spatial learning and memory. Irritability, depression, disturbance of motor functions, anxiety.	No	Miller et al. (2007)
3xtg AD	Single-cell embryos from mice with knock-in of PSEN1 with the PS1M146V mutation were injected with two human transgenes (APP with the Swedish mutation and MAPT with the P30IL mutation). Transgenes integrated at a single locus under the control of the mouse Thy1 promoter.	Age-related, progressive neuropathology including amyloid plaques (accumulation of intraneuronal Aβ), neurofibrillary tangles and microgliosis. Cognitive impairment, episodic memory loss, circadian changes, anxiety. No neuronal loss in the hippocampus.	No	Oddo et al. (2003)
5xFAD	Two transgenes: mutant human APP with the APP Swedish, Florida and London mutations and containing the 5′ untranslated region driven by the mouse Thy1 promoter and mutant human PSEN1 including the M146L and L286V mutations driven by the mouse Thy1 promoter.	Amyloid plaques, including accumulation of intraneuronal Aβ. Gliosis and synapse degeneration. Neuron loss in cortical layer 5 and subiculum. No neurofibrillary tangles. Age-dependent memory deficits. Motor phenotype and reduced anxiety.	No	Ayadi et al. (2012)

[a] Most widely used genetic mouse models of Alzheimer's disease are listed; for complete list of AD models please go to http://www.alzforum.org/.
[b] Relevance of each listed model applies to a corresponding human condition.
[c] Mice ≥ 18 months of age.
[d] Maximum of 5 relevant references listed; listed references include selected relevant model development and characterization publications.

in AD pathogenesis as well as for developing anti-ApoE4 strategies (Holtzman et al., 2000; Michaelson, 2014). So far these studies have utilised apoE$^{-/-}$ mice (Holtzman et al., 2000; Bales et al., 1997; Bales, 1999) and mice expressing human apoE2, apoE3 or apoE4 (Holtzman et al., 2000; Fagan et al., 2002). Using knock-in and targeted replacement technologies, humanised ApoE murine models have been developed that express human ApoE2/3/4 genes under the control of the murine ApoE regulatory sequence (see the currently available models at http://www.taconic.com/transgenic-mouse-model/). Humanised AD models thus may represent a more relevant model both for familial and sporadic AD as they express the gene of interest under its endogenous promoter. Although humanised murine models would potentially be less acute than the current transgenic models and would need more "ageing" to develop the AD-like pathology, they could identify more relevant drug targets to develop successful therapies against AD. As we evidence novel genetic risk factors of SAD, in addition to apoE4 allele, other risk genes may also be used to better model SAD (reviewed in Medway et al. (Medway and Morgan, 2014)).

2.3. Cardiovascular diseases

Ageing is also one of the main risk factors in the development of cardiovascular diseases (CVD) given that it causes functional alterations in the vasculature as a result of deregulation of the molecular longevity pathways. The ageing heart in mice is comparable with that of humans (Dai and Rabinovitch, 2009) but generally require an additional genetic modification for atherosclerosis to occur, as outlined below. Vascular ageing is particularly associated with endothelial dysfunction, arterial stiffening and remodeling, impaired angiogenesis, defective vascular repair, and an increased prevalence of atherosclerosis (Erusalimsky, 2009; Lakatta and Levy, 2003; Novella et al., 2013). Experimental models of cardiovascular ageing include senescence-accelerated mouse (SAM) model with two substrains: SAM-prone (SAMP) and SAM-resistant (SAMR), each of which exhibits characteristic disorders (Butterfield and Poon, 2005; Takeda et al., 1997). SAMP8 shows an age-related deterioration of learning and memory at an earlier age, compared with the senescence-accelerated resistant strain (SAMR1) (Butterfield and Poon, 2005). Vascular studies using these models in male (Novensa, 2010) and female (Novella et al., 2013; Novensa, 2010; Novella, 2010) mice have shown morphological alterations and mechanical and endothelial dysfunction, and they are suitable models for the study of vascular physiological changes during ageing. In addition, studies in mouse models of genes associated with ageing have also been used to understand the connection between ageing and CVD progression. In particular, mice deficient for Sirtuin1 (*Sirt1*), which would mimic the decreased activity associated with ageing, exhibit enhanced injury in response to ischemia reperfusion studies. Consistently, *Sirt1* transgenic mice display reduced

injury and cardiac *Sirt1*-overexpressing mice exhibited delayed cardiomyopathies associated with ageing (summarized in (North and Sinclair, 2012)).

Atherosclerosis is the most common cause of CVD. Mouse models of this process have been generated by genetic manipulation of lipoprotein metabolism genes which resulted in mice exhibiting hypercholesterolemia and atherosclerosis, providing a useful tool to study lesion progression. Thus, the low-density lipoprotein receptor-deficient (*Ldlr*-/-) mouse (Ishibashi, 1993) is a model of familiar hypercholesterolemia with a plasma lipoprotein profile similar to humans and atheroma lesions induced by a high caloric Western diet. The human apoB response to a high-fat feeding (Purcell-Huynh, 1995). The most widely used atherosclerotic mouse model is the apolipoprotein E-deficient (*ApoE*-/-) mice (Plump, 1992; Zhang et al., 1992; Onozuka, 2002; Hartley, 2000) that develops hypercholesterolemia and spontaneous atherosclerosis with a complexity in the lesions resembling those observed in human atherosclerosis (Zaragoza, 2011). The combination of apoE-deficiency with inactivation of other genes has advanced the knowledge of the underlying pathogenesis of the atherosclerotic process. Whilst this model has been very useful, the rapid onset of atherosclerosis in the mouse model compared to humans (weeks versus years) limits the utility of the model in drug or treatment development. Similarly, the *ApoE*-/- model does not take into account the effects of ageing on the physiology and the inflammatory response to atherosclerotic lesions; this appears as a serious modeling shortcoming given a strong age-dependent evolution of the immune system toward the pro-inflammatory environment. Despite the significance of CVD in age-related diseases, few mouse models have been developed that integrate physiological ageing element as the basic setting. Available mouse CVD models are summarized in Table 4.

Several experimental models and methods have been developed to address other cardiac complications.

Heart failure (HF) is a complex syndrome than can be caused by multiple factors, but the consequences of an ageing of the population and the improvement of treatments for ischemic cardiac disease, are aged patients at risk for HF. HF is characterized by a decreased ability of the heart to provide sufficient cardiac output to support the normal functions of the tissues because of impaired filling and/or ejection of blood (Houser et al., 2012). Research to identify novel targets for HF therapy usually requires preclinical testing in appropriate HF animal models.

HF models were originally developed in rats because of the numerous potential advantages inherent in a small animal model (Patten and Hall-Porter, 2009), although the advent of transgenic strategies has made the mouse an invaluable tool to study the pathogenesis of heart failure and to identify novel therapeutic targets. Whereas the rat models have been used extensively to explore the potential for novel pharmacological or molecular agents for the treatment of HF, using animal models can establish causality, confirm proof-of-principal for a particular therapeutic approach, and help people to understand the multifactorial bases for CVD (Yutzey and Robbins, 2007). Mouse models of HF are usually non genetically altered models subjected to experimental manipulations such as coronary artery ligation, cardiac pressure overload, cardiac volume overload, viral myocarditis, or cardiotoxic cardiomyopathy (Wang et al., 2004). However, genetically engineered murine models are being developed in which the genes involved are those related to a variety of proteins including cytoskeletal or sarcomeric components, neurohumoral receptors, cell signalling molecules, calcium-regulating proteins, and to extracellular matrix proteins (Wang et al., 2004).

In mice that have undergone coronary artery ligation the time course of HF is affected not only by the infarcted area but also by the age of animals. Two-month-old C57BL/6N mice tolerate coronary artery occlusion without HF signs, whereas 14-month-old mice develop HF, with only 36% of animals surviving for more than 8 weeks (Gould et al., 2002). The same limitation occurs with the mice with homozygous null mutations in the high-density lipoprotein receptor SR-BI (scavenger receptor class B, type I) and ApoE, a model of hyperlipidaemia and atherosclerosis which manifests multiple myocardial infarction and HF (Braun, 2002). These mice survive only a few weeks after birth, limiting their use in HF research.

The senescence-accelerated strain, SAMP8, has also been proposed as a suitable model for the study of cardiac ageing. SAMP8 mice have diastolic dysfunction associated with ageing similar to that observed in humans (Reed et al., 2011), an increase in age-associated oxidative damage in RNA and DNA in heart (Gan et al., 2012), alterations in glucose transport (Kurokawa et al., 1998), and present pro-inflammatory cytokines associated with the pathogenesis of cardiovascular diseases (Forman et al., 2010, 2011).

2.4. Metabolic dysfunction

A variety of metabolic dysfunctions, such as impaired glucose tolerance, insulin resistance (IR), and type 2 diabetes mellitus (T2DM) develop with age. Persistence of diabetes increases the risk of a cluster of chronic life-threatening metabolic diseases such CVD, hepatic steatosis, chronic kidney disease and central nervous system deterioration. The pathogenic mechanisms of age-associated T2DM include impaired insulin secretion from β cells, loss of proper insulin/insulin-like growth factor (IGF1)-signalling mediated by the insulin receptor substrates (IRS) (White, 2014), and an increase in body weight owing to a reduction in energy expenditure and/or nutrient sensing associated with ageing (Manini, 2010). A mechanistic insight of carbohydrate metabolism has been obtained from mouse models with genetic manipulations in these pathways (Taniguchi et al., 2006). Thus, mutant mice for *db* ($Lepr^{db/db}$) or *ob* ($Lep^{ob/ob}$) genes have a deficiency in the leptin hormone sensing system and develop an early-onset obesity, hyperglycemia and IR due to a slower rate of catabolism (Gonzalez-Navarro et al., 2007). Other diabetes-related mouse models are the insulin receptor (Insr)-deficient mice which display severe hyperinsulinemia but die within a few days after birth and the insulin receptor substrate 1 (IRS1)-null mice (a downstream effector of insulin) which develop mild IR. A mouse model that recapitulates most characteristics of T2DM is the *Irs2*-deficient mouse which is characterized by IR, hyperinsulinemia, hyperglucemia and β-cell failure. *Irs2*-/- females also develop obesity produced by dysregulation of leptin sensitivity (Gonzalez-Navarro et al., 2007). In addition, mouse models with double deficiencies in *Insr* or *Irs2* genes in combination with ApoE- or LDLr-inactivation shed light into the underlying pathogenesis of the relationship between CVD, lipid and carbohydrate metabolism deterioration and insulin-signalling (Baumgartl, 2006; Gonzalez-Navarro, 2007; Han, 2006; Gonzalez-Navarro et al., 2008; Martinez-Hervas, 2014). These studies have shown that impaired insulin/IGF1-signalling produces life-threatening diseases in mice similar to those in humans. However, reduced insulin/IGF1-signalling can extend life span in lower metazoans and seem to be in conflict with the pathogenic effect in mouse and humans (White, 2014). Recent studies in brain-specific *Irs2*-null mice, which resulted in reduced insulin/IGF1 signalling, showed an increased life-span despite glucose and energy homeostasis imbalance and obesity demonstrating the key role of insulin/IGF1-IRS2 pathway in coordinating metabolism and longevity (Taguchi et al., 2007).

