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Immunotherapy for Tauopathies

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Abstract

Pathological tau protein is found in Alzheimer's disease and related tauopathies. The protein is hyperphosphorylated and/or mutated which leads to aggregation and neurotoxicity. Because cognitive functions correlate well with the degree of tau pathology, clearing these aggregates is a promising therapeutic approach. Studies pioneered by our laboratory and confirmed by others have shown that both active and passive immunization targeting disease-related tau epitopes successfully reduce tau aggregates *in vivo* and slow or prevent behavioral impairments in mouse models of tauopathy. Here, we summarize recent advances in this new field.

Keywords

Tau; tangles; immunization; immunotherapy; Alzheimer's disease; tauopathies; mice

Introduction

In the past decade, immunotherapy has become very attractive for clearing abnormal protein aggregates in various diseases. A majority of these studies has focused on Alzheimer's disease (AD), which is the most common form of dementia affecting the elderly population. Two major pathological hallmarks of AD brains are extracellular senile plaques containing amyloid-β (Aβ) deposits and intracellular neurofibrillary tangles (NFTs) containing aggregated tau proteins. Most AD immunotherapy studies have focused on targeting Aβ because its initial pathology may precede tau lesions. Both active and passive immunizations to clear Aβ have shown encouraging results in animal studies (Schenk et al., 1999;Bard et al., 2000;Janus et al., 2000;Morgan et al., 2000;Sigurdsson et al., 2001;DeMattos et al., 2001;Das et al., 2003;Sigurdsson et al., 2004;Lemere and Masliah, 2010). These approaches successfully reduce Aβ burden in various transgenic mouse models and improve cognitive functions. The promising results in mouse studies led to a series of clinical trials in AD patients (reviewed in Lemere and Masliah, 2010). However, less robust effects have been observed in these human studies but it should be noted that many of these trials are in their early stages focusing on safety. In the first active immunization trial, AN1792, clearance of Aβ plaques from the brain did not appear to slow the progression of dementia (Holmes et al., 2008). The two most advanced passive immunization trials using humanized monoclonal antibodies, bapineuzumab from Elan and solanezumab from Lilly, have also found very

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limited effects on prevention of disease progression (Kerchner and Boxer, 2010;Siemers et al., 2010). It may be too late to start Aβ immunotherapy once cognitive impairments are pronounced. However, the outcome of larger Phase III trials with these Aβ antibodies is eagerly awaited, as those should be able to detect more subtle benefits.

The other main target for immunotherapy in AD is the tau protein, and it is the key target in other tauopathies. It is mostly expressed in neurons and normally binds to and stabilizes microtubules and thereby promotes axonal transport. Abnormal tau protein forms aggregates, leading to the formation of paired helical filaments (PHFs), which are the major components of NFTs. These aggregates are implicated in the pathology of a variety of neurodegenerative diseases collectively called tauopathies. In AD, tau is not mutated but hyperphosphorylated, while various mutations of tau proteins are known to cause frontotemporal dementia (FTD) (Goedert and Jakes, 2005). The mutations and/or hyperphosphorylation of tau promote its aggregation into PHFs and eventually NFTs. It is unclear which type of aggregate is the most toxic but it is reasonable to expect the smaller aggregates to be more toxic based on their larger surface area compared to NFTs. The overall effect is disruption of microtubule integrity and axonal transport that leads to synaptic loss and eventually neuronal death. Importantly, tau pathology correlates better than amyloid-β pathology with cognitive impairments in patients (Wilcock and Esiri, 1982;Arriagada et al., 1992). Considering that tau and Aβ pathologies may have synergetic effects resulting in neurodegeneration (Frautschy et al., 1991;Sigurdsson et al., 1996;Sigurdsson et al., 1997;Gotz et al., 2001;Lewis et al., 2001;Ribe et al., 2005;Pearson and Powell, 1989;Delacourte et al., 2002;Roberson et al., 2007), tackling both pathologies is likely to lead to a more efficacious treatment.

