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Immunotherapy Targeting Pathological Tau Protein in Alzheimer's Disease and Related Tauopathies

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Abstract

Immunotherapies that target the amyloid- β (A β) peptide in Alzheimer's disease (AD) have shown promise in animal and human studies. Although the first clinical trial was halted because of adverse reactions, this approach has been refined and additional trials are underway. Another important target in AD is the neurofibrillary tangles, composed primarily of hyperphosphorylated tau proteins, which correlate well with the degree of dementia. As A β and tau pathologies are likely synergistic, targeting both should be more effective and may be essential as early diagnosis prior to cognitive decline is currently not available. Also, A β immunotherapy only results in a very limited indirect clearance of tau aggregates in dystrophic neurites, showing the importance of developing a separate therapy that directly targets pathological tau. Our findings in two tangle mouse models indicate that immunization with a phospho-tau derivative reduces aggregated tau in the brain and slows progression of the tangle-related behavioral phenotype. These antibodies enter the brain and bind to pathological tau within neurons. We are currently clarifying further the mechanism of action of this promising therapeutic approach and determining its epitope specificity.

Keywords

Amyloid- β ; tau; immunotherapy; vaccine; immunization

INTRODUCTION

An emerging therapeutic approach for protein conformational disorders is immune modulation to clear the characteristic assemblies and aggregates of the pathological proteins [114]. This promising approach was originally based primarily on studies showing that immunization with aggregated A β_{1-42} reduces A β plaque burden and associated pathology in mouse brains [110]. Prior and subsequent studies indicated that this effect was likely to be antibody-mediated [11,14,23,25,67,116,120,122], and resulted in cognitive improvements [30,56,62,86]. Following and during these promising mouse studies, clinical trials were initiated using aggregated A β_{1-42} along with QS-21 adjuvant that promotes cytotoxic T-cell response [57]. These trials were subsequently halted because of meningoencephalitis observed in a small subset of patients [96,109]. The clinical symptoms, when they occurred, and subsequent

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Holmes C. et al. (Lancet 372 (2008), 180–182) recently reported that additional subjects from the initial Phase I AN1792 A β immunotherapy trial appeared to have substantial or near complete removal of A β plaques while having severe end-stage dementia at the time of death. These disappointing results suggest that targeting A β may not be helpful once cognitive impairments are evident, and further support the feasibility of therapeutic approaches targeting pathological tau proteins.

histopathological analysis in two patients indicated that the encephalitis was likely T-cell mediated directly related to the vaccination, caused by the antigen and/or adjuvant and probably not related to the A β antibodies *per se* [36,90,96]. However, positive preliminary findings have emerged from this trial, and refinement of this approach is currently underway. Four autopsies from the trial have shown plaque clearance but vascular amyloid and most of the tau pathology remained [36,79,89,90]. Tau aggregates within plaque-associated dystrophic neurites appeared to have been cleared as those neurites disappeared with the removal of the plaques. However, tangles and neurophil threads remained, emphasizing the need for therapy that directly targets pathological tau. Two of the four autopsy subjects did not develop encephalitis, indicating that reduced amyloid burden is not a consequence of brain inflammation. Regarding cognitive improvements, in the Zurich cohort there was a positive correlation between the presence of antibodies that recognized A β in tissue sections [51] and a less pronounced cognitive decline [52]. More recently, a report from the Phase I study of AN-1792 showed less decline in a cognitive test compared to untreated age-matched controls [15]. In the larger Phase IIa trial, cognitive improvement was not obvious although z-score analyses across the neuropsychological test battery indicated that the antibody responders differed from the placebo subjects [42].

Overall, these preliminary findings on cognitive effects and A β clearance raise hopes for the future of A β -based immunotherapy. A β derivatives/antibodies and other adjuvants are being explored with the aim of reducing potential side effects while maintaining or improving therapeutic efficacy. However, it should be stressed that the current findings from the A β vaccine trials indicate as well that it is unlikely that targeting A β alone will be sufficient in most subjects that are already experiencing cognitive decline.

