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Murine models of Alzheimer's disease and their use in developing immunotherapies

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Abstract

Alzheimer's disease (AD) is one of the categories of neurodegenerative diseases characterized by a conformational change of a normal protein into a pathological conformer with a high β-sheet content that renders it resistant to degradation and neurotoxic. In AD, the normal soluble amyloid β (sAβ) peptide is converted into oligomeric/fibrillar Aβ. The oligomeric forms of Aβ are thought to be the most toxic, while fibrillar Aβ becomes deposited as amyloid plaques and congophilic angiopathy, which both serve as neuropathological markers of the disease. An additional important feature of AD is the accumulation of abnormally phosphorylated tau as soluble toxic oligomers and as neurofibrillary tangles. Many therapeutic interventions are under investigation to prevent and treat AD. The testing of these diverse approaches to ameliorate AD pathology has been made possible by the existence of numerous transgenic mouse models which each mirror specific aspects of AD pathology. None of the current murine models is a perfect match of the human disease. Perhaps the most exciting of the therapeutic approaches being developed is immunomodulation targeting the aggregating proteins, Aβ and tau. This type of AD therapy is currently being assessed in many transgenic mouse models, and promising findings have led to clinical trials. However, there is a discrepancy between results in murine models and ongoing clinical trials, which highlight the limitations of these models and also of our understanding of the underlying etiology and pathogenesis of AD. Because of these uncertainties, Tg models for AD are continuously being refined with the aim to better understand the disease and to enhance the predictive validity of potential treatments such as immunotherapies.

Keywords

Transgenic mice; Amyloid β; Congophilic angiopathy; tau; Immunization; Neurofibrillary tangles; Immunomodulation; Alzheimer's disease

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1. Introduction

Treatments for AD currently available provide largely symptomatic relief with only minor effects on the course of the disease; hence, there is an urgent need for better therapeutic interventions. Besides immunomodulation, numerous other approaches are being studied, which include anti-Aβ aggregation agents, secretase inhibitors/modulators blocking Aβ production, tau aggregation blockers, agents targeting mitochondria, stem cell therapies, and various neuroprotective strategies [1,2]. Currently, it appears that the greatest hope for an intervention that will significantly affect disease progression in the near future comes from immunization approaches [3–5]. In AD, Tg mouse models' Aβ-directed immunization has been hugely successful using a wide variety of methods. Despite this, significant unanswered questions remain for the current and future human trials as to what is the best design of a vaccine, what is the best target, and when should therapy start. A key issue that needs to be addressed is how to target the early initiating events in AD and not just the tombstone lesions that are the result of a long chain of pathological processes.

2. Pathogenesis of familial and sporadic Alzheimer's disease

The diagnostic neuropathological lesions of AD are the accumulation of Aβ as neuritic plaques and congophilic angiopathy, as well as aggregation of abnormally phosphorylated tau in the form of neurofibrillary tangles (NFTs). Missense mutations in APP or in the presenilin (PS) genes PS1 and 2 can cause early onset, familial forms of AD (FAD) affecting <4% of AD patients. The most common form of AD is sporadic and late onset. The dominant theory for the causation of AD has been the amyloid cascade hypothesis [6,7]. This theory currently suggests that accumulation of Aβ peptides particularly in a highly toxic oligomeric form is the primary pathogenic driver that downstream leads to tau hyperphosphorylation, NFT formation, and, ultimately, synaptic and neuronal loss. Extensive evidence supports this hypothesis in FAD patients and in models of FAD: (1) inherited forms of AD linked with mutations in the APP gene or in the PS1 or 2 genes are associated with changes in APP processing that favor over production of sAβ or production of more aggregation-prone forms of sAβ such as Aβ1–42 [8]. (2) Down's syndrome, where there is an extra copy of the APP gene due to trisomy 21, is associated with AD-related pathology at a very early age [9]. (3) In transgenic and other models of coexpressed amyloid β and tau, amyloid β oligomer formation precedes and accentuates tau-related pathology, consistent with the hypothesis that NFT formation is downstream from Aβ aggregation [10–15].(4) In transgenic mouse models of mutant APP over-expression (where there is no tau pathology), therapeutic prevention and/or removal of Aβ is associated with cognitive benefits in experimental mice [16–21]. Importantly, in transgenic mouse models of both mutant APP and tau overexpression (with both amyloid and tau-related pathology), prevention of Aβ pathology leads to both amelioration of cognitive deficits and attenuation of early but not late tau pathology [22–24]. In addition, it has been shown that reducing the level of endogenous mouse tau can prevent behavioral deficits in APP Tg mice without affecting Aβ levels [25] and that exogenous Aβ extracted from AD Tg mice can accelerate plaque deposition in predisposed young Tg mice [26]. However, evidence proving that Aβ is central in the common late-onset sporadic form of AD is more limited: (1) A correlation has been shown between biochemically extracted Aβ peptide species from sporadic AD brains with cognitive decline [27]. A comparison of several neuropathological features with cognitive states in AD revealed that the strongest predictor of cognitive dysfunction was Aβ load in the entorhinal cortex [28]. (2) Isolated Aβ peptide dimers/oligomers from sporadic AD brains have been documented to impair synaptic structure and function [29]. (3) Aβ extracted from sporadic AD patients has been shown to induce amyloid deposits when injected into transgenic mice [30]. A significant problem for the amyloid cascade hypothesis comes from the autopsy data from the initial human active vaccination trial targeting full-length Aβ. Postmortem analysis was available from nine subjects in the active immunization arm [31].