The growth hormone receptor/binding protein (Ghr/bp) KO (GHR-KO) mouse constitutes another relevant model to study regulation of insulin-associated signalling pathways during ageing. GHR-KO mice display decreased GH hormonal signalling and hepatic production of insulin-like growth factor 1 (IGF-1), which leads

Table 4
Mouse models displaying cardiovascular disease.

Mouse model[a]	Cardiovascular alteration[b]	Clinical relevance[c]	Tested in Aged Mice[d]	Relevant References[e]
SAMP8 mice	Mechanical and endothelial dysfunction; Diastolic dysfunction and cardiac fibrosis	yes	no	Novella et al. (2013),Butterfield and Poon (2005),Takeda et al. (1997),Novensa (2010),Reed et al. (2011)
Sirt1-/- mice	Enhanced injury in ischemia reperfusion studies; Dilated cardiomyopathy	no	no	Novella (2010),Miranda (2015)
Sirt1-Tg mice	Delayed cardiomyopathy	no		Novella (2010)
Ldlr-/- mice	Increased atherosclerosis	yes	no	North and Sinclair (2012)
ApoB-Tg mice	Increased atherosclerosis	yes		Ishibashi (1993)
apoE-/- mice	Increased atherosclerosis; cardiomyopathy	yes	no	Purcell-Huynh (1995),Plump (1992),Zhang et al. (1992),Onozuka (2002),Hartley (2000)
VSMC-specific Sirt1-TgapoE-/-	Increased DNA damage and atherosclerosis	yes	no	Gao et al. (2014)
Foxo1-/-apoE-/-	Endothelial dysfunction and atherosclerosis	no	no	McDonnell et al. (2015)

[a] Most common experimental setups are listed.
[b] Impact of the genetic manipulation in the indicated metabolic characteristics.
[c] Relevance of each listed model applies to a corresponding human condition.
[d] Mice ≥ 18 months of age.
[e] Maximum of 5 relevant references listed.

to a markedly reduced level of circulating IGF-1, reduced growth rate and adult body weight (Zhou, 1997) as well as longer lifespan (Coschigano, 2003). GHR-KO animals also exhibit decreased plasma insulin level and consequently, higher insulin sensitivity, in part due to decreased proliferation of β cells (Liu, 2004). Of note, specific suppression of insulin sensitivity in these mice attenuates phenotypic features of slow ageing (Arum, 2014).

Reactive oxygen species (ROS), mitochondrial by-products of oxidative energy metabolism, are considered to be important drivers of the age-related decline; ROS can damage DNA directly or indirectly, resulting in a wide variety of oxidative DNA lesions which accumulate with age in different tissues. In turn, mutations affecting DNA repair further lead to more lesions and premature ageing (Gurkar and Niedernhofer, 2015; Wang et al., 2012). As such, mouse models bearing genetic mutations of antioxidant enzymes may help in determining its effects on ageing and lifespan. For instance, transgenic mice overexpressing mitochondrial catalase show increased lifespan and reduced oxidative damage (Schriner et al., 2005). Still, different mouse models have described contradictory and/or inconsistent results, suggesting that mutation of a unique antioxidant enzyme or even that oxidative damage alone may not contribute in full to the ageing phenotype and longevity. Nevertheless, mitochondrial dysfunction appears to possess strong mechanistic links with age-induced metabolic dysfunction, including impaired fatty acid oxidation (FAO), ROS-induced oxidative damage, inflammation and diabetes (Gao et al., 2014; McDonnell et al., 2015). Indeed, the decline in mitochondrial function during ageing is concomitant with the development of hyperglycemia and hyperinsulinemia (Petersen et al., 2003), while the prevalence of diabetes is increased in aged individuals. Sirtuin 3 (*Sirt3*) KO mice present an excellent opportunity to study metabolic changes associated with mitochondrial dysfunction. SIRT3 is a mitochondrial deacetylase that increases mitochondrial energy metabolism by regulating ROS detoxification, ATP generation, mitochondrial dynamics, nutrient oxidation, and the mitochondrial unfolded protein response (UPR) (McDonnell et al., 2015; Brenmoehl and Hoeflich, 2013). Therefore, SIRT3 plays a key role in regulating fat metabolism and whole-body energy homeostasis; livers of SIRT3 KO mice accumulate lipid and acylcarnitine metabolites and show impaired fatty acid oxidation (FAO) (Hirschey, 2010). Moreover, when placed on a high-fat diet (HFD), SIRT3 KO mice exhibit accelerated development of several hallmarks of the metabolic syndrome, including weight gain, impaired glucose tolerance, and insulin resistance. In fact, these mice also show hampered insulin secretion in response to glucose, suggesting a diet-induced pancreatic β cell dysfunction and the likelihood of SIRT3 protecting β cells from nutritional stress (Hirschey, 2011).

SAMP1 mice also display several features of dysfunctional energy metabolism. For instance, aged SAMP1 mice display lower oxygen consumption and fat oxidation in parallel with higher plasma glucose, insulin, leptin, and lower adiponectin concentrations, when compared with age-matched SAMR1 mice. Additionally, decreased fatty acid catabolism in the muscles and liver, and increased inflammation and oxidative stress in the adipose tissue, constitute early events in ageing SAMP1 mice (Haramizu et al., 2011). This characteristic underscores the usefulness of SAMP1 mice in studying factors impacting on the metabolic syndrome during ageing.

The mammalian sodium-coupled citrate transporter NaCT (mINDY), is predominantly expressed in the liver cells and acts as a transporter of Krebs cycle intermediates (Rogers and Rogina, 2015). Interestingly, mINDY$^{-/-}$ mice are protected from HFD-induced and age-associated insulin resistance, at least in part, by activation of 5′ AMP-activated protein kinase (AMPK) and subsequent induction of mitochondrial biogenesis *via* peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α), leading to augmented energy expenditure associated with an increased hepatic lipid oxidation and reduced lipogenesis (Birkenfeld, 2011). As a result, mINDY$^{-/-}$ mice display reduced adiposity and liver and skeletal muscle lipid accumulation. The above highlights the value of this model in studying age-associated nonalcoholic fatty liver disease (NAFLD), obesity, and type 2 diabetes.

Taurine depletion has been shown to accelerate skeletal muscle senescence leading to early death in mice (Ito et al., 2014a) and administration of taurine affords several beneficial effects in obesity and its comorbidities, including type 2 diabetes. Taurine transporter (TauT) KO (TauTKO) mice exhibit lower body weight and abdominal fat mass compared with WT animals, suggesting that they are resistant to ageing-dependent obesity when maintained on a normal diet. In addition, they also possess more pancreatic β cells and enhanced glucose disposal, despite lower serum insulin levels, implying deterioration in tissue energy metabolism (Ito et al., 2015). Finally, TauTKO mice also display impaired metabolic adaptation to exercise in the skeletal muscles (Ito et al., 2014b). As such, this model may help to better understand to which extent the crosstalk between the different metabolic

Table 5
Mouse models of metabolic dysfunction.

Genetic deficiency[a]	Metabolic alteration and impact on life-span[b]	Clinical relevance[c]	Tested in Aged Mice[d]	Relevant References[e]
$Lepr^{db/db}$, $Lep^{ob/ob}$	Impaired leptin sensing, insulin resistance, obesity and diabetes	no	no	Taniguchi et al. (2006),Gonzalez-Navarro et al. (2007)
Insr-/- mice	Severe hyperinsulinemia and death at few days of birth	no	no	Taniguchi et al. (2006),Gonzalez-Navarro et al. (2007)
Irs1-/- mice	Impaired insulin-signalling, mild insulin resistance	no	no	Taniguchi et al. (2006),Gonzalez-Navarro et al. (2007)
Irs2-/- mice	Insulin resistance, hyperinsulinemia, hyperglucemia and b-cell failure and death within few months	yes	no	Taniguchi et al. (2006),Gonzalez-Navarro et al. (2007)
brain-specific Irs2-/- mice	glucose and energy homeostasis imbalance, obesity and delayed ageing	yes	yes	Taguchi et al. (2007)
LDLr-/-macrophageInsr-/- mice	Insulin resistance and accelerated atherosclerosis	yes	no	Han (2006)
apoE-/-Irs2-/-, apoE-/-Irs2+/- mice	Metabolic syndrome features, increased inflammation and increased atherosclerosis	yes	no	Baumgartl (2006),Gonzalez-Navarro (2007),Gonzalez-Navarro et al. (2008),Martinez-Hervas (2014)
GHR-/- mice	Decreased insulin levels, b-cell proliferation and body weight and longer lifespan and increased insulin sensitivity	yes	yes	Zhou (1997),Coschigano (2003)
mitCatalaseTg	Decreased oxidative stress and delayed ageing	no	yes	Schriner et al. (2005)
Sirt3-/- mice	Increased energy metabolism and weight gain, insulin resistance, b-cell dysfunction	no	no	McDonnell et al. (2015),Brenmoehl and Hoeflich (2013),Hirschey (2011)
SAMP1	Lower oxygen consumption, enhanced glucose, insulin, leptin and decreased adiponectin	no	yes	Haramizu et al. (2011)
mINDY-/- mice	Augmented energy expenditure and decreased lipogenesis	no	no	Birkenfeld (2011)
TauT-/- mice	Lower body weight, insulin levels and enhanced glucose disposal	no	no	Ito et al. (2015)

[a] Most common experimental setups are listed.
[b] Impact of the genetic manipulation in the indicated metabolic characteristics.
[c] Relevance of each listed model applies to a corresponding human condition.
[d] Mice ≥ 18 months of age.
[e] Maximum of 5 relevant references listed.

tissues impacts the development of obesity and/or diabetes with ageing.

Interestingly, mouse models of ageing genes have also been used to investigate the tangled relationship between CVD, metabolic derangement and ageing. In some of these studies Sirtuin 1 (sirt1) was found to be protective in age-associated diseases. In *apoE-/-* mice, for example, the specific vascular Sirtuin 1 (Sirt1) deficiency, accelerated atherosclerosis (Gorenne, 2013) or cardiomyopathy (Planavila et al., 2012), while activation of the Sirt1 provided atheroprotection in the same model (Miranda, 2015). Mice overexpressing Sirt1 or specific activation of Sirt1 protected from metabolic disorders such as diabetes and liver steatosis and mice displayed healthy ageing (Herranz, 2010; Feige, 2008). Gene inactivation of Foxo1, a transcription factor that regulates longevity genes and is modulated by Sirt1, in *apoE-/-* mice aggravated atherosclerosis and produced endothelial dysfunction (Qiang, 2012).

