

# Tau-based Therapies for Alzheimer's Disease: Wave of the Future?

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## ABSTRACT

*The development of effective neuroprotective agents for sporadic Alzheimer's disease is a formidable challenge because this disease is multifactorial and heterogeneous. Tau-mediated neurotoxicity has been implicated as a downstream effector of Abeta pathology and as an increasingly compelling target for Alzheimer's disease therapies. The tau hypothesis of pathogenesis of Alzheimer's disease proposes that dysregulation of tau phosphorylation, misfolding and subsequent aggregation of tau and tau fibrillization may play a significant role in causing synaptic loss and neuronal loss. Thus, reducing hyperphosphorylation of tau, reducing aggregation of tau and promoting clearance of hyperphosphorylated tau and tau aggregates may reduce neurotoxicity and may be important in the treatment of Alzheimer's disease. An expanding number of tau-based therapies (eg, kinase inhibitors, microtubule stabilizers) are being investigated by researchers in both the pharmaceutical industry and academia. Research in the next few years may soon bring the full potential of tau-based therapies for Alzheimer's disease in sight.*

## INTRODUCTION

There are two major neuropathologic hallmarks of Alzheimer's disease. Extracellular senile plaques are largely composed of  $\beta$ -amyloid (A $\beta$ ) deposits. Intracellular flame-shaped neurofibrillary tangles (NFTs) are bundles of paired helical filaments (PHFs) whose main constituent is the abnormally hyperphosphorylated tau protein (hptau).<sup>1</sup> Other generally accepted pathologic features of Alzheimer's disease

## FOCUS POINTS

- Protein tau is necessary for normal synaptic and neuronal function.
- Tau dysfunction has been implicated in the pathogenesis of Alzheimer's disease.
- Tau-based therapies are currently being investigated for treatment of Alzheimer's disease.
- Combining tau-based therapies with amyloid-based therapies may be needed for effective treatment of Alzheimer's disease.

include synaptic and neuronal loss. NFTs were first recognized in 1906 by Alois Alzheimer as the diagnostic hallmark of Alzheimer's disease.<sup>1</sup> In the 1960s, the composition of these insoluble proteinaceous deposits as PHFs were identified by electron microscopy.<sup>2</sup> By the end of the 1980s, the identification of tau protein as the principle component of these filaments allowed for the immunohistologic recognition of tau in numerous other neurodegenerative conditions. The Table provides a list of tauopathies.

The debate over whether tau dysfunction can cause neuronal death and dementia was settled with the landmark discoveries in 1998 of tau gene mutations pathogenic for hereditary fronto-temporal dementia (FTD) with parkinsonism linked to chromosome 17, or FTDP-17.<sup>3</sup> The development of transgenic mouse models of tauopathies have increased efforts to develop tau-based therapies for Alzheimer's disease and related tauopathies.

This article briefly reviews the normal function of tau, the potential role tau may play in the pathogenesis of Alzheimer's disease, tau-based therapies that have been studied to date, and limitations of current research.

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## NORMAL TAU FUNCTION

Microtubules (MTs) represent one of the three main components of the eukaryotic cellular cytoskeleton. MTs serve a wide variety of essential structural and transport functions in the neurons. The proper regulation of MT dynamics is essential in order for MTs to perform their many critical cellular functions. Cells have evolved a host of regulatory MT-associated proteins

**TABLE**  
**MOST PREVALENT TAUOPATHIES**  
**(DYSFUNCTIONAL PROTEIN: TAU)**

<i>Name</i>	<i>Type</i>	<i>Typical Cognitive Dysfunction</i>	<i>Movement Disorder</i>
<i>Predominantly tau pathology</i>			
Pick's disease	Frontal atrophy, pick bodies	Frontal dysexecutive syndrome, PNFA, SD	Rare
FTDP-17	Varies, frontal atrophy often seen with tau-positive neuronal and glial inclusions	Frontal behavioral syndrome	Parkinsonism
PSP	NFTs in basal ganglia, diencephalon, and brain stem	Frontal dysexecutive	Supranuclear gaze palsy, falls, parkinsonism
CBD	Parietofrontal or frontotemporal atrophy and pallor in substantia nigra, tau-aggregates	Cortical sensory loss, apraxia	Asymmetric akinetic rigid syndrome
Argyrophilic grain disease	Cortical and subcortical granular changes in the neuropil	Memory and personality problems (Limbic dementia)	Absent
<i>Associated with amyloid deposition</i>			
Alzheimer's disease	Hippocampal and medial temporal Hippocampal and medial temporal atrophy and amyloid plaques, NFTs	Amnesic, cortical	Rare
Down's syndrome	Hippocampal and medial temporal atrophy and amyloid plaques, NFTs	Amnesic, cortical	Rare
Dementia pugilistica	A $\beta$ and NFT deposition in cortical and subcortical regions	Amnesic, cortical (following traumatic brain injury in boxers)	Parkinsonism