All these individuals showed partial or near-complete plaque removal and reduced Aβ load compared to age-matched nonimmunized controls. Despite this, there were no differences between placebo and active immunization groups in terms of long-term survival outcome, time to severe dementia, and in outcome measures such as ADAS-Cog, MMSE, or DAD. This may be related to immunization having begun too late in the disease process; alternatively, one can use these data to suggest that the amyloid cascade hypothesis is an oversimplification. A number of investigators have suggested alternative theories, whereby accumulation of Aβ and tau hyperphosphorylation are dual pathways both downstream from a common upstream pathogenic deficit (which remains to be identified) [32–34]. In such a scenario, it is essential for immunotherapy to address both of these pathologies to be highly effective. In this review, we discuss the various approaches that have been tried to target parenchymal amyloid deposition, vascular amyloid, oligomeric Aβ, and tau-related pathology.

3. Overview of transgenic mouse models

3.1. A. Models of amyloid plaque deposition

The majority of successful models to generate Aβ deposits have used transgenes for human APP with missense mutations found in the familial form of Alzheimer's disease (FAD; see Table 1). The first transgenic model (PDAPP), published by Games et al. [35], used the Indiana mutation V717F under the control of the PDGF promoter. This model shows a robust increase of Aβ deposition between 6 and 9 months, with the expression of APP being ~18-fold greater than endogenous levels. Minimal CAA can be found in these mice from about 18 months. In old mice, the size of amyloid fibrils and the association of plaques to dystrophic neurites were shown to be analogous to the pathology detected in patients with AD [36]. The next AD transgenic model to be developed used the Swedish APP mutation (APP 695, K670N/M671L) under the control of the PrP mouse promoter [37]. This model is referred to as Tg2576 and is the most widely studied Tg model of amyloid deposition. The brain Aβ levels start increasing at 6 months and Aβ parenchymal deposits start developing between 9 and 12 months [37,38]. Congophilic angiopathy can be abundant in these mice at advanced ages (> 18 months) [39]. The overexpression of the mutant APP is about 5-fold. This model was extensively used to examine the role of inflammation, including astrogliosis [40], microgliosis [41], cytokine production [42], and oxidative stress [43,44]. Several behavioral tests have shown age-dependent impairment with cognitive tasks [18,20,37,45–47]. Further models such as the APP23 were generated using the APP751 isoform, expressed under control of the murine Thy-1 promoter with 7-fold overexpression [48]. Plaques are evident at 6 months of age in the hippocampus and cortex, with older animals having plaques also in the thalamus and olfactory nucleus. Another line, APP22, expresses the Swedish (APP 695, mutated K670N/M671L) and London mutation (APP V717I) under control of Thy-1 promoter. These Tg mice develop amyloid deposits at 8 months with 2-fold overexpression of APP. The transgenic CRND8 mouse line was generated under the control of the PrP promoter using the Swedish and the Indiana mutations (V717F) [49]. Amyloid β deposits start quite early (from the age of 3 months) since the two mutations involve both the β and γ secretase APP cleavage sites. In these mice, the pathology starts in the subiculum and the frontal cortex, followed by spread to the rest of the cortex and hippocampus and then the thalamus, striatum, and cerebral vasculature. The mThy-1 APP 751 mouse [50] is analogous in terms of spread of the pathology to the CRND8 line. A comparison of transgenic mice overexpressing mutated (V717I and Swedish mutation) and wild type human APP showed that cognitive deficits could be seen as early as 3 months, well before amyloid deposition, suggesting that Aβ peptide-soluble aggregates could be related to these phenotypic traits [51]. Other single Tg lines were generated by expression of either the Flemish (APPA692G) or the Dutch mutation (APPE693Q) [52]. These FAD mutations are associated with extensive CAA, but in the Tg mice, they led to behavioral abnormalities in the absence of amyloid deposition.

The next step in creating Tg models of Aβ parenchymal deposition was to cross APP mutation lines with Tg mice expressing FAD linked presenilin (PS) 1 mutations. More than 160 mutations in PS-1, located on chromosome 14q, and 11 mutations on PS-2, located on chromosome 1, have been linked to FAD [53]. PS is part of the γ-secretase complex and FAD-linked mutations are associated with an increase in Aβ42 production [54–56]. Crossing PS1 mutation mice with APP Tg models dramatically increases amyloid deposition, thought to be due to increased Aβ42 production [57–60]. In these various Tg models, the ratio of Aβ 40 to 42, as well as the expression of "chaperone" proteins, affects the type and distribution of amyloid deposits [61–63]. The critical role of Aβ42 in "seeding" amyloid deposition was illustrated in Tg mice that express Aβ1–40 or Aβ1–42 in the absence of human APP overexpression by the fusion of Aβ42 and Aβ40 to the C-terminal end of the BRI protein [64]. Mutations in BRI are associated with the cerebral amyloidoses of British and Danish dementias [65,66]. The Aβ1–42 expressing mice developed extensive cored plaques, diffuse plaques and CAA (at older ages), in contrast to the Aβ1–40 mice that did not develop amyloid deposits at any age [64]. Although Aβ42 appears to be essential for seeding, Aβ40 can influence the amount of CAA, perhaps related to the fact that the major biochemical component of CAA is Aβ40 [67].

