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Tau-targeting therapies for Alzheimer disease

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Abstract

Alzheimer disease (AD) is the most common form of dementia. Pathologically, AD is characterized by amyloid plaques and neurofibrillary tangles in the brain, with associated loss of synapses and neurons, resulting in cognitive deficits and eventually dementia. Amyloid-β (Aβ) peptide and tau protein are the primary components of the plaques and tangles, respectively. In the decades since Aβ and tau were identified, development of therapies for AD has primarily focused on Aβ, but tau has received more attention in recent years, in part because of the failure of various Aβ-targeting treatments in clinical trials. In this article, we review the current status of tau-targeting therapies for AD. Initially, potential anti-tau therapies were based mainly on inhibition of kinases or tau aggregation, or on stabilization of microtubules, but most of these approaches have been discontinued because of toxicity and/or lack of efficacy. Currently, the majority of tau-targeting therapies in clinical trials are immunotherapies, which have shown promise in numerous preclinical studies. Given that tau pathology correlates better with cognitive impairments than do Aβ lesions, targeting of tau is expected to be more effective than Aβ clearance once the clinical symptoms are evident. With future improvements in diagnostics, these two hallmarks of the disease might be targeted prophylactically.

Introduction

Alzheimer disease (AD) represents a major health crisis, with an estimated 5.4 million people currently affected in the USA alone[1]. With an ageing population in the USA and elsewhere, the problem will only grow worse. The search for disease-modifying therapies for AD has centred on the two main hallmarks of the disease: the extracellular plaques composed primarily of amyloid-β (Aβ), and the intraneuronal neurofibrillary tangles (NFTs), the main constituent of which is the tau protein (Fig. 1). Unfortunately, attempts to

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Author contributions

Both authors researched data for the article, made substantial contributions to discussion of the content, wrote the article, developed the figures and table, and reviewed and edited the manuscript before submission.

Competing interests statement

E.M.S. is an inventor on various patents on immunotherapies and related diagnostics that are assigned to New York University. Some of those focusing on the tau protein are licensed to and are being co-developed with H. Lundbeck A/S. E.E.C. declares no competing interests.

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alter the disease course by removing Aβ or reducing its production have been largely unsuccessful. Thus, interest in tau-targeting strategies is increasing.

Under normal conditions, tau provides microtubule stability and contributes to the regulation of intracellular trafficking[2,3]. However, in AD and a range of other conditions, including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick disease, frontotemporal dementia (FTD), traumatic brain injury (TBI), stroke and ischaemia, the normal function of tau is disrupted, which ultimately leads to the development of NFT pathology. Although tau lesions are present in each of these conditions, many aspects of tau pathology, including the initial location, progression, associated symptoms, cell types affected, and even the ultrastructure of the tau filaments, are disease-dependent.

The development of tau pathology is a complex multifactorial process, presenting multiple points where therapeutic intervention is possible. In this Review, we will discuss some of the mechanisms that promote tau pathology and are being targeted in clinical trials, including post-translational modifications, cytoskeletal disruption and impairments in protein degradation mechanisms. We focus on AD, given that it is the most common tauopathy and has been the main focus of research and clinical development to date. Current and discontinued efforts to address tau pathology are discussed, and an overview of the results of clinical trials is provided.

Pathological processes in tauopathies

Pathological tau can be seen in the brain decades before the onset of symptoms, with the development of phosphorylated pre-tangles and neuropil threads[4–6]. NFTs, which can be visualized with the Gallyas silver stain, appear at a later stage. Even before the formation of tangles, tau undergoes a series of post-translational modifications, including hyperphosphorylation[7], acetylation[8] *N*-glycosylation[9] and truncation[10], which differentiate it from the normal tau that is seen in healthy brains (see Fig. 2 for a depiction of tau pathology in AD). In AD, deposition of tau aggregates follows a highly stereotyped pattern, beginning in the entorhinal cortex and hippocampus before spreading to other regions[11,12]. However, hippocampal-sparing and limbic-predominant subtypes are thought to constitute ~25% of AD cases[13]. Another potential pre-AD tau pathology subtype, termed primary age-related tauopathy (PART), has also been characterized[14]. People with PART have limited if any Aβ deposition, and many do not show cognitive impairments.

The polymers that constitute tau lesions are a heterogeneous mixture, the composition of which depends on the disease and stage. In AD, tau exists as monomers, small oligomeric species, paired helical filaments (PHFs) and straight filaments[15–17]. NFTs in familial tauopathy can contain fibrils with a twisted ribbon morphology that is distinct from the typical PHFs, whereas straight filaments predominate in Pick disease[18]. The isoform composition of tau also differs between the various tauopathies. Neurons in the adult CNS express six tau isoforms, which differ in the inclusion or exclusion of two amino-terminal exons, and contain three or four amino acid repeat sequences in the microtubule-binding domain[19,20]. In AD and PART, the tau aggregates are a mixture of three-repeat and four-

repeat tau isoforms, whereas four-repeat sequences dominate in PSP and CBD and three-repeat sequences predominate in Pick disease[14,18,19,21].

Targetable pathological events

Post-translational modifications

Post-translational modifications of tau — with the exception of *O*-GlcNAcylation (see below) —interfere with tau–microtubule binding and promote tau misfolding. Thus, targeting of any of these modifications, alone or in combination, has the potential to prevent tau aggregation and restore normal function to the protein (Fig. 2). As these processes begin long before symptoms appear, development of further pathology might be prevented if treatment can be administered in the prodromal phase.

Hyperphosphorylation.—Concurrently with the identification of tau as the primary component of AD-associated NFTs[15], the aggregated tau was discovered to be hyperphosphorylated[7]. Previous reports had shown that phosphorylation of the tau protein affects its ability to bind tubulin and promote microtubule assembly[22]. Since the initial reports, multiple phosphorylation sites and kinases have been identified. In AD the pattern of phosphorylation changes as the disease progresses. Early phosphorylation events disrupt the association of tau with microtubules and promote relocation of tau to the somatodendritic compartment. Phosphorylation at sites such as Ser199, Ser202/205, Thr231 and Ser262 seems to be associated with pre-tangles in the neuronal processes[23,24]. Subsequently, levels of somatic tau increase and additional epitopes such as phospho-Ser422 (pSer422) become evident. At both of these stages, phosphorylation can precede cleavage at Asp421, which renders the tau protein prone to aggregation, although phosphorylation at Ser422 inhibits this cleavage step[25]. Phosphorylation at other sites, such as Ser396, is more prominent later in the disease[24,26]. Adding to the complexity of this process, phosphorylation at some sites might prime other sites, leading to the formation of large multisite epitopes or promoting conformational changes[21,27]. The pattern of phosphorylation differs between tauopathies[21], and in the case of familial tauopathies, the causative mutations might induce conformational changes that make tau a more favourable substrate for certain kinases.

Hyperphosphorylation of tau is one of the earliest events in the development of AD, and the degree of phosphorylation reflects abnormal activity of both protein kinases and phosphatases. Changes in the levels of active kinases in the brains of individuals with AD can be the result of upregulation of the kinase itself or disruption of its regulation. For example, evidence from post-mortem tissue from the brains of patients with AD indicates that levels of active cyclin-dependent-like kinase 5 (CDK5) and cyclin-dependent kinase 5 activator 1, p25 — a truncated form of a CDK5 regulator — are increased in disease[28]. Similarly, active glycogen synthase kinase-3β (GSK3β)[29] and its regulator c-JUN N-terminal kinase (JNK)[30] are associated with neurofibrillary pathology and are upregulated in AD. Because each of these kinases is responsible for phosphorylating different sites, the emergence of specific phospho-epitopes might indicate the stages at which increased activity is most pronounced.

In addition to their role in tau phosphorylation, aberrantly activated kinases can promote neurodegeneration through other mechanisms. CDK5 activity is implicated in the deposition of Aβ, indirect reduction of nerve growth factor (NGF), exacerbation of oxidative stress, promotion of aberrant cell cycle re-entry, and activation of JNK (reviewed elsewhere[31,32]). Overactive GSK3β induces inflammation via nuclear factor κB (NFκB), promoting apoptosis and impairment of axonal transport. These findings demonstrate that enhanced kinase activity can contribute to pathology in multiple ways, making these enzymes an attractive target for intervention.

Although many tau kinases have been identified, protein phosphatase 2A (PP2A) is one of only a few tau phosphatases, and is responsible for over 70% of the total tau phosphatase activity[33]. Expression of PP2A and its activators is significantly reduced in the brains of individuals with AD compared with age-matched controls, whereas PP2A inhibitors are upregulated[34]. Interestingly, PP2A also regulates GSK3β, CDK5 and JNK, providing an additional route to influence tau phosphorylation[34].