A few tau immunotherapy studies have been reported recently showing positive effects of such approaches in animal studies, suggesting its feasibility for treating tauopathies. We will briefly review these recent developments and mention as well more preliminary findings reported at various conferences.

Animal studies of tau immunotherapy

In 2007, our laboratory published the first study on an active immunization approach targeting pathological tau proteins in a tangle mouse model (JNPL3) that overexpresses human tau protein with the P301L mutation (Asuni et al., 2007). This mutation was originally identified in FTD patients as a causative factor in the disease, and the homozygous mice we employed exhibit pre-tangles, NFTs, neuronal loss and motor deficits (Lewis et al., 2000). The functional impairments are thought to be related to tau aggregation in the spinal cord, brain stem and perhaps the motor cortex as well. As an immunogen, we selected a highly immunogenic 30 amino acid fragment (Tau379-408) of the tau protein containing two phosphorylated sites (P-Ser396, 404), which are prominent in tauopathies. The mice elicited a robust immune response against the immunogen, administered in alum adjuvant, and the antibodies purified from the immunized mice recognized tau aggregates on brain sections from patients, suggesting their selectivity for pathological tau. Immunized mice exhibited significantly less tau pathology in multiple brain regions, including motor cortex, dentate gyrus, and brain stem. Likewise, biochemical analysis of the left hemisphere showed a shift from insoluble tau to soluble tau. Importantly, the treated animals performed significantly better in tests of motor function than control mice, and there was a good correlation between tau pathology and performance on the tasks. Detailed cognitive assessment could not be performed in these animals as most of those tests require extensive maze navigation and, therefore, intact motor abilities. Nevertheless, this study demonstrated the efficacy and feasibility of tau immunotherapy.

Subsequently, in 2010, Boimel and colleagues reported on the beneficial effects of a similar active tau immunization approach (Boimel et al., 2010). In their study, an analogous transgenic mouse model was used, which expresses a double mutated tau (K257T/P301S). They used as immunogen a mixture of three phosphorylated tau segments, Tau 195-213 (P-Ser202, 205), Tau 207-220 (P-Thr212, Ser 214), and Tau 224-238 (P-Ser 238), which are also prominent in tauopathies. A substantial immune response was observed and the antibodies detected pathological tau protein. Their phospho-tau approach also successfully reduced tau aggregates in multiple brain regions, including cortex, hippocampus, and brain stem. Effects of the therapy on tau fractions on Western blots or on animals' function were not assessed. Interestingly, decreased immunohistochemical detection of the lysosomal proteases cathepsin D and L was observed in the immunized mice, which perhaps may be a consequence of diminished tau pathology.

As mentioned above, the major disadvantage of the JNPL3 model is that their tangle-related motor impairments make it impossible to thoroughly assess their cognitive status, and if it is impacted by tau immunotherapy. To look into this important issue, we considered first the htau model, which overexpresses all six isoforms of human tau on a mouse tau knockout background. It was previously described to develop AD-like tauopathy, with hyperphosphorylated tau proteins forming aggregates in cortical and hippocampal regions (Andorfer et al., 2003). At the time it was unclear if these mice would develop memory impairments but recent findings indicate that they indeed do (Polydoro et al., 2009). Compared to the homozygous JNPL3 model, the htau mice have a later age of onset and slower progression of tau pathology which nicely follows a similar timeline as in AD but increases the length and cost of therapeutic studies. To address this issue, our laboratory developed a novel transgenic tauopathy model, htau/PS1, by crossing htau mice with presenilin-1 (PS1) mutant M146L mice to generate htau/PS1 model on a mouse tau knockout background. The htau/PS1 mice exhibit earlier onset and faster progression of tau pathology (Boutajangout et al., 2010b), and we are studying the mechanism behind this phenomenon. As importantly, these mice develop substantial cognitive impairments without motor deficits and, therefore, are ideally suited to assess cognitive benefits of tau immunotherapy. The same immunogen, Tau 379-408 (P-Ser396, 404), as in the JNPL3 study elicited a strong antibody response in the htau/PS1 model without any evident detrimental effects. Like in the JNPL3 model, the tau immunotherapy in the htau/PS1 model resulted in reduced tau pathology on brain sections and Western blots. Furthermore, three cognitive tests, radial arm maze, object recognition, and closed field symmetrical maze, all showed clearly that the therapy completely prevented cognitive impairments in this model. A good correlation among antibody titer, the amount of tau aggregates in the brain and performance in cognitive tests was also demonstrated in this study, suggesting that the prevention of memory deficits was directly related to antibody-mediated clearance of tau aggregates (Boutajangout et al., 2010b).

