## Title
Targeting tau: Clinical trials and novel therapeutic approaches



## Authors
VandeVrede, Lawren
Boxer, Adam L
Polydoro, Manuela

## Publication Date
2020-07-01

## DOI
10.1016/j.neulet.2020.134919

Peer reviewed

HHS Public Access

Author manuscript

*Neurosci Lett*. Author manuscript; available in PMC 2022 June 21.

Published in final edited form as:

*Neurosci Lett*. 2020 July 13; 731: 134919. doi:10.1016/j.neulet.2020.134919.

# Targeting tau: Clinical trials and novel therapeutic approaches

**Lawren VandeVrede**[a],

**Adam L. Boxer**[a],

**Manuela Polydoro**[b,*]

[a]Memory and Aging Center, Department of Neurology, University of California, San Francisco (UCSF), San Francisco, CA, USA

[b]Casma Therapeutics, Cambridge, MA, USA

## Abstract

Tauopathies are a group of over 20 clinicopathological neurodegenerative diseases including Alzheimer's disease (AD), the most common type of dementia, progressive supranuclear palsy, Pick's disease, corticobasal degeneration, among others. Tauopathies are defined by neurodegeneration and the presence of tau aggregates in affected brains regions. Interestingly, regional tau aggregation burden correlates with clinical phenotype and predicts cognitive status. Autosomal dominant mutations in the *MAPT* gene lead to tau deposition and clinical FTD syndromes with cognitive, behavioral, and motor impairment. Polymorphisms in or around the *MAPT* gene have also been strongly linked to other proteinopathies including synucleinopathies. Taken together these findings suggests that tau plays a critical role in neurodegeneration and proteinopathies, supporting the idea that tau targeted approaches can be disease-modifying and lead to clinically meaningful benefits in slowing or reversing disease progression. Increasingly, human clinical trials are testing this hypothesis. This article reviews tau-targeted therapies tested in clinical trials as well as agents currently in active development based on publicly disclosed information. We describe the therapeutic approaches of these trials based on the potential pathogenic mechanism they target.

### Keywords

Tauopathies; Tau; Alzheimer's disease; Frontotemporal dementia; Progressive supranuclear palsy; Pick's disease; Corticobasal degeneration; Parkinsonism

## 1. Introduction

Neurodegenerative diseases cause disability and death in millions of people worldwide. [1] The cost of treating these illnesses exceeds a quarter of a trillion dollars in the United States alone [2]. Despite numerous approaches having been tested in clinical trials, available therapeutic options for neurodegenerative diseases remain limited and many syndromes lack even symptomatic treatment options. Disease-modifying therapies

*Corresponding author. mpolydoro@casmatx.com (M. Polydoro).

that can alter the underlying biology and slow or arrest disease progression are urgently needed. One approach is targeting tau proteins, which have been implicated in a variety of neurodegenerative diseases through both clinical/pathological correlations as well as genetic studies.

A group of neurological disorders collectively referred to as tauopathies have aggregates of tau protein as a core neuropathologic feature (see Table 1) [3]. In Alzheimer's disease (AD), the most common and best studied tauopathy, tau aggregation into neurofibrillary tangles (NFTs) is one of two pathological hallmarks of the disease, the other being beta amyloid (Aβ) plaques [4]. Tau aggregation in the brainstem and entorhinal cortex has been shown to be the earliest histopathological finding in the neuropathology of AD, which can spread to other brain regions as the disease progresses over time and increases in severity [5-7]. Recent advances in tau-sensitive PET imaging have demonstrated that tau aggregation correlates neuroanatomically with both symptoms and severity in AD [8]; these findings are consistent with Braak staging in clinicopathological studies that have demonstrated regional tau burden correlates with clinical phenotype and predicts cognitive status [9,10].

Further critical support for the tau hypothesis of neurodegeneration came from a series of discoveries showing that mutations in the gene encoding tau (*MAPT*) were pathogenic for a hereditary neurodegenerative syndrome called frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). Subsequently, a variety of autosomal dominant mutations in the *MAPT* gene were found to lead to tau deposition and frontotemporal lobar degeneration (FTLD) related syndromes with cognitive, behavioral, and motor impairment, supporting the hypothesis that tau may be the proximal etiology leading to clinical symptoms. Polymorphisms in or around the *MAPT* gene have also been strongly linked to other proteinopathies including synucleinopathies, suggesting that tau may play an important role in other neurodegenerative proteinopathies. [11]

A number of pathogenic *MAPT* mutations associated with FTDP-17 can alter tau's binding kinetics, increasing the levels of unbound tau and therefore its propensity to misfold and aggregate. Although it has been previously hypothesized that the disassociation of tau from microtubules, reflective of its loss of function, could potentially play a role in the pathogenesis of the disease, the current view in the field is that the deleterious effects of tau pathology are due to toxic gain of function of tau. This is consistent with the observation that tau knockout mice are essentially healthy. Furthermore, Tau reduction has been found to be not only safe but also neuroprotective in mouse models of excitotoxicity and seizures. [12,13] Thus, it is clear that tau toxicity plays a critical role in the pathogenesis of tauopathies, however the molecular mechanisms of this toxicity remains unclear. There is limited understanding of what forms of tau confer its toxicity and how tau aggregates interfere with cellular function leading to neurodegeneration. The main reason for this gap in our knowledge comes from the complexity of tau proteins and the heterogeneous patterns of tau pathology presented in different tauopathies. Different isoforms are affected in different tauopathies leading to aggregates with distinct structures, which accumulate in different cell types.

Tau proteins are expressed from a single gene (*MAPT*) on chromosome 17, resulting in six isoforms after alternative splicing that differ by N-terminal insertions and the number of repeats of microtubule binding repeat (MTBR) domains at the carboxy-terminal. [11] Importantly, three- or four-repeat MTBR isoforms (3R-tau or 4R-tau) arise from inclusion or exclusion of exon 10, and in the healthy adult brain 3R- and 4R-tau proteins are equally expressed [14]. In 1998, thirteen families with a clinical syndrome with cognitive, behavioral, and motor symptoms called frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) were found to have *MAPT* mutations that increased expression and aggregation of 4R-tau isoforms, [15-17] and these patients provided the first direct evidence for a causal link between tau dysfunction and neurodegenerative disease.

Subsequently, in patients without mutations, similar accumulations of 4R-tau were found to lead to diverse clinical phenotypes also with cognitive, behavioral, and motor involvement, collectively termed 4R-tauopathies, which include progressive supranuclear palsy (PSP), [18] corticobasal degeneration (CBD) [19], and argyrophilic grain disease (AGD) [20]. Accumulation of the 3R isoforms has also been linked to pathologic aggregation, as seen in Pick's disease (a 3R-tauopathy), and a limited number of *MAPT* mutations. [21] Equal expression of 3R- and 4R-tau, is found in AD and chronic traumatic encephalopathy (CTE). Although tau inclusions are present in a group of neurodegenerative diseases, patients with different tauopathies show distinctive clinical symptoms and patterns of tau aggregation. Tau pathology is presented in various forms, in different brain regions, cell types, as well as subcellular localization depending on the disease [22]. Tau isoforms have diverse contributions and specific filament conformations lead to ultrastructure conformation in each of the tauopathies [23,24]. The implication is that a particular tau aggregate strain is the culprit in each specific Tauopathy. The pathological diversity of tauopathies imposes a challenge in finding a common treatment that can be applied to all diseases in which tau plays a toxic role.

After transcription and alternative splicing, tau undergoes extensive post-translational modification by processes such as phosphorylation, O-GlcNAcylation, acetylation, and proteolytic cleavage by caspases and other proteases [25]. PTM regulates tau's diverse functions, and phosphorylated tau (pTau) plays a crucial role in normal physiology, including tau binding to microtubules [26]. In contrast, abnormal phosphorylation patterns (e.g. hyperphosphorylation) are associated with pathologic tau aggregation, primarily in AD [27]. It has been proposed that physiologic clearance of tau is also partially dependent on PTM, typically via ubiquitination and routing of tau to the proteasome. Acetylation of tau at lysine residues prevents ubiquitination and clearance, allowing hyperphosphorylation and tau aggregation [28]. In human AD brains, increased acetylation has been demonstrated in tau aggregates, raising the possibility that an acetylation inhibitor may increase the physiologic clearance of tau and prevent tau aggregation [29].

## 2. Therapeutic approaches

Taken together, this body of work supports the idea that therapies that modulate tau levels or function have the potential to lead to clinically meaningful benefits in slowing or reversing disease progression. Increasingly, human clinical trials are testing this hypothesis.

This article aims to review the potential tau pathological mechanisms in neurodegenerative disease, and the current tau-directed therapeutic agents that have reached the clinical phase of development. In primary tauopathies, tau is an obvious target given the evidence of its direct cause of the disease. It is also clear that the tau is an attractive target in secondary tauopathies such as AD, and the failure of multiple phase III clinical trials in Alzheimer's disease (AD) with drugs targeting Aβ has fueled increasing interest in alternative therapeutic approaches, especially those targeting tau pathology. Given that tau pathology is a better correlate with cognitive impairments than Aβ plaques, targeting tau can be more effective than Aβ clearance.

Six main approaches are being tested, including reducing *MAPT* gene expression, modulating post-translational modification, preventing tau aggregation, immune neutralization or clearance of different tau species via either active or passive strategies, and stabilizing microtubules (Fig. 1). The overarching hypotheses being tested through these studies are 1) the predominant hypothesis that tauopathies are caused by a toxic gain of tau function (post-translational modification, misfolding, aggregation and or altered expression) leading to neuronal dysfunction and death, [12] which would require prevention, disruption and/or clearance; or 2) neurodegeneration is in part a consequence of loss of normal tau function, e.g. binding to and stabilizing microtubules or other cellular functions, which would require agents to supplement this function [30]. Importantly, these mechanisms of tau toxicity are not mutually exclusive, e.g. toxic tau gain of function could interfere with physiological tau function leading to secondary loss of function.

At the time of this review, 24 therapeutics identified as tau-targeted by clinical trial sponsors have been tested in Phase 1 or later clinical trials, with 15 agents currently in active development based on publicly available data (see Table 2). Below, each potential pathogenic mechanism and relevant therapeutic approaches that are in or nearing human clinical trials are discussed.

## 3. Therapeutic approaches to toxic tau gain of function

### 3.1. Approach 1: reduce tau gene expression (gene therapy)

RNA-targeted therapeutic approaches have provided an exciting new treatment for other genetic diseases, and recent successes with anti-sense oligonucleotides (ASOs) in spinal muscular atrophy [31] and Huntington’s disease [32] raise the possibility of reducing tau transcript expression as a therapeutic approach in tauopathies. Given the diverse roles of tau in the human brain, complete knockdown has been approached cautiously, but in many mouse models, complete tau knockout has no overt phenotype, suggesting that reduction of tau expression may not be deleterious and well tolerated [12,33-35]. These data are complemented by findings that tau reduction may also be protective against seizure activity in pre-clinical models [36].

**3.1.1. Anti-sense Oligonucleotides (ASOs)—**Based on the above rationale, Ionis developed BIIB080 (IONISMAPT Rx), an ASO delivered intrathecally that reduces total tau gene expression. In P301S transgenic mice that express human tau, 50% reduction in tau mRNA levels by BIIB080 reversed tau aggregation, with a concomitant decrease in

the rate of hippocampal atrophy, neuronal loss, and nesting behavioral deficits. [37] These encouraging preclinical findings led to an ongoing Phase 1/2 in 46 mild AD patients, who will be treated with BIIB080 for 36 weeks (NCT03186989). Additional studies support the hypothesis that 4R-tau may be a particularly pathologic species, especially in 4R-tauopathies such as PSP and CBD, leading to development of ASOs for the selective knockdown of 4R-tau, though this approach remains in preclinical development [38].

Published data from a clinical trial for Huntington's disease using RG6042, an ASO developed by Roche and Ionis to reduce mutant huntingtin, showed up to 60% lowering of mutant HTT in cerebral spinal fluid. There was 55% to 85% reduction in the cortex, but 20% to 50% in the caudate, and deeper brain regions. Depending on the distribution of ASOs in the brain they may be more efficient in tauopathies with a cortical involvement as opposed to caudate, putamen and thalamic nuclei such as in PSP. The upcoming Phase 3 trial of RG6042 will test whether lowering the levels of a mutant form of huntingtin (mHTT) translates into clinical improvement. [39]

### 3.2. Approach 2: modulate tau post-translational modification (PTM)

Tau can undergo a variety of post-translational modifications including phosphorylation, acetylation, methylation, ubiquitylation, SUMOylation, glycation, glycosylation, nitration, and truncation. There are over 90 identified phosphorylation sites alone, and a host of putative sites for additional modifications. These PTMs can take place in all 6 isoforms of tau found in the brain and the possible combinations in one particular molecule of tau are nearly infinite. It is therefore extremely difficult to determine if and which PTMs are responsible for tau toxicity. The overall hypothesis has been that PTMs, phosphorylation in particular, interfere with tau–microtubule binding thereby enhancing the propensity of tau to misfold and aggregate. The availability of phospho-tau antibodies and the correlation between increased tau phosphorylation and disease progression gave rise to the hypothesis that phosphorylation plays a critical role in tau pathophysiology.

