Animal models for Alzheimer's disease and frontotemporal dementia: a perspective

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ABSTRACT

In dementia research, animal models have become indispensable tools. They not only model aspects of the human condition, but also simulate processes that occur in humans and hence provide insight into how disease is initiated and propagated. The present review discusses two prominent human neurodegenerative disorders, Alzheimer's disease and frontotemporal dementia. It discusses what we would like to model in animals and highlights some of the more recent achievements using species as diverse as mice, fish, flies and worms. Advances in imaging and therapy are explored. We also discuss some anticipated new models and developments. These will reveal how key players in the pathogenesis of Alzheimer's disease and frontotemporal dementia, such as the peptide Aβ (amyloid β) and the protein tau, cause neuronal dysfunction and eventually, neuronal demise. Understanding these processes fully will lead to early diagnosis and therapy.

Key words: Alzheimer's disease, amyloid, Caenorhabditis elegans, Drosophila, frontotemporal dementia, mouse, rat, tau, TAR DNA-binding protein 43 (TDP-43), transgenic, zebrafish.

INTRODUCTION

The present review is based on a Plenary Lecture given by J.G. at the 12th ICAD (International Conference on Alzheimer’s Disease) in Vienna in July 2009.

Animal models have become indispensable in basic and biomedical research (Götz and Ittner, 2008). The following definitions found on the web underscore two important attributes of a model: the open-source platform Wikipedia states that an animal model is “a non-human animal that has a disease or injury that is similar to a human condition” (http://en.wikipedia.org/wiki/Animal_model; accessed 7 July 2009). Another site highlights a second important aspect by defining an animal model as “a laboratory animal used in research that simulates processes comparable to those that occur in humans” (http://science.education.nih.gov/supplements/nih4/self/other/glossary.htm; accessed 7 July 2009). Applying these definitions, e.g. to neurodegenerative disorders, illustrates that models are valuable because they represent a certain stage of disease and because processes that lead to this stage can be monitored longitudinally.

In modelling AD (Alzheimer’s disease), the most important form of dementia, and FTD (frontotemporal dementia), which in prevalence ratings comes second (Baillo et al., 2007), familial forms of these diseases, as well as histopathological and clinical features in the human patient, provide guidance.

In the present review, first, we discuss the genes that cause FAD (familial AD) and FTD as remarkably enough a subset of these genes also encode the proteins within the major lesions that define the two diseases. In FAD, which accounts for less than 1% of all cases, autosomal-dominant mutations have been identified in three genes: APP (amyloid precursor protein), PSEN1 (presenilin 1) and PSEN2 (presenilin 2) (Bertram and Tanzi, 2008). APP is a membrane-associated protein from which the peptide Aβ (amyloid β) is derived by proteolytic cleavage. The presenilins are components of the γ-secretase complex that, together with β-secretase, generates Aβ, while β-secretase activity precludes Aβ formation. In addition to the three FAD genes, a series of susceptibility genes have been identified in SAD (sporadic AD); these include APOE (apolipoprotein E) as the most established risk gene (Bertram and Tanzi, 2008). Very recently, three...
additional risk factor genes have been found, CLU encoding clusterin, PICALM encoding the phosphatidylinositol-binding clathrin assembly protein and CR1, the complement component (3b/4b) receptor 1 (Harold et al., 2009; Lambert et al., 2009). Compared with AD, FTD is a much more heterogeneous group of related dementias, which is reflected both by the types of genes that are mutated and by the proteins that are deposited. The first mutations identified in FTD were in FTDP-17 (familial FTD with parkinsonism linked to chromosome 17), where they were found in the MAPT gene that encodes the microtubule-associated protein tau (Cruts and Van Broeckhoven, 2008). This subset of FTD cases is characterized by tau inclusions (see below). Another subset of familial FTD is characterized by mutations in the PGRN gene that encodes the pleiotropic protein progranulin, and in the VCP gene that encodes valosin-containing protein; these cases are characterized by inclusions of the TDP-43 (TAR DNA-binding protein 43), a highly conserved hnRNP (heteronuclear ribonucleoprotein) (Neumann et al., 2006). Finally, mutations in CHMP2B, encoding chromatin-modifying protein 2B, lead to FTD in the absence of either tau or TDP-43 inclusions (Cruts and Van Broeckhoven, 2008). For detailed information, we refer to http://www.molgen.ua.ac.be/ADMutations and http://www.molgen.ua.ac.be/FTDMutations as a constantly updated source of mutations in FAD and FTD, as well as of the families in which they occur.

Histopathologically, AD is characterized by Aβ plaques and neurofibrillary lesions. Aβ in the plaques is fibrillar. Neurofibrillary lesions contain hyperphosphorylated, fibrillar aggregates of tau that are found in cell bodies and apical dendrites as NFTs (neurofibrillary tangles), in distal dendrites as neurofil processes, and in the abnormal neurites that are associated with some Aβ plaques. Truncation of tau, in addition to hyperphosphorylation (Chen et al., 2004a), has been linked to pathogenesis (Horowitz et al., 2004). Tau is generally perceived as a neuronal protein, with a mainly axonal localization, but this concept needs to be revisited as discussed below. In addition to plaques and neurofibrillary lesions, the AD brain is also characterized by massive neuronal cell and synapse loss at specific predilection sites (Selkoe, 2002). With regard to the formation of plaques and neurofibrillary lesions, sporadic cases of AD are not different from familial cases, whether they carry mutations in APP, PSEN1 or PSEN2. Hence, this led to the notion that understanding the pathogenesis of familial cases would also provide insight into the sporadic cases.