IMPROVING THE SAFETY OF A β IMMUNOTHERAPY

Prior to the side effects in the AN-1792 trial, we raised concerns about administering full-length A β_{1-42} in humans, and we advocated the use of adjuvants that favor a Th2 response promoting antibody production instead of a Th1 response which mediates a cytotoxic T-cell response [120]. The primary objective in designing our A β derivatives was to maintain antibody epitopes while reducing their β -sheet content compared to A β to eliminate direct toxicity and amyloid seeding potential. These modifications also altered or removed potential T-cell epitopes; hence, modulation of the immune response was to be expected. Interestingly, recent findings in the prion field indicate also that immune responses to α -helical structures appear to involve more the Th2 pathway whereas β -sheet conformation favors Th1 activation [58].

Our initial report was on K6A β_{1-30} which contains 6 lysines to increase immunogenicity and reduce β -sheet propensity. This peptide elicited a similar antibody response as A β_{1-42} in mice which resulted in a comparable therapeutic efficacy [120]. Our findings with other A β derivatives with diminished T-cell reactivity and modest anti-A β antibody titers indicate that a robust immune response towards A β is not needed to improve cognition, and for certain immunogens, IgM response correlated with reduction in A β burden [9,111,116]. As IgM is unlikely to enter the brain because of its size, that particular study [116] supported the view put forward by us and others that antibody-mediated peripheral clearance of A β may at least in part explain the therapeutic effect [25,120].

We are currently evaluating the immunogenicity and efficacy of our A β derivatives in lemur primates [115,129], which develop both A β plaques and tau aggregates as observed in AD [41,83]. Our present findings indicate that most of our A β derivatives elicit a substantial antibody response in primates, and importantly this effect is reversible which enhances the safety profile of our approach. Also, A β levels in plasma in the immunized groups correlated

with their antibody response, demonstrating an *in vivo* effect of the vaccination. In future studies, our tau-based immunotherapy could be evaluated as well in this model.

A β clearing effects and/or favorable immune responses of unaltered A β fragments as vaccine components have recently been described by others [1,22,38,40,49,66,68,77,112,113,138]. This approach is currently in Phase I clinical trials but one of these studies was recently halted, at least temporarily, because of skin rashes that developed in one subject [128]. It is unclear at this point if this reaction was related to the immunogen and/or adjuvant or neither. Other types of A β targeting therapies that may diminish adverse reactions include administering monoclonal antibodies [14] that recently entered Phase III clinical trials, as well as the use of proteolytic antibodies [97]. Furthermore, IVIg that contains some anti-A β antibodies has shown promise in a Phase I trial [103].

TARGETING PATHOLOGICAL TAU PROTEIN BY IMMUNOTHERAPY

Neurofibrillary tangle pathology results in a loss of axonal integrity which leads to a decline in connectivity and synapses, that consistently correlates well with dementia in AD [43,126]. These intracellular tangles are found extracellularly after neuronal death, and are primarily composed of hyperphosphorylated tau protein. Tau is a soluble protein that normally promotes tubulin assembly, microtubule stability, and cytoskeletal integrity; hence, tau pathology leads to dysfunction of neurons and glia. The causative role of tau pathology in neurodegeneration has been unequivocally shown with the identification of tau mutations in frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17) [100,124].

The objective of immunotherapy for tau pathology is to generate antibodies that selectively or specifically recognize the pathological hyperphosphorylated tau protein. These antibodies should result in clearance of tau aggregates that may then improve neuronal function. Potential side effects may be that targeting tau may also prevent it from performing its normal cellular functions but we have not seen any indications of that in our studies, perhaps because our prototype immunogen was designed to elicit generation of antibodies that primarily recognize pathological tau protein. Furthermore, tau knock-out animals appear remarkably normal indicating that other microtubule associated protein can perform similar functions [26], and reducing endogenous tau has been shown to ameliorate A β induced dysfunction in transgenic mice [106].

