Article:
Ameen-Ali, K.E., Wharton, S.B., Simpson, J.E. et al. (3 more authors) (2017) Neuropathology and behavioural features of transgenic murine models of Alzheimer's disease. Neuropathology and Applied Neurobiology, 43 (7). pp. 553-570. ISSN 0305-1846

https://doi.org/10.1111/nan.12440

Neuropathology and Applied Neurobiology (2017), **43**, 553–570 doi: 10.1111/nan.12440

Review: Neuropathology and behavioural features of transgenic murine models of Alzheimer's disease

K. E. Ameen-Ali*, S. B. Wharton†, J. E. Simpson†, P. R. Heath†, P. Sharp* and J. Berwick*

**Department of Psychology, and †Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, UK*

K. E. Ameen-Ali, S. B. Wharton, J. E. Simpson, P. R. Heath, P. Sharp and J. Berwick (2017) *Neuropathology and Applied Neurobiology* **43**, 553–570
Neuropathology and behavioural features of transgenic murine models of Alzheimer's disease

Our understanding of the underlying biology of Alzheimer's disease (AD) has been steadily progressing; however, this is yet to translate into a successful treatment in humans. The use of transgenic mouse models has helped to develop our understanding of AD, not only in terms of disease pathology, but also with the associated cognitive impairments typical of AD. Plaques and neurofibrillary tangles are often among the last pathological changes in AD mouse models, after neuronal loss and gliosis. There is a general consensus that successful treatments need to be applied before the onset of these pathologies and associated cognitive symptoms. This review discusses the different types of AD mouse models in terms of the temporal progression of the disease, how well they replicate the pathological changes seen in human AD and their cognitive defects. We provide a critical assessment of the behavioural tests used with AD mice to assess cognitive changes and decline, and discuss how successfully they correlate with cognitive impairments in humans with AD. This information is an important tool for AD researchers when deciding on appropriate mouse models, and when selecting measures to assess behavioural and cognitive change.

Keywords: Alzheimer's disease, amyloid, behavioural tests, cognitive decline, mouse models, tau

Introduction

Dementia is a term used to describe a syndrome, caused by various diseases of the brain, characterized by significant decline in multiple cognitive areas including memory, language, social cognition, executive and perceptual functions. The most recent Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM–V) introduces the term 'Major Neurocognitive Disorders', with some changes in criteria compared to DSM–IV [1], including more specific details on the degree of impairment observed in the aforementioned cognitive domains, and the inability to explain such impairments by any other means [2]. Population-based studies show that Alzheimer's disease (AD), dementia with Lewy bodies and vascular dementia are the most common pathological substrates for dementia [3–6]. AD is the most common type of dementia and is associated with a decline in cognitive abilities, such as memory and visuo-spatial skills. Early-onset familial AD accounts for <1% of AD diagnoses, and typically occurs before the age of 65 years [7]. Late-onset AD most often occurs over the age of 65 years and is much more common.

Murine models of AD recapitulate aspects of the disease, often through gene mutations associated with familial AD, and can powerfully elucidate critical aspects of pathogenesis. Although this type of AD is less common, the pathological phenotypes are similar to sporadic AD. Extracellular beta amyloid plaques, intracellular hyperphosphorylated tau, synaptic and

Correspondence: Kamar Ameen-Ali, Department of Psychology, University of Sheffield, Floor D, Cathedral Court, 1 Vicar Lane, Sheffield S1 2LT, UK. Tel: +44 114 22 26540; E-mail: k.ameen-ali@sheffield.ac.uk

neuronal loss and neuroinflammation, are all associated with the disease [8]. The amyloid cascade hypothesis [9,10] proposed that amyloid (Aβ) plaque deposition is key to the pathogenesis of AD, with tau pathology, inflammation and subsequent cell damage as contributing factors. Neuronal and neurotransmitter changes follow Aβ deposition, leading eventually to cell death. Cognitive decline may be a result of neuronal dysfunction from toxic soluble Aβ [11], or inhibited synapse remodelling linked to Aβ oligomers [12]. Therapeutic trials have targeted the clearance of Aβ, with some success in both murine models [13,14] and in humans [15,16]. However, immunotherapy targeting Aβ has not yet translated into improved cognitive functioning [17–19]. A greater understanding of the role of Aβ molecular forms, their temporal role in AD development and their interaction with other pathogenic factors is required.

Oxidative stress is a key factor in AD, whereby the balance between oxidants and antioxidants is disrupted, leading to an excess of oxidants [20,21]. Several mechanisms may contribute towards oxidative stress, including dysfunction of mitochondria [22,23], accumulation of Aβ [22,24] and hyperphosphorylated tau [25,26] and neuroinflammation [27,28]. Biomarkers of oxidative stress in AD have been identified; however, a relatively recent systematic review by Chang *et al.* [29] concluded that although serum markers of lipid peroxidation are elevated in AD, there is insufficient evidence to justify the use of biomarkers as predictors of AD severity or outcome.

Recent studies have investigated the interacting and modifying factors of the defining pathological features of AD; Jonsson *et al.* [30] reported that a coding mutation (A673T) in the amyloid precursor protein (APP) gene has a protective effect against AD and cognitive decline. Genome-wide association studies have reported AD genetic risk factors, with Chapuis *et al.* [31] recently identifying a gene (FERMT2) that has a role in regulating APP metabolism and Aβ production. Researchers are yet to fully explore the interacting and modifying factors of AD pathogenesis using AD mouse models in great detail.

The current review will discuss how well, and in what aspects, murine models of AD recapitulate the physiological, neuropathological and cognitive changes associated with human AD. A complete critical analysis of all AD models and their phenotypes is beyond the scope of this review, so the particular focus will be on commonly used amyloid-based transgenes (overexpressors of APP and/or its processing enzymes), wild-type human tau or mutant microtubule associated protein tau (*MAPT*) expressors, and selected combined and triple transgenes.

Murine models of AD

AD pathology primarily consists of amyloid plaques and neurofibrillary tangles (NFT). Other pathological features of AD include neuronal and synaptic loss, dystrophic neurites, reactive astrocytes, activated microglia and BBB dysfunction [32].

Mutations in three genes have been identified as causing autosomal dominant AD [APP, presenilins (*PSEN1* and *PSEN2*)] through altering Aβ production, and share similar pathological features to sporadic AD [33]. These gene mutations have therefore been the focus of many AD mouse models. Transgenic animals based on amyloid production typically express high levels of Aβ peptide usually through altering the processing of APP [34]. Altered APP processing is usually achieved through introduction of human APP (hAPP), or a *PSEN* gene mutation, which affects γ-secretase enzyme activity, and subsequently alters the cleavage of APP to Aβ1-42 [35,36]. Cleavage of APP occurs by both β-secretase enzyme [also known as β-site amyloid-cleaving enzyme 1 (BACE1)] at the N-terminus of the Aβ peptide, and the γ-secretase enzyme (Aβ C-terminus) activity [36], resulting in a 42 amino acid peptide. This peptide makes up the extracellular fibrillar Aβ which forms the senile, compact plaques with dense cores. The ratio between Aβ40 and Aβ42, rather than just overall Aβ expression, is thought to be a significant factor in determining plaque load and toxicity [34]. α-secretase activity is involved in cleavage of APP to Aβ fragments between residues 16 and 17 of the Aβ peptide, resulting in a truncated Aβ17-40 or Aβ17-42 fragment. *PSEN* genes also have several other functions in addition to cleavage of γ-secretase, and there is current debate over whether they may be altered by gene mutations leading to AD [37], rather than, or in addition to, changes to the Aβ40/Aβ42 ratio [38].

Single mutations in the *PSEN1* or *PSEN2* genes cause APP processing by γ-secretase activity to shift towards the more toxic Aβ 1-42 rather than Aβ 1-40 [39], although these mice do not develop plaques unless crossed with APP overexpressor lines [40].

PSEN1 and *PSEN2* gene mutations are functionally similar, although *PSEN1* is more severe [41].

Neurofibrillary tangles are also a significant hallmark of AD, and are composed of hyperphosphorylated forms of tau protein [35]. There are no known *MAPT* gene mutations associated with sporadic AD, but they do occur in fronto-temporal dementia (FTLD-tau) and Parkinson's disease, linked to chromosome 17 (FTDP-17; [42]). Tau protein binds microtubules stabilizing them in the axons, but in some disease states hyperphosphorylated tau dissociates from the microtubules and forms prefibrillar oligomeric and fibrillary aggregates such as NFTs and paired helical filaments ([43]). Aβ oligomers have been reported to contribute to tau oligomerization [44]. Improved animal models are essential for further understanding the relationship between amyloid and tau pathology. Transgenic mice that recapitulate the NFT therefore express either wild-type human tau or mutant *MAPT* [35]. A number of double-transgenic mice models go one step further and attempt to model the functional interaction between APP and mutant MAPT expression, to more closely mimic the overall pathology seen in AD, with triple transgenes also including a *PSEN1* gene mutation.

AD mouse models that exhibit one or more of the main features of the disease also exhibit additional neuropathological changes associated with the disease, such as changes to cells within the neurovascular unit [45]. For example astrocytes, which are typically involved in cerebral homoeostasis, become activated in AD [46] and co-localize with amyloid plaques [47]. Early astrocyte damage and dysfunction have been linked to AD pathogenesis [48–50]. Microglia are immune cells that also become activated and co-localize with amyloid plaques [51,52]. Some AD mouse models associated with altered Aβ production are known to develop cerebral amyloid angiopathy (CAA) whereby amyloid deposition builds up on arterial walls. It is a pathological feature of AD that can also be found in the elderly without AD, and can be associated with cerebral haemorrhage [53]. Mouse models that exhibit CAA (such as TgAPP23 and TgCRND8) are useful for assessing small vessel disease and cerebral haemorrhage in relation to AD, but interpreting causal links between pathological and behavioural phenotypes can be difficult, as symptoms may be due to cerebral abnormalities [11].

Testing cognition in animals

The hippocampal formation is one of the earliest brain regions to be affected by AD, with impairments in working memory and declarative memory among the first symptoms to be reported by AD patients [54]. Tests of visuo-spatial processing are useful measures of cognitive impairment in the disease, however, by the point in which patients undergo neuropsychological assessment, neuropathology may have been present for years without notable symptomatology [55].