In addition to AD, NFTs are also abundantly present in a significant subset of FTD such as FTDP-17, in which there is an absence of overt plaques. Another subset of FTD with tau-negative and ubiquitin-positive lesions, also in the absence of plaques, has been termed FTLD-U or FTDU-17 (Cruts and Van Broeckhoven, 2008). Here, TDP-43 has been identified in ubiquitin-positive inclusions; these have also been found in sporadic ALS (amyotrophic lateral sclerosis). Similar to tau, TDP-43 in the aggregates is hyperphosphorylated, ubiquitinated and C-terminally truncated (Neumann et al., 2006). Both types of protein aggregates can be visualized under the light microscope either by immunohistochemistry, thioflavin S or silver impregnation methods such as those developed by Gallyas and Bielschowsky [as described previously (Ittner et al., 2008)]. Massive protein aggregation and, in particular, Gallyas reactivity was one of the defining hallmark aspects of the human pathology that the early animal models tried to achieve, but in which they failed: although tau formed aggregates as the mice aged, NFTs did not develop (Figure 1A) (Götz and Ittner, 2008).

Another defining feature of the human pathology is the characteristic spreading of the hallmark lesions in the AD brain that, in the case of tau, is subject to little inter-individual variation and provides a basis for distinguishing six stages: the transentorhinal stages I and II representing silent cases; the limbic stages III and IV; and the neocortical stages V and VI (Braak and Braak, 1991). A similar type of staging has subsequently been defined for the Aβ pathology (Thal et al., 2002) and is now also available for the Lewy body pathology in PD (Parkinson’s disease) (Braak et al., 2003). The spreading of the major histopathological hallmarks of AD, associated with selective neuronal cell loss, is not well understood at the cellular and molecular level. The Braak staging implies selective vulnerability of distinct neuronal populations (Götz et al., 2009). This staging is a feature one definitely would like to recapitulate in animals, as neuronal and synapse loss at specific predilection sites causes the clinical features that discriminate AD from FTD (Figure 1B). In the AD brain, atrophy is initiated in the hippocampus and entorhinal cortex, followed by the association cortices and subcortical structures, including the amygdala and NBM (nucleus basalis of Meynert). The histopathology is reflected by the clinical features that characterize AD: early memory deficits that are followed by a gradual erosion of other cognitive functions (Arnold et al., 1991). Atrophy in the FTD brain is mainly found in frontal and/or temporal cortices. Hence, in contrast with AD, FTD is associated predominantly with behavioural and/or language impairment, with memory impairment mostly found only late in disease (Cruts and Van Broeckhoven, 2008). A significant subset of FTD is characterized by parkinsonism (Figure 1C), an aspect that has been modelled in animals as outlined below.

A further remarkable aspect one would like to model in animals is that of the distinct age of onset and disease duration until death that, e.g. discriminates carriers of PGRN mutations from those of MAPT mutations (Cruts and Van Broeckhoven, 2008) (Figure 1D).

In understanding the aetiology of the sporadic cases of AD and FTD, a lot of hypotheses have been put forward (addressing an important aspect highlighted by the second definition we have presented above). These include the amyloid cascade hypothesis, oxidative stress/mitochondrial dysfunction, transport/synaptic dysfunction, mitosis failure, proteasome dysfunction, and stress response and inflammation hypotheses. They have been tackled by a series of ‘omics’ approaches which encompass lipidomics, proteomics, transcriptomics and genomics (Noorbakhsh et al., 2009).
VERTEBRATE AND INVERTEBRATE ANIMAL MODELS

The mouse is the major species used in AD and FTD research, but significant additional insight has been provided from species such as the roundworm Caenorhabditis elegans, the fruit fly Drosophila melanogaster, and two types of fish, the sea lamprey and the zebrafish (Götz et al., 2007).

As far as rodents are concerned, there are non-transgenic models available such as the SAM (senescence-accelerated mice), or chemically induced lesion models, but these lack the characteristic hallmark lesions of AD (Van Dam and De Deyn, 2006). These have been modelled by transgenesis (Ittner and Götz, 2007), almost exclusively in mice, as reviewed recently (Götz and Ittner, 2008), although there are a few transgenic rat models available (Zlika et al., 2006; Koson et al., 2008). Although the list of strains that were discussed in Götz and Ittner (2008) is long, it is still incomplete, since a myriad of

Figure 1  Aspects of AD and FTD one would like to model in animals
Animal models have become indispensable in basic and biomedical research. They reproduce aspects of AD and FTD (A–D), but also allow for testing the many hypotheses that have been put forward to determine what exactly causes these diseases (E). In both AD and FTD, protein aggregation leads to lesions that can be visualized under the light microscope either by immunohistochemistry, by dyes such as thioflavin S, or by silver impregnation methods such as those developed by Gallyas and Bielschowsky, an aspect to be modelled (as indicated by the ‘M’) in animals (A). A second aspect is that of the spreading of the key histopathological hallmarks of AD, the Aβ plaques and the tau tangles (NFTs) that has led to the definition of the Braak stages (B). A third is the distinct clinical features such as memory impairment in AD or parkinsonism that characterizes a subset of FTD cases (C). The fourth is the distinct age of onset and disease duration that discriminates, e.g. carriers of mutations in the tau-encoding MAPT gene compared with those in the progranulin-encoding PGRN gene (D) based on data in (Cruts and Van Broeckhoven, 2008). The list of hypotheses in the field is led by the amyloid cascade hypothesis, but animal models provide support for all proposed hypotheses (E).
AD and FTD mouse strains has been generated since the early 1990s and it is impossible to present them all.

