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Tau-targeting therapies for Alzheimer disease: current status and future directions

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Abstract

Alzheimer disease (AD) is the most common cause of dementia in older individuals. AD is characterized pathologically by amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the brain, with associated loss of synapses and neurons, which eventually results in dementia. Many of the early attempts to develop treatments for AD focused on Aβ, but a lack of efficacy of these treatments in terms of slowing disease progression led to a change of strategy toward targeting of tau pathology. Given that tau shows a stronger correlation with symptom severity than does Aβ, targeting of tau is more likely to be efficacious once cognitive decline begins. Anti-tau therapies initially focused on post-translational modifications, inhibition of tau aggregation and stabilization of microtubules. However, trials of many potential drugs were discontinued because of toxicity and/or lack of efficacy. Currently, the majority of tau-targeting agents in clinical trials are immunotherapies. In this Review, we provide an update on the results from the initial immunotherapy trials and an overview of new therapeutic candidates that are in clinical development, as well as considering future directions for tau-targeting therapies.

Introduction

Since the publication of our previous review on tau-targeting therapies in 2018[1], the number of people in the USA with Alzheimer disease (AD) has increased from an estimated 5.4

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

E. M. S. in an inventor on various patents related to the topic of this review that are assigned to New York University. Some of the patents on tau immunotherapies are licensed to H. Lundbeck. The other authors declare no competing interests.

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million to 6.5 million, making it a major health issue[2]. Worldwide, around 57 million people are thought to have dementia, with AD probably contributing to 60–70% of these cases[3]. In addition to the direct impact on patients, AD and related illnesses cost hundreds of billions of dollars to care-givers and the health-care system[2]. As the population continues to age, the need for effective therapies will only increase.

Early efforts to find a disease-modifying therapies for AD focused on amyloid-β (Aβ), the main component of the extracellular plaques that accumulate in the brain in this condition. However, both immunotherapies and secretase modifiers have been largely ineffective or detrimental[4,5]. The main exceptions are lecanemab[6,7] and donanemab[8,9], both of which produced modest but significant slowing of cognitive decline in phase III trials. The limited success of Aβ-targeting therapies led to a change in focus towards the tau protein — the main component of the neurofibrillary tangles (NFTs) that comprise the other major pathological hallmark of AD. This decision was supported by the fact that tau pathology correlates better with the degree of dementia than does Aβ deposition[10–17].

The presence of tau pathology in many conditions other than AD, including the primary tauopathies progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick disease, frontotemporal dementia (FTD), and primary age-related tauopathy[18,19], makes it an appealing target for therapeutic development. The progression of tau lesions is thought to involve both loss and gain of function for the protein, offering multiple points for intervention. In this Review, we briefly discuss these aspects of tau pathology, highlighting data published since our previous Review[1]. We summarize the latest results from ongoing and completed clinical trials and provide information on trials that have recently been initiated. In addition, we discuss strategies for improving tau-targeting therapies, in particular immunotherapies, and future directions for the field.

Targetable aspects of tau pathology

Numerous aspects of tau pathology could be targeted in AD (Fig. 1). Phosphorylated tau (p-tau) pre-tangles and neuropil threads can be seen in brain tissue decades before the symptoms of AD manifest[20]. The pathology commonly begins in the entorhinal cortex and hippocampus and spreads in a stereotypical pattern; however, several atypical variants of AD exist, accounting for up to 45% of all cases[21,22]. Monomeric, oligomeric and aggregated tau species are observed in all tauopathies, although AD and the various primary tauopathies differ with regard to tau isoform composition and multimer morphology[18,19,23,24].

Post-translational modifications

The pathological tau in AD is characterized in part by extensive post-translational modifications (Fig. 1). Here, we focus on the modifications that have been the subject of clinical development, namely, hyperphosphorylation, acetylation, truncation and glycosylation.

Hyperphosphorylation.—The tau hyperphosphorylation that is seen in AD results from increased activity of tau kinases[25–30], combined with reduced activity of protein phosphatase 2A (PP2A)[31,32]. Tau kinases have been shown to be activated directly or indirectly by

Aβ, and Aβ can induce tau phosphorylation and aggregation in vivo[33–44]. The outcome is increased occupancy at multiple phosphorylation sites, the prevelance of phosphorylation at specific sites and overall extent of phosphorylation changes with disease stage[20,45–53]. Patterns of phosphorylation also differ between tauopathies, and familial mutations in the tau-encoding gene *MAPT* can promote phosphorylation[54–56]. The consequences of increased phosphorylation include mislocalization of tau to the somatogenic compartment, decreased microtubule binding and promotion of tau misfolding[57].

Acetylation.—Although not seen as consistently as hyperphosphorylation, enhanced tau acetylation in AD and other tauopathies can impair microtubule binding, decrease solubility, promote cleavage and impair degradation of the protein[58–60]. Salsalate and diflunisal reduce tau acetylation through inhibition of p300 acetyltransferase[61,62], and were initially identified owing to their association with decreased incidence of AD in patients[62–65].

Truncation.—The distribution of cleaved tau fragments is complex, with some species appearing in both AD and healthy individuals, some only in AD and other tauopathies others only in non-AD tauopathies[66]. Aβ can promote tau truncation through caspase activation but is not required for this process, as truncated tau is also found in non-AD tauopathies. Cleavage promotes tau assembly, reduces microtubule binding, promotes synaptic and organelle dysfunction, and acetylation of tubulin, and might promote tau secretion[66,67]. Two caspase inhibitors, minocycline and VX-765, have shown positive results in AD models[68–71], and minocycline has entered clinical trials in patients with AD (see below).

Glycosylation.—*O*-GlcNAcylation, a specialized protective type of *O*-glycosylation, promotes microtubule binding, prevents phosphorylation and reduces aggregation of tau, and is found to be reduced in AD[60,72]. By contrast, *N*-glycosylation and non-enzymatic glycosylation (glycation) are increased in AD and other tauopathies. These modifications promote tau phosphorylation and misfolding while impairing microtubule binding and protein digestion[60]. To date, *O*-GlcNAcylation is the only glycosylation mechanism to be targeted in clinical trials.

Tau aggregation

Tau multimers include small soluble aggregates, paired helical filaments (PHFs), straight filaments and twisted ribbons. Post-translational modifications and mutations influence the structure of these aggregates, which can be faithfully transmitted during seeding[60,73–79].