There are relatively few reports on the development of therapy targeting pathological tau conformers compared to the numerous studies on A β targeting approaches. In Down syndrome, A β plaques are observed before tau pathology which can be explained by gene dosage effect as those individuals have three copies of the gene for the amyloid- β protein precursor (A β PP) [53,78,87,134]. A similar scenario can be envisioned in familial forms of AD with A β PP mutations. However, in sporadic cases of AD, it is unclear if A β pathology precedes tau pathology and it may depend on the individual. Regardless of which occurs first, histological analyses in AD brains and in mouse models indicate synergism between these pathologies [24,45,69,93,104,117,118]. Hence, targeting both is likely to substantially increase treatment efficacy. Furthermore, analysis of brains from normal individuals has shown tangle formation in the temporal lobe without any A β plaques [17]. These findings demonstrate that at least in some individuals tangle formation precedes the development of A β plaques. Several diverse experimental therapies targeting tau are currently in development [27,46,55,84,91,98,137]. All of these approaches are certainly worth pursuing but as with immunotherapy targeting tau, the major concerns are target selectivity and potential toxicity. We hope that our approach targeting pathological tau diminishes the likelihood of these complications.

In the AN-1792 trial, A β plaque clearance did not appear to affect tau pathology [36,79,89,90], although plaque-associated dystrophic neurites disappeared as plaques were removed.

However, a recent mouse study showed that A β immunotherapy indirectly resulted in clearance of early tau pathology but hyperphosphorylated tau aggregates remained [93], as in the human studies. Furthermore, immunotherapy targeting A β that led to reduction of both soluble A β and soluble tau has been shown to improve cognition in mice with plaques and tangles whereas the same type of therapy that only reduced soluble A β did not improve cognition [95]. As tangle pathology correlates better with the degree of dementia than A β burden [7,133], these observations clearly underscore the importance of developing therapy that directly targets pathological tau conformers.

As we and others have observed in A β plaque mouse models, it may not be necessary to clear plaques to observe a cognitive benefit; removal of the more toxic early stage smaller A β assemblies may be more important [59,64]. This concept may also apply to tau pathology, as suppressed expression of transgenic tau has been shown to improve memory in a tangle mouse model although neurofibrillary tangles were not cleared [108]. In addition, loss of synapses and microglial activation has been shown to precede tangle formation in a Tg P301S tauopathy mouse model [135]. These observations in mouse models show that it is likely to be of the most therapeutic benefit to clear the early stage pathological tau aggregates. These smaller assemblies should be removed more easily than tightly bound NFT that may take years to develop. Our published findings in the P301L tangle model also support the feasibility of tau immunotherapy. Our active immunization with an AD specific phosphorylated tau epitope reduces brain levels of aggregated tau and slows the progression of tangle-related behavioral phenotype [8]. Furthermore, we have now shown that this approach prevents cognitive impairments in another tangle model with associated reduction in aggregated tau in the brain [16,119].

MECHANISM OF CLEARANCE

Regarding the mechanism of this effect, it has been established that about 0.1% of circulating IgG can be detected within the central nervous system (CNS) [88], and it may enter through regions deficient in blood brain barrier (BBB) [12,19], as shown for an antibody targeting A β [13]. Also, IgG can cross the BBB via adsorptive-mediated transcytosis [140]. It is likely that a substantially higher percentage of IgG can be found within the brain under pathological conditions. For example, the BBB is known to be compromised in several neurological disorders that are associated with inflammation such as AD [139]. This phenomenon has also been observed in AD model mice that deposit A β plaques [65,99], but BBB permeability has not been thoroughly assessed in tangle AD model mice. However, our findings indicate that the BBB is likely to be impaired in the P301L model because intracarotid injection of FITC labeled IgG readily entered the brain of these mice but not in wild-type mice [8]. Furthermore, we measured age-related increase in tau autoantibodies in plasma of this tangle model as tau pathology advanced which may be explained by diminished immunoprivilege of the CNS because of increased BBB permeability. Another way for antibodies to get into the brain is through antibody-secreting-cells that can enter the brain and may secrete the antibodies locally [60]. In the mouse immunotherapy studies targeting A β , IgG has been routinely found within the brain associated with extracellular A β deposits and phagocytic microglia [14,109], and in our published findings we have detected neuronal antibodies within the brain in tangle model mice by immunohistochemistry [8].

