Animal models of Alzheimer's disease and frontotemporal dementia

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Abstract | Insoluble protein aggregates have been linked to Alzheimer's disease (AD) and frontotemporal dementia (FTD). Recent work in transgenic mice has shed light on the role of these aggregates by identifying soluble oligomeric species that may interfere with essential cellular mechanisms at an early disease stage. This review summarizes what we have learned about the roles of these proteins from transgenic mice and invertebrate species such as flies and worms. Proteomic and transcriptomic analyses of tissue from these animal models have identified new molecules with crucial roles in disease. Moreover, transgenic animals have been instrumental in defining drug targets and designing novel therapeutic strategies. With advanced imaging techniques that can be used in both humans and mice an early, preclinical diagnosis of AD and FTD could be within reach.

Nucleus basalis of Meynert
A group of cholinergic nerve cells in the basal forebrain, with numerous projections to the cortex.

Disinhibition
A reduced capacity to control and coordinate the immediate impulsive response to a distinct situation.

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Dementia is defined as a loss of intellectual abilities that is severe enough to interfere with social or occupational functioning. Alzheimer's disease (AD) is the most common cause of dementia, comprising 50–70% of all cases. Frontotemporal dementia (FTD) is less common, but makes up 50% of dementia cases presenting before age 60 (REF. 1). At present neither can be cured.

Drugs that are currently prescribed for AD can have severe side-effects in patients with FTD[2]. Furthermore, FTD itself includes several clinical entities that require better biochemical characterization. Therefore, it is imperative to develop tools that enable an early, differential diagnosis.

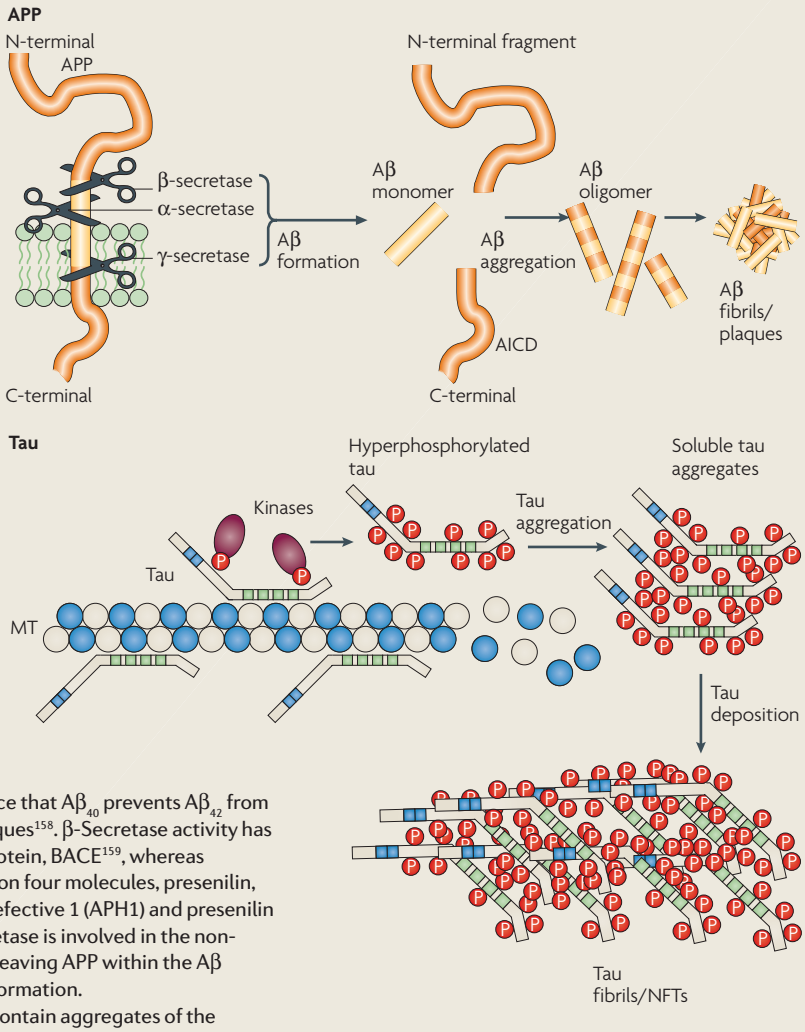
Animal models have been useful in dissecting the pathogenic mechanisms of AD and FTD. Here we introduce the neuropathology, genetics and clinical features of AD and FTD, and describe what we have learned about these diseases from transgenic vertebrate and invertebrate models. This Review focuses on recent developments and aims to integrate functional genomics, novel imaging techniques and new concepts in therapy.

A brief overview of AD and FTD

Clinical features. AD is characterized by early memory deficits, followed by the gradual erosion of other cognitive functions. The most severe neuropathological changes occur in the hippocampus, followed by the association cortices and subcortical structures, including the amygdala and nucleus basalis of Meynert[3]. In contrast to AD, which is characterized predominantly by memory loss, FTD is associated mainly with behavioural impairment such as disinhibition, loss of initiative or apathy. Loss of interest in the environment, severe loss in judgement and insight, negligence of personal hygiene, verbal and physical aggressiveness, alcohol abuse, restlessness, hyperorality and stereotypical behaviour are additional features of FTD[4]. The average age of diagnosis of FTD is about 60, which is around 10 years before the average sporadic AD (SAD) patient is diagnosed[5,6]. Patients with FTD often display asymmetrical atrophy of the frontal and temporal cortex. There is evidence that motor neuron disease and FTD coexist, and that the motor symptoms might precede, coincide or follow the development of cognitive and behavioural changes[1]. Furthermore, late-onset parkinsonism is observed in a significant subset of patients with FTD.

Neuropathology. The AD brain is characterized by massive neuronal cell and synapse loss at specific sites[7], as well as β-amyloid plaques and neurofibrillary lesions. The major protein component of plaques is the polypeptide Aβ that is derived from amyloid precursor protein (APP; BOX 1). The neurofibrillary lesions contain hyperphosphorylated aggregates of the microtubule-associated protein tau and are found in cell bodies and apical dendrites as neurofibrillary tangles (NFTs), in distal dendrites as neuropil threads, and in the abnormal neurites that are associated with some β-amyloid plaques. NFTs are also abundant in FTD, in which there is an absence of overt plaques[8].

Box 1 | **APP processing and tau phosphorylation**



β-Amyloid plaques and neurofibrillary tangles (NFTs) are hallmark lesions of Alzheimer's disease (AD). The major protein component of the plaques is a 40–42 amino acid polypeptide termed Aβ ($Aβ_{40}$ and $Aβ_{42}$), that is derived by proteolytic cleavage from the amyloid precursor protein, APP[155,156] (see figure, top). β-Secretase generates the amino terminus of Aβ and γ-secretase dictates its length, with $Aβ_{40}$ being the more common and $Aβ_{42}$ the more fibrillogenic and neurotoxic species. Aβ forms toxic oligomeric aggregates and eventually deposits as plaques. Additional products of APP processing are an N-terminal fragment that is released by shedding, and the Aβ intracellular cytoplasmic domain (AICD)[7]. $Aβ_{42}$-transgenic mice develop plaques, whereas $Aβ_{40}$-transgenic mice do not[157]. There is further evidence that $Aβ_{40}$ prevents $Aβ_{42}$ from aggregating and forming plaques[158]. β-Secretase activity has been attributed to a single protein, BACE[159], whereas γ-Secretase activity depends on four molecules, presenilin, nicastrin, anterior pharynx-defective 1 (APH1) and presenilin enhancer 2 (PEN2)[160]. α-Secretase is involved in the non-amyloidogenic pathway by cleaving APP within the Aβ domain, thus precluding Aβ formation.

The neurofibrillary lesions contain aggregates of the microtubule (MT)-associated protein tau. Under physiological conditions tau is mainly localized to the axon for stabilization of MTs[161]. In tauopathies such as progressive supranuclear palsy or corticobasal degeneration, tau also forms aggregates in non-neuronal cells[39]. Tau is a phosphoprotein owing to its high numbers of serine and threonine residues, and is therefore a substrate of many kinases (see also FIG. 3). Under pathological conditions, tau is hyperphosphorylated, which means that it is phosphorylated to a higher degree at physiological sites, as well as at additional 'pathological' sites (see figure, bottom)[39]. Hypophosphorylated tau dissociates from MTs, causing them to depolymerize, while tau is deposited in aggregates such as NFTs. There is increasing evidence that at early stages of the disease toxicity is exerted by soluble and lower order Aβ and tau species rather than by Aβ plaques and NFTs.