On the other hand, ablation of the genes *Cdkn2a/Cdkn2b* (whose expression increases with age (Krishnamurthy, 2004)) encoded by the *Ink4/Arf* locus promoted atherosclerosis in *apoE-/-* and *Ldlr-/-* mice (Gonzalez-Navarro, 2010; Kuo et al., 2011). Consistently, overexpression of the *Cdkn2a/Cdkn2b* genes restored insulin-signalling and sensitivity associated with ageing (Gonzalez-Navarro, 2013) and diminished hepatic steatosis and IR in 1 year-aged *Irs2+/−* mice (Vinue, 2015). Therefore, these mouse studies indicate a protective role of *Cdkn2a/Cdkn2b* genes in metabolic age-associated diseases. Telomere attrition, a process linked to ageing, restrained proliferation of leukocytes and atheroma progression in *apoE-/-* mice (Poch, 2004). The study of mouse models with metabolic deficiencies either in lipid metabolism (in apoE, LDLr, apoB), in insulin-signalling (GH/insulin/IGF1-signalling) and altered mitochondrial dysfunction in combination or not with other age-related processes (such as premature senescence, decreased or absence of Sirtuins) have provided many mechanistic insight about the ageing process and age-related chronic diseases. Most commonly used mouse models of metabolic derangements are listed in Table 5.

2.5. Sleep and ageing

Ageing is characterized by impairments in physiological functions, reduced ability to react adaptively to environmental stimuli and increased susceptibility to disease (Troen, 2003; Vanhooren and Libert, 2013), therefore it is not surprising that it brings with it alterations in sleep physiology. The percentage of global elderly population will increase in the next three decades and it has been reported that over 40% of people over 65, suffer from sleep disturbances (Foley et al., 2004). Normal ageing is accompanied by changes in the sleep quality, its duration and architecture. Specifically, a decrease in the proportion of the deeper, more restorative, slow-wave sleep (SWS) and rapid eye movement (REM) sleep in the healthy elderly has been suggested. Furthermore, sleep latency and sleep fragmentation (waking up during the night) increments with age, leading to an increase of risk of developing physical and psychiatric illnesses. Indeed, sleep disturbance can induce depression (Jaussent et al., 2011; Tranah et al., 2010; Paudel et al., 2008) and increase the risk of neurodegeneration (Singletary and Naidoo, 2011) and mortality (Cappuccio et al., 2010) in the elderly population. Therefore, a crucial issue is to understand which risk factors can lead to sleep disturbances. To gain a better insight into this relevant question many mouse models have been developed to study

the biology of ageing and neurodegeneration in association with sleep disturbances.

Experimental evidence suggests that sleep deprivation and disturbances in circadian rhythms may promote oxidative stress and play a role in the occurrence of hypertension, type 2 diabetes and neurodegenerative disorders. Most experimental evidence was obtained from different animal species, mainly rats and mice. Recent findings show that severe astrogliosis, oxidative damage and synaptic degeneration occur in *Bmal1* mouse model; deletion in *Bmal1* gene constitutes one of the core elements of the circadian transcriptional-translational feedback loop (TTFL). These data suggest that a decline in the circadian function, as seen in normal ageing, can exacerbate neurodegeneration via decreased BMAL1-mediated transcription (Musiek et al., 2015).

Diabetes, hypertension and metabolic syndrome are well known co-morbidities of neurodegenerative diseases frequently found in the elderly. Although there are many different models of diabetes their sleep patterns have not been well studied and the related evidence is scarce. The ob/ob mouse shows a sleep disordered breathing that appears to exacerbate the already present pathology. The Zucker fatty rat is widely used in research to study type 2 diabetes and shows mutation in the leptin receptor (Phillips et al., 1996) leading to obesity, hyperphagia and hyperinsulinemia. Recent evidence shows that Zucker fatty rats present a longer daily period of SWS suggesting that obesity and/or insulin resistance influences sleep patterns (Megirian et al., 1998).

Disturbances of both sleep and circadian rhythms have long been associated with many neurological and psychiatric ageing-related diseases, including Alzheimer's disease. Alzheimer's diseasepatients show alterations in sleep–wake cycle activity. As described above, Alzheimer's diseaseis the most common age-related neurodegenerative disorder. Recent research has provided evidence that chronic sleep restrictions can exacerbate Aβ pathology and can induce tau phosphorylation and synaptic injury in mouse models of Alzheimer's disease (Rothman et al., 2013; Di Meco et al., 2014). Furthermore, recent studies in transgenic mice demonstrated that an increase of amyloid deposition and tau intracellular aggregation may impair sleep patterns, and consequently promote amyloid plaque formation. Abnormalities in the normal sleep architecture consists of phase delay (Duncan et al., 2012), altered nocturnal activity level (Sterniczuk et al., 2010a, 2010b) and changes in non-REM sleep (Jyoti et al., 2010). Thus, Alzheimer's diseasemouse models show sleep disturbances which are also present in AD patients.

In addition to Alzheimer's disease, Parkinson's Disease is a progressive disease of the nervous system marked by tremors,

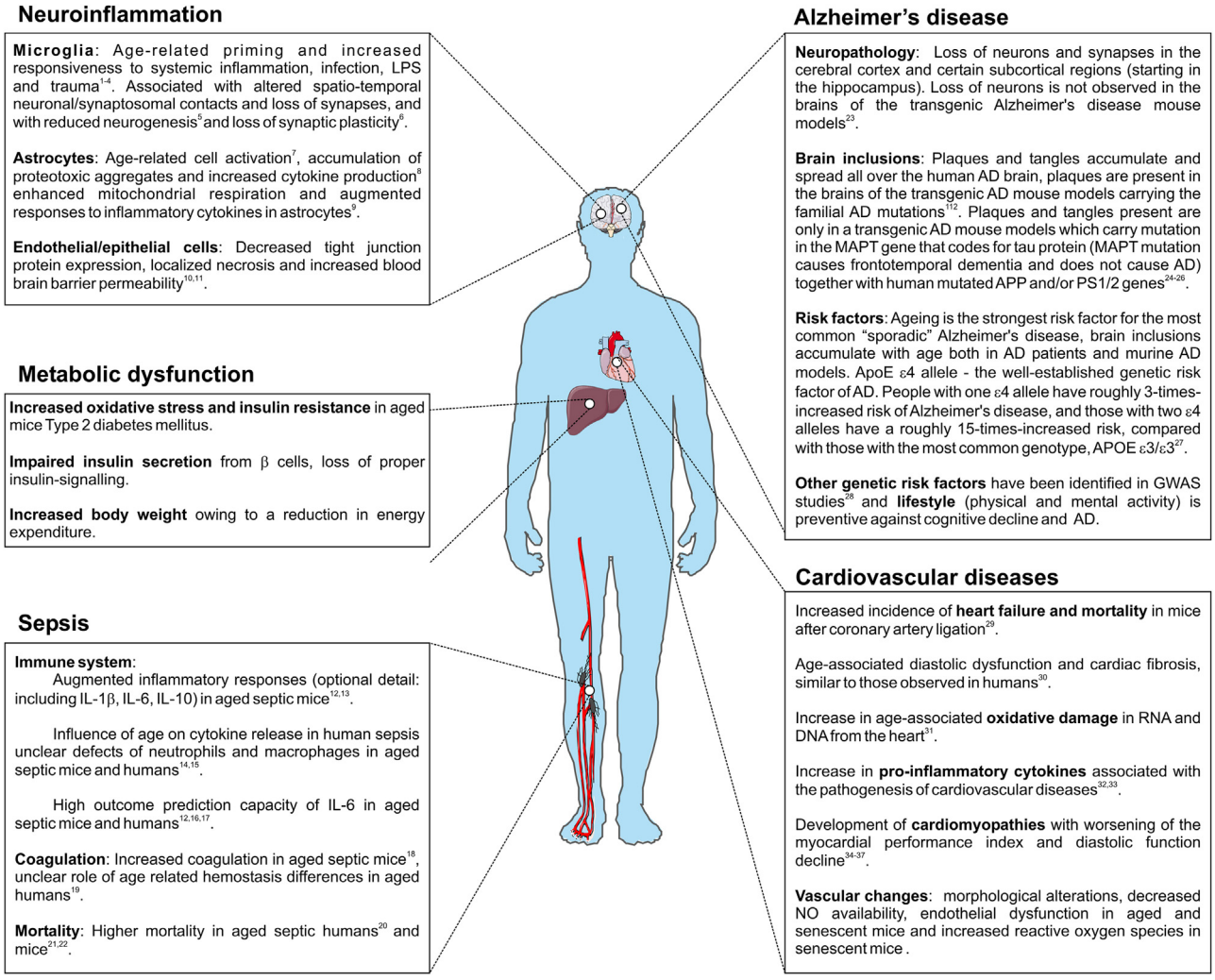

Fig. 1. A summary figure highlighting the effects of ageing on different disease areas. Also included are similarities or differences between human disease and current mouse models where appropriate. (Loffredo et al., 2013; Barrientos et al., 2015; Matt and Johnson, 2016; Ziebell et al., 2016; Ojo et al., 2015; Lynch, 2015; Salminen et al., 2011; Jiang and Cadenas, 2014; Gorle et al., 2016; Minogue et al., 2014; Gomez et al., 2008; Kovacs, 2009; Marti et al., 2007; Kumar et al., 2009; Starr et al., 2015; Kale et al., 2010; Martin et al., 2006; Turnbull et al., 2009; Lloréns et al., 2007).

muscular rigidity, slow and imprecise movements. Parkinson's Disease patients experience a severe impairment in normal sleep activity characterized by insomnia, excessive daytime sleepiness, increase number of nocturnal awakenings and REM-sleep behaviour disorder (Schrempf et al., 2014). Several findings, using a dopamine-transporter KO mouse demonstrated a suppression of normal REM sleep (Lima et al., 2008; Dzirasa et al., 2006) although motor functions were not affected by the diminished dopaminergic tone. Furthermore, other evidence suggests that dopaminergic neurons of the ventral mesencephalic tegmentum may be important for REM sleep (Maloney et al., 2002). In addition, it has been demonstrated using rat model that blockage of dopaminergic D(2) receptors produced decrease of REM but not of the slow wave sleep after REM sleep deprivation (Lima et al., 2008). Thanks to recent studies carried out in rodent animal models, it can be suggested that PD and sleep may be intertwined, either as predictors or consequences of dopaminergic neurodegeneration.

