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Immunotherapeutic approaches for Alzheimer's disease in transgenic mouse models

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Abstract

Alzheimer's disease (AD) is a member of a category of neurodegenerative diseases characterized by the 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 the case of AD the normal soluble amyloid β (sA β) peptide is converted into oligomeric/fibrillar A β . The oligomeric forms of A β are thought to be the most toxic, while fibrillar A β becomes deposited as amyloid plaques and congophilic angiopathy, which both serve as neuropathological markers of the disease. In addition, the accumulation of abnormally phosphorylated tau as soluble toxic oligomers and as neurofibrillary tangles is an essential part of the pathology. 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 different aspects of AD pathology. Perhaps the most exciting of these approaches is immunomodulation. Vaccination is currently being tried for a range of age associated CNS disorders with great success being reported in many transgenic mouse models. However, there is a discrepancy between these results and current human clinical trials which highlights the limitations of current models and also uncertainties in our understanding of the underlying pathogenesis of AD. No current AD Tg mouse model exactly reflects all aspects of the human disease. Since the underlying etiology of sporadic AD is unknown, the process of creating better Tg models is in constant evolution. This is an essential goal since it will be necessary to develop therapeutic approaches which will be highly effective in humans.

Keywords

Transgenic mice; Amyloid β ; Congophilic angiopathy; Tau; Vaccination; Immunomodulation; Alzheimer's disease

Introduction

Currently available treatments for AD provide largely symptomatic relief with only minor effects on the course of the disease. There is an urgent need for better therapeutic interventions. Besides immunomodulation, numerous other approaches are being studied, which include anti-A β aggregation agents, secretase inhibitors/modulators blocking A β production, tau aggregation blockers, agents targeting mitochondria, stem cell therapies and various neuroprotective strategies (Biran et al. 2009; Rafii and Aisen 2009). Currently, it appears that the greatest hope for an intervention that will significantly impact disease progression in the near future comes from the vaccination approaches (Brody and Holtzman 2008; Wisniewski and Boutajangout 2009; Wisniewski and Konietzko 2008). In AD Tg mouse models A β 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 which needs to be addressed is how to target the early initiating events in AD and not just the tombstone lesions which are the end result of a long chain of pathological processes.

Pathogenesis of familial and sporadic Alzheimer's disease

The pathological hallmarks of AD are the accumulation of A β as neuritic plaques and congophilic angiopathy, as well as accumulation of abnormally phosphorylated tau in the form of neurofibrillary tangles (NFTs). Missense mutations in APP or in the presenilin genes PRES 1 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 (Hardy and Selkoe 2002; Tanzi and Bertram 2005). This theory currently suggests that accumulation of A β peptides particularly in a highly toxic oligomeric form is the primary pathogenic driver, that downstream leads to tau hyperphosphorylation, NFT formation and ultimately to 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 PRES1 or two genes are associated with changes in APP processing that favor over production of sA β or production of more aggregation prone forms of sA β such as A β 1-42 (Hardy 2006). (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 (Lemere et al. 1996). (3) In transgenic and other models of co-expressed amyloid β and tau, amyloid β oligomer formation precedes and accentuates tau related pathology, consistent with the hypothesis that NFT formation is downstream from A β aggregation (Gotz et al. 2001b; King et al. 2006; Oddo et al. 2003b). (4) In transgenic mouse models of mutant APP over-expression (where there is no tau pathology) therapeutic prevention and/or removal of A β is associated with cognitive benefits in experimental mice (Janus et al. 2000; Morgan et al. 2000; Schenk et al. 1999; Sigurdsson et al. 2001a). Importantly, in transgenic mouse models of both mutant APP and tau over-expression (with both amyloid and tau related pathology) prevention of A β pathology leads to both amelioration of cognitive deficits and tau related pathology (Blurton-Jones and LaFerla 2006; McKee et al. 2008; Oddo et al. 2006). In addition, it has been shown that reducing the level of endogenous mouse tau can prevent behavioral deficits in APP Tg mice without affecting A β levels (Roberson et al. 2007) and that exogenous A β extracted from AD Tg mice can accelerate plaque deposition in predisposed young Tg mice (Eisele et al. 2009). However, evidence proving that A β is central in the common late-onset sporadic form of AD is more limited: (1) a correlation has been shown between biochemically extracted A β peptides species from sporadic AD brains with cognitive decline (Naslund et al. 2000). (2) Isolated A β peptide dimers/oligomers from sporadic AD brains have been documented to impair synaptic structure and function