However, a few select models may provide a flavour of what has been achieved so far. Of the many APP mutant mice that have been generated in the past, strains such as the PDAPP, J20, APP23 or Tg2576 mice are good representatives as they are widely used owing to their robust APP/Aβ pathology (Games et al., 1995; Hsiao et al., 1996; Sturchler-Pierrat et al., 1997; Mucke et al., 2000). Representative models with NFT formation are strains such as the JNPL3 or pR5 mice, both of which express P301L mutant tau that previously has been identified in FTDP-17 (Lewis et al., 2000; Götz et al., 2001a). Aβ in the above plaque mice is fibrillar, as is tau in the NFTs of the P301L mutant strains; in both instances, the histopathology is associated with behavioural impairment, following assessment of hippocampus- and amygdala-dependent tasks (Götz and Ittner, 2008). In conclusion, the aggregation of both Aβ and tau has been faithfully reproduced in vivo, with the hallmark lesions of AD and FTD being visible at a light microscopic level. Similarly, aspects of memory impairment have been reproduced.

The microtubule-associated protein tau is generally perceived as a neuronal protein, however, tauopathies such as CBD (corticobasal degeneration) and PSP (progressive supranuclear palsy) are characterized by a pronounced glial tau pathology that is often even more pronounced than the concomitant neuronal pathology (Götz, 2001; Kurotsi and Götz, 2002). The glial tau pathology has been modelled, e.g. in mice that express wild-type human tau in astrocytes (Forman et al., 2005). Not only do these mice develop glial lesions that are remarkably similar to the human pathology, with tufted astrocytes and astrocytic plaques, but the authors also report on a focal neuronal degeneration. In other words, a glial pathology causes a neuronal pathology. The glial lesions were Gallyas-positive, as in the human patients. Similar inclusions were obtained by expressing P301L mutant tau in astrocytes; this again was associated with a neuronal pathology as evidenced by impaired axonal transport shown for the optic nerve (Higuchi et al., 2005).

While these studies model tau aggregation and NFT or GFT (glial fibrillary tangle) formation, other models addressed the question of how, if at all, the tau aggregates are related to disease (Götz et al., 2008a). To this end, a CaMKII (Ca²⁺/calmodulin-dependent protein kinase II) promoter-driven transactivator system was employed, achieving a 15-fold overexpression of P301L mutant tau (Ramden et al., 2005; Santacruz et al., 2005). This resulted in NFT formation, neuronal loss and memory impairment. NFT formation was linked to the appearance of a 64 kDa ‘toxic’ tau species termed tau*. When tau expression was suppressed after supplementing the drinking water with doxycycline, this resulted in a lower, 2.5-fold overexpression. Interestingly, memory functions recovered, but NFTs continued to accumulate. In more recent work it was shown that, in the young brain, elevation of the levels of phosphorylated tau species per se was not sufficient to cause a lasting tau pathology (Dickey et al., 2009). A CaMKII promoter-driven transactivator system was also employed to express truncated forms of tau comprising mainly the C-terminal microtubule-binding domain. Both a pro- and an anti-aggregation mutant were generated, with the former resulting in neuronal loss (Mocanu et al., 2008). An interesting observation was that human ‘pro-aggregation’ tau co-aggregated with mouse tau, the possibility of tau forming mixed aggregates being an issue of discrepancy in the field for quite some time. For comparison, previous work including a BAC (bacterial artificial chromosome) transgenic approach combined with a tau knockout had suggested that endogenous mouse tau is inhibitory to the aggregation of transgenic human tau (Andorfer et al., 2003). In the pro-aggregation mouse model, again, when the mice were fed with doxycycline, tau levels went down, while NFTs persisted (Mocanu et al., 2008). In related work in flies, overexpression of both wild-type and R406W mutant tau was shown to cause premature death, with mutant tau showing an earlier age of onset (Wittmann et al., 2001). Cholinergic neurons (a major target of the cholinergic therapy in AD) were found to be degenerating in the flies. Interestingly, the tau-associated pathology occurred in the absence of NFT formation, suggesting that their formation may not be required for tau to execute its toxic effects.