Genetics. In familial AD (FAD), which accounts for less than 1% of the total number of AD cases, autosomal dominant mutations have been identified in three genes: *APP*, *presenilin 1* (*PSEN1*) and *presenilin 2* (*PSEN2*). The presenilins are components of the proteolytic γ-secretase complex that, together with β-secretase, generates Aβ. By contrast, α-secretase activity precludes Aβ formation (BOX 1). Most FAD cases are caused by mutations in *PSEN1* and *PSEN2*, of which over 130 have been identified. Of the more than 20 pathogenic mutations that have been identified in *APP*, several, including the V717I 'London' mutation[9], V717F 'Indiana' mutation[10], K670D/M671L 'Swedish or APP^{swe}' mutation[11] and E693G 'Arctic' mutation[12], have been expressed in transgenic mice (FIG. 1 and Supplementary Information S1 (table)). In SAD, various susceptibility genes have been identified, including *apolipoprotein E* (*APOE*)[13]. Other than age of onset, the clinical and histopathological features of early-onset FAD cannot be discriminated from those of late-onset SAD.

Although no mutations in the gene encoding tau, *MAPT*, have been identified in patients with AD, both exonic and intronic mutations in *MAPT* have been found in patients with FTD with Parkinsonism linked to chromosome 17 (FTDP-17)[14–16]. The discovery of these mutations established that tau dysfunction can cause neurodegeneration and dementia. Of the 42 known mutations in *MAPT*[17], several have been expressed in

Autosomal dominance
An inheritance pattern in which an abnormal copy of a gene from one parent gives rise to the trait, even though the copy inherited from the other parent is normal.

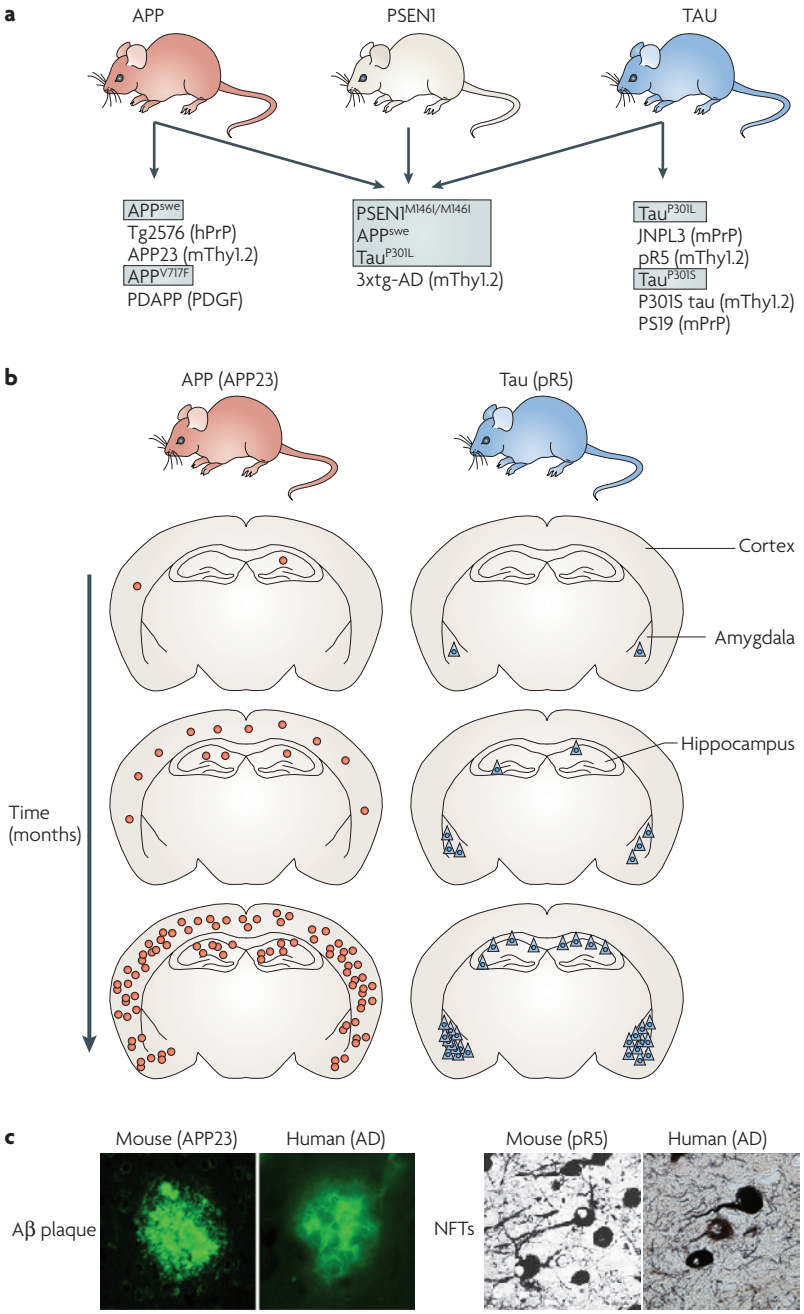


Figure 1 | **Reproducing plaques and NFTs in transgenic mice. a** | Plaques are produced by expressing mutant amyloid precursor protein (APP), as found in patients with familial Alzheimer's disease (FAD), both with and without mutant *PSEN1*, and neurofibrillary tangles (NFTs) are produced by expressing mutant tau, as found in patients with frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). A few exemplary mutations are listed (grey boxes) together with their strain names and the promoters (in brackets) that were used for expression (strains reviewed in REF. 31). More strains are listed in the Supplementary information S1. **b** | Progression of the pathology in APP23 and pR5 mice. NFT formation in pR5 mice is initiated in the amygdala and eventually found in the hippocampus, whereas the cortex is virtually spared. Plaque formation in the APP23 mice is prominent in the cortex and in the hippocampus. This reflects, to some extent, the situation in the brain of patients with AD, in which plaques and NFTs are anatomically separated. **c** | Representative Aβ plaques from an APP23 and a human AD brain visualized with the dye thioflavin S are shown on the left. For comparison, NFTs from a pR5 and a human AD brain, visualized with the Gallyas silver impregnation technique, are shown on the right. These images highlight the similarities of the brain lesions in transgenic mice and in patients with AD.

transgenic mice (FIG. 1 and Supplementary Information S1 (table)). These include N279K, ΔK280, P301L, P301S, V337 and R406W.

The existence of a subgroup of patients with FTD with no tau aggregation was enigmatic for some time. This dementia, characterized by tau-negative and ubiquitin-positive lesions, is now termed FTLD-U or FTDU-17, although the implication of this nomenclature that the lesions in tau-positive FTD are ubiquitin-negative is misleading. Most cases of FTDU-17 are sporadic, yet groundbreaking work showed that FTDU-17 can be caused by loss-of-function mutations in *progranulin* (*PGRN*)[18,19]. Soon after, the TAR DNA-binding protein TDP-43 was identified in ubiquitin-positive inclusions in both FTLD-U and sporadic amyotrophic lateral sclerosis (ALS), suggesting that the pathology of these two disorders overlaps[20]. Mutations in the gene encoding TDP-43, *TARDBP*, in both familial and sporadic cases of ALS have since been identified[21–23]. Similar to tau, the TDP-43 found in the lesions is hyperphosphorylated, ubiquitinated and carboxy-terminally truncated[20].

FTD with inclusion body myopathy and Paget disease of bone is a rare, autosomal-dominant disorder caused by mutations in valosin-containing protein (*VCP*), an essential component of the ER-associated degradation (ERAD) process[24]. TDP-43, but not VCP, accumulates in the ubiquitin-positive inclusions of this disorder. TDP-43 thus seems to be a common pathological substrate in various types of FTLD-U that are caused by different genetic alterations[25]. Neither VCP nor TDP-43 have been expressed in transgenic mice so far, and although *PGRN* knockout mice have been generated, aspects related to FTD have not been addressed[26]. To date, 11 mutations have been identified in *VCP*, 9 in *TARDBP*, 62 in *PGRN* and 42 in *MAPT*[17].