Hippocampal-dependent tasks measure early cognitive changes in mouse models of neurodegenerative diseases and so will be the sole focus of the review, with a comprehensive overview of these and other tasks being reported elsewhere [56,57]. Tasks used in mouse models of AD include the Morris water maze [58,59], the radial arm maze (RAM) [60], the T-maze/Y-maze [61] and the spontaneous object recognition (SOR) task [62].

The Morris water maze is a test of hippocampal-dependent spatial memory whereby rodents typically have to locate a submerged platform using external visual cues (Figure 1). Escape latency and/or search path are used as measures of learning acquisition, in which good spatial learning is reflected by a decrease in escape latency and/or the search path used to locate the platform. Hippocampal-dependent spatial working memory has been measured using a number of paradigms, particularly the RAM, which involves baiting the arms of the maze with food that does not get replenished. Efficient searching through reduced entries to previously visited arms suggests that the animal remembers where it has previously visited. Alternation tasks using the T-maze or the Y-maze utilize the animal's natural exploratory behaviour to measure the animal's tendency to enter the less recently visited arm (s). These spatial alternation tasks require minimal training in contrast to the RAM.

The SOR task relies on rodent's innate preference for novelty, as they demonstrate recognition for a familiar object through preferential exploration of a novel object. The SOR task is not typically hippocampal-dependent, unless the time delay between the sample and test phases is increased from minutes to hours [63]. Rodent behavioural tasks are thought to rely on the same neural mechanisms as in humans, so they can provide a reliable measure of cognitive function in animal models of neurodegeneration that closely

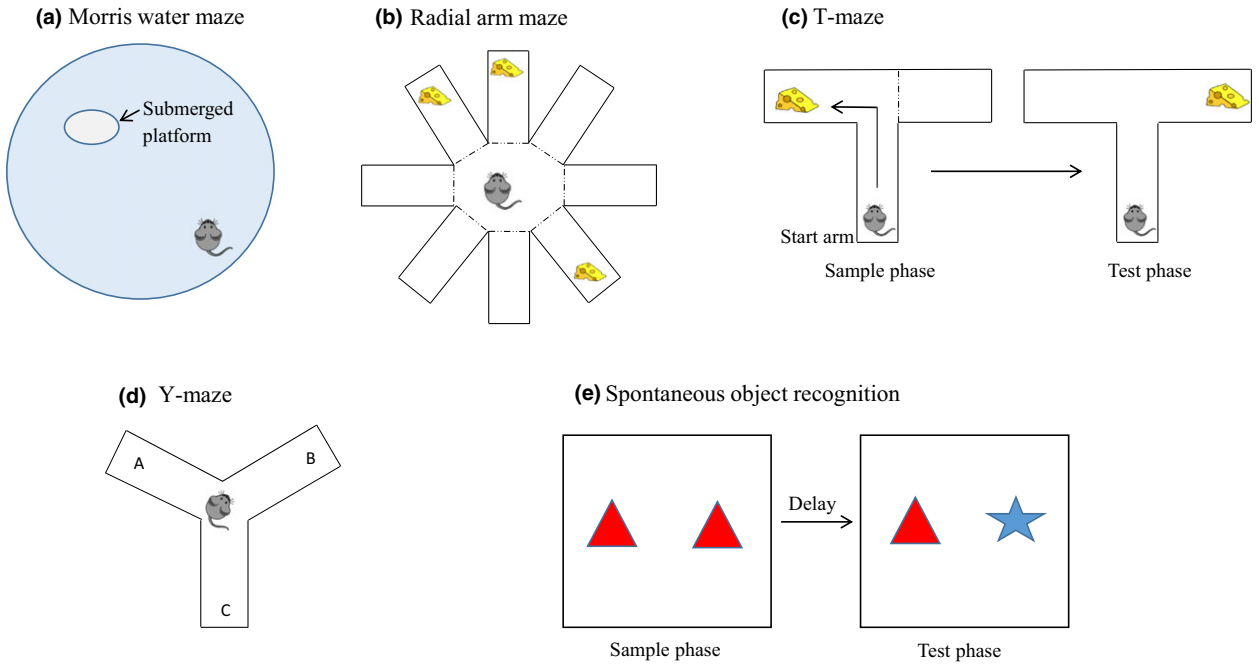

Figure 1. Test apparatus for a series of rodent cognitive tasks. (**a**) The Morris water maze. Animals are required to locate a submerged (hidden) platform. Escape latency and/or search path are used as measures of spatial memory. Memory impairment is demonstrated through no decrease in escape latency. (**b**) Radial arm maze. The animal begins in the centre of the maze, with each arm baited with food. The animal can explore these arms and consume the food reward, but the food is not replenished. Spatial working memory is assessed through the number of times unbaited arms are re-entered. Memory impairment is demonstrated when unbaited arms are repeatedly visited. The dashed lines represent the line to be crossed for an arm entry to be counted. (**c**) T-maze alternation task. During a sample phase, the animal begins in the start arm and is forced to enter either the right or left arm (in this example, the left), receiving a food reward. For the test phase, the animal again begins in the start arm, but has the choice between previously entered arm and the novel arm. The animal receives a food reward for entering the arm not previously visited during the sample phase. Memory impairment is demonstrated if the animal fails to alternate between the arms from sample to test phase. The dashed line represents the door blocking entry to the right arm during the sample phase. (**d**) Y-maze alternation task. The animal begins in the centre of the maze in this continuous version of the alternation task. For a period of time (e.g. 10 min) the animal can freely explore the three arms of the maze (labelled here as 'A', 'B' and 'C'). Memory impairment is demonstrated if the animal fails to display a tendency to alternate between the less visited arms. (**e**) Spontaneous object recognition. Animals can freely explore two copies of an object in an open field in a sample phase. Following a delay (of minutes or hours), the animal is returned to the open field and exposed to a copy of the sample object and a novel object in the test phase. Recognition of the familiar object is shown through greater exploration of the novel object over the familiar object. Memory impairment is demonstrated through equal exploration of both objects at test.

reflects the cognitive decline seen in human neurological disease.

How well do models of AD recapitulate physiological, neuropathological and behavioural changes associated with the disease?

Specific mouse models, categorized as those that overexpress Aβ, those with mutations affecting secretase processing of APP and those with NFT pathology (through introducing human wild-type tau or mutant *MAPT*), will now be discussed, considering how well they reflect human AD in terms of pathology and cognitive changes.

Altering Aβ through APP processing

Human APP mutations mainly occur at one or both of the two cleavage sites that result in Aβ production. For example, γ-secretase cleavage site mutations, such as V717I and V717F, alter the ratio between Aβ40 and Aβ42 production to favour the more toxic Aβ42 [34], but many express the K670N/M671L Swedish double mutation at the β-secretase cleavage site which results in increased BACE cleavage and production of Aβ40

and Aβ42. Others combine both the Swedish mutation with a γ-secretase cleavage site mutation [38].

PDAPP

The first transgenic mouse model to develop robust amyloid plaque deposition was generated by Games *et al.* [64], and contained hAPP with mutations associated with familial, early-onset AD (FAD V717F Indiana) using C57Bl/6, DDA/2J and Swiss-Webster mouse strains (Table 1). The PDAPP (platelet-derived growth factor promoter amyloid precursor protein) mice exhibit amyloid deposition from 6 to 9 months of age, with further pathologies characteristic of AD such as dystrophic neurites (immunoreactive against phosphorylated tau; [65]), the co-localization of activated astrocytes and microglia with plaques and a decrease in synaptic density [64]. There is no development of NFTs or neuronal loss up to at least 18 months of age [66].

There is an age-related memory impairment in the SOR task, with all PDAPP mice initially performing as well as controls in discriminating between novel and familiar objects at 3 months of age, but by 6 months onwards, the homozygous PDAPP mice fail to successfully discriminate between objects. When tested in the RAM, only homozygous PDAPP mice show significant reference memory impairments through entering incorrect unbaited arms more often than controls, but PDAPP mice show working memory impairments through revisiting previously baited arms more often than controls [35]. Chen *et al.* [67] reported spatial memory impairments in the Morris water maze with 3-month-old PDAPP mice impaired at learning the first platform location. Dodart *et al.* [68] reported sensorimotor impairments in PDAPP mice from 3 months of age, as they failed to habituate to an open field typically exhibited through a decrease in locomotor activity levels over time.

The reported cognitive and behavioural impairments all precede the onset of disease pathology in PDAPP mice, which suggests there is early dysfunction to mechanisms linked to these impairments, and may contribute to the plaque and cellular pathology which is typical of AD.

Tg2576

Tg2576 mice were developed by Hsiao *et al.* [69], overexpressing the Swedish APP mutation (K670N/M671L) on a C57Bl/6 × SJL background [35]. These mice show an increase in Aβ levels at 6 months, and plaque deposition between 9 and 12 months of age across the cortex and hippocampus [70]. These mice recapitulate

Table 1. Timeline of onset of amyloid pathology and cognitive test impairments in transgenic mouse models of AD

Transgenic mouse model	*Mutation*	*Amyloid deposition (months)*	*SOR (months)*	*Water maze (months)*	*T-maze (months)*	*Y-maze (months)*
PDAPP	APP (Indiana V717F)	6–9	6	3		
Tg2576	APP (Swedish K670N-M671L)	9–12	12–15	6	10	10
TgAPP23	APP (Swedish K670N-M671L)	6–12	3–4	3		
TgCRND8	APP (Swedish K670N-M671L and Indiana V717F)	3–5	3–5	3		
J20	APP (Swedish K670N-M671L and Indiana V717F)	5–7	4	6–9		
APP + PSEN1	APP (Swedish K670N-M671L), PSEN1 M146L	6–8		15–17		3
TAPP	APP (Swedish K670N-M671L), MAPT P301L	6		7–8		
Tg2576n/VLW tau	APP (Swedish K670N-M671L), G272V, *MAPT* P301L, R406W	9		16		
3xTgAD	APP (Swedish K670N-M671L), *MAPT* P301L, PSEN1 M146V	5	Intact at 11 months		6–9	

AD, Alzheimer's disease; SOR, spontaneous object recognition; APP, amyloid precursor protein; PDAPP, platelet-derived growth factor promoter amyloid precursor protein; PSEN1, presenilin; MAPT, microtubule associated protein tau; TAPP, tau amyloid precursor protein.

many of the neuropathological features of AD, including astrogliosis [71], microgliosis [72] and dystrophic neurites [71]. Similar to the PDAPP mice, there is no observed neuronal loss; however, there is also no significant decrease in synaptic density [73,74]. Aβ increases may be linked to synaptic dysfunction, if not necessarily synapse loss [73,75].