Coming back to NFT formation, this has been linked by several groups to phosphorylation of tau at distinct epitopes including AT100 (Thr212/Ser214) and pS422 (Ser422) (Götz and Nitsch, 2001; Götz et al., 2001b; Allen et al., 2002; Ferrari et al., 2003; Guillozet-Bongaarts et al., 2006; Le Corre et al., 2006; Deters et al., 2008, 2009). The notion that phosphorylation of tau at specific sites is both necessary and sufficient for tau to form filaments has been recently challenged, again by work in flies. First it was shown that tau simultaneously pseudo-phosphorylated at 14 sites (E14 tau) was more toxic than wild-type tau. Next, these sites were mutated to alanine residues, both in combination and alone. The analysis of individual alanine point mutations suggested that tau phosphorylation sites rather than working ‘in isolation’ act ‘in concert’ in order to promote toxicity (Steinhilb et al., 2007). However, the final word is not yet spoken, especially as toxicity may depend on species and cell types. From a therapeutic perspective, whether general rather than site-specific phosphorylation needs to be impaired to prevent tau from aggregating has important implications, as boosting the activity of more promiscuous phosphatases may be a preferred strategy compared with reducing the activity of phospho-site-specific kinases (Iqbal and Grundke-Iqbal, 2008).

Similar to the tau field, with a hunt for what is thought to be the ‘toxic species’, there is also an ongoing search for the toxic species in the Aβ field [reviewed in (Götz et al., 2008b; Yankner and Lu, 2009)]. Here, a dodecameric form of Aβ termed Aβ56 has been identified in mutant APP transgenic Tg2576 mice that appeared when memory impairment was initiated and that disappeared when memory decline was
Stabilized. When a preparation enriched for Aβ*56 was injected into young recipient rat brains this was shown to disrupt memory (Lesne et al., 2006). However, in more recent work, fibrillar Aβ was identified as a pathogenic entity that altered neuronal membrane properties such that there was hyperexcitability of pyramidal cells, culminating in epileptiform activity (Minkeviciene et al., 2009). Moreover, an analysis of mitochondrial impairment suggests that both oligomeric and fibrillar species of Aβ exert a similar degree of toxicity (Eckert et al., 2008).

While this addresses memory impairment as the major clinical feature characterizing AD, another clinical feature, parkinsonism, that characterizes a significant subset of FTD cases, has also been modelled in mice. Several mini-gene tau constructs have been used to establish a series of transgenic mouse strains, of which one particular strain reproduced tau accumulation in astrocytes and neurons including these of the nigro-striatal pathway (Dawson et al., 2007). The rate-limiting enzyme in dopamine synthesis, TH (tyrosine hydroxylase), was found to accumulate in varicosities (axonal swellings). Furthermore, the mice showed memory and motor impairment (Dawson et al., 2007). A second model was based on the identification of the K369I mutation of tau in a patient with Pick’s disease, an extreme form of FTD (Neumann et al., 2001). The tau lesions in Pick’s disease (and also in the brain of this particular patient) show a remarkable feature: they are Bielschowsky-positve and Gallyas-negative; in addition tau is phosphorylated at many epitopes but 12E8 (Ser262/Se239). This distinct Pick pathology was reproduced in the K3 mouse strain that expresses K369I mutant tau (Ittner et al., 2008). The transgenic mice also model early-onset parkinsonism (resting tremor, bradykinesia, postural instability and gait anomalies). They show an increased cateleptic response to haloperidol and an early, but not late, response to L-Dopa, with similarities to the efficacy of the treatment in FTD patients using this form of medication.

In the K3 mice, axonal transport is impaired. Indeed in recent years, impaired axonal transport emerged as a central pathomechanism in AD (Stokin et al., 2005; Götz et al., 2006; Magnani et al., 2007; Thies and Mandelkow, 2007; Dixit et al., 2008; Pigino et al., 2009). Impaired axonal transport is conceptually linked to oxidative stress and mitochondrial dysfunction: mitochondria are a major organelle that needs to be efficiently transported along the long processes for neurons to function and they are a major source of ROS (reactive oxygen species) (Su et al., 2008; Tatsuta and Langer, 2008). In the K3 mice, there is a selectively impaired axonal transport of distinct cargos, such as mitochondria and TH-containing vesicles (Ittner et al., 2008). This is because a component of the kinesin motor machinery, the scaffold/adapter protein JIP1 (c-Jun N-terminal kinase-interacting protein 1), is trapped by elevated tau, preventing it from executing its physiological function. In a follow-up study a pathological interaction between tau and JIP1 was also revealed in AD and not control brain (Ittner et al., 2009). Interestingly, this pathological interaction requires phosphorylation of tau. Since JIP1 is involved in regulating cargo binding to kinesin motors, these findings may, at least in part, explain how hyperphosphorylated tau mediates impaired axonal transport in AD and FTD, before tau starts to aggregate (Ittner et al., 2009). This presents inhibition of abnormal hyperphosphorylation of tau as a promising therapeutic target for the development of disease-modifying drugs (Iqbal and Grundke-Iqbal, 2008).

Another interesting aspect of tau that has recently emerged is that of the transmission, secretion and spreading of tau. Using a stereotactic injection approach (Clavaguera et al., 2009), a donor brain extract was derived from 6-month-old NFT-forming P301S mice (Allen et al., 2002) and injected into brains of 3-month-old ALZ17 mice (Probst et al., 2000; Götz and Nitsch, 2001), a (wild-type) tau transgenic strain, that develops a tau-associated amyotrophy, but fails to develop NFTs (Clavaguera et al., 2009). The study found that the donor extract induced NFTs in the recipient brain, a feature termed ‘transmission’. Secondly, NFT induction was not confined to the injection site, a feature referred to by the investigators as ‘spreading’. Finally, insoluble rather than soluble tau was found to be responsible for these effects (Clavaguera et al., 2009). In related work, it has been shown that extracellular tau aggregates can transmit a misfolded state from the outside to the inside of a cell, similar to prions (Frost et al., 2009). These features of tau are supported by work in the sea lamprey, a marine fish characterized by so-called giant neurons, which can be injected with plasmids encoding tau expression constructs. Work spanning one and a half decades support the notion that tau is secreted and reproduces aspects of the staging that characterizes the tau pathology (Hall and Cohen, 1983; Hall et al., 2001; Kim et al., 2009). Similar aspects have been reported for α-synuclein, a protein with a structure very much like tau, that induced inclusion formation and neuronal cell death through interneuronal transmission (Desplats et al., 2009). Taken together, these data contribute to an understanding of how, in human disease, Aβ and tau impair cellular functions, which eventually leads to neuronal loss.