Transgenic mouse models of dementia

The finding that, in the familial forms of AD and FTD, the genes that encode the proteins that are deposited in plaques and NFTs (*APP* and *MAPT*, respectively) are mutated suggested a causal role for these proteins in disease and led to the generation of transgenic animal models[27] (Supplementary Information S1 (table)). Here we focus on the most recent advances and the new insights into the disease that these models have provided. Five recent key publications are highlighted in BOX 2.

Tau models. The first tau transgenic mouse model (Supplementary Information S1 (table)) expressed the longest human wild-type (WT) tau isoform in neurons[28]. Pre-tangle formation and hyperphosphorylation of tau was observed. However, it was another 5 years before the expression of human FTD mutant P301L tau reproduced aggregation and NFT-formation in mice[29,30] (FIG. 1). These mice have become a widely used tool to study disease-related pathogenic mechanisms[27,31] and recent models have built on their success.

In an elegant study, it was shown that suppression of P301L tau expression in rTg4510 tau transgenic mice, which normally express the mutant protein at a

Box 2 | **Selected recent advances provided by animal models**

Tau reduction blocks Aβ-mediated toxicity

Tau pathology in Alzheimer's disease (AD) was thought to be downstream of Aβ. However, slightly higher tau levels increase the AD risk[162]. When human amyloid precursor protein (hAPP)-expressing mice were crossed onto *tau* knockout backgrounds this prevented behavioural deficits, without altering the high Aβ levels[40]. Tau reduction also protected mice against pentylene-tetrazole (PTZ)-mediated excitotoxicity[40]. Reducing tau levels could therefore be a powerful treatment option[40]. Earlier findings in cultured hippocampal neurons derived from *tau*$^{-/-}$ and transgenic mice support this notion[139]. A mechanistic explanation is eagerly awaited.

Common mechanisms of Aβ and prions

Prions are infectious and intracerebral injection causes them to spread in the brain. Intracerebral injections of AD-patient and APP23 transgenic brain extracts induced Aβ deposits in APP23 transgenic mice[163]. Subsequent injections of APP23 and APP/PSEN1 extracts into APP23 and APP/PSEN1 mice resulted in four different types of pathology. This shows that, similar to prion disease[159], exogenously induced amyloidosis depends on both the host and the source of the agent, suggesting the existence of polymorphic Aβ strains reminiscent of prion strains[163].

Inducible transgenic system puts NFTs into perspective

The rTg4510 tau transgenic model examined whether NFT formation is related to functional impairment[32]. These mice express doxycycline-repressible human P301L mutant tau and develop NFTs, neuron loss and behavioural impairment. Following a reduction of transgenic tau, memory function was recovered and the number of neurons stabilized, but NFTs continued to accumulate. This shows that elevated levels of tau impair memory function but that NFTs are not sufficient to cause cognitive decline or neuronal death.

The search for toxic species

Natural Aβ oligomers that disrupt cognitive function in rats[165] were identified, followed by the Aβ*56 species in Tg2576 mice[164]. The appearance of Aβ*56 correlated with memory loss at 6 months. Aβ*56 infusion into young rat brains transiently disrupted short-term but not spatial memory. Aβ*56 impaired memory independently of Aβ plaques or neuronal loss, and might contribute to cognitive deficits associated with AD[164]. Aβ*56 has since been correlated with memory impairment in additional APP mouse models[166].

BACE branches out

The role of the β-secretase BACE as a therapeutic target in AD is contradictory. BACE is required to cleave Aβ from its precursor but this study shows that it also has a role in myelinating axons[167]. BACE is required for processing of neuregulin (NRG1), an axonally expressed factor required for glial cell development and myelination[167]and implicated in schizophrenia[168]. It remains to be seen whether BACE has other substrates that are associated with disease[169].

high level, reverses behavioural impairments in these mice, although NFT formation continues[32]. This suggested that soluble tau rather than NFTs, is neurotoxic (BOXES 1,2). It should however be noted that even under these suppressed conditions P301L tau expression was only reduced to levels comparable to other strains of transgenic mice that express P301L tau under control of a non-inducible promoter and develop NFTs (Supplementary Information S1 (table)).

Both oligodendrocytes and astrocytes contain filamentous tau inclusions in patients with FTD. This was modelled *in vivo* by expressing P301L and WT human tau under the control of the 2′,3′-cyclic nucleotide 3′-phosphodiesterase and glial fibrillary acidic protein (GFAP) promoters, respectively[33,34]. Both strains presented neuronal dysfunction and axonal degeneration, showing that glial tau pathology also affects neurons.

Neuronal loss is lower in the P301L tau models than in P301S tau mice, consistent with the early onset of FTD in patients carrying the P301S mutation[35] (FIG. 1). In one P301S strain, in which the mouse prion protein (PrP) promoter was used, tau expression caused pronounced neuronal loss in several brain areas and ventricular enlargement, as in patients with FTD[36]. Impaired synaptic function and synapse loss preceded neurodegeneration by several months. Furthermore, the increased cytokine expression and early microglial activation seen in this model suggests that neuroinflammation might be associated with tau pathology[36,37,38]. In P301S tau mice, tau pathology was attenuated and survival improved upon immunosuppression with FK506[36].

Taken together, these tau transgenic models of FTD proved that FTDP-17 mutations accelerate tau aggregation, and cause nerve-cell dysfunction and loss *in vivo* (Supplementary Information S1 (table)). Furthermore, tau transgenic mice model an important aspect of FTDs such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD): they exhibit glial pathology that affects neuronal function, and hence behavioural read-outs[39]. Finally, these transgenic models are also valuable tools for AD research, as aspects of their pathology such as synapse loss or inflammation are also features of AD.

Modelling the Aβ–tau axis. Mice expressing mutant APP, which reproduce β-amyloid plaque formation and memory impairment, have become the most widely used tool to study AD-related pathogenic mechanisms *in vivo* (FIGS 1,2; Supplementary Information S1 (table)). Aβ can promote a tau pathology, although recent data show that tau reduction blocks Aβ-mediated toxicity[40] (BOX 2). Crossing the APP transgenic strain Tg2576 with the P301L tau transgenic strain JNPL3, or intracerebral injection of the long form of Aβ, $Aβ_{42}$, into a second P301L tau transgenic strain, pR5, increased tau phosphorylation and a pre-existing NFT pathology[30,41]. Similarly, NFT formation was aggravated by infusing JNPL3 mice intracerebrally with brain extracts from aged APP mutant mice (APP23 mice), or by crossing APP23 and JNPL3 mice[42]. This effect could be mediated by the tau kinase glycogen synthase kinase 3β (GSK3β)[43], which also appears to regulate APP processing[44]. Similarly, studies in mice lacking the *cis/trans*-isomerase PIN1, which modulates tau phosphorylation[45], have revealed that this enzyme promotes the cleavage of APP by α-secretase[46]. By combining the expression of APP^{swe} and P301L tau on a $PSEN1^{M146V/-}$ background the 3xtg-AD mouse model was generated; this model closely recapitulates human AD pathology[47] (FIG. 1). Furthermore, a knock-in approach was used to create the APP(SL)PS1KI mice, which combines mutations in *PSEN1* with overexpresssion of a mutant form of human *APP*, resulting in a 50% loss of CA1 neurons at 10 months of age[48]. These combinatorial approaches have proven to be very successful in modelling AD. Although *MAPT* mutations are not found in FAD, expression of FTDP-17 mutant tau together with mutant APP resulted in a complete AD-like pathology in mice, which could not be achieved by mere overexpression of either WT or mutant *APP* alone.

ER-associated degradation (ERAD). Pathway which targets misfolded proteins from the endoplasmic reticulum for degradation by the proteasome.

Pre-tangle
A somatic accumulation of hyperphosphorylated tau without fibrillar deposition. Pre-tangles represent early stages of NFT formation.