The expression of several Aβ binding proteins can also influence Aβ deposition and clearance. In particular, the expression of apolipoprotein E (apoE) isoforms is a significant factor [63, 68]. Many studies have shown that the inheritance of the apoE4 allele is the single most important genetic risk factor for late-onset AD identified so far [63,68]. The role of apoE in AD is complex with it being involved in both the aggregation state of Aβ and its clearance [62,63,68,69]; however, one suggested role for apoE has been as a "pathological chaperone" that can induce a β-sheet conformation in Aβ [70–73]. The critical role of apoE in Aβ deposition was shown when PDAPP and Tg2576 mice were crossed to murine apoE knockout (KO) mice resulting in a complete lack of true amyloid plaques [74,75]. The effects of different human apoE isoforms on Aβ deposition are somewhat more complex. In PDAPP mice expressing human apoE, there was a marked delay in amyloid deposition compared to murine apoE expressing mice or apoE KO mice; however, the apoE4-expressing mice had increased levels of Aβ deposits compared to apoE3 mice [39,76,77]. These crosses have also been performed using mice that express human apoE isoforms under the control of endogenous mouse regulatory elements to examine this issue under more physiological conditions. When these knock-in apoE3 and apoE4 mice were crossed to Tg2576 mice or more recently in PDAPP mice, the apoE4 mice had significantly more parenchymal amyloid deposition and more CAA than the apoE3 mice [78,79]. In humans, the significance of apoE expression has been well documented by autopsy studies and by neuroimaging, showing that apoE4-expressing individuals have a higher amyloid burden and glucose utilization abnormalities even in presymptomatic stages of AD [80–83]. The expression of different apoE isoforms is an important consideration for immunomodulation, as current human data suggest that apoE4 carriers are more likely to experience inflammatory/hemorrhagic complications from immunomodulation, and in some clinical trials, apoE4 carriers are being excluded or are limited to lower doses of anti-Aβ antibodies[4,5,84]. The effect of immunomodulation in different human apoE isotype-expressing AD Tg models is a subject of ongoing investigation.

One of the limitations of the existing Tg amyloid models is the relative lack of neuronal loss, contrasting to what is found in AD [41,85,86]. Three Tg lines with some neuronal loss are the APP23 mice [48,87], a line with both the Swedish and London FAD APP mutations, along with two PS1 mutations (M233T/L235P) [88], and a model that expresses five familial AD mutations, three of those within the APP gene (Swedish, Florida, and London) and two within the PS1 gene (M146L and L286V) ("Vassar" or 5xFAD Tg mice) [89]. In the APP23 mice, there is limited neuronal loss in old animals in the direct vicinity of thioflavin-positive amyloid plaques in the CA1 sector of the hippocampus. In the model described by Casas et al. [88],

there is ~50% loss in the CA1/2 sectors of the hippocampus correlating with the accumulation of intraneuronal Aβ rather than extracellular plaques. In the Vassar model, large pyramidal neurons in cortical layer 5 and subiculum are lost. Synaptic markers decrease as well in these models with age. Many other Tg lines that do not develop extensive neuronal loss have shown age-associated synaptic degeneration [60,85,86,90,91]. In the widely used Tg2576 mice, synaptophysin immunoreactivity loss occurs in 21- to 25-month-old mice with associated electrophysiological changes suggesting synaptic dysfunction [92]. In addition, elegant 3D multiphoton microscopy studies in Tg2576 and APP/PS1 Tg mice have shown neurite displacement, dendritic spine loss, thinning of dendrites, and dendritic breakage adjacent to amyloid plaques, suggesting that dense-cored amyloid plaques do contribute at least partially to the cognitive abnormalities found in these mice [92,93]. However, it is likely that small soluble aggregates of Aβ are a more important cause of neuronal dysfunction since cognitive deficits in these mouse lines occur well before the appearance of widespread cored amyloid plaques. This hypothesis is supported by a series of Tg lines produced by Mucke et al. [94] expressing wild type and mutant APP which do not have amyloid deposition but have age-associated synaptophysin immunoreactivity loss that correlates with brain-soluble Aβ levels. It should be mentioned, however, that overexpression of APP may conceivably have synaptotoxic effects by itself or through other APP fragments other than Aβ. The lack of more marked synaptic and neuronal loss in APP and APP/PS1 mice, unless multiple mutations are expressed, is likely related to the fact that none of these Tg lines develop significant tau-related pathology. Phosphorylated tau epitopes have been noted in dystrophic neurites adjacent to cored amyloid deposits [35,37,59]. In particular, the S199/S202 site recognized by the monoclonal Ab AT8 is found in many mice, but not the more AD-specific phosphorylation sites such as those at residues S396, S404, and S422. An additional important factor determining the degree of neuronal loss and tau pathology in Tg AD models may be the expression of other genes that play a significant role in disease that are downstream from Aβ accumulation. For example, APPSw crossed with mice with a KO of nitric oxide synthetase 2 (NOS2) have 30% hippocampal neuronal loss that correlates with behavioral abnormalities [95]. It has been recently shown that active vaccination with Aβ1–42 with Freund's adjuvant can prevent the neuronal loss found in these mice [96].

3.2. B. Transgenic models of vascular amyloid deposition

Most AD patients have some degree of congophilic angiopathy (CAA) at autopsy, with approximately 20% of AD patients having “severe” CAA [97]. Furthermore, CAA is present in about 33% of cognitively normal elderly, control populations [98]. The population-based Honolulu Asia Aging Study has shown a significant correlation between cognition and the presence of CAA [99]. Many of the Tg models of parenchymal amyloid discussed above and listed in Table 1 also have some vascular amyloid deposition with a variable age of onset [100]. However, the Tg model with the most extensive vascular amyloid in association with lower levels of parenchymal amyloid is the APPSwDI mouse that incorporates 3 APP mutations: Swedish, Dutch E693Q, and Iowa D694N [101–103]. These Dutch and Iowa mutations are associated with hereditary cerebral hemorrhage with amyloidosis (HCHWA) [104,105]. The parenchymal Aβ deposits in these mice largely do not stain with Congo red and represent nonfibrillar, diffuse amyloid similar to the neuropathology of HCHWA-Dutch [106]. A caveat with the APPSwDI mice is that the vascular amyloid deposition is mainly in capillaries, in contrast to AD CAA, which is primarily in arterioles with less capillary involvement. Interestingly, in human autopsy tissue, it is the capillary CAA level that correlates best with the presence of other AD-related pathology [107]. When the APPSwDI mice were crossed with NOS2 KO mice, there was an increase in amyloid deposition in association with a 30% neuronal loss in the hippocampus [96]. The Tg2576 and the APPSwDI mice with and without NOS2 KO have been shown to have significant blood–brain barrier abnormalities, which mirror what is found in AD autopsy tissue [108]. Importantly, the neuronal loss and