(Shankar et al. 2008). (3) A β extracted from sporadic AD patients has been shown to induce amyloid deposits when injected into transgenic mice (Meyer-Luehmann et al. 2006). A significant problem for the amyloid cascade hypothesis comes from the autopsy data from the initial human active vaccination trial. Post-mortem analysis was available from nine subjects in the active immunization arm (Holmes et al. 2008). All these individuals showed some degree of plaque removal and reduced A β load compared to comparable non-immunized 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 this data to suggest that the amyloid cascade hypothesis is an oversimplification. A number of investigators have suggested alternative theories, whereby accumulation of A β and tau hyperphosphorylation are dual pathways both downstream from a common upstream pathogenic deficit (which remains to be identified) (Castellani et al. 2008; Shioi et al. 2007; Small and Duff 2008). 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 which have been tried to target parenchymal amyloid deposition, vascular amyloid, oligomeric A β and tau related pathology.

Overview of transgenic mouse models

Models of parenchymal amyloid deposition

The successful models to generate amyloid β deposits have used transgenes for human APP with missense mutations found in familial form of Alzheimer's disease (FAD) (see Table 1). The first transgenic models (PDAPP) developed by Games et al. (1995), used the Indiana mutation V717F, under the control of the PDGF promoter. These mice show a robust increase of amyloid β 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 (Masliah et al. 2001). The next AD transgenic model was developed by using a Swedish APP mutation (APP 695, K670N/M671L). This model is referred to as Tg 2576 and is the most studied Tg model of amyloid deposition. The transgene is under the control of the PrP mouse promoter (Hsiao et al. 1996). The brain amyloid β levels start increasing at 6 months and A β parenchymal deposits start developing between 9 and 12 months (Hsiao et al. 1996; Kawarabayashi et al. 2001). Congophilic angiopathy can be abundant in these mice at advanced ages (>18 months) (Fryer et al. 2003). The over-expression of the mutant APP is about 5-fold. This model was extensively used to examine the role of inflammation, including astrogliosis (Irizarry et al. 1997a), microgliosis (Frautschy et al. 1998), cytokine production (Tan et al. 1999), and oxidative stress (Pappolla et al. 1998; Smith et al. 1998). Several behavioral tests have shown age-dependent impairment with cognitive tasks (Arendash et al. 2001; Hsiao et al. 1996; Lesne et al. 2006; Morgan et al. 2000; Sigurdsson et al. 2004; Tagliavini et al. 1991). Further models such as the APP23 were generated using the APP751 isoform, expressed under control of the murine thy-1 promoter with 7-fold over-expression (Sturchler-Pierrat et al. 1997). 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 over-expression of APP. The transgenic CRND8 mouse line was generated under the control of the PrP promoter using the Swedish and the Indiana mutations (V717F) (Chishti et al. 2001). 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 (Rockenstein et al. 2001) is analog in term of spread of the pathology to the CRND8 line. A comparison of transgenic mice over-expressing 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 A β peptide soluble aggregates could be related to these phenotypic traits (Moechars et al. 1999). Other single Tg lines were generated by expression of either the Flemish (APPA692G) or the Dutch mutation (APPE693Q) (Kumar-Singh et al. 2000). 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 A β parenchymal deposition was to cross APP mutation lines with Tg mice expressing FAD linked presenilin (PS) 1 mutations. Over 160 mutations in PS-1, located on chromosome 14q, and 11 mutations on PS-2, located on chromosome 1, have been linked to FAD (Brouwers et al. 2008). PS is part of the γ -secretase complex and FAD linked mutations are associated with an increase in A β 42 production (Borchelt et al. 1996; Citron et al. 1997; Wolfe 2009). Crossing PS1 mutation mice with APP Tg models dramatically increases amyloid deposition, thought to be due to increased A β 42 production (Borchelt et al. 1997; Duff et al. 1996; Holcomb et al. 1998; Radde et al. 2006). In these various Tg models the ratio of A β 40–42, as well as the expression of “chaperone” proteins affects the type and distribution of amyloid deposits (McGowan et al. 