Secretase models. By genetically interfering with β- and γ-secretase activity, the role of these enzymes in APP processing, Aβ deposition and memory impairment has been established, with implications for treatment strategies (Supplementary Information S1 (table)). Altering γ-secretase activity by expression of M146L PSEN1 in an APP transgenic background increased $Aβ_{42}$ formation and deposition. Behavioural deficits and neuronal loss were also observed, even before Aβ was deposited[49,50]. Surprisingly, this effect was even more pronounced upon removal of endogenous mouse PSEN1 in PSEN1$^{M146V/-}$ knock-in mice, suggesting that WT PSEN1 is protective[51].

Reducing the activity of the β-secretase BACE by crossing APP transgenic mice onto a *BACE*$^{-/-}$ background reduced Aβ formation and deposition[52,53],

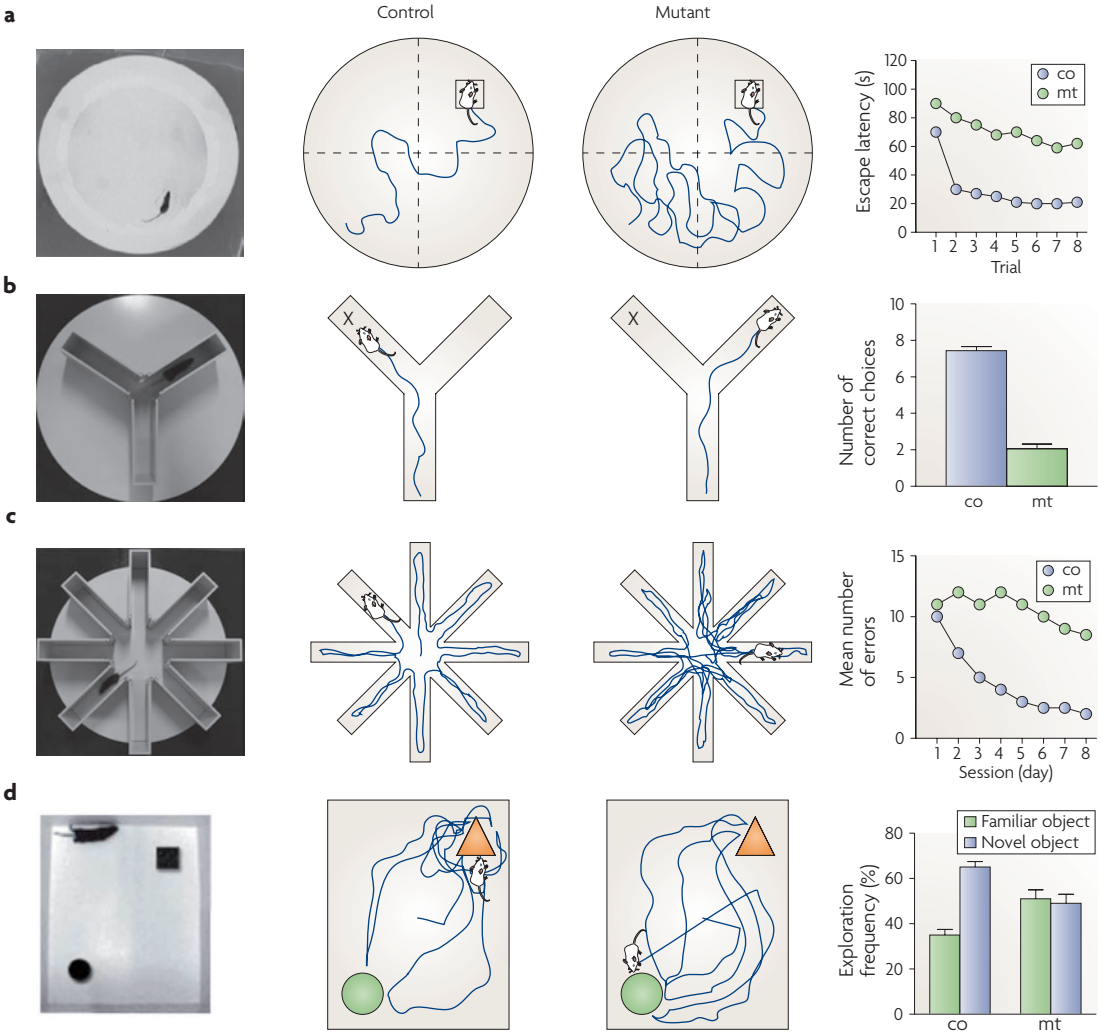


Figure 2 | **Behavioural tests used to assess memory functions in AD mouse models.** Behavioural tests are essential to functionally validate Alzheimer's disease (AD) models and assess treatments. Some routine methods to assess hippocampus-dependent memory functions are shown. **a** | The Morris water maze measures spatial reference memory. Mice are trained in a circular pool filled with an opaque liquid. Distant visual cues are provided for navigation around the pool. A platform is hidden just below the water surface. Mice swim until they find the platform. There are different ways to perform the test and also many parameters to assess memory, including path length and time to find the platform (escape latency). The test can be divided into two phases, an acquisition phase followed by a reversal phase during which the platform is moved to the opposite corner. **b** | The Y-maze measures spatial working memory. One arm is blocked off while the mouse explores the other two arms for about 15 minutes. After several hours, the blocked arm is uncovered and the mouse is allowed to explore the maze. Memory is judged to be better when the mouse does not enter the arm it has entered before but explores the 'novel' arm (X). **c** | The radial arm maze measures short-term working memory. During training, a food pellet is placed at the end of each arm. In the test phase, which is without pellets, the mouse must go down each arm only once to successfully complete the maze, using short-term memory and spatial cues to remember which arms have already been visited. **d** | In the novel object recognition test the mouse is placed in an enclosure where it is exposed to two objects for a defined time. The mouse is removed and later re-tested in the same environment, in which one of the two previously used objects has been replaced with a novel object. The time spent on exploring the new object is recorded and reflects ability to remember what is new and what is old. co, control; mt, mutant.

conversely transgenic BACE overexpression increased Aβ generation and plaque formation in APP/BACE mice[54]. *BACE*-deficiency also reversed the behavioural changes observed in several APP transgenic strains[52,55]. Expression of the α-secretase ADAM10 in APP transgenic mice also reduced Aβ formation, ameliorated behavioural deficits and enhanced LTP impairment, providing *in vivo* evidence for ADAM10 as a functional α-secretase[56].

ApoE models. The allele *APOEε4* is a major risk factor for AD. Crossing APP transgenic PDAPP (platelet-derived growth factor promoter-expressing APP) mice onto an *ApoE*$^{-/-}$ background strongly reduced Aβ levels and deposition in the brain[57], whereas lentiviral delivery of *ApoE4* increased Aβ formation[58]. The state of ApoE lipidation and solubility also impacts on amyloidogenesis[59–61], as shown in three independent studies that crossed different transgenic APP mice with mice lacking ATP-binding cassette transporter A1 (ABCA1), a protein that removes cholesterol and phospholipids from cells (Supplementary Information S1 (table)). *ABCA1*$^{-/-}$ mice have lower cerebral ApoE levels; however, the remnant ApoE is mainly carbonate-insoluble, which increases its amyloidogenic potential[59–61]. Transgenic *ABCA1* overexpression in PDAPP mice significantly reduced Aβ levels and plaque burden[62].

Axonal transport models. Axonal transport along microtubules is mediated by kinesin and dynein proteins[63]. Disrupted axonal transport has been implicated in the pathology of AD and axonal transport defects have been observed in tau and APP transgenic mice[33,64,65]. Moreover, reduction of kinesin light chain in *Klc*$^{+/-}$ mice increased axonal defects and amyloidogenic APP processing when crossed with APP transgenic mice[65]. Both tau and APP might be directly involved in axonal transport: tau regulates motor-protein binding to microtubules and APP links motor proteins to cargos[66–68]. However, to what extent increased tau binding to microtubules contributes to the transport defects in AD[66], is unclear: in AD, tau is hyperphosphorylated, which reduces its association with microtubules[69]. Another possibility is that tau interacts directly with proteins of the motor complex, thereby altering axonal transport[70].

Beyond the rodent models

Studies in fruit flies. Invertebrate models, and in particular the fly, have emerged as a powerful tool for studying neurodegeneration[71]. A dozen different transgenic lines can be generated simultaneously, eliciting some enviousness in researchers working with mice. Here we highlight some of the recent insights into disease pathology that have emerged from this work.