PNFA=progressive nonfluent aphasia; SD=semantic dementia; FTDP-17=fronto-temporal dementia with parkinsonism linked to chromosome 17; PSP=progressive supranuclear palsy; NFTs=neurofibrillary tangles; CBD=cortico-basal degeneration; A $\beta$ = $\beta$ -amyloid.

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(MAPs) that fine tune MT dynamics, including tau, MAP2, MAP1A/B, MAP4, SCG10, and stathmin.<sup>4</sup>

The MAP tau (MAPT) is a 352-441 amino acid protein. There are six isoforms of tau expressed in the adult human brain, all of which are derived from a single gene called MAPT gene through alternative RNA splicing.

Tau has a well-established role in regulating the stability of MTs.<sup>5</sup> In addition, normal tau function is also important in allowing signalling molecules, trophic factors, and so forth, to travel along the axons.<sup>6</sup> Under normal physiologic conditions, tau is in a constant dynamic equilibrium, binding to MTs for a short time and then getting phosphorylated by kinases, leading to detachment from MTs for a short time and then reattaching after getting dephosphorylated by phosphatases.<sup>7</sup> Frequent cycles of such binding and detachment may be needed to allow effective axonal transport.

## TAU PATHOLOGY IN ALZHEIMER'S DISEASE

Tau is one of a growing category of proteins that are predisposed to conformational change (ie, folding) and self-assembly into pathologic aggregates.<sup>8</sup> Other proteins that have been rigorously studied include A $\beta$  (causing amyloidopathies such as Alzheimer's disease),  $\alpha$ -synuclein (causing synucleinopathies such as dementia with Lewy bodies) and prion protein (causing prionopathies such as Creutzfeldt Jacob disease).

The important early events in NFT formation are thought to be relocation of tau protein from axonal to somatodendritic compartments; detachment from microtubules; and hyperphosphorylation of tau accompanied initially by synaptic dysfunction and then synaptic loss, followed by neuronal loss.<sup>8,9</sup> The sequence in which these three events occur is not clear. To date, efforts to find mutations involving MAPT that cause Alzheimer's disease have been unsuccessful. Several factors influencing these early events have been identified. These include but are not limited to A $\beta$  neurotoxicity, genetic factors, neuroinflammation, oxidation, atherosclerosis, exposure to toxins (eg, nicotine, aluminum), altered cholesterol metabolism, nutritional factors, depression, and stress.<sup>10-31</sup> The formation of tangles precedes deposition of A $\beta$  into plaques.<sup>10</sup> However, in the absence of A $\beta$  plaques, the neurofibrillary changes are relatively slow and are largely restricted to medial temporal lobe structures. Tau accumulation in Alzheimer's disease is probably a consequence of A $\beta$ -amyloidogenic neuronal damage rather than a primary event.<sup>11</sup> Appearance of A $\beta$  is associated with spreading of tangles to the neocortex.<sup>8</sup> In preclinical Alzheimer's disease cases, which have substantial number of plaques but do not yet show any cognitive decline, there is evidence that the rate of increase of tangles with age is greater than in cases with few or no plaques.<sup>32</sup> Blocking A $\beta$ 42