Tg2576 mice show repetitive exploration behaviours from 10 months of age in the spontaneous Y-maze alteration task [69], and from 10 months onwards in the T-maze alternation task [75]. Tg2576 mice exhibit soluble Aβ before 6 months of age, but do not develop progressive spatial acquisition and memory performance impairments until 6 months onwards [76]. In the SOR task, Tg2576 mice fail to discriminate between novel and familiar objects after a 24 h delay compared to controls at 12–15 months of age [77]. Tg2576 mice exhibited greater exploration in an open field [75] and an increased interest in exploring the central areas [78]. Tg2576 mice have also been reported to show increased aggression towards cage mates [79].

Cognitive impairments in the Tg2576 mice occur much later than the PDAPP mice, which may be related to the significant decrease in synaptic density observed in the PDAPP mice. Similar to the PDAPP mice, the cognitive and behavioural impairments in the Tg2576 mice either precede or coincide with the Aβ pathology, again suggesting there is early dysfunction occurring prior to plaque deposition and glial response.

TgAPP23

TgAPP23 AD mice were generated using the Swedish double mutation (K670N/M671L) altering the β-secretase cleavage site, and the London (V717I) mutation altering the γ-secretase cleavage site, on a C57Bl/6 × DBA/2 background [80]. These mice overexpress hAPP across the hippocampus and cortex and are notable for their cerebrovascular phenotype [81]. Amyloid deposition is present from 6 months of age and substantial by 12 months, particularly in cerebral vessels which progressively decreases cerebral blood flow and alters vessel morphology [82,83]. TgAPP23 mice also display reactive gliosis and astrocytosis, dystrophic neurites, and synaptic loss [81], as well as a degree of neuronal loss in older TgAPP23 mice [84].

TgAPP23 mice show spatial impairments in water maze latencies and path lengths from 3 months of age prior to substantial plaque deposition [85]. In the SOR task, TgAPP23 mice fail to discriminate between novel and familiar objects after a 24 h delay at 3–4 months of age [86]. Both SOR and water maze task impairments occur from around 3 months of age, therefore, preceding amyloid deposition. This is similar to the PDAPP and Tg2576 mice, though with slightly different ages of onset.

TgAPP23 mice exhibit a cerebrovascular phenotype making them a useful model for AD with CAA, but it is unclear how much of the neuropathology and cognitive profiles can be attributed to the hAPP mutation or the cerebrovascular changes [11].

TgAPP23 mice exhibit a decrease in exploratory behaviour in the open field, at 6–8 weeks, 3 and 6 months of age, while also showing significant impairments relative to control animals on the rotarod at 3 and 6 months [85]. TgAPP23 mice have also been reported to show increased aggression from 6 months of age, after the onset of both amyloid plaques and other discussed behavioural impairments [87].

TgCRND8

TgCRND8 mice were developed on a C57Bl/6 × C3H background and contained both the APP Swedish double mutation (K670N-M671L) and the V717F Indiana mutation [35]. These mice present with Aβ deposition at 3 months of age, with dense core plaques present by 5 months in the cortex and hippocampus [88,89], spreading to the cerebellum and brainstem by 8–9 months of age [11], which is associated with increased inflammatory response [90]. In addition, astrocytic gliosis and microglial activation in regions around plaques have been reported [89].

Chishti *et al.* [89] reported that these mice have significant acquisition impairments in hidden platform testing at 11 weeks, with longer swim paths and search latencies compared to controls. In addition, TgCRND8 mice show spatial reference memory impairments at 6–8 months of age, but were able to overcome this impairment when the hidden platform was visibly cued [91].

At 3–5 months of age, TgCRND8 mice fail to discriminate between novel and familiar objects on the SOR task with a 1 h delay [92], and in the Y-maze task, TgCRND8 mice perform comparably to controls up to around 11 months of age, demonstrating intact short-term spatial memory capacity [93]. Overall, and

similar to the previously discussed AD models, any significant cognitive impairments reported in the TgCRND8 mice coincide with amyloid deposition, occurring at an early age of around 3 months. However, the Aβ pathology does occur at a younger age compared to the previous models, so the timeline from when the cognitive impairments are observed, to when amyloid deposition occurs, is much shorter, almost occurring simultaneously.

J20

The J20 transgenic mouse features a high level of Aβ1-42 overexpression resulting from the introduction of both the Swedish (K670N and M671L) and Indiana (V7171F) hAPP mutations in a C57Bl/6 × DBA2J background. Diffuse amyloid deposits appear from 5 to 7 months of age in the hippocampus and the neocortex, with larger neuritic plaques appearing after 9 months of age (Figure 2). J20 mice also exhibit a decrease in synaptophysin immunoreactivity indicating changes in synaptic function [11]. J20 mice are also a useful epilepsy model, due to abnormal neural hyperexcitability [94], and cerebrovascular function and neurovascular coupling in relation to neurodegeneration [95,96].

On the SOR task, J20 mice successfully discriminate between novel and familiar objects after a 1 h delay up to 15–16 months of age [97], but are unable to recognize familiar objects after a 4 h delay at 6–8 months of age [98]. When the delay is extended to 24 h, J20 mice are impaired from as early as 4 months old [99]. Overall, these findings suggest that J20 AD mice are able to successfully recognize a previously encountered object following a delay of up to 1 h, but not after a delay of over 4 h.

Palop *et al.* [100] reported that J20 mice aged 6–9 months of age are impaired in water maze hidden platform location as well as spatial location retention in probe trials. An alternative measure of spatial memory that relies on the animal's natural exploratory behaviour is the object-location (OL) task (a spatial variant of the SOR paradigm). AD mice with APP mutations show impairments on the OL from around 5 months of age [101]. Unlike the previously discussed AD models, the age of onset for spatial memory impairments in the water maze is not as early. Spatial memory impairments in the OL task are observed at a slightly younger age, so it can be concluded that, overall, impairments observed on both recognition and spatial memory appear to coincide closely with the deposition on amyloid in the hippocampus and cortex, from around 4 months onwards.

Secretases

Specific mutations in the *PSEN* genes (*PSEN1* and *PSEN2*; [102,103] result in changes in γ-secretase activity leading to preferential processing of Aβ1–42

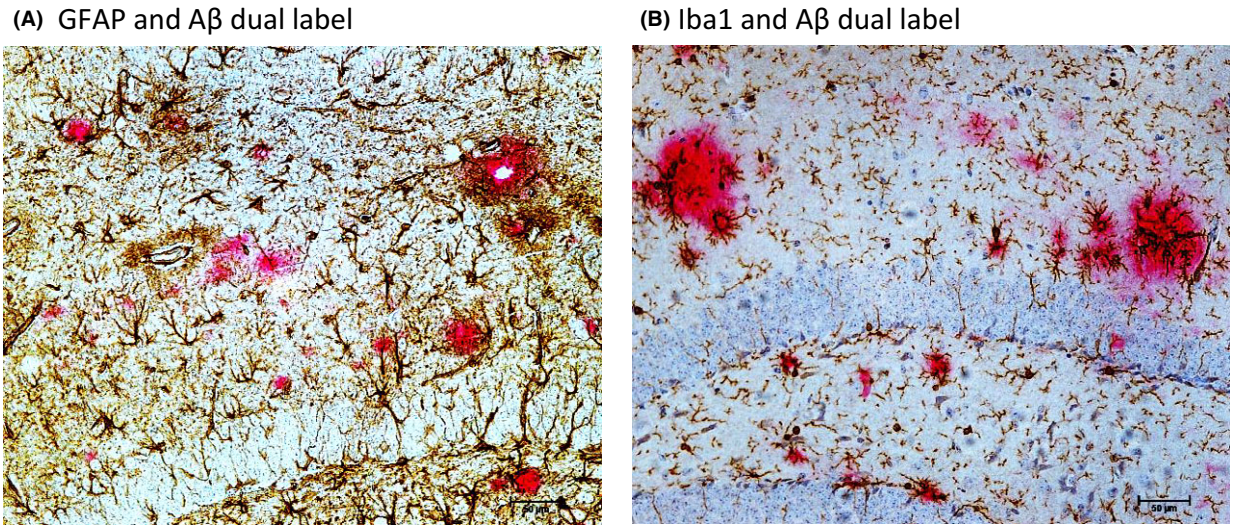

Figure 2. Glial pathology associated with Aβ plaques in the hippocampus of a 12-month-old hAPP-J20 mouse. Aβ plaques (6E10, red) are associated with (**A**) reactive astrocytes (GFAP, brown) and (**B**) microglia (Iba-1, brown). Scale bar represents 50 μm. Images are contrast enhanced.

fragments. Most *PSEN* gene mouse models are derived from *PSEN1* mutations.

APP + PSEN1

Holcomb *et al.* [40] crossed the *PSEN1* transgene (M146L) with hAPP Tg2576 mice, and at 4–5 months of age APP + *PSEN1* mice had detectable insoluble Aβ. At 6–8 months of age, APP + *PSEN1* mice show elevated levels of Aβ compared to single transgenic Tg2576 littermates [40]. Spatial memory impairments appear as early as 12–14 weeks of age, with APP + *PSEN1* mice showing a significant reduction in the number of alternations on the Y-maze spatial task [104]. Arendash *et al.* [105] further supported these findings, reporting that APP + *PSEN1* mice showed a significant reduction in the number of alternations in the Y-maze task at 5–7 months of age, but also showed impairments in acquisition of spatial locations in the water maze at 15–17 months of age.