Acetylation.—In addition to being hyperphosphorylated, tau from patients with AD and other tauopathies is more heavily acetylated than in the brains of cognitively normal individuals[8]. Like phosphorylation, tau acetylation can arise through multiple mechanisms, including histone acetyltransferase p300 (p300 HAT), cAMP-responsive element-binding protein (CREB)-binding protein, or auto-acetylation, with sirtuin 1 and histone deacetylase 6 acting to deacetylate tau[35]. Dysregulation of this process produces dysfunction in multiple systems, thereby contributing to neurodegeneration. Acetylation also contributes to tau pathology by inducing tau cleavage, preventing ubiquitin binding and impeding tau turnover[8,35]. Thus, tau becomes cytosolic, more aggregation-prone, and more difficult for the cell to remove.

Carboxy-terminal truncation.—During the characterization of PHFs isolated from the brains of individuals with AD, it was discovered that tau had undergone carboxy-terminal truncation by caspase-3[36,37]. A similar phenomenon was observed in other tauopathies[37]. In the case of AD, Aβ promotes caspase activation, thereby providing a link between the two main pathologies[36]. Although cleavage of tau at Asp421 by caspase 3 is the most studied mechanism, tau has several other caspase cleavage sites in the amino terminus[36] (caspase 6) and at Asp314[38] (caspase 2), and activated caspase 3, 6 and 9 colocalize with tau pathology. In addition, tau can be cleaved by other proteases, including calpains and cathepsins.

Cleaved tau is also present in PSP, FTD, CBD and Pick disease, although the pattern is different from that observed in AD. A 35 kDa tau fragment is seen in brain extracts from individuals with PSP, FTD or CBD, but is not present in Pick disease or AD. In addition, a greater number of tau fragment sizes in the 35–64 kDa range is observed in non-AD tauopathies than in AD[25]. Like phosphorylation and acetylation, truncation inhibits the ability of tau to bind to microtubules, and also promotes tau aggregation[36,37], mitochondrial dysfunction[37] and synaptic deficits[39].

O-GlcNAcylation and N-glycosylation.—Unlike other tau post-translational modifications, *O*-GlcNAcylation, a type of *O*-glycosylation, seems to be protective against

tauopathies. In brain tissue from patients with AD, compared with healthy elderly controls, levels of *O*-GlcNAcylated tau are reduced[40]. Conversely, *N*-glycosylation of tau, which is thought to promote phosphorylation and pathological conformational changes, is increased in AD[9,35].

Cytoskeletal dysfunction

Disruption of the tau-microtubule association can potentially affect microtubule dynamics and transport. Indeed, cytoskeletal dysfunction is a common feature of multiple neurodegenerative disorders, including AD. In AD, brain neurons show a reduction in the number and length of microtubules[41], reduced levels of acetylated tubulin[42,43] (a marker of stable microtubules), and axonal swellings containing vesicles and organelles[44]. Furthermore, tau influences the movement of kinesin and dynamin along the axon[2,3], and has been shown to inhibit the transport of organelles and amyloid precursor protein (APP)[45]. Data from cell and animal models show that tau is also a mediator of Aβ-induced toxicity[46–48].

Tau aggregation

Post-translational modifications and loss of microtubule binding lead to elevated levels of cytosolic tau, thereby increasing the potential for tau-tau interactions and polymerization. In AD and other tauopathies, the brain tissue contains a variety of tau multimer species, including the classic PHFs, straight filaments, twisted ribbons and small oligomeric aggregates[15–17]. The variations in conformation can be attributed to mutations, differing patterns of post-translational modification between diseases, and the presence of different polymerization inducers. Overall, in humans, tau aggregation and the presence of NFTs correlate more closely with symptom severity and neuron loss than do Aβ lesions[49].

Large fibrils might contribute to cell dysfunction via molecular crowding and effects on cell metabolism[50,51]. Neurons containing tangles also have fewer synapses and reduced levels of synaptophysin mRNA compared with tangle-free neurons[52,53]. However, the mature filaments are unlikely to be the primary toxic species: current evidence suggests that small soluble species are more detrimental to cells (reviewed previously[54,55]). Indeed, larger aggregates might exert beneficial effects by sequestering misfolded monomers and soluble aggregates. This phenomenon could account for the seemingly paradoxical findings regarding tau levels in the cerebrospinal fluid (CSF) of patients with AD. Although CSF tau levels are higher in AD than in controls, the levels decrease as the disease progresses, despite the accrual of NFTs[56]. These observations might be explained by decreased tau secretion and/or release, possibly resulting from assembly of tau into larger, more stable filaments within the neurons, as well as from loss of synapses and neurons. CSF tau levels are not increased in non-AD tauopathies[57–60], suggesting that extracellular tau is not a primary target in these conditions. These well-established findings should be taken into account in biomarker and therapeutic studies. For example, the documented decrease in CSF tau with pathology progression in patients with AD might impede the detection of drug-induced reductions in CSF tau. It also raises concerns about the validity of targeting extracellular tau in the later stages of the disease. Furthermore, detailed information on tau fragments obtained by mass spectroscopy could provide additional insight into therapy-

related changes in CSF tau levels that are not detected with current enzyme-linked immunosorbent assays. This information will also guide which epitopes can be targeted extracellularly.

Oligomeric tau has emerged as the probable candidate for the most toxic species in tauopathies, and is present in the brain at early stages of mild cognitive impairment (MCI) and AD[54,55,61]. Tau oligomers promote toxicity in cell models to a greater extent than filamentous tau, and are linked to neurodegeneration and cognitive phenotypes in vivo[54,55] Soluble tau aggregates might also affect the integrity of membranes[62,63]. In addition, tau oligomers are implicated in the spreading of tau pathology. For example, in cell models, soluble oligomeric tau can induce seeding of native tau[54,64], and small tau aggregates isolated from patients or animals with AD can induce tau pathology in mice[54,64,65]. Thus, compounds that prevent or reverse tau aggregation have the potential to improve cell health and prevent the spread of tau pathology to other brain regions.

Protein degradation pathway impairment

In addition to changes to the tau protein itself, other factors can promote the development of tau pathology (Fig. 2). Impairment of protein degradation pathways, including autophagy (reviewed previously[66–68]), is found in a host of neurodegenerative diseases. In MCI and AD, the pattern of kinase activation in the mechanistic target of rapamycin (mTOR) pathway is altered[69–71] and expression of other key autophagy-related proteins is reduced[72] in the brain. Disruption of autophagic flux and a failure of autophagosomes to fuse with lysosomes leads to a build-up of vesicles, which can be seen in dystrophic neurites and cell bodies in AD, CBD and PSP, as well as in tauopathy models[73–76]. Impaired flux also directly contributes to AD pathology. Autophagosomes contain APP, presenilin and γ-secretase, and disruption of autophagosome processing in neurons can lead to increased production of Aβ[77], which can in turn further inhibit protein digestion[78,79]. As tau is a target of autophagy[80], any deficiencies in processing could lead to increased levels of intracellular tau, including misfolded, damaged or aggregated protein.

The ubiquitin-proteasome system is also dysfunctional in AD, leading to a build-up of ubiquitinated proteins including tau[81,82]. Alterations in proteasome efficiency also affect learning and memory via the CREB pathway. Digestion of the regulatory subunit of cAMP-dependent protein kinase A (PKA) in the proteasome results in increased PKA activity and phosphorylation of CREB[83]. Tau pathology and cognitive deficits can be either exacerbated[84] or reduced[85,86] in model animals through the use of inhibitors or enhancers of proteasome function. Interestingly, as with autophagic degradation, tau inhibits proteasome activity[87] suggesting that tau pathology can become self-perpetuating once aggregates are present in neurons.

Tau-targeting drugs

Each stage in the development of tau pathology, from the expression of tau itself to post-translational modifications, aggregation and impairments in clearance, presents opportunities for intervention. In addition to AD, some of the candidate treatments have been examined in other tauopathies such as PSP, FTD and CBD, which involve similar processes. Thus,

treatments that prove efficacious in one condition could have wider applications. Aβ is not a confounding variable in the non-AD tauopathies and, as rare conditions, their therapies qualify for orphan drug status (treatments for conditions affecting ≤200,000 people) and fast tracking for FDA approval. In this section, we review the diverse potential tau-targeting therapies that have reached the clinical trial stage for AD and other tauopathies (Table 1).