accumulation has been found to delay the onset and progression of tau pathology.<sup>33</sup> There is also evidence that somatodendritic tau accumulation is dependent on the A $\beta$  deposits.<sup>34</sup> Taken together, evidence to date suggests that high concentration of A $\beta$  in plaques may have a role in production of hptau and increased tangles formation in Alzheimer's disease. These findings also raise the possibility that tau dysfunction may be essential to A $\beta$ -induced neurotoxicity.<sup>35</sup> A $\beta$  immunotherapy leads to clearance of early, but not late, hptau aggregates in transgenic mice.<sup>36</sup> This also suggests that therapies to lower A $\beta$  may reduce neurotoxicity caused by tau misfunction early in the disease. Later in the disease, the impact of lowered A $\beta$  may not be so effective and a combination of amyloid-based and tau-based therapies may be necessary for successful outcomes. Tau aggregation may self-perpetuate once they reach a critical formative stage, meaning that neurotoxicity mediated by tau misfunction may accelerate even if A $\beta$  or amyloid plaque can be reduced. Although the precise mechanisms underlying the effect of A $\beta$  on development of tau pathology are unclear, it may involve alterations in the levels of C terminus of heat shock protein 70 (Hsp70)-interacting protein (CHIP).<sup>37</sup>

Neuroinflammation may also play a critical role in tau pathogenesis. Immunosuppression of young mutant tau transgenic mice attenuated tau pathology and increased lifespan, thereby linking neuroinflammation to early progression of Alzheimer's disease.<sup>19</sup> There is evidence suggesting that neuroinflammation is responsible for an abnormal secretion of proinflammatory cytokines that trigger signaling pathways that activate brain tau hyperphosphorylation in residues that are not modified under normal physiologic conditions.<sup>38</sup> Products of neuroinflammation might change the substrate specificity of kinases/phosphatases leading to tau phosphorylation at pathologic sites.<sup>39</sup>

When disengaged from an MT, tau seems to be a promiscuous binder that is prone to heterogenous interactions (especially phosphorylation). This may lead to protein misfolding and aggregation.<sup>40</sup> Misfolded tau has impaired ability to stabilize MTs. Misfolded tau has enhanced ability to form larger and larger aggregates, initially forming "pretangles" leading to formation of PHFs with a  $\beta$  sheet-containing structure which, in turn, aggregates to form large compact bundles filling the entire cytoplasm as classic NFTs.<sup>40</sup> In addition to the intracellular lesions in the neuronal perikaryon, hptau in Alzheimer's disease also exists as PHFs in neuropil threads (derived from dendritic processes; also called "ghost tangles,") and in dystrophic neurites surrounding neuritic plaque A $\beta$  cores.<sup>41</sup>

The topographic distribution and progression of NFT pathology in Alzheimer's disease has been described by Braak and Braak<sup>42</sup> and divided into six distinct stages assigned as follows: In stage 1, NFT is confined to the transentorhinal cortex (layer 4); in stage 2, NFT is in the entorhinal cortex (layer 2); in stage 3, NFT is in the hippocampus (CA1 and

subiculum); in stage 4, NFT is in the temporal lobe association neocortex (mild); in stage 5, NFT is in the temporal association neocortex (moderate to severe); and in stage 6, NFT is in the temporal association neocortex (severe) and primary visual cortex. Braak stage 0 was assigned in the absence of NFT. Braak stages 0–2 have been considered as low limbic stages with pathologic changes consistent with typical aging. Braak staging is based on the presence of any NFT in a certain region, not quantitative NFT load (ie, tau burden). Tau burden is significantly correlated to Braak stage, although tau burden varies to a large degree in each Braak stage.<sup>43</sup>

## THE TAU HYPOTHESIS OF ALZHEIMER'S DISEASE NEURODEGENERATION

The tau-hypothesis of Alzheimer's disease pathogenesis proposes that tau misfunction mediates neurotoxicity and neurodegeneration and that this is an important contributor to the pathogenesis of Alzheimer's disease. This is supported by several important findings. The appropriate pathologic correlate of synaptic and neuronal (gray matter) loss in Alzheimer's disease is tangles, not plaques.<sup>10</sup> Synaptic dysfunction and loss develops long before neuronal loss, and synaptic loss is the best correlate of cognitive decline in Alzheimer's disease.<sup>44</sup> A substantial number of tangles develop in the entorhinal cortex (layers 2 and 4) and hippocampus (area CA1)—precisely the same neurons that slightly later show extensive degeneration characterizing the early stage of Alzheimer's disease development and correspond to initial clinical symptoms of impaired memory. In the superior temporal cortex, plaques develop early in Alzheimer's disease, but both tangles or neuronal degeneration develop together in more severe stages of Alzheimer's disease.<sup>45</sup> This suggests that tau aberrations and aggregations may be involved in the process of cell degeneration, either as a causative factor or as a contributory factor of neuronal degeneration. In one study,<sup>46</sup> genetically reducing tau expression (thus, reducing endogenous levels of tau) in Alzheimer's disease mouse models that overexpress human amyloid resulted in prevention of behavioral disturbances and memory loss in the mice without altering the accumulation of amyloid plaques. This study showed that even partial reduction of tau prevented memory problems despite the persistence of high levels of amyloid. Thus, aberrant tau may play a role in neurodegeneration in Alzheimer's disease. If so, understanding the mechanisms by which aberrant tau mediates neurodegeneration in Alzheimer's disease is critical to any development of tau-based therapies. The importance of tau aggregation intermediates (eg, tau dimer, tau multimer, and granular tau oligomer) in Alzheimer's disease pathogenesis has been suggested by recent studies. These studies<sup>47</sup> indicate that the smaller aggregates of tau may be neurotoxic; NFTs