2006; Wilhelmus et al. 2007; Wisniewski and Sadowski 2008). The critical role of A β 42 in “seeding” amyloid deposition was illustrated in Tg mice that express A β 1-40 or A β 1-42 in the absence of human APP over-expression by the fusion of A β 42 and A β 40 to the C-terminal end of the BRI protein (McGowan et al. 2005). Mutations in BRI are associated with the cerebral amyloidoses of British and Danish dementias (Vidal et al. 1999; Vidal et al. 2000). The A β 1-42 expressing mice developed extensive cored plaques, diffuse plaques and CAA (at older ages), in contrast to the A β 1-40 mice which did not develop amyloid deposits at any age (McGowan et al. 2005). Although A β 42 appears to be essential for seeding, A β 40 can influence the amount of CAA, perhaps related to the fact that the major biochemical component of CAA is A β 40 (Prelli et al. 1988). The expression of several A β binding proteins can also influence A β deposition and clearance. In particular the expression of apolipoprotein E (apoE) isoforms is a significant factor (Kim et al. 2009; Wisniewski and Sadowski 2008). 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 (Kim et al. 2009; Wisniewski and Sadowski 2008). The role of apoE in AD is complex with it being involved in both the aggregation state of A β and its clearance (Kim et al. 2009; Mahley and Huang 2009; Wilhelmus et al. 2007; Wisniewski and Sadowski 2008); however, one suggested role for apoE has been as a “pathological chaperone” that can induce a β -sheet conformation in A β (Sadowski et al. 2006; Wisniewski et al. 1993, 1994; Wisniewski and Frangione 1992). The critical role of apoE in A β deposition was shown when PDAPP and Tg2576 mice were crossed to murine apoE knock-out (KO) mice resulting in a complete lack of true amyloid plaques (Bales et al. 1997, 1999). The affects of different human apoE isoforms on A β deposition is 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 A β deposits compared to apoE3 mice (Fryer et al. 2003; Holtzman et al. 1999, 2000). 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 (Bales et al. 2009; Fryer et al. 2005). 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 (Kok et al. 2009; Reiman et al. 1996, 2004, 2009). 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 (Wisniewski and Boutajangout 2009; Wisniewski and Konietzko 2008). The effect of immunomodulation in different human apoE isotype expressing AD Tg models is a subject of on-going 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 (Frautschy et al. 1998; Irizarry et al. 1997b; Takeuchi et al. 2000). Two Tg lines with some neuronal loss are the APP23 mice (Calhoun et al. 1998; Sturchler-Pierrat et al. 1997) and a line with both the Swedish and London FAD APP mutations, along with two PS1 mutations (M233T/L235P) (Casas et al. 2004). 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. (2004) there is ~50% loss in the CA1/2 sectors of the hippocampus correlating with the accumulation of intraneuronal A β rather than extracellular plaques. In contrast to the lack of neuronal loss, many Tg lines have shown age associated synaptic degeneration (Calon et al. 2004; Dzieczapolski et al. 2009; Irizarry et al. 1997b; Radde et al. 2006; Takeuchi et al. 2000). In the widely used Tg2576 mice synaptophysin immunoreactivity loss occurs in 21–25-month-old mice with associated electrophysiological changes suggesting synaptic dysfunction (Spires et al. 2005). In addition, elegant 3D multi-photon 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 (Spires et al. 2005; Tsai et al. 2004). However, it is likely that small soluble aggregates of A β 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. (2000) expressing wild-type and mutant APP which do not have amyloid deposition but have age associated synaptophysin immunoreactivity loss that correlates with brain soluble A β levels. The lack of more marked synaptic and neuronal loss in APP and APP/PS1 mice 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 (Games et al. 1995; Holcomb et al. 1998; Hsiao et al. 1996). 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 or 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 is downstream from A β accumulation. APPSw crossed with mice with a KO of nitric oxide synthetase 2 (NOS2) have 30% hippocampal neuronal loss that correlates with behavioral abnormalities (Colton et al. 2006). It has been recently shown that active vaccination with A β 1–42 with Freund's adjuvant can prevent the neuronal loss found in these mice (Wilcock et al. 2009a).