Several aspects of the human AD and FTD pathology have been modelled in the nematode C. elegans (Morcos and Hutter, 2009). This roundworm has a number of features that make it a powerful research tool: (i) it is easy to culture as it feeds on bacteria grown on agar plates; (ii) it reproduces and develops rapidly: within 3 days it develops from an egg to an adult worm, with approx. 300 progenies originating from one self-fertilized hermaphrodite; (iii) its small size allows assays in microtitre format, studying hundreds of animals in a single well; (iv) the worm is transparent, which is ideal for the use of fluorescence markers in vivo; (v) it is a complex multicellular animal: an adult hermaphrodite has exactly 959 somatic cells that form different organs, including 302 neurons forming the nervous system; (vi) it has a short life span of 2–3 weeks, allowing studies in aged animals within a reasonable time frame (mice, in comparison, often need to age for 1 year or even longer before they develop a phenotype); and (vii) genetic modifications, such as transgenic expression or RNAi
(RNA interference)-mediated gene knockdown are quite easy compared with other in vivo systems. Furthermore, most human disease genes and pathways are present in C. elegans (Kaletta and Hengartner, 2006). This includes the APP homologue APL-1, a mutation of which results in early larval lethality (Hornsten et al., 2007). C. elegans has two PSEN homologues, SEL-12 and HOP-1 (Levitan and Greenwald, 1995; Li and Greenwald, 1997), and a single tau-like protein called PTL-1 (protein with tau-like repeats) (Goedert et al., 1996; McDermott et al., 1996).

C. elegans has been successfully used as model organism to study pathomechanisms in MND (motor neuron disease) and FTD; e.g. expression of SOD1 (superoxide dismutase 1) carrying a human pathogenic mutation identified in familial MND results in severe locomotor deficits in transgenic C. elegans (Wang et al., 2009). Expression of wild-type SOD1, however, does not affect motor behaviour. Similarly, expression of human tau carrying FTD mutations, but not wild-type tau, in C. elegans results in neurodegeneration with an accumulation of hyperphosphorylated tau and associated uncoordinated locomotion (Umc) (Kraemer et al., 2003; Miyasaka et al., 2005; Brandt et al., 2009). C. elegans is not capable of producing endogenous Aβ. The first published transgenic model targeted Aβ to the body wall of muscle cells, causing progressive paralysis (Link, 1995). Aβ deposition in another model was associated with oxidative stress (Drake et al., 2003). A further aspect linked to oxidative stress is that is evident from studies in C. elegans is the similarity between diabetes mellitus and AD, in particular with regards to the formation of AGEs (advanced glycation end-products) (Morcos and Hutter, 2009). Together this demonstrates the potential of C. elegans as a model organism in AD and FTD research. The findings obtained in the worm are complemented by studies in Drosophila, that in addition has shown its potential as a model and a powerful system to screen for modifiers that either enhance or suppress an AD-associated pathology (Shulman and Feany, 2003; van de Hoe et al., 2009).

That farm animals are also attractive as AD models is illustrated by the recent establishment of a porcine model: while the transgene was found to be expressed in brain, the authors speculate that it may take until the age of 1–2 years until Aβ may accumulate in the porcine brain (Krath et al., 2009).

THE Aβ–TAU AXIS

A central hypothesis in AD research is the amyloid cascade hypothesis as revisited by Hardy (2006). Animal models were central in providing support for this hypothesis that claims, in simplified terms, that an Aβ pathology causes a tau pathology (Figure 2). While initially plaques and NFTs were thought to be the key players, in recent years the focus has shifted from these end-stage lesions to the precursors, oligomeric forms of Aβ and soluble forms of tau, as the major (but not exclusive) culprit. When P301L mutant tau transgenic JNPL3 mice were crossed with APP mutant Tg2576 mice, this caused a 7-fold NFT induction, but no increased Aβ pathology (Lewis et al., 2001) (Figure 2A). Similarly, stereotactic injections of fibrillar preparations of Aβ42 into the hippocampus and somatosensory cortex of P301L tau mutant pR5 mice caused a 5-fold induction of NFTs in the amygdala, a site which projects to the CA1 neurons in the hippocampus (Götz et al., 2001b) (Figure 2B). The pathology in the amygdala is reflected by an impairment in amygdala-dependent tasks (PENNANEN et al., 2004, 2006). Injections of Aβ42 into wild-type tau transgenic ALZ17 mice that lack an NFT pathology (PROBST et al., 2000) failed to induce NFTs, suggesting that the toxic effect of Aβ is dependent on a pre-existing tau pathology (Götz et al., 2001b).