behavioral abnormalities have been shown to be preventable in the APPSwDI/NOS2 KO mice by Aβ1–42 vaccination [96].

3.3. C. Transgenic models of tau pathology

A number of tau mutations have been reported to be associated with frontal temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), but none has been shown to produce AD pathology [109,110]. A number of transgenic mice models that express human tau with FTDP-17 mutations have been produced [111]. Some of these mice display neurofibrillary tangles, neuronal death, and behavioral deficits [112–124]. In most of these models, there is presumably a disruption of axonal transport due to the mutated tau expression and aggregation that induce synaptic and neuronal loss. In addition, one Tg mouse model that expresses a mutated (N279K) tau shows behavioral deficits without formation of NFTs or neuronal loss [125]. The distribution of tau pathology in many of these tauopathy models is distinct from AD, with pretangles and tangles often prominent in regions such as the brain stem and spinal cord, with lesser involvement of hippocampal and cortical regions [111].

An additional tau mutation model is the triple transgenic line (3×Tg-AD) that expresses the PS1M146V, APPSwe, and TauP301L transgenes. This model develops extracellular amyloid deposits from 6 months of age, and tau-related pathology starting at 10 to 12 months of age [11,126], first in the hippocampus and then progresses to the cortex [126]. Deficits in long-term synaptic plasticity correlate with the accumulation of intraneuronal Aβ [11]. Recently, it has been reported that spatial and contextual learning and memory were affected in the 3×Tg-AD mice in an age-dependent manner, and the accumulation of intraneuronal Aβ correlates with cognitive deficits [127]. Variability in the pathology of this model has been reported [128]. Some lines have delayed pathology, with plaque deposition starting at 15 months [128].

To generate a more ideal model for AD, other researchers have used a single wild-type human tau to generate a transgenic model; however, most of these models did not develop NFTs, with the exception of two models: one expressing ON3R wild-type tau with a few NFTs in aged animals [116] and another with abundant NFTs that expresses all six human tau isoforms on a knockout background for murine tau [129,130] that develops age-related cognitive deficits [131]. The relative absence of tau pathology in mice that express wild-type human tau is likely due to the endogenous tau inhibiting the formation of NFT-like pathology.

Recently, a new model has been generated by crossing htau mice (with expression of six tau isoforms) with mice expressing the M146L PS1 mutation [57]. This model maintained on a mouse tau knockout background shows earlier and more advanced tau pathology than the htau model and develops more severe cognitive deficits as well [132,133].

4. Immunotherapy targeting parenchymal amyloid deposits

4.1. Active immunization

Supporting data for AD immunotherapy initially showed that anti-Aβ antibodies could inhibit Aβ peptide fibrillization/oligomerizaton and prevent cell culture-based neurotoxicity [134, 135]. This leads to vaccination of AD Tg mice with Aβ1–42 or Aβ homologous peptides coinjected with Freund's adjuvant, which demonstrated striking reduction in Aβ deposition and, as a consequence, elimination of behavioral deficits (Table 2) [16–21]. This has also been done with Aβ encoding DNA vaccines and Aβ peptide fragment (EFRH) phage vaccines [136–138]. Similar effects on Aβ load and behavior have been demonstrated in AD Tg mice by peripheral injections of anti-Aβ monoclonal antibodies indicating that the therapeutic effect of the vaccine can be based primarily on eliciting a humoral response [139,140]. In the initial preclinical studies, no toxicity was evident in the treated mice; however, some investigators