Oligomeric tau has emerged as the primary pathogenic species, resulting in acute toxicity[80–83] as well as impairments in nuclear stability and gene transcription, mitochondrial health, neurotransmission, synaptic function and protein degradation[80,81,83–86]. Extracellular oligomers can initiate templated seeding of tau following uptake into naive cells[80–84]. Larger NFT aggregates might initially represent a compensatory protective mechanism, but in the longer term, NFT-bearing neurons exhibit changes in gene expression, as well as synapse loss, inhibition of axonal transport and energy deficits[87–90]. Multiple groups have developed small-molecule inhibitors with the goal of preventing or reversing tau aggregation and reducing the spread of pathology[91–93].

Cytoskeletal dysfunction

Compared with control neurons, NFT-bearing neurons from patients with AD show reduced tubulin expression, microtubule length and overall tubule numbers, as well as increased acetylation of tubulin[90,94,95]. Tubulin from patients with AD is slower to assemble and has increased GTPase activity compared with that from healthy controls[96]. In AD, the dynamic removal and restoration of the external tyrosine residues of tubulin are impaired leading, to a build-up of detyrosinated tubulin[97,98]. Together, these data point towards disruption of the microtubule network, resulting from the loss of tau binding and other pathological processes, as a potential target for therapeutic intervention.

Protein degradation pathway impairment

Defects in macroautophagy (autophagy), endosomal microautophagy and chaperone-mediated autophagy have been observed in AD and other tauopathies[99–101]. Reduced expression of autophagy and endosomal microautophagy components, reduced chaperone-mediated autophagy activity, impaired lysosomal fusion, decreased lysosomal activity, increased concentrations of ubiquitinated protein and disruption of key signalling pathways are all observed in AD[58,99–107].

Once established, tau pathology can also affect its own clearance. Tau can inhibit autophagy induction and autophagosome formation, impair autophagosome–lysosome fusion, and sequester pathway components[108–113]., and can also prevent endosomal uptake of proteins and increase endosomal leakage[114–119]. These effects underscore the importance of removing tau aggregates from neurons.

Targeting tau pathology

Since our previous Review on tau-targeting therapies[1], several trials have concluded or been initiated. In this section, we discuss strategies that target various aspects of tau pathology [Fig. 1], and in the next section, we focus specifically on immunotherapies, in particular, antibody-based therapies, which have been the subject of most of the clinical trials to date Fig. 2. Our group has worked extensively in the tau immunotherapy field from its infancy so we are ideally placed to provide an expert opinion on this topic. Figure 2 provides a breakdown of the different treatment strategies, and how far each has advanced in clinical testing. Supplementary Tables 1 and 2 list the non-immunotherapy and immunotherapy trials, respectively, and Table 1 lists the potential advantages and disadvantages of each treatment type.

Reducing tau expression

Tau antisense oligonucleotides (ASOs) target human *MAPT* mRNA to reduce the expression of tau[120]. In 2017, a phase Ib trial (NCT03186989) was initiated to study the safety, tolerability, pharmacokinetics and pharmacodynamics of the tau ASO $MAPT_{Rx}$ (also known as BIIB080) in patients with mild AD. At a 2021 press conference, the drug was reported to be safe and to reduce total tau (t-tau) and p-tau levels in the cerebrospinal fluid (CSF) in a dose-dependent manner[121]. Additional data from phase I testing, presented in 2023, showed dose-dependent decreases in t-tau and p-tau in the CSF[122]. PET scans from

participants who received a high dose of the drug showed a decrease in tau levels to below baseline values in all brain regions analysed[122]. Adverse events were predominately mild to moderate. In addition, reductions in tau phosphorylated at residue 181 (p-tau181), the inflammatory marker YKL40 and the ratio of t-tau to $A\beta_{42}$ in the CSF were reported[123]. Despite the decrease in CSF measures, however, no significant improvements in cognitive, functional, psychiatric or neurological impairments were observed[123]. Phase II testing has been initiated in patients with mild cognitive impairment (MCI) due to AD or with mild AD (NCT05399888), with cognitive changes as the primary outcome, and will run through to December 2026.

NIO752 is another tau ASO that is currently in two trials to examine safety, tolerability, and pharmacokinetics in people with PSP (NCT04539041), MCI or early AD (NCT05469360). The results are anticipated in 2023 and 2024, respectively.

Targeting tau protein modifications

Phosphatase modifiers.—As we outlined in our previous Review, memantine has various mechanisms of action, including enhancement of PP2A activity[1,124]. No updates on clinical trials of memantine in AD or other tauopathies have been provided since our earlier article.

Sodium selenate has been shown to reduce tau phosphorylation in animal models[125–127], but in a clinical trial in people with mild-to-moderate AD, only modest benefits were detected on diffusion MRI[128]. A phase Ib open-label study (ACTRN12617001218381) in 12 individuals with behavioural variant FTD was completed in 2021[129]. Small declines in MRI, cognitive and behavioural measures were observed, with no changes in t-tau, p-tau or the neurodegeneration biomarker neurofilament light chain (NfL) in the CSF. Two phase IIb trials are examining the safety, tolerability and efficacy of sodium selenate in FTD (ANZCTR12620000236998) and PSP (ACTRN12620001254987)[130,131]. Outcome measures will include tau levels in CSF, serum and plasma; tau PET; MRI for brain atrophy and midbrain mean diffusivity; and cognitive and functional measures. These studies are expected to be completed in 2025.

Kinase inhibitors.—Lithium chloride is widely used to treat bipolar disorder and has also been shown to inhibit glycogen synthase kinase 3β (GSK3β) — an enzyme that phosphorylates tau[132,133]. In a pilot study in patients with MCI (NCT02601859), no adverse reactions to lithium chloride treatment were reported, although GSK3β activity was not significantly changed, suggesting that the dose was too low to be effective [134]. A phase II trial (NCT02862210) has been extended to 2023 to assess the effects of this drug on behavioural symptoms of FTD. Additional outcomes include changes in motor symptoms, adverse events and serum biomarkers. The results of this trial have yet to be reported.

Acetylation inhibitors.—Salsalate is a small-molecule non-steroidal anti-inflammatory drug that has been shown to inhibit tau acetylation [62]. In a transgenic mouse model of tauopathy, this drug reduced levels of t-tau and acetylated tau, prevented hippocampal atrophy and reduced memory deficits [61]. A phase I open-label study (NCT02422485) evaluated safety, tolerability and CSF biomarkers in patients with PSP who were

treated with salsalate[135]. The drug was well tolerated but failed to elicit any significant improvements. A second phase I trial in patients with AD (NCT03277573) is assessing adverse effects, changes in CSF biomarkers, and imaging and cognitive measures. Although the estimated completion date was December 2021, the results have yet to be reported.