are cells' attempts to protect themselves from the neurotoxic effects of these smaller tau aggregates by sequestering the "abnormal" phospho-tau microaggregates, thereby rendering them harmless.

In Alzheimer's disease, disease onset and progression are dynamic processes that take place over time (probably over 2–3 decades). Aggregation of altered tau may produce a range of different effects at various stages of the disease. Thus, early in the pathogenesis of Alzheimer's disease, detrimental effects due to loss of normal tau function may be the primary driver of neurodegeneration. As the disease progresses, toxic effects of tau aggregates may accelerate the neurodegeneration. Misfolded, truncated tau protein promotes activation of microglia and leukocyte infiltration in the transgenic rat model of tauopathy.<sup>48</sup> Besides neuroinflammation, tau-mediated neurodegeneration may occur through impaired axonal transport, oxidative stress, or a combination of these processes.<sup>35,49-51</sup>

## POTENTIAL PATHWAYS TO CORRECT TAU-BASED NEURODEGENERATION

There are several potential targets to ameliorate tau-mediated neurotoxicity in Alzheimer's disease. Research<sup>52</sup> using phosphorylation modulators (genetically enhanced kinases, or kinase inhibitors) has shown that phosphorylation can enhance the pathogenic progress; importantly, pharmacologic inhibition of this process can reverse or prevent further worsening of Alzheimer's disease, making the development of compounds that prevent abnormal phosphorylation of tau (eg, kinase inhibitors) for therapeutic use worthwhile. Modulation of phosphorylation is, thus, an important avenue to find tau-based therapies. Kinase inhibitors (eg, glycogen synthase kinase [GSK], cyclin-dependent kinase 5 [CDK-5], protein kinase A) are currently being investigated as potential tau-based therapies for Alzheimer's disease. Numerous phosphatases, including protein phosphatase (PP)1, PP2A, PP2B, and PP2C, have also been identified as potential targets for identifying tau-based therapies. Compounds that promote MT stabilization may attenuate altered tau-mediated neurotoxicity in Alzheimer's disease. MT stabilizers such as paclitaxel or related compounds that are safer than paclitaxel are currently being investigated for treatment of Alzheimer's disease.<sup>53</sup> Compounds that promote binding of chaperones (eg, heat shock proteins [HSPs]) may protect against neurotoxicity of htau by promoting clearance of pathologically altered tau.<sup>54</sup> The ability of tau proteins to form a  $\beta$ -structure and aggregate may be a primary determinant of tau-mediated toxicity.<sup>55</sup> Thus, aggregation inhibitors and compounds that prevent fragmentation of tau hold promise for treatment of Alzheimer's disease. Removing A $\beta$  and attenuating neuroinflammation may also reduce tau-mediated neurodegeneration.

## TRIALS OF TAU-BASED THERAPIES

Santacruz and colleagues<sup>56</sup> conducted one of the initial studies targeting abnormal tau, creating transgenic mice expressing mutant tau that could be suppressed with doxycycline. They found that mice expressing a repressible human tau variant developed progressive age-related NFTs, neuronal loss, and behavioral impairments. After the suppression of transgenic tau with doxycycline, memory function recovered and neuron numbers stabilized but NFTs continued to accumulate. They concluded that NFTs are not sufficient to cause cognitive decline or neuronal death in this model of tauopathy.