These two recent studies by us and Rosenmann's group further support the efficacy and feasibility of active immunization targeting pathologically hyperphosphorylated tau proteins. Several other groups are also exploring tau immunotherapy, with preliminary findings reported at recent conferences. Novak reported at the 2009 and 2010 ICAD conferences in Vienna and Hawaii that vaccination with a recombinant misfolded truncated tau protein or an unspecified phospho-tau immunogen, respectively, reduced tau pathology and delayed behavioral impairments in a rat tangle model (Novak, 2009;Novak, 2010). Theunis and colleagues presented at the 2011 AD/PD meeting in Barcelona that liposome-based vaccines carrying an unspecified phospho-tau epitope lead to a strong and specific antibody response against phosphorylated tau protein in P301L mice, with preliminary data suggesting therapeutic efficacy (Theunis et al., 2011) Liposome-based Aβ vaccine had previously been reported to elicit antibody response and restore memory deficits in APP/PS1 mice (Muhs et

al., 2007). At the same conference, Troquier and colleagues showed that active tau immunization with a tau fragment phosphorylated at position 422 (P-Ser422) reduced tau pathology and improved memory in THY-Tau22 transgenic mouse model (Troquier et al., 2011). These mice express double mutated human tau (G272V/P301S) under a Thy1.2 promoter and have tau pathology and memory deficits without motor dysfunction (Schindowski et al., 2006). A third report at this meeting by Higuchi indicated that an unspecified form of tau vaccination slowed progression of tau pathologies in transgenic tangle mice (Higuchi, 2011).

Passive immunization with monoclonal tau antibodies is also being employed. Our laboratory initially studied passive tau immunization with PHF1, a mouse monoclonal that recognizes an epitope encompassing P-Ser396, 404 (Otvos, Jr. et al., 1994), which is within the region we used as an immunogen in our reports (Asuni et al., 2007;Boutajangout et al., 2010b). At ICAD 2010, we showed that JNPL3 mice treated intraperitoneally with PHF1 have reduced tau pathology and improved motor function compared to controls (Boutajangout et al., 2010a), and a manuscript based on these findings was recently published (Boutajangout et al., 2011). Subsequently, Kayed and colleagues demonstrated at the 2010 SFN meeting in San Diego that a novel tau oligomer-specific monoclonal antibody, administered by the same route in the same JNPL3 model, reduced tau oligomer load and improved motor test performance (Castillo et al., 2010). Further support for the passive approach came at the 2011 AD/PD meeting, at which Morgan and colleagues indicated that intracerebral injection of tau-5, a monoclonal antibody against a non-phosphorylated epitope in the middle region of tau, effectively and acutely reduced intracellular tau pathology (Morgan et al., 2011).