Neurodegenerative and metabolic disorders associated with ageing lead to sleep disturbances in humans. The opportunity to reproduce age-related disorders with mutations and complex genome manipulation, give the possibility to further investigate the potential mechanisms that are responsible for sleep disturbances in elderly patients. The importance of investigating multimorbidities in mouse models is demonstrated by the observation that disrupted circadian rhythms can result in osteoarthritis (Gossan et al., 2013). Thus, it is entirely feasible that a disease such as Alzheimer's disease can cascade through a disrupted circadian rhythm to promote susceptibility to other type of diseases such as osteoarthritis with the overarching age-related changes strongly contributing.

3. Looking to the future

Mouse studies continue to deliver insight into disease through a variety of physiological systems, and with the pressure of an ageing society it is certain that we will face an increased use of mice in ageing studies in the near future. The influence of ageing in the development of selected disease is summarized in Fig. 1, including areas where there are differences between current models and patients. Ageing mouse studies, however present us with several problems, primarily cost and time. Ageing mice is expensive and time consuming, and results in difficulties in obtaining sufficient funding. It is therefore important to critically assess models on a continuous basis to determine their utility for clinically-relevant studies and determine whether new models are needed and/or deeper phenotypic information on existing models is required. This is particularly relevant as we learn more about co-morbidities associated with individual diseases. Furthermore, to study an ageing phenotype within the confines of a standard three year project grant would mean ideally having ageing mice already available when the grant starts, which is rarely feasible. There is therefore a need for flexibility in funding streams and funding proportionate to the increased costs of ageing mice. However, as funding is always highly competitive, we must also explore mechanisms for cost saving. One potential for cutting costs, and allowing the immediate availability of aged animals, is to have a centralised access to ageing mice, which may include the most common strains and models of age-relevant conditions. Building on the theme of centralisation, many studies are focused on a single phenotype and yet we often observe comorbidities in the aged (Fabbri et al., 2015), and therefore providing central facilities with a wide range pf phenotypic capabilities will allow a deeper analysis of phenotypes in a single model. The range of phenotypes associated with ageing is emphasised by the limited examples of models highlighted above. Ideally, a range of phenotypic assays would be applied to aged mouse models to provide a centralised comprehensive phenotypic analysis of mutants under different test conditions, similar to the Mouse Clinic model (Ayadi et al., 2012) or Intervention Testing Programme (Miller et al., 2007; Warner et al., 2000). Developing such resources will be a challenge but infrastructures supporting mouse research (Consortium, 2015) provide a stepping stone and centralised expertise and services would no doubt facilitate the study of ageing and age-related disease. Furthermore, as highlighted here, more work is needed to understand the relevance and utility of the various models to study age-related diseases. This effort will continue within the recently formed MouseAGE COST action to provide this information in an easily accessible form with consensus recommendations from experts in the various fields.

Acknowledgments

"This article is based upon work from COST Action (BM1402: MouseAGE), supported by COST (European Cooperation in Science and Technology)". Dr Susanne Dreschler is supported by FWF, Austria.

References

Ahrenholz, D.H., Simmons, R.L., 1980. Fibrin in peritonitis: I. Beneficial and adverse effects of fibrin in experimental *E. coli* peritonitis. Surgery 88, 41–47.
Angus, D.C., van der Poll, T., 2013. Severe sepsis and septic shock. N. Engl. J. Med. 369, 840–851, http://dx.doi.org/10.1056/NEJMra1208623.
Angus, D.C., 2001. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit. Care Med. 29, 1303–1310.
Arum, O., 2014. Specific suppression of insulin sensitivity in growth hormone receptor gene-disrupted (GHR-KO) mice attenuates phenotypic features of slow aging. Aging cell 13, 981–1000.
Ayadi, A., et al., 2012. Mouse large-scale phenotyping initiatives: overview of the european mouse disease clinic (EUMODIC) and of the welcome trust sanger institute mouse genetics project. Mamm. Genome 23, 600–610, http://dx.doi.org/10.1007/s00335-012-9418-y.
Bales, K.R., et al., 1997. Lack of apolipoprotein E dramatically reduces amyloid beta-peptide deposition. Nat. Genet. 17, 263–264, http://dx.doi.org/10.1038/ng1197-263.
Bales, K.R., 1999. Apolipoprotein E is essential for amyloid deposition in the APP(V717F) transgenic mouse model of Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 96, 15233–15238.
Barrett, J.P., Costello, D.A., O'Sullivan, J., Cowley, T.R., Lynch, M.A., 2015. Bone marrow-derived macrophages from aged rats are more responsive to inflammatory stimuli. J. Neuroinflammation 12 (67), http://dx.doi.org/10.1186/s12974-015-0287-7.
Barrientos, R.M., et al., 2002. Memory for context is impaired by a post context exposure injection of interleukin-1 beta into dorsal hippocampus. Behav. Brain Res. 134, 291–298 (S0166432802000438[pii]).
Barrientos, R.M., Kitt, M.M., Watkins, L.R., Maier, S.F., 2015. Neuroinflammation in the normal aging hippocampus. Neuroscience 309, 84–99, http://dx.doi.org/10.1016/j.neuroscience.2015.03.007.
Barrientos, R.M., 2006. Peripheral infection and aging interact to impair hippocampal memory consolidation. Neurobiol. Aging 27, 723–732.
Baruch, K., et al., 2013. CNS-specific immunity at the choroid plexus shifts toward destructive Th2 inflammation in brain aging. Proc. Natl. Acad. Sci. U. S. A. 110, 2264–2269, http://dx.doi.org/10.1073/pnas.1211270110.
Baruch, K., et al., 2014. Aging-induced type I interferon response at the choroid plexus negatively affects brain function. Science 346, 89–93, http://dx.doi.org/10.1126/science.1252945.
Baumgartl, J., 2006. Myeloid lineage cell-restricted insulin resistance protects apolipoproteinE-deficient mice against atherosclerosis. Cell Metab. 3, 247–256.
Birkenfeld, A.L., 2011. Deletion of the mammalian INDY homolog mimics aspects of dietary restriction and protects against adiposity and insulin resistance in mice. Cell Metab. 14, 184–195.
Boomer, J.S., Green, J.M., Hotchkiss, R.S., 2014. The changing immune system in sepsis: is individualized immuno-modulatory therapy the answer? Virulence 5, 45–56, http://dx.doi.org/10.4161/viru.26516.
Braun, A., 2002. Loss of SR-BI expression leads to the early onset of occlusive atherosclerotic coronary artery disease, spontaneous myocardial infarctions, severe cardiac dysfunction, and premature death in apolipoprotein E-deficient mice. Circ. Res. 90, 270–276.
Brenmoehl, J., Hoeflich, A., 2013. Dual control of mitochondrial biogenesis by sirtuin 1 and sirtuin 3. Mitochondrion 13, 755–761.
Brookmeyer, R., Johnson, E., Ziegler-Graham, K., Arrighi, H.M., 2007. Forecasting the global burden of Alzheimer's disease. Alzheimers Demen. 3, 186–191, http://dx.doi.org/10.1016/j.jalz.2007.04.381.