15–17-month-old APP + *PSEN1* mice exhibited sensorimotor deficits through a significant impairment on a balance beam test, and increased activity in the open field [105]. A more recent study by Wang *et al.* [106] measured sensorimotor gating in the APP + *PSEN1* mice at 3, 7 and 22 months of age, using the prepulse inhibition (PPI) of the startle response (attenuated startle response from a preceding stimulus). PPI was found to be lower in 7- and 22-month-old APP + *PSEN1* mice compared to age-matched controls, with the 7-month-old APP + *PSEN1* mice also exhibiting memory impairments in the water maze task and increased Aβ plaque deposition compared to 3-month-old APP + *PSEN1* mice.

Correlating the onset of Aβ pathology and impairments in spatial memory in the water maze suggest that these phenotypes are linked, with onset occurring around 6–7 months of age. However, spatial memory performance in the Y-maze reveals impairments from as early as 3 months of age, highlighting how task-specific demands can vary in sensitivity.

BACE1 KO × APP

Luo *et al.* [107] developed the BACE1 knock out on a hAPP Tg2576 background. BACE1$^{-/-}$Tg2576^{+} phenotypically should be 'normal', in that they show no significant disease-associated pathology. These mice do not develop plaques or produce soluble Aβ peptides [108]. In the Y-maze alternation task, BACE1$^{-/-}$ Tg2576^{+} mice at 4–6 months of age performed as well as wild-type controls and significantly better than Tg2576 mice who exhibit brain amyloid Aβ (but not plaque deposition) at this age. These results suggest that BACE1 deficiency in a hAPP transgenic mouse model results in improved performance on the Y-maze alternation task, which may be linked to reduced Aβ levels.

Tau and triple transgenes

Most transgenic mouse models used to investigate tau and the formation of NFTs involve either introducing a gene for human wild-type tau, or mutant *MAPT* [35]. It is important to note that single transgenic mice with FTD-associated tau (e.g. the JNPL3 line expressing the P301L FTD-associated tau mutation) are better understood as models of FTD, rather than AD [38]. A number of studies have also modelled tau propagation through transgenic lines that overexpress P301L restricted to regions such as the entorhinal cortex where neurons are first affected by NFTs [109], or through injecting tau preformed fibrils into specific brain regions of PS19 transgenic mice overexpressing human P301S mutant tau, for example [110].

TAPP

Lewis *et al.* [111] crossed the hAPP Tg2576 mouse line with the JNPL3 mouse line expressing the most common FTD-associated human tau mutation (P301L), forming the TAPP (tau amyloid precursor protein) bigenic line. The TAPP mice develop Aβ plaque deposition comparable to Tg2576 mice and as early as 6 months of age [111], but the NFT pathology is more severe than JNPL3 mice, suggesting that the APP pathology may contribute towards exacerbating tangle formation [111]. Cognitive performance is not widely reported in this model, but they do have various motor disturbances [111]. Yuzwa *et al.* [112] recently reported TAPP mice were impaired on the water maze task at 7–8 months of age, which is at a slightly later age of onset to Aβ deposition and in contrast to previously discussed AD models.

Tg2576/VLW tau

Amyloid overexpressing Tg2576 mice were crossed with VLW mice with mutant 4R *MAPT* [113] containing a

triple mutation (G272V, P301L, R406W) on a C57Bl/6 × CBA background. These mice exhibit widespread Aβ accumulation initially at 9 months of age, with widespread deposition, and neuronal loss in the entorhinal cortex and CA1 region of the hippocampus from 16 months of age [113]. Spatial memory tested in the Morris water maze reveals longer escape latencies compared to wild-type controls initially at 9 months of age, but predominantly from 16 months of age [113]. The spatial memory impairments in the water maze are first observed at a comparable age of onset relative to Aβ deposition, but this is still at a later age of onset compared to previously discussed AD models.

3xTgAD

The 3xTgAD mouse line was developed by Oddo *et al.* [114], who generated a triple transgenic model by coinjecting two transgenes containing APP (Swedish) and *MAPT* P301L FTDP-17 mutations into embryonic cells from PS1M146V knock-in mice. 3xTgAD mice exhibit increased levels of Aβ1-40 and Aβ1-42, and NFTs. Amyloid plaques are present as early as 3 months of age, with NFTs appearing much later at 12 months of age in the hippocampus and cortex [114]. These mice also have altered synaptic function which progresses with age [114], and spatial memory impairments on the water maze from 6 months of age [115]. Davis *et al.* [116] reported intact recognition memory at 11 months of age, despite the presence of intracellular Aβ from 5 months. In addition, 3xTgAD mice showed impairments on the T-maze task (being unable to successfully distinguish between novel and familiar arms), and the radial arm water maze from between 6 and 9 months of age [117]. Overall, Aβ deposition occurs early in 3xTgAD mice prior to any significant cognitive impairments, which are reported from around 6 months of age. This is in contrast to the previously discussed AD models. NFTs also develop later, at around 12 months of age. Though 3xTgAD mice present with the two main features of AD, these findings suggest poor correlation between behavioural impairments and disease pathology, perhaps because Aβ and tau develop independently of one another.

Translation into therapeutic developments

There are currently only a select number of drugs available to treat AD, focusing on alleviating symptoms, with no new drugs being approved since 2003. No drug has yet been identified to significantly alter the course of the disease, and translate successfully into clinical applications. This may be due to significant differences between rodent models and humans in terms of how they metabolise the drugs, how the drugs act upon certain mechanisms, and fundamental differences in neural circuitry between species [118].

Immunotherapy has been investigated preclinically in AD mouse models as a potential therapeutic strategy through preventing Aβ aggregation. For example, administration of the monoclonal antibody bapineuzumab in PDAPP resulted in a reduction in both soluble and insoluble levels of Aβ [119]. Immunotherapies targeting amyloid plaques have progressed to clinical trials, showing some promising reductions in rate of cognitive decline [120], and levels of Aβ and tau following neuropathological investigations [18], but no trials have shown results that are both significantly efficacious and nonharmful. For example, a recent meta-analysis highlighted the lack of clinical efficacy of bapineuzumab [121] which failed Phase III trials, alongside similar monoclonal antibody solanezumab [122].

BACE1 is another therapeutic target, with administration of TAK-070 (a nonpeptidic BACE1 inhibitor) to Tg2576 mice resulting in a reduction in both soluble and insoluble Aβ, and a reduction in cognitive impairments [123]. However, promising BACE1 inhibitor verubecestat has recently failed in clinical trial, although a trial with patients at an earlier stage of the disease continues [124]. Hung and Fu [125] have recently published a comprehensive review of AD drugs in clinical trials up to June 2017, including the therapeutic targets, trial status and clinical outcomes.

Stem cells have been investigated as a potential therapeutic strategy for AD. Administration of haplotype-matched murine neuronal stem cells to aged 3xTgAD mice reduced cognitive impairments, but had no significant effect on Aβ or tau pathology [126].

There have also been recent advances in the use of optogenetics, a technique which modulates neuronal activity, as a therapeutic approach for neurodegenerative diseases, including AD [127]. However, this research is currently in the very early stages of research.

In summary, a number of therapeutic strategies have been developed in AD mouse models and have shown

promising results in terms of reducing Aβ or tau, for example, showing that these models are good for recapitulating disease pathology. However, none of these strategies have yet successfully translated to clinical outcomes in AD patients, so there is a need for more advanced animal models that better model disease complexity.

Discussion

No one model provides an ideal and complete characterization of AD as observed in humans, however, different models are useful for answering questions about specific aspects of the disease.

Within each type of AD model there are variations in terms of the onset of pathological features and cognitive decline, of which some can be accounted for by background strains as well as differing baseline abilities in terms of learning, memory and locomotion [39]. Even with AD models of the same genetic background, many cognitive tests are sensitive to small variations in task protocol, which can yield contrasting results [128]. Rodents are nocturnal and do not primarily rely on vision, but olfaction, which raises issues around their abilities to perform in tasks such as the Morris water maze [129]. Mice, in particular, are known to perform poorly in the water maze compared to rats, due to tendencies to swim nearer to the wall (a classic hallmark of anxiety; [130] and to be more buoyant [131]. The age of the animals is also a determining factor in water maze performance [132], which may be related to an age-related decline in motor abilities.

No AD mouse model exhibits the full range of pathological phenotypes, making it difficult to correlate cognitive decline and pathological changes. Only a small number of AD models exhibit neuronal loss [39], with it being rarely reported in APP models, such as PDAPP and Tg2576 [67, 72], but more often reported in APP models combined with *PSEN1* gene mutations [133]. Aβ impairs synaptic function, which is likely to be a major contributor to the cognitive impairments reported [36]. Studies have described a loss in synaptophysin-immunoreactivity around compact plaques in both PDAPP and Tg2576 mice, indicating changes to synapse function relating to Aβ [72]. Soluble Aβ may contribute towards cognitive impairments, which would account for why they are observed prior to compact plaque deposits [77]. Pathological and behavioural features need consideration when selecting an AD model to test a specific hypothesis, and will depend on the precise mechanisms being investigated.

It is not clear how accurately the time course of amyloid plaque deposition and cognitive decline reflects human AD. Behavioural impairments are often reported prior to plaque deposition across AD mouse models, but it is likely that Aβ pathology is present prior to the onset of cognitive impairments in humans [134]. It may, however, be likely that subtle changes in cognition occur prior to patients reporting the first notable changes with their physician.

Transgenic mice expressing both amyloid and tau pathology (e.g. TAPP and 3xTgAD) may seem like the ideal models to study human AD as they more closely reflect the disease. Although these mice present with the two main features of AD, these pathologies are reported as developing independently [38], and so do not fully mimic the disease progression seen in humans.

A number of emerging hypotheses linking other health conditions to dementia and AD present an opportunity for AD models to be utilized as models for other diseases. For example, recent studies suggest that Aβ may play a role in promoting cerebrovascular atherosclerosis [135], which would make an APP mouse model suitable for studying this relationship and a number of other cerebrovascular and neurodegenerative diseases, particularly as such conditions rarely present independently in humans.

Two genetic variations which are important risk factors for sporadic AD are the allelic variations of apolipoprotein (APOE), and the R47H allele of the triggering receptor expressed on myeloid cells 2 (TREM2; [136]). APOE colocalizes with Aβ and microglia. Mice that are haploinsufficient for human APOE show a significant decrease in plaque deposition in APP/*PSEN1* (L166P) and J20 mice [137,138], and APOE-knockout mice have been reported to clear Aβ faster than control mice [139]. Disrupting the interaction between APOE and Aβ may be a viable potential therapeutic approach to reduce Aβ deposition.