There is limited information available on antibody transport within the CNS but transport of IgG within and across cells in the periphery is crucial for humoral immunity [61,81,92,101,123]. Furthermore, numerous studies have shown that antibodies can be found within neurons, which supports the feasibility of our approach; for example [2,28,32-35,37,47,48,54,74,82,85,102,105,127,130,131,136]. The antibodies may be taken up into cells by pinocytosis (e.g., receptor-mediated endocytosis or fluid-phase endocytosis) [75]. When surface antigens are not

recognized by the antibody, as is likely the case for tau antibodies, receptor-mediated uptake may be through Fcγ or FcRn receptors [75], and Fcγ receptors have been located on neurons [3,85]. In some cases, the initial uptake can occur outside the CNS. For example, motor neurons send projections from the CNS to the periphery and their synapses have been shown to take up IgG via Fc receptors [32-34,85]. The antibodies then enter the CNS by retrograde axonal transport. Other receptors found on neurons can also mediate antibody uptake such as the Thy1.1 receptor [33] and the lipoprotein receptor-related protein (LRP) [50,63]. Interestingly, LRP-mediated endocytosis has been shown to result in lysosomal degradation [44]. Indeed, antibodies have been detected within lysosomes by immunoelectron microscopy [82]. In addition to binding to these receptors found on neurons, intracellular targets of the antibodies have been identified in some of the studies mentioned above. For example, antibodies to double stranded DNA [131], Hu nuclear antigen [54], Hsp27 [127] and certain viruses [28].

Regarding the site of antibody-tau interaction within the cell, tau is normally found in the cytosol but following its hyperphosphorylation and subsequent aggregation, it has been located in or near subcellular vesicles that are increased in numbers and size compared to normal neurons. For example, in a detailed study on the ultrastructural neuronal pathology in transgenic mice expressing mutant P301L human tau, lysosomal and autophagic structures were prevalently associated with tau filaments [72]. We used that particular mouse model in our first tau immunotherapy study [8]. Lysosomal complexes have also been observed near tau filaments in neurons expressing the longest tau isoform with G272V, P301L and R406W mutations [71]. Hence, the scenario outlined in Figure 1 can be put forward. Tau aggregation is likely to lead to activation of the endosomal-lysosomal pathway to facilitate its clearance which may indirectly enhance receptor-mediated endocytosis that may in turn increase uptake of antibodies into the neuronal cytoplasm (Figure 1A). Abnormally folded tau is likely to end up in lysosomes for degradation in which it may interact with antibodies. Initially, the antibodies will be in the endosomal compartment following their receptor-mediated endocytosis. Eventually, the endosomes will fuse with the lysosomes, and the binding of the antibodies to the tau assemblies may then enhance their lysosomal degradation. In tandem, tau antibodies may diffuse through damaged membranes of neurons under stress because of tau pathology (Figure 1B). This pool of antibodies may then recognize and cross-link tau filaments that are associated with the inner phase of the neuronal plasma membrane. As a matter of fact, tau has been shown to be associated with neural plasma membrane components in addition to microtubules, and there is evidence that this interaction is influenced by phosphorylation of tau at sites that are modified in paired helical filaments (PHFs) [18,29,31,76]. Also, tau interacts with actin [21] and spectrin [20], which may provide another link to the neural membrane. Our findings support the observation by these investigators, as tau and/or IgG can often be observed outlining the perikarya (inner face of the plasma membrane) of the neurons in the P301L mice [8].

Concurrent with the intracellular interaction, clearance of extracellular tangles by antibodies may also reduce associated pathology. This could be envisioned to occur in a similar way as Aβ plaque clearance by antibodies, either by direct antibody-mediated disassembly or antibody binding to the tangles may promote clearance by microglia. It should also be mentioned that tau and its fragments are detected in cerebrospinal fluid, likely as a result of cellular degradation. Antibody-mediated clearance of this pool may also have beneficial effects by reducing the overall tau burden within the brain.