Reducing tau expression

As tau is not only directly toxic to cells but is also a mediator of Aβ toxicity[88], reducing tau levels would seem to be a logical therapeutic approach for AD. In mouse models, tau knockout has few adverse effects[89], presumably because other microtubule-associated proteins can, to a large extent, compensate for loss of the tau protein. If the level of tau monomers in cells decreases, the equilibrium that governs aggregate formation dictates that the tau assemblies will depolymerize, leading to reductions in oligomeric tau and larger aggregates such as PHFs. Tau expression can be reduced with small interfering RNA (siRNA) or antisense oligonucleotides (ASOs). In cell and animal models, siRNA was found to reduce tau pathology and associated functional impairments[37]. Although this approach has not yet been tested in clinical trials for AD or other tauopathies, it has been used for other conditions, including cancer[90,91]. ASOs were a popular experimental approach about 25 years ago but fell out of favour because of adverse effects. However, the recent success of this approach in attenuating the progression of spinal muscular atrophy is likely to lead to a resurgence of this type of therapy for various conditions, including tauopathies[92,93].

Targeting tau protein modifications

Phosphatase modifiers.—Memantine was first used as an agent to lower blood sugar levels, but was later discovered to function as an *N*-methyl-D-aspartate receptor antagonist[94,95]. In addition, memantine enhances PP2A activity by blocking inhibitor 2[96] (also known as I_2^{PP2A}). In early clinical trials, memantine produced some improvements in patients who were in a coma[97,98]. In patients with moderate to severe AD, memantine promoted small short-term improvements in cognition[99,100], and it also seemed to provide modest benefits in FTD[101]. The drug might be more effective if administered in combination with cholinesterase inhibitors[102].

Sodium selenate increases PP2A activity via activation of the regulatory B subunit, and reduces phosphorylation of tau in models of AD[103–105], epilepsy[106,107] and TBI[108]. In a phase IIa clinical trial in patients with mild to moderate AD, sodium selenate showed some benefits on diffusion MRI but not on other measures, including CSF levels of tau and Aβ, cognition, volumetric MRI and PET imaging[109].

Kinase inhibitors.—Some of the earliest work to develop CDK5 inhibitors came from the cancer field, leading to the identification of compounds such as flavopiridol (alvocidib)[110] and roscovitine (seliciclib)[111]. Both of these compounds compete with ATP for binding to CDK5, resulting in reduced activation of this kinase[112]. These inhibitors prevent cell death in various models[113], and roscovitine prevents tau phosphorylation in animal models of AD and encephalitis[114]. Both compounds cross the blood-brain barrier and have been tested in various cancer trials, but not yet for AD or other neurodegenerative diseases[114,115].

Tideglusib is an irreversible inhibitor of GSK3β that does not compete with ATP binding[116,117]. In animal models of AD, tideglusib reduces tau phosphorylation, Aβ plaque burden, memory deficits, cell death and astrocytosis[118,119]. In a pilot clinical study[120], patients with AD who received 1,000 mg tideglusib daily showed significant improvements in cognition compared with placebo-treated patients[121]. In a larger phase II study, tideglusib treatment was associated with significant cognitive improvement and a reduction in CSF levels of β-secretase in a subgroup of patients with mild AD[122]. However, when the entire study cohort was analysed, tideglusib was found to be well tolerated but produced no significant improvements[122]. Another phase II trial of this drug[123] was carried out in patients with PSP over 52 weeks, and no clinical improvements were observed[124].

Lithium chloride (or 'lithium') was widely known as a treatment for bipolar disorder long before its identification as an inhibitor of GSK3β[125,126]. In cultured cells, lithium can prevent Aβ-induced toxicity and tau phosphorylation[127]. Transgenic animals treated with lithium show reduced phospho-tau levels, and also Aβ reduction in some studies[127]. Clinical studies of lithium treatment in patients with MCI or AD have been small, but have produced some positive results. Preliminary testing has shown few adverse effects in elderly patients with AD[127]. In short-term trials, increased serum levels of brain-derived neurotrophic factor and CSF levels of glial cell line-derived neurotrophic factor, both of which act as neuroprotectants, were observed, in addition to cognitive improvements[127]. In patients with MCI, lithium treatment significantly reduced phospho-tau levels in CSF and improved cognitive performance[127,128]. In a recent study[129], patients with AD were given very low doses of lithium (300 μg daily) for 15 months. This treatment resulted in a stabilization of cognitive symptoms, whereas placebo-treated patients showed cognitive decline. Additional trials are planned in MCI[130] and FTD[131].

Inhibiting tau acetylation.—Salsalate is a small-molecule NSAID that inhibits acetylation of tau at Lys174 by p300 HAT[132]. In preclinical testing, salsalate reduced p300 HAT activity, leading to reduced tau pathology, preserved hippocampal volume and improved cognition in transgenic mice. Phase I testing of salsalate in patients with PSP was expected to be completed by March 2017, but the results have yet to be published[133]. The trial involves a 6-month open-label course of salsalate, and assessments of brain volume, motor functioning, CSF biomarkers and cognition.

Inhibiting tau deglycosylation.—MK-8719 is a small-molecule inhibitor of the *O*-GlcNAcase (OGA) enzyme. The human dosage was determined in preclinical studies in various species, using intravenous and oral administration[134]. Subsequently, safety, pharmacokinetics and pharmacodynamics were evaluated in healthy individuals, who received ascending oral doses of the drug. Efficacy was also assessed by measuring *O*-GlcNAcylated protein levels in peripheral blood mononuclear cells, which increased in a dose-dependent manner. The drug was well tolerated and the findings support further development[134]. In 2016, the FDA granted MK-8719 orphan drug status, and plans are underway to develop the drug for the treatment of PSP[135].

Inhibiting tau truncation.—Broad caspase inhibitors have been used to reduce pathology in models of Huntington disease, ischaemia and amyotrophic lateral sclerosis (ALS)[136].

Although no specific caspase inhibitors are in clinical trials for tauopathies, several of these agents that have been used in vitro and in vivo have advanced to the clinical trial stage in ALS and Parkinson disease[136].

Tau aggregation inhibitors

Methylene blue blocks the polymerization of tau in vitro by trapping the tau monomers in an aggregation-incompetent conformation[137,138]. This agent was effective at reducing tau pathology and improving cognitive phenotypes in transgenic mouse models of tauopathy[137]. Methylene blue crosses the blood–brain barrier and has a long history of use in humans, so it would seem to be a promising drug candidate.

Initial safety data for methylene blue in the context of AD were collected in healthy individuals[139] before phase II testing[140]. Three different doses of an oxidized form of the molecule were administered to patients with AD for an initial period of 24 weeks[141], which was later extended to 50 weeks[142]. Although some notable treatment effects were observed in initial testing, in two phase III clinical trials of the methylene blue derivative LMTX (also known as LMTM or TRx0237)[143,144], none of the treatment groups experienced significant benefits. Although the authors claimed benefits in patients with mild or moderate AD who received LMTX in the absence of other AD medications[145], these results were widely called into question[146] owing to concerns over use of statistics and unsuitable controls. Data from the second completed phase III trial is expected to be forthcoming, although the first results presented at the Clinical Trials on Alzheimer's Disease (CTAD) Congress in 2016 did not show slowing of disease progression with LMTX treatment[147]. An additional clinical trial was recently terminated that was recruiting individuals with AD and FTD who had already completed a previous trial, and was assessing the long-term safety of the drug[148].

Curcumin is a natural product of the *Curcuma longa* plant, and has been used in cooking and herbal medicine for centuries. Its antioxidant and anti-inflammatory properties, as well as its history of safety in humans, made it an attractive candidate for clinical development. In addition to these properties, it can bind to proteins in β-sheet conformation and prevent aggregation[149,150]. In animal models, it can reduce tau and Aβ pathology and ameliorate cognitive deficits[149,150].

In two phase II trials[151,152] in patients with AD, curcumin had no effect on cognition or CSF biomarkers[149], and a third study in patients with MCI was terminated[153]. A larger phase II study, in which patients with MCI will receive one of three doses of curcumin for 18 months, is ongoing[154], and an additional trial of a combined course of curcumin and exercise is currently recruiting[155]. In both trials, patients will be assessed for biomarkers of AD, and for changes on PET and MRI scans.