One approach at lowering the tau burden involves reducing the activity of the kinases that phosphorylate tau. Although several kinases have been implicated as key players involved in tau hyperphosphorylation, GSK inhibitors have received most attention. Two variants of GSK exist, referred to as GSK3 $\alpha$  and GSK3 $\beta$ . In addition to the latter's well-described role in the phosphorylation of tau, reports also suggest that GSK3 $\alpha$  may regulate amyloid precursor protein processing and A $\beta$  formation. GSK3 promotes the production of inflammatory molecules and cell migration, while GSK3 inhibition provides protection from inflammatory conditions in animal models.<sup>57</sup> Thus, GSK3 may contribute not only to primary pathologies in Alzheimer's disease, but also to the associated inflammation, suggesting that GSK3 inhibitors may have multiple effects influencing these conditions. Microglia play a prominent role in the brain's inflammatory response to injury or infection by migrating to affected locations, secreting inflammatory molecules, and phagocytosing damaged tissue. GSK3 promotes microglial responses to inflammation and the microglial responses to inflammatory stimulation were greatly attenuated by GSK3 inhibitors, demonstrating that the utilization of GSK3 inhibitors provides a means to limit the inflammatory actions of microglia.<sup>58</sup> Lithium is currently being investigated for treatment of tauopathies. Inhibition of GSK3 $\beta$  by lithium not only reduced tau phosphorylation *in vivo*, but also lowered the level of aggregated tau, compared with controls.<sup>59</sup> Lithium may also reduce A $\beta$  production, possibly through inhibition of GSK3 $\alpha$ , which is required for maximal processing of the precursor of A $\beta$ , amyloid precursor protein.<sup>60</sup> Progression of the tauopathy could be prevented by administration of lithium when the first signs of neuropathology appear.<sup>61</sup> Engel and colleagues<sup>62</sup> investigated the therapeutic efficacy of chronic lithium administration in a triple transgenic mouse model of Alzheimer's disease that harbored both plaques and tangles. They found that though lithium reduced tau phosphorylation, it did not significantly alter the A $\beta$  load or improve deficits in working memory. *In vivo* and *in vitro* findings of lithium-mediated reductions in GSK3 $\beta$  and cyclin-dependent kinase 5 activities, tau phosphorylation, apoptotic activity, and cell death provide a strong rationale for the use of lithium as a potential

treatment in neurodegenerative diseases.<sup>63</sup> Rametti and colleagues<sup>64</sup> showed that exposure of cultured cortical neurons to lithium decreased tau protein levels linked to a reduction in tau mRNA levels and markedly reduced pre-aggregated A $\beta$ -induced neuronal apoptosis. Their findings raise the possibility that lithium could exert its neuroprotective effect against A $\beta$  toxicity through the downregulation of tau proteins. A phase 2 trial using lithium and divalproex to inhibit GSK3 activity is being sponsored by the National Institute of Neurological Disorders and Stroke. Other novel kinase inhibitors are being developed. One such selective GSK3 $\beta$  inhibitor is 1-aza-9-oxafluorenes.<sup>65</sup> Indirubins are being designed as novel analogues of 6-bromo-indirubin-3'-oxime with increased hydrophilicity based on the GSK3/indirubins co-crystal structures. The new derivatives with an extended amino side chain attached at position 3' showed potent GSK3 inhibitory activity, enhanced selectivity, and dramatically increased water solubility. Furthermore, some of them displayed little or no cytotoxicity. The new indirubins inhibit GSK3 in a cellular reporter model.<sup>66</sup>

The removal of phosphorylated tau could be a relevant therapeutic strategy in Alzheimer's disease. The CHIP, an ubiquitin ligase that interacts directly with Hsp70/90, induces ubiquitination of tau and also increases tau aggregation. Tau lesions in human postmortem tissue were found to be immunopositive for CHIP. Conversely, induction of Hsp70 through treatment with either geldanamycin or heat shock factor 1 (HSF1) leads to a decrease in tau steady-state levels and a selective reduction in detergent insoluble tau.<sup>67</sup> Furthermore, 30-month-old mice overexpressing inducible Hsp70 show a significant reduction in tau levels.