POTENTIAL TOXICITY

Potential problems associated with tau immunotherapy are primarily toxicity because of cellular uptake of antibodies and binding to normal tau that may result in destabilization of the microtubules and subsequent interference with axonal transport and cytoskeletal integrity. We

have not observed any toxicity in our mice with high titer against phosphorylated tau epitope. Furthermore, tau knock-out animals appear remarkably normal indicating that other microtubule associated protein can perform similar functions [26], and reducing endogenous tau has been shown to ameliorate A β induced dysfunction in transgenic mice [106]. By basing our immunogens on AD specific epitopes, the likelihood of this type of toxicity is diminished. Accordingly, our findings indicate that the antibodies generated in response to the vaccine specifically/selectively recognize tau aggregates and NOT normal tau on brain sections [8]. The fact that the P301L model develops autoantibodies against tau with age makes it difficult to thoroughly evaluate antibody specificity in this model. Occasionally, these autoantibodies in control mice recognize tau aggregates on brain sections.

Besides antibody specificity, the pathological state seems to facilitate access of the antibodies and their clearance. In support of this view, it is interesting to note that in our hands, normal neurons do not appear to take up appreciable amounts of antibodies (or those antibodies are rapidly degraded) as we have not observed uptake/binding of anti-tau antibodies in neuroblastoma cells and primary cultures that do not have tau pathology [10]. This observation suggests that adverse effects of this type of therapy are less likely as normal neurons are not targeted. Also, in a healthy individual, the intact BBB would limit antibody access to the brain. Furthermore, prior studies by us and others have not observed any toxicity following passive immunization with monoclonal antibodies against the prion protein (PrP) [121,132]. PrP is a ubiquitous transmembrane protein and as such should be more accessible than the tau protein.

However, tauopathy-like abnormalities and neurological deficits have been reported in wild-type mice that were immunized with tau protein [107]. In this preliminary study, the mice were inoculated with recombinant human tau protein in complete Freund's adjuvant (CFA) and with pertussis toxin (PT). Six of eleven tau immunized mice developed some neurological deficits based on a severity scale used to assess experimental autoimmune encephalomyelitis (EAE). Semi-quantitative analysis indicated some tau pathology in these animals. A possible explanation for this apparent toxicity is both the choice of very strong adjuvants and the use of full length human tau protein that differs from the endogenous mouse sequence. Also, because recombinant proteins are unphosphorylated, this approach could not be used to specifically or selectively target AD phosphorylated tau. This adjuvant combination with human A β has been shown to induce autoimmune encephalomyelitis in wild-type mice [39], probably for the same reasons. In our studies, we have been using Alzheimer's specific/selective phosphorylated fragment of the human tau protein in mice that express the human protein. Furthermore, we employed alum adjuvant that is the only adjuvant approved for human use. Alum is a relatively mild immunostimulant that primarily promotes an antibody response [73], whereas CFA and PT induce a strong cytotoxic T-cell response that has toxic effects.

IMMUNOTHERAPIES TARGETING OTHER INTRACELLULAR PROTEINS

While our tau immunotherapy studies were underway or under review, other findings from related fields supported the validity of our approach and our findings. Masliah's group showed that immunization with recombinant α -synuclein removed intracellular aggregates of the same sequence in Parkinson's disease model mice [80]. The clearance most likely occurred through the endosomal-lysosomal pathway. Another more recent report by Gouras' group demonstrated that anti-A β antibodies can be internalized in neuronal culture models that contain intracellular A β aggregates [125]. The antibodies promoted A β clearance also via the endosomal-lysosomal pathway which in turn protected against synaptic alterations [125]. Related work by Solomon and colleagues showed an internalization of an antibody against the β -secretase cleavage site into CHO cells expressing human APP751, which was associated with reduced A β levels in the media and within the cells [6]. Furthermore, Oddo et al. showed clearance of extra- and intracellular A β following direct intrahippocampal injection of anti-A β antibody. However, it

is unclear if the antibody entered the neurons and they speculated that the clearance of the intracellular A β was due to a dynamic relationship between these two pools of A β [94].