Subsequently, the so-called 3xtg-AD mice (P301L tau/APPsw/PSEN1M146I–knock-in) were generated that combine an NFT and plaque pathology (Figure 2C). Their formation was found to be preceded by synaptic and LTP (long-term potentiation) deficits (Oddo et al., 2003). The clinical features were correlated with intraneuronal Aβ formation (Billings et al., 2005), and blocking of Aβ was shown to delay onset and progression of the tau pathology (Oddo et al., 2008). A stereotoxic approach was used, not by injecting synthetic Aβ preparations (Götz et al., 2001b), but by injecting extracts from Aβ plaque-forming APP23 mice into P301L tau mutant JNPL3/B6 mice (Figure 2D). This induced a tau pathology in areas with a neuronal projection to the injection site (Bolmont et al., 2007). When the injections were performed in APP23/JNPL3/B6 mice with both a plaque and NFT pathology, a more pronounced tau pathology was induced in areas with a high Aβ plaque load (Bolmont et al., 2007) (Figure 2D).

While this supports the amyloid cascade hypothesis in mice, there is also a role for tau (Figure 3). Several years ago, Aβ toxicity in primary neuronal cultures was shown to depend on the presence of tau: wild-type neurons were found to degenerate when incubated with Aβ42 as did tau-transfected neurons (Figures 3A and 3B). However, primary neurons derived from tau knockout mice turned out to be resistant to the toxic effects of Aβ (Rapoport et al., 2002) (Figure 3C). This was translated in vivo by breeding APP mutant J20 mice on to a tau-knockout background (Roberson et al., 2007). Most, if not all, APP mutant strains with a robust Aβ plaque pathology are characterized by premature death of unknown cause (Palop et al., 2007; Minkeviciene et al., 2009; Palop and Mucke, 2009) (Figure 3D). Roberson and colleagues reported the remarkable finding that tau reduction ameliorates the premature lethality of the J20 mice, increases the resistance to excitotoxin-induced seizures and prevents behavioural deficits in the Morris water maze (Roberson et al., 2007) (Figure 3E).

Taken together, these studies suggest that Aβ and tau contribute synergistically to neurodegeneration in AD (Götz...
et al., 2007). The findings further indicate that a combinatorial therapy targeting both Aβ and tau may be useful (Golde et al., 2009).

**ADVANCES IN ANIMAL IMAGING AND THERAPY**

The preclinical diagnosis of AD depends on neuropsychological testing and, increasingly, the use of imaging techniques and biomarkers in CSF (cerebrospinal fluid) and blood. The major imaging techniques are PET (positron emission tomography), CT (computed tomography), MRI (magnetic resonance imaging) and multiphoton imaging. The field has been boosted significantly with the development of the PET tracer PIB (Pittsburgh Compound-B), a thioflavin T derivative. Using four-dimensional multiphoton imaging of transgenic mouse brain, PIB was shown to enter the brain extremely rapidly, Aβ was targeted within 1 min, and unbound florescence cleared within several minutes (Bacskai et al., 2003). This was soon followed by the first study using PIB in humans (Klunk et al., 2004). While PET has its undisputed beauty, there are, however, some major drawbacks, especially when PET is compared with MRI: it takes around 45 min for an entire scan (a situation with which healthy people are not comfortable let alone patients suffering from dementia); a cyclotron needs to be close to the imaging facility as the $t_{1/2}$ (half-life) of carbon-20 is only 20 min, and finally, PET is approx. 50 times as expensive as MRI. Multiphoton imaging has also been used to determine that plaque formation in mice can be a surprisingly rapid process, with an Aβ plaque forming within 24 h (Meyer-Luehmann et al., 2008).

Imaging assists in diagnosis, but has its place also in monitoring the efficacy of therapies. The current treatment rests on the use of AChE (acetylcholine esterase) inhibitors and memantine, an NMDA ($N\text{-methyl-D-aspartate}$) receptor antagonist. The AD major advocacy forum, AlzForum, at the time of writing this article lists 39 ongoing clinical trials which include NGF (nerve growth factor), DHA (docosahexanoic acid), vitamin A, anti-Aβ antibodies, $\gamma$-secretase inhibitors, $\alpha$-secretase activators, oestrogen, natural IgG, melatonin, a calcium channel agonist, anti-inflammatory...
substances [NSAIDs (non-steroidal anti-inflammatory drugs)], a nicotinic a7 agonist, statins and the chelator PBT2 (http://www.alzforum.org).

Many of these therapies have their foundation in animal work. This includes the vaccination approach, which has been pioneered by researchers of the biotech company Elan. Using both an active and passive immunization approach, existing plaques/Aβ pathology could be removed, the formation of plaques/Aβ pathology prevented, and age-dependent learning deficits reduced or prevented (Schenk et al., 1999; Bard et al., 2000). In follow-up work in 3xtg-AD mice, which present with a combined Aβ plaque and NFT pathology, these improvements were correlated with reductions in soluble Aβ and tau (Oddo et al., 2006). The last years have seen many modifications of the initial approach that has been tested in mice, using different routes of administration, changes to the peptide, alterations to the adjuvans, a DNA vaccination strategy, or as has been done recently, by coupling of Aβ to retro-particles (Bach et al., 2009). As the brain is generally conceived to be immune-privileged, the efficacy of the Aβ-targeted immunization approach came as a surprise, most likely also for those who had initiated the first vaccinations.