Bruunsgaard, H., Andersen-Ranberg, K., Hjelmborg, J., Pedersen, B.K., Jeune, B., 2003. Elevated levels of tumor necrosis factor alpha and mortality in centenarians. Am. J. Med. 115, 278–283.
Butterfield, D.A., Poon, H.F., 2005. The senescence-accelerated prone mouse (SAMP8): a model of age-related cognitive decline with relevance to alterations of the gene expression and protein abnormalities in Alzheimer's disease. Exp. Gerontol. 0, 774–783.
Cappuccio, F.P., D'Elia, L., Strazzullo, P., Miller, M.A., 2010. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep 33, 585–592.
Choudhry, M.A., 2005. Gender differences in acute response to trauma-hemorrhage. Shock 24 (Suppl. 1), 101–106.
Clarke, R.M., 2008. A pivotal role for interleukin-4 in atorvastatin-associated neuroprotection in rat brain. J. Biol. Chem. 283, 1808–1817.
Consortium, I., 2015. INFRAFRONTIER–providing mutant mouse resources as research tools for the international scientific community. Nucleic Acids Res. 43, D1171–1175, http://dx.doi.org/10.1093/nar/gku1193.
Coschigano, K.T., 2003. Deletion, but not antagonism, of the mouse growth hormone receptor results in severely decreased body weights, insulin, and insulin-like growth factor I levels and increased life span. Endocrinology 144, 3799–3810.
Cowley, T.R., et al., 2012. Rosiglitazone attenuates the age-related changes in astrocytosis and the deficit in LTP. Neurobiol. Aging 33, 162–175, http://dx.doi.org/10.1016/j.neurobiolaging.2010.02.002.
Cribbs, D.H., et al., 2012. Extensive innate immune gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration: a microarray study. J. Neuroinflammation 9 (179), http://dx.doi.org/10.1186/1742-2094-9-179.
Curran, B., O'Connor, J.J., 2001. The pro-inflammatory cytokine interleukin-18 impairs long-term potentiation and NMDA receptor-mediated transmission in the rat hippocampus in vitro. Neuroscience 108, 83–90.
Dai, D.F., Rabinovitch, P.S., 2009. Cardiac aging in mice and humans: the role of mitochondrial oxidative stress. Trends Cardiovasc. Med. 19, 213–220, http://dx.doi.org/10.1016/j.tcm.2009.12.004.
Davis, C.G., et al., 2011. Increased susceptibility to Candida infection following cecal ligation and puncture. Biochem. Biophys. Res. Commun. 414, 37–43, http://dx.doi.org/10.1016/j.bbrc.2011.09.017.
Dejager, L., Pinheiro, I., Dejonckheere, E., Libert, C., 2011. Cecal ligation and puncture: the gold standard model for polymicrobial sepsis? Trends Microbiol. 19, 198–208, http://dx.doi.org/10.1016/j.tim.2011.01.001.
Demeestere, D., Libert, C., Vandenbroucke, R.E., 2015. Clinical implications of leukocyte infiltration at the choroid plexus in (neuro)inflammatory disorders. Drug Discovery Today 20, 928–941, http://dx.doi.org/10.1016/j.drudis.2015.05.003.
Di Meco, A., Joshi, Y.B., Pratico, D., 2014. Sleep deprivation impairs memory, tau metabolism, and synaptic integrity of a mouse model of Alzheimer's disease with plaques and tangles. Neurobiol. Aging 35, 1813–1820, http://dx.doi.org/10.1016/j.neurobiolaging.2014.02.011.
Donegan, J.J., Girotti, M., Weinberg, M.S., Morilak, D.A., 2014. A novel role for brain interleukin-6: facilitation of cognitive flexibility in rat orbitofrontal cortex. J. Neurosci. 34, 953–962, http://dx.doi.org/10.1523/JNEUROSCI.3968-13.2014.
Drechsler, S., et al., 2012. Relationship between age/gender-induced survival changes and the magnitude of inflammatory activation and organ dysfunction in post-traumatic sepsis. PLoS One 7, e51457, http://dx.doi.org/10.1371/journal.pone.0051457.
Duncan, M.J., et al., 2012. Effects of aging and genotype on circadian rhythms, sleep, and clock gene expression in APPxPS1 knock-in mice, a model for Alzheimer's disease. Exp. Neurol. 236, 249–258, http://dx.doi.org/10.1016/j.expneurol.2012.05.011.
Dzirasa, K., et al., 2006. Dopaminergic control of sleep-wake states. J. Neurosci. 26, 10577–10589, http://dx.doi.org/10.1523/JNEUROSCI.1767-06.2006.
Erusalimsky, J.D., 2009. Vascular endothelial senescence: from mechanisms to pathophysiology. J. Appl. Physiol. 106, 326–332 (1985).
Esposito, A.L., Pennington, J.E., 1983. Effects of aging on antibacterial mechanisms in experimental pneumonia. Am. Rev. Respir. Dis. 128, 662–667, http://dx.doi.org/10.1164/arrd.1983.128.4.662.
Fabbri, E., et al., 2015. Aging and multimorbidity: new tasks priorities, and frontiers for integrated gerontological and clinical research. J. Am. Med. Dir. Assoc. 16, 640–647, http://dx.doi.org/10.1016/j.jamda.2015.03.013.
Fagan, A.M., et al., 2002. Human and murine ApoE markedly alters A beta metabolism before and after plaque formation in a mouse model of Alzheimer's disease. Neurobiol. Dis. 9, 305–318, http://dx.doi.org/10.1006/nbdi.2002.0483.
Feige, J.N., 2008. Specific SIRT1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation. Cell Metab. 8, 347–358.
Foley, D., Ancoli-Israel, S., Britz, P., Walsh, J., 2004. Sleep disturbances and chronic disease in older adults: results of the 2003 national sleep foundation sleep in America survey. J. Psychosom. Res. 56, 497–502, http://dx.doi.org/10.1016/j.jpsychores.2004.02.010.
Fontana, L., Partridge, L., Longo, V.D., 2010. Extending healthy life span-from yeast to humans. Science 328, 321–326, http://dx.doi.org/10.1126/science.1172539.
Forman, K., et al., 2010. Cardiological aging in SAM model: effect of chronic treatment with growth hormone. Biogerontology 11, 275–286, http://dx.doi.org/10.1007/s10522-009-9245-z.
Forman, K., et al., 2011. Effect of a combined treatment with growth hormone and melatonin in the cardiological aging on male SAMP8 mice. J. Gerontol. A. Biol. Sci. Med. Sci. 66, 823–834, http://dx.doi.org/10.1093/gerona/glr083.
Franceschi, C., Campisi, J., 2014. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J. Gerontol. A. Biol. Sci. Med. Sci. 69 (Suppl 1), S4–S9, http://dx.doi.org/10.1093/gerona/glu057.
Frank, M.G., et al., 2009. IL-1RA blocks *E. coli*-induced suppression of Arc and long-term memory in aged F344xBN F1 rats. Brain Behav. Immun.
Frasca, D., Blomberg, B.B., 2015. Inflammaging decreases adaptive and innate immune responses in mice and humans. Biogerontology, http://dx.doi.org/10.1007/s10522-015-9578-8.
Frohlich, M., et al., 2014. Epidemiology and risk factors of multiple-organ failure after multiple trauma: an analysis of 31,154 patients from the TraumaRegister DGU. J. Trauma Acute Care Surg. 76, 921–927, http://dx.doi.org/10.1097/ta.0000000000000199, Discussion 927–928.
Gan, W., et al., 2012. Age-dependent increases in the oxidative damage of DNA RNA, and their metabolites in normal and senescence-accelerated mice analyzed by LC–MS/MS: urinary 8-oxoguanosine as a novel biomarker of aging. Free Radical Biol. Med. 52, 1700–1707, http://dx.doi.org/10.1016/j.freeradbiomed.2012.02.016.
Gao, A.W., Canto, C., Houtkooper, R.H., 2014. Mitochondrial response to nutrient availability and its role in metabolic disease. EMBO Mol. Med. 6, 580–589.
Gentile, L.F., et al., 2013. Identification and description of a novel murine model for polytrauma and shock. Crit. Care Med. 41, 1075–1085, http://dx.doi.org/10.1097/CCM.0b013e318275d1f9.
Gentile, L.F., et al., 2014. Protective immunity and defects in the neonatal and elderly immune response to sepsis. J. Immunol. 192, 3156–3165, http://dx.doi.org/10.4049/jimmunol.1301726.
Gibertini, M., Newton, C., Friedman, H., Klein, T.W., 1995. Spatial learning impairment in mice infected with *Legionella pneumophila* or administered exogenous interleukin-1-beta. Brain Behav. Immun. 9, 113–128.
Giovannini, S., et al., 2011. Interleukin-6 C-reactive protein, and tumor necrosis factor-alpha as predictors of mortality in frail, community-living elderly individuals. J. Am. Geriatr. Soc. 59, 1679–1685, http://dx.doi.org/10.1111/j.1532-5415.2011.03570.x.
Godbout, J.P., et al., 2005. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. FASEB J. 19, 1329–1331, http://dx.doi.org/10.1096/fj.05-3776fje.
Gomez, C.R., Nomellini, V., Faunce, D.E., Kovacs, E.J., 2008. Innate immunity and aging. Exp. Gerontol. 43, 718–728, http://dx.doi.org/10.1016/j.exger.2008.05.016.
Gonzalez-Navarro, H., Burks, D.J., Andres, V., 2007. Murine models to investigate the influence of diabetic metabolism on the development of atherosclerosis and restenosis. Front. Biosci. 12, 4439–4455.
Gonzalez-Navarro, H., et al., 2008. Molecular mechanisms of atherosclerosis in metabolic syndrome: role of reduced IRS2-dependent signaling. Arterioscler. Thromb. Vasc. Biol. 28, 2187–2194.
Gonzalez-Navarro, H., 2007. Plasma insulin levels predict the development of atherosclerosis when IRS2 deficiency is combined with severe hypercholesterolemia in apolipoprotein E-null mice. Front. Biosci. 12, 2291–2298.
Gonzalez-Navarro, H., 2010. p19(ARF) deficiency reduces macrophage and vascular smooth muscle cell apoptosis and aggravates atherosclerosis. J. Am. Coll. Cardiol. 55, 2258–2268.
Gonzalez-Navarro, H., 2013. Increased dosage of Ink4/Arf protects against glucose intolerance and insulin resistance associated with aging. Aging cell 12, 102–111.
Gorenne, I., 2013. Vascular smooth muscle cell sirtuin 1 protects against DNA damage and inhibits atherosclerosis. Circulation 127, 386–396.
Gorle, N., Van Cauwenberghe, C., Libert, C., Vandenbroucke, R.E., 2016. The effect of aging on brain barriers and the consequences for Alzheimer's disease development. Mamm. Genome, http://dx.doi.org/10.1007/s00335-016-9637-8.
Goshen, I., Yirmiya, R., 2009. Interleukin-1 (IL-1): a central regulator of stress responses. Front. Neuroendocrinol. 30, 30–45.
Gossan, N., et al., 2013. The circadian clock in murine chondrocytes regulates genes controlling key aspects of cartilage homeostasis. Arthritis Rheum. 65, 2334–2345, http://dx.doi.org/10.1002/art.38035.
Gotz, J., et al., 2007. A decade of tau transgenic animal models and beyond. Brain Pathol. 17, 91–103, http://dx.doi.org/10.1111/j.1750-3639.2007.00051.x.
Gould, K.E., et al., 2002. Heart failure and greater infarct expansion in middle-aged mice: a relevant model for postinfarction failure. Am. J. Physiol. Heart Circ. Physiol. 282, H615–H621, http://dx.doi.org/10.1152/ajpheart.00206.2001.
Griffin, R., 2006. The age-related attenuation in long-term potentiation is associated with microglial activation. J. Neurochem. 99, 1263–1272.
Guarente, L., 2014. Aging research-where do we stand and where are we going? Cell 159, 15–19, http://dx.doi.org/10.1016/j.cell.2014.08.041.
Gurkar, A.U., Niedernhofer, L.J., 2015. Comparison of mice with accelerated aging caused by distinct mechanisms. Exp. Gerontol. 68, 43–50.
Hagberg, L., 1983a. Contribution of adhesion to bacterial persistence in the mouse urinary tract. Infect. Immun. 40, 265–272.
Hagberg, L., 1983b. Ascending, unobstructed urinary tract infection in mice caused by pyelonephritogenic *Escherichia coli* of human origin. Infect. Immun. 40, 273–283.
Han, S., 2006. Macrophage insulin receptor deficiency increases ER stress-induced apoptosis and necrotic core formation in advanced atherosclerotic lesions. Cell Metab. 3, 257–266.