There are conflicting reports regarding the effect of TREM2 on overall Aβ plaque deposition which has been characterized in the APP/*PSEN1* and 5xFAD mouse models [140,141]. Ulrich *et al.* [142] reported that TREM2 haploinsufficient APP/*PSEN1* mice of 3 and 7 months of age showed no significant Aβ

deposition in the cortex. Further research supports these findings with Jay *et al.* [143] reporting that 4-month-old TREM2$^{-/-}$ APP/*PSEN1* mice showed no significant cortical Aβ deposition, and a decrease in hippocampal Aβ deposition compared to TREM2$^{+/+}$ APP/*PSEN1* mice (26). In comparison, Wang *et al.* [144] reported that 8-month-old TREM2$^{-/-}$ 5xFAD mice exhibited an increase in hippocampal Aβ deposition, with no significant effect on cortical Aβ. Further work is needed to elucidate the roles of APOE and TREM2 gene variations in AD, and refining animal models will be key to progressing how the function of these genes relate to certain pathological features of AD.

Touchscreen technology [145] could present as a way of standardizing and improving rodent cognitive and behavioural tests. A range of computer-automated cognitive tasks have been developed for rodents which are designed to mimic the neuropsychological tasks used with humans, improving their translational capability. Such tasks are carried out in the same apparatus with the same type of stimuli, improving the ability to compare performance across tasks. Romberg *et al.* [146] reported that TgCRND8 mice showed no impairment on a visual discrimination test, but were impaired on a test of object recognition, even with a short delay of 1 min. It is possible that the touchscreen version of the object recognition task is more difficult than the standard version, potentially due to rodents naturally being more dependent on olfaction than visual acuity, but the technology remains promising.

There have been varying results regarding the effect of sexual differences on AD mouse model phenotypes, but it is necessary to understand how such differences may contribute to making one sex more vulnerable or protected from disease. Research suggests that female AD mice have an increased vulnerability to AD phenotypes, but Dubal *et al.* [147] propose this may be more closely related to a greater beneficial effect of male hormones, and a more deleterious effect of female hormones in the brain of AD mouse models.

Developments in genome editing technology known as CRISPR/Cas9 allows for mice to be genetically engineered much more efficiently [148], as multiple gene variations can be introduced simultaneously. This technology is particularly significant for developing mouse models of late-onset AD, which is likely to involve multiple gene variations. Improved predictive models should lead to better translation between preclinical and clinical studies, particularly for the more common late-onset AD.

Conclusion

Mouse models of AD continue to be a central component in furthering our understanding of the disease and identifying new therapeutic targets for existing and novel compounds. It is important, however, to treat AD models as a reductionist tool for understanding the pathogenesis of AD, and research should be guided by human studies to look for the causal relationships human work cannot often provide.

Acknowledgements

KA-A wrote the manuscript, with contributions and editing from SBW, JES, PRH, PS and JB. This work was funded by an Alzheimer's Research UK Interdisciplinary Research Grant (ARUK-IRG2014-10).

Ethical approval

All original research carried out under the Alzheimer's Research UK Interdisciplinary Research Grant (ARUK-IRG2014-10) was given ethical approval through the University of Sheffield's Animal Welfare and Ethical Review Body. All original research from this grant was carried out in accordance with the U.K. Animals (Scientific Procedures) Act (1986) and associated guidelines.

Conflict of interest

The authors declare no conflict of interest.

References

1 Sachdev PS, Mohan A, Taylor L, Jeste DV. DSM–5 and mental disorders in older individuals: an overview. *Harv Rev Psychiatry* 2015; **23**: 320–8
2 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th edn. Washington, DC: American Psychiatric Association, 2013
3 Esiri MM, Matthews F, Brayne C, Ince PG, Matthews FE, Xuereb JH, Broome JC, McKenzie J, Rossi M, McKeith IG, Lowe J, Morris JH. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet* 2001; **357**: 169–75

4 Helmes E, Bowler JV, Merskey H, Munoz DG, Hachinski VCI. Rates of cognitive decline in Alzheimer's disease and dementia with Lewy bodies. *Dement Geriat Cogn* 2003; **15**: 67–71

5 Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. *PLoS Med* 2009; **6**: e1000180

6 Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. *Arch Med Res* 2012; **43**: 600–8

7 Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *Lancet* 2006; **368**: 387–403

8 Wright AL, Zinn R, Hohensinn B, Konen LM, Beynon SB, Tan RP, Clark IA, Abdipranoto A, Vissel B. *PLoS ONE* 2013; **8**: e59586

9 Hardy J. Testing times for the 'amyloid cascade hypothesis'. *Neurobiol Aging* 2002; **23**: 1073–4

10 Hardy J. Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. *J Alzheimers Dis* 2006; **9**: 151–3

11 Kobayashi DT, Chen KS. Behavioral phenotypes of amyloid-based genetically modified mouse models of Alzheimer's disease. *Genes Brain Behav* 2005; **4**: 173–96

12 Freir DB, Fedriani R, Scully D, Smith IM, Selkoe DJ, Walsh DM, Regan CM. Aβ oligomers inhibit synapse remodelling necessary for memory consolidation. *Neurobiol Aging* 2011; **32**: 2211–18

13 Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Liao Z, Lieberburg I, Motter R, Mutter L, Soriano F, Shopp G, Vasquez N, Vandevert C, Walker S, Wogulis M, Yednock T, Games D, Seubert P. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 1999; **400**: 173–7

14 Sevigny J, Chiao P, Bussiere T, Weinreb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, O'Gorman J, Qian F, Arastu M, Li M, Chollate S, Brennan MS, Quintero-Monzon O, Scannevin RH, Moore Arnold H, Engber T, Rhodes K, Ferrero J, Hang Y, Mikulskis A, Grimm J, Hock C, Nitsch RM, Sandrock A. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* 2016; **537**: 50–6

15 Boche D, Denham N, Holmes C, Nicoll JA. Neuropathology after active $A\beta_{42}$ immunotherapy: implications for Alzheimer's disease pathogenesis. *Acta Neuropathol* 2010; **120**: 369–84

16 Nicoll JA, Wilkinson D, Holmes C, Steart P, Markham H, Weller RO. Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: a case report. *Nat Med* 2003; **9**: 448–52

17 Abbott A, Dolgin E. Failed Alzheimer's trial does not kill leading theory of disease. *Nature* 2016; **540**: 15–16

18 Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JAR. Long-term effects of $A\beta_{42}$ immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *Lancet* 2008; **372**: 216–23

19 Pasquier F, Sadowsky C, Holstein A, Leterme Gle P, Peng Y, Jackson N, Fox NC, Ketter N, Liu E, Ryan JM; ACC-001(QS-21) Study Team. Two phase 2 multiple ascending-dose studies of vanutide cridificar (ACC-001) and QS-21 adjuvant in mild-to-moderate Alzheimer's disease. *J Alzheimers Dis* 2016; **51**: 1131–43

20 Behl C, Moosmann B. Antioxidant neuroprotection in Alzheimer's disease as preventive and therapeutic approach. *Free Radic Biol Med* 2002; **33**: 182–91.

21 Moosmann B, Behl C. Antioxidants as treatment for neurodegenerative disorders. *Expert Opin Investig Drugs* 2002; **11**: 1407–35

22 Zhao Y, Zhao B. Oxidative stress and the pathogenesis of Alzheimer's disease. *Oxid Med Cell Longev* 2013; doi: 10.1155/2013/316523

23 Wang X, Su B, Siedlak SL, Moreira PI, Fujioka H, Wang Y, Casadesus G, Zhu X. Amyloid-beta overproduction causes abnormal mitochondrial dynamics *via* differential modulation of mitochondrial fission/fusion proteins. *Proc Natl Acad Sci USA* 2008; **105**: 19318–23

24 Yan MH, Wang X, Zhu X. Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. *Free Radic Biol Med* 2013; **62**: 90–101

25 Dias-Santagata D, Fulga TA, Duttaroy A, Feany MB. Oxidative stress mediates tau-induced neurodegeneration in Drosophila. *J Clin Invest* 2007; **117**: 236–45

26 Stamer K, Vogel R, Thies E, Mandelkow E, Mandelkow EM. Tau blocks traffic of organelles, neurofilaments, and APP vesicles in neurons and enhances oxidative stress. *J Cell Biol* 2002; **156**: 1051–63

27 Candore G, Bulati M, Caruso C, Castiglia L, Colonna-Romano G, Di Bona D, Dura G, Lio D, Matranga D, Pellicano M, Rizzo C, Scapagnini G, Vasto S. Inflammation, cytokines, immune response, apolipoprotein E, cholesterol, and oxidative stress in Alzheimer disease: therapeutic implications. *Rejuvenation Res* 2010; **13**: 301–13

28 Lee YJ, Han SB, Nam SY, Oh KW, Hong JT. Inflammation and Alzheimer's disease. *Arch Pharm Res* 2010; **33**: 1539–56

29 Chang Y-T, Chang W-N, Tsai N-W, Huang C-C, Kung C-T, Su Y-J, Lin W-C, Cheng B-C, Su C-M, Chiang Y-F, Lu C-H. The roles of biomarkers of oxidative stress and antioxidant in Alzheimer's disease: a systematic review. *Biomed Res Int* 2014; **182303**: 1–14.