In the case of tau, one would think that efficacy would be even more difficult to achieve as, different from Aβ, tau is intracellular and hence, at least at first sight, not seen by the immune system. However, it seems as if tau is presented as an antigen or released into the extracellular space, because immunization of tau transgenic mice with the PHF1 phospho-tau-peptide (which contains the phospho-sites Ser396 and Ser404) causes a reduction of aggregated tau levels, a shift from the insoluble to the soluble pool of tau and a slowing of the progression of an NFT-related motor phenotype (Asuni et al., 2007).

The fact that our way of life affects our health in old age comes as no surprise. Several recent studies in mice address stress, diet, exercise and environmental enrichment. One of the earliest studies addressing the impact of an enriched environment used the APPsw/PS1D9 mice with a plaque pathology. Housing of the mice was in large cages and they were given running wheels, coloured tunnels, toys and chewable material to play with. This caused reductions in Aβ levels and plaque load; furthermore, levels of the Aβ-degrading enzyme neprilysin and of learning-related genes were up-regulated (Lazarov et al., 2005). When plaque-forming

| Tau   | X Aβ/APP | Observations                                      | References            |
|-------|----------|--------------------------------------------------|-----------------------|
| A.    | wt       | Aβ                                              | Neuronal Degeneration | Rapoport et al., PNAS 2002 |
| B.    | Tau KO   | Aβ                                              | NO Neuronal Degeneration | Rapoport et al., PNAS 2002 |
| C.    | Tau Transfer | Aβ                                           | Neuronal Degeneration | Rapoport et al., PNAS 2002 |
| D.    |          | J20                                             | • Premature lethality  | Roberson et al., Science 2007 |
|       |          |                                                 | • Sensitive to excitotoxin-induced seizures | |
|       |          |                                                 | • Behavioral deficits | |
| E.    | Tau -/-  | J20                                             | • Ameliorates premature lethality of APP mice | Roberson et al., Science 2007 |
|       | Tau +/−  | J20                                             | • Increases resistance to excitotoxin-induced seizures | |
|       |          |                                                 | • Prevents behavioral deficits | |

**Figure 3** Critical role for tau in Aβ toxicity

That tau is critical for Aβ-mediated toxicity, has been shown in primary neuronal cultures: wild-type (wt) neurons (A) degenerated when incubated with Aβ42, as did tau-transfected neurons (C). Primary neurons derived from tau knockout (KO) mice, however, were resistant to the toxic effects of Aβ (B). This has been translated in vivo. Most, if not all, APP mutant strains with a robust Aβ plaque pathology are characterized by premature death of unknown cause. This includes APP mutant J20 mice (D). By crossing these on to a hetero- or homo-zygous tau knockout background many clinical features could be ameliorated (E).
Tg2576 mice were fed with the green tea active compound EGCG (epigallocatechin gallate), this had similar effects: again, Aβ levels and plaque load were reduced, and this was dependent on the up-regulation of the α-secretase ADAM (α disintegrin and metalloproteinase) 10 (Rezai-Zadeh et al., 2005; Obregon et al., 2006).

The deacetylase Sir2 is a critical regulator of the ageing process. SIR2 is a longevity gene and SIRT1 is its human homologue. Resveratrol, a well-known active compound in red wine, activates SIRT1. When p25 transgenic mice [p25 is an activator of the kinase cdk5 (cyclin-dependent kinase 5)] were intra-hippocampally injected with SIRT1 lentiviruses, this protected the p25 mice from neurodegeneration (Kim et al., 2007). Finally, the typical Western diet is not well balanced with a ratio of unsaturated fatty acids of n–3 (omega-3)/n–6 (omega-6)=1:24, whereas the ideal diet would be 1:5. When Tg2576 mice were fed with n–3, this reduced Aβ levels by 70% and the plaque burden by 40% (Lim et al., 2005). Taken together this indicates a role for environmental factors in the progression of AD.

Both tau and APP are phospho-proteins, and phosphorylation is regulated by a balanced interplay of kinases and phosphatases; hence, numerous molecules which interfere with their function have been tested in vitro and in animals (Pei et al., 2008). Very recently, a zebrafish model has been established which reproduced tau hyperphosphorylation, NFT formation, and neuronal and behavioural disturbances, as well as cell death. Of the many inhibitors of the kinase GSK3β (glycogen synthase kinase 3β) tested in the fish model, AR–534 turned out to reduce tau hyperphosphorylation in vivo (Paquet et al., 2009).

Another strategy is the targeting of phosphatases as has been suggested recently (Iqbal and Grundke-Iqbal, 2008). Here, PP2A (protein phosphatase 2A) is particularly attractive, as instead of modulating general catalytic activity it may be possible to activate specifically the one of its many regulatory subunits that confers specificity for tau as a substrate (Kins et al., 2001; Schild et al., 2006). Together this presents a strategy that modulates either kinases or phosphatases as an attractive therapeutic approach (Iqbal and Grundke-Iqbal, 2008).

WHAT HAVE WE ACHIEVED SO FAR AND WHAT DOES THE FUTURE HOLD?