Transgenic models of congophilic angiopathy (CAA)

CAA is an important part of the pathology of AD being present in virtually all AD cases, with approximately 20% of AD patients having “severe” CAA (Jellinger 2002). Furthermore CAA is present in about 33% of cognitively normal elderly, control populations (Zhang-Nunes et al. 2006). The population based Honolulu Asia Aging Study has shown a

significant correlation between cognition and the presence of CAA (Pfeifer et al. 2002a). Many of the Tg models of parenchymal amyloid discussed above and listed in Table 1 also have some degree of vascular amyloid deposition with a variable age of onset (Domnitz et al. 2005). However, the Tg model with the most extensive vascular amyloid in association with lower levels of parenchymal amyloid is the APPSwDI mouse which incorporates three APP mutations: Swedish, Dutch E693Q and Iowa D694N (Davis et al. 2004, 2006; Xu et al. 2007). These Dutch and Iowa mutations are associated with hereditary cerebral hemorrhage with amyloidosis (HCHWA) (Grabowski et al. 2001; Levy et al. 1990). The parenchymal A β deposits in these mice largely does not stain with Congo red and represents non-fibrillar, diffuse amyloid similar to the neuropathology of HCHWA-Dutch (Kumar-Singh 2009). 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 which correlates best to the presence of other AD related pathology (Attems and Jellinger 2004). 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 (Wilcock et al. 2009a). The Tg 2576 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 (Wilcock et al. 2009b). The neuronal loss and behavioral abnormalities have been shown to be preventable in the APPSwDI/NOS2 KO mice by A β 1–42 vaccination (Wilcock et al. 2009a).

Transgenic models of tau pathology

Several tau mutations have been reported to be associated with frontal temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), but none have been associated with AD (Gendron and Petrucelli 2009; Iqbal et al. 2009). A number of transgenic mice models that express human tau with FTDP-17 mutations have been produced (Zilka et al. 2009). Some of these mice display NFTs, neuronal death and behavioral deficits (Egashira et al. 2005; Gotz et al. 2000, 2001a; Gotz and Ittner 2008; Ishihara et al. 2001; Lee et al. 2005; Lewis et al. 2001; Murakami et al. 2006; Tanemura et al. 2001; Yoshiyama et al. 2007). In addition, 1 Tg mice model that expresses a mutated (N279K) tau shows behavioral deficits without formation of NFTs or neuronal loss (Taniguchi et al. 2005). In most of these models there is disruption of axon transport due to the tau expression that induces synaptic and neuronal loss. Another Tg tau mice model was developed expressing the mutated P301S tau which shows synaptic loss that precedes tangles formation (Yoshiyama et al. 2007). The distribution of NFTs in most of these tauopathies models are distinct from AD, since NFT are localized in different brain regions such as the brain stem, spinal cord or in fronto-temporal cortex instead of the entorhinal region, hippocampus and neocortex as observed in AD (Zilka et al. 2009). An additional tau model is the triple transgenic line (3 $\times$ Tg-AD) which expresses the PS1M146V, APPSwe and TauP301L transgenes. This model develops extracellular amyloid deposits from 6 months of age, and tau related pathology starting at 10–12 months of ages (Oddo et al. 2003a, b). In this model, the tau pathology is observed first in the hippocampus and then progresses to the cortex (Oddo et al. 2003a). Deficits in long-term synaptic plasticity correlate with accumulation of intraneuronal A β (Oddo et al. 2003b). Recently, it has been reported that spatial and contextual learning and memory was affected in the 3 $\times$ Tg-AD mice in an age depend manner, and the accumulation of intraneuronal A β correlates with cognitive deficits (Billings et al. 2005).

In order 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 (Ishihara et al. 2001) and another with abundant NFTs that

expresses all six human tau isoforms on a knockout background for murine tau (Andorfer et al. 2003, 2005). The absence of tangles in mice that express a single wild-type human tau is likely due to the endogenous tau inhibiting the formation of NFT-like pathology. Another transgenic mouse line (Tg30tau), expressing two pathogenic mutations (P301S and G272V), develop age-dependent brain and hippocampal atrophy, central and peripheral axonopathy, progressive motor impairment with neurogenic muscle atrophy, and NFTs and had decreased survival (Schindowski et al. 2006).

A tau Tg mouse model expressing the mutated P301S tau was generated which shows synaptic loss that precedes tangles formation (Yoshiyama et al. 2007). Changes in tau interactions with cytoskeletal actin can also contribute to the early stages of neurodegenerative diseases. Recently, new model has been generated by crossing htau (with expression of six tau isoforms) with a mutated presenilin. This model shows early tau pathology (Boutajangout et al. 2008).