However, to date there is no clear evidence that phosphorylation is necessary or sufficient for tau-mediated neurodegeneration. Based on the hypothesis that hyperphosphorylation of tau is an early driver of tau pathology, one of the initial therapeutic approaches was to target kinases, which were seen as a traditional drug target in the oncology field. Drug screenings were practical and straight forward, therefore, several kinase inhibitors were developed and moved into human trials. Numerous of publications implicate protein kinases with pathological phosphorylation of tau in AD, including glycogen synthase kinase 3 beta (GSK-3β), Fyn, and Abl, among others. [40,41] However, even if phosphorylation plays a role in toxicity, developing specific and safe kinase inhibitors is extremely challenging specially for long term treatment needed for Tauopathies. Moreover, even if phosphorylation is a critical it is still unclear which kinase is responsible or if there is a single or multiple kinases.

PTM can also affect tau activity by blocking phosphorylation by O-GlcNAcylation, which is the attachment of N-acetylglucosamine (GlcNAc) moieties to serine/threonine residues by O-GlcNAcase (OGA); this process can attenuate subsequent hyperphosphorylation by kinases. [42] In the human AD brain, levels of O-GlcNAcylation were found to

be reduced 50% compared to healthy controls, and this inversely correlated with tau hyperphosphorylation, supporting OGA inhibition and increasing O-GlcNAcylation as a therapeutic mechanism [43].

**3.2.1. Kinase inhibitors—**Kinase inhibitors were some of the first drugs to be tested to treat tauopathies for several reasons. Even though phosphorylation has not been proven to play a role in toxicity, hyperphosphorylated tau was originally seen as an attractive target because it is an early marker of the disease that precedes aggregation in AD. Kinase inhibition was accessible, as enzymes are traditional druggable targets and kinase inhibitors had been developed for many years for the treatment of cancer and psychiatric disorders. However, kinase inhibitors have also been historically difficult to develop outside of the oncology field because they are often unspecific and similar related kinases are also inhibited. Kinases also have many roles and numerous substrates, so even in the event that an inhibitor is specific, the unintended off-target effects may still represent an important liability.

The first kinase inhibitors tested in clinical trials targeted GSK3β, a serine/threonine kinase involved in a wide range of cellular processes including differentiation, growth, motility, and apoptosis, [44] known to be dysregulated in Alzheimer's disease [45]. Lithium, a small molecule that is FDA-approved as a mood stabilizer, was found to reduce tau hyperphosphorylation and aggregation in P301L transgenic mice via a mechanism that was dependent on GSK3β inhibition [46]. These data led to national and international Phase 2 trials in AD, but after 10 weeks of treatment with lithium, no effect was found on cognition, mood, or CSF biomarkers (pTau or Aβ) [47]. In a later trial in patients with PSP or CBS, lithium was poorly tolerated, and only one patient was able to complete 28 weeks of treatment (NCT00703677).

Though no clinical benefit of lithium has been demonstrated in completed clinical trials, it was argued that target engagement was not established, and a Phase 2 trial was initiated under the hypothesis that replicating the positive effect seen in epidemiological data may require longer treatment and initiation earlier in the disease process. Thus, 80 patients with mild cognitive impairment (MCI) are undergoing treatment with lithium for two years, with progression assessed using cognitive testing, CSF biomarkers (GSK3β, ptau), and brain atrophy via 7 T MRI (NCT03185208). Another ongoing trial is assessing the effect of lithium on agitation and aggression in 60 patients with bvFTD (NCT02862210), though the mechanism of this effect is not necessarily tau-mediated.

Valproate (Depakote, divalproex, valproic acid), another small molecule FDA-approved mood stabilizer and anti-epileptic, was also found to inhibit GSK3β, [48] and, in amyloid transgenic mice, it rescued behavioral deficits [49]. However, in a Phase 3 study involving 313 patients with probable AD, treatment with valproate for 24 months resulted in accelerated brain atrophy and cognitive impairment [50], with significant toxic effects, and no effect on agitation or psychosis [51]. A later Phase 2 study in 28 patients with PSP showed no difference in disease progression, with possible worsening on measures of gait, suggesting valproate was poorly tolerated and inefficacious in this population [52]. Due to these negative results, valproate is no longer in clinical development for treatment of

tauopathies, and available evidence recommends against its use. It should be noted that both lithium and valproate are non-specific for GSK3β, and thus observed toxicity may be due to off-target effects, and it is also possible that GSK3β was not inhibited to the extent that would be predicted to have a significant effect on tau phosphorylation and therefore a clinically meaningful effect.

Tideglusib (NP031112, Nypta, Zentylor, NP12) was a novel small molecule specifically designed as a GSK3β inhibitor, [53] and in a double transgenic mouse model overexpressing human amyloid and tau proteins ($APP^{swe}$-$tau^{vlw}$), tideglusib reduced tau hyperphosphorylation and aggregation, protected against neuronal loss, and prevented memory deficits. [54] Tideglusib was well-tolerated in an early trial in 30 patients with mild to moderate AD [55], but in ARGO, a larger Phase 2 trial enrolling 306 CE patients, treatment with tideglusib for 26 weeks did not show clinical efficacy despite apparent pharmacodynamic effect as measured by changes in BACE1 levels in the CSF [56]. Similar results were seen in TAUROS, a Phase 2 trial in 146 patients with progressive supranuclear palsy, where 52 weeks of treatment with tideglusib was well-tolerated but lacked efficacy in the primary outcome of disease progression (PSP Rating Scale) [57,58]. Due to the results of the ARGO and TAUROS trials, tideglusib is no longer in development for neurodegenerative disease, though ongoing trials are evaluating efficacy in myotonic dystrophy (NCT02858908) and autism spectrum disorder (NCT02586935).

Fyn, another kinase implicated in post-translational modification of tau, belongs to the Src family of tyrosine kinases, and in AD overactivation of Fyn has been hypothesized to cause pathologic tau phosphorylation (Tyr18) and synaptic loss via a mechanism dependent on oligomeric Aβ (oAβ) and cellular prion protein ($PrP^{C}$). [59] A small molecule Fyn inhibitor called saracatinib (AZD0530) was initially developed by AstraZeneca for treatment of various cancers [60]. In transgenic mouse models overexpressing amyloid ($APP^{swe}/PS1^{\Delta E9}$), saracatinib also prevented synaptic loss and rescued memory deficits, and, in the 3xTg triple transgenic mouse, it reduced tau aggregation. [61] A Phase 1 trial in 24 patients with AD showed saracatinib was well-tolerated and showed CNS penetration via oral dosing [62], and these findings led to CONNECT (NCT02167256), a 12-month Phase 2 trial in 159 patients with mild AD, with a primary outcome of $^{18}$F-FDGPET. No effect was seen on primary or secondary outcomes, and GI side effects led to discontinuation in a quart of particpants [63].

The most recent kinase being tested in clinical trials is Nilotinib (Tysigna, AMN107), a small molecule Abl inhibitor that is FDA-approved for chronic myeloid leukemia. Abl is a tyrosine kinase that phosphorylates tau on an alternative pathologic site, Tyr394, leading to increased tau aggregation into paired helical fragments. [64] In a small Phase 1/2 trial in patients with Parkinson's disease dementia (PDD) and dementia with lewy bodies (DLB), nilotinib reduced CSF levels of tau and amyloid in exploratory studies [65]. Based on these results, a Phase 2 trial in 42 patients with mild to moderate AD is underway, with a primary outcome of safety and tolerability (NCT02947893).

**3.2.2. O-GlcNAcase inhibitors—**Supporting the hypothesis that targeting O-GlcNAcylation can decrease tau hyperphosphorylation, an OGA inhibitor (Thiamet-G) was found to reduce the levels of pathologic tau aggregates in P301 L transgenic mice.

[66] Subsequently, the small molecule OGA inhibitor MK-8719 was developed by Alectos Therapeutics in collaboration with Merck, which showed similar effects in transgenic mouse models, and, in a follow-up Phase 1 trial in 16 healthy controls, MK-8719 was found to be well-tolerated and engaged the target, as demonstrated by use of a novel radiotracer [$^{18}$F]MK-8553 [67]. In 2016, Alectos announced they would be moving MK-8719 into clinical trials for patients with progressive supranuclear palsy [68], however the trial was never initiated and Merck has since discontinued development.

Another OGA inhibitor, ASN120290 (ASN-561), has been developed by Asceneuron, with preclinical data in P301S transgenic mice showing a more than two-fold increase in O-GlcNAcylated tau and a decrease in phosphorylated tau. [69] Results from a subsequent Phase 1 trial in 61 healthy controls was announced in 2018, demonstrating safety and tolerability [70]. ASN120290 has since been awarded orphan drug status, and Asceneuron announced in July 2018 that it will enter into Phase 2 clinical trials for the treatment of PSP, though this trial has not yet been initiated.

**3.2.3. Acetylation inhibitors—**As described above, abnormal acetylation at lysine residues can prevent physiologic clearance of tau, and K174 was identified as an important acetylation site critical for tau homeostasis. In PS19 transgenic mice that express human tau gene with the P301S mutation, treatment with salsalate, a small molecule anti-inflammatory agent that precedes the FDA approval process, was found to reduce tau acetylation at K174, decrease tau aggregations, and rescue memory deficits. [71] These preclinical data led to two Phase 1/2 trials for salsalate, and the first trial (SAL-AD) will look at safety and pharmacokinetics after 12 months of treatment in 40 mild to moderate AD patients (NCT03277573). The second trial screened for treatment effect in 10 patients with PSP, but no evidence of efficacy was found after treatment for 6 months [72].

### 3.3. Approach 3: disrupt tau aggregation

While natively unfolded, the MTBR tandem repeat region (3R/4R) can undergo tau-tau binding resulting in the paired helical filaments seen in NFTs, forming a cross-β structure similar to that seen in amyloid plaques. [73] Methylene blue (MB) is a small molecule phenothiazine initially developed in the late 1800s for treatment of malaria and still used in modern medicine. In 1996, MB was found to disrupt these high affinity tau-tau bonds, preventing aggregation. [74] MB was then tested in P301S and Tau$^{\Delta K}$ transgenic mice, where it was found to decrease phosphorylated tau aggregates and rescue memory deficits, though only when given prior to symptom onset. [75,76] Later studies posited an increase in clearance via upregulation of autophagy as a potential mechanism for the benefits seen in mouse models [77].

**3.3.1. Tau aggregation inhibitors—**Based on the preclinical data, methylene blue was rebranded as Rember by TauRx Therapeutics, and moved into a Phase 2 clinical trial involving 321 mild to moderate Alzheimer's patients, where positive results were seen on a measure of cognition (ADAS-Cog) after 24 weeks on the middle dose (138 mg/day), but no clinical effect was seen at the highest dose, halting further clinical development. [78] A reduced formulation of MB called LMTM (LMT-X, TRx0237) was developed, which

showed different pharmacokinetics in animal models and limited human studies involving healthy controls [79].

Unfortunately, in two companion Phase 3 trials involving nearly 1700 patients with mild Alzheimer's and a separate Phase 3 trial in 220 patients with behavioral variant frontotemporal dementia (the largest trial ever in this cohort), treatment with 200 mg LMTM did not have any effect on pre-specified primary outcome measures compared to placebo controls. [80-82] However, methylene blue and related compounds are colorants that turn urine and feces blue, and all previous studies had included a low dose of active compound (8 mg daily) in placebo groups to improve blinding. Due to the possibility that this low dose may itself be effective, which would be a confound in previous analyses, an alternative active placebo was developed and a Phase 3 trial (LUCIDITY) is ongoing to test the low dose of LMTM in 450 patients with early AD (NCT03446001).

### 3.4. Approaches 4 and 5: blocking cell-to-Cell tau transmission

Tau is mainly an intracellular protein, however in recent years there is growing evidence that tau is found in the extracellular space under physiological conditions. [83,84] It has been proposed that tau is regulated by neuronal activity and that extracellular tau may play a role in regulating synaptic function and excitability. Studies from animal and cellular models suggest that pathogenic tau can propagate between neighboring brain cells or synaptically connected neurons following a prion-like spreading mechanism [85-87]. It is hypothesized that tau species with seeding capability can be transmitted from cell-to-cell and recruit soluble tau into growing aggregates, and that this process may play a critical role in the pathogenesis of tau and the neurodegenerative process.