Deglycosylation inhibitors.—*O*-GlcNAcylation of tau produces protective effects in tauopathies by preventing tau phosphorylation and aggregation[136,137]. ASN120290 is an *O*-GlcNAcase (OGA) inhibitor that was determined to be safe and well-tolerated in a phase I trial conducted in healthy adults[138,139]. Drug concentrations were comparable in the CSF and plasma, indicating that the compound readily enters the brain. In 2018, ASN120290 was given an orphan drug designation for the treatment of PSP. ASN-51 is a second-generation, longer-lasting version of ASN120290 that was assessed in a phase I trial (NCT04759365) aimed at evaluating its safety, tolerability, pharmacokinetics and pharmacodynamics in healthy individuals. The trial was terminated in August 2022 citing various logistic reasons, and the findings from enrolled patients have yet to be reported.

Through the use of PET radioligands, the OGA inhibitor LY3372689 was shown to efficiently penetrate the brain after a single dose in rats, and this research is now being extended to healthy volunteers with LY3372689 showing brain penetration and occupancy[140,141]. Additional studies of both single (NCT03819270) and multiple (NCT04106206) ascending doses in healthy volunteers have shown that LY3372689 is safe[142–144]. An ongoing phase II trial, which includes cognitive assessments and imaging, is determining the efficacy, safety and tolerability of this drug in patients with early AD (NCT05063539) will be completed in 2024.

Another OGA inhibitor, MK-8719 was discussed our previous Review[1], but no further updates are available on this drug at present.

Caspase inhibitors.—A multicentre phase II study of two different doses of the caspase inhibitor minocycline (ISRCTN16105064) was conducted in patients over 50 years of age with mild AD[145]. The treatment failed to slow cognitive decline, and the higher dose was associated with increased adverse effects; and treatment was discontinued.

Tau aggregation inhibitors

Curcumin reduces tauopathy in animal models and prevents tau aggregation in vitro[146–148]. A phase II clinical trial (NCT01383161) examined the effects of curcumin treatment in patients with MCI and healthy adults[149]. Improvements in long-term memory, visual memory and attention were noted in the individuals who received the drug. Furthermore, significant associations were observed between improved cognition and decreases in PET ligand binding to pathological tau and Aβ. A second phase II study (NCT01811381) is examining the effects of curcumin, alone or with yoga, in people with MCI or subjective cognitive impairment. The endpoints include blood-based biomarkers, changes on PET imaging and adverse events. The study was scheduled to be completed in 2020 but the results have yet to be released.

LMTX (also known as TRx0237) is a derivative of methylene blue that crosses the blood–brain barrier (BBB), and In animal models, reduced tau aggregation and improved cognition[150,151]. Several phase III trials of this drug have been initiated in people with mild-to-moderate AD, along with an open-label extension study for individuals who completed the earlier trials[152–155]. Although none of the trials produced positive results, a revised report was released that purported to show efficacy[153,155,156]. However, this report used statistical analysis based on a small subset of the total sample that lacked proper control groups[154,155]. The open-label extension study (NCT02245568) was terminated early.

A phase III trial of LMTX in patients with AD (NCT03446001) was completed in April 2023 and will be followed by a 1-year open-label extension study. The primary outcomes are adverse events and changes in cognition and daily functioning. Additional outcomes include brain atrophy and findings on ^{18}F-fluorodeoxyglucose-PET scans. The results have yet to be reported.

Tau Morphomer (also known as ACI3024) is a small-molecule inhibitor that selectively targets tau aggregates. A phase I trial (ISRCTN18150742) to examine safety and tolerability in healthy adults was completed in 2020. The drug was found to enter the brain and its levels in the CSF increased in a dose-dependent manner[157]. No further data or future clinical trial plans have been reported.

Microtubule stabilizers

TPI-287 (also known as abeotaxane) is a microtubule stabilizer that has been shown to be safe and effective in cancer trials[158]. Two phase I trials, one in people with in AD (NCT01966666) and the other in people with CBD or PSP (NCT02133846), were combined to examine the safety, tolerability, pharmacokinetics and pharmacodynamics of the drug[159]. The AD group had a lower maximum tolerated dose than the CBD and PSP groups. In the AD group, the treatment was associated with reduced cognitive decline compared with placebo, however the authors attributed this to the greater than expected cognitive decline in the placebo group. Although the patients with CBD or PSP patients tolerated a higher dose, the treated individuals showed increased falls and worsening dementia symptoms. Brain penetrance of TPI-287 could not be confirmed as it was not detected in the CSF 1 week after the final infusion. No trials of this drug are currently in progress.

NAP (also known as davunetide) is a neuroprotective peptide that has been shown to reduce tau and Aβ burden and improve cognition in animals[160]. A phase II trial (NCT01056965), examining its safety, tolerability, cognition, imaging and CSF biomarkers in various tauopathies, including PSP, FTD, CBD and non-fluent aphasia, was reported to be completed in 2012, but the results have yet to be released.

Tau immunotherapies

The first successful reports of vaccine and antibody therapies targeting tau were made by our group[161–164]. Subsequently, numerous papers have reported effective targeting of multiple tau epitopes, including the amino-terminus, the mid-domain, the microtubule-binding

region, misfolded tau, p-tau202, p-tau231, p-tau396/404, p-tau409, p-tau413, p-tau422 and oligomeric tau species[57,165–172].

Immunotherapy can be active or passive and can function through extracellular or intracellular mechanisms (Fig. 3). Active immunotherapy delivers a tau immunogen as a vaccine, and the advantages of this approach are its low cost, promotion of a polyclonal antibody response and lasting efficacy. However, because tau is an endogenous protein, the potential exists for adverse and potentially irreversible autoimmune responses. Detrimental effects were seen in early mouse studies that used full-length recombinant tau with strong adjuvants that would never be approved for human use[173,174]. Multiple immunizations with the p-tau396/404 immunogen in alum adjuvant led to increased mortality in 3×Tg but not JNPL3 mice[162,175]. With fewer immunizations, 3×Tg mice showed a strong sustained antibody response with clearance of Aβ and tau and the animals remained healthy. No safety issues have been reported in other preclinical studies or ongoing clinical trials of active tau immunization.