Safety of tau immunotherapy has not been thoroughly studied but is of a concern as with any other self immunogen, particularly considering the adverse reactions in the Aβ immunotherapy trials (Orgogozo et al., 2003;Kerchner and Boxer, 2010). In our two active studies and the PHF1 passive study, we have not observed any obvious side effects (Asuni et al., 2007;Boutajangout et al., 2010b;Boutajangout et al., 2010a;Boutajangout et al., 2011). Importantly, astrogliosis which is a sensitive marker of neurotoxicity, does not seem to be increased in association with the clearance of the tau aggregates in these studies. However, Rosenmann and colleagues examined previously if injections of recombinant tau protein can induce an autoimmune response. Indeed, it appeared to lead to delayed neurological deficits when administered with two strong adjuvants (Rosenmann et al., 2006). As stated in the article, the objective of that study was to assess if tau could induce a neuroautoimmune disorder in mice. In their more recent study, which is similar to our approach, mice immunized with phospho-tau epitopes using the same strong adjuvants to assess safety did not show such adverse reactions (Boimel et al., 2010). It is conceivable that phospho-tau epitopes raise tauopathy-specific/selective immune responses and do not cause autoimmune-related toxic reactions. However, the difference in the adjuvant used in these studies should also be noted. Rosenmann's group used complete Freund's adjuvant (CFA) and pertussis toxin (PT), which are very strong adjuvants and prohibited in human use. An Aβ active immunization study using CFA and PT as adjuvants also found encephalomyelitis in mice (Furlan et al., 2003). The strong adjuvants, which elicit cytotoxic T-cell response, could be at least in part responsible for the adverse reactions. It is encouraging that none were seen when the immunogen consisted of phospho-epitopes of tau (Boimel et al., 2010). On the other hand, we have exclusively used milder alum adjuvant in our active tau immunization studies, which promotes antibody response over cytotoxic T-cell response. The choice of adjuvant needs to be carefully considered to maintain the safety of tau immunotherapy.

Mechanisms of antibody-mediated clearance

For tau immunotherapy to work, the antibodies have to get into the brain. It is known that a small percentage (about 0.1%) of circulating IgG can enter the central nervous system, presumably mainly through the circumventricular organs (Nerenberg and Prasad, 1975;Broadwell and Sofroniew, 1993). Moreover, the blood-brain barrier (BBB) is thought to be compromised in AD and other neurodegenerative diseases (Bell and Zlokovic, 2009), which should lead to greater access of antibodies into the brain. Importantly, our study in JNPL3 tauopathy mice found that intracarotid injected FITC-labeled tau antibodies entered the brain and bound to tau aggregates within neurons (Asuni et al., 2007). Interestingly, FITC-labeled antibodies were only detected in the brains of transgenic mice but not wild-type mice, indicating that these tauopathy mice have a defective BBB. Aβ immunotherapy studies have also demonstrated the ability of antibodies to cross BBB and bind to Aβ deposits in transgenic mice (Bard et al., 2000;Wang et al., 2011).

Although tau is generally an intracellular protein, extracellular ghost tangles are well known in tauopathies and the tau protein is detected as well in cerebrospinal fluid. Importantly, extracellular tau aggregates appear to be taken up into cells/neurons, induce intracellular tau misfolding and thus spread tau pathology throughout the brain (Frost et al., 2009;Clavaguera et al., 2009). Once entering the central nervous system, tau antibodies would readily bind to extracellular aggregates and trigger microglia-related clearance. The removal of extracellular tau aggregates would then presumably halt the propagation of tau pathology. Concurrently, since tau aggregates are likely to be secreted by neurons, their rapid extracellular clearance by antibodies may facilitate further secretion and thereby indirectly clear intracellular tau aggregates. There is also evidence that neurons can endocytose antibodies via various receptors which have affinity for the Fc fraction of IgG (for review, see Sigurdsson, 2009). Antibody entry into cells, including neurons, is likely to be an integral and important component of the immune system. This pathway will allow antibodies to neutralize intracellular pathogens such as viruses and to pass through tissue to the site of insult. With tau immunotherapy, we are taking advantage of this endogenous pathway. Upon internalization into neurons, we have detected antibodies co-localized with tau aggregates and endosomal/lysosomal markers (Asuni et al., 2007;Krishnamurthy et al., 2010). Furthermore, Rosenmann's group detected less cathepsin D and L immunoreactivity in the brain of mice immunized with phospho-tau epitopes (Boimel et al., 2010), which may be a consequence of the clearance of tau aggregates as we alluded to earlier. These findings are consistent with reports that suggested the involvement of this pathway in antibody-mediated clearance of intracellular Aβ and α-synuclein (Masliah et al., 2005;Tampellini et al., 2007). While these studies point to the importance of the endosomal/autophagic/lysosomal pathways in antibody-mediated clearance of intracellular aggregates, the proteosome pathway may participate in antibody-mediated clearance of soluble misfolded proteins. Recently, a novel intracellular antibody receptor was described (Mallery et al., 2010), TRIM21 (tripartite motif-containing 21), which has relatively high affinity for IgG and IgM and interestingly targets antibody-antigen to the proteosome for degradation. Hence, there are at least three potential pathways within the brain for antibody-mediated clearance of pathological tau.