Expression of either WT or R406W human tau in flies produces adult onset, progressive neurodegeneration and premature death, and enhances the accumulation and toxicity of FTDP-17 tau expressed panneuronally or in cholinergic neurons[72]. The neurodegeneration occurs without NFT formation, which is consistent with studies in mice[32] (BOX 2). A neurofibrillary pathology with tau filaments was observed when WT tau-expressing flies co-expressed the *Drosophila melanogaster* GSK3 kinase homologue Shaggy, indicating that increased tau phosphorylation promoted tau filament formation[73]. This study highlights a role for GSK3 in mediating the effects of Aβ on tau in AD[40].

Oxidative stress has been implicated in AD and FTD. Genetic downregulation of antioxidant defence pathways in R406W tau flies enhanced tau toxicity and neuronal death[74]. Administration of the anti-oxidant α-tocopherol (vitamin E) suppressed tau-induced neurotoxicity. In R406W tau flies in which oxidative stress was induced by genetic manipulation of anti-oxidant enzymes, the c-Jun N-terminal kinase (JNK) pathway and the cell cycle were activated[74]. This links oxidative stress to cell-cycle activation and supports the hypothesis that AD might involve a failure of mitosis[75]. Data from WT and R406W tau flies suggest that cell-cycle activation is downstream of tau phosphorylation and that activation of TOR (target of rapamycin kinase) by tau overexpression induced neurodegeneration in a cell-cycle-dependent manner[76]. As Aβ causes oxidative stress these findings also have implications for AD.

From a therapeutic point of view it is unclear whether specific tau kinases and phosphatases, or overall tau phosphorylation should be targeted (FIG. 3). Specific phosphorylation sites in tau have been linked to tau toxicity and NFT formation[30,77], but new work in *D. melanogaster* indicates that multiple phosphorylation sites might work in concert to promote neurotoxicity[78].

Actin-containing Hirano bodies are found in many neurodegenerative diseases and they are predominantly localized to the CA1 region of the hippocampus. R406W tau-induced neurodegeneration was shown to be associated with the accumulation of filamentous actin-containing rods[79], many of which contained cofilin and phosphorylated tau. Rods were also found in the brain of rTg4510 mice, in which tau expression is inducible[79] (Supplementary Information S1 (table)), and the changes in actin structure were shown to occur downstream of tau phosphorylation[79]. The effects of tau were potentiated by Aβ, and this synergistic effect also required tau phosphorylation[79].

In *D. melanogaster*, the protein components of γ-secretase are highly conserved[80], whereas β-secretase activity is very low or absent[81]. An APP-like protein (APPL) is present in flies, although, as in mice, the Aβ domain is not conserved. Transgenic expression of WT or mutated human APP increased cell death in the larval brain[81]. This toxicity depended on both Aβ and the carboxy-terminal tail of APP. Discussions about the relative toxicity of fibrillar, protofibrillar and oligomeric Aβ species are ongoing. The recent development of antibodies that are specific for distinct types of aggregates, might provide a tool to address this question[82–84].

Ubiquilin variants have been associated with an increased risk for SAD[85], but independent studies are awaited to confirm their role. In *D. melanogaster*, overexpression of ubiquilin rescued a degenerative eye phenotype caused by overexpression of presenilin and

Drosophila melanogaster
Often simply termed Drosophila, belongs to the family of fruit-flies and is widely used as a genetic model organism.

Hirano body
Intraneuronal, often rod-like aggregate of actin and associated proteins found in certain neurodegenerative disorders, such as Alzheimer's disease and Creutzfeldt-Jakob disease.

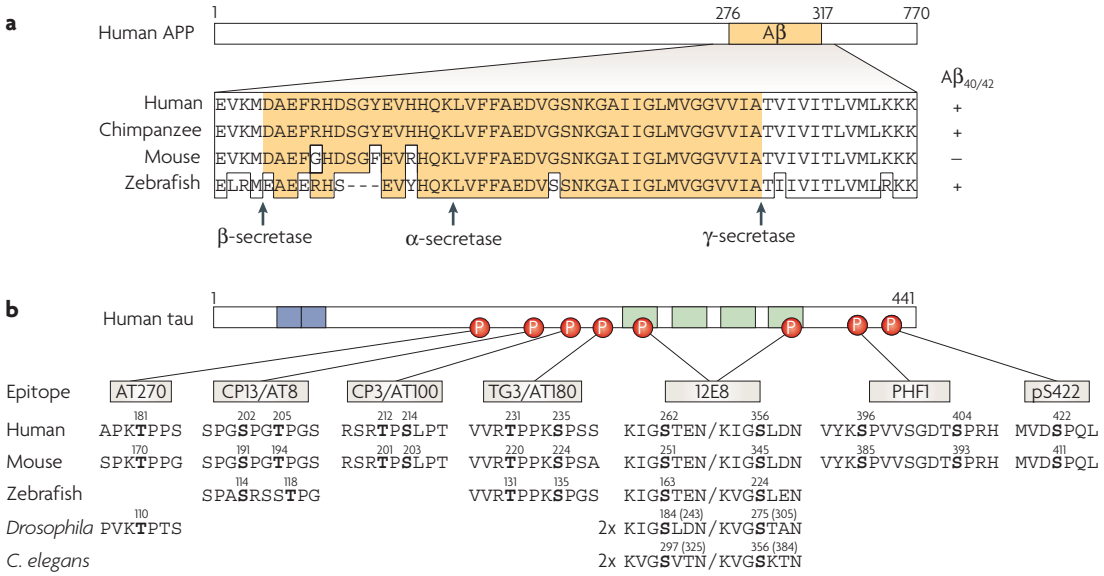


Figure 3 | **Sequence alignment of Aβ and tau from vertebrate and invertebrate species. a** | Sequence alignment of Aβ and flanking sequences from the human, chimpanzee, mouse and zebrafish. Owing to the sequence, all but mouse amyloid precursor protein (APP) can be proteolytically cleaved to form $Aβ_{40/42}$. **b** | The longest human tau isoform, htau40, contains two amino-terminal inserts (blue) and four microtubule-binding domains (green). Routinely used phosphorylation-dependent anti-tau antibodies are listed (grey boxes) along with the respective phosphorylation-site and flanking sequences. As can be seen from the alignment of the tau sequences in five species, mouse and human tau are highly homologous, which explains why most of the phosphorylation-dependent antibodies that are listed react with both human and murine tau.

co-expression of ubiquilin with human APP reduced APP levels[86].

The relative contribution of the two forms of Aβ ($Aβ_{40}$ and $Aβ_{42}$) to disease is a matter of debate. In *D. melanogaster*, $Aβ_{42}$ expression caused the formation of diffuse amyloid deposits, age-dependent learning deficits and neurodegeneration. $Aβ_{40}$ caused similar learning deficits without aggregation and neurodegeneration[87]. Rational mutagenesis applied to the $Aβ_{42}$ peptide confirmed that the rate of aggregate formation *in vitro* is linked to brain toxicity[88]. Furthermore, flies expressing WT $Aβ_{42}$ or E22G $Aβ_{42}$ had a median survival of 24 and 8 days, respectively, whereas $Aβ_{40}$-expressing flies had a median survival of 30 days, indicating that $Aβ_{40}$ is non-toxic and possibly protective[87].

In humans, *PSEN* mutations cause FAD with an age of onset ranging from 24 to 65 years. When *PSEN* mutations were introduced into *D. melanogaster PSEN*, the activities of the mutant presenilins were linked to the age of onset of AD, suggesting that disease severity in humans is caused primarily by the mutations and not by unlinked genetic or epigenetic modifiers[89].

D. melanogaster is an excellent system for drug screening. The flies' short lifespan, combined with their small size and low cost, allows a single laboratory to keep several hundred thousand simultaneously[90]. For example, to develop γ-secretase inhibitors as AD drugs, side-effects related to impaired Notch signalling need to be precluded. The binding site of the γ-secretase inhibitor DAPT is conserved in *D. melanogaster* and DAPT administration causes a phenotype similar to that elicited by mutations in the Notch signalling pathway, suggesting that *D. melanogaster* is a suitable system for *in vivo* pre-screening of candidate γ-secretase inhibitors[91].