suggested that use of nonfibrillogenic, nontoxic Aβ homologous peptides along with approaches that stimulate primarily humoral, Th_2 immunity, in contrast to a primary Th_1 cell-mediated response might reduce potential toxicity [141–143]. The dramatic biological effect of vaccination in preclinical testing encouraged Elan/Wyeth in April 2000 to launch a randomized, multiple-dose, dose-escalation, double-blind phase I clinical trial with a vaccine designated as AN1792, which contained preaggregated Aβ1–42 and QS21 as an adjuvant. This type of vaccine design was aimed to induce a strong cell-mediated immune response, since QS21 is known to be a strong inducer of Th_1 lymphocytes [144]. The initial trial was conducted in the United Kingdom and involved 80 patients with mild to moderate AD [145]. This trial was designed to assess the antigenicity and the toxicity of multiple-dose immunization with the full-length Aβ1–42 peptide with the QS21. About 53% of patients developed an anti-Aβ humoral response. During the later stages of the phase I trial, the emulsifier polysorbate 80 was added, causing a more pronounced proinflammatory Th_1 response [146]. In the subsequent phase IIa trial, begun in October 2001, 372 patients were enrolled, with 300 receiving the aggregated Aβ1–42 (AN1792) with QS21 in the polysorbate 80 formulation. This trial was prematurely terminated in January 2002 when 6% of vaccinated patients manifested symptoms of acute meningoencephalitis (18/298 subjects) [144,147,148]. Autopsies performed on a limited number of trial patients suggested that striking Aβ clearance of parenchymal plaques had occurred, similar to what had been reported in the animal studies, confirming the validity of this approach for amyloid clearance in humans [148–153]. In these cases, extensive areas of cerebral cortex were devoid of plaques, with residual plaques having a “moth-eaten” appearance or persisting as “naked” dense cores. This amyloid clearance in most cases was in association with microglia that showed Aβ immunoreactivity, suggesting phagocytosis. Additional striking features were the persistence of amyloid in cerebral vessels in most patients, as well as limited effects on tau immunoreactive NFTs and neuropil threads in regions of cerebral cortex where plaque clearing had apparently occurred, compared to regions without clearing [151–154]. A recent study of five patients who had participated in the phase IIa Elan trial showed a reduction in dystrophic neurites as well as a reduction in PHF-1 immunolabeled NFTs, but no reduction in Alz50 or thioflavin-2-positive tangles [155]. Furthermore, more neuritic dystrophy was found associated with the dense-cored plaques that remained in the vaccinated AD patients [155]. Hence, this initial vaccination approach has not sufficiently addressed either NFT-related or vascular pathology. Some cases also showed a deleterious T-cell reaction surrounding some cerebral vessels, suggestive of an excessive Th_1 immune response. It appeared that the immune reaction triggered by AN1792 was a double-edged sword, where the benefits of a humoral response against Aβ were overshadowed in some individuals by a detrimental T-cell-mediated inflammatory response [148,156]. The likely involvement of an excess cell-mediated response in mediating toxicity was supported by analysis of peripheral blood mononuclear cells from trial patients, which were stimulated in vitro with the Aβ peptide, followed by quantification of cytokine secretion by enzyme-linked immunosorbent spot assay [146]. The cells of most responder trial patients mounted IL-2- and IFN--γ-positive responses, indicative of a class II ($CD4^+$) Th_1-type response [146]. Not all patients who received AN1792 responded with antibody production. The majority mounted a humoral response and showed a modest but statistically significant cognitive benefit, demonstrated as an improvement on some cognitive testing scales compared to baseline and a slowed rate of disease progression compared to the patients who did not form antibodies [145,157], although the effect on cognition was not clearly evident when subjects from several different sites were analyzed together [158]. The follow-up data from the Zurich cohort, who are a subset of the Elan/Wyeth trial [157,159], indicated that the vaccination approach might be beneficial for human AD patients. In agreement with the findings in the Zurich cohort, immune responders with high antibody titers in the multicenter cohort scored significantly better in composite scores of memory functions as compared to low- and nonresponders or to the placebo group of patients [146]. Active vaccination approaches under development in Tg mouse models are aiming to avoid the excessive Th_1 stimulation associated with the human

trial. Concurrently, the formulation of any active vaccine also has to overcome the problem of immunosenescence in the target patient population. One promising approach taken by several investigators is to alter the sequence of the Aβ peptide immunogen to remove or alter the major Th_1 stimulator sites in the carboxyl terminus and the middle portion of Aβ, while focusing on the major Th_2 stimulator site in the amino terminus [20,21,142,160–162]. These Aβ homologous peptide immunogens can be combined with various costimulator epitopes. An example of this approach is a combination with a synthetic, non-natural Pan HLA DR-binding epitope PADRE [162] or linkage to viral-like particles (VLPs) [163–165] to induce a primarily humoral immune response. These can be further combined with other immunostimulator carriers. For example, the Aβ Th_2 amino terminal epitope can be combined with PADRE and macrophage-derived chemokine (MDC) in a DNA epitope vaccine to drive robust Th_2 responses [166]. The choice of adjuvant is also an important consideration. The use of polysorbate 80 and a strong Th_1 stimulate adjuvant (QS21) in the AN1792 trial is one likely contributing factor to the encephalitis in a minority of patients. Use of adjuvants such as alum that drive primarily a Th_2 response is preferable [21,167]. The route of immunization also plays an important role. Stimulating mucosal immunity by vaccinating nasally, via the gut or transcutaneously, has been shown to be beneficial and may favor a Th_2 response [168–173].

A difficulty with active immunization aimed at just the removal or prevention of parenchymal amyloid deposition is the autopsy data from the human trial. Despite the apparent success in amyloid clearance indicated by the limited autopsy data, the clinical cognitive benefits were very modest when the active vaccination group was compared to the placebo group [158]. No difference between the antibody responders and the placebo group was found on the ADAS-Cog, Disability Assessment for Dementia, Clinical Dementia Rating scale, MMSE, or on the Clinical Global Impression of Change. It was only on a nine-item composite NTB that antibody responders had a slight benefit compared to the placebo group. These data can be used to suggest that vaccination in this cohort was started too late, at a time point when irreversible neurodegeneration has already occurred; hence, tau-related pathology was largely unaffected by vaccination, and thus, the cognitive benefits were small. Alternatively, it can be suggested that the amyloid cascade hypothesis must be an oversimplification of the pathogenesis of sporadic AD. The latter view is supported by the follow-up study of the 80 patients in the initial phase I AN1782 trial, of whom 8 came to autopsy [31]. This study showed that despite evidence of very significant amyloid plaque removal in 6 out of the 8 autopsy subjects, which correlated with the anti-Aβ titer, in the overall group, there was no evidence of improved survival or attenuation of dementia progression [31].