The concept of tau spreading created an opportunity for novel therapeutic strategies targeting extracellular tau. The underlying mechanisms for tau transmission and how much this process contributes to the progression of tauopathies in humans is still an open question in the field. The nature of interstitial tau and processes taking place within the brain parenchyma are extremely challenging to study. However, even without answers to the basic biological questions around tau propagation, several companies have developed therapeutic approaches focusing on preventing the cellular release, uptake, clearance or neutralization of extracellular tau. Immunotherapy is the primary approach used in the clinic to target extracellular to clear it or neutralize it in order to prevent propagation.

### 3.5. Approach 4: active immune clearance of tau

Harnessing the immune system to clear protein aggregates was one of the earliest and most exciting therapeutic targets for Alzheimer's disease, and numerous immunotherapy approaches targeting both amyloid and tau have since been developed. [88] However, while immunological interventions targeting amyloid have been in trials since 2000, treatments specifically targeting tau have only begun to be tested in humans in the last five years. Active immunization provides an attractive therapeutic approach as it potentially would require fewer administrations by inducing a sustained autologous antibody response, and if effective it could potentially be used as a preventative agent in a manner similar to vaccines currently available for a host of infectious diseases. Additionally, unlike

passive immunization, treatment effect would not be limited by the generation of anti-drug antibodies [89].

However, one past trial targeting amyloid with active immunotherapy (AN1792), caused a life-threatening T-cell mediated meningoencephalitis in 6% of patients, leading to trial termination and subsequent caution regarding this approach. [90] Early studies using full-length human tau inoculation in mouse models also provoked inflammation and further tau aggregation, further limiting initial enthusiasm for active immunization [91]. Subsequent vaccination strategies have avoided full-length tau, employing tau fragments, which have not demonstrated off-target immune response, though efficacy has yet to be evaluated.

**3.5.1. Vaccinations—**The first tau-directed vaccine tested in clinical trials was AADvac1, developed by Axon Neuroscience SE. The vaccine development approach used a truncated tau protein (151–391/4R) hypothesized to be the pathologic fragment triggering misfolding and aggregation. [92] A novel monoclonal antibody (DC8E8) was raised against this fragment and found to disrupt the tau-tau interactions that lead to pathologic tau agreggation [93]. The specific epitope for DC8E8 was found to be in the MTBR repeat region, and AADvac1 was developed by attaching a peptide fragment recapitulating the structural epitope to a carrier protein that drives a B-cell mediated immune response. In transgenic rat models expressing truncated tau protein, AADvac1 reduced tau aggregation and improved sensorimotor function [94].

A Phase 1 first-in-human trial of AADvac1 in 30 patients with mild to moderate AD showed excellent immunogenicity after 6 doses given over 24 weeks, with 29 of 30 patients demonstrating a robust IgG antibody response, with adverse effects including one seizure and one patient with existing microhemorrhages showing new microhemorrhages. [95] A subsequent 72 week follow-up trial (FUNDAMANT) showed sustained immune response after augmentation with 48- and 72-week boosters, and high antibody titers were associated with a decrease in hippocampal atrophy [96]. A larger Phase 2 trial enrolled 208 mild AD patients for 24 months of treatment (ADAMANT, NCT02579252), and a press release in September 2019 announced successful immunization without adverse events and a trend towards efficacy on functional outcomes, but results have not been published. A similar Phase 1 trial in 30 patients with non-fluent variant of primary progressive aphasia will assess safety and immunogenicity in this population (AIDA, NCT03174886), with results expected in late 2020.

ACI-35, an alternative vaccination agent, was initially developed by AC Immune and later licensed by Janssen. ACI-35 employs a liposomebased delivery strategy to anchor a tau fragment (393–408) with several phosphorylated serine residues (S396/S404) known to be pathologically phosphorylated by GSK3 kinases. [97] In P301 L mice, treatment with ACI-35 showed robust immunogenicity, with a reduction in phosphorylated forms of tau, and improvement in motor deficits [97]. ACI-35 started an international Phase 1 clinical trial in patients with mild to moderate AD (ISRCTN13033912), which concluded in June 2017, but results have not been announced.

### 3.6. Approach 5: passive immune clearance of tau

Passive immune clearance is the largest area of active intervention and excitement in the field, with eight novel monoclonal antibodies targeting tau undergoing testing in clinical trials and many more in preclinical development. However, the appropriate tau epitope to target for clearance remains controversial. As mentioned previously, in addition to the classic intraneuronal hyperphosphorylated NFT aggregates, tau is also secreted extracellularly, often in truncated form (eTau), and studies on cerebrospinal fluid from AD patients have found N-terminal fragments and mid-domain regions, without appreciable full length tau or C-terminal fragments. [98] Recent studies have suggested that eTau may induce neuronal hyperexcitability and mediate the transcellular spreading of tau pathology, supporting its role as the pathologic species [99]. This prion-like initial “seeding” of misfolded eTau followed by cell-to-cell propagation along neuronal networks has significant support [85,100], and eTau presents an attractive target for antibody infusion precisely because it is an extracellular process.

Current tau monoclonal antibody targets include N-terminal, mid-domain regions, and specific phosphorylated epitopes in NFTs. However, the only currently published clinical trial results for a monoclonal antibody targeting tau come from antibodies against the N-terminal region, and no long-term data on efficacy have yet been published. Many tau epitope targets remain unexplored.

**3.6.1. Monoclonal antibodies—**One of the first completed trials using a passive antibody approach for tau clearance was a Phase 1 study involving RG7345 (RO 6,926,496), which targeted a phosphorylated epitope at serine 422 (pS422) near the C-terminal end of tau. The rationale for the development of this epitope target was that pS422 was thought to undergo phosphorylation only in pathologic tau aggregates, e.g. NFTs. [101] This hypothesis was supported by preclinical work targeting passive immunization with a monoclonal antibody against pS422 that resulted in selective clearance of pS422 in triple transgenic mouse models (TauPS1APP) [102]. Unfortunately, despite trial completion in October 2015, results from the Phase 1 study were not released, but Hoffman La-Roche discontinued development.

BIIB092 (BMS-986168, IPN007; Gosuranemab) is a monoclonal IgG4 antibody against the N-terminal region initially developed from IPN002, a mouse antibody with a specific epitope spanning N-terminal amino acids 15–24, which has been found to reduce levels of both full length tau and secreted eTau in cell culture and transgenic animal models. [99] Phase 1 studies in 65 health controls demonstrated safety and tolerability, with dose-related reductions in N-terminal fragments, though four patients developed anti-drug antibodies (ADA) [103]. A subsequent Phase 1 study in 48 PSP patients was announced to be well-tolerated at a dose of 2100 mg infused monthly for three doses (NCT02460094). Importantly, this study demonstrated target engagement of N-terminal tau fragments by BIIB092 [104].

Three follow-up efficacy trials for BIIB092 have been initiated based on these data. Two studies were in patients with 4R-tauopathy, including PASSPORT (NCT03068468), which enrolled 490 PSP patients, and the TauBasket study (NCT03658135), which enrolled 22

patients with diverse clinical syndromes including CBS, nfvPPA, MAPT, and TES. In December 2019, Biogen announced that PASSPORT would be stopped after an interim futility analysis showed no efficacy on primary or secondary endpoints, and the TauBasket study was terminated at the same time. A parallel trial in AD-related tauopathy, TANGO (NCT03352557) remains open, with a goal to enroll 654 patients for 76 weeks of treatment, with safety as a primary endpoint and CDR as a secondary endpoint, and this study is expected to run through 2024.

C2N 8E12 (ABBV-8E12) is a monoclonal IgG4 antibody derived from a mouse antibody (HJ8.5), that blocked tau propagation *in vitro*, with an epitope mapped to N-terminal amino acids 25-30. It was developed by C2N Diagnostics and AbbVie and moved into clinical trials based on preclinical data in P301S transgenic mouse models showing reduction in tau aggregation and rescue of cognitive deficits. [105-107] A Phase 1 study in 32 PSP patients showed C2N 8E12 was well-tolerated without development of ADA [108], prompting a follow-up Phase 2 efficacy study (NCT02985879) treating 378 PSP patients for 12 months, but in July 2019, AbbVie terminated the trial after it tailed an interim futility analysis. In a separate trial, 453 early AD patients are being treated for 96 weeks with safety and CDR as primary endpoints, and several clinical biomarkers as secondary endpoints, was planned to end summer 2021.

Unlike amyloid, tau does not associate with blood vessels, and the neuroinflammation leading to the amyloid related imaging abnormalities (ARIA) seen with some monoclonal amyloid antibodies has not been seen with tau antibodies. However, overactivation of the immune system remains a theoretical concern, and RO 7,105,705 (RG 6100) is a monoclonal IgG4 antibody against the N-terminal that was developed with reduced effector function to limit microglia activation, under the rationale that sequestration of eTau may be sufficient to prevent further seeding. [109] Reportedly, high doses were tolerated in the Phase 1 study on 74 healthy controls and patients with mild AD (NCT02820896), and a follow-up study Phase 2 study TAURIEL (NCT03289143) has been started in 360 patients with prodromal or mild AD, with results expected in September 2022.

The most recent monoclonal antibody against the N-terminal region to enter clinical trials is LY3303560, but the specific epitope has not been released. In the only publicly available data, LY3303560 was shown to preferentially bind tau aggregates over monomers and had acceptable pharmacokinetic properties in preclinical animal models. [110] A Phase 1/2 trial in 110 healthy controls and patients with mild AD concluded in July 2018, but results have not yet been reported (NCT02754830). A second early Phase 1 study started in January 2017, and enrolled 24 patients with MCI for six months of treatment, with concurrent administration of treatment plus amyloid and tau PET tracers (NCT03019536). Lilly's Phase 2 trial in 285 early AD patients will treat for 80 weeks with a primary clinical endpoint, but tau PET has been included as a secondary endpoint, marking the first use of this imaging biomarker for a tau therapeutic (NCT03518073). The trial is expected to conclude in late 2021.

Biogen has a second monoclonal antibody targeting tau, BIIB076, but the epitope has not been reported. Limited preclinical pharmacokinetic data describes BIIB076 as a "pan-tau"

antibody targeting monomers and fibrils. [111] Biogen is currently running a Phase 1 trial in 56 healthy controls and mild AD patients, with a primary outcome of safety and tolerability, which is expected to conclude in early 2020 (NCT03056729).

The mid-region of tau, closer to the MTBR, is an alternative target to N-terminal regions. In April 2018, researchers from UCB Biopharma described results from a seeding model in which PHFs were injected into transgenic mouse models, and antibodies that targeted the mid-domain were able to suppress aggregation, while N-terminal antibodies were not. [112] Following from these data, UCB is further developing UCB0107, a monoclonal antibody to the tau mid-domain (amino acids 235–246), which completed Phase 1 studies in December 2018 (NCT03464227). Janssen also has a mid-region antibody (JNJ-63733657) in a Phase 1 clinical trial (NCT03375697). Preclinical data showed that a UCB anti-tau antibody that recognize a mid-domain region epitope on tau, is more efficacious at blocking pathology induced by Alzheimer's disease brain-derived material in vivo than a tau antibody which recognizes an N-terminal epitope [113].

## 4. Therapeutic approaches for tau loss of function

### 4.1. Approach 6: replace tau physiologic function

Following the hypothesis that tau dysfunction in tauopathies results from a loss of normal tau function, an agent that stabilizes microtubules and prevents axonal/dendritic degeneration may restore function and ameliorate symptoms. Three agents have been developed following this hypothesis, but only one remains in active development.

**4.1.1. Microtubule stabilizers—**Davunetide (NAP, AL-108) is an eight amino acid peptide derived from the activity-dependent neurotrophic protein (ADNP), a growth factor with diverse neuroprotective activity. [114] In several transgenic mouse models, administration of davunetide increased the amount of microtubule-associated tau and reversed cognitive deficits [115,116]. In a Phase 2 trial in 144 MCI patients, treatment with davunetide for 12 weeks was safe and well-tolerated, but no improvement was seen in pre-specified composite batteries of cognition [117]. However, improvements were seen on individual tests of working memory, tasks known to be profoundly impacted in patients with PSP [118]. These data supported further development in this population, and davunetide entered the first Phase 2/3 trial for PSP, but in 360 patients treated for 52 weeks, no differences were found in primary or secondary outcomes, and development of davunetide was discontined [119].

Epothilone D (BMS-241027) is a macrolide compounds isolated from myxobacterium *Sorangium cellulosum* that acts through microtubule stabilization. Epothilones have strong antitumor activity against several human cancer cells. Although the epothilones share some similarities with the taxanes, the epothilones have significant antitumor activity against taxane-resistant human cancer cells. Taxanes have poor blood-brain barrier (BBB) permeability, while Epothilone D crosses the BBB, and in PS19 tau transgenic mice, it increased microtubule density and reduced cognitive deficits. [120] In a Phase 1 study with healthy females, Epothilone D, which had been known to produce adverse effects at higher dose in vandevoncologic trials, only produced a single Grade 3 hypersensitivity reaction

[121]. A follow-up Phase 1/2 study in 40 mild AD patients given Epithilone D or placebo for 10 weeks concluded in October 2013 (NCT01492374), but results were never published and development was subsequent discontinued.