Studies in nematodes. *Caenorhabditis elegans* also has a short life span and modifier screens and RNA interference (RNAi) are easier in worms than flies, as they can be grown on agar plates containing genetically modified bacteria. Here we outline some of the ways in which these experiments have enhanced our understanding of AD and FTD.

Expression of WT and mutant tau in *C. elegans* leads to behavioural and synaptic abnormalities, with mutant tau causing an earlier and more severe phenotype[92,93]. The role of the tau ubiquitin-ligase CHIP in the formation of insoluble tau filaments (which was first shown in mice), was confirmed by results of an RNAi-mediated downregulation of CHIP in nematodes[94]. In addition, the *C. elegans* homologue of the cytoskeletal regulatory protein Enabled, UNC-34, was identified by a forward genetic screen for mutations that ameliorate the tau-induced coordination phenotype[95]. *C. elegans* was also instrumental in identifying aph-1 and pen-2 as components of the γ-secretase complex[96].

Egg-laying in *C. elegans* is controlled by a simple motor programme and thus, provides a straightforward read-out of motor behaviour[97]. A defective egg-laying phenotype can be caused by mutations in the *PSEN* homologue, *sel-12*. A suppressor screen revealed that a transcription factor, a histone deacetylase and a histone demethylase could suppress the egg-laying defect and

Rational mutagenesis
Targeted mutation of a gene of interest based on previous analysis (for example, sequence alignment or functional domains/motifs), often using site-directed mutagenesis.

Caenorhabditis elegans
A roundworm (nematode) that has become a major model organism for molecular and developmental biology.

Modifier screen
Screen in which random mutations are introduced into an organism with a pre-existing phenotype, using a mutagen such as *N*-ethyl-*N*-nitrosourea (ENU). Mutants that modify (enhance or suppress) the pre-existing phenotype are then isolated.

RNA interference
(RNAi). A method by which double-stranded RNA is used to cause rapid degradation of endogenous RNA thereby precluding translation. This provides a simple way of studying the effects of the absence of a gene product.

Forward genetic screen
A genetic analysis that proceeds from phenotype to genotype by positional cloning or candidate-gene analysis

hence rescue the mutant presenilin-related phenotype[98]. A relatively high throughput method of assessing egg-laying has been developed by measuring the chitinase that is released by hatching eggs[99].

Animal models and functional genomics

Transcriptomics and proteomics are increasingly being applied to both patients and animal models of AD and FTD, where they have allowed the identification of novel differentially regulated genes and proteins[100] (FIG. 4). These methods can be used to re-define and subdivide AD and FTD on the basis of biochemical criteria. The analyzed material includes human brain, cerebrospinal fluid (CSF) and plasma, as well as tissue culture cells and brain and spinal cord tissue from animal models[101,102]. Whereas transcriptomics offers the possibility of examining single cells or even subcellular compartments, proteomics has not yet attained this level of sensitivity[101]. Here, we describe how the analysis of animal models by these techniques has contributed to the understanding of AD and FTD.

Wild-type mice provide the setting. To provide a framework for the analysis of transgenic brains it is sensible to analyze WT mice and identify subregion- or cell type-specific transcripts. In animal models, tissue can be dissected without the postmortem delay required for human tissue. When subregion-specific RNA transcripts were compared within the mouse hippocampus, the maximal difference observed was 7.6-fold (that was *Est1* enriched in dentate gyrus) and no gene was exclusively expressed in any one region[103]. A related study compared gene expression in the cortex, cerebellum and midbrain, and showed that less than 1% of the genes examined were enriched in any area[104]. The hippocampus, amygdala and entorhinal cortex showed similar expression profiles[104]. Another study identified differentially enriched genes in the amygdala that exhibited boundaries of expression corresponding to cyto-architectonically defined subnuclei[105]. Although regional gene/protein expression differences are not the sole basis of selective vulnerability, studies like these, together with determining differential activity patterns, should help us to understand why certain brain regions are more prone to degeneration in diseases such as AD and FTD.

Focusing on mitochondria. Several explanations of the neurodegeneration found in AD have been proposed, some of which have also been also implicated in FTD. Genetic, clinical and biochemical evidence supports the amyloid cascade hypothesis in FAD[106], whereas the oxidation damage hypothesis is attractive in SAD. This hypothesis overlaps with the axon transport failure hypothesis: mitochondria are both a target and source of reactive oxygen species (ROS) and their transport is impaired in disease[107].

A mass-spectrometric analysis of pR5 mice (FIG. 1) revealed deregulation of mitochondrial respiratory chain complex components (including complex V) and antioxidant enzymes, and mitochondrial dysfunction[108]. Furthermore, decreased complex V levels have been found in the brains of patients carrying the P301L tau mutation[108]. Studies on *Sod2*$^{-/-}$ mice that lack the detoxifying enzyme superoxide dismutase 2 showed that mitochondrial stress can cause tau hyperphosphorylation[109]. This implies that a vicious cycle of alterations in tau and oxidative stress can cause neurodegeneration.

Crossing transgenic mice overexpressing the mitochondrial enzyme Aβ-binding alcohol dehydrogenase (ABAD) with APP mutant J20 mice has been shown to cause the generation of ROS and spatial learning and memory deficits[110]. As AD is associated with synapse failure[7], synaptosomal fractions from Tg2576 mice have been analyzed by mass spectrometry[111] (FIGS 1,4). Significant differences were found in *mitochondrial hsp70*. When synaptic and nonsynaptic mitochondria were purified from Tg2576 brains and compared, numerous differences in the protein subunit composition of respiratory chain complexes I and III were found. Functional examination revealed impairment in state 3 respiration and uncoupled respiration in brain mitochondria from young Tg2576 mice[111], similar to those observed in pR5 mice[108]. As this impairment occurred before NFT formation and Aβ plaque deposition, mitochondria are thought to be early targets of Aβ and tau aggregates.

Focusing on stress response and inflammation. An upregulation of oxidative stress-related, apoptosis-related and pro-inflammatory signalling genes has been found in the CA1 region of the brains of patients with AD[112]. Similarly, in three APP transgenic models, genes encoding proteins involved in the immune response, carbohydrate metabolism and proteolysis were deregulated. Screening JNPL3 mice (FIG. 1) identified deregulated inflammation mediators and apoptosis inhibitors[113]. In the pR5 strain[114], *glyoxalase I* (GLO1) was found to be the only upregulated gene[115]. Glyoxalase I is essential for the detoxification of dicarbonyl compounds, preventing the formation of advanced glycation end (AGE) products that promote the formation of ROS. Comparative proteomics applied to $A\beta_{42}$-treated P301L tau expressing neuroblastoma cells and the amygdala of pR5 mice stereotaxically injected with $A\beta_{42}$ identified proteins involved in the stress-response that are associated with protein folding, including VCP[116]. In both mice and *D. melanogaster*, a puromycin-sensitive aminopeptidase (PSA) was identified as a suppressor of tau-induced neurodegeneration. However, unlike tau, PSA did not alter APP levels *in vitro*[117]. PSA is the major peptidase responsible for digesting polyglutamine sequences released by proteasomes during protein degradation.

Learning and memory-related genes. When APP/PSEN1 transgenic mice were analyzed for differential mRNA expression several genes that are essential for long-term potentiation (LTP) and memory formation were found to be downregulated in Aβ plaque-containing areas. As there were no apparent changes in synaptic structure, memory loss in these mice might model the early memory dysfunction that is seen in patients with AD before synapses and neurons degenerate[118]. Epidemiological

Suppressor screen
A system used to identify genes that, when overexpressed, lead to the suppression of a mutant phenotype.

Transcriptomics
Large-scale studies of the expression of genes at the mRNA level, typically carried out using microarray technology.

Proteomics
Large-scale studies of the proteome, which comprises all proteins produced by an organism or system. This might also include the analysis of protein function, structures and secondary modifications, using techniques such as mass-spectrometry.

Mass-spectrometric analysis
A technique used to identify and measure biological and chemical compounds. It involves ionization, followed by the use of a magnetic or electrical field. Applications include the identification of proteins and sequencing of oligosaccharides.