Conclusion

Overall, immunotherapy targeting tau has a great potential as treatment for tauopathies. As the field is novel, several questions remain. Dissecting the mechanism and epitope specificity of antibody-mediated clearance of tau aggregates within and outside cells will provide valuable information to improve the efficacy and safety of this promising approach.

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References

Andorfer C, Kress Y, Espinoza M, de Silva R, Tucker KL, Barde YA, Duff K, Davies P. Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms. J Neurochem. 2003; 86:582–590. [PubMed: 12859672]

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology. 1992; 42:631–639. [PubMed: 1549228]

Asuni AA, Boutajangout A, Quartermain D, Sigurdsson EM. Immunotherapy targeting pathological tau conformers in a tangle mouse model reduces brain pathology with associated functional improvements. J Neurosci. 2007; 27:9115–9129. [PubMed: 17715348]

Bard F, et al. Peripherally administered antibodies against amyloid β-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. Nat Med. 2000; 6:916–919. [PubMed: 10932230]

Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathol. 2009; 118:103–113. [PubMed: 19319544]

Boimel M, Grigoriadis N, Lourbopoulos A, Haber E, Abramsky O, Rosenmann H. Efficacy and safety of immunization with phosphorylated tau against neurofibrillary tangles in mice. Exp Neurol. 2010; 224:472–485. [PubMed: 20546729]

Boutajangout A, Ingadottir J, Davies P, Sigurdsson EM. Passive tau immunotherapy diminishes functional decline and clears tau aggregates in a mouse model of tauopathy. Alzheimer's & Dementia. 2010a; 6:S578.

Boutajangout A, Ingadottir J, Davies P, Sigurdsson EM. Passive immunization targeting pathological phospho-tau protein in a mouse model reduces functional decline and clears tau aggregates from the brain. Journal of Neurochemistry. 2011; 118:658–67. Epub ahead of print June 3. [PubMed: 21644996]

Boutajangout A, Quartermain D, Sigurdsson EM. Immunotherapy targeting pathological tau prevents cognitive decline in a new tangle mouse model. J Neurosci. 2010b; 30:16559–16566. [PubMed: 21147995]

Broadwell RD, Sofroniew MV. Serum proteins bypass the blood-brain fluid barriers for extracellular entry to the central nervous system. Exp Neurol. 1993; 120:245–263. [PubMed: 8491281]

Castillo DL, Lasagna-Reeves C, Guerrero-Munoz MJ, Estes DM, Barrett A, Dineley K, Jackson GR, Kayed R. Modulation of tau oligomers by passive vaccination. Soc Neurosci. 2010 Abstr 347.11.