Microtubule stabilizers

Epithilone D belongs to a class of molecules that were originally identified as antifungal agents, but were later discovered to also stabilize microtubules[156]. In preclinical testing, epithilone D increased microtubule numbers and reduced the number of axons with abnormal morphology in young[157] and aged[158] tau transgenic mice. In other mouse models of tauopathy, the drug improved cognition, and reduced tau pathology and tau-related

changes in microtubule dynamics[159]. A phase I clinical trial[160] was initiated to assess the safety, efficacy and pharmacodynamics of epithilone D in patients with AD. However, this trial was discontinued, presumably due to adverse effects.

Davunetide, also known as NAP, is an eight-amino-acid fragment of activity-dependent neuroprotective peptide. Both the full-length peptide and NAP have been shown to improve cognitive performance in wild-type animals and to protect against damage in a mouse model of TBI. In transgenic AD models, NAP reduced tau and amyloid pathology and improved cognition and axonal transport[161]. In a phase II trial, patients with MCI were treated with an ascending dose of NAP for 12 weeks. The drug was well tolerated, but no significant differences relative to placebo were seen at either dose, although a trend towards improvements in working memory and attention was observed. In the latest phase II/III study[162], patients with PSP were treated with NAP for 52 weeks, but no differences were found between placebo-treated and NAP-treated patients[163].

Two clinical trials of the microtubule-stabilizing compound TPI 287 (abeotaxane)[164,165] are ongoing. TPI 287 has been shown to cross the blood–brain barrier in a mouse model of cancer metastasis[166], and it has some efficacy in stabilization of tumours in the human brain[167,168]. This drug is currently being trialled in patients with mild to moderate AD, PSP or CBD. Patients received one of three doses of TPI 287 for 9 weeks with the option to continue treatment for a further 6 weeks[164,165]. The treatment is expected to be completed in December 2018. Outcome measures include CSF levels of TPI 287, tau and Aβ, cognitive testing and MRI.

Modulating protein degradation

Rolipram, a phosphodiesterase E4 (PDE4) inhibitor, was initially developed as an antidepressant[169], but early human trials were discontinued owing to a narrow therapeutic window and gastrointestinal adverse effects. However, the drug has been shown to improve cognition and reduce pathology in Aβ and tauopathy mice, and in rats treated with exogenous Aβ, suggesting its potential utility for treating AD[85]. The APP/PS1 mouse model of AD develops long-term potentiation (LTP) deficits, but rolipram-treated APP/PS1 mice showed comparable LTP induction to wild-type animals[85]. In addition, increased phosphorylation of PKA — a mediator of proteasome function — and proteasome subunits was seen after rolipram treatment, indicating enhancement of the proteasome system[170].

To apply these results in the clinical setting, BPN14770, a related PDE4 inhibitor with fewer adverse effects, was developed. To assess the safety of this agent, two phase I trials using three different doses were carried out in healthy individuals[171,172]. At the low and mid-range doses, improvements in two measures of working memory were reported. Although the tests were conducted in a small number of healthy individuals, the results were promising enough to plan phase II testing in patients with AD (trial not yet registered).

Tau immunotherapies

To date, Aβ immunotherapies have been largely unsuccessful, possibly because they were only administered once the symptoms of AD had become apparent[173–178]. Although there is

still some hope that patients at earlier stages of AD might benefit from this approach, tau immunotherapies could be the most prudent course of action once the symptomatic phase is underway.

Some data indicate that Aβ immunotherapy has noteworthy but modest effects on tau pathology. In the first active immunization trial, the AN-1792 vaccine seemed to show some ability to clear Aβ plaque-associated tau lesions through plaque removal[179–181], and in phase II trials, the anti-Aβ antibody bapineuzumab reduced CSF phospho-tau levels in patients with AD[182,183]. Unfortunately, these results did not extend to phase III trials, in which bapineuzumab had no effect on tau pathology[184]. Likewise, solanezumab did not alter tau levels in treated individuals in any of the trials. These data indicate that any clearance of Aβ during active or passive immunization cannot reduce tau levels sufficiently to alter the course of disease, and direct targeting of tau is the next logical step.

The first reports of successful active and passive immunization against tau in a tauopathy mouse model, using a phospho-tau peptide comprising the pSer396/404 epitope or the PHF1 antibody against this epitope[185–188], came from our group. Immunization with these agents reduced pathological tau levels and attenuated the behavioural phenotypes associated with the tauopathy, demonstrating the feasibility of these related interventions. Subsequently, the efficacy of these approaches has been confirmed and extended by multiple groups, as detailed below.

Active tau immunization has been shown to reduce tau pathology by targeting single[185, 187, 189–193] or multiple[194] phospho-epitopes, the amino terminus[195], full-length normal and mutant tau[196, 197], or aggregated tau[198]. Reductions in pathological tau are achieved with few reported adverse effects, and the long-lasting immune response makes active immunization a promising option. However, elicitation of antibodies against a native protein always carries the risk of adverse immune reactions and detrimental targeting of the normal protein. In mice, tau vaccination has been reported to cause toxicity when administered in conjunction with strong T-helper 1-inducing adjuvants[199,200], which are not approved for use in humans. Similar tau immunogens administered with a milder adjuvant or fewer immunizations do not produce such adverse reactions[194,196], emphasizing the need to use mild adjuvants with tau immunogens, as we have always advocated[185].

Passive immunization offers a potential solution to the safety concerns that arise from active strategies. Patients will not develop their own antibodies, and the effects of immunization are likely to be transient, which reduces the risk of immunological adverse effects. Passive immunization also offers greater specificity for the epitope that is being targeted. Because the epitope profile changes over the course of the disease, once diagnostics advance sufficiently, treatments could be tailored to the individual according to the disease stage. As mentioned above, the pSer396/404 region was the first to be studied and has since been targeted by several groups[186, 188,201–208]. In addition, monoclonal antibodies against the amino-terminal or repeat domain (306–320) region[209–215], oligomeric tau[216,217], misfolded tau[201,218,219], pSer202[220,221], pThr231[208] pSer409[222], pSer413[223] and pSer422[224] have proved to be efficacious in tauopathy models. Moreover, antibody fragments have been shown to reduce tau levels in vivo[225,226].

The fact that NFTs are intracellular could potentially limit the utility of anti-tau antibodies as therapeutic agents. However, several groups have reported that antibodies, including anti-tau antibodies, can enter neurons, and that extracellular tau might be important for the spread of tau pathology[227–229]. Our group and others have shown that anti-tau antibodies can cross into the brain and enter neurons, where they primarily colocalize with endosomal and lysosomal markers[185,202–204,206,219,224,230]. The entry of these antibodies into neurons is mainly receptor-mediated but can also occur via bulk endocytosis to some extent. Fc receptors are expressed on neurons[231,232] and seem to be the main route of entry for anti-tau antibodies: blockade of low-affinity Fcγ II/III receptors largely prevents antibody uptake[202,219]. Of note, binding of a tau–antibody complex to a cytosolic Fc receptor, E3 ubiquitin-protein ligase TRIM21, promotes proteosomal degradation of the complex, thereby inhibiting intracellular seeded tau aggregation[233].

Antibodies could also modify disease progression by blocking the spread of tau pathology. Researchers have known for decades that tau lesions begin in specific brain regions, before spreading to other areas[11,12]. Tau-expressing cells secrete normal and pathological tau[234], which can be taken up by other cells and induce seeding of tau pathology[54,64,228]. In animal models that express tau only in certain brain regions, or that are injected with exogenous tau, spreading of tau pathology to anatomically connected regions occurs over time[54,64,228]. This type of spreading mechanism is thought to govern disease propagation in all amyloid diseases and related proteinopathies[235]. Furthermore, tau is now known to be present in the interstitial space both in tauopathy animal models[234] and in the human brain[236]. This phenomenon can also be seen in cultured cells: even healthy cells can release tau into the culture medium, where it can be endocytosed[234,237]. Multiple groups have employed antibodies in cell and animal models to block this spreading by targeting extracellular tau[238]. Tau exocytosis provides a pool of pathologically relevant tau that can be targeted without requiring internalization. Indeed, several reports are available of antibodies that are capable of reducing tau levels and preventing spreading without apparently entering neurons[216,218,239]. However, the most effective antibodies will probably be those that can also target tau inside the cell, where most of the pathological protein is located (Fig. 3 illustrates the potential intracellular and extracellular mechanisms).

The promising results in animal models have prompted many different groups to move tau vaccines and antibodies into clinical development. In the sections that follow, we will discuss the antibodies that had reached clinical trials at the time of writing (Table 2).