Together, these data demonstrate that the Hsp70/CHIP chaperone system plays important roles in the pathogenesis of tauopathies, regulation of tau turnover, and selective elimination of abnormal tau species, and also represents a potential therapeutic target. In another study,<sup>68</sup> inhibition of Hsp90 led to decreases in p-tau levels independent of HSF1 activation. The peripheral administration of a novel Hsp90 inhibitor promoted selective decreases in p-tau species in a mouse model of tauopathy, further suggesting a central role for the Hsp90 complex in the pathogenesis of tauopathies.<sup>68</sup>

Methyl thioninium chloride (MTC), also known as methylene blue, is a reducing agent manufactured by the Singapore-based TauRx Therapeutics. MTC inhibits the heparin-induced filament formation of 4repeat and 3repeat tau in a concentration-dependent manner.<sup>69</sup> It also has antioxidant properties by competitive inhibition of the reduction of molecular oxygen to superoxide by acting as an alternative electron acceptor.<sup>70</sup> Wischik and colleagues<sup>71</sup> presented preliminary results of a phase 2 study at the International Conference on Alzheimer's Disease held July 2008 in Chicago, Illinois. A total of 321 patients with mild-to-moderate Alzheimer's disease were

given MTC in 30, 60, or 100 mg doses TID or randomized to placebo. The 60 mg dose produced the most significant effect and the patients showed an almost seven-point difference over 50 weeks for symptoms of dementia. In the study, an 81% difference in the rate of mental decline was observed compared with those not taking the treatment; at 19 months there was no significant decline in mental function in patients taking the drug. According to Wischik and colleagues,<sup>71</sup> MTC interferes with tau aggregation by acting on self-aggregating truncated tau fragments and imaging data suggest the drug may have its effect in the parts of the brain responsible for memory. Patients taking cholinesterase inhibitors and memantine were excluded. For patients with moderate Alzheimer's disease on placebo, there was a roughly 5.5 point decline on the Alzheimer's Disease Assessment Scale-Cognitive versus a 1.5-point decline in the MTC group over 24 weeks. This study has not been published and all the data are not available for independent review. Larger trials of the drug are planned to start in 2009, and research is also ongoing as to whether the drug has a preventive role in Alzheimer's disease.

AL-108 (developed by Allon Therapeutics), delivered in a nasal spray, targets phosphorylated tau. AL-108 contains an eight-amino acid peptide derived from activity-dependent neuroprotective protein, which participates in neurodevelopment and neuroprotection.<sup>72</sup> The phase 2 study<sup>73</sup> involved 144 subjects with mild cognitive impairment who were randomly assigned to receive placebo, 5 mg BID AL-108, or 15 mg BID AL-108 for 12 weeks. Subjects receiving high-dose AL-108 showed a statistically significant improvement in a memory test after 12 weeks and 62.4% improvement from baseline by week 16. This study also awaits full publication and peer review.

Another recent therapeutic strategy reported in two tangle mouse models indicates 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 pathologic tau within neurons.<sup>74</sup>

## THE FUTURE PROSPECTS OF TAU-BASED THERAPIES: A HOLISTIC APPROACH

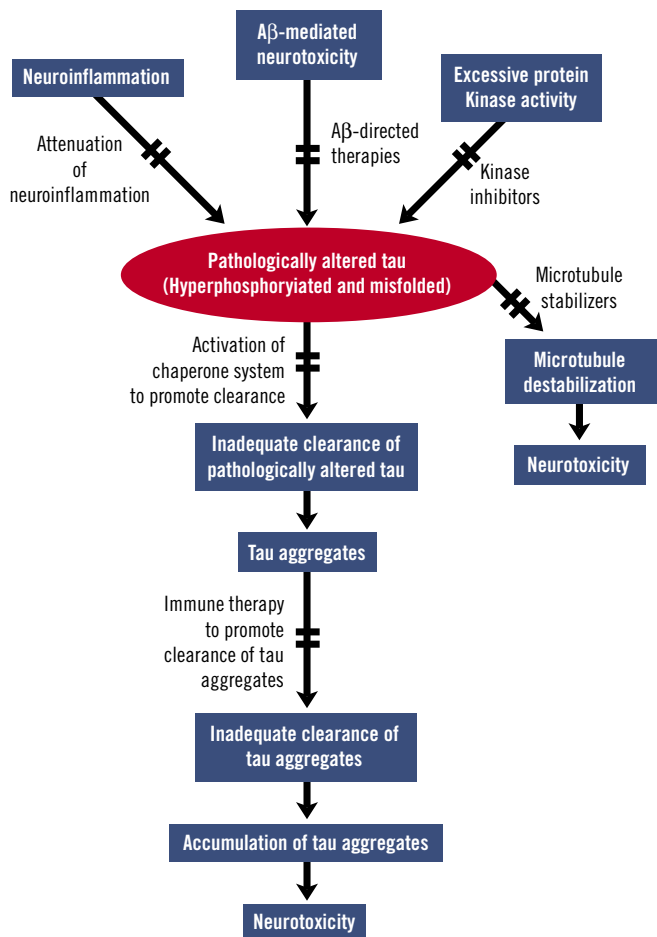
Potential therapeutic targets to ameliorate tau-based neurotoxicity in Alzheimer's disease are shown in the Figure. Alzheimer's disease may result from several different etiopathogenic mechanisms.<sup>75</sup> Hence, most experts believe that effective treatment of Alzheimer's disease will probably require multiple targets. These targets include A $\beta$  aggregates, tau dysfunction, and neuronal and synaptic loss—mechanisms that contribute to A $\beta$  and tau-mediated inflammation and immune dysregulation.<sup>76</sup>