Clavaguera F, Bolmont T, Crowther RA, Abramowski D, Frank S, Probst A, Fraser G, Stalder AK, Beibel M, Staufenbiel M, Jucker M, Goedert M, Tolnay M. Transmission and spreading of tauopathy in transgenic mouse brain. Nat Cell Biol. 2009; 11:909–913. [PubMed: 19503072]

Das P, Howard V, Loosbrock N, Dickson D, Murphy MP, Golde TE. Amyloid-beta immunization effectively reduces amyloid deposition in FcRγ-/- knock-out mice. J Neurosci. 2003; 23:8532–8538. [PubMed: 13679422]

Delacourte A, Sergeant N, Champain D, Wattez A, Maurage CA, Lebert F, Pasquier F, David JP. Nonoverlapping but synergetic tau and APP pathologies in sporadic Alzheimer's disease. Neurology. 2002; 59:398–407. [PubMed: 12177374]

DeMattos RB, Bales KR, Cummins DJ, Dodart JC, Paul SM, Holtzman DM. Peripheral anti-Aβ antibody alters CNS and plasma Aβ clearance and decreases brain Aβ burden in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A. 2001; 98:8850–8855. [PubMed: 11438712]

Frautschy SA, Baird A, Cole GM. Effects of injected Alzheimer β-amyloid cores in rat-brain. Proc Natl Acad Sci (USA). 1991; 88:8362–8366. [PubMed: 1924295]

Frost B, Jacks RL, Diamond MI. Propagation of tau misfolding from the outside to the inside of a cell. J Biol Chem. 2009; 284:12845–12852. [PubMed: 19282288]

Furlan R, Brambilla E, Sanvito F, Roccatagliata L, Olivieri S, Bergami A, Pluchino S, Uccelli A, Comi G, Martino G. Vaccination with amyloid-β peptide induces autoimmune encephalomyelitis in C57/BL6 mice. Brain. 2003; 126:285–291. [PubMed: 12538398]

Goedert M, Jakes R. Mutations causing neurodegenerative tauopathies. Biochim Biophys Acta. 2005; 1739:240–250. [PubMed: 15615642]

Gotz J, Chen F, Van Dorpe J, Nitsch RM. Formation of neurofibrillary tangles in P301L tau transgenic mice induced by Aβ 42 fibrils. Science. 2001; 293:1491–1495. [PubMed: 11520988]

Higuchi M. Molecular mediators of amyloidosis-inflammation coupling in Alzheimer's disease: In vivo evidence in humans and animal models. Neurodegenerative Diseases. 2011; 8(Suppl 1)

Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JAR. Long-term effects of Aβ(42) immunisation in Alzheimer's disease: Follow-up of a randomised, placebo-controlled phase I trial. Lancet. 2008; 372:216–223. [PubMed: 18640458]

Janus C, Pearson J, McLaurin J, Mathews PM, Jiang Y, Schmidt SD, Chishti MA, Horne P, Heslin D, French J, Mount HT, Nixon RA, Mercken M, Bergeron C, Fraser PE, George-Hyslop P, Westaway D. Aβ peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. Nature. 2000; 408:979–982. [PubMed: 11140685]

Kerchner GA, Boxer AL. Bapineuzumab. Expert Opin Biol Ther. 2010; 10:1121–1130. [PubMed: 20497044]

Krishnamurthy PK, Deng Y, Mathews PM, Sigurdsson EM. Mechanistic studies of antibody mediated clearance of tau aggregates using an ex vivo brain slice model. Alzheimer's & Dementia. 2010; 6:S276.

Lemere CA, Masliah E. Can Alzheimer disease be prevented by amyloid-β immunotherapy? Nat Rev Neurol. 2010; 6:108–119. [PubMed: 20140000]

Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, Hardy J, Hutton M, McGowan E. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science. 2001; 293:1487–1491. [PubMed: 11520987]

Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van Slegtenhorst M, Gwinn-Hardy K, Paul MM, Baker M, Yu X, Duff K, Hardy J, Corral A, Lin WL, Yen SH, Dickson DW, Davies P, Hutton M. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. Nat Genet. 2000; 25:402–405. [PubMed: 10932182]