A taxane derivative, TPI 287 (abeotaxane), was developed with excellent BBB penetrance, and underwent testing in oncologic trials for brain metastases. [122] TP 287 has also been proposed as a microtubule stabilizer that may have efficacy in tauopathies, and this hypothesis has led to two Phase 1 studies looking at safety and tolerability in 44 CBS or PSP patients (NCT02133846) and 33 mild to mod AD patients (NCT01966666). Both trials ended in 2017, and immune hypersensitivity reactions limited dosing in the AD arm, and a dose-related worsening of falls and cognitive outcomes was found in the 4R-tauopathy cohort, and this agent is no longer in clinical development [123].

## 5. Conclusion

A total of 60 clinical trials have been conducted on 24 tau-directed therapeutics, and 13 trials are ongoing at the time of publication, with more likely to follow (Table 3), incorporating diverse mechanisms (Fig. 1). Tau represents an important target in the treatment of neurodegenerative disease, and the ultimate goal is to find a treatment that prevents the relentless progression of cognitive and motor symptoms. To this end, numerous hypotheses regarding tau biology are being tested in clinical trials for the first time, representing the dawn of a new age of drug development for tau, though numerous barriers remain to seeing a tau therapeutic in the clinic.

The first hurtle for a tau therapeutic in clinical trials is pharmacokinetics. For neurodegenerative diseases, the blood brain barrier (BBB) presents a formidable obstacle to ensuring adequate drug reaches its intended target in the CNS, and while intrathecal approaches such as ASOs circumvent the BBB, the cost of administration is a necessary consideration given the prevalence of neurodegeneration. However, the BBB provides a major limitation to antibody therapies as only very low levels, approximately 0.1-0.2%, distribute to the brain from the systemic circulation after passive immunization. [104] Thus, in order to achieve efficacy, antibodies need to have extremely high affinity to tau. Very high doses need to be used to achieve proper target coverage and antibody production becomes exceptionally expensive.

In order to circumvent these challenges, companies are using gene therapy approaches by vectorizing antibodies to directly express them in the brain. Companies are developing novel AAV capsids that cross the blood-brain barrier after systemic administration, and engineering the viruses to improve transduction of cells in the CNS for enhanced cellular specificity. Preclinical studies will need to address the feasibility of this approach. These antibodies could possibly be actively transported out of the brain even if they are locally produced. Moreover, potential deleterious effects of expressing antibodies in cells that do not typically have this function will need to be addressed before being tested in the clinic.

Using small molecules that cross the blood brain barrier is an attractive approach. Thus far the compounds tested have clear limitations include off-target effects specially for

kinase inhibitors. Examples include studies on lithium and valproate, which have action on kinases in the CNS but also involve other diverse mechanisms, which led to side effects such as the toxicity seen in the valproate trials. Even approaches where the mechanism is limited to a single kinase will likely lead to a pleotropic effect given the complexity of cell signaling, though the sum total of this effect may be beneficial. Recently published studies revealing the Cryo-EM structure of tau aggregates provide valuable knowledge of the atomic coordinates of tau filaments. [24] The structural information of tau aggregates could be helpful in rational design of specific tau aggregation inhibitors. These structures are also useful for the design of tau binders that can be used as part of the PROteolysis TArgeting Chimeras (PROTACs) approach. PROTACs is a strategy to degrade proteins by hijacking the ubiquitin-proteasome system (UPS). PROTAC is a bifunctional-hybrid molecule that on one side binds to E3 ubiquitin ligase and on the other side to a target protein. This bifunctional binder allows exposed lysine on the target protein to be ubiquitinated by the E3 ubiquitin ligase complex, followed by UPS-mediated protein degradation of aberrant tau in frontotemporal dementia patient-derived neuronal cell models [124,125].

Generally, positive preclinical pharmacokinetic data supports further development, but showing a pharmacodynamic effect in the preclinical stage in neurodegenerative tauopathies has been difficult to translate in the clinical setting. One root of the problem is the poor translatability of animal models to the human condition. These models often focus on overexpression of a single mutant tau isoform and would only recapitulate one particular tertiary and quaternary filament structure which are not relevant to all tauopathies. It is postulated that tau filaments present distinct ultrastructural polymorphs in different tauopathies. [23,24] Therefore, therapeutic agents optimized against a particular conformation may not be generalizable to all tauopathies broadly, posing a significant limitation for aggregation inhibitors and neutralizing antibodies which target a particular aggregation domain or epitope. Broad application and cross-purposing of therapeutics may prove problematic, and perhaps specialized therapeutics need to be developed for 3R- and 4R-tauopathies.

A significant challenge is demonstrating target engagement and selecting an appropriate dose. Even when a potential drug has a known mechanism, demonstrating target engagement to evaluate efficacy remains challenging, and a critical gap in tau drug development as a whole is the lack of appropriate biomarkers for target engagement and pharmacodynamics. Despite the term “tau” often used interchangeably, many populations of tau species exist in dynamic equilibrium. Few human biomarkers are available to distinguish between the transcriptional splice variants (3R/4R); how tau has been post-translationally modified (phosphorylated, O-GlyNAcylated, acetylated, ubiquitinated, truncated); whether it is exists as a soluble protein, an oligomer, or has been deposited as part of an insoluble aggregate; and where the particular tau species is localized (intracellular compartments, extracellular space, circulating in the CSF, released into the blood). Each of these tau populations is distinct though related, and the exact pathologic species is a matter of intense debate and are very likely different in the diverse tauopathies. [126]

This distinction is even more important when developing immunotherapeutic approaches to tau, specifically when determining the appropriate tau epitope to target for clearance.

Although robust assays that can measure some forms of tau found in CSF and blood, these tau species do not necessarily represent the relevant pathological tau found in the brain parenchyma. Therefore, antibodies could target the correct disease relevant tau epitope in the brain but if the epitope is absent from CSF and blood, it is impossible to measure target engagement, making the clinical development of such antibodies extremely difficult. Several PET ligands are being tested, but not without challenges. Longitudinal tau tracer studies will further inform on the kinetics of tau aggregation, but current results from these studies and evidence from post-mortem Braak staging indicate that the rate of aggregation is likely slow and may be challenging to use as a proximal pharmacodynamic biomarker.

After the pre-clinical development stage, without appropriate measures of target engagement, determining the effect of the current monoclonal antibodies cannot be assessed in the absence of a robust clinically meaningful effect over a short period of time, a thus far elusive goal in neurodegenerative diseases. If target engagement and clear effects on diverse tau populations can be demonstrated, clinical trials will be informative whether or not they produce positive results, because they will provide important insights to human tau pathophysiology that can guide future work.

The development of new biomarkers to supplement our current clinical measures of function will therefore be critical to enable measurement of target engagement, help evaluate other pharmacodynamic effects, and measure disease progression. For amyloid-targeted AD therapies, pharmacodynamic biomarkers such as amyloid PET imaging have helped identify whether therapies that engage the target have clear pharmacodynamic effects that correlate with clinical status. [127] Improved tau biomarkers would allow smaller, shorter trials, and basket designs, such as in the TauBasket and TPI 257 trial which allowed unbiased evaluation in diverse tauopathies. Much of the focus is appropriately on Alzheimer’s disease as the most prevalent tauopathy, but observing drug effect in other tauopathies, especially where tau is the sole neuropathologic etiology, may be more informative regarding tau’s role in these disparate diseases.

Rigorous clinical trial design is especially important as tau trials move out of early clinical stages and are being investigated for signs of efficacy. Though we may be years from an effective tau-directed therapeutic, once an effective treatment is found, additional trials will need to be done to determine which populations will benefit, and perhaps whether combination therapies with multiple tau therapeutics or other non-tau therapeutics may be necessary. In addition to the ongoing clinical trials for current therapeutic approaches, there are several new strategies in the pre-clinical stage trying to tackle the challenges of treating tauopathies, but these efforts are at an early stage, and it may be some time before they are tested in the clinic. However, the rapid pace of development of novel tau directed therapies over the past five years is encouraging and suggests that we will eventually see a tau therapeutic in clinical use.

## Acknowledgements

This work was funded by the National Institute on Aging (NIA) through 5T32AG023481 (L.V.), 5R01AG038791-09, and 1U19AG063911-01 (A.L.B.), and the Tau Consortium (A.L.B.)

## References


[1]. Erkkinen MG, Kim MO, Geschwind MD, Clinical neurology and epidemiology of the major neurodegenerative diseases, Cold Spring Harb. Perspect. Biol 10 (4) (2018).

[2]. Gooch CL, Pracht E, Borenstein AR, The burden of neurological disease in the United States: a summary report and call to action, Ann. Neurol 81 (4) (2017) 479–484. [PubMed: 28198092]

[3]. Lee VM, Goedert M, Trojanowski JQ, Neurodegenerative tauopathies, Annu. Rev. Neurosci 24 (2001) 1121–1159. [PubMed: 11520930]

[4]. Wood JG, Mirra SS, Pollock NJ, Binder LI, Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau), Proc. Natl. Acad. Sci. U. S. A 83 (11) (1986) 4040–4043. [PubMed: 2424015]

[5]. Braak H, Braak E, Frequency of stages of Alzheimer-related lesions in different age categories, Neurobiol. Aging 18 (4) (1997) 351–357. [PubMed: 9330961]

[6]. Braak H, Thal DR, Ghebremedhin E, Del Tredici K, Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years, J. Neuropathol. Exp. Neurol 70 (11) (2011) 960–969. [PubMed: 22002422]

[7]. Grinberg LT, Rub U, Ferretti RE, et al. , The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset? Neuropathol. Appl. Neurobiol 35 (4) (2009) 406–416. [PubMed: 19508444]

[8]. Ossenkoppele R, Schonhaut DR, Scholl M, et al. , Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease, Brain 139 (Pt 5) (2016) 1551–1567. [PubMed: 26962052]

[9]. Giannakopoulos P, Herrmann FR, Bussiere T, et al. , Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease, Neurology 60 (9) (2003) 1495–1500. [PubMed: 12743238]

[10]. Nelson PT, Alafuzoff I, Bigio EH, et al. , Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature, J. Neuropathol. Exp. Neurol 71 (5) (2012) 362–381. [PubMed: 22487856]

[11]. Goedert M, Spillantini MG, Jakes R, Rutherford D, Crowther RA, Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease, Neuron 3 (4) (1989) 519–526. [PubMed: 2484340]

[12]. Roberson ED, Scearce-Levie K, Palop JJ, et al. , Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model, Science 316 (5825) (2007) 750–754. [PubMed: 17478722]

[13]. Gheyara AL, Ponnusamy R, Djukic B, et al. , Tau reduction prevents disease in a mouse model of Dravet syndrome, Ann. Neurol 76 (3) (2014) 443–456. [PubMed: 25042160]

[14]. Goedert M, Jakes R, Expression of separate isoforms of human tau protein: correlation with the tau pattern in brain and effects on tubulin polymerization, EMBO J. 9 (13) (1990) 4225–4230. [PubMed: 2124967]

[15]. Hutton M, Lendon CL, Rizzu P, et al. , Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17, Nature 393 (6686) (1998) 702–705. [PubMed: 9641683]

[16]. Poorkaj P, Bird TD, Wijsman E, et al. , Tau is a candidate gene for chromosome 17 frontotemporal dementia, Ann. Neurol 43 (6) (1998) 815–825. [PubMed: 9629852]

[17]. Spillantini MG, Bird TD, Ghetti B, Frontotemporal dementia and Parkinsonism linked to chromosome 17: a new group of tauopathies, Brain Pathol. 8 (2) (1998) 387–402. [PubMed: 9546295]

[18]. Flament S, Delacourte A, Verny M, Hauw JJ, Javoy-Agid F, Abnormal Tau proteins in progressive supranuclear palsy. Similarities and differences with the neurofibrillary degeneration of the Alzheimer type, Acta Neuropathol. 81 (6) (1991) 591–596. [PubMed: 1831952]

[19]. Ksiezak-Reding H, Morgan K, Mattiace LA, et al. , Ultrastructure and biochemical composition of paired helical filaments in corticobasal degeneration, Am. J. Pathol 145 (6) (1994) 1496–1508. [PubMed: 7992852]

[20]. Tolnay M, Sergeant N, Ghestem A, et al. , Argyrophilic grain disease and Alzheimer's disease are distinguished by their different distribution of tau protein isoforms, Acta Neuropathol. 104 (4) (2002) 425–434. [PubMed: 12200631]

[21]. Delacourte A, Robitaille Y, Sergeant N, et al. , Specific pathological Tau protein variants characterize Pick's disease, J. Neuropathol. Exp. Neurol 55 (2) (1996) 159–168. [PubMed: 8786374]

[22]. Arendt T, Stieler JT, Holzer M, Tau and tauopathies, Brain Res. Bull 126 (Pt 3) (2016) 238–292. [PubMed: 27615390]

[23]. Arakhamia T, Lee CE, Carlomagno Y, et al. , Posttranslational modifications mediate the structural diversity of tauopathy strains, Cell 180 (4) (2020) p. 633–644 e12. [PubMed: 32032505]

[24]. Fitzpatrick AWP, Falcon B, He S, et al. , Cryo-EM structures of tau filaments from Alzheimer's disease, Nature 547 (7662) (2017) 185–190. [PubMed: 28678775]

[25]. Gong CX, Liu F, Grundke-Iqbal I, Iqbal K, Post-translational modifications of tau protein in Alzheimer's disease, J. Neural Transm. Vienna (Vienna) 112 (6) (2005) 813–838.