30 Jonsson T, Atwal JK, Steinberg S, Snaedal J, Jonsson PV, Bjornsson S, Stefansson H, Sulem P, Gudbjartsson D, Maloney J, Hoyte K, Gustafson A, Liu Y, Lu Y, Bhangale T, Graham RR, Huttenlocher J, Bjornsdottir G, Andreassen OA, Jonsson EG, Palotie A, Behrens TW, Magnusson OT, Kong A, Thorsteinsdottir U, Watts RJ, Stefansson K. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. *Nature* 2012; **488**: 96–9
31 Chapuis J, Flaig A, Grenier-Boley B, Eysert F, Pottiez V, Deloison G, Vandeputte A, Ayral A-M, Mendes T, Desai S, Goate AM, Kauwe JSK, Leroux F, Herledan A, Demiautte F, Bauer C, Checler F, Petersen RC, Blennow K, Zetterberg H, Minthon L. Genome-wide, high-content siRNA screening identifies the Alzheimer's genetic risk factor FERMT2 as a major modulator of APP metabolism. *Acta Neuropathol* 2017; **133**: 955–66
32 Elder GA, Gama Sosa MA, De Gasperi R. Transgenic mouse models of disease. *Mt Sinai J Med* 2010; **77**: 69–81
33 Goate A, Chartier-Harlin M-C, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor M, Owen M, Hardy J. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991; **349**: 704–6
34 Charier-Harlin MC, Crawford F, Houlden H, Warren A, Hughes D, Fidani L, Goate A, Rosser M, Roques P, Hardy J, Mullan M. Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. *Nature* 1991; **358**: 844–6
35 Eriksen JL, Janus CG. Plaques, tangles, and memory loss in mouse models of neurodegeneration. *Behav Genet* 2007; **37**: 79–100
36 Wild-Bode C, Yamazaki T, Capell A, Leimer U, Steiner H, Ihara Y, Haass C. Intracellular generation and accumulation of amyloid beta-peptide terminating at amino acid 42. *J Biol Chem* 1997; **272**: 16085–8
37 Xia XF, Wang P, Sun XY, Soriano S, Shum WK, Yamaguchi H, Trumbauer ME, Takashima A, Koo EH, Zheng H. The aspartate-257 of presenilin 1 is indispensable for mouse development and production of β-amyloid peptides through β-catenin-independent mechanisms. *Proc Natl Acad Sci USA* 2002; **99**: 8760–5
38 Hall AM, Roberson ED. Mouse models of Alzheimer's disease. *Brain Res Bull* 2012; **88**: 3–12
39 Vetrivel KS, Zhang YW, Xu H, Thinakaran G. Pathological and physiological functions of presenilins. *Mol Neurodegener* 2006; **1**: 4
40 Holcomb L, Gordon MN, McGowan E, Yu X, Benkovic S, Jantzen P, Wright K, Saad I, Mueller R, Morgan D, Sanders S, Zehr C, O'Campo K, Hardy J, Prada CM, Eckman C, Younkin S, Hsiao K, Duff K. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. *Nat Med* 1998; **4**: 97–100
41 Bertram L, Tanzi RE. The current status of Alzheimer's disease genetics: what do we tell the patients? *Pharmacol Res* 2004; **50**: 385–96
42 Haugarvoll K, Wszolek ZK, Hutton M. The genetics of frontotemporal dementia. *Neurol Clin* 2007; **25**: 697–715
43 Cardenas-Aguayo MC, Gomez-Virgilio L, DeRosa S. The role of tau oligomers in the onset of Alzheimer's disease neuropathology. *ACS Chem Neurosci* 2014; **5**: 1178–91
44 Lasagna-Reeves CA, Castillo-Carranza DL, Guerrero-Muoz MJ, Jackson GR, Kayed R. Preparation and characterization of neurotoxic tau oligomers. *Biochemistry* 2010; **49**: 10039–41
45 Sweeney MD, Ayyadurai S, Zlokovic BV. Pericytes of the neurovascular unit: key functions and signaling pathways. *Nat Neurosci* 2016; **19**: 771–83
46 Steardo L Jr, Bronzuoli MR, Iacomino A, Esposito G, Steardo L, Scuderi C. Does neuroinflammation turn on the flame in Alzheimer's disease? Focus on astrocytes. *Front Neurosci* 2015; **9**: 1–6
47 Armstrong RA. The molecular biology of senile plaques and neurofibrillary tangles in Alzheimer's disease. *Folia Neuropathol* 2009; **47**: 289–99
48 Garwood CJ, Ratcliffe LE, Simpson JE, Heath PR, Ince PG, Wharton SB. Review: astrocytes in Alzheimer's disease and other age associated dementias: a supporting player with a central role. *Neuropath Appl Neurobiol* 2017 l; **43**: 281–98
49 Simpson JE, Ince PG, Haynes LJ, Theaker R, Gelsthorpe C, Baxter L, Forster G, Lace GL, Shaw PJ, Matthews FE, Savva GM, Brayne C, Wharton SB. Population variation in oxidative stress and astrocyte DNA damage in relation to Alzheimer-type pathology in the ageing brain. *Neuropath Appl Neurobiol* 2010; **36**: 25–40
50 Simpson JE, Ince PG, Shaw PJ, Heath PR, Raman R, Garwood CJ, Gelsthorpe C, Baxter L, Forster G, Matthews FE, Brayne C, Wharton SB. Microarray analysis of the astrocyte transcriptome in the aging brain: relationship to Alzheimer's pathology and APOE genotype. *Neurobiol Aging* 2011; **32**: 1795–807
51 Akiyama H, Mori H, Saido T, Kondo H, Ikeda K, McGeer PL. Occurrence of the diffuse amyloid beta-protein (Abeta) deposits with numerous Abeta-containing glial cells in the cerebral cortex of patients with Alzheimer's disease. *Glia* 1999; **25**: 324–31
52 Mackenzie IR, Hao C, Munoz DG. Role of microglia in senile plaque formation. *Neurobiol Aging* 1995; **16**: 797–804

53 Carare RO, Hawkes CA, Jeffrey M, Kalaria RN, Weller RO. Review: cerebral amyloid angiopathy, prion angiopathy, CADASIL and the spectrum of protein elimination failure angiopathies (PEFA) in neurodegenerative disease with a focus on therapy. *Neuropathol Appl Neurobiol* 2013; **39**: 593–611
54 Nestor PJ, Fryer TD, Hodges JR. Declarative memory impairments in Alzheimer's disease and semantic dementia. *NeuroImage* 2006; **3**: 1010–20
55 Braak H, Feldengut S, Del Tredici K. Pathogenesis and prevention of Alzheimer's disease. When and in what way does the pathological process begin? *Nervenarzt* 2013; **84**: 477–82
56 Shepherd A, Tyebji S, Hannan AJ, Burrows EJ. Translational assays for assessment of cognition in rodent models of Alzheimer's disease and dementia. *J Mol Neurosci* 2016; **60**: 371–82
57 Webster SJ, Bachstetter AD, Nelson PT, Schmitt FA, Van Eldik LJ. Using mice to model Alzheimer's dementia: an overview of the clinical disease and the preclinical behavioral changes in 10 mouse models. *Front Genet* 2014; **5**: 1–23
58 Morris RGM. Spatial localisation does not require the presence of local cues. *Learn Motiv* 1981; **12**: 239–60
59 Morris R. Developments of a water-maze procedure for studying spatial learning in the rat. *J Neurosci Methods* 1984; **11**: 47–60
60 Olton DS, Samuelson RJ. Remembrance of places passed – spatial memory in rats. *J Exp Psychol* 1976; **2**: 97–116
61 Rawlins JN, Olton DS. The septo-hippocampal system and cognitive mapping. *Behav Brain Res* 1982; **5**: 331–58
62 Ennaceur A, Delacour J. A new one-trial rest for neurobiological studies of memory in rats. 1: behavioral data. *Behav Brain Res* 1988; **31**: 47–59
63 Hammond RS, Tull LE, Stackman RW. On the delay-dependent involvement of the hippocampus in object recognition memory. *Neurobiol Learn Mem* 2004; **82**: 26–34
64 Games D, Adams D, Alessandrini R, Barbour R, Berthelette P, Blackwell C, Carr T, Clemens J, Donaldson T, Gillespie F, Guido T, Hagopian S, Johnsonwood K, Khan K, Lee M, Leibowitz P, Lieberburg I, Little S, Masliah E, McConlogue L, Montoyazavala M, Mucke L, Paganini L, Penniman E, Power M, Schenk D, Seubert P, Snyder B, Soriano F, Tan H, Vitale J, Wadsworth S, Wolozin B, Zhao J. Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. *Nature* 1995; **373**: 523–7
65 Masliah E, Sisk A, Mallory M, Games D. Neurofibrillary pathology in transgenic mice overexpressing V717F β-amyloid precursor protein. *J Neuropathol Exp Neurol* 2001; **60**: 357–68
66 Irizarry MC, Soriano F, McNamara M, Page KJ, Schenk D, Games D, Hyman BT. Abeta deposition is associated with neuropil changes, but not with overt neuronal loss in the human amyloid precursor protein V717F (PDAPP) transgenic mouse. *J Neurosci* 1997; **17**: 7053–9
67 Chen GQ, Chen KS, Knox J, Inglis J, Bernard A, Martin SJ, Justice A, McConlogue L, Games D, Freedman SB, Morris RGM. A learning deficit related to age and beta amyloid plaques in a mouse model of Alzheimer's disease. *Nature* 2000; **408**: 975–9
68 Dodart JC, Meziane H, Mathis C, Bales KR, Paul SM, Ungerer A. Behavioral disturbances in transgenic mice overexpressing the V717F beta-amyloid precursor protein. *Behav Neurosci* 1999; **113**: 982–90
69 Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G. Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. *Science* 1996; **274**: 99–102
70 Kawarabayashi T, Younkin LH, Saido TC, Shoji M, Ashe KH, Younkin SG. Age-dependent changes in brain, CSF, and plasma amyloid (beta) protein in the Tg2576 transgenic mouse model of Alzheimer's disease. *J Neurosci* 2001; **21**: 372–81
71 Irizarry MC, McNamara M, Fedorchak K, Hsiao K, Hyman BT. APPSw transgenic mice develop age-related Abeta deposits and neuropil abnormalities, but no neuronal loss in CA1. *J Neuropathol Exp Neurol* 1997; **56**: 965–73
72 Frautschy SA, Yang F, Irrizarry M, Hyman B, Saido TC, Hsiao K, Cole GM. Microglial response to amyloid plaques in APPsw transgenic mice. *Am J Pathol* 1998; **152**: 307–17
73 King DL, Arendash GW. Maintaining synaptophysin immunoreactivity in Tg2576 transgenic mice during aging: correlations with cognitive impairment. *Brain Res* 2002; **926**: 58–68
74 Takeuchi A, Irizarry MC, Duff K, Saido TC, Hsiao Ashe K, Hasegawa M, Mann DM, Hyman BT, Iwatsubo T. Age-related amyloid beta deposition in transgenic mice overexpressing both Alzheimer mutant presenilin 1 and amyloid beta precursor protein Swedish mutant is not associated with global neuronal loss. *Am J Pathol* 2000; **157**: 331–9
75 Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, Younkin L, Good MA, Bliss TV, Hyman BT, Younkin SG, Hsiao KK. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. *Nat Neurosci* 1999; **2**: 271–6
76 Westerman MA, Cooper-Blacketer D, Mariash A, Kotilinek L, Kawarabayashi T, Younkin LH, Carlson GA, Younkin SG, Ashe KH. The relationship between Abeta and memory in the Tg2576 mouse model of Alzheimer's disease. *J Neurosci* 2002; **22**: 1858–67