The main advantage of passive immunotherapy is flexibility. Premade antibodies can target specific epitopes, which could allow treatment to be tailored to the disease stage. The antibodies can also be optimized, for example, by changing the IgG subclass or through modifications to improve uptake and/or alter tau binding. Passive immunotherapy is also relatively reversible as any adverse effects should subside following antibody clearance, with minimal to no T cell activation. Disadvantages include the high cost and the need for chronic administration, which increases the likelihood of an anti-idiotypic response and associated adverse effects. Monoclonal targeting might also be less effective than the active polyclonal response. Antibodies could prevent or clear tau pathology through several mechanisms, as reviewed extensively elsewhere[167]. In brief, antibodies can work extracellularly to sequester pathological tau or promote its clearance via the periphery or by microglia. Intracellularly, tau antibodies could promote disaggregation of tau polymers and their degradation through cellular clearance pathways.

In preclinical testing, pretreatment of pathological tau with antibodies or addition of an antibody and tau to cultures simultaneously dampened seeding of pathological tau[176–186], possibly through the formation of tau–antibody complexes that prevented uptake of the tau seeds by neighbouring neurons. These complexes could be phagocytosed by microglia or cleared from the interstitial space via the BBB and/or the circumventricular organs. Antibody treatment can increase serum tau levels, which might indicate removal from the brain via Fc receptors or, more likely, the increased half-life of antibody bound tau[187–189]. Microglia also phagocytose antibody–tau complexes, typically in an Fc-dependent manner, with clearance being impaired by effectorless antibodies or fragments or by blocking the Fc receptors[181,189–194].

Despite concerns about antibodies with effector functions promoting glial activation, either human IgG1 antibodies did not increase cytokine levels in cultured glia compared with tau alone, or the activation pattern was different from that induced by bacterial antigens[191,192]. However, glia might behave differently in culture than in situ, and differentiating the impact of antibody treatments from the effects of tau-induced cytokine production is difficult.

Furthermore, an effectorless tau antibody, gosuranemab, seemed to promote glial activation in humans, although the small number of patients prevents firm conclusions from being drawn[195]. Data from patients with tauopathy demonstrate the complexity of the glial response. Glial activation has been observed in early stages and is thought to be both a result and a mediator of pathology[196–198]. Activated glia are found in association with plaques and NFT-bearing cells, with some studies showing a stronger correlation of glial activation with tau pathology compared to Aβ[196,199–203]. In some studies, a progressive increase in glial activation was seen over time[199]. However, some reports suggest that increased baseline rates of glial tracer binding early in disease reflect a protective response, and other studies found distinct waves of glial activation in MCI and AD[201,204–207]. Ultimately, these data highlight the need for further research, ideally in vivo, into the role of glia in tauopathies.

Multiple groups have shown that antibodies can enter neurons and colocalize with pathological tau[162,182–184,208–216]. This uptake could occur through several different mechanisms (Fig. 3). Neurons express Fcγ receptors and tripartite motif containing 21 (TRIM21), a high-affinity cytosolic Fc receptor[162,208,212,217–226]. Antibodies or antibody-bound tau can bind to surface receptors, which facilitate uptake from the extracellular space in a clathrin-dependent manner and enable delivery to the endosomal–lysosomal system. Antibodies or antibody–tau complexes can also enter the cell via non-specific bulk endocytosis. Colocalization between antibodies and tau or other protein targets in this compartment has been shown in cell and animal models[182,183,208,209,211,213–215,227–230]. Multiple groups have demonstrated neuronal uptake of therapeutic antibodies against other intracellular targets, and of autoantibodies and circulating IgGs[228–242]. Once internalized, antibodies might exert protective effects in the endosome or the cytosol. By binding to endosomal tau, antibodies could prevent tau-induced endosomal membrane disruption and promote disassociation of aggregates, thereby facilitating lysosomal enzyme access for digestion. Antibodies might also enter the cytosol following disruption of the endosomal membrane or through translocation. Endosomal–lysosomal membrane integrity is compromised in the presence of pathological tau, Aβ, exosomes or reactive oxygen species, and any increased permeability might also allow antibodies to escape[114,117–119,243–248] Antigens and antigen–antibody complexes are transported from the endosome to the cytosol in dendritic cells[249–251], and a similar mechanism could exist in neurons.

Once in the cytosol, antibody-bound tau can be ubiquitinated for proteasomal degradation through its association with TRIM21[194,212]. Specifically, an antibody against p-tau422 has been shown to reduce the levels of insoluble tau in vivo, but its efficacy is lost in the absence of TRIM21, further highlighting the importance of antibody-mediated intracellular clearance of tau[194]. Both endosomal–lysosomal and proteasomal clearance can also be aided by antibody-mediated blockage or reversal of tau polymerization, as smaller aggregates or monomers are more easily cleared[227,252–254].

In the sections that follow, we discuss the clinical trials of tau immunotherapies that have been initiated or published since our previous Review[1].

Active immunotherapy

AADvac1.—AADvac1 is an active vaccine designed to target N-terminally truncated tau fragments[255,256]. It consists of a synthetic peptide encompassing amino acids 294–305 of the tau protein coupled to keyhole limpet hemocyanin with an aluminum hydroxide adjuvant. Four clinical studies of AADvac1 have been completed, three in patients with mild-to-moderate AD and the fourth in patients with non-fluent, agrammatic variant progressive aphasia (naPPA), the pathology of which resembles AD and FTD[257].

In a phase I trial (NCT01850238) found that AADvac1 was safe and well tolerated in patients with AD[256]. No deleterious immunological responses were elicited. All but one of 30 patients developed an IgG response with no encephalitis or vasogenic oedema. Five patients in the treatment group experienced serious adverse events, with two patients from this group withdrawing from the trial with complications thought to be unrelated to treatment. Cognitive scores remained stable in all patients. Overall, AADvac1 had excellent immunogenicity and a favourable safety profile.

A follow-up phase I study (NCT02031198, FUNDAMANT) revealed a similar safety profile[258]. Antibody titres declined after the six-dose vaccination regimen, but booster doses restored IgG levels. Higher IgG titres were significantly correlated with reduced hippocampal atrophy and cognitive decline. An association between cognitive benefit and IgG titre was observed in patients with positive AD biomarkers.

A phase II trial (NCT02579252, ADAMANT) was conducted in patients with mild AD[259–261]. AADvac1 was safe and well tolerated and induced a strong IgG response. The vaccine did not alter cognition or brain atrophy rates but was associated with a 58% attenuation of plasma NfL increase. In patients who provided CSF samples, levels of the p-tau217 epitope were significantly reduced, with trends for clearance of p-tau181 and t-tau, in the AADvac1 group. In a subgroup of patients who were predicted to have both Aβ and tau pathology, AADvac1 reduced clinical and functional decline and plasma NfL levels[260]. These results suggested that larger stratified studies are needed to evaluate the clinical efficacy of this vaccine.