Mallery DL, McEwan WA, Bidgood SR, Towers GJ, Johnson CM, James LC. Antibodies mediate intracellular immunity through tripartite motif-containing 21 (TRIM21). Proc Natl Acad Sci U S A. 2010; 107:19985–19990. [PubMed: 21045130]

Masliah E, Rockenstein E, Adame A, Alford M, Crews L, Hashimoto M, Seubert P, Lee M, Goldstein J, Chilcote T, Games D, Schenk D. Effects of α-synuclein immunization in a mouse model of Parkinson's disease. Neuron. 2005; 46:857–868. [PubMed: 15953415]

Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C, Hardy J, Duff K, Jantzen P, DiCarlo G, Wilcock D, Connor K, Hatcher J, Hope C, Gordon M, Arendash GW. Aβ peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. Nature. 2000; 408:982–985. [PubMed: 11140686]

Morgan D, Lee D, Brownlow M, Selenica M-L, Reid P, Alvarez J, Gordon MN. Opposing roles of microglial activation in amyloid depositing and tau depositing transgenic mice. Neurodegenerative Diseases. 2011; 8(Suppl 1)

Muhs A, Hickman DT, Pihlgren M, Chuard N, Giriens V, Meerschman C, van der Auwera I, van Leuven F, Sugawara M, Weingertner MC, Bechinger B, Greferath R, Kolonko N, Nagel-Steger L, Riesner D, Brady RO, Pfeifer A, Nicolau C. Liposomal vaccines with conformation-specific amyloid peptide antigens define immune response and efficacy in APP transgenic mice. Proc Natl Acad Sci U S A. 2007; 104:9810–9815. [PubMed: 17517595]

Nerenberg ST, Prasad R. Radioimmunoassays for Ig classes G, A, M, D, and E in spinal fluids: Normal values of different age groups. J Lab Clin Med. 1975; 86:887–898. [PubMed: 1185045]

Novak M. Tau vaccine: Active immunization with misfolded tau protein attenuates tau pathology in the transgenic rat model of tauopathy. Alzheimer's & Dementia. 2009; 5:P93.

Novak M. Tau transgenic rat model and response to tau vaccine. Alzheimer's & Dementia. 2010; 6:S118.

Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C. Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization. Neurology. 2003; 61:46–54. [PubMed: 12847155]

Otvos L Jr. Feiner L, Lang E, Szendrei GI, Goedert M, Lee VM. Monoclonal antibody PHF-1 recognizes tau protein phosphorylated at serine residues 396 and 404. J Neurosci Res. 1994; 39:669–673. [PubMed: 7534834]

Pearson RCA, Powell TPS. The neuroanatomy of Alzheimer's disease. Rev Neurosci. 1989; 2:101–122. [PubMed: 21561251]

Polydoro M, Acker CM, Duff K, Castillo PE, Davies P. Age-dependent impairment of cognitive and synaptic function in the htau mouse model of tau pathology. J Neurosci. 2009; 29:10741–10749. [PubMed: 19710325]

Ribe EM, Perez M, Puig B, Gich I, Lim F, Cuadrado M, Sesma T, Catena S, Sanchez B, Nieto M, Gomez-Ramos P, Moran MA, Cabodevilla F, Samaranch L, Ortiz L, Perez A, Ferrer I, Avila J, Gomez-Isla T. Accelerated amyloid deposition, neurofibrillary degeneration and neuronal loss in double mutant APP/tau transgenic mice. Neurobiol Dis. 2005; 20:814–822. [PubMed: 16125396]

Roberson ED, Scearce-Levie K, Palop JJ, Yan FR, Cheng IH, Wu T, Gerstein H, Yu GQ, Mucke L. Reducing endogenous tau ameliorates amyloid β-induced deficits in an Alzheimer's disease mouse model. Science. 2007; 316:750–754. [PubMed: 17478722]