[26]. Wang Y, Mandelkow E, Tau in physiology and pathology, Nat. Rev. Neurosci 17 (1) (2016) 5–21. [PubMed: 26631930]

[27]. Kopke E, Tung YC, Shaikh S, Alonso AC, Iqbal K, Grundke-Iqbal I, Microtubule-associated protein tau. Abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease, J. Biol. Chem 268 (32) (1993) 24374–24384. [PubMed: 8226987]

[28]. Min SW, Cho SH, Zhou Y, et al. , Acetylation of tau inhibits its degradation and contributes to tauopathy, Neuron 67 (6) (2010) 953–966. [PubMed: 20869593]

[29]. Cohen TJ, Guo JL, Hurtado DE, et al. , The acetylation of tau inhibits its function and promotes pathological tau aggregation, Nat. Commun 2 (2011) 252. [PubMed: 21427723]

[30]. Khanna MR, Kovalevich J, Lee VM, Trojanowski JQ, Brunden KR, Therapeutic strategies for the treatment of tauopathies: hopes and challenges, Alzheimers Dement. 12 (10) (2016) 1051–1065. [PubMed: 27751442]

[31]. Finkel RS, Mercuri E, Darras BT, et al. , Nusinersen versus sham control in infantile-onset spinal muscular atrophy, N. Engl. J. Med 377 (18) (2017) 1723–1732. [PubMed: 29091570]

[32]. I. Ionis Pharmaceuticals, IONIS-HTT Rx (RG6042) Top-line Data Demonstrate Significant Reductions of Disease-Causing Mutant Huntingtin Protein in People With Huntington's Disease, (2018).

[33]. Lei P, Ayton S, Finkelstein DI, et al. , Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export, Nat. Med 18 (2) (2012) 291–295. [PubMed: 22286308]

[34]. Morris M, Hamto P, Adame A, Devidze N, Masliah E, Mucke L, Age-appropriate cognition and subtle dopamine-independent motor deficits in aged tau knockout mice, Neurobiol. Aging 34 (6) (2013) 1523–1529. [PubMed: 23332171]

[35]. Lei P, Ayton S, Moon S, et al. , Motor and cognitive deficits in aged tau knockout mice in two background strains, Mol. Neurodegener 9 (2014) 29. [PubMed: 25124182]

[36]. DeVos SL, Goncharoff DK, Chen G, et al. , Antisense reduction of tau in adult mice protects against seizures, J. Neurosci 33 (31) (2013) 12887–12897. [PubMed: 23904623]

[37]. DeVos SL, Miller RL, Schoch KM, et al. , Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy, Sci. Transl. Med 9 (374) (2017).

[38]. Schoch KM, DeVos SL, Miller RL, et al. , Increased 4R-Tau induces pathological changes in a human-tau mouse model, Neuron 90 (5) (2016) 941–947. [PubMed: 27210553]

[39]. Fischbeck KH, Wexler NS, Oligonucleotide treatment for huntington's disease, N. Engl. J. Med 380 (24) (2019) 2373–2374. [PubMed: 31059640]

[40]. Hanger DP, Anderton BH, Noble W, Tau phosphorylation: the therapeutic challenge for neurodegenerative disease, Trends Mol. Med 15 (3) (2009) 112–119. [PubMed: 19246243]

[41]. Dolan PJ, Johnson GV, The role of tau kinases in Alzheimer's disease, Curr. Opin. Drug Discov. Devel 13 (5) (2010) 595–603.

[42]. Liu F, Iqbal K, Grundke-Iqbal I, Hart GW, Gong CX, O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease, Proc. Natl. Acad. Sci. U. S. A 101 (29) (2004) 10804–10809. [PubMed: 15249677]

[43]. Liu F, Shi J, Tanimukai H, et al. , Reduced O-GlcNAcylation links lower brain glucose metabolism and tau pathology in Alzheimer's disease, Brain 132 (Pt 7) (2009) 1820–1832. [PubMed: 19451179]

[44]. Forde JE, Dale TC, Glycogen synthase kinase 3: a key regulator of cellular fate, Cell. Mol. Life Sci 64 (15) (2007) 1930–1944. [PubMed: 17530463]

[45]. Flaherty DB, Soria JP, Tomasiewicz HG, Wood JG, Phosphorylation of human tau protein by microtubule-associated kinases: GSK3beta and cdk5 are key participants, J. Neurosci. Res 62 (3) (2000) 463–472. [PubMed: 11054815]

[46]. Noble W, Planel E, Zehr C, et al. , Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo, Proc. Natl. Acad. Sci. U. S. A 102 (19) (2005) 6990–6995. [PubMed: 15867159]

[47]. Hampel H, Ewers M, Burger K, et al. , Lithium trial in Alzheimer's disease: a randomized, single-blind, placebo-controlled, multicenter 10-week study, J. Clin. Psychiatry 70 (6) (2009) 922–931. [PubMed: 19573486]

[48]. Chen G, Huang LD, Jiang YM, Manji HK, The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3, J. Neurochem 72 (3) (1999) 1327–1330. [PubMed: 10037507]

[49]. Qing H, He G, Ly PT, et al. , Valproic acid inhibits Abeta production, neuritic plaque formation, and behavioral deficits in Alzheimer's disease mouse models, J. Exp. Med 205 (12) (2008) 2781–2789. [PubMed: 18955571]

[50]. Fleisher AS, Truran D, Mai JT, et al. , Chronic divalproex sodium use and brain atrophy in Alzheimer disease, Neurology 77 (13) (2011) 1263–1271. [PubMed: 21917762]

[51]. Tariot PN, Schneider LS, Cummings J, et al. , Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease, Arch. Gen. Psychiatry 68 (8) (2011) 853–861. [PubMed: 21810649]

[52]. Leclair-Visonneau L, Rouaud T, Debilly B, et al. , Randomized placebo-controlled trial of sodium valproate in progressive supranuclear palsy, Clin. Neurol. Neurosurg 146 (2016) 35–39. [PubMed: 27136096]

[53]. Martinez A, Alonso M, Castro A, Perez C, Moreno FJ, First non-ATP competitive glycogen synthase kinase 3 beta (GSK-3beta) inhibitors: thiadiazolidinones (TDZD) as potential drugs for the treatment of Alzheimer's disease, J. Med. Chem 45 (6) (2002) 1292–1299. [PubMed: 11881998]

[54]. Sereno L, Coma M, Rodriguez M, et al. , A novel GSK-3beta inhibitor reduces Alzheimer's pathology and rescues neuronal loss in vivo, Neurobiol. Dis 35 (3) (2009) 359–367. [PubMed: 19523516]

[55]. del Ser T, Steinwachs KC, Gertz HJ, et al. , Treatment of Alzheimer's disease with the GSK-3 inhibitor tideglusib: a pilot study, J. Alzheimers Dis 33 (1) (2013) 205–215. [PubMed: 22936007]

[56]. Lovestone S, Boada M, Dubois B, et al. , A phase II trial of tideglusib in Alzheimer's disease, J. Alzheimers Dis 45 (1) (2015) 75–88. [PubMed: 25537011]

[57]. Tolosa E, Litvan I, Hoglinger GU, et al. , A phase 2 trial of the GSK-3 inhibitor tideglusib in progressive supranuclear palsy, Mov. Disord 29 (4) (2014) 470–478. [PubMed: 24532007]

[58]. Hoglinger GU, Huppertz HJ, Wagenpfeil S, et al. , Tideglusib reduces progression of brain atrophy in progressive supranuclear palsy in a randomized trial, Mov. Disord 29 (4) (2014) 479–487. [PubMed: 24488721]

[59]. Nygaard HB, van Dyck CH, Strittmatter SM, Fyn kinase inhibition as a novel therapy for Alzheimer's disease, Alzheimers Res. Ther 6 (1) (2014) 8. [PubMed: 24495408]

[60]. Hennequin LF, Allen J, Breed J, et al. , N-(5-chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5- (tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine, a novel, highly selective, orally available, dual-specific c-Src/Abl kinase inhibitor, J. Med. Chem 49 (22) (2006) 6465–6488. [PubMed: 17064066]

[61]. Kaufman AC, Salazar SV, Haas LT, et al. , Fyn inhibition rescues established memory and synapse loss in Alzheimer mice, Ann. Neurol 77 (6) (2015) 953–971. [PubMed: 25707991]

[62]. Nygaard HB, Wagner AF, Bowen GS, et al. , A phase Ib multiple ascending dose study of the safety, tolerability, and central nervous system availability of AZD0530 (saracatinib) in Alzheimer's disease, Alzheimers Res. Ther 7 (1) (2015) 35. [PubMed: 25874001]

[63]. van Dyck CH, Nygaard HB, Chen K, et al. , Effect of AZD0530 on cerebral metabolic decline in alzheimer disease: a randomized clinical trial, JAMA Neurol. (2019).

[64]. Derkinderen P, Scales TM, Hanger DP, et al. , Tyrosine 394 is phosphorylated in Alzheimer's paired helical filament tau and in fetal tau with c-Abl as the candidate tyrosine kinase, J. Neurosci 25 (28) (2005) 6584–6593. [PubMed: 16014719]

[65]. Pagan F, Hebron M, Valadez EH, et al. , Nilotinib effects in parkinson's disease and dementia with Lewy bodies, J. Parkinsons Dis 6 (3) (2016) 503–517. [PubMed: 27434297]

[66]. Yuzwa SA, Shan X, Macauley MS, et al. , Increasing O-GlcNAc slows neurodegeneration and stabilizes tau against aggregation, Nat. Chem. Biol 8 (4) (2012) 393–399. [PubMed: 22366723]

[67]. Smith SM, Struyk A, Jonathan D, et al. , Early clinical results and preclinical validation of the O-GlcNAcase (OGA) inhibitor MK-8719 as a novel therapeutic for the treatment of tauopathies, Alzheimer's and Dementia 12 (7) (2016) P261.

[68]. A. Therapeutics, Alectos Therapeutics Announces FDA Orphan Drug Designation for MK-8719: An Investigational Small-molecule OGA Inhibitor for Treatment of Progressive Supranuclear Palsy, (2016).

[69]. Permanne B, Quattropani A, Hantson J, et al. , Pharmacological intervention with the novel o-glcnacase inhibitor ASN-561 reduces pathological tau in transgenic mice, Alzheimer's and Dementia 11 (7) (2015) P227.

[70]. Ryan JM, Quattropani A, Abd-Elaziz K, et al. , Phase 1 study in healthy volunteers of the O-glcnacase inhibitor ASN120290 as a novel therapy for progressive supranuclear palsy and related tauopathies, Alzheimer's and Dementia 14 (7) (2018) P251.

[71]. Min SW, Chen X, Tracy TE, et al. , Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits, Nat. Med 21 (10) (2015) 1154–1162. [PubMed: 26390242]

[72]. VandeVrede LDM, Fields S, Frank M, Hare E, Heuer HW, Keith K, Koestler M, Ljubenkov PA, McDermott D, Ohanesian N, Richards J, Rojas JC, Thijssen EH, Walsh C, Wang P, Wolf P, Quinn JF, Tsai R, Boxer AL, Open-label phase 1 futility studies of salsalate and young plasma in progressive supranuclear palsy, Mov. Disord. Clin. Pract (2020) (in press).