4.2. Passive immunization

The easiest way to fulfill the goal of providing monoclonal anti-Aβ antibodies without risk of uncontrolled Th_1-mediated autoimmunity is by passive transfer. AD Tg model mice treated this way had a significantly reduced Aβ level and demonstrated cognitive benefit [139,140, 174–176]. Potential problems with passive immunization include the need for repeated injections in a chronic disease, high cost, proper selection of antigen targets, blood–brain barrier penetration, the risk of hemorrhages, and the development of an immune response to the injected antibodies. Several passive immunization trials are underway with the most advanced being the phase III bapineuzumab trial begun in December 2007 [4]. The phase II trial using this anti-Aβ monoclonal antibody was a randomized, double-blind, placebo-controlled trial testing 3 doses in 240 participants. In each of the escalating doses of the antibody, approximately 32 subjects received active agent and 28 placebos. Although the study did not attain statistical significance on the primary efficacy end point in the whole study population, in the subgroup of non-apoE4 carriers, clinically significant benefits were documented using a number of scales including the Mini Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale Battery, during the 18-month trial period. In addition, among non-

apoE4 carriers, evaluation of the MRI results showed less loss of brain volume in treated versus control patients. However, it was reported that some patients in the treatment group developed vasogenic edema, a significant adverse reaction. The phase III trial is targeting to recruit 800 patients and run until December 2010.

A particular concern in association with passive immunization is cerebral microhemorrhage. The mechanism of this hemorrhage is thought to be related to Aβ deposition in the form of congophilic amyloid angiopathy (CAA) that causes degeneration of smooth muscle cells and weakening of the blood vessel wall. A number of reports have shown an increase in microhemorrhages in different AD mouse models following passive intraperitoneal immunization with different monoclonal antibodies with high affinity for Aβ plaques and CAA [177–179]. Microhemorrhages following active immunization in animal models have also been reported in three studies [96,180,181]. In particular, in the APPSwDI/NOS2 KO mouse model with the most extensive vascular amyloid, vaccination with Aβ1–42, while reducing the amyloid burden in association with behavioral benefits, led to a marked increase in microhemorrhages [96]. While this increase in microhemorrhages does not appear to be symptomatic in the mouse models, this would be much less likely in humans. Strategically placed microhemorrhages in patients have been shown to correlate with cognitive deficits [182,183]. Interestingly, gentler clearance of Aβ with immunogens eliciting moderate antibody response may prevent further cerebral bleeding. For example, vaccination of the Tg2576 model with an Aβ derivative, K6Aβ1–30, reduced Aβ burden and improved cognition without increase in microhemorrhages [21].

In transgenic mouse models, Aβ antibodies can in theory both prevent the deposition of vascular amyloid and remove it, with the former scenario contributing to vascular repair, whereas the latter may potentially promote bleeding. However, clearance of parenchymal Aβ complicates the picture because several mouse studies suggest it may lead to enhanced vascular amyloidosis, thereby canceling any direct effect of the antibodies on Aβ deposits in vessels. On the other hand, the autopsies from the AN1792 trial indicated no clearance of vascular amyloid, and in one of these cases, numerous cortical bleeds were found, which are typically rare in AD patients, [150]. This is an important issue since CAA is present in virtually all AD cases, with approximately 20% of AD patients having “severe” CAA [97]. The need for vascular repair and regeneration during Aβ immunotherapy represents another argument for early treatment as well as an argument favoring subtle clearance over a longer period.

5. Immunotherapy targeting tau pathology

Neurofibrillary tangles (NFTs) are intraneuronal inclusion bodies that consist of an accumulation of paired helical filaments (PHFs), which are mainly composed of abnormally phosphorylated tau. NFTs are a major pathologic hallmark of AD. Recently, there has been an increased focus on phosphorylated tau as an immunotherapeutic target [184–187]. In the CNS, human tau is expressed in six isoforms arising from alternative mRNA splicing from a single gene on chromosome 17q21, containing 16 exons [188,189]. The size range of the six isoforms is between 352 and 441 amino acids, which differ by the absence or presence of 29 (exon 2) or 58 (exon 2 + exon 3) amino acids inserts in the amino-terminal. The carboxy-terminal half of tau contains three or four semihomologous repeats of 31 or 32 amino acids, encoded by exon 10. The repeats (3R, 4R) correspond to the microtubule-binding region of protein tau. Stabilization of microtubules by tau is essential for the maintenance of neuronal cell morphology and for transport within the neuron. In addition, tau has other roles such as interactions with kinesin-1 and the complex dynactin/dynein [190,191]. Tau also plays a crucial role in neuronal cell architecture by interacting with the plasma membrane as well as cytoskeleton proteins such as actin, spectrin, and neurofilament proteins. Several mutations have been detected in the tau gene in FTDP-17 and other tauopathies; however, none has been

linked to AD [109]. Most of these mutations affect the binding of tau to microtubules or enhance the aggregation of tau into fibrils. Other intronic mutations that affect the splicing of exon 10 induce an increase of isoforms with four repeats. In AD, tau is hyperphosphorylated at many phosphorylation sites with nine phosphates per molecule in comparison to normal brain tau that has two to three phosphorylated residues [192]. Other studies suggested that changes in tau splice forms are related to neurodegeneration. In some animal models expressing mutated tau, there is an increase of 4R versus 3R tau [193]. The functional significance of a shift in the 3Rtau/4Rtau ratio remains unclear, but four-repeat tau binds microtubules with a higher affinity than three-repeat tau [194].