Immunotherapy targeting parenchymal amyloid deposits

Active immunization

Initial data supporting immunotherapy for AD showed that anti-A β antibodies could inhibit A β peptide fibrillization/oligomerization and prevent cell culture based neurotoxicity (Solomon et al. 1997; Solomon 2007). This led to vaccination of AD Tg mice with A β 1-42 or A β homologous peptides co-injected with Freund's adjuvant which demonstrated striking reduction in A β deposition and as a consequence elimination of behavioral impairments (Asuni et al. 2006; Janus et al. 2000; Morgan et al. 2000; Schenk et al. 1999; Sigurdsson et al. 2001a, 2004). This has also been done with A β encoding DNA vaccines and A β peptide fragment (EFRH) phage vaccines (Frenkel et al. 2003; Lavie et al. 2004; Schiltz et al. 2004). Similar effects on A β load and behavior have been demonstrated in AD Tg mice by peripheral injections of anti-A β monoclonal antibodies indicating that the therapeutic effect of the vaccine is based primarily on eliciting a humoral response (Bard et al. 2000; DeMattos et al. 2001). In the initial preclinical studies no toxicity was evident in the treated mice; however, some investigators suggested that use of non-fibrillogenic, non-toxic A β 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 (Lemere et al. 2001; Sigurdsson et al. 2001b, 2002). 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 pre-aggregated A β 1-42 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 (Wisniewski and Frangione 2005). The initial trial was conducted in the UK and involved 80 patients with mild to moderate AD (Bayer et al. 2005). This trial was designed to assess the antigenicity and the toxicity of multiple-dose immunization with the full length A β 1-42 peptide with the QS21. 53% of patients developed an anti-A β humoral response. During the later stages of the phase I trial, the emulsifier polysorbate 80 was added causing a greater shift from a Th2 biased response to a proinflammatory Th1 response (Pride et al. 2008). In the subsequent phase IIa trial, begun in October 2001, 372 patients were enrolled with 300 receiving the aggregated A β 1-42 (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 out of 298 subjects) (Boche and Nicoll 2008; Wisniewski 2005; Wisniewski and Frangione 2005). Autopsies performed on a limited number of trial patients suggested that striking A β 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 (Boche and Nicoll 2008; Bombois et al.

2007; Ferrer et al. 2004; Masliah et al. 2005a; Nicoll et al. 2005, 2006). 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 A β immunoreactivity, suggesting phagocytosis. Additional striking features were the persistence of amyloid in cerebral vessels, as well as unaltered tau immunoreactive NFTs and neuropil threads in regions of cerebral cortex where plaque clearing had apparently occurred, compared to regions without clearing (Masliah et al. 2005a; Nicoll et al. 2005, 2006). Hence, this initial vaccination approach did not address vascular amyloid or NFT related 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-edge sword, where the benefits of a humoral response against A β were overshadowed in some individuals by a detrimental T-cell mediated inflammatory response (Boche and Nicoll 2008; Sadowski and Wisniewski 2007). 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 A β peptide, followed by quantification of cytokine secretion by enzyme-linked immunosorbent spot assay (Pride et al. 2008). 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 (Pride et al. 2008). 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 comparing to baseline and a slowed rate of disease progression comparing to the patients who did not form antibodies (Bayer et al. 2005; Hock et al. 2003). The follow-up data from the Zurich cohort, who are a subset of the Elan/Wyeth trial (Hock et al. 2002, 2003), indicated that the vaccination approach may be beneficial for human AD patients. In agreement with the findings in the Zurich cohort, immune responders with high antibody titers in the multi-center cohort scored significantly better in composite scores of memory functions as compared to low- and non-responders or to the placebo group of patients (Pride et al. 2008). Active vaccination approaches under development in Tg mouse models are aiming to avoid the excessive Th1 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 A β peptide immunogen in order to remove or alter the major Th1 stimulator sites in the carboxyl terminus and the middle portion of A β , while focusing on the major Th2 stimulator site in the amino terminus (Agadjanyan et al. 2005; Cribbs et al. 2003; Maier et al. 2006; Sigurdsson et al. 2001b, 2004). These A β homologous peptide immunogens can be combined with various co-stimulator epitopes. An example of this approach is a combination with a synthetic, non-natural Pan HLA DR-binding epitope PADRE (Agadjanyan et al. 2005) or linkage to viral-like particles (VLP) (Chackerian et al. 2006; Jennings and Bachmann 2008; Zamora et al. 2006) to induce a primarily humoral immune response. These can be further combined with other immunostimulator carriers. For example the A β Th2 amino-terminal epitope can be combined with PADRE and macrophage derived chemokine (MDC) in a DNA epitope vaccine to drive robust Th2 responses (Movsesyan et al. 2008). The choice of adjuvant is also an important consideration. The use of polysorbate 80, a strong Th1 stimulate adjuvant, in the AN1792 trial is one likely contributing factor to the encephalitis in a minority of patients. Use of adjuvants such as alum which drive primarily a Th2 response is preferable (Asuni et al. 2006; Head et al. 2008). The route of immunization also plays an important role. Stimulating mucosal immunity by vaccinating nasally, via the gut or transcutaneously has been shown to drive strong Th2 responses (Hara et al. 2004; Lemere et al. 2002; Nikolic et al. 2007; Seabrook et al. 2006; Weiner et al. 2000) (Tables 2, 3).