Active immunization

AADvac1.—The epitope for development of the tau vaccine AADvac1 was selected on the basis of in vitro experiments using a monoclonal antibody, DC8E8, which prevents tau oligomerization[240]. Epitope mapping revealed that DC8E8 binds a six-amino-acid sequence, HXPGGG, which is found in each of the microtubule-binding repeats of tau. Immunization of transgenic tauopathy rats with a vaccine based on this sequence (KLH-linked Tau294–305) elicited tau antibodies that bound to tau in the brain, reduced the levels of pathological tau and improved behaviour, compared with animals that received alum adjuvant only[197].

Adverse effects were limited to inflammation at the injection site, and the treatment did not produce any deleterious immunological responses.

On the basis of these results, human trials were initiated. In phase I testing, patients with mild to moderate AD were given three doses of AADvac1 in alum adjuvant over a 12-week period[241,242]. Almost all of the participants (29 of 30) developed an immunoglobulin G response, and no instances of encephalitis or oedema were reported. However, two patients withdrew owing to adverse reactions (seizure and viral infection), which might have been treatment-related, and an episode of microhaemorrhage was reported in one patient with a history of this condition. A follow-up trial to monitor these patients for additional 18 months and to provide booster vaccination is ongoing[243].

A larger phase II trial of AADvac1 in patients with mild AD is underway[244,245]. Patients in the treatment group will be given six doses of AADvac1 over 6 months, with two additional booster injections. Assessments for safety, changes in clinical symptoms and AD biomarkers in blood and CSF will be conducted.

ACI-35.—ACI-35 targets the pSer396/404 epitope of tau and is delivered in a liposome-based adjuvant. This vaccine was tested in Tau.P301L mice — a transgenic tauopathy model that develops progressive motor impairment[190]. Serum samples from Tau.P301L mice that were given two doses of ACI-35 contained antibodies that selectively bound pSer396/404 over the non-phosphorylated version of the epitope and could detect tau pathology when used in immunostaining experiments. The vaccinated animals showed a delay in the emergence of the motor phenotype, and also displayed a significant reduction in soluble tau phosphorylated at Ser396, but not at other amino acid residues. There was no evidence of an astrocyte response or significant differences in body weight in the vaccinated mice compared with vehicle-treated animals. Phase I testing is currently being carried out in patients with mild to moderate AD to assess the tolerability and immunogenicity of ACI-35[246].

Passive immunization

RG7345.—RG7345 is a humanized antibody that recognizes tau phosphorylated at Ser422, and was originally derived from a rabbit monoclonal antibody. In transgenic mice, RG7345 was shown to enter neurons and reduce tau pathology[224]. The antibody was administered to healthy young individuals in a phase I trial to assess safety[247]. However, the results of this trial have not been released and the drug has been discontinued by Roche, presumably because of an unfavourable pharmacokinetic profile, because no safety or efficacy concerns seem to have been raised during the trial.

BMS-986168.—The developers of BMS-986168 observed that neurons derived from stem cells of patients with familial AD secreted amino-terminal tau fragments, termed e-tau[215]. When added to the media of cultured neurons, these fragments induced hyperactivity and increased Aβ production, and these effects were blocked by the application of an antibody recognizing residues 9–18 of e-tau. The ability of the antibody to enter neurons was not assessed. In animals, administration of BMS-986168 significantly reduced the levels of tau in the interstitial space and soluble $A\beta_{1–40}$ in the brain.

Four clinical trials of BMS-986168 have been registered. A phase I trial in healthy individuals[248] and patients with PSP[249] has been completed. This trial used a single ascending dose methodology, and was designed to assess tolerability, with effects on CSF tau as a secondary outcome. A second phase I trial in patients with PSP, involving a multiple ascending dose paradigm, is underway at several centres in the USA[249], with follow-up studies planned for those who participated in the earlier trial[250]. A phase II trial aiming to study the clinical efficacy of BMS-986168 in 400 patients with PSP began recruiting in March 2017. In April 2017, BMS-986168 was licensed by Biogen, with plans to proceed with phase II testing[251].

C2N-8E12.—C2N-8E12 recognizes amino acids 25–30 of the tau protein and, similar to BMS-986168, it was intended to work extracellularly. In cell culture, C2N-8E12 prevented pathological tau seeding caused by exogenous tau aggregates[212]. Infusion of this antibody into the brain in a transgenic mouse model of tauopathy reduced the levels of aggregated and hyperphosphorylated tau, and also improved cognition[213]. Similar results were seen when a higher dose was delivered systemically[239]. No adverse immune reactions were seen; in fact, microglial activation was reduced in the treated animals[213,239].

Phase I testing of C2N-8E12 in patients with PSP did not show any major adverse effects or safety issues compared with placebo[252]. In 2016, two phase II trials were initiated, one in 330 patients with PSP[253] and the other in 400 patients with early stage AD[254]. The studies are expected to run until 2019 and 2020, respectively, with patients being assessed on multiple cognitive and behavioural measures. The trial descriptions do not indicate whether CSF analysis and/or brain imaging will be included. In view of its potential utility in PSP, the FDA has granted fast-track status to C2N-8E12.

RO 7105705.—The epitope of RO 7105705 has not been disclosed, but this antibody probably targets pSer409 on the tau protein[222]. Phase I safety assessments of RO 7105705 are being conducted in healthy individuals and patients with AD[255]. The participants will receive either a single dose or multiple doses of the antibody to assess tolerability, and the antibody concentration in serum will be measured to determine the pharmacokinetics. In addition, patients with AD will be assessed using the Clinical Dementia Rating scale. As an early-stage trial, the number of participants is insufficient for efficacy assessment. Early reports from the Alzheimer's Association International Conference in 2017 showed that the antibody was well tolerated in patients at doses up to 16.8 g, and the antibody was detectable in the CSF[256].

LY3303560.—Eli Lilly initiated two phase I trials to study the safety and pharmacokinetics of the anti-tau antibody LY3303560, one in healthy individuals and patients with AD[257], and the other in patients with MCI or AD[258]. LY3303560 possibly targets a conformational epitope, although this information has not been officially disclosed[259]. In the first trial, individuals will be given a single dose of LY3303560, and the concentrations of the antibody in serum and CSF will be monitored. In the second trial, patients with MCI or AD will receive multiple doses of LY3303560, and levels of the antibody in serum and CSF will be assessed, as will the uptake ratio of the Aβ-binding compound ^{18}F-florbetapir in the brain. These studies are expected to end in 2017 and 2020, respectively.

Future prospects

Newly initiated and forthcoming trials.—Recently, it was announced that two new antibodies were entering human testing. Janssen Pharmaceuticals has begun a phase I clinical trial of passive immunization with JNJ-63733657[260]. The trial is recruiting healthy individuals and patients with AD to assess the safety, tolerability and pharmacological profile of this anti-tau antibody. We are not aware of any preclinical data on this antibody, but it seems to bind to the middle region of tau and has been designed to prevent tau seeding and spreading[261]. Also advancing into human trials is UCB0107, a tau antibody developed by UCB Biopharma[262]. Preclinical testing showed that this antibody binds to amino acids 235–246 in the proline-rich region of tau, and that the antibody was effective in preventing seeding and spreading of pathological tau[261]. The trial is currently recruiting healthy individuals.

Several additional promising tau immunotherapies are set to enter clinical trials in the near future[227,238,263]. For example, Lundbeck is currently developing a broad portfolio of anti-tau antibodies, targeting both total tau and pathological hyperphosphorylated PHF-tau. The first of these antibodies, a humanized mouse monoclonal antibody that specifically targets pathological hyperphosphorylated tau, has entered clinical development for the treatment of AD (Jan T. Pedersen, H. Lundbeck A/S, personal communication). Developments in the field of tau immunotherapy are occurring at a rapid pace, and several additional trials are likely to start in the near future.

Additional considerations.—Various factors govern the efficacy of anti-tau antibodies, the most important of which are probably the epitope (normal or primarily pathological) and the site of action (extracellular and intracellular, or extracellular only). Although the pathological epitopes seen in AD are common to most if not all of the tauopathies, the pathogenesis of these conditions is likely to differ. Of note, CSF tau levels are increased in AD but not in the other tauopathies[57–60], suggesting that extracellular spread of tau pathology is not a prominent feature of non-AD tauopathies. In addition, mass spectroscopy studies indicate that CSF tau predominantly consists of tau fragments spanning amino acids 150–250 of the tau protein, with the amino and carboxyl termini presumably having been digested[264,265]. Therefore, anti-tau antibodies that primarily work extracellularly should probably target amino acids 150–250, and might only work in AD. The most efficacious antibodies are likely to be those that can target all pools of pathological tau protein, both intracellularly and extracellularly. Finally, it is unclear how closely tau seeding and spread are linked to tau toxicity. Hence, an antibody selected to prevent tau seeding and spread may not necessarily block tau toxicity.