A separate 24-month open-label phase I pilot trial (NCT03174886) was conducted in patients with naPPA. The primary objective was to assess the safety of AADvac1 with immunogenicity as a second objective. Exploratory outcomes included clinical, cognitive, and biomarker readouts. The results have not yet been disclosed.

ACI-35.—ACI-35 is a liposome-based vaccine that targets the p-tau396/404 epitope[262]. A phase Ib study (ISRCTN13033912) completed in 2017 found ACI-35 to be safe and well tolerated in patients with mild-to-moderate AD. However, the immune response was weak, even after booster shots[261]. A second-generation vaccine, ACI-35.030, was developed, which included a second adjuvant and an epitope to activate T helper cells. The redesigned vaccine has better immunogenicity, and the antibodies generated specifically bind to p-tau and recognize PHFs from the brains of individuals with AD[261].

A phase Ib/IIa trial (NCT04445831) to test the safety and immunogenicity of ACI-35.030 in early AD is ongoing. A separate arm was added to evaluate JACI-35.054, which uses the same p-tau396/404 peptide linked to a carrier protein. The primary outcomes are adverse events and plasma antibody titres, with cognition and behaviour as secondary outcomes. The interim results from the ACI-35.030 cohorts showed that all groups developed a potent antibody response that was specific for p-tau and PHFs[263–267]. The ACI-35.030-induced immune response was sustained when boosted periodically for up to 72 weeks, with no clinically relevant safety concerns[268]. JACI-35.054 also generated encouraging interim safety, tolerability and immunogenicity results in the low-dose cohort[266]. However, ACI-35.030 has been selected for further development, given that its antibody response was stonger relative to JACI-35.054[268].

Passive immunotherapy

APNmAb005.—APNmAb005 is an anti-tau IgG antibody (subclass not reported). According to a preclinical preprint, the mouse version of this antibody preferentially recognized synaptic oligomeric and insoluble tau in brain lysates from individuals with AD and pathological tau in brain tissue from people with 3R and 4R tauopathies[269]. The antibody prevented tau seeding in culture and partially rescued synaptic and neuronal loss and increased tau levels in brain lysate in a mouse model of tauopathy, indicating that the antibody prevented toxicity in vivo without promoting tau clearance.

In May 2022, a phase I study (NCT05344989) was initiated to evaluate the safety profile of a single dose of APNmAb005 in healthy participants. The trial is expected to be completed in July 2024.

Bepranemab.—Bepranemab (UCB0107) is an IgG4 antibody that binds to amino acids 235–250 of tau near the microtubule-binding region. The mouse version was found to block tau seeding in culture[270] and in two mouse models of tauopathy when pre-incubated with tau [271].

Three phase I trials evaluated the safety, tolerability and pharmacokinetics of bepranemab. The first trial (NCT03464227) in healthy individuals showed no drug-related safety issues or anti-drug antibodies, and a dose-dependent increase in UCB0107 levels was observed in serum and CSF[272,273]. A second phase I trial (NCT03605082), also in healthy individuals, had safety and pharmacokinetics as primary endpoints. The results have not been released. The third phase I trial (NCT04185415), in patients with PSP, raised no safety issues[274]. An open-label extension study (NCT04658199) was registered to evaluate the long-term safety and tolerability of UCB0107 in patients with PSP and is scheduled to run until 2025.

A phase II trial of bepranemab in patients with MCI or mild AD (NCT04867616) is ongoing and expected to run until 2025. The primary outcome is the cognitive score, and the secondary outcomes are adverse events, other cognitive measures, tau PET and pharmacokinetics.

BIIB076.—BIIB076 is an IgG1 antibody that recognizes the mid-domain of tau. It was reported to block tau seeding in culture after immunodepletion and to inhibit tau propagation between neurons[177].

A phase I trial of BIIB076 (NCT03056729) was conducted in healthy volunteers and individuals with mild or probable AD. In June 2019, the trial protocol was modified by eliminating the more advanced AD cohort and adopting adverse events as the sole primary outcome. Adverse events prompted the investigators to reduce the highest dose[275,276]. BIIB076 reduced mid-region-containing tau in CSF 1 week after infusion, suggesting target engagement[275]. However, the development of BIIB076 was terminated in July 2022 for business reasons[277].

E2814.—E2814 is an IgG1 antibody that recognizes HVPGG motifs in the second and fourth repeats of the tau microtubule-binding domain and binds to extracellular tau[178]. This antibody (or its murine version) has been reported to prevent tau seeding and aggregation in vitro, attenuate deposition of tau aggregates in mice injected with tau fibrils, and reduce free tau containing the mid-domain in non-human primates[178,278]. Interestingly, in mice that had received intracerebral tau seed injections, a 3 week course of intraperitoneal injections of the mouse version of E2814 reduced insoluble tau levels on the contralateral but not the ipsilateral side of the seed injections, raising efficacy concerns[178]. A longer-term study using the same seeding method and peripheral antibody injections for 12 weeks showed significant reductions in insoluble tau on both the ipsilateral and contralateral sides at the highest dose, and target engagement in the CSF[279]. Neither study reported on soluble tau levels.

A phase I trial (NCT04231513) completed in 2020 tested the safety, tolerability and immunogenicity of E2814 in healthy individuals. No significant drug-related adverse events were reported, although two participants developed anti-E2814 antibodies. Serum and CSF pharmacokinetics were proportional to antibody dose, with a dose-related increase of antibody–tau association in the CSF, which persisted for at least 1 month[278,280,281]. In 2021, a multiple-ascending-dose phase was added to the study. The trial ended in March 2023, and the results have yet to be released.

In 2021, E2814 was chosen to be evaluated in the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) prevention trial, the participants of which carry pathogenic amyloid precursor protein or presenilin mutations[282]. A phase Ib/II trial (NCT04971733) aims to enroll thirteen DIAN patients with mild-to-moderate cognitive impairment. This trial will assess safety, tolerability, target engagement and pharmacokinetics, as well as anti-drug antibodies, and will run until April 2025. Preliminary results from this trial were presented at the Alzheimer's Association International Conference (AAIC) in 2023[283,284]. The antibody was safe and well tolerated with favourable pharmacokinetics, and showed target engagement with tau in the CSF. After 3 months, the treated individuals showed a significant decrease in CSF tau 243–254, a tau fragment that strongly correlates with tau PET scan data[283,285]. Importantly, E2814 binds outside the 243–254 region, thereby ensuring that the CSF data are not confounded by the treatment itself[283]. In vivo, the antibody might bind to a larger tau fragment extracellularly and/or intracellularly.