Normal tau and PHF tau differ in molecular weight and banding pattern. Normal tau has six bands between 45 and 68 kDa, while PHF-tau has four bands between 60 and 74 kDa [195, 196]. The diversity of tau isoforms is related to various posttranslational modifications such as phosphorylation, glycosylation, glycation, ubiquitination, and nitration [197]. Tau has multiple phosphorylation sites that have been characterized using phospho-tau-dependent antibodies. Of the 85 potential phosphorylated sites, 71 have been shown to be phosphorylated in physiological or pathological conditions [198,199]. More than 20 protein kinases have been implicated in the phosphorylation of tau proteins, with glycogen synthase kinase-3β (GSK-3β) and cyclin-independent kinase (cdk5) thought to play the most important role in phosphorylation under pathological condition [198–201].

Recently, it has been shown that active immunization of homozygous Tg JNPL3 P301L mice [202] with a phospho-tau peptide (containing the phosphorylated PHF-1 epitope Ser 396, Ser 404) for 3–6 months could reduce tau-related pathology (Table 3) [203]. This particular phospho-epitope was chosen because of its immunogenicity and prominent involvement in tau pathology [187]. Histological and biochemical analyses showed a reduction of aggregated tau in the brain and improved performance on motor tasks [203]. Motor impairments are prominent in this model as tau pathology is particularly advanced in brain stem and spinal cord. This study clearly documented that it is possible to reduce tau-related pathology with active immunization. Purified antibodies from high-titer mice entered the brain and neurons following an intracarotid injection and bound to pathological tau.

At first examination, it is difficult to understand how an antibody response to a protein, which is accumulating intracellularly, can have beneficial effects. However, such an outcome is supported by a study of immunization in a Parkinson's disease transgenic mouse model with α-synuclein showing a reduction of intracellular α-synuclein aggregates [204]. Another study has shown that antibodies against Aβ can be internalized in AD neuronal culture models of Aβ accumulation and clear intraneuronal Aβ aggregates via the endosomal–lysosomal pathway [205]. Furthermore, recent evidence has shown that extracellular tau aggregates can be internalized and promote the fibrillization of intracellular full-length tau in a tissue culture model [206]. In addition, injection of fibrillar tau brain extract into the brains of transgenic wild-type expressing mice can induce the formation of human tau into filaments, as well as the spread of pathology from the site of injection into neighboring brain regions [207]. This type of “infectivity” of abnormal protein conformation from outside the cell has also been demonstrated for polyglutamine aggregates [208] and is well characterized in prion disease [209,210]. Aβ has also been shown to have such “infectious” properties in vivo, being able to induce an acceleration of both further Aβ and tau-related pathology [13–15,26,211,212]. Hence, if the spread of PHF pathology in AD can occur via such a prion-like mechanism, antiphosphorylated tau antibodies would not need to enter cells to be effective.

6. Immunotherapy by stimulation of the innate immune system

An alternative, nonmutually exclusive approach to enhance vaccine design is to stimulate innate immunity and enable microglia/macrophages to clear amyloid and/or NFTs. More than 20 years ago, H. Wisniewski noted that while brain-resident macrophages were unable to phagocytose amyloid, brain-infiltrating macrophages are plaque-competent [213]. A number of recent studies suggest that only a small percentage of plaques are associated with peripheral origin macrophages and that these are required for plaque clearance [214–216]. Vaccination approaches based on this knowledge are now being developed. Stimulation of peripheral macrophages to enter the CNS and phagocytose amyloid has been achieved by stimulation of the Toll-like receptor 9 using unmethylated cytosine-guanosine oligonuceotides (CpG) [217, 218], via blockade of the CD40/CD40L interaction [219] and by blockade of TGFβ-Smad2/3 innate signaling pathway [220]. Significantly, amyloid clearance by CpG stimulation was effective against CAA and parenchymal amyloid without any associated increase in cerebral microhemorrhages [217]. These innate immunity stimulatory approaches can be used alone or in combination with adaptive immunity stimulation. Stimulating the innate immune system has the added potential advantage that it could be effective against both Aβ and tau-related pathologies. Studies to address whether stimulation of the innate immune system will be effective to inhibit tau-related pathology are underway.

7. Immunization targeting Aβ and tau oligomers

Abundant evidence both in vivo and in vitro suggests that the most toxic species of Aβ are oligomers or Aβ-derived diffusible ligands (ADDLs) [221,222] with a similar line of evidence suggesting that tau oligomers are the most toxic form of phosphorylated tau [120,186]. Active vaccination or use of monoclonal antibodies that specifically target Aβ oligomers, tau oligomers, or preferably both would be an ideal way to block AD-related toxicity. A small number of preclinical studies targeting Aβ oligomers suggest that this methodology is potentially powerful and in the need of further development [223–227]. However, various proteins/peptides exist to some extent in a β-sheet conformation, which raises concerns about possible side effects of this otherwise promising approach [228]. On the other hand, indiscriminate clearance of all forms of Aβ may not be ideal because emerging evidence suggests that monomeric Aβ peptides have normal physiological functions in the brain such as neuroprotection and modulating LTP [229,230], with normally phosphorylated tau also having a role [185]. Targeting only oligomeric Aβ or tau would avoid potential interference with these physiological functions. A novel immunotherapeutic approach is to target the shared abnormal β-sheet conformation of amyloid proteins using conformationally specific antibodies or active immunization that favors such a conformational response [223,224,231,232]. Such an approach has the advantage that both Aβ and tau-related pathologies would be addressed concurrently.