A striking problem 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 (Gilman et al. 2005). 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; hence, tau related pathology was unaffected by vaccination and thus the cognitive benefits were small. Alternatively it can be suggested that the amyloid cascade hypothesis must be an over-simplification 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 eight came to autopsy (Holmes et al. 2008). This study showed that despite evidence of very significant amyloid plaque removal in six out of the eight autopsy subjects, which correlated with the anti-A β titer, in the overall group there was no evidence of improved survival or an improvement in the time to severe dementia (Holmes et al. 2008).

Passive immunization

Passive transfer of exogenous monoclonal anti-A β antibodies appears to be the easiest way to fulfill the goal of providing anti-A β antibodies without risk of uncontrolled Th-1 mediated autoimmunity. AD Tg model mice treated this way had a significantly reduced A β level and demonstrated cognitive benefit (Bard et al. 2000; DeMattos et al. 2001; Dodart et al. 2002; Levites et al. 2006; McLaurin et al. 2002). 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 Dec 2007 (Wisniewski and Konietzko 2008). The Phase II trial using this anti-A β monoclonal antibody was a randomized, double-blind, placebo controlled trial testing three 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 endpoint in the whole study population, in the sub-group 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, over 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 A β 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 A β plaques and CAA (Pfeifer et al. 2002b; Racke et al. 2005; Wilcock et al. 2004). Microhemorrhages following active immunization in animal models have also been reported in three studies (Petrushina et al. 2008; Wilcock et al. 2007, 2009a). In particular in the APPSwDI/NOS2 KO mouse model with the most extensive vascular amyloid, vaccination with A β 1-42, while reducing the amyloid burden in association with behavioral benefits, led to a marked

increase in microhemorrhages (Wilcock et al. 2009a). 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 (Kramer et al. 2002; Vermeer et al. 2003).

In transgenic mouse models, A β antibodies can both prevent the deposition of vascular amyloid, and remove it thus contributing to vascular repair. 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 (Ferrer et al. 2004). This is an important issue since CAA is present in virtually all AD cases, with approximately 20% of AD patients having “severe” CAA (Jellinger 2002). The need for vascular repair and regeneration during A β immunotherapy represents another argument for early treatment as well as an argument favoring subtle clearance over a longer time period.

Immunotherapy targeting tau pathology

Neurofibrillary tangles (NFTs) are a major pathologic hallmark of AD. NFTs are intraneuronal inclusion bodies that consist of an accumulation of paired helical filaments (PHFs), which biochemically are mainly composed of abnormally phosphorylated tau. Recently there is increasing focus on phosphorylated tau as an immunotherapeutic target (Kayed and Jackson 2009; Noble et al. 2009; Sigurdsson 2008, 2009). 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 (Goedert et al. 1988, 1989). 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 semi-homologous repeat 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 transport of organelles. In addition, tau has other roles such as interactions with kinesin-1 and the complex dynactin/dynein (Magnani et al. 2007; Utton et al. 2005). 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 have been linked to AD (Gendron and Petrucelli 2009). 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 2–3 phosphorylated residues (Morishima-Kawashima et al. 1995). 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 (Sergeant et al. 1997). 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 (Butner and Kirschner 1991).