Further phase II/III trials (NCT05269394 and NCT01760005) will test E2814 treatment alone or concurrently with anti-Aβ treatment (lecanemab) in DIAN patients with early-onset AD. These trials will evaluate safety, tolerability, biomarkers and cognitive and other functional efficacy of E2814 alone or with lecanemab. Both trials are expected to be completed in October 2027.

Gosuranemab.—Gosuranemab (BIIB092) is an IgG4 antibody that binds human tau at residues 15–22[286]. It was raised against extracellular N-terminal tau fragments (eTau) isolated from human neurons differentiated from pluripotent stem cells derived from patients with familial AD[186,287]. The antibody was shown to decrease free tau in brain interstitial fluid and CSF in tauopathy mice after intraperitoneal injections but its potential effect on clearing tau in brain tissue was not reported[186].

In a phase I trial to evaluate the safety of gosuranemab in healthy volunteers (NCT02294851), no severe adverse events were reported[288]. The antibody significantly decreased unbound tau in CSF, with sustained reduction of eTau fragments for up to 12 weeks at higher doses. In a phase Ib trial in patients with PSP (NCT02460094), gosuranemab was safe and well tolerated, with mild-to-moderate adverse effects, and showed dose-dependent accumulation in serum and plasma[289]. All doses decreased free eTau by more than 90%, and this decrease was sustained for 85 days after treatment. An open-label extension (NCT02658916) was offered to phase Ib study participants to evaluate long-term safety and tolerability. However, this trial was terminated when a follow-up phase II trial (NCT03068468, PASSPORT) failed to meet its primary endpoint[290]. The phase II study was conducted to evaluate the efficacy of gosuranemab in 490 patients with PSP. In December 2019, it was announced that gosuranemab showed no efficacy, as assessed on the PSP Rating Scale, which measures movement difficulties. However, the antibody did reduce CSF free N-terminal tau fragments by 98%.

Gosuranemab also failed to show efficacy in a phase Ib ‘basket’ trial (NCT03658135) in four different primary tauopathies: Aβ PET-negative corticobasal syndrome, naPPA, frontotemporal lobar degeneration with *MAPT* mutation and traumatic encephalopathy syndrome[287,291]. No adverse events were reported and the treatment cleared most of the free eTau from the CSF but had no effect on exploratory measures of disease severity. Both this trial and the aforementioned phase II trial were terminated in December 2019[291,292].

In a preliminary study of tissue from gosuranemab-treated individuals with primary tauopathies, treatment-related glial responses were reported, with no clearance of neuronal tau inclusions[195]. However, only a few individuals underwent autopsies and their treatment regimens and times to death following the last dose differed substantially.

Another phase II study (NCT03352557, TANGO) was conducted in patients with MCI or mild AD. This trial was designed to evaluate long-term safety and efficacy of three different doses of gosuranemab and generation of anti-drug antibodies. The treatment either failed to change or worsened cognitive scores[275,293], and all three dose groups had poorer cognitive outcomes than the placebo group[275]. This trial and further development of gosuranemab were terminated[293].

JNJ-63733657.—JNJ-63733657 is an IgG1 antibody with a high affinity for p-tau217. It has been reported to neutralize tau seeds and inhibit pathological spreading in mouse models of tauopathy, but these data have not been peer reviewed[294].

A phase I trial of JNJ-63733657 (NCT03375697) was conducted in healthy individuals and patients with prodromal or mild AD[294,295]. No safety or tolerability issues were raised. The pharmacokinetics were similar between healthy participants and those with AD, with dose-dependent reductions of p-tau217 in the CSF. Two other phase I trials (NCT03689153 and NCT05407818) to assess the safety, tolerability and pharmacokinetics of JNJ-63733657 in healthy participants have been completed but the results have not yet been published.

A phase II study (NCT04619420) is also ongoing to evaluate efficacy, safety, and tolerability of JNJ-63733657 in patients with early-stage AD who have a positive tau PET scan is also ongoing. The primary outcome is change in cognition, and secondary outcomes include other functional measures, brain tau burden, CSF tau, safety and pharmacokinetics. This trial will run until 2025.

Lu AF87908.—Lu AF87908 is an IgG1 antibody raised against p-tau396/404. The mouse version, C10.2, reduced tau seeding in vitro and in mice when pathological tau was pre-incubated with or immunodepleted by the antibody[179]. In cultured microglia, C10.2 promoted tau uptake and lysosome-mediated degradation[191]. The humanized version showed highly specific and sensitive tau binding in post-mortem brain tissue from people with AD or primary tauopathies[296]. A phase I study (NCT04149860) to test the safety, tolerability and pharmacokinetics of Lu AF87908 in healthy individuals and patients with AD concluded in July 2023.

MK-2214.—The precise epitope for MK-2214 has not been reported, but this antibody might be derived from a mouse antibody that recognizes p-tau413 and was found to bind AD tau and showed efficacy in animal models[297,298]. Two phase I trials have been initiated to examine its safety, tolerability, pharmacokinetics and pharmacodynamics in healthy individuals (jRCT2031220627) or patients with MCI or mild-to-moderate AD (NCT05466422), and are expected to be completed in 2024[298].

PNT001.—PNT001 recognizes *cis* p-tau231 which is reported to be a highly neurotoxic form of pathological tau [214,299]. *Cis* p-tau231 has been detected in brain tissue from people with AD or traumatic brain injury (TBI) and was shown to have a role in tau aggregation and neurodegeneration[214,300–302]. Preclinical studies indicated that peripheral anti-*cis* p-tau231 treatment cleared pathological tau from the brain and ameliorated neuronal degeneration and some cognitive impairments in mouse models of tauopathy, vascular dementia and TBI[214,300,303].

A phase II study (NCT04096287) evaluated the safety and tolerability of PNT001 in healthy individuals. The antibody was well tolerated, with dose-dependent serum and CSF exposure[274]. Another phase I trial (NCT04677829) to examine safety and tolerability in patients with acute TBI was also registered, but was terminated soon after the first participant enrolled and no results have been disclosed.