Rosenmann H, Grigoriadis N, Karussis D, Boimel M, Touloumi O, Ovadia H, Abramsky O. Tauopathy-like abnormalities and neurologic deficits in mice immunized with neuronal tau protein. Archives of Neurology. 2006; 63:1459–1467. [PubMed: 17030663]

Schenk D, et al. Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature. 1999; 400:173–177. [PubMed: 10408445]

Schindowski K, Bretteville A, Leroy K, Begard S, Brion JP, Hamdane M, Buee L. Alzheimer's disease-like tau neuropathology leads to memory deficits and loss of functional synapses in a novel mutated tau transgenic mouse without any motor deficits. Am J Pathol. 2006; 169:599–616. [PubMed: 16877359]

Siemers ER, Friedrich S, Dean RA, Gonzales CR, Farlow MR, Paul SM, DeMattos RB. Safety and changes in plasma and cerebrospinal fluid amyloid β after a single administration of an amyloid β monoclonal antibody in subjects with Alzheimer disease. Clin Neuropharmacol. 2010; 33:67–73. [PubMed: 20375655]

Sigurdsson EM. Tau-focused immunotherapy for Alzheimer's disease and related tauopathies. Curr Alzheimer Res. 2009; 6:446–450. [PubMed: 19874269]

Sigurdsson EM, Knudsen E, Asuni A, Fitzer-Attas C, Sage D, Quartermain D, Goni F, Frangione B, Wisniewski T. An attenuated immune response is sufficient to enhance cognition in an Alzheimer's disease mouse model immunized with amyloid-β derivatives. J Neurosci. 2004; 24:6277–6282. [PubMed: 15254082]

Sigurdsson EM, Lee JM, Dong XW, Hejna MJ, Lorens SA. Bilateral injections of amyloid-β 25-35 into the amygdala of young Fischer rats: Behavioral, neurochemical, and time dependent histopathological effects. Neurobiol Aging. 1997; 18:591–608. [PubMed: 9461057]

Sigurdsson EM, Lorens SA, Hejna MJ, Dong XW, Lee JM. Local and distant histopathological effects of unilateral amyloid-beta 25-35 injections into the amygdala of young F344 rats. Neurobiol Aging. 1996; 17:893–901. [PubMed: 9363801]

Sigurdsson EM, Scholtzova H, Mehta PD, Frangione B, Wisniewski T. Immunization with a non-toxic/non-fibrillar amyloid-β homologous peptide reduces Alzheimer's disease associated pathology in transgenic mice. Am J Pathol. 2001; 159:439–447. [PubMed: 11485902]

Tampellini D, Magrane J, Takahashi RH, Li F, Lin MT, Almeida CG, Gouras GK. Internalized antibodies to the Aβ domain of APP reduce neuronal Aβ and protect against synaptic alterations. J Biol Chem. 2007; 282:18895–18906. [PubMed: 17468102]

Theunis C, Biel N Crespo, Borghgraef P, Devijver H, Gafner V, Philgren M, Hickman DT, Chuard N, Deber MP Lopez, Reis P, Buccarello AL, Adolfsson O, Pfeifer A, Muhs A, Van Leuven F. Protein

tau, target for immunotherapy: Pre-clinical evaluation in transgenic mice. Neurodegenerative Diseases. 2011; 8 in press.

Troquier L, Burnouf S, Belarbi K, Caillierez R, Blum D, Buee L. Modulation of tau pathology in THY-Tau22 transgenic mice: From physical exercise to immunotherapy. Neurodegenerative Diseases. 2011; 8(Suppl 1)

Wang A, Das P, Switzer RC III, Golde TE, Jankowsky JL. Robust amyloid clearance in a mouse model of Alzheimer's disease provides novel insights into the mechanism of amyloid-β immunotherapy. J Neurosci. 2011; 31:4124–4136. [PubMed: 21411653]

Wilcock GK, Esiri MM. Plaques, tangles and dementia: A quantitative study. Journal of the Neurological Sciences. 1982; 56:343–356. [PubMed: 7175555]