State 3 respiration
Active respiration after adding a limited amount of ADP. The rate after all the ADP has been phosphorylated to ATP is termed state 4 respiration.

Uncoupled respiration
Respiration upon adding a reagent such as oligomycin (complex V inhibitor) that uncouples from ATPase.

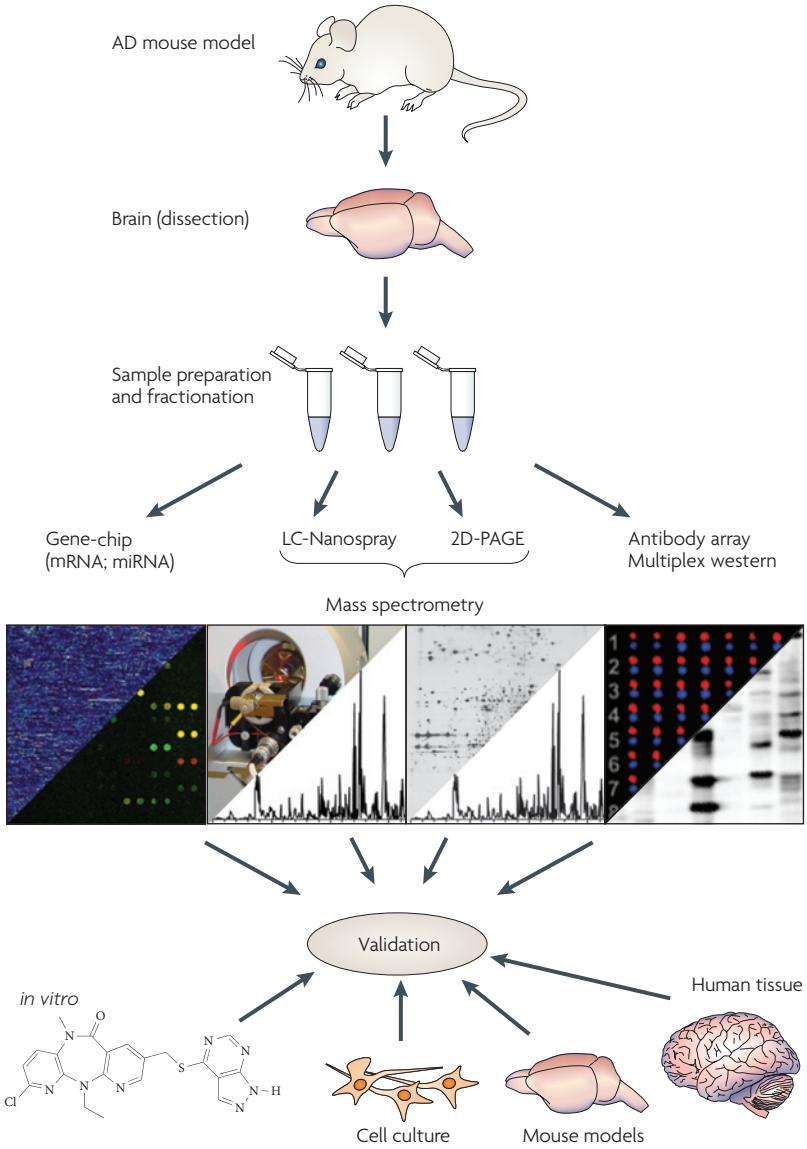


Figure 4 | **Application of functional genomics to AD mouse models.** Functional genomics is increasingly being applied to animal models of Alzheimer's disease (AD)[100]. In most instances some kind of pre-fractionation is required to reduce the complexity of the sample or to remove overtly abundant mRNAs or proteins. Pre-fractionation can be at the level of subcellular compartments, based on biochemical or biophysical characteristics, or by dissecting subregions of the brain. Gene-chips determine differences in mRNA and, more recently, in micro RNA (miRNA) levels[100]. Mass spectrometry might involve prior separation on two-dimensional poly-acrylamide gels (2D-PAGE) and cutting out of protein spots or, alternatively, protein mixtures might be fed, through liquid chromatography (LC)-nanospray, directly into the mass spectrometer. Antibody arrays and multiplex Western blotting are biased mass-scale approaches to quantitatively determine differences in protein levels and post-translational modifications, such as phosphorylation. Functional genomics data are highly dependent on a proper normalization and validation, both functionally and in human and animal tissue; this can be done using techniques such as Western blotting and immunohistochemistry[101].

evidence suggests that activity and exercise are correlated with a later onset of AD and placing APP/PSEN1 mutant transgenic mice in an environmentally enriched environment significantly reduced the Aβ plaque burden. Many of the genes that were specifically upregulated in APP/PSEN1 mutant mice living in the enriched environment are involved in learning and memory, neurogenesis and cell survival pathways, implying that activity has a positive effect on plasticity-related genes[119].

Although some functional genomics studies of transgenic models of dementia reveal few deregulated gene/protein-categories, others indicate that many functional categories are deregulated, often related to processes known to be important in AD pathophysiology[120]. This is, in part, due to differences in tissue complexity, statistical stringency and annotation softwares[101]. The challenge for the future is to identify early changes both with respect to age of onset and the tissue or cellular compartment in which pathology is initiated, which will offer the possibility of a targeted interference with the disease process.

Imaging animal models

The clinical diagnosis of AD and FTD remains vague and includes recording the patient history, exclusion of depression and other causes of dementia, laboratory tests (to rule out diabetes for example), neurological and mental examinations and increasingly, imaging techniques. The techniques that are used for preclinical diagnosis include positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI) and multiphoton imaging. Although multiphoton imaging is compatible with human and mouse tissue — neurons and Aβ plaques have a similar dimension in both species — the former techniques require a higher resolution in animals due to their much smaller brain structures. In principle, imaging in animals provides a tool to non-invasively monitor pathological changes and to correlate these with behavioural changes.

Visualizing Aβ deposition *in vivo* might contribute to a definitive diagnosis of AD and to monitoring the success of treatments. An early probe was a dye called BSB ((*trans*,*trans*)-1-bromo-2,5-bis-(3-hydroxycarbonyl-4-hydroxy)styrylbenzene), which was used to label Aβ plaques in Tg2576 mice[121]. In recent years the novel PET tracer ^{11}C-labelled Pittsburgh Compound-B (PIB), which binds to Aβ plaques, has aroused significant attention[122]. PIB was shown to enter the brain quickly and label plaques within minutes[123]. It was used as a PET tracer in APP transgenic mice but initially failed to reflect the amount of Aβ[124]. Eventually, in APP23 mice, an age-dependent increase in radioligand binding was found to be consistent with progressive Aβ accumulation[125]. Importantly, Aβ reductions upon vaccination with an anti-Aβ-antibody were reflected by reduced binding of ^{11}C-PIB.

However, there are several limitations of PET, including a high variability in normal controls, low spatial resolution, the need for probes that must be synthesized, purified and quickly used, and the high cost. In addition, PET studies require up to 45 minutes of scanning, which poses particular problems for the elderly and patients with dementia. By contrast, MRI is up to 50-fold cheaper, the resolution is high, the probes or contrast enhancers can be stored for extended

periods and there is no radioactive exposure[126]. When Tg2576 mice were administered the ^{19}F-containing amyloidophilic Congo red-type compound FSB ((E,E)-1-fluoro-2,5-bis-(3-hydroxycarbonyl-4-hydroxy)styrylbenzene) intravenously, Aβ plaques could be visualized by MRI. Furthermore, magnetic resonance spectroscopy can be used to measure alterations in metabolites that are prognostic markers for neurodegeneration[127].

What is now needed are PET tracers for pathological structures other than plaques (such as the NFTs), at a resolution that is compatible with the size of mouse brain structures. It is expected that imaging, together with the development of biomarkers in CSF and blood, will lead to an early differential diagnosis of AD.

Therapeutic strategies

There is no cure for AD or FTD and the available treatment is only symptomatic. However, clinical trials that are based on the underlying biology of disease are on the way (see Further information). These include vaccination, anti-inflammatory drugs and modulators of formation, aggregation and clearance of Aβ and tau. Many of the new therapeutic strategies have their foundation in transgenic animal work[128]; we highlight a few of these here.