8. Conclusions

Many studies are underway in AD Tg mouse models aiming to improve the efficacy and safety profile of immunomodulation in patients. Approaches that concurrently address the three AD-related pathologies, namely, neuritic plaques, CAA, and NFTs, will have the greatest chance of success. Abnormal protein conformation is thought to be not only the underlying pathogenesis of AD but also of a long list of neurodegenerative conditions, such as prion disease, Parkinson's disease, and Huntington's chorea, with immunomodulation having the potential to be a disease-altering therapeutic approach for all these disorders [5]. For example, it has been shown that prion-directed mucosal vaccination can prevent infection from an exogenous source [234,235]. The development of safe and effective immunomodulation methods in Tg models that direct the immune system to clear highly toxic abnormal oligomeric

conformers that underlie the pathogenesis of multiple neurodegenerative diseases has the greatest potential to halt the progression of a wide spectrum of human neurodegenerative conditions.

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Table 1

Summary of some reported AD Tg mouse models developed, with the approximate timing of parenchymal and vascular amyloid deposition, as well as timing of cognitive deficits (abbreviations: Morris water maze [MWM], radial arm maze [RAM], Barnes maze [BM], spontaneous alternation Y-maze [SAYM]).

Transgenic Line	Mutations	Isoforms	Promotor	Expression level of APP transgene	Neuron loss	CAA severity	Age at onset of cognitive deficit and test used	Time of development of cerebral amyloid angiopathy	Age at which Aβ plaque deposits start	Reference
PDAPP	V717F	695	PDGF-β promoter.	18-fold	−	+	6 months (MWM)	24 months	6 months	[35]
Tg2576	KM670/671 N	695	Hamster PrP	5-fold	−	+	9 months (MWM)	16 months	9–12 months	[37]
APP23	KM670/671 N	751	Thy1.2	7-fold	+	++	3 months (MWM)	12 months	6 months	[48]
APPPS1	KM670/671 N, M146L	695	PDGF-β, Hamster PrP	5	−	+	8 months (RAM)	6 months	4 months	[59]
APP V717I	V717I	695	Thy1	2- to 5-fold	−	++	3 months (MWM)	16 months	13 months	[51]
APP Flemish	A682G	770	Thy1	2- to 14-fold	−	+	3 months (MWM)	none	none	[52]
APP Dutch	E693Q									
Tg CRND8	KM670/671 N; V717F		PrP	5	−	++	11 weeks (MWM)	11 months	5 months	[49]
Tg2576	KM670/671 N	695	Hamster PrP	5-fold		+	12 months (MWM)	> 18 months	7–10 months	[39]
PDAPP	V717F									
Apoe−/−										
J20 APP	KM670/671 N	695	PDGF-β	10-fold		+	7 months (MWM)	12 months	6 months	[94]
Swe/Indiana	V717F									
APP/Swe/	Swedish K670N/M671L,	770	Thy1.2	0.5-fold	−	+++	3 months (BM)	4 months	6 months (diffuse only)	[101,103]
Dutch/Iowa	Dutch/Iowa E693Q/D694N									
APP PS1	KM670/671 N, L166P	751	Thy1	3-fold	−	+	8 months (RAM)	8 months	6 weeks	[60]
APP^{SL}PS1KI	APP K670N/M671L (Swedish) + V717I (London) and PS1 M233T + L235P	751	Thy1	5-fold	++	+	?	8 months	2.5 months	[88]
5XFAD	APP K670N/M671L (Swedish) + 1716V (Florida) +V717I (London) and PS1 M146L + L286V	695	Thy1	Variable depending on which line but less than Tg2576	++	+	4 months (SAYM)	6 months	2 months	[89]
APP E693Δ	APP E693Δ	695	PrP	2-fold	+	None	8 months (MWM)	None	None (Aβ oligomers accumulate intracellularly)	[236]

Table 2

This table shows a summary of some of the active and passive immunization approaches that have been used in different AD Tg models.

Model	Antigen or antibody	Type of immunization	Reference
PDAPP (V717F)	Aβ1–42	Subcutaneously + adjuvant	[16]
APP (V717F)	Aβ1–42	Nasal	[168]
APP (V717F)	Antibodies to Aβ1–6, Aβ3–6	Passive	[139]
APP (V717F	Antibody to Aβ13–28	Passive	[140,174]
APP (V717F)	Antibody to Aβ 4–10	Passive	[175]
APP(K670N, M671L, V717F) Tg CRND8	Aβ1–40 and Aβ1–42 Specific antibodies	Passive	[176]
APP(K670N, M671L), Tg 2576	Aβ encoding DNA vaccine	Intramuscularly	[138]
APP(K670N, M671L), Tg 2576	Recombinant adenoassociated virus vector expressing Aβ1–21	Oral	[170]
APP(K670N, M671L), Tg 2576	Antibody to oligomeric Aβ	Passive	[237]
APPK670N, M671L V717F (CDND8)mice, APP K670N, M671L, PS1 M146L	Aβ1–42	Subcutaneously + adjuvant	[18,19]
APP(K670N, M671L), Tg 2576	K6Aβ1–30	Subcutaneously + adjuvant	[17]
APP(K670N, M671L), Tg 2576	K6Aβ1–30[$E_{18}E_{19}$]	Subcutaneously + adjuvant	[20]
	Aβ1–30[$E_{18}E_{19}$]		
APP(K670N, M671L), Tg 2576	K6Aβ1–30	Subcutaneously + adjuvant	[21]
APP(K670N, M671L), Tg	K6Aβ1–30 × 4	Oral	[173]
APPAwDI/NOS2−/−	Aβ1–42	Subcutaneously + adjuvant	[96]

Table 3

Shows studies of active immunization directly targeting tau pathology.

Tg model used	Immunogen	Route of immunization	Reference
P301L tau	Tau Peptide 379–408, phosphorylated at Ser 396, Ser 404	Subcutaneously with alum adjuvant	[203]
Human tau PS1	Tau Peptide 379–408, phosphorylated at Ser 396, Ser 404	Subcutaneously with alum adjuvant	[233]