77 Oules B, Del Prete D, Greco B, Zhang X, Lauritzen I, Sevalle J, Moreno S, Paterlini-Brechot P, Trebak M, Checler F, Benfenati F, Chami M. Ryanodine receptor blockade reduces amyloid-beta load and memory impairments in Tg2576 mouse model of Alzheimer disease. *J Neurosci* 2012; **32**: 11820–34
78 Lalonde R, Lewis TL, Strazielle C, Kim H, Fukuchi K. Transgenic mice expressing the betaAPP695SWE mutation: effects on exploratory activity, anxiety, and motor coordination. *Brain Res* 2003; **977**: 38–45
79 Alexander G, Hanna A, Serna V, Younkin L, Younkin S, Janus C. Increased aggression in males in transgenic Tg2576 mouse model of Alzheimer's disease. *Behav Brain Res* 2011; **216**: 77–83
80 Andra K, Abramowski D, Duke M, Probst A, Wiederhold KH, Burki K, Goedert M, Sommer B, Staufenbiel M. Expression of APP in transgenic mice: a comparison of neuron-specific promoters. *Neurobiol Aging* 1996; **17**: 183–90
81 Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mistl C, Rothacher S, Ledermann B, Burki K, Frey P, Paganetti PA, Waridel C, Calhoun ME, Jucker M, Probst A, Staufenbiel M, Sommer B. Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. *Proc Natl Acad Sci USA* 1997; **94**: 13287–92
82 Beckmann N, Schuler A, Mueggler T, Meyer EP, Wiederhold KH, Staufenbiel M, Krucker T. Age-dependent cerebrovascular abnormalities and blood flow disturbances in APP23 mice modeling Alzheimer's disease. *J Neurosci* 2003; **23**: 8453–9
83 Mueggler T, Sturchler-Pierrat C, Baumann D, Rausch M, Staufenbiel M, Rudin M. Compromised hemodynamic response in amyloid precursor protein transgenic mice. *J Neurosci* 2002; **22**: 7218–24
84 Calhoun ME, Wiederhold KH, Abramowski D, Phinney AL, Probst A, Sturchler-Pierrat C, Staufenbiel M, Sommer B, Jucker M. Neuron loss in APP transgenic mice. *Nature* 1998; **395**: 755–6
85 Van Dam D, D'Hooge R, Staufenbiel M, Van Ginneken C, Van Meir F, De Deyn PP. Age-dependent cognitive decline in the APP23 model precedes amyloid deposition. *Eur J Neurosci* 2003; **17**: 388–96.
86 Huang SM, Mouri A, Kokubo H, Nakajima R, Suemoto T, Higuchi M, Matthias Staufenbiel M, Noda Y, Yamaguchi H, Nabeshima T, Saido TC, Iwata N. Neprilysin-sensitive synapse-associated amyloid-beta peptide oligomers impair neuronal plasticity and cognitive function. *J Biol Chem* 2006; **281**: 17941–51
87 Vloeberghs E, Van Dam D, Coen K, Staufenbiel M, De Deyn PP. Aggressive male APP23 mice modelling behavioral alterations in dementia. *Behav Neurosci* 2006; **120**: 1380–3.
88 Janus C, Pearson J, McLaurin J, Mathews PM, Jiang Y, Schmidt SD, Chishti MA, Horne P, Heslin D, French J, Mount HT, Nixon RA, Mercken M, Bergeron C, Fraser PE, St George-Hyslop P, Westaway D. A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. *Nature* 2000; **408**: 979–82
89 Chishti MA, Yang DS, Janus C, Phinney AL, Horne P, Pearson J, Strome R, Zuker N, Loukides J, French J, Turner S, Lozza G, Grilli M, Kunicki S, Morissette C, Paquette J, Gervais F, Bergeron C, Fraser PE, Carlson GA, St George-Hyslop P, Westerway D. Early-onset amyloid deposition and cognitive deficits in transgenic mice expressing a double mutant form of amyloid precursor protein 695. *J Biol Chem* 2001; **276**: 21562–70
90 Chauhan NB, Siegel GJ, Lichtor T. Effect of age on the duration and extent of amyloid plaque reduction and microglial activation after injection of anti-Abeta antibody into the third ventricle of TgCRND8 mice. *J Neurosci Res* 2004; **78**: 732–41
91 Janus C. Search strategies used by APP transgenic mice during spatial navigation in the Morris water maze. *Learn Mem* 2004; **11**: 337–46
92 Ambree O, Richter H, Sachser N, Lewejohann L, Dere E, De Souza Silva MA, Herring A, Keyvani K, Paulus W, Schabitz W-R. Levodopa ameliorates learning and memory deficits in a murine model of Alzheimer's disease. *Neurobiol Aging* 2009; **30**: 1192–204
93 Hyde LA, Kazdoba TM, Grilli M, Lozza G, Brusa R, Zhang Q, Wong GT, McCool MF, Zhang L, Parker EM, Higgins GA. Age-progressing cognitive impairments and neuropathology in transgenic CRND8 mice. *Behav Brain Res* 2005; **160**: 344–55
94 Bomben V, Holth J, Reed J, Cramer P, Landreth G, Noebels J. Bexarotene reduces network excitability in models of Alzheimer's disease and epilepsy. *Neurobiol Aging* 2014; **35**: 2091–5
95 Ongali B, Nicolakakis N, Tong X-K, Aboulkassim T, Papadopoulos P, Rosa-Neto P, Lecrux C, Imboden H, Hamel E. Angiotensin II type 1 receptor blocker losartan prevents and rescues cerebrovascular, neuropathological and cognitive deficits in an Alzheimer's disease model. *Neurobiol Dis* 2014; **68**: 126–36
96 Royea J, Zhang L, Tong X-K, Hamel E. Angiotensin IV receptors mediate the cognitive and cerebrovascular benefits of losartan in a mouse model of Alzheimer's disease. *J Neurosci* 2017; **37**: 5562–73
97 Karl T, Bhatia S, Cheng D, Kim WS, Garner B. Cognitive phenotyping of amyloid precursor protein transgenic J20 mice. *Behav Brain Res* 2012; **228**: 392–7
98 Cisse M, Sanchez PE, Kim DH, Ho K, Yu GQ, Mucke L. Ablation of cellular prion protein does not ameliorate abnormal neural network activity or cognitive dysfunction in the J20 line of human amyloid precursor protein transgenic mice. *J Neurosci* 2011; **31**: 10427–31
99 Escribano L, Simon AM, Perez-Mediavilla A, Salazar-Colocho P, Del Rio J, Frechilla D. Rosiglitazone

reverses memory decline and hippocampal glucocorticoid receptor down-regulation in an Alzheimer's disease mouse model. *Biochem Biophys Res Commun* 2009; **379**: 406–10

100 Palop JJ, Jones B, Kekonius L, Chin J, Yu GQ, Raber J, Masliah E, Mucke L. Neuronal depletion of calcium dependent proteins in the dentate gyrus is tightly linked to Alzheimer's disease-related cognitive deficits. *Proc Natl Acad Sci USA* 2003; **100**: 9572–7

101 Beauquis J, Vinuesa A, Pomilio C, Pav P, Galvan V, Saravia F. Neuronal and glial alterations, increased anxiety, and cognitive impairment before hippocampal amyloid deposition in PDAPP mice, model of Alzheimer's disease. *Hippocampus* 2014; **24**: 257–69

102 De Strooper B. Aph-1, Pen-2, and nicastrin with presenilin generate an active gamm-Secretase complex. *Neuron* 2003; **38**: 9–12

103 Francis R, McGrath G, Zhang J, Ruddy DA, Sym M, Apfeld J, Nicoll M, Maxwell M, Hai B, Ellis MC, Parks AL, Xu W, Li J, Gurney M, Myers RL, Himes CS, Hiebsch R, Ruble C, Nye JS, Curtis D. aph-1 and pen-2 are required for Notch pathway signalling, gamma-secretase cleavage of betaAPP, and presenilin protein accumulation. *Dev Cell* 2002; **3**: 85–97

104 Holcomb LA, Gordon MN, Jantzen P, Hsiao K, Duff K, Morgan D. Behavioral changes in transgenic mice expressing both amyloid precursor protein and presenilin-1 mutations: lack of association with amyloid deposits. *Behav Genet* 1999; **29**: 177–85

105 Arendash GW, King DL, Gordon MN, Morgan D, Hatcher JM, Hope CE, Diamond DM. Progressive, age-related behavioral impairments in transgenic mice carrying both mutant amyloid precursor protein and presenilin-1 transgenes. *Brain Res* 2001; **891**: 42–53

106 Wang H, He J, Zhang R, Zhu S, Wang J, Kong L, Tan Q, Li X-M. Sensorimotor gating and memory deficits in an APP/PS1 double transgenic mouse model of Alzheimer's disease. *Behav Brain Res* 2012; **233**: 237–43

107 Luo Y, Bolon B, Damore MA, Fitzpatrick D, Liu H, Zhang J, Yan Q, Vasser R, Citron M. BACE1 (beta-secretase) knockout mice do not acquire compensatory gene expression changes or develop neural lesions over time. *Neurobiol Dis* 2003; **14**: 81–8

108 Ohno M, Sametsky EA, Younkin LH, Oakley H, Younkin SG, Citron M, Vassar R, Disterhoft JF. BACE1 deficiency rescues memory deficits and cholinergic dysfunction in a mouse model of Alzheimer's disease. *Neuron* 2004; **41**: 27–33