Haramizu, S., Ota, N., Hase, T., Murase, T., 2011. Aging-associated changes in physical performance and energy metabolism in the senescence-accelerated mouse. J. Gerontol. 66, 646–655.
Harris, T.B., 1999. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am. J. Med. 106, 506–512.
Hartley, C.J., 2000. Hemodynamic changes in apolipoprotein E-knockout mice. Am. J. Physiol. Heart Circ. Physiol. 279, H2326–2334.
Hayakawa, N., Kato, H., Araki, T., 2007. Age-related changes of astorocytes, oligodendrocytes and microglia in the mouse hippocampal CA1 sector. Mech. Ageing Dev. 128, 311–316.
Hein, A.M., et al., 2009. Sustained hippocampal IL-1beta overexpression impairs contextual and spatial memory in transgenic mice. Brain Behav. Immun.
Herranz, D., 2010. Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer. Nat. Commun. 1, 3.
Heyser, C.J., Masliah, E., Samimi, A., Campbell, I.L., Gold, L.H., 1997. Progressive decline in avoidance learning paralleled by inflammatory neurodegeneration in transgenic mice expressing interleukin 6 in the brain. Proc. Natl. Acad. Sci. U. S. A. 94, 150–1505.
Hirschey, M.D., 2010. SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. Nature 464, 121–125.
Hirschey, M.D., 2011. SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Mol. Cell 44, 177–190.
Holtzman, D.M., et al., 2000. Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 97, 2892–2897, http://dx.doi.org/10.1073/pnas.050004797.
Houser, S.R., et al., 2012. Animal models of heart failure: a scientific statement from the American Heart Association. Circ. Res. 111, 131–150, http://dx.doi.org/10.1161/RES.0b013e3182582523.
Hubbard, W.J., 2005. Cecal ligation and puncture. Shock 24 (Suppl 1), 52–57.
Hyde, S.R., McCallum, R.E., 1992. Lipopolysaccharide-tumor necrosis factor-glucocorticoid interactions during cecal ligation and puncture-induced sepsis in mature versus senescent mice. Infect. Immun. 60, 976–982.
Ishibashi, S., 1993. Hypercholesterolemia in low density lipoprotein receptor knockout mice and its reversal by adenovirus-mediated gene delivery. J. Clin. Invest. 92, 883–893.
Ito, T., et al., 2014a. Tissue depletion of taurine accelerates skeletal muscle senescence and leads to early death in mice. PLoS One 9, e107409.
Ito, T., Yoshikawa, N., Schaffer, S.W., Azuma, J., 2014b. Tissue taurine depletion alters metabolic response to exercise and reduces running capacity in mice. J. Amino Acids 2014, 964680.
Ito, T., Yoshikawa, N., Ito, H., Schaffer, S.W., 2015. Impact of taurine depletion on glucose control and insulin secretion in mice. J. Pharmacol. Sci. 129, 59–64.
Jaussent, I., et al., 2011. Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. Sleep 34, 1103–1110, http://dx.doi.org/10.5665/SLEEP.1170.
Jiang, T., Cadenas, E., 2014. Astrocytic metabolic and inflammatory changes as a function of age. Aging cell 13, 1059–1067, http://dx.doi.org/10.1111/acel.12268.
Jyoti, A., Plano, A., Riedel, G., Platt, B., 2010. EEG, activity, and sleep architecture in a transgenic AbetaPPswe/PSEN1A246E Alzheimer's disease mouse. J. Alzheimers Dis. 22, 873–887, http://dx.doi.org/10.3233/JAD-2010-100879.
Kahlke, V., et al., 2000. Immune dysfunction following trauma-haemorrhage: influence of gender and age. Cytokine 12, 69–77, http://dx.doi.org/10.1006/cyto.1999.0511.
Kahlke, V., 2000. Reversal of sexual dimorphism in splenic T lymphocyte responses after trauma-hemorrhage with aging. Am. J. Physiol. Cell Physiol. 278, C509–516.
Kale, S., et al., 2010. The effects of age on inflammatory and coagulation-fibrinolysis response in patients hospitalized for pneumonia. PLoS One 5, e13852, http://dx.doi.org/10.1371/journal.pone.0013852.
Kelly, R.J., et al., 2013. Glial activation in a beta PP/PS1 mice is associated with infiltration of IFN gamma-producing cells. J. Alzheimers Dis. 37, 63–75, http://dx.doi.org/10.3233/Jad-130539.
Kleber, C., et al., 2015. Temporal profile of inflammatory response to fracture and hemorrhagic shock: proposal of a novel long-term survival murine multiple trauma model. J. Orthop. Res. 33, 965–970, http://dx.doi.org/10.1002/jor.22857.
Kohama, S.G., Goss, J.R., Finch, C.E., McNeill, T.H., 1995. Increases of glial fibrillary acidic protein in the aging female mouse brain. Neurobiol. Aging 16, 59–67 (019745809580008F[pii]).
Kovacs, E.J., Grabowski, K.A., Duffner, L.A., Plackett, T.P., Gregory, M.S., 2002. Survival and cell mediated immunity after burn injury in aged mice. J. Am. Aging Assoc. 25, 3–9, http://dx.doi.org/10.1007/s11357-002-0001-4.
Kovacs, E.J., Plackett, T.P., Witte, P.L., 2004. Estrogen replacement, aging, and cell-mediated immunity after injury. J. Leukoc. Biol. 76, 36–41, http://dx.doi.org/10.1189/jlb.1103538.
Kovacs, E.J., 2005. Aging, traumatic injury, and estrogen treatment. Exp. Gerontol. 40, 549–555, http://dx.doi.org/10.1016/j.exger.2005.04.009.
Kovacs, E.J., 2009. Aging and innate immunity in the mouse: impact of intrinsic and extrinsic factors. Trends Immunol. 301, 319–324.
Krishnamurthy, J., 2004. Ink4a/Arf expression is a biomarker of aging. J. Clin. Invest. 114, 1299–1307.
Kumar, A.T., et al., 2009. Cytokine profile in elderly patients with sepsis. Indian J. Crit. Care Med. 13, 74–78, http://dx.doi.org/10.4103/0972-5229.56052.
Kumar, A., et al., 2013. Traumatic brain injury in aged animals increases lesion size and chronically alters microglial/macrophage classical and alternative activation states. Neurobiol. Aging 34, 1397–1411, http://dx.doi.org/10.1016/j.neurobiolaging.2012.11.013.
Kuo, C.L., et al., 2011. Cdkn2a is an atherosclerosis modifier locus that regulates monocyte/macrophage proliferation. Arterioscler. Thromb. Vasc. Biol. 31, 2483–2492.
Kurokawa, T., Ozaki, N., Ishibashi, S., 1998. Difference between senescence-accelerated prone and resistant mice in response to insulin in the heart. Mech. Ageing Dev. 102, 25–32.
LaFerla, F.M., Green, K.N., 2012. Animal models of Alzheimer disease. Cold Spring Harb. Perspect. Med. 2, http://dx.doi.org/10.1101/cshperspect.a006320.
Lakatta, E.G., Levy, D., 2003. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part I: aging arteries: a set up for vascular disease. Circulation 107, 139–146.
Langlois, J.A., Rutland-Brown, W., Wald, M.M., 2006. The epidemiology and impact of traumatic brain injury: a brief overview. J. Head Trauma Rehabil. 21, 375–378.
Lee, C.K., Weindruch, R., Prolla, T.A., 2000. Gene-expression profile of the ageing brain in mice. Nat. Genet. 25, 294–297, http://dx.doi.org/10.1038/77046.
Lewis, J., et al., 2001. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science 293, 1487–1491, http://dx.doi.org/10.1126/science.1058189.
Li, X.Z., et al., 2009. Effects of IL-6 secreted from astrocytes on the survival of dopaminergic neurons in lipopolysaccharide-induced inflammation. Neurosci. Res. 65.
Lima, M.M., et al., 2008. Blockage of dopaminergic D(2) receptors produces decrease of REM but not of slow wave sleep in rats after REM sleep deprivation. Behav. Brain Res. 188, 406–411, http://dx.doi.org/10.1016/j.bbr.2007.11.025.
Linton, P.J., Haynes, L., Klinman, N.R., Swain, S.L., 1996. Antigen-independent changes in naive CD4T cells with aging. J. Exp. Med. 184, 1891–1900.
Liu, J.L., 2004. Disruption of growth hormone receptor gene causes diminished pancreatic islet size and increased insulin sensitivity in mice. Am. J. Physiol. 287, E405–413.
Livingston, D.H., et al., 2003. Bone marrow failure following severe injury in humans. Ann. Surg. 238, 748–753, http://dx.doi.org/10.1097/01.sla.0000094441.38807.09.
Lloréns, S., de Mera, R.M., Pascual, A., Prieto-Martín, A., Mendizábal, Y., de Cabo, C., Nava, E., Jordán, J., 2007. The senescence-accelerated mouse (SAM-P8) as a model for the study of vascular functional alterations during aging. Biogerontology. 8 (6), 663–672.
Loane, D.J., 2009. Interleukin-4 mediates the neuroprotective effects of rosiglitazone in the aged brain. Neurobiol. Aging 30, 920–931.
Loffredo, F.S., et al., 2013. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. Cell 153, 828–839, http://dx.doi.org/10.1016/j.cell.2013.04.015.
Lord, J.M., et al., 2014. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet 384, 1455–1465, http://dx.doi.org/10.1016/S0140-6736(14)60687-5.
Lynch, A.M., et al., 2007. Eicosapentaenoic acid confers neuroprotection in the amyloid-beta challenged aged hippocampus. Neurobiol. Aging 28, 845–855, http://dx.doi.org/10.1016/j.neurobiolaging.2006.04.006.
Lynch, M.A., 2010. Age-related neuroinflammatory changes negatively impact on neuronal function. Front Aging Neurosci. 1 (6), http://dx.doi.org/10.3389/neuro.24.006.2009.
Lynch, M.A., 2014. Neuroinflammatory changes negatively impact on LTP: A focus on IL-1beta. Brain Res., http://dx.doi.org/10.1016/j.brainres.2014.08.040.
Lynch, M.A., 2015. Neuroinflammatory changes negatively impact on LTP: A focus on IL-1beta. Brain Res. 1621, 197–204, http://dx.doi.org/10.1016/j.brainres.2014.08.040.
Lyons, A., et al., 2007. CD200 ligand receptor interaction modulates microglial activation in vivo and in vitro: a role for IL-4. J. Neurosci. 27, 8309–8313, http://dx.doi.org/10.1523/JNEUROSCI.1781-07.2007.
Lyons, A., et al., 2009. Fractalkine-induced activation of the phosphatidylinositol-3 kinase pathway attentuates microglial activation in vivo and in vitro. J. Neurochem. 110, 1547–1556, http://dx.doi.org/10.1111/j.1471-4159.2009.06253.x.
Maher, F.O., Nolan, Y., Lynch, M.A., 2005. Downregulation of IL-4-induced signalling in hippocampus contributes to deficits in LTP in the aged rat. Neurobiol. Aging 26, 717–728.
Maher, F.O., Clarke, R.M., Kelly, A., Nally, R.E., Lynch, M.A., 2006. Interaction between interferon gamma and insulin-like growth factor-1 in hippocampus impacts on the ability of rats to sustain long-term potentiation. J. Neurochem. 96, 1560–1571.
Maloney, K.J., Mainville, L., Jones, B.E., 2002. c-Fos expression in dopaminergic and GABAergic neurons of the ventral mesencephalic tegmentum after paradoxical sleep deprivation and recovery. Eur. J. Neurosci. 15, 774–778.
Manini, T.M., 2010. Energy expenditure and aging. Ageing Res. Rev. 9, 1–11.
Mares, C.A., et al., 2010. Attenuated response of aged mice to respiratory *Francisella novicida* is characterized by reduced cell death and absence of subsequent hypercytokinemia. PLoS One 5, e14088, http://dx.doi.org/10.1371/journal.pone.0014088.
Marti, L., et al., 2007. Cytokine-release patterns in elderly patients with systemic inflammatory response syndrome. Gerontology 53, 239–244, http://dx.doi.org/10.1159/000101436.