Conclusions

In the search for disease-modifying therapies for AD and other tauopathies, multiple avenues have been and continue to be explored (Fig. 4, Table 1 and Table 2 show ongoing, completed and discontinued trials). Adding to the complexity is the fact that many of the compounds under investigation might exert effects through more than one pathway. On numerous occasions, preclinical success in animal models has failed to translate into benefits

in humans. For example, despite encouraging results in preclinical studies, the clinical data on methylene blue derivatives are not very promising. Furthermore, curcumin is limited by its bioavailability, and has yet to demonstrate efficacy in humans with tauopathy.

With many trials ongoing or awaiting analysis, the next few years will provide a clearer picture of which, if any, of the various tau-targeting approaches are the most viable. In initial tests in humans, MK-8719 was able to increase the levels of *O*-GlcNAcylated proteins, and the results of efficacy studies are eagerly awaited. In the area of immunotherapy, we expect to see the results of multiple active and passive immunization trials in the near future. In general, both strategies have been well tolerated and have not produced the types of adverse effects that led to trial termination or dosing adjustments in some of the Aβ immunotherapy trials. In addition, multiple groups have tau antibodies in development, but not yet in clinical trials. Antibody engineering and combined targeting of tau and Aβ might also improve treatment efficacy in the future.

A shift in the timing of intervention to the MCI stage or the very early stages of AD has been a feature of many recent trials, and as diagnostic methods continue to improve, treatment before symptom onset might be feasible. To some extent, this strategy is already possible, as has been shown in Aβ-targeting clinical trials involving carriers of mutations associated with familial AD, and in control individuals with PET evidence of Aβ accumulation. However, research to develop therapies that are effective once symptoms have progressed will always be needed. In addition, the continuation of basic research into the underlying causes of AD and the mechanisms of tau dysfunction is essential to identify new targets for intervention.

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Key points

- Therapies for Alzheimer disease in clinical trials are gradually shifting from amyloid-β (Aβ)-targeting to tau-targeting approaches.
- Early anti-tau therapies were based mainly on inhibition of kinases or tau aggregation, or on stabilization of microtubules, but most of these approaches have been discontinued because of toxicity and/or lack of efficacy.
- Most of the tau-targeting approaches that are currently in clinical trials are immunotherapies.
- Tau is likely to be a better target than Aβ once cognitive deficits manifest, because the tau burden correlates better with clinical impairments than does the Aβ burden.
- Eventually, with continued improvements in diagnostics, both Aβ and tau are likely to be targeted prophylactically for clearance.

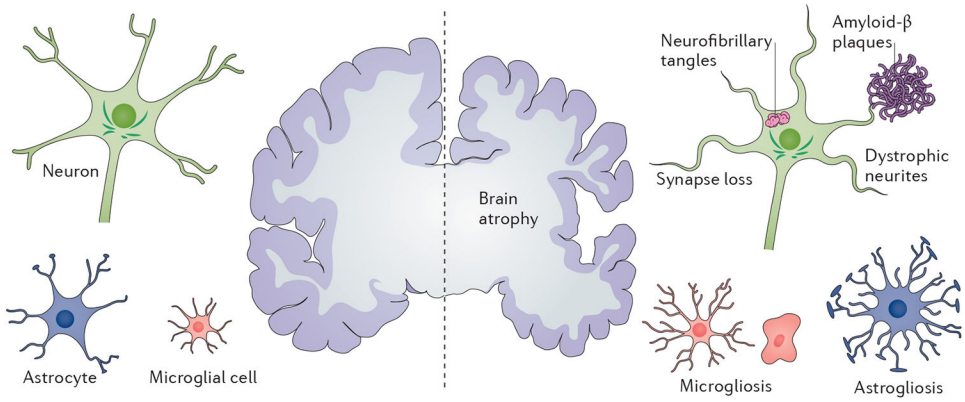

Figure 1 |. The defining pathological hallmarks of Alzheimer disease.

At the gross anatomical level, the disease is characterized by brain atrophy associated with loss of synapses and neurons. At the microscopic level, deposition of extracellular amyloid-β plaques and intraneuronal neurofibrillary tangles is observed, in association with dystrophic neurites and loss of synapses, as well as microgliosis and astrogliosis.

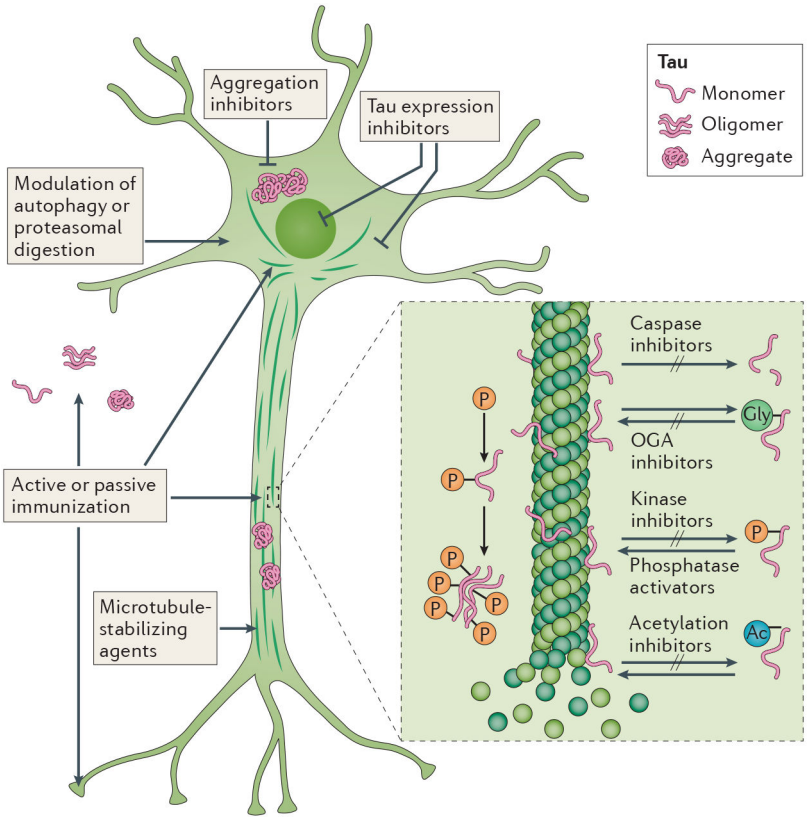

Figure 2 |. Tau-related therapeutic targets.

Drugs in preclinical or clinical development include active and passive immunotherapies; inhibitors of *O*-deglycosylation, aggregation, kinases, acetylation, caspases or tau expression; phosphatase activators; microtubule stabilizers; and modulators of autophagy or proteosomal degradation. Ac, acetyl group, Gly, glycosyl group; OGA, O-GlcNAcase; P, phosphate. Figure adapted with permission from ref. 266, Springer Nature.