[73]. Berriman J, Serpell LC, Oberg KA, Fink AL, Goedert M, Crowther RA, Tau filaments from human brain and from in vitro assembly of recombinant protein show cross-beta structure, Proc. Natl. Acad. Sci. U. S. A 100 (15) (2003) 9034–9038. [PubMed: 12853572]

[74]. Wischik CM, Edwards PC, Lai RY, Roth M, Harrington CR, Selective inhibition of Alzheimer disease-like tau aggregation by phenothiazines, Proc. Natl. Acad. Sci. U. S. A 93 (20) (1996) 11213–11218. [PubMed: 8855335]

[75]. Hochgrafe K, Sydow A, Matenia D, et al. , Preventive methylene blue treatment preserves cognition in mice expressing full-length pro-aggregant human Tau, Acta Neuropathol. Commun 3 (2015) 25. [PubMed: 25958115]

[76]. Stack C, Jainuddin S, Elipenahli C, et al. , Methylene blue upregulates Nrf2/ARE genes and prevents tau-related neurotoxicity, Hum. Mol. Genet 23 (14) (2014) 3716–3732. [PubMed: 24556215]

[77]. Congdon EE, Wu JW, Myeku N, et al. , Methylthioninium chloride (methylene blue) induces autophagy and attenuates tauopathy in vitro and in vivo, Autophagy 8 (4) (2012) 609–622. [PubMed: 22361619]

[78]. Wischik CM, Harrington CR, Storey JM, Tau-aggregation inhibitor therapy for Alzheimer's disease, Biochem. Pharmacol 88 (4) (2014) 529–539. [PubMed: 24361915]

[79]. Baddeley TC, McCaffrey J, Storey JM, et al. , Complex disposition of methylthioninium redox forms determines efficacy in tau aggregation inhibitor therapy for Alzheimer's disease, J. Pharmacol. Exp. Ther 352 (1) (2015) 110–118. [PubMed: 25320049]

[80]. Gauthier S, Feldman HH, Schneider LS, et al. , Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial, Lancet 388 (10062) (2016) 2873–2884. [PubMed: 27863809]

[81]. Wilcock GK, Gauthier S, Frisoni GB, et al. , Potential of low dose leuco-methylthioninium bis(Hydromethanesulphonate) (LMTM) monotherapy for treatment of mild alzheimer's disease: cohort analysis as modified primary outcome in a phase III clinical trial, J. Alzheimers Dis 61 (1) (2018) 435–457. [PubMed: 29154277]

[82]. T. Pharmaceuticals, TRX-237 Phase 3 Clinical Trial Update, (2016).

[83]. Pooler AM, Phillips EC, Lau DH, Noble W, Hanger DP, Physiological release of endogenous tau is stimulated by neuronal activity, EMBO Rep. 14 (4) (2013) 389–394. [PubMed: 23412472]

[84]. Yamada K, Cirrito JR, Stewart FR, et al. , In vivo microdialysis reveals age-dependent decrease of brain interstitial fluid tau levels in P301S human tau transgenic mice, J. Neurosci 31 (37) (2011) 13110–13117. [PubMed: 21917794]

[85]. Clavaguera F, Bolmont T, Crowther RA, et al. , Transmission and spreading of tauopathy in transgenic mouse brain, Nat. Cell Biol 11 (7) (2009) 909–913. [PubMed: 19503072]

[86]. de Calignon A, Polydoro M, Suarez-Calvet M, et al. , Propagation of tau pathology in a model of early Alzheimer's disease, Neuron 73 (4) (2012) 685–697. [PubMed: 22365544]

[87]. Frost B, Jacks RL, Diamond MI, Propagation of tau misfolding from the outside to the inside of a cell, J. Biol. Chem 284 (19) (2009) 12845–12852. [PubMed: 19282288]

[88]. Gallardo G, Holtzman DM, Antibody therapeutics targeting abeta and tau, Cold Spring Harb. Perspect. Med 7 (10) (2017).

[89]. Pineda C, Castaneda Hernandez G, Jacobs IA, Alvarez DF, Carini C, Assessing the immunogenicity of biopharmaceuticals, BioDrugs 30 (3) (2016) 195–206. [PubMed: 27097915]

[90]. Gilman S, Koller M, Black RS, et al. , Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial, Neurology 64 (9) (2005) 1553–1562. [PubMed: 15883316]

[91]. Rosenmann H, Grigoriadis N, Karussis D, et al. , Tauopathy-like abnormalities and neurologic deficits in mice immunized with neuronal tau protein, Arch. Neurol 63 (10) (2006) 1459–1467. [PubMed: 17030663]

[92]. Paholikova K, Salingova B, Opattova A, et al. , N-terminal truncation of microtubule associated protein tau dysregulates its cellular localization, J. Alzheimers Dis 43 (3) (2015) 915–926. [PubMed: 25147106]

[93]. Kontsekova E, Zilka N, Kovacech B, Skrabana R, Novak M, Identification of structural determinants on tau protein essential for its pathological function: novel therapeutic target for tau immunotherapy in Alzheimer's disease, Alzheimers Res. Ther 6 (4) (2014) 45. [PubMed: 25478018]

[94]. Kontsekova E, Zilka N, Kovacech B, Novak P, Novak M, First-in-man tau vaccine targeting structural determinants essential for pathological tau-tau interaction reduces tau oligomerisation and neurofibrillary degeneration in an Alzheimer's disease model, Alzheimers Res. Ther 6 (4) (2014) 44. [PubMed: 25478017]

[95]. Novak P, Schmidt R, Kontsekova E, et al. , Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: a randomised, double-blind, placebo-controlled, phase 1 trial, Lancet Neurol. 16 (2) (2017) 123–134. [PubMed: 27955995]

[96]. Novak P, Schmidt R, Kontsekova E, et al. , FUNDAMANT: an interventional 72-week phase 1 follow-up study of AADvac1, an active immunotherapy against tau protein pathology in Alzheimer's disease, Alzheimers Res. Ther 10 (1) (2018) 108. [PubMed: 30355322]

[97]. Theunis C, Crespo-Biel N, Gafner V, et al. , Efficacy and safety of a liposomebased vaccine against protein Tau, assessed in tau.P301L mice that model tauopathy, PLoS One 8 (8) (2013) e72301. [PubMed: 23977276]

[98]. Meredith JE Jr, Sankaranarayanan S, Guss V, et al. , Characterization of novel CSF Tau and ptau biomarkers for Alzheimer's disease, PLoS One 8 (10) (2013) e76523. [PubMed: 24116116]

[99]. Bright J, Hussain S, Dang V, et al. , Human secreted tau increases amyloid-beta production, Neurobiol. Aging 36 (2) (2015) 693–709. [PubMed: 25442111]

[100]. Brettschneider J, Del Tredici K, Lee VM, Trojanowski JQ, Spreading of pathology in neurodegenerative diseases: a focus on human studies, Nat. Rev. Neurosci 16 (2) (2015) 109–120. [PubMed: 25588378]

[101]. Bussiere T, Hof PR, Mailliot C, et al. , Phosphorylated serine422 on tau proteins is a pathological epitope found in several diseases with neurofibrillary degeneration, Acta Neuropathol. 97 (3) (1999) 221–230. [PubMed: 10090668]

[102]. Collin L, Bohrmann B, Gopfert U, Oroszlan-Szovik K, Ozmen L, Gruninger F, Neuronal uptake of tau/pS422 antibody and reduced progression of tau pathology in a mouse model of Alzheimer's disease, Brain 137 (Pt 10) (2014) 2834–2846. [PubMed: 25085375]

[103]. Qureshi IA, Tirucherai G, Ahlijanian MK, Kolaitis G, Bechtold C, Grundman M, A randomized, single ascending dose study of intravenous BIIB092 in healthy participants, Alzheimers Dement. N. Y. (N Y) 4 (2018) 746–755.

[104]. Boxer AL, Qureshi I, Ahlijanian M, et al. , Safety of the tau-directed monoclonal antibody BIIB092 in progressive supranuclear palsy: a randomised, placebo-controlled, multiple ascending dose phase 1b trial, Lancet Neurol. 18 (6) (2019) 549–558. [PubMed: 31122495]

[105]. Yanamandra K, Jiang H, Mahan TE, et al. , Anti-tau antibody reduces insoluble tau and decreases brain atrophy, Ann. Clin. Transl. Neurol 2 (3) (2015) 278–288. [PubMed: 25815354]

[106]. Yanamandra K, Kfoury N, Jiang H, et al. , Anti-tau antibodies that block tau aggregate seeding in vitro markedly decrease pathology and improve cognition in vivo, Neuron 80 (2) (2013) 402–414. [PubMed: 24075978]

[107]. Yanamandra K, Patel TK, Jiang H, et al. , Anti-tau antibody administration increases plasma tau in transgenic mice and patients with tauopathy, Sci. Transl. Med 9 (386) (2017).

[108]. West T, Hu Y, Verghese PB, et al. , Preclinical and clinical development of ABBV-8E12, a humanized anti-tau antibody, for treatment of alzheimer's disease and other tauopathies, J. Prev. Alzheimers Dis 4 (4) (2017) 236–241. [PubMed: 29181488]

[109]. Lee SH, Le Pichon CE, Adolfsson O, et al. , Antibody-mediated targeting of tau in vivo does not require effector function and microglial engagement, Cell Rep. 16 (6) (2016) 1690–1700. [PubMed: 27475227]

[110]. Alam R, Driver D, Wu S, et al. , Preclinical characterization of an antibody [LY3303560] targeting aggregated tau, Alzheimer's and Dementia 13 (7) (2017) P592–P593.

[111]. Czerkowicz J, Chen W, Wang Q, Shen C, Wager C, Stone I, Stebbins C, Lamb M, Setser J, Cantone G, Graham D, Pan-tau antibody Biib076 exhibits promising safety and biomarker profile in cynomolgus monkey toxicity study [abstract P4-039], Alzheimers Dement. 13 (7 Suppl) (2018) P1271.

[112]. Courade JP, Angers R, Mairet-Coello G, et al. , Epitope determines efficacy of therapeutic anti-Tau antibodies in a functional assay with human Alzheimer Tau, Acta Neuropathol. 136 (5) (2018) 729–745. [PubMed: 30238240]

[113]. Albert M, Mairet-Coello G, Danis C, et al. , Prevention of tau seeding and propagation by immunotherapy with a central tau epitope antibody, Brain 142 (6) (2019) 1736–1750. [PubMed: 31038156]

[114]. Gozes I, Bassan M, Zamostiano R, et al. , A novel signaling molecule for neuropeptide action: activity-dependent neuroprotective protein, Ann. N. Y. Acad. Sci 897 (1999) 125–135. [PubMed: 10676441]

[115]. Matsuoka Y, Jouroukhin Y, Gray AJ, et al. , A neuronal microtubule-interacting agent, NAPVSIPQ, reduces tau pathology and enhances cognitive function in a mouse model of Alzheimer's disease, J. Pharmacol. Exp. Ther 325 (1) (2008) 146–153. [PubMed: 18199809]

[116]. Shiryaev N, Jouroukhin Y, Giladi E, et al. , NAP protects memory, increases soluble tau and reduces tau hyperphosphorylation in a tauopathy model, Neurobiol. Dis 34 (2) (2009) 381–388. [PubMed: 19264130]

[117]. Morimoto BH, Schmechel D, Hirman J, et al. , A double-blind, placebo-controlled, ascending-dose, randomized study to evaluate the safety, tolerability and effects on cognition of AL-108 after 12 weeks of intranasal administration in subjects with mild cognitive impairment, Dement. Geriatr. Cogn. Disord 35 (5-6) (2013) 325–336. [PubMed: 23594991]

[118]. Litvan I, Cognitive disturbances in progressive supranuclear palsy, J. Neural Transm Suppl. 42 (1994) 69–78.

[119]. Boxer AL, Lang AE, Grossman M, et al. , Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial, Lancet Neurol. 13 (7) (2014) 676–685. [PubMed: 24873720]

[120]. Brunden KR, Zhang B, Carroll J, et al. , Epothilone D improves microtubule density, axonal integrity, and cognition in a transgenic mouse model of tauopathy, J. Neurosci 30 (41) (2010) 13861–13866. [PubMed: 20943926]

[121]. Malamut R, Wang J-S, Savant I, et al. , A randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, tolerability and pharmacokinetics of a microtubule stabilizer (BMS-241027) in healthy females, Alzheimer's and Dementia 9 (4) (2013) P668–P669.

[122]. Fitzgerald DP, Emerson DL, Qian Y, et al. , TPI-287, a new taxane family member, reduces the brain metastatic colonization of breast cancer cells, Mol. Cancer Ther 11 (9) (2012) 1959–1967. [PubMed: 22622283]

[123]. Tsai RM, Miller Z, Koestler M, et al. , Reactions to multiple ascending doses of the microtubule stabilizer TPI-287 in patients with alzheimer disease, progressive supranuclear palsy, and corticobasal syndrome: a randomized clinical trial, JAMA Neurol. (2019).

[124]. Kargbo RB, Treatment of alzheimer’s by PROTAC-Tau protein degradation, ACS Med. Chem. Lett 10 (5) (2019) 699–700. [PubMed: 31097984]

[125]. Silva MC, Ferguson FM, Cai Q, et al. , Targeted degradation of aberrant tau in frontotemporal dementia patient-derived neuronal cell models, Elife 8 (2019).