What has been achieved so far? Depending on how much emphasis is placed on the different aspects of AD modelling in animals (symbolized by the ‘M’ in Figure 4), the balance of

![Figure 4 Modelling in animals and what has been achieved so far](image)
achievements will vary. The difference in emphasis is not meant to be taken at face value, but should rather provide an idea for further opportunities of advancement.

In discussing what the future holds, we would like to highlight two selected aspects, selective vulnerability and the functional domains of APP. Selective vulnerability characterizes AD and FTD but the cellular and molecular basis of it is not at all understood (Götz et al., 2009). In AD, both the Braak staging outlined above (Braak and Braak, 1991) and the distribution of NFTs reflect selective vulnerability. Interestingly, in the AD brain some areas are spared from degeneration until very late in disease. Also, in the basal forebrain all neurons that die appear to contain NFTs (Cullen and Halliday, 1998), whereas in the CA1 region, up to 20% of the neuronal loss cannot be explained by NFT formation, suggesting that modes of death differ (Gomez-Isla et al., 1997; Kri et al., 2002; Giannakopoulos et al., 2003). How can transgenic mouse models be exploited to dissect selective vulnerability and identify genes and proteins that either protect from degeneration or confer an increased risk? This is exemplified for two selected mouse models, one characterized by memory impairment and the other in addition by parkinsonism (Figure 5): rTg(tauP301L)E510 mice with an inducible and hence very strong P301L mutant tau expression are characterized by massive brain weight loss and gross atrophy of the forebrain (Santacruz et al., 2005). By 5.5 months, 60% of CA1 hippocampal pyramidal neurons are lost, and by 8.5 months only 23% remain (Santacruz et al., 2005). K3 mice are characterized by loss of TH-positive, K369I tau-expressing neurons in the substantia nigra, long after the first clinical symptoms become apparent (Ittner et al., 2008, 2009). Interestingly, this loss is only partial, with 60% of the TH neurons lost by 24 months of age. What protects a subset of morphologically indistinguishable neurons within this brain area from cell death while others degenerate?

We previously used the tools of functional genomics to dissect pathogenic mechanisms, including mitochondrial dysfunction and AGE formation that not only operate in the transgenic mouse but also in human diseased brain (Chen et al., 2004b; Hoernndl et al., 2004; David et al., 2005a, 2005b; Hoernndl et al., 2005; David et al., 2006; Hoernndl et al., 2007). Functional genomics not only assists in dissecting disease mechanisms, but also emerges as a powerful tool in identifying cell-type-specific gene expression, which ultimately may be useful to understand selective vulnerability. In an impressive study, Sugino and colleagues used four GFP (green fluorescent protein)–expressing transgenic mouse lines to obtained eleven fluorescently labelled neuronal populations from different brain areas (Sugino et al., 2006). They triturated the neurons and by an elaborate panning process, manually isolated between 30 and 120 neurons from each brain area that they had characterized previously using current-clamp recordings. The subsequent analysis of the transcriptomic profile allowed them to construct a taxonomic tree that showed clear distinctions between neuronal cell types such as cortical interneurons and projection neurons (Sugino et al., 2006). We believe that crossing GFP-marked mice with AD or FTD mouse models such as those described above should allow identification of genes that confer susceptibility to or protection from neuronal degeneration. Ultimately, these genes can be reintroduced into the germine of mice for a functional validation (Figure 5).

Another aspect which is likely to receive more attention in the future is the realization that in pathogenesis functional domains of APP, other than Aβ, may have a role. APP overexpression causes an axonal transport defect (Stokin et al., 2005, 2008). However, by fusing the Aβ domain with the BRI protein, it could be shown that the APP-induced axonal defects are not caused by Aβ as one might have expected (Stokin et al., 2008). Similarly, in more recent work, APP was found to be a ligand of the DR (death receptor). Binding of an N-terminal APP fragment was further shown to trigger neuronal degeneration, leading to the notion that an extracellular APP fragment, in addition to Aβ, contributes to AD (Nikolaev et al., 2009).

Therefore it is obvious that more transgenic models are needed to dissect the role of the different functional domains of APP. Certainly, for any gene implicated in AD and FTD, more sophisticated cell-type–specific and/or inducible transgenic systems need to be developed. Animals need to be humanized by using BAC-transgenic approaches as has been done previously (Andorfer et al., 2003). More tools need to be developed, such as additional conformation- and epitope-specific antibodies, to better characterize and isolate toxic species (Habicht et al., 2007; Glabe, 2008). Finally, insight gained from the various animal species needs to be fully

Figure 5 Selective vulnerability examined in two mouse models with neuronal loss

Selective vulnerability characterizes two selected mouse strains, one characterized by memory impairment [rTg(tauP301L)E510 line] and the other, in addition, by parkinsonism (K369I tau mutant K3 strain). The rTg(tauP301L)E510 mice lose 60% of CA1 hippocampal pyramidal neurons by 5.5 months, and only 23% remain by 8.5 months. In the K3 mice, loss of TH neurons is also only partial, with 60% lost by 24 months of age. What protects a subset of morphologically indistinguishable neurons within the respective brain area from cell death while others degenerate?
integrated, taking into consideration the species-inherent limitations, but also the complementary potential. In conclusion, animal models will continue to be an important tool in AD and FTD research. While the mouse is likely to remain the major species, a larger contribution of invertebrate models can be foreseen.

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