109 de Calignon A, Polydoro M, Sua′rez-Calvet M, William C, Adamowicz DH, Kopeikina KJ, Pitstick R, Sahara N, Ashe KH, Carlson GA, Spires-Jones TL, Hyman BT. Propagation of tau pathology in a model of early Alzheimer's disease. *Neuron* 2012; **73**: 685–97

110 Iba M, McBride JD, Guo JL, Zhang B, Trojanowski JQ, Lee VM-Y. Tau pathology spread in PS19 tau transgenic mice following locus coeruleus (LC) injections of synthetic tau fibrils is determined by the LC's afferent and efferent connections. *Acta Neuropathol* 2015; **130**: 349–62

111 Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, Hardy J, Hutton M, McGowan E. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. *Science* 2001; **293**: 1487–91

112 Yuzwa SA, Shan X, Jones BA, Zhao G, Woodward ML, Li X, Yanping Zhu Y, McEachern EJ, Silverman MA, Watson NW, Gong C-X, Vocadlo DJ. Pharmacological inhibition of O-GlcNAcase (OGA) prevents cognitive decline and amyloid plaque formation in bigenic tau/APP mutant mice. *Mol Neurodegener* 2014; **9**: 1–14

113 Ribe EM, Perez M, Puig B, Gich I, Lim F, Cuadrado M, Sesma T, Catena S, Sanchez B, Nieto M, Gomez-Ramos P, Moran MA, Cabodevilla F, Samaranch L, Ortiz L, Perez A, Ferrer I, Avila J, Gomez-Isla T. Accelerated amyloid deposition, neurofibrillary degeneration and neuronal loss in double mutant APP/tau transgenic mice. *Neurobiol Dis* 2005; **20**: 814–22

114 Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron* 2003; **39**: 409–21

115 Billings LM, Oddo S, Green KN, McGaugh JL, LaFerla FM. Intraneuronal Abeta causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. *Neuron* 2005; **45**: 675–88

116 Davis KE, Easton A, Eacott MJ, Gigg J. Episodic-like memory for what-where-which occasion is selectively impaired in the 3xtTgAD mice mouse model of Alzheimer's disease. *J Alzheimers Dis* 2013; **33**: 681–98

117 Davis KE, Burnett K, Gigg J. Water and T-maze protocols are equally efficient methods to assess spatial memory in 3xTg Alzheimer's disease mice. *Behav Brain Res* 2017; **331**: 54–66

118 Van Dam D, De Deyn PP. Animal models in the drug discovery pipeline for Alzheimer's disease. *Br J Pharmacol* 2011; **164**: 1285–300.

119 Bard F, Cannon C, Barbour R, Burke RL, Games D, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Lieberburg I, Motter R, Nguyen M, Soriano F, Vasquez N, Weiss K, Welch B, Seubert P, Schenk D, Yednock T. Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat Med* 2000; **6**: 916–19

120 Vellas B, Black R, Thal LJ, Fox NC, Daniels M, McLennan G, Tompkins C, Leibman C, Pomfret M, Grundman M. Long-term follow-up of patients immunized with AN1792: reduced functional decline in antibody responders. *Curr Alzheimer Res* 2009; **6**: 144–51
121 Abushouk AI, Elmaraezy A, Aglan A, Salama R, Fouda S, Fouda R, AlSafadi AM. Bapineuzumab for mild to moderate Alzheimer's disease: a meta-analysis of randomized controlled trials. *BMC Neurol* 2017; **17**: 1–13
122 Hawkes N. Promise of new Alzheimer's drug is dashed after lack of evidence. *BMJ* 2016; **355**: i6362
123 Fukumoto H, Takahashi H, Tarui N, Matsui J, Tomita T, Hirode M, Sagayama M, Maeda R, Kawamoto M, Hirai K, Terauchi J, Sakura Y, Kakihana M, Kato K, Iwatsubo T, Miyamoto M. A noncompetitive BACE1 inhibitor TAK-070 ameliorates Abeta pathology and behavioral deficits in a mouse model of Alzheimer's disease. *J Neurosci* 2010; **30**: 11157–66
124 Mullard A. BACE inhibitor bust in Alzheimer trial. *Nat Rev Drug Discov* 2017; **16**: 155
125 Hung S-Y, Fu W-M. Drug candidates in clinical trials for Alzheimer's disease. *J Biomed Sci* 2017; **24**: 47
126 Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Muller FJ, Loring JF, Yamasaki TR, Poon WW, Green KN, LaFerla FM. Neural stem cells improve cognition *via* BDNF in a transgenic model of Alzheimer disease. *Proc Natl Acad Sci USA* 2009; **106**: 13594–9
127 Vann KT, Xiong Z-G. Optogenetics for neurodegenerative diseases. *Int J Physiol Pathophysiol Pharmacol* 2016; **8**: 1–8
128 Ameen-Ali KE, Easton A, Eacott MJ. Moving beyond standard procedures to assess spontaneous recognition memory. *Neurosci Biobehav Rev* 2015; **53**: 37–51
129 Reid IC, Morris RG. The enigma of olfactory learning. *Trends Neurosci* 1993; **16**: 17–20
130 Gerlai R, Clayton NS. Analysing hippocampal function in transgenic mice: an ethological perspective. *Trends Neurosci* 1999; **22**: 47–51
131 Whishaw IQ, Tomie J. Of mice and mazes: similarities between mice and rats on dry land but not water mazes. *Physiol Behav* 1996; **60**: 1191–7
132 Bergado JA, Almaguer W, Rojas Y, Capdevila V, Frey JU. Spatial and emotional memory in aged rats: a behavioral-statistical analysis. *Neuroscience* 2011; **172**: 256–69
133 Schmitz C, Rutten BP, Pielen A, Schafer S, Wirths O, Tremp G, Czech C, Blanchard V, Multhaup G, Rezaie P, Korr H, Steinbusch HWM, Pradier L, Bayer TA. Hippocampal neuron loss exceeds amyloid plaque load in a transgenic mouse model of Alzheimer's disease. *Am J Pathol* 2004; **164**: 1495–502
134 Price JL, Morris JC. Tangles and plaques in nondemented aging and 'preclinical' Alzheimer's disease. *Ann Neurol* 1999; **45**: 358–68
135 Gupta A, Iadecola C. Impaired Aβ clearance: a potential link between atherosclerosis and Alzheimer's disease. *Front Aging Neurosci* 2015; **7**: 1–8
136 Onos KD, Sukoff Rizzo SJ, Howell GR, Sasner M. Toward more predictive genetic mouse models of Alzhiemer's disease. *Brian Res Bull* 2016; **122**: 1–11
137 Kim J, Jiang H, Park S, Eltorai AEM, Stewart FR, Yoon H, Basak JM, Finn MB, Holtzman DM. Haploinsufficiency of human APOE reduces amyloid deposition in a mouse model of amyloid-beta amyloidosis. *J Neurosci* 2011; **31**: 18007–12
138 Bien-Ly N, Gillespie AK, Walker D, Yoon SY, Huang Y. Reducing human apolipoprotein E levels attenuates age-dependent Abeta accumulation in mutant human amyloid precursor protein transgenic mice. *J Neurosci* 2012; **32**: 4803–11
139 DeMattos RB, Cirrito JR, Parsadanian M, May PC, O'Dell MA, Taylor JW, Harmony JA, Aronow BJ, Bales KR, Paul SM, Holtzman DM. ApoE and clusterin cooperatively suppress Abeta levels and deposition: evidence that ApoE regulates extracellular Abeta metabolism in vivo. *Neuron* 2004; **41**: 193–202
140 Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, Guillozet-Bongaarts A, Ohno M, Disterhoft J, Van Eldik L, Berry R, Vassar R. Intraneuronal b-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. *J Neurosci* 2006; **26**: 10129–40
141 Radde R, Bolmont T, Kaeser SA, Coomaraswamy J, Lindau D, Stoltze L, Calhoun ME, Jäggi F, Wolburg H, Gengler S, Haass C, Ghetti B, Czech C, Holscher C, Mathews PM, Jucker M. Abeta42- driven cerebral amyloidosis in transgenic mice reveals early and robust pathology. *EMBO Rep* 2006; **7**: 940–6
142 Ulrich JD, Finn MB, Wang Y, Shen A, Mahan TE, Jiang H, Stewart FR, Piccio L, Colonna M, Holtzman DM. Altered microglial response to Ab plaques in APPPS1-21 mice heterozygous for TREM2. *Mol Neurodegener* 2014; **9**: 20
143 Jay TR, Miller CM, Cheng PJ, Graham LC, Bemiller S, Broihier ML, Xu G, Margevicius D, Karlo JC, Sousa GL, Cotleur AC, Butovsky O, Bekris L, Staugaitis SM, Leverenz JB, Pimplikar SW, Landreth GE, Howell GR, Ransohoff RM, Lamb BT. TREM2 deficiency eliminates TREM2 + inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. *J Exp Med* 2015; **212**: 287–95
144 Wang Y, Cella M, Mallinson K, Ulrich JD, Young KL, Robinette ML, Gilfillan S, Krishnan GM, Sudhakar S, Zinselmeyer BH, Holtzman DM, Cirrito JR, Colonna M. TREM2 lipid sensing sustains the microglial

response in an Alzheimer's disease model. *Cell* 2015; **160**: 1061–71

145 Bussey TJ, Saksida LM, Rothblat LA. Discrimination of computer- graphic stimuli by mice: a method for the behavioral characterization of transgenic and gene-knockout models. *Behav Neurosci* 2001; **115**: 957–60

146 Romberg C, Horner AE, Bussey TJ, Saksida LM. A touch screen-automated cognitive test battery reveals impaired attention, memory abnormalities, and increased response inhibition in the TgCRND8 mouse model of Alzheimer's disease. *Neurobiol Aging* 2013; **34**: 731–44

147 Dubal DB, Broestl L, Worden K. Sex and gonadal hormones in mouse models of Alzheimer's disease: what is relevant to the human condition? *Biol Sex Differ* 2012; **2**: 1–17

148 Sander JD, Joung JK. CRISPR-Cas systems for editing, regulating and targeting genomes. *Nat Biotechnol* 2014; **32**: 347–55

Received 12 June 2017
Accepted after revision 4 September 2017
Published online Article Accepted on 7 September 2017