CONCLUSIONS AND FUTURE DIRECTIONS

Our promising findings indicate that active immunization with an Alzheimer's specific phosphorylated tau epitope results in high antibody titer and reduces cerebral tau aggregates *in vivo* as well as slows progression of the tangle-related behavioral phenotype [8]. We have now confirmed these findings in a different tangle model and shown prevention of cognitive impairments using three different tests [119]. Furthermore, we show that these antibodies enter the brain, in which they should have best access to extracellular tangles but should also reach intracellular tau and tangles based on numerous reports on neuronal uptake of antibodies [2, 28,32-35,37,47,48,54,74,82,85,102,105,127,130,131,136], and our published findings [8]. The access to and clearance of intracellular targets is also supported by recent immunotherapy studies targeting α -synuclein and A β [80,125]. The extracellular tangles are expected to be cleared to a similar extent as extracellular amyloid burden in Tg A β PP mice following immunization with A β or its derivatives, as several laboratories including ours have observed. The reduction in intracellular tangles may depend on regional differences or variations between different types of neurons in antibody uptake. Even if the antibodies would only be able to reduce the extent of extracellular tangles, this may still delay disease onset in the mice. The reason is that tangle-associated inflammation that can have detrimental effect on surrounding tissue (such as "bystander lysis") is expected to reduce concurrently. Based on these observations, a possible scenario for a therapeutic use of immunotherapy targeting pathological tau would be as follows. The best effect would obviously be obtained if individuals could be immunized as a prophylactic measure. In a healthy subject, the BBB would be relatively impermeable to the anti-phospho tau antibodies. As tau pathology would start to accumulate, associated inflammatory changes and cellular stress should facilitate antibody uptake into the brain and subsequently into neurons. The outcome would be gradual removal of pathological tau as it forms that would then delay the onset of the disease.

We expect the immunotherapy to be also effective in other tangle models such as the htau mice that more closely resemble AD in the distribution, age of onset and rate of progression of tau pathology. The cognitive improvements we have observed with this approach in the newly developed htau/PS1 model are also very promising [16,119]. Compared to the homozygous P301L mice, the htau mice have a slower progression of pathology that more closely resembles AD [4,5,70] and may be more amenable to clearance. Hence, the impressive 28–96% reduction (depending on their age, brain region analyzed and model) in tau aggregates in the aggressive homozygous P301L model [8], or the accelerated htau/PS1 model [119] may translate into a reversal of tau pathology in the htau mice and eventually in AD. However, this approach is unlikely to benefit dying neurons with advanced tangle formation.

Overall, our tau immunotherapy studies may lead to a more efficacious combination therapy that targets the two major hallmarks of AD, tau- and A β aggregates.

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Figure 1 is based on a figure designed by Johanna Ingadottir, a former student in my laboratory. I thank her for allowing me to use it as a template.

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Figure 1. Potential mechanisms for clearance of pathological tau within neurons

A: 1) Aggregated tau within neurons activates protein quality control mechanisms within neurons which results in the generation of phagosomes that encapsulate the aggregates. 2) Anti-tau antibodies are transported into the cell via receptor-mediated endocytosis through the Thy 1.1 receptor, the lipoprotein receptor-related protein (LRP) and/or the Fc receptor (FcR). 3) The antibody-endosomes fuse with the tau-phagosomes and, 4) subsequently fuse with lysosomes in which 5) the antibodies and the tau aggregates are degraded.

B: Anti-tau antibodies may enter the neuron through passive diffusion that may be more prominent in damaged neurons. 1) Tau aggregates are often found near the inner lumen of the neuronal plasma membrane by which they could bind to the antibodies. 1) The complex would then be engulfed by endosomes/phagosomes, 2) fuse with lysosomes and, 3) be degraded as in A.