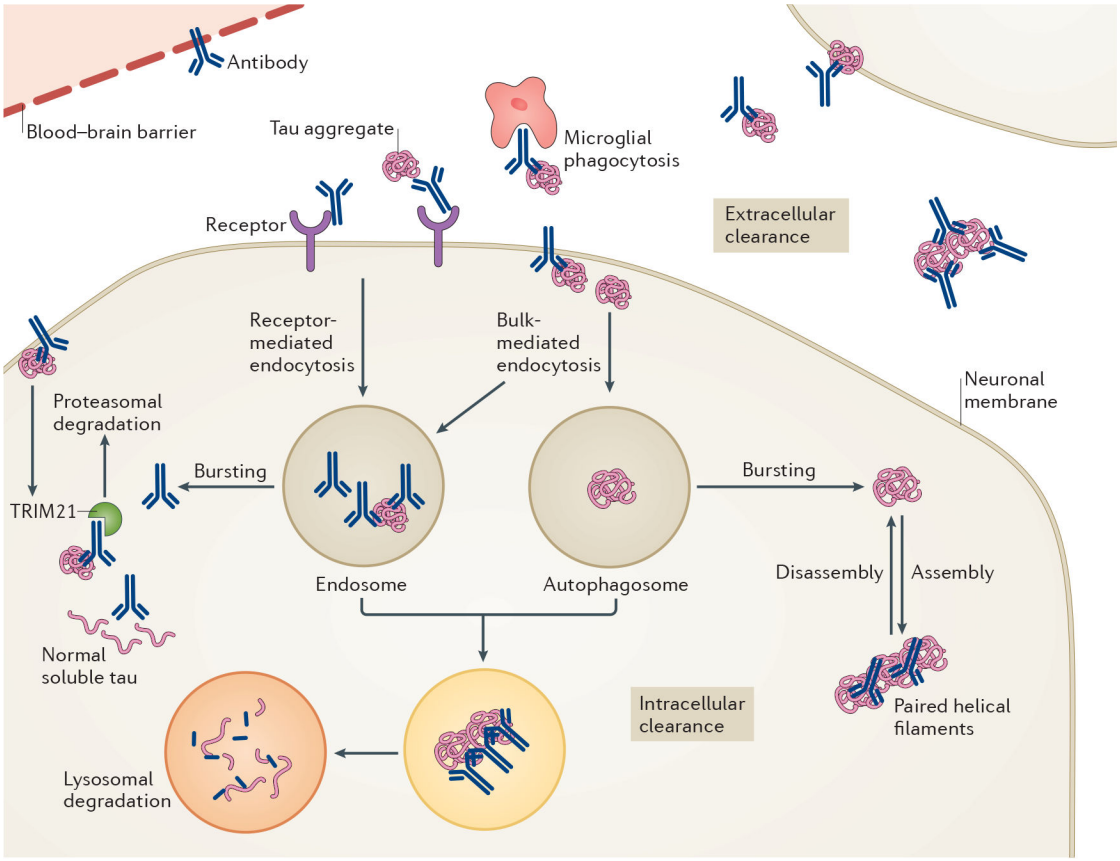

Figure 3 |. Proposed modes of action of anti-tau antibodies.

Antibodies can target tau both extracellularly and intracellularly. Pathological tau mostly resides within neurons but in certain individuals and/or tauopathies, it is also evident in other cell types, primarily glia (in particular, astrocytes and oligodendrocytes). A much smaller pool of tau aggregates is found extracellularly, in the form of small aggregates that are not easily detected or as remnants of neurofibrillary tangles following the death of the neuron. Some anti-tau antibodies are not readily taken up into neurons, presumably because of their unfavourable charge and, therefore, they work principally in the extracellular compartment. Within this compartment, antibodies might sequester tau aggregates, interfere with their assembly and promote microglial phagocytosis, with the overall effect of blocking the spread of tau pathology between neurons. Other antibodies are easily detected within neurons, in association with tau, and have been shown to work both intracellularly and extracellularly. Within the cells, these antibodies could bind to tau aggregates within the endosomal–lysosomal system and promote their disassembly, leading to enhanced access of lysosomal enzymes to degrade the aggregates; sequester tau assemblies in the cytosol and prevent their release from the neuron; or promote proteosomal degradation via E3 ubiquitin–protein ligase TRIM21 binding. The most efficacious antibodies are likely to target more than one pathway and/or pool of tau.

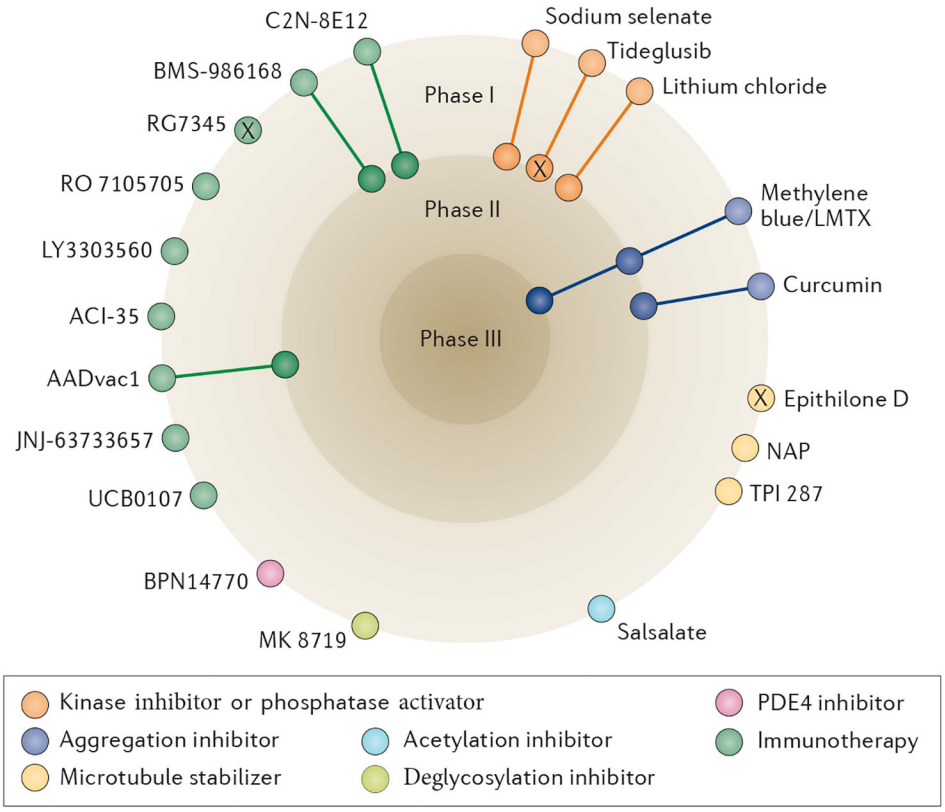

Figure 4 |. Current status of clinical trials of drugs that target tau pathology.

At the time of writing, the most active field is tau immunotherapy, with two active vaccines (AADvac1 and ACI-35) and six antibodies (LY3303560, RO 7105705, BMS-986168, C2N-8E12, JNJ-63733657 and UCB0107) in clinical trials, although most of these therapies are still in the early stages of development. Several of the other compounds in trials have complex or incompletely defined mechanisms of action; in this diagram, these compounds are categorized according to their presumed tau-related mode of action. ‘X’ indicates trials that, to our knowledge, have been halted or terminated, as detailed in the main text, although their current status is difficult to determine. PDE4, phosphodiesterase E4.

Table 1 |

Clinical trials of tau-targeting small molecule therapies for Alzheimer disease and other tauopathies

Drug	Clinical trial identifier	Dates	Trial description	Trial status
PP2A activators				
Memantine	NCT00097916	2004–2006	Phase III randomized, double-blind, placebo-controlled, interventional study in moderate to severe AD (n = 34)	Completed
	NCT00187525	2004–2006	Phase IV non-randomized, open-label, interventional study in frontotemporal lobar degeneration	Completed
	NCT00120874	2005–2011	Phase IV randomized, single-blind, parallel assignment, interventional study in AD	Completed
	NCT00235716	2005–2012	Phase III randomized, quadruple-blind, placebo-controlled, interventional study in AD (n = 613)	Completed
	NCT00255086	2005–2009	Phase III randomized, quadruple-blind, placebo-controlled interventional study in AD (n = 17)	Completed
	NCT00322153	2006–2008	Phase III randomized, double-blind, placebo-controlled interventional study in moderate to severe AD (n = 677)	Completed
	NCT00334906	2006–2008	Phase IV non-randomized, open-label interventional study in moderate AD (n = 75)	Completed
	NCT00401167	2006–2010	Phase IV non-randomized, open-label, interventional study in severe AD (n = 32)	Completed
	NCT00469456	2007–2009	Phase IV randomized, double-blind, placebo-controlled interventional study in AD (n = 265)	Completed
	NCT00476008	2007–2012	Phase IV randomized, double-blind, parallel-assessment interventional study in mild AD (n = 60)	Completed
	NCT00505167	2007–2008	Phase IV randomized, single-blind, memantine versus donepezil in mild to moderate AD (n = 64)	Completed
	NCT00545974	2007–2012	Phase IV randomized, double-blind, placebo-controlled interventional study in FTD (n = 81)	Completed
	NCT00594737	2008–2012	Phase III open-label interventional pilot study in FTD (n = 17)	Completed
	NCT00857233	2009–2012	Phase III open-label extension study on efficacy and safety in moderate to severe AD (n = 297)	Terminated
	NCT00857649	2009–2013	Phase III randomized, double-blind, parallel-assignment interventional study in moderate to severe AD (n = 369)	Terminated
	NCT00862940	2009–2012	Phase IV randomized, double-blind, parallel assessment intervention study in AD (n = 277)	Completed
	NCT00933608	2009–2014	Phase IV randomized, parallel-assessment intervention study in patients at risk of AD (n = 17)	Completed
	NCT01409694	2011–2016	Phase III randomized, parallel, quadruple masking intervention study in moderate AD (n = 90)	Completed
	NCT02553928	2015–2016	Phase IV randomized, double-blind interventional study in AD (n = 62)	Completed
	NCT02854917	2016–2018	Case–control retrospective study (n = 20)	Completed
	NCT03168997	2017–2018	Phase IV open-label, parallel-group interventional study (n = 222)	Not yet recruiting
Sodium selenate	ACTRN12611001200976	2011–2012	Phase IIa randomized, double-blind, placebo-controlled safety and efficacy study in mild to moderate AD (n = 20)	Completed