Vaccination targeting Aβ. Vaccination trials targeting Aβ in mice and humans have been reviewed in REF. 129. In brief, both active and passive vaccination strategies have been successful in Aβ plaque-forming mice. Vaccination of young PDAPP mice with the $A\beta_{42}$ peptide, for example, prevents the development of neuritic Aβ plaques, and in older mice it significantly reduces them[130]. An Aβ-directed passive vaccination approach was also effective[131]. Vaccination reduced age-dependent learning deficits, which correlated with reductions in both soluble Aβ and tau[132].

Encouraged by the efficacy in mice, a clinical trial was launched with AN-1792-containing pre-aggregated synthetic $A\beta_{42}$ and the adjuvant QS-21 (REF. 133). The Phase IIa trial was halted prematurely as 6% of the patients who had received the vaccine developed meningoencephalitis; however, as some patients developed Aβ-antibody titres that correlated with a slowed cognitive decline[134], the development of antibody fragments and humanized Aβ-specific antibodies is ongoing and some are currently in clinical trials (see Further information).

Reduction of tau. At first sight, a tau-directed vaccination approach does not appear feasible, because tau is primarily an intracellular protein. Therefore it was surprising, and encouraging, to find that vaccination of JNPL3 mice with a tau peptide containing the PHF1 phospho-epitope reduced aggregated tau levels and slowed progression of an NFT-related motor phenotype[135]. In this study, anti-tau antibodies entered the brain and bound to pathological tau[136]. An independent tau vaccination study is awaited and clinical trials have not yet started.

To compensate for the loss of tau's microtubule-stabilizing function (as when it is phosphorylated it has less microtubule-binding capacity), intraperitoneal injections of the microtubule-binding and stabilizing drug paclitaxel, were administered to mice overexpressing WT tau[137]. This restored fast axonal transport in spinal cord axons and ameliorated motor impairment [137]. When NFT-forming P301S tau mice (PS19 mice, Supplementary Information S1 (table)), in which microglial activation precedes NFT formation, were treated with the immunosuppressant FK506, an increase in survival, an attenuation of neuroinflammation, and an amelioration of the tau pathology was observed[36]. Similarly, FK506 improved memory functions in Tg2576 mice[138]. Another recent finding is that the increased lethality of Aβ-producing transgenic mice could be prevented by breeding the APP transgene onto a tau-deficient background (BOX 2). This strengthens the idea that a reduction of tau could be an effective treatment strategy for AD[40,139].

Role of diet. The role of diet in preventing AD has gained increased recognition. Caloric restriction (CR) reduced Aβ plaque numbers in two APP transgenic strains and reduced astrocyte activation[140]. Both intermittent fasting and CR ameliorated the behavioural phenotype of 3xtg-AD mice[141]. Aβ levels and tau phosphorylation were not altered in the intermittent fasting group, suggesting that this strategy might provide protection downstream of tau and Aβ.

One protein implicated in CR-mediated longevity is the deacetylase sirtuin 1 (SIRT1). When mice overexpressing p25, an activator of the tau kinase cdk5, were injected with the anti-oxidant resveratrol, hippocampal neurodegeneration was reduced, learning deficiencies were prevented and a decrease in the acetylation of the known SIRT1 substrates PGC-1α and p53 was observed[142].

Other dietary strategies include the use of antioxidants such as *Ginkgo biloba* or the green tea component epigallocatechin-3-gallate, which reduce Aβ generation in Tg2576 mice, possibly by activating the α-secretase pathway[143]. A diet enriched in omega-3 polyunsaturated fatty acids (PFAs) reduced Aβ plaques in Tg2576 mice possibly by influencing the lateral membrane mobility of APP and its secretases, as well as secretase activity[144]. Zinc metabolism has also been implicated in β-amyloid plaque formation[145]. Neonatal omega-3 PFA deficiency caused overexpression of the zinc transporter ZnT3 in rats and alterations in brain and plasma zinc levels[145].

Whether our growing understanding of the importance of diet in AD will lead to lifestyle changes is questionable; however the finding that moderate consumption of red wine attenuates Aβ neuropathology and memory impairment in Tg2576 mice might be easier to translate into daily practice[146]. Whether the red wine should be consumed with Aβ-expressing transgenic potatoes, the feeding of which has been shown to elicit an immune response and partially reduce Aβ plaques in Tg2576 mice, remains to be seen[147].

Positron emission tomography
(PET). *In vivo* imaging technique used for diagnostic examination that involves the acquisition of physiological images based on the detection of positrons, which are emitted from a radioactive substance previously administered to the patient.

Computed tomography
Imaging technique that exploits the differences in absorption of X-rays by different tissues to give high-contrast images of anatomical structures. Computed tomography has relatively poor soft-tissue contrast, so iodinated contrast agents, which perfuse different tissue types at different rates, are commonly used to delineate tumours.

Magnetic resonance imaging
A non-invasive method used to obtain images of living tissue. It uses radio-frequency pulses and magnetic field gradients; the principle of nuclear magnetic resonance is used to reconstruct images of tissue characteristics (for example, proton density or water diffusion parameters).

Multiphoton imaging
A non-invasive form of microscopy in which a fluorochrome that would normally be excited by a single photon is stimulated quasi-simultaneously by several photons of lower energy. Under these conditions, fluorescence increases as a function of the square of the light intensity, and decreases approximately as the square of the distance from the focus. Because of this behaviour, only fluorochrome molecules near the plane of focus are excited, greatly reducing light scattering and photodamage.

Other strategies targeting Aβ and tau. Further therapeutic strategies that have been tested in mice include reducing Aβ production by inhibiting β- and γ-secretase activity, or by promoting its clearance through neprilysin or insulin-degrading enyzme[148]. Other therapies employ the use of muscarinic agonists and chelating agents[149,150]. Antioxidants and inhibitors of the proteases caspase-3 and calpain have been considered, as APP and tau are both substrates of these enzymes[151]. Similarly, non-steroidal anti-inflammatory drugs (NSAIDs) are considered for treatment and prevention of AD and have been tested in animal models[152]. As tau is hyperphosphorylated in both AD and FTD, kinases are promising targets, although targeting these enzymes is not trivial, because they have multiple substrates in many organs[44]. Lithium is used to treat bipolar disorder and there is conflicting evidence regarding whether it is effective in AD. Chronic administration in aged 3xTg-AD mice reduced tau phosphorylation by reducing GSK3 activity, but did not alter Aβ levels or memory functions[153]. In a related study lithium reduced APP phosphorylation and hence, Aβ levels[154].

When all treatment strategies in mice are considered we conclude that animal experimentation is absolutely essential. However, the lesson learned from the Aβ-directed vaccinations is to be particularly careful in directly translating animal findings to the human patient.

Outlook

Animal models continue to have a central role in AD research. Recently, a major focus has been on combinatorial approaches that rely on a limited number of basic models with a pronounced pathology. The models might not accurately reproduce the anatomical distribution of the lesions in human brain, but biochemically they are very similar to the human condition. As far as memory and motor functions, neuroanatomy and the endocrine system are concerned, the mouse models are superior to the invertebrate ones. However, recent work in invertebrate species highlights their advantages for dissecting signalling pathways, performing modifier screenings or analyzing families of mutations in parallel.

What will the future bring? We expect that there will be a wider application of imaging techniques to animal models. Several teams have applied functional genomics to their models and with the advent of antibody arrays and the emerging role of miRNAs becoming clear, it is likely that the coming years will see a massive increase in the use of these techniques. The near future will show whether the current clinical trials will be fruitful and lead to a real cure of AD and FTD. Finally, unexpected results in animal models could overturn some of the current hypotheses.

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
APOE | GLO1 | *MAPT* | *PGRN* | *PSEN1* | *PSEN2* | *TARDBP* | *VCP* |
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Alzheimer's disease | amyotrophic lateral sclerosis | frontotemporal dementia |
UniProtKB: http://ca.expasy.org/sprot
ABCA1 | ADAM10 | APP | APPL | BACE | CHIP | GSK3β | INK | PIN1 | SIRT1 | tau | TDP-43 |

FURTHER INFORMATION

Jürgen Götz's homepage: http://www.bmri.org.au/alzheimer.html
Alzforum index of drugs in clinical trials: http://www.alzforum.org/drg/drc/default.asp

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