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 (Brion et al. 1986; Brion 2006). The diversity of tau isoforms is related to various post-translational modifications such as phosphorylation, glycosylation, glycation, ubiquitination, nitration (Wang and Liu 2008). Tau has multiple phosphorylation sites that were characterized using phospho-tau dependant antibodies. 71 out of the 85 potential phosphorylated sites have been shown to be phosphorylated in physiological or pathological conditions (Buee et al. 2000; Sergeant et al. 2008). More than 20 protein kinases have been implicated in the

phosphorylation of tau proteins, with glycogen synthase kinase-3 β (GSK-3 β) and cyclin-independent kinase (cdk5) thought to play the most important role in phosphorylation under pathological condition (Baumann et al. 1993; Buee et al. 2000; Hamdane et al. 2003; Sergeant et al. 2008).

Recently, it has been shown that active immunization of Tg mice P301L with a phospho-tau peptide (containing the phosphorylated PHF-1 epitopes Ser 396, Ser 404) for 2–5 months could prevent tau related pathology (Asuni et al. 2007). These particular phosphorylation epitopes were chosen since these sites have been shown to increase the fibrillogenic nature of tau and contribute to paired helical filaments formation (Eidenmuller et al. 2001; Fath et al. 2002; Sigurdsson 2009). Histological and biochemical analyses showed a reduction of aggregated tau in the brain and improved performance on motor tasks (Asuni et al. 2007). This study clearly documented that it is possible to reduce tau related pathology with active immunization.

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 (Masliah et al. 2005b). Another study has shown that antibodies against A β can be internalized in AD neuronal culture models of A β accumulation and clear intraneuronal A β aggregates via the endosomal–lysosomal pathway (Tampellini et al. 2007). 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 (Frost et al. 2009) and that 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 (Clavaguera et al. 2009). This type of “infectivity” of abnormal protein conformation from outside the cell has also been demonstrated for polyglutamine aggregates (Ren et al. 2009) and is well characterized in prion disease (Aguzzi 2009; Sadowski et al. 2008). A β has also been shown to have such “infectious” properties in vivo, being able to induce an acceleration of both further A β and tau related pathology (Bolmont et al. 2007; Eisele et al. 2009; Wisniewski et al. 1995). Hence, if the spread of PHF pathology in AD can occur via such a prion like mechanism, anti-phosphorylated tau antibodies would not need to enter cells in order to be effective.

Immunotherapy by stimulation of the innate immune system

An alternative, non-mutually exclusive approach to enhance vaccine design is to stimulate innate immunity and enable microglia/macrophages to clear amyloid and/or NFTs. Over 20 years ago, H. Wisniewski noted that while brain-resident macrophages were unable to phagocytose amyloid, brain-infiltrating macrophages are plaque competent (Frackowiak et al. 1992). 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 (Butovsky et al. 2007; El et al. 2007; Jucker and Heppner 2008). 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 nine using unmethylated cytosine-guanosine oligonucleotides (CpG) (Scholtzova et al. 2009; Tahara et al. 2006), via blockade of the CD40/CD40L interaction (Obregon et al. 2008) and by blockade of TGF β -Smad2/3 innate signaling pathway (Town et al. 2008). Significantly amyloid clearance by CpG stimulation was effective against CAA and parenchymal amyloid without any associated increase in cerebral microhemorrhages (Scholtzova et al. 2009). 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 A β and tau related pathologies. Studies to address whether stimulation of the innate immune system will be effective to inhibit tau related pathology are underway.

Immunization targeting A β and tau oligomers

Abundant evidence both in vivo and in vitro suggests that the most toxic species of A β are oligomers or A β derived diffusible ligands (ADDLs) (Glabe 2008; Klybin et al. 2008) with a similar line of evidence suggesting that tau oligomers are the most toxic form of phosphorylated tau (Kayed and Jackson 2009; Yoshiyama et al. 2007). Active vaccination or use of monoclonal antibodies that specifically target A β oligomers, tau oligomers or preferably both would be an ideal way to block AD related toxicity. A small number of pre-clinical studies targeting A β oligomers suggest that this methodology is potentially powerful and in the need of further development (Lambert et al. 2009, 2007; Lee et al. 2006; Mamikonyan et al. 2007; Moretto et al. 2007). An additional important factor to consider is that emerging evidence suggests that monomeric A β peptides have normal physiological functions in the brain such as neuroprotection and modulating LTP (Giuffrida et al. 2009; Puzzo et al. 2008), with phosphorylated tau also having a normal role (Noble et al. 2009). Targeting only oligomeric A β 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 (Lee et al. 2006; Moretto et al. 2007; Wisniewski et al. 2009). Such an approach has the advantage that both A β and tau related pathologies would be addressed concurrently.