PRX005.—PRX005 is an IgG1 antibody targeting the microtubule-binding region in both the 3R and 4R tau isoforms[304,305]. According to a conference presentation, PRX005 recognizes both unphosphorylated and phosphorylated tau, and NFTs and dystrophic neurites in AD brain tissue[304,305]. It blocks binding of tau to heparan sulfate proteoglycan, thereby preventing tau transmission between cells, and was also shown to inhibit tau aggregation and p-tau accumulation in mouse models of tauopathy and amyloidosis.

A phase I study to evaluate the safety and tolerability of PRX005 is ongoing. The top-line results from a single-ascending-dose study in healthy individuals was announced in a press release and in poster at the AAIC in 2023[305,306]. The antibody was shown to be safe, with dose-dependent plasma and CSF exposure. A multiple-ascending-dose study in patients with AD has been initiated.

RG7345.—RG7345 targets p-tau422, and, preclinical studies, chronic administration reduced tau pathology in transgenic mice[211]. A phase I trial (NCT02281786) was initiated in healthy individuals to assess the safety, tolerability and pharmacokinetics of this antibody. Presumably it did not assess target engagement because the pSer422 epitope is found at very low levels or not at all in healthy individuals[45,307,308]. This trial was discontinued, probably because of unfavourable pharmacokinetics, and the results have not been published[309].

Semorinemab.—Semorinemab (RO7105705) is an IgG4 antibody that targets the N-terminus of monomeric and oligomeric tau. The mouse version was shown to target extracellular tau and reduced one phospho-tau epitope on brain sections, but had no effect on tau in western in a mouse model of tauopathy[193,310]. Effects on insoluble tau and on behaviour were not reported. Interestingly, the version of semorinemab with effector function cleared tau at a lower dose than the effectorless version, and neither antibody subclass increased astrogliosis or microgliosis[193,310]. Nevertheless, the effectorless version was selected for clinical trials, presumably because unlike the version with effector function, its mouse version does not cause fragmentation of microtubule-associated protein 2 — a protein that is important for microtubule assembly and stabilization in neurons in culture[193,310].

A phase I trial of semorinemab (NCT02820896) was conducted in healthy individuals and patients with mild-to-moderate AD. All dosing and administration paradigms were safe and well tolerated[311]. No severe adverse effects were reported, and dose-dependent plasma and CSF antibody exposure was observed.

A phase II trial (NCT03289143, TAURIEL) was conducted in patients with prodromal or mild AD. The antibody was safe; however, it missed both the primary and secondary efficacy endpoints[312]. Antibody administration also failed to slow NFT accumulation, although its pharmacokinetics were dose-proportional[274].

Another phase II trial (NCT03828747, LAURIET) enrolled patients with moderate AD. This study was completed in August 2023. The primary outcome was change in cognitive scores, and secondary outcomes include additional cognitive tests and behaviour, adverse events, serum concentration and immunogenicity. The top-line results showed that semorinemab

treatment slowed decline on one cognitive test, but no changes in other cognitive and functional outcomes were noted[313], and tau burden based on PET signal was not altered although CSF tau was reduced[313,314]. A decision on phase III testing is pending.

Tilavonemab.—Tilavonemab (CN2–8E12) is an IgG4 antibody that recognizes an N-terminal tau epitope comprising residues 25–30 and has been reported to work extracellularly[180,181,185,315]. In culture, tilavonemab blocked tau seeding and prevented propagation of tau pathology when preincubated with the tau seeds[181,185]. In a mouse model of tauopathy, the drug substantially reduced levels of p-tau and insoluble tau and rescued contextual fear conditioning deficits[180]. A second study showed reduced levels of insoluble tau and decreased brain atrophy, as well as improved motor function, in mice treated with tilavonemab[189].

In a phase I trial in patients with PSP (NCT02494024), tilavonemab was shown to be safe[316]. The drug had a serum half-life of 27–37 days and dose-dependent blood exposure. An open-label extension study (NCT03413319) was performed to determine the long-term safety and tolerability of the drug, as well as the eligibility of participants for a subsequent phase II trial.

A phase II trial (NCT02985879) to evaluate the safety and efficacy of tilavonemab was conducted in patients with PSP. A 4-year extension (NCT03391765) was initiated in participants who had completed the placebo-controlled treatment phase. Tilavonemab provided no benefit over placebo, although it had target engagement and a favourable tolerability profile[317,318]. The extension studies, as well as an expanded access programme in patients with CBD, were subsequently halted[317,319].

Another phase II trial of tilavonemab (NCT02880956) was conducted in patients with early-stage AD. An extension study (NCT03712787) on long-term safety and tolerability was offered to participants who completed the initial testing. In the extension study, which ended in July 2021, the treatment did not halt cognitive decline or improve functional outcomes, nor did it slow brain atrophy or lower plasma NfL levels[275,320]. Given the lack of efficacy in all trials, development of tilavonemab was terminated[315].

Zagotenemab.—Zagotenemab (LY3303560) is a humanized form of the MC1 antibody, which recognizes an early form of misfolded tau[321,322]. In preclinical testing in tau transgenic mice, chronic injections of zagotenemab reduced insoluble p-tau levels in the spinal cord and p-tau immunoreactivity in brainstem and spinal cord, and improved motor phenotypes[321]. The single-chain variable fragment (scFv) of the antibody also reduced tau pathology in mice when administered in an AAV construct as a gene therapy[323].

Two phase I trials assessed the safety and pharmacokinetics of zagotenemab. The first (NCT02754830) evaluated safety and serum drug concentration in healthy individuals and patients with MCI or mild-to-moderate AD. A second trial (NCT03019536) assessed multiple ascending doses in the same AD cohort. Adverse effects and pharmacokinetics were evaluated. The results have not been published.

A phase II efficacy trial of zagotenemab (NCT03518073) was also conducted in patients with gradual and progressive memory decline. Primary outcomes included changes in cognition and secondary outcomes were additional functional measures and anti-drug antibodies. This trial missed its primary endpoint, and development of zagotenemab was discontinued[324].

Factors influencing antibody efficacy

The results from human testing raise the issue of how to maximize antibody efficacy. Multiple factors affect antibody efficacy, including mechanism of action, IgG subclass, epitope and the patient population being treated.