Drug	Clinical trial identifier	Dates	Trial description	Trial status
	ACTRN12613000170729	2012–2013	Open-label extension study (n = 20)	Completed
GSK3β inhibitors				
Tideglusib	NCT00948259	2008–2009	Phase I randomized, double-blind, placebo-controlled, dose escalation study in mild to moderate AD (n = 30)	Completed
	NCT01049399	2009–2011	Phase II randomized, double-blind, parallel assessment intervention study in mild to moderate PSP (n = 146)	Completed
	2010-023322-21	2013–2015	Phase II randomized, double-blind, placebo-controlled, four- arm efficacy study in mild to moderate AD (n = 306)	Completed
Lithium chloride	NCT00088387	2004–2005	Phase II assessment of the effects of lithium and divalproex on cerebrospinal fluid tau in AD (n = 35)	Completed
	NCT00703677	2008–2010	Phase I/II non-randomized, single-group efficacy study in PSP and CBD (n = 17)	Completed
	NCT02601859	2016	Open-label, single-group efficacy study in MCI (n = 20)	Not yet recruiting
	NCT02862210	2016–2020	Phase II randomized, double-blind, placebo-controlled low dose efficacy study in FTDP (n = 60)	Not yet recruiting
Acetylation inhibitors				
Salsalate	NCT02422485	2015–2017	Phase I open-label pilot in PSP (n = 10)	Active, not Recruiting
OGA inhibitors				
MK-8719	Not registered	2016	Phase I single ascending dose safety and tolerability study in healthy individuals (n = 16)	Completed
Aggregation inhibitors				
LMTX	NCT01626391	2012–2013	Phase II randomized, double-blind, placebo-controlled, safety and tolerability study in patients with mild to moderate AD already taking medication (n = 9)	Terminated
	NCT01689233	2012–2016	Phase III randomized, double-blind, placebo-controlled, parallel-group, single-dose efficacy study in mild AD (n = 800)	Completed
	NCT01689246	2013–2015	Phase III randomized, double-blind, placebo-controlled, parallel-group, single-dose efficacy study in mild to moderate AD (n = 891)	Completed
	NCT02245568	2014–2018	Phase III open-label extension study for patients in previous trials (n = 1,000)	Terminated
Curcumin	NCT00099710	2003–2007	Phase II randomized, double-blind, placebo-controlled, parallel-assessment safety and tolerability study in mild to moderate AD (n = 33)	Completed
	NCT00164749	2004–2006	Phase II randomized, double-blind, parallel-assessment pilot study in AD (n = 36)	Completed
	NCT00595582	2005–2008	Single-group, open-label, dietary supplement in MCI (n = 10)	Terminated
	NCT01383161	2012–2017	Phase II randomized, double-blind, placebo-controlled, parallel-assessment efficacy study in MCI (n = 132)	Active not recruiting
	NCT01811381	2014–2018	Phase II randomized, double-blind, placebo-controlled, factorial-assignment prevention study in MCI (n = 80)	Recruiting
Microtubule stabilizers				

Drug	Clinical trial identifier	Dates	Trial description	Trial status
Epithilone D	NCT01492374	2012–2013	Phase I randomized, double-blind, placebo-controlled trial in mild AD (n = 40)	Completed
NAP	NCT00422981	2007–2008	Phase II randomized, double-blind, placebo-controlled, parallel-assignment efficacy study in MCI (n = 144)	Completed
	NCT01110720	2010–2012	Phase II/III randomized, double-blind, placebo-controlled interventional study in PSP (n = 313)	Completed
	NCT01056965	2010–2017	Phase II randomized, double-blind, placebo-controlled, interventional study in FTDP, PSP, CBD and Niemann–Pick type A (n = 12)	Active, not recruiting
TPI 287	NCT01966666	2013–2017	Phase I randomized, double-blind, placebo-controlled, sequential-cohort dose-ranging study in mild AD (n = 33)	Active, not recruiting
	NCT02133846	2014–2017	Phase I randomized, double-blind, placebo-controlled, sequential-cohort dose-ranging study in CBD and PSP (n = 44)	Active, not recruiting
PDE4 inhibitors				
BPN14770	NCT02648672	2015–2016	Phase I randomized, double-blind, placebo-controlled, single ascending dose study in healthy individuals (n = 32)	Completed
	NCT02840279	2016	Phase I randomized, double-blind, placebo-controlled, multiple ascending dose study in healthy elderly individuals (n = 77)	Completed

AD, Alzheimer disease; CBD, corticobasal degeneration; FTD, frontotemporal dementia; FTDP, frontotemporal dementia and parkinsonism; MCI, mild cognitive impairment; PSP, progressive supranuclear palsy; GSK3β, glycogen synthase kinase 3β; OGA, O-GlcNAcase; PDE4, phosphodiesterase E4; PP2A, protein phosphatase 2A.

Table 2 |

Clinical trials of tau-targeting immunotherapies for Alzheimer disease

Agent	Clinical trial identifier	Dates	Trial description	Trial status
Active immunotherapy				
AADvac1	NCT01850238	2013–2015	Phase I randomized, double-blind, placebo-controlled safety and tolerability study in mild to moderate AD (*n* =30)	Completed
	NCT02031198	2014–2016	Phase I unmasked 18-month follow-up for patients in previous study (*n* = 25)	Completed
	NCT02579252	2016–2019	Phase II randomized, double-blind, placebo-controlled, safety and efficacy study in mild AD (*n* = 185)	Recruiting
ACI-35	ISRCTN13033912	Started 2013	Phase I randomized, double-blind, placebo-controlled safety, tolerability and immunogenicity study in mild to moderate AD (*n* = 24)	Completed
Passive immunotherapy				
RG7345	NCT02281786	2015	Phase I randomized, double-blind single ascending dose safety study in healthy individuals (*n* = 48)	Completed
BMS-986168	NCT02294851	2014–2016	Phase I randomized double-blind, placebo-controlled safety and tolerability study in healthy individuals (*n* = 65)	Completed
	NCT02460094	2015–2017	Phase I randomized, double-blind, placebo-controlled, multiple ascending dose study in PSP (*n* =48)	Completed
	NCT02658916	2016–2019	Phase I extension study for participants in previous trial (*n* = 48)	Enrolling by invitation
	NCT03068468	2017–2020	Phase II randomized, double-blind, placebo-controlled, parallel-group efficacy study in PSP (*n* =396)	Active, not enrolling
C2N-8E12	NCT02494024	2015–2016	Phase I randomized, double-blind, placebo-controlled, single ascending dose safety and tolerability study in PSP (*n* = 32)	Active, not recruiting
	NCT02985879	2016–2019	Phase II randomized, double-blind, placebo-controlled, multiple-dose safety and efficacy study in PSP (*n* = 330)	Recruiting
	NCT02880956	2016–2020	Phase II randomized, double-blind, placebo-controlled efficacy and safety study in early AD (*n* = 400)	Recruiting
RO 7105705	NCT02820896	2016–2017	Phase I randomized, double-blind, placebo-controlled, single or multiple ascending dose safety and efficacy study in healthy individuals and patients with mild to moderate AD (*n* = 74)	Completed
LY3303560	NCT02754830	2016–2017	Phase I randomized, double-blind, placebo-controlled, single-dose escalation study to assess safety in healthy individuals and patients with mild to moderate AD (*n* = 90)	Active, not recruiting
	NCT03019536	2017–2020	Phase I randomized, parallel-assignment, multiple-dose escalation safety and efficacy study in mild cognitive impairment and mild to moderate AD (*n* = 132)	Recruiting
JNJ-63733657	NCT03375697	Started 2017	Phase I randomized safety and tolerability trial in healthy individuals and patients with prodromal or mild AD (*n* = 64)	Recruiting
UCB0107	NCT03464227	Started 2018	Phase I randomized safety and tolerability trial in healthy individuals (*n* = 52)	Recruiting

AD, Alzheimer disease; PSP, progressive supranuclear palsy.