## LIMITATIONS OF CURRENT RESEARCH

Substantial limitations exist in our current understanding of the physiologic role of tau in neuronal function and precise steps in the pathogenesis of Alzheimer's disease. Some researchers have suggested that neuropathologic changes in the brains of people with Alzheimer's disease may not be central to pathogenesis; rather, pathology may even be the anti-pathogenesis and, rather than causing the disease, the pathology may be protecting from the disease.<sup>77,78</sup> Although focus on kinase inhibitors dominate current research for tau-based Alzheimer's disease therapy, a study<sup>79</sup> showing that kinase MARK2 rescued degeneration of synapses caused by abnormal sorting of tau in neurons (probably by correcting the redistribution of tau from axons to cell body and dendrites) highlights the complexity of

### FIGURE

#### POTENTIAL THERAPUTIC TARGETS CURRENTLY UNDER INVESTIGATION TO AMELIORATE TAU-MEDIATED NEUROTOXICITY IN ALZHEIMER'S DISEASE



A $\beta$ = $\beta$ -amyloid.

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normal tau function. Although it may be desirable to suppress mutant forms of tau in hereditary tauopathies or in tauopathies with an abnormal ratio of 3R versus 4R tau isoforms, reducing tau levels in Alzheimer's disease—especially to a degree that compromises MT stability and dynamics—may have long-term deleterious effects that may offset short-term benefits. Many kinase inhibitors (eg, GSK3) of tau are promiscuous; they bind to other protein within cells that play a role in normal neuronal function. This poses the challenge of designing kinase inhibitors that are specific to tau and that do not suppress constitutive neuronal activity.<sup>80</sup>

## FUTURE RESEARCH ON DEVELOPMENT OF TAU-BASED THERAPIES

To design clinical trials for Alzheimer's disease, knowledge about measurement of disease progression is needed to estimate power and enable the choice of optimal outcome measures. Positron emission tomography scans using FDDNP fluorescent probes can be used to detect tangles besides plaques.<sup>81</sup> In the future, measuring and mapping tau before and after a treatment may be one indicator of whether tau-based therapies are working. Levels of soluble and insoluble tau may be indicative of overall levels of tau phosphorylation and may be useful markers to evaluate the effects of tau-based therapies for Alzheimer's disease.<sup>82</sup> Future clinical trials may need to involve "enriched population" or stratification of patients at risk for Alzheimer's disease.<sup>83</sup> Stratification of patients at risk for future Alzheimer's disease involves separating them into different subgroups based on amyloid load (eg, through amyloid imaging), htau load (eg, through tau imaging), genetics (eg, through genotyping), cerebrofluid tau and A $\beta$ , findings from magnetic resonance imaging of the brain, and lifestyle and cardiovascular factors. This may markedly increase the success in developing specific and potent therapeutic drugs for Alzheimer's disease.

## CONCLUSION

There are several tau-based potential avenues worthy of investigation for therapeutic potential in the treatment of patients with Alzheimer's disease. Tau-based therapies may also have a role in treatment of non-Alzheimer's disease tauopathies such as Pick's disease, cortico-basal degeneration, and progressive supranuclear palsy.<sup>84</sup> **PP**

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