[126]. Holmes BB, Furman JL, Mahan TE, et al. , Proteopathic tau seeding predicts tauopathy in vivo, Proc. Natl. Acad. Sci. U. S. A 111 (41) (2014) E4376–85. [PubMed: 25261551]

[127]. Sevigny J, Chiao P, Bussiere T, et al. , The antibody aducanumab reduces Abeta plaques in Alzheimer’s disease, Nature 537 (7618) (2016) 50–56. [PubMed: 27582220]

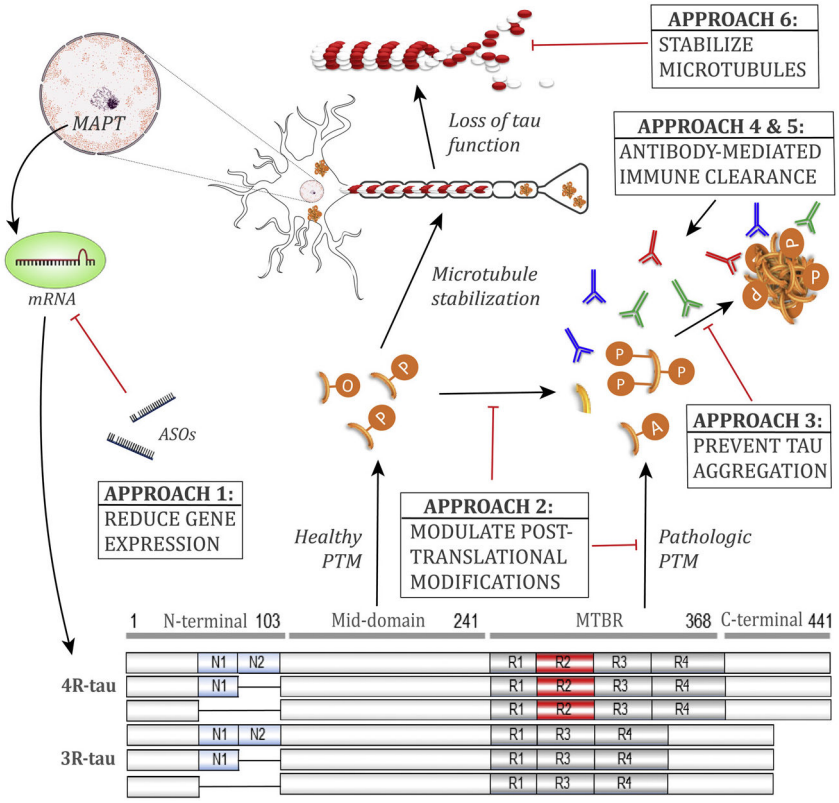


**Fig. 1.**

Tau-directed approaches currently being tested in clinical trials. In Approach 1–5, toxic tau gain of function is targeted by removal or modulation of toxic tau species. In Approach 1, anti-sense oligonucleotides (ASOs) are directed against mRNA from the *MAPT* gene, thereby reducing translation and decreasing tau gene expression. In Approach 2, healthy post-translational modification (PTM) pathways are supported by blocking hyperphosphorylation by kinases, inhibiting removal of O-GlcNAc, and preventing tau acetylation. In Approach 3, toxic tau aggregates are prevented from forming and existing tau aggregates are disrupted by autophagy. In Approach 4 and 5, antibodies are used to clear or sequester pathologic tau species, preventing cell to cell transmission. In contrast to the prior approaches, in Approach 6 tau loss of function is addressed by restoring microtubule stabilization.

**Table 1**

Neuropathological tauopathies and associated clinical syndromes.

| Tauopathy | Associated clinical syndrome |
|---|---|
| Neurofibrillary tangles (NFTs) | Mild cognitive impairment (MCI), Alzheimer's disease (AD), Down Syndome, logopenic variant primary progressive aphasia (lvPPA), corticobasal syndrome (CBS), non-fluent variant of primary progressive aphasia (nfvPPA), behavioral variant frontotemporal dementia (bvFTD) |
| Chronic traumatic encephalopathy (CTE) | Executive mild cognitive impairment (MCI), traumatic encephalopathy syndrome (TES) |
| Argyrophilic grain disease (AGD) | Amnestic MCI, bvFTD |
| Progressive supranuclear palsy (PSP) | PSP Richardson's syndrome (PSP-RS), CBS, nfvPPA, bvFTD |
| Corticobasal degeneration (CBD) | CBS, PSP-RS, nfvPPA, bvFTD |
| Pick's disease (PiD) | bvFTD, nfvPPA, CBS, PSP-RS, semantic variant of primary progressive aphasia (svPPA) |
| *MAPT* mutation | Frontotemporal dementia with parkinsonism syndrome (FTDP-17) and diverse others |

**Table 2**

Tau-directed therapeutics tested in clinical trials.

| Therapeutic | Synonyms | Mechanism | Rationale (Ref #) | Preclinical Data (Ref #) | Furthest Development Phase |
|---|---|---|---|---|---|
| **GENE EXPRESSION** | | | | | |
| **BIIB080** | IONIS-MAPTRx, ISIS 814907 | ASO targeting decreased total tau expression | 12, 31, 34 | 37 | AD (Phase 2) |
| **KINASE INHIBITOR** | | | | | |
| **Lithium** | | GSK-3β inhibitor | 44, 45 | 46 | AD (Phase 2 - D/C), PSP (Phase 2- D/C), CBS (Phase 2-D/C), MCI (Phase 2), BvFTD (Phase 2) |
| **Valproate** | Depakote, divalproex, valproic acid | GSK-3β inhibitor | 48 | 49 | AD (Phase 3 - D/C), PSP (Phase 2 - D/C) |
| **Tideglusib** | NP031112, Nypta, Zentylor, NP12 | GSK-3β inhibitor | 53 | 54 | AD (Phase 2 - D/C), PSP (Phase 2 - D/C) |
| **Saracatinib** | AZD0530 | Fyn inhibitor | 59, 60 | 61 | AD (Phase 2) |
| **Nilotinib** | Tasigna, AMN107 | Abl inhibitor | 64 | 65 | AD (Phase 2) |
| **OGA INHIBITOR** | | | | | |
| **MK-8719** | | O-GlcNAcase inhibitor | 66 | 67 | Healthy Controls (Phase 1 – D/C) |
| **ASN120290** | ASN-561 | O-GlcNAcase inhibitor | 66 | 69 | Healthy Controls (Phase 1) |
| **ACETYLATION INHIBITOR** | | | | | |
| **Salsalate** | | Tau acetylation inhibitor | 28, 29 | 71 | AD (Phase 2) PSP (Phase 2 – D/C) |
| **TAU AGGREGATION INHIBITOR** | | | | | |
| **Rember TM** | Methylene Blue, methylthioninium (MT), TRx-0014 | Tau aggregation inhibitor (TAI) | 74 | 75, 76 | AD (Phase 2 - D/C) |
| **LMTM** | TRx0237, LMT-X | Tau aggregation inhibitor (TAI) | 74 | 79 | AD (Phase 3), BvFTD (Phase 3 – D/C) |
| **ACTIVE IMMUNIZATION (VACCINATION)** | | | | | |
| **AADvac-1** | | Tau fragment of MTBR conjugated to keyhole limpet hemocyanin | 92, 94 | 94 | AD (Phase 2), NfvPPA (Phase 2) |
| **ACI-35** | | Ptau fragment anchored on liposome | – | 97 | AD (Phase 2) |
| **PASSIVE IMMUNIZATION (ANTIBODY TRANSFUSION)** | | | | | |
| **RG7345** | RO6926496 | mAb to tau pS422 near C-terminal | 101 | 102 | Healthy Controls (Phase 1 - D/C) |
| **BIIB092** | BMS-986168, IPN007 | mAb to tau N-terminal (aa 15-24) | 85, 99 | 99 | PSP (Phase 2 – D/C), AD (Phase 2), Tauopathies (Phase 2 – D/C) |
| **C2N 8E12** | ABBV-8E12 | mAb to tau N-terminal (aa 25-30) | 85 | 105-107 | PSP (Phase 2 – D/C), AD (Phase 2) |

| Therapeutic | Synonyms | Mechanism | Rationale (Ref #) | Preclinical Data (Ref #) | Furthest Development Phase |
|---|---|---|---|---|---|
| RO7,105,705 | Semorinemab, RG 6100 | mAb to tau N-terminal (reduced effector function) | 85, 109 | 109 | AD (Phase 2) |
| **LY3303560** | Zagotenemab | mAb to tau N-terminal (tau aggregates) | 85 | 110 | AD (Phase 2) |
| **BIIB076** | NI-105, 6C5 huIgG1/λ | mAb to “pan-tau” (monomers and fibrils) | – | 111 | AD (Phase 2) |
| **UCB0107** | UCB 0107 | mAb to tau mid domain (aa 235-246) | – | – | Healthy Controls (Phase 1) |
| **JNJ-63733657** | | mAb to tau mid domain | – | – | AD (Phase 2) |
| **MICROTUBULE STABILIZATION** | | | | | |
| **Davunetide** | NAP, AL-108 | Growth factor derived neuropeptide | 114 | 115, 116 | MCI (Phase 2 - D/C), PSP (Phase 3 - D/C), Tauopathies (Phase 2 - D/C) |
| **Epothilone D** | BMS-241027 | Taxane derivitive that stabilizes microtubules | – | 120 | AD (Phase 2 - D/C) |
| **TPI 287** | | Taxane derivitive that stabilizes microtubules | 122 | – | AD (Phase 2 – D/C), CBS (Phase 2 – D/C), PSP (Phase 2 – D/C) |

**Table 3**

Clinical trials of tau-directed therapeutics.

| Therapeutic | Company/Sponsor | Trial | Stage | Cohort | Treatment Length | Outcome Measures | Trial End | Result (Ref #) |
|---|---|---|---|---|---|---|---|---|
| **GENE EXPRESSION** | | | | | | | | |
| **BIIB080** | Biogen, IONIS Pharmaceuticals | NCT03186989 | Phase 1/2 | 46 mild AD | 36 weeks | 1°: safe/tol<br>2°: PK | May-22 * | |
| **KINASE INHIBITOR** | | | | | | | | |
| **Lithium** | NINDS, ADDF, Columbia University | NCT00088387 | Phase 2 | 35 AD | 6 weeks | CSF tau | Mar-20 | |
| | | ISRCTN72046462 | Phase 2 | 71 mild AD | 10 weeks | 1°: CSF ptau, GSK-3β<br>2°: CSF Aβ/tau, ADAS-Cog, NPI, safe/tol | Jul-20 | [47] |
| | | NCT00703677 | Phase 1/2 | 17 PSP or CBD | 28 weeks | 1°: safe/tol<br>2°: CSF tau, BDNF, GSK-3β, PSP-RS, UPDRS, QoL, FAB, GDS | Jan-20 | |
| | | NCT02862210 | Phase 2 | 60 bvFTD | 12 weeks | 1°: agitation/NPI<br>2°: CGI, NPI, AEs, BDNF | Mar-21 * | |
| | | NCT03185208 | Phase 4 | 80 MCI | 2 years | 1°: NPSY, GSK-3β, BDNF, 7 T MRI<br>2°: 7 T MRI, CSF ptau | Mar-22 * | |
| **Valproate** | NINDS | NCT00088387 | Phase 2 | 35 AD | 6 weeks | CSF tau | Mar-20 | |
| | | NCT00071721 (VALID) | Phase 3 | 313 prob AD | 24 months | 1°: agitation/NPI<br>2°: ADAS-cog, ADL, CDR, CMAI, CGI | Dec-20 | [50,51] |
| | | NCT00385710 | Phase 2 | 28 poss or prob PSP | 24 months | 1°: PSP-RS<br>2°: NPSY | Jul-20 | [52] |
| **Tideglusib** | Zeltia Group, Neuropharma, Noscira | NCT00948259 | Phase 1/2 | 30 mild to mod AD | 20 weeks | 1°: safe/tol<br>2°: Cognition and mood | Nov-20 | [55] |
| | | NCT01049399 (TAUROS) | Phase 2 | 146 poss or prob PSP | 12 months | 1°: PSP-RS<br>2°: safety, NPSY, UPDRS, CGI | Nov-20 | [57,58] |
| | | NCT01350362 (ARGO) | Phase 2 | 306 mild to mod AD | 6 months | 1°: ADAS-cog<br>2°: safe/tol, ADL, MMSE, fluency, NPI, GDS, CGI, EQ-5D, RUD, urinary incont | Oct-20 | [56] |
| **Saracatinib** | AstraZeneca | NCT01864655 | Phase 1 | 24 mild AD | 4 weeks | 1°: safe/tol, PK<br>2°: NPSY, FDG-PET | Mar-20 | [62] |
| | | NCT02167256( CONNECT) | Phase 2 | 159 mild AD | 12 months | 1°: safe/tol, PET<br>2°: ADAS-cog, MMSE, ADL, CDR, MRI, CSF Aβ/tau, ApoE | Feb-20 | [63] |