Martin, G.S., Mannino, D.M., Moss, M., 2006. The effect of age on the development and outcome of adult sepsis. Crit. Care Med. 134, 15–21.
Martinez-Hervas, S., 2014. Insulin resistance aggravates atherosclerosis by reducing vascular smooth muscle cell survival and increasing CX3CL1/CX3CR1 axis. Cardiovasc. Res. 103, 324–336.
Matt, S.M., Johnson, R.W., 2016. Neuro-immune dysfunction during brain aging: new insights in microglial cell regulation. Curr. Opin. Pharmacol. 26, 96–101, http://dx.doi.org/10.1016/j.coph.2015.10.009.
Mawhinney, L.J., de Rivero Vaccari, J.P., Dale, G.A., Keane, R.W., Bramlett, H.M., 2011. Heightened inflammasome activation is linked to age-related cognitive impairment in Fischer 344 rats. BMC Neurosci. 12, 123, http://dx.doi.org/10.1186/1471-2202-12-123.
McConnell, K.W., et al., 2011. The role of heat shock protein 70 in mediating age-dependent mortality in sepsis. J. Immunol. 186, 3718–3725, http://dx.doi.org/10.4049/jimmunol.1003652.
McDonnell, E., Peterson, B.S., Bomze, H.M., Hirschey, M.D., 2015. SIRT3 regulates progression and development of diseases of aging. ABBV Trends Endocrinol. Metab. 26, 486–492.
Medway, C., Morgan, K., 2014. Review: the genetics of Alzheimer's disease; putting flesh on the bones. Neuropathol. Appl. Neurobiol. 40, 97–105, http://dx.doi.org/10.1111/nan.12101.
Mees, S.T., et al., 2007. Age- and gender-related differences of the immune function in a murine model of hemorrhagic shock: IL-10 restores immunodepression in aged females without reduction of mortality. Langenbecks Arch. Surg. 392, 629–638, http://dx.doi.org/10.1007/s00423-007-0152-y.
Mees, S.T., et al., 2008. Influence of sex and age on morphological organ damage after hemorrhagic shock. Shock 29, 670–674, http://dx.doi.org/10.1097/shk.0b013e31815c3ea0.
Megirian, D., Dmochowski, J., Farkas, G.A., 1998. Mechanism controlling sleep organization of the obese Zucker rats. J. Appl. Physiol. 84, 253–256.
Michaelson, D.M., 2014. APOE epsilon4: the most prevalent yet understudied risk factor for Alzheimer's disease. Alzheimers Demen. 10, 861–868, http://dx.doi.org/10.1016/j.jalz.2014.06.015.
Miller, R.A., Nadon, N.L., 2000. Principles of animal use for gerontological research. J. Gerontol. A. Biol. Sci. Med. Sci. 55, B117–123.
Miller, R.A., et al., 2007. An aging interventions testing program: study design and interim report. Aging Cell 6, 565–575, http://dx.doi.org/10.1111/j.1474-9726.2007.00311.x.
Miller, R.A., 1996. The aging immune system: primer and prospectus. Science 273, 70–74.
Minogue, A.M., Lynch, A.M., Loane, D.J., Herron, C.E., Lynch, M.A., 2007. Modulation of amyloid-beta-induced and age-associated changes in rat hippocampus by eicosapentaenoic acid. J. Neurochem. 103, 914–926, http://dx.doi.org/10.1111/j.1471-4159.2007.04848.x.
Minogue, A.M., et al., 2014. Age-associated dysregulation of microglial activation is coupled with enhanced blood-brain barrier permeability and pathology in APP/PS1 mice. Neurobiol. Aging 35, 1442–1452, http://dx.doi.org/10.1016/j.neurobiolaging.2013.12.026.
Miranda, M.X., 2015. The Sirt1 activator SRT3025 provides atheroprotection in Apoe-/- mice by reducing hepatic Pcsk9 secretion and enhancing Ldlr expression. Eur. Heart J. 36, 51–59.
Mohler, M.J., Fain, M.J., Wertheimer, A.M., Najafi, B., Nikolich-Zugich, J., 2014. The Frailty syndrome: clinical measurements and basic underpinnings in humans and animals. Exp. Gerontol. 54, 6–13, http://dx.doi.org/10.1016/j.exger.2014.01.024.
Moore, A.H., Wu, M., Shaftel, S.S., Graham, K.A., O'Banion, M.K., 2009. Sustained expression of interleukin-1beta in mouse hippocampus impairs spatial memory. Neuroscience.
Muenzer, J.T., et al., 2006. Pneumonia after cecal ligation and puncture: a clinically relevant two-hit model of sepsis. Shock 26, 565–570, http://dx.doi.org/10.1097/01.shk.0000235130.82363.ed.
Musiek, E.S., Xiong, D.D., Holtzman, D.M., 2015. Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease. Exp. Mol. Med. 47, e148, http://dx.doi.org/10.1038/emm.2014.121.
Nacionales, D.C., et al., 2015. A detailed characterization of the dysfunctional immunity and abnormal myelopoiesis induced by severe shock and trauma in the aged. J. Immunol. 195, 2396–2407, http://dx.doi.org/10.4049/jimmunol.1500984.
Niccoli, T., Partridge, L., 2012. Ageing as a risk factor for disease. Curr. Biol. 22, R741–R752, http://dx.doi.org/10.1016/j.cub.2012.07.024.
Nimmerjahn, A., Kirchhoff, F., Helmchen, F., 2005. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308, 1314–1318.
Nolan, Y., 2005. Role of interleukin-4 in regulation of age-related inflammatory changes in the hippocampus. J. Biol. Chem. 280, 9354–9362.
Nomellini, V., Faunce, D.E., Gomez, C.R., Kovacs, E.J., 2008. An age-associated increase in pulmonary inflammation after burn injury is abrogated by CXCR2 inhibition. J. Leukoc. Biol. 83, 1493–1501, http://dx.doi.org/10.1189/jlb.1007672.
North, B.J., Sinclair, D.A., 2012. The intersection between aging and cardiovascular disease. Circ. Res. 110, 1097–1108.
Novella, S., et al., 2013. Aging-related endothelial dysfunction in the aorta from female senescence-accelerated mice is associated with decreased nitric oxide synthase expression. Exp. Gerontol. 48, 1329–1337, http://dx.doi.org/10.1016/j.exger.2013.08.003.
Novella, S., 2010. Gathering of aging and estrogen withdrawal in vascular dysfunction of senescent accelerated mice. Exp. Gerontol. 45, 868–874.
Novensa, L., 2010. Equine estrogens impair nitric oxide production and endothelial nitric oxide synthase transcription in human endothelial cells compared with the natural 17{beta}-estradiol. Hypertension 56, 405–411.
Nulsen, M.F., Finlay-Jones, J.J., Skinner, J.M., McDonald, P.J., 1983. Intra-abdominal abscess formation in mice: quantitative studies on bacteria and abscess-potentiating agents. Br. J. Exp. Pathol. 64, 345–353.
Oddo, S., Caccamo, A., Kitazawa, M., Tseng, B.P., LaFerla, F.M., 2003. Amyloid deposition precedes tangle formation in a triple transgenic model of Alzheimer's disease. Neurobiol. Aging 24, 1063–1070.
Oddo, S., 2003. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron 39, 409–421.
Oitzl, M.S., van Oers, H., Schobitz, B., de Kloet, E.R., 1993. Interleukin-1 beta, but not interleukin-6, impairs spatial navigation learning. Brain Res. 613, 160–163.
Ojo, J.O., Rezaie, P., Gabbott, P.L., Stewart, M.G., 2015. Impact of age-related neuroglial cell responses on hippocampal deterioration. Front Aging Neurosci. 7 (57), http://dx.doi.org/10.3389/fnagi.2015.00057.
Onozuka, H., 2002. In vivo echocardiographic detection of cardiovascular lesions in apolipoprotein E-knockout mice using a novel high-frequency high-speed echocardiography technique. Circ. J. 66, 272–276.
Onyszchuk, G., He, Y.Y., Berman, N.E., Brooks, W.M., 2008. Detrimental effects of aging on outcome from traumatic brain injury: a behavioral, magnetic resonance imaging, and histological study in mice. J. Neurotrauma 25, 153–171, http://dx.doi.org/10.1089/neu.2007.0430.
Ostan, R., et al., 2008. Immunosenescence and immunogenetics of human longevity. Neuroimmunomodulation 15, 224–240, http://dx.doi.org/10.1159/000156466.
Osuchowski, M.F., et al., 2014. Abandon the mouse research ship? Not just yet! Shock 41, 463–475, http://dx.doi.org/10.1097/SHK.0000000000000153.
Patten, R.D., Hall-Porter, M.R., 2009. Small animal models of heart failure: development of novel therapies, past and present. Circ. Heart Fail 2, 138–144, http://dx.doi.org/10.1161/CIRCHEARTFAILURE.108.839761.
Paudel, M.L., et al., 2008. Association between depressive symptoms and sleep disturbances in community-dwelling older men. J. Am. Geriatr. Soc. 56, 1228–1235, http://dx.doi.org/10.1111/j.1532-5415.2008.01753.x.
Petersen, K.F., et al., 2003. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science 300, 1140–1142 (New York, N. Y.).
Phillips, M.S., et al., 1996. Leptin receptor missense mutation in the fatty Zucker rat. Nat. Genet. 13, 18–19, http://dx.doi.org/10.1038/ng0596-18.
Plackett, T.P., et al., 2003. Aging enhances lymphocyte cytokine defects after injury. FASEB J. 17, 688–689, http://dx.doi.org/10.1096/fj.02-0452fje.
Planavila, A., et al., 2012. Dilated cardiomyopathy and mitochondrial dysfunction in Sirt1-deficient mice: a role for Sirt1-Mef2 in adult heart. J. Mol. Cell. Cardiol. 53, 521–531, http://dx.doi.org/10.1016/j.yjmcc.2012.07.019.
Plotnikov, E.Y., et al., 2013. Protective effect of mitochondria-targeted antioxidants in an acute bacterial infection. Proc. Natl. Acad. Sci. U. S. A. 110, E3100–E3108, http://dx.doi.org/10.1073/pnas.1307096110.
Plump, A.S., 1992. Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. Cell 71, 343–353.
Poch, E., 2004. Short telomeres protect from diet-induced atherosclerosis in apolipoprotein E-null mice. FASEB J. 18, 418–420.
Purcell-Huynh, D.A., 1995. Transgenic mice expressing high levels of human apolipoprotein B develop severe atherosclerotic lesions in response to a high-fat diet. J. Clin. Invest. 95, 2246–2257.
Qiang, L., 2012. Increased atherosclerosis and endothelial dysfunction in mice bearing constitutively deacetylated alleles of Foxo1 gene. J. Biol. Chem. 287, 13944–13951.
Ransohoff, R.M., Perry, V.H., 2009. Microglial physiology: unique stimuli, specialized responses. Annu. Rev. Immunol. 27, 119–145, http://dx.doi.org/10.1146/annurev.immunol.021908.132528.
Reed, A.L., et al., 2011. Diastolic dysfunction is associated with cardiac fibrosis in the senescence-accelerated mouse. Am. J. Physiol. Heart Circ. Physiol. 301, H824–H831, http://dx.doi.org/10.1152/ajpheart.00407.2010.
Remick, D.G., Newcomb, D.E., Bolgos, G.L., Call, D.R., 2000. Comparison of the mortality and inflammatory response of two models of sepsis: lipopolysaccharide vs cecal ligation and puncture. Shock 13, 110–116.
Rogers, R.P., Rogina, B., 2015. The role of INDY in metabolism, health and longevity. Front. Genet. 6 (204).
Rothman, S.M., Herdener, N., Frankola, K.A., Mughal, M.R., Mattson, M.P., 2013. Chronic mild sleep restriction accentuates contextual memory impairments, and accumulations of cortical Abeta and pTau in a mouse model of Alzheimer's disease. Brain Res. 1529, 200–208, http://dx.doi.org/10.1016/j.brainres.2013.07.010.
Saito, H., Sherwood, E.R., Varma, T.K., Evers, B.M., 2003. Effects of aging on mortality, hypothermia, and cytokine induction in mice with endotoxemia or sepsis. Mech. Ageing Dev. 124, 1047–1058.
Salminen, A., et al., 2011. Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. Eur. J. Neurosci. 34, 3–11, http://dx.doi.org/10.1111/j.1460-9568.2011.07738.x.
Sampalis, J.S., et al., 2009. Assessment of mortality in older trauma patients sustaining injuries from falls or motor vehicle collisions treated in regional level I trauma centers. Ann. Surg. 249, 488–495, http://dx.doi.org/10.1097/SLA.0b013e31819a8b4f.