Conclusions

Numerous studies are underway in AD Tg mouse models in order to improve immunomodulation so it will ultimately have greater efficacy and a better safety profile in patients. Approaches which address all three AD related pathologies: neuritic plaques, CAA and NFTs will have the greatest chance of being successful. 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. For example it has been shown that prion directed mucosal vaccination can prevent infection from an exogenous source (Goni et al. 2008; Wisniewski and Sigurdsson 2007). The testing of immunomodulation methods in Tg models that direct the immune system to clear the highly toxic abnormal oligomeric conformers that characterize multiple neurodegenerative diseases has the greatest potential to dramatically alter the course of a wide spectrum of human age associated diseases.

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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

Transgenic line	Mutations	Isoforms	Promotor	Expression level of APP transgene	Neuron loss	CAA severity	Time of development of cerebral amyloid angiopathy (months)	Age at which A β plaque deposits start	Reference
PDAPP	V717F	695	PDGF- β promoter	18-fold	-	+	24	6 months	Games et al. (1995)
Tg2576	KM670/671N	695	Hamster PrP	5-fold	-	+	16	9-12 months	Hsiao et al. (1996)
APP23	KM670/671N	751	Thy1.2	7-fold	+	++	12	6 months	Sturchler-Pierrat et al. (1997)
APPPS1	KM670/671N, M146L	695	PDGF- β , Hamster PrP	5	-	+	6	4 months	Holcomb et al. (1998)
APP V717I	V717I	695	Thy1	2- to 5-fold	-	++	16	13 months	Moechars et al. (1999)
APP Flemish	A682G	770	Thy1	2- to 14-fold	-	+	-	-	Kumar-Singh et al. (2000)
APP Dutch	E693Q								
Tg CRND8	KM670/671N; V717F		PrP	5-fold	-	++	11	5 months	Chishti et al. (2001)
Tg2576	KM670/671N	695	Hamster PrP	5-fold	-	+	>18	7-10 months	Fryer et al. (2003)
PDAPP	V717F								
Apoe $^{-/-}$									
APP/Swe/Dutch/Iowa	Swedish K670N/M671L, Dutch/Iowa E693Q/D694N	770	Thy1.2	0.5-fold	-	+++	4	6 months (diffuse only)	Davis et al. (2004)
APP PS1	KM670/671N, L166P	751	Thy1	3-fold	-	+	8	6 weeks	Radde et al. (2006)

Table 2

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)	A β 1-42	Subcutaneously + adjuvant	Schenk et al. (1999)
APP (V717F)	A β 1-42	Nasal	Weiner et al. (2000)
APP (V717F)	Antibodies to A β 1-6, A β 3-6	Passive	Bard et al. (2000)
APP (V717F)	Antibody to A β 13-28	Passive	DeMattos et al. (2001), Dodart et al. (2002)
APP (V717F)	Antibody to A β 4-10	Passive	McLaurin et al. (2002)
APP(K670N, M671L, V717F) Tg CRND8	A β 1-40 and A β 1-42 Specific antibodies	Passive	Levites et al. (2006)
APP(K670N, M671L), Tg 2576	A β encoding DNA vaccine	Intramuscularly	Schiltz et al. (2004)
APP(K670N, M671L), Tg 2576	Recombinant adeno- associated virus vector expressing A β 1-21	Oral	Hara et al. (2004)
APP(K670N, M671L), Tg 2576	Antibody to Oligomeric A β	Passive	Lee et al. (2005)
APPK670N, M671L, V717F (CDND8)mice, APP K670N, M671L,PS1 M146L	A β 1-42	Subcutaneously + adjuvant	Morgen et al. (2000), Janus et al. (2000)
APP(K670N, M671L), Tg 2576	K6A β 1-30	Subcutaneously + adjuvant	Sigurdsson et al. (2001)
APP(K670N, M671L), Tg 2576	K6A β 1-30	Subcutaneously + adjuvant	Asuni et al. (2006)
APP(K670N, M671L), Tg	K6A β 1-30 $\times$ 4	Oral	Boutajangout et al. (2009)
APPawDI/NOS2-/-	A β 1-42	Subcutaneously + adjuvant	Wilcock et al. (2009a)

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	Asuni et al. (2007)
Human tau PS1	Tau peptide 379–408, phosphorylated at Ser 396, Ser 404	Subcutaneously with alum adjuvant	Boutajangout et al. (2008)