| Therapeutic | Company/Sponsor | Trial | Stage | Cohort | Treatment Length | Outcome Measures | Trial End | Result (Ref #) |
|---|---|---|---|---|---|---|---|---|
| **Nilotinib** | Novartis, Georgetown University | NCT02947893 | Phase 2 | 42 mild to mod AD | 12 months | 1°: safe/tol<br>2°: PK | Feb-20 * | |
| **OGA INHIBITOR** | | | | | | | | |
| **MK-8719** | Alectos Therapeutics | | Phase 1 | 16 healthy ctrls | | 1°: safe/tol<br>2°:PK | | [67] |
| **ASN120290** | Asceneuron | | Phase 1 | 61 healthy ctrls | 10 days | 1°: safe/tol<br>2°:PK | | [70] |
| **ACETYLATION INHIBITOR** | | | | | | | | |
| **Salsalate** | UCSF | NCT03277573 (SAL-AD) | Phase 1 | 40 mild to mod AD | 12 months | 1°: safe/tol<br>2°: PK, MRI, CSF tau, NfL, NPSY, ADL, CDR | Feb-21 * | |
| | | NCT02422485 | Phase 1 | 10 prob or poss PSP | 6 months | 1°: safe/tol<br>2°: PSP-RS, CDR, CGI, RBANS, MRI, CSF NfL | Mar-20 | [72] |
| **TAU AGGREGATION INHIBITOR** | | | | | | | | |
| **Rember TM** | TauRx Therapeutics Ltd | NCT00515333 | Phase 2 | 323 mild or mod AD | 24 weeks | 1°: ADAS-cog<br>2°: NPI, CGI, CDR, MMSE,BADLs, SPECT/PET | Dec-20 | [78,79] |
| | | NCT00684944 | Extension | 111 mild or mod AD | 12 months | 1°: ADAS-cog, MMSE<br>2°: CDR, ADFACS | Dec-20 | |
| **LMTM** | TauRx Therapeutics Ltd | NCT01626391 | Phase 1/2 | 9 mild to mod AD | 4 weeks | 1°: safe/tol | Mar-20 | |
| | | NCT01689246 | Phase 3 | 891 mild to mod AD | 65 weeks | 1°: safe/tol, ADL, ADAS-cog<br>2°: CGI, MMSE, MRI | Nov-20 | [80] |
| | | NCT01689233 | Phase 3 | 800 mild AD | 78 weeks | 1°: safe/tol, ADL, ADAS-cog<br>2°: CGI, MMSE, NPI, MADRS, MRI | May-20 | [81] |
| | | NCT01626378 | Phase 3 | 220 bvFTD | 12 months | 1°: ACE-R, FAQ, MRI<br>2°: UPDRS, FRS, CGI, safe/ tol | Feb-20 | |
| | | NCT02245568 | Extension | 913 AD or bvFTD | 34 months | 1°: safe/tol<br>2°: EQ-5D, RUD | May-20 | |
| | | NCT03446001 (LUCIDITY) | Phase 3 | 450 early AD | 12 month | 1°: ADAS-cog, ADL, safe/tol<br>2°: MRI, FDG PET, ADAS-cog, ADL | Dec-22 * | |
| **ACTIVE IMMUNIZATION (VACCINATION)** | | | | | | | | |
| **AADvac-1** | Axon Neuroscience SE | NCT01850238 | Phase 1 | 30 mild to mod AD | 3 months | 1°: safe/tol<br>2°: Ab titers | Mar-20 | [95] |
| | | NCT02031198 (FUNDAMANT) | Extension | 25 mild to mod AD | 18 months | 1°: long-term safe/tol<br>2°: Ab titers, ADAS-cog, COWAT | Dec-20 | [96] |

| Therapeutic | Company/Sponsor | Trial | Stage | Cohort | Treatment Length | Outcome Measures | Trial End | Result (Ref #) |
|---|---|---|---|---|---|---|---|---|
| | | NCT02579252 (ADAMANT) | Phase 2 | 208 mild AD | 24 months | 1°: safe/tol<br>2°: CDR, NPSY, ADL, Ab titers | Jun-20 | |
| | | NCT03174886 (AIDA) | Phase 1 | 33 nfv-PPA | 24 months | 1°: safe/tol, Ab titers | Nov-20 * | |
| **ACI-35** | AC Immune SA, Janssen | ISRCTN13033912 | Phase 1 | Mild to mod AD | 6 month + 16 month booster | 1°: safe/tol, Ab titers | Jun-20 | |
| **PASSIVE IMMUNIZATION (ANTIBODY TRANSFUSION)** | | | | | | | | |
| **RG7345** | Hoffmann-La Roche | NCT02281786 | Phase 1 | 48 healthy ctrls | 16 weeks | 1°: safe/tol<br>2°: PK | Oct-20 | |
| **BIIB092** | Biogen, Bristol-Myers Squibb | NCT02294851 (Healthy ctrls) | Phase 1 | 65 healthy ctrls | Single dose | 1°: safe/tol | Apr-20 | [103] |
| | | NCT02460094 | Phase 1 | 48 poss or prob PSP | 12 weeks | 1°: safe/tol<br>2°: CSF tau, Ab titers, PK | Oct-20 | [104] |
| | | NCT02658916 | Extension | 48 poss or prob PSP | 1.5 years+ | 1°: long-term safe/tol<br>2°: PK, Ab titers, CSF tau | Feb-20 | |
| | | NCT03658135 (TauBasket) | Phase 1 | 22 CBS, nfvPPA, MAPT, and TES | 20 weeks | 1°: safe/tol<br>2°: PK, CSF tau | Feb-20 | |
| | | NCT03068468 (PASSPORT) | Phase 2 | 490 poss or prob PSP | 48 weeks + 156 week OLE | 1°: PSP-RS, safe/tol<br>2°: UPDRS, CGI, RBANS, QoL, SEADL, NPSY, MOCA, Ab titers, MRI | Feb-20 | |
| | | NCT03352557 (TANGO) | Phase 2 | 654 MCI or early AD | 76 weeks | 1°: safe/tol<br>2°: CDR, Ab titers | Mar-24 * | |
| **C2N 8E12** | AbbVie, C2N Diagnostics, LLC | NCT02494024 | Phase 1 | 32 poss or prob PSP | 4 months | 1°: safe/tol<br>2°: PK, Ab titers | Aug-20 | [108] |
| | | NCT03413319 | Extension | 3 poss or prob PSP | 29 months | 1°: safe/tol | Nov-20 | |
| | | NCT02985879 (PSP) | Phase 2 | 378 poss or prob PSP | 12 months | 1°: PSP-RS, safe/tol<br>2°: PK, CGI, MRI, UPDRS, SEADL | Nov-20 | |
| | | NCT03391765 | Extension | 378 poss or prob PSP | 5 years | 1°: PSP-RS<br>2°: UPDRS, CGI, SEADL | Nov-20 | |
| | | NCT02880956 | Phase 2 | 453 early AD | 96 weeks | 1°: safe/tol, CDR<br>2°: UPSA, PK, MMSE, ADL, FAQ, RBANS, CGI, ADAS-cog, NPI | Jul-21 * | |
| | | NCT03712787 | Extension | 360 early AD | 5.5 years | 1°: safe/tol | Aug-20 6 * | |
| **RO 7,105,705** | AC Immune SA, Genentech, Hoffmann-La Roche | NCT02820896 | Phase 1 | 74 healthy ctrls and mild AD | 19 weeks | 1°: safe/tol, C-SSRS<br>2°: CDR, Ab titers, PK, MMSE | Jun-20 | |
| | | NCT03289143 (TAURIEL) | Phase 2 | 457 prodromal to mild AD | 73 weeks | 1°: CDR, safe/tol<br>2°: RBANS, ADAS-cog, ADL,PK, Ab titers | Sep-22 * | |

| Therapeutic | Company/Sponsor | Trial | Stage | Cohort | Treatment Length | Outcome Measures | Trial End | Result (Ref #) |
|---|---|---|---|---|---|---|---|---|
| **LY3303560** | Eli Lilly & Co. | NCT02754830 | Phase 1 | 110 healthy ctrls and mild AD | 85 days | 1°: safe/tol<br>2°: PK | Jul-20 | |
| | | NCT03019536 | Phase 1 | 24 MCI or early AD | 64 weeks | 1°: safe/tol<br>2°: PK | Jun-20 | |
| | | NCT03518073 | Phase 2 | 285 early AD | 80 weeks | 1°: iADRS<br>2°: ADAS-cog, ADL, CDR, MMSE, tau PET, MRI, CSSRS, Ab titers | Oct-21 * | |
| **BIIB076** | Biogen, Neurimmune | NCT03056729 | Phase 1 | 56 healthy ctrls and mild AD | 20 weeks | 1°: safe/tol<br>2°: PK, Ab titers | Mar-20 | |
| **UCB0107** | UCB S.A. | NCT03464227 | Phase 1 | 52 healthy ctrls | 20 weeks | 1°: safe/tol<br>2°: PK | Dec-20 | |
| | | NCT03605082 | Phase 1 | 24 healthy Japanese ctrls | 20 weeks | 1°: safe/tol, PK | Mar-20 | |
| **JNJ-63733657** | Janssen | NCT03375697 | Phase 1 | 72 healthy ctrls and mild AD | 21 weeks | 1°: safe/tol<br>2°: PK, CSF tau | Dec-20 | |
| **MICROTUBULE STABILIZATION** | | | | | | | | |
| **Davunetide** | Allon Therapeutics Inc., Paladin Labs Inc. | NCT00422981 | Phase 2 | 144 MCI | 12 weeks | 1°: NPSY (12 weeks)<br>2°: NPSY (16 weeks) | Jan-20 | [117] |
| | | NCT01056965 | Phase 1 | 12 PSP, CBS, nfvPPA, and sMAPT | 12 weeks | 1°: safe/tol<br>2°: PSP-RS, CGI, SEADL, MRI, RBANS, UPDRS, NPI, GDS, CSF Aβ/tau, saccades, CDR, FAQ | Jul-20 | |
| | | NCT01110720 | Phase 2/3 | 313 PSP | 12 months | 1°: PSP-RS, SEADL, safe/tol<br>2°: CGI, MRI | Dec-20 | [119] |
| **Epothilone D** | Bristol-Myers Squibb | NCT01492374 | Phase 1 | 40 mild AD | 10 weeks | 1°: safe/tol, CSF tau<br>2°: CSF tau/NfL, NPSY, PK,MRI | Oct-20 | |
| **TPI 287** | Cortice Biosciences | NCT02133846 | Phase 1 | 44 CBS or PSP | 9 weeks | 1°: safe/tol<br>2°: PK | Mar-20 | [123] |
| | | NCT01966666 | Phase 1 | 33 mild to mod AD | 9 weeks | 1°: safe/tol<br>2°: PK | Nov-20 | [123] |

* = estimated data of completion at time of publication. Abbreviations: antibody (Ab), beta amyloid (Aβ), Addenbrooke's Cognitive Examination - Revised (ACE-R), Alzheimer's Disease Assessment Scale-cognitive Subtest (ADAS-cog), Alzheimer's Disease Functional Assessment and Change Scale (ADFACS), Alzheimer's Disease Cooperative Study Activities of Daily Living (ADL), adverse events (AE), apolipoprotein E (ApoE), basic activities of daily living (BADLs), brain-derived neurotrophic factor (BDNF), cerebrospinal fluid (CSF), Clinical Global Impression of Change (CGI), Cohen-Mansfield Agitation Inventory (CMAI), Controlled oral word association test (COWAT), Columbia Suicide Severity Rating Scale (C-SSRS), European Quality of Life Instrument (EQ-5D), Frontal Assessment Battery (FAB), Functional Activities Questionnaire (FAQ), Frontotemporal Dementia Rating Scale (FRS). Geriatric Depression Scale (GDS), glycogen synthase kinase-3 beta (GSK-3β), integrated Alzheimer's Disease Rating Scale (iADRS), Montgomery-Asberg Depression Rating Scale (MADRS), Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), magnetic resonance imaging (MRI), neurofilament light chain (NfL), Neuropsychiatric Inventory (NPI), neuropsychological testing (NPSY), pharmacokinetics (PK), Progressive Supranuclear Palsy Rating Scale (PSP-RS), PSP-Quality of Life Scale (QoL), Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS), Resource Utilization in Dementia (RUD), safety and tolerability (safe/tol), Schwab and England Activities of Daily Living (SEADL), Unified Parkinson Disease Rating Scale (UPDRS), University of California's Performance Based Skills Assessment, Brief Version (UPSA).