Schneider, C.P., Schwacha, M.G., Chaudry, I.H., 2006. Influence of gender and age on T-cell responses in a murine model of trauma-hemorrhage: differences between circulating and tissue-fixed cells. J. Appl. Physiol. 100, 826–833, http://dx.doi.org/10.1152/japplphysiol.00898.2005.
Schneider, C.P., Schwacha, M.G., Chaudry, I.H., 2007. Impact of sex and age on bone marrow immune responses in a murine model of trauma-hemorrhage. J. Appl. Physiol. 102, 113–121, http://dx.doi.org/10.1152/japplphysiol.00848.2006.
Schoeneberg, C., et al., 2014. Mortality in severely injured elderly patients: a retrospective analysis of a German level 1 trauma center (2002–2011). Scand. J. Trauma Resuscitation Emerg. Med. 22 (45), http://dx.doi.org/10.1186/s13049-014-0045-3.
Schrempf, W., Brandt, M.D., Storch, A., Reichmann, H., 2014. Sleep disorders in Parkinson's disease. J. Parkinsons Dis. 4, 211–221, http://dx.doi.org/10.3233/JPD-130301.
Schriner, S.E., et al., 2005. Extension of murine life span by overexpression of catalase targeted to mitochondria. Science 308, 1909–1911 (New York, N. Y.).
Seitz, D.H., et al., 2011. Inflammatory alterations in a novel combination model of blunt chest trauma and hemorrhagic shock. J. Trauma 70, 189–196, http://dx.doi.org/10.1097/TA.0b013e3181d7693c.
Seok, J., et al., 2013. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc. Natl. Acad. Sci. U. S. A. 110, 3507–3512, http://dx.doi.org/10.1073/pnas.1222878110.
Shivshankar, P., Boyd, A.R., Le Saux, C.J., Yeh, I.T., Orihuela, C.J., 2011. Cellular senescence increases expression of bacterial ligands in the lungs and is positively correlated with increased susceptibility to pneumococcal pneumonia. Aging Cell 10, 798–806, http://dx.doi.org/10.1111/j.1474-9726.2011.00720.x.
Singletary, K.G., Naidoo, N., 2011. Disease and degeneration of aging neural systems that integrate sleep drive and circadian oscillations. Front. Neurol. 2 (66), http://dx.doi.org/10.3389/fneur.2011.00066.
Sparkman, N.L., 2006. Interleukin-6 facilitates lipopolysaccharide-induced disruption in working memory and expression of other proinflammatory cytokines in hippocampal neuronal cell layers. J. Neurosci. 26, 10709–10716.
Starr, M.E., Saito, H., 2014. Sepsis in old age: review of human and animal studies. Aging Dis. 5, 126–136, http://dx.doi.org/10.14336/AD.2014.0500126.
Starr, M.E., et al., 2014. A new cecal slurry preparation protocol with improved long-term reproducibility for animal models of sepsis. PLoS One 9, e115705, http://dx.doi.org/10.1371/journal.pone.0115705.
Starr, M.E., et al., 2015. Increased coagulation and suppressed generation of activated protein C in aged mice during intra-abdominal sepsis. Am. J. Physiol. Heart Circ. Physiol. 308, H83–H91, http://dx.doi.org/10.1152/ajpheart.00289.2014.
Sterniczuk, R., Antle, M.C., Laferla, F.M., Dyck, R.H., 2010a. Characterization of the 3xTg-AD mouse model of Alzheimer's disease: part 2. Behavioral and cognitive changes. Brain Res. 1348, 149–155, http://dx.doi.org/10.1016/j.brainres.2010.06.011.
Sterniczuk, R., Dyck, R.H., Laferla, F.M., Antle, M.C., 2010b. Characterization of the 3xTg-AD mouse model of Alzheimer's disease: part 1. Circadian changes. Brain Res. 1348, 139–148, http://dx.doi.org/10.1016/j.brainres.2010.05.013.
Taguchi, A., Wartschow, L.M., White, M.F., 2007. Brain IRS2 signaling coordinates life span and nutrient homeostasis. Science 317, 369–372 (New York, N.Y).
Takeda, T., Hosokawa, M., Higuchi, K., 1997. Senescence-accelerated mouse (SAM): a novel murine model of senescence. Exp. Gerontol. 32, 105–109.
Taniguchi, C.M., Emanuelli, B., Kahn, C.R., 2006. Critical nodes in signalling pathways: insights into insulin action. Nat. Rev. Mol. Cell Biol. 7, 85–96.
Timaru-Kast, R., et al., 2012. Influence of age on brain edema formation, secondary brain damage and inflammatory response after brain trauma in mice. PLoS One 7, e43829, http://dx.doi.org/10.1371/journal.pone.0043829.
Tranah, G.J., et al., 2010. Circadian activity rhythms and mortality: the study of osteoporotic fractures. J. Am. Geriatr. Soc. 58, 282–291, http://dx.doi.org/10.1111/j.1532-5415.2009.02674.x.
Troen, B.R., 2003. The biology of aging. Mt. Sinai J. Med. 70, 3–22.
Turnbull, I.R., et al., 2009. Effects of aging on the immunopathologic response to sepsis. Crit. Care Med. 37, 1018–1023, http://dx.doi.org/10.1097/CCM.0b013e3181968f3a.
Turnbull, I.R., 2003. Effects of age on mortality and antibiotic efficacy in cecal ligation and puncture. Shock 19, 310–313.
Vanhooren, V., Libert, C., 2013. The mouse as a model organism in aging research: usefulness, pitfalls and possibilities. Ageing Res. Rev. 12, 8–21, http://dx.doi.org/10.1016/j.arr.2012.03.010.
Vincent, J.L., 2006. Sepsis in European intensive care units: results of the SOAP study. Crit. Care Med. 34, 344–353.
Vinue, A., 2015. Ink4/Arf locus restores glucose tolerance and insulin sensitivity by reducing hepatic steatosis and inflammation in mice with impaired IRS2-dependent signalling. Biochim. Biophys. Acta 1852, 1729–1742.
Wafaisade, A., et al., 2011. Epidemiology and risk factors of sepsis after multiple trauma: an analysis of 29,829 patients from the Trauma Registry of the German Society for Trauma Surgery. Crit. Care Med. 39, 621–628, http://dx.doi.org/10.1097/CCM.0b013e318206d3df.
Wang, Q.D., Bohlooly, Y.M., Sjoquist, P.O., 2004. Murine models for the study of congestive heart failure: implications for understanding molecular mechanisms and for drug discovery. J. Pharmacol. Toxicol. Methods 50, 163–174, http://dx.doi.org/10.1016/j.vascn.2004.05.005.
Wang, J., Clauson, C.L., Robbins, P.D., Niedernhofer, L.J., Wang, Y., 2012. The oxidative DNA lesions 8,5'-cyclopurines accumulate with aging in a tissue-specific manner. Aging cell 11, 714–716.
Warner, H.R., Ingram, D., Miller, R.A., Nadon, N.L., Richardson, A.G., 2000. Program for testing biological interventions to promote healthy aging. Mech. Ageing Dev. 115, 199–207.
Weksler, M.E., Goodhardt, M., Szabo, P., 2002. The effect of age on B cell development and humoral immunity. Springer Semin. Immunopathol. 24, 35–52.
White, M.F., 2014. IRS2 integrates insulin/IGF1 signalling with metabolism, neurodegeneration and longevity. Diabetes Obesity Metab. 16 (Suppl. 1), 4–15.
Wichmann, M.W., Ayala, A., Chaudry, I.H., 1998. Severe depression of host immune functions following closed-bone fracture, soft-tissue trauma, and hemorrhagic shock. Crit. Care Med. 26, 1372–1378.
Wichmann, M.W., 1996. Immune function is more compromised after closed bone fracture and hemorrhagic shock than hemorrhage alone. Arch. Surg. 131, 995–1000.
Yutzey, K.E., Robbins, J., 2007. Principles of genetic murine models for cardiac disease. Circulation 115, 792–799, http://dx.doi.org/10.1161/CIRCULATIONAHA.106.682534.
Zantl, N., 1998. Essential role of gamma interferon in survival of colon ascendens stent peritonitis, a novel murine model of abdominal sepsis. Infect. Immun. 66, 2300–2309.
Zaragoza, C., 2011. Animal models of cardiovascular diseases. J. Biomed. Biotechnol. 2011, 497841.
Zhang, S.H., Reddick, R.L., Piedrahita, J.A., Maeda, N., 1992. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. Science 258, 468–471, New York, N.Y.
Zhou, Y., 1997. A mammalian model for Laron syndrome produced by targeted disruption of the mouse growth hormone receptor/binding protein gene (the Laron mouse). Proc. Natl. Acad. Sci. U. S. A. 94, 13215–13220.
Ziebell, J.M., et al., 2016. Aging with a traumatic brain injury: could behavioral morbidities and endocrine symptoms be influenced by microglial priming? Brain Behav. Immun., http://dx.doi.org/10.1016/j.bbi.2016.03.008.