Tilavonemab, gosuranemab, semorinemab, and zagotenemab which were found in preclinical testing to work only extracellularly and to solely or partially target the N-terminus of tau, have not provided functional benefits in clinical trials, suggesting that extracellular targeting of tau epitopes will not be sufficient. Although tau spreading is a valid clinical target, extracellular tau is only a small proportion of the tau in AD[325,326]. Most tau, including its pathological forms, is found within neurons. Therefore, removing extracellular tau is unlikely to reverse intracellular pathology, although the extracellular and intracellular pools might exist in equilibrium. In addition, in the CSF patients with AD or primary tauopathy, N-terminal tau is found at much lower levels than tau containing the mid-domain[327–330]. Furthermore, tilavonemab and gosuranemab were tested in patients with PSP, who, unlike patients with AD, do not have elevated CSF tau levels[328,331–336]. These factors could all have contributed to the lack of efficacy of the antibodies. Patients with primary tauopathy were shown to have decreased CSF levels of the microtubule-binding region of tau[337], suggesting that extracellular antibodies against this region would not be beneficial in these individuals.

The optimal tau epitopes to target in AD remain open to debate. Mass spectroscopy has revealed relatively low levels of carboxy-terminal tau in the CSF in AD, indicating that extracellular antibodies targeting this region are likely to be ineffective[280,328–330,337,338]. Mid-domain tau (approximately aa 150–250) comprises the largest fraction of tau in the CSF, suggesting that this region would be a better target[327,328]; however, as stated above, even the largest fraction of extracellular tau is a minuscule proportion of the tau in the brain.

Intracellularly, the N-terminus might not be the optimal target for immunotherapies[339]. Preventing or reversing aggregation of tau can reduce seeding and make the protein easier to digest; therefore, selecting epitopes from the core of aggregates could be more beneficial, but these epitopes often have limited accessibility owing to their hydrophobic nature. Cryo-electron microscopy has clarified the core structure and sequence of filaments from different tauopathies[55,340–342]. Although the structures differ, they all consist of the microtubule-binding region and C-terminus of the molecule. Thus, antibodies targeting epitopes in these regions might be appealing candidates, assuming that they can work intracellularly. Like C-terminal tau, the microtubule-binding region of tau is primarily found intraneuronally. An additional challenge for immunotherapies that target phospho-epitopes is the shifting prevalence of these epitopes over time, with some being more prominent in early-stage disease and others increasing during disease progression.

In addition to differences in CSF tau, the pathology seen in primary tauopathies and AD differs in many respects, including the brain regions affected and the types of tau lesions[18,19]. Therefore, these patient populations should not be considered interchangeable during the development and testing of immunotherapies. Tau filaments can assume different morphologies with unique core structures, and phospho-epitope profiles might also vary between and within tauopathies [54,55,340–343]. In addition to neuronal tau, primary tauopathies also feature glial tau deposits. These inclusions, such as oligodendrocyte coiled bodies and tufted astrocytes, are distinct from the pathological tau that is seen in neurons. The type of astrocytic pathology is also disease-dependent[18,344], which has consequences for synaptic function, provision of trophic support, inflammation and maintenance of myelination[344,345]. Glial tau pathology might propagate independently of neurons[346,347]. Targeting of non-neuronal inclusions with immunotherapies is unlikely to be straightforward, as the optimal epitopes might be different from those in neurons, and antibodies optimized for neurons may not be internalized by glia. Clearing this pool of tau may require a more direct focus, such as using gene therapy to specifically express antibodies in glial cells[323].

Current human trials utilize either IgG1 or IgG4 antibody subclasses. Unlike IgG1, IgG4 antibodies mostly lack effector function, which might increase safety but reduce their efficacy. Although Lee at al. argued that effector function was unnecessary, their antibody with effector functions promoted tau clearance at a lower dose than its effectorless counterpart[193,310]. Mukadam et al. showed that in slice cultures, an antibody mutated to lack Fc binding, which mediates effector function, was less effective than its unmodified counterpart[194]. In cultured microglia, a direct comparison between humanized IgG1 and IgG4 versions of the same antibody showed that the IgG1 variant was more efficacious at promoting tau phagocytosis[192]. When the same tau binding region was cloned into all four mouse IgG subclasses (IgG1, IgG2a, IgG2b and IgG3), IgG1 and IgG2a (the human IgG1 analogue) were the most effective at preventing tau toxicity and promoting tau clearance, and the effectorless variant IgG3 (human IgG4 analogue) was the least effective[348]. Some of those efficacy differences might relate to variable Fc-mediated neuronal uptake of the IgG subclasses. In addition to Fc binding, the IgG subclass influences antibody catabolism rates, self-association and stability[349–352], and changing the IgG subclass can affect antigen binding even when the variable regions are unchanged[182,348,353–368]. These findings could have major implications for antibodies that underwent preclinical testing before being humanized, sometimes into a different subclass. IgG4 can also split and form heterodimers with other IgG4 antibodies, and it is unclear whether this possibility was considered for the antibodies reviewed above [369,370].

Thorough testing of humanized antibodies in mouse models is not feasible because species differences increase the likelihood of development of anti-idiotypic antibodies and related adverse effects. These problems could be minimized to some extent by using mouse models with humanized immune systems crossed with tauopathy models, although no such hybrid models have been described in the literature. Some humanized antibodies have been examined in non-human primates, but they have limited utility as these animals are not prone to develop tau pathology.

Antibody charge and affinity should also be considered during antibody design, although. affinity for the antigen and efficacy do not necessarily correspond. For example, a lower-affinity antibody against p-tau396/404 was more efficacious than a higher affinity antibody against the same epitope[182,183,348,371]. Though not directly comparable, the low-affinity MC1 antibody showed greater efficacy in vivo than a higher-affinity antibody against a different tau epitope[372]. However, such findings are not universal, as a higher-affinity antibody specific for tau truncated at Asp421 was more effective than a lower-affinity antibody against the same epitope (E.E.C., E.M.S. et al, unpublished work). Charge also influences every aspect of antibody function, including binding, uptake into cells or across the BBB, what cell type the antibody targets, and how quickly the antibody is degraded[182,373–378]. Of note, an antibody's ability to prevent tau seeding does not necessarily relate to its ability to prevent tau toxicity[182,325].

These findings highlight the need for further research into optimal antibody design and demonstrate the challenge of translating results from the laboratory to human patients. Many of these questions have been explored more thoroughly in other fields, notably in the development of cancer immunotherapies, and merit greater study. In the sections that follow, we discuss how antibodies and their fragments might be modified to enhance tau clearance[379–402].

New immunotherapy approaches

Antibody fragments

Currently, only whole IgGs are being tested in clinical trials, but antibody fragments show potential as therapeutic and imaging agents. scFvs and single-domain antibodies (sdAbs) are much smaller (approximately 25 kDa and 13 kDa, respectively) than whole IgGs (150 kDa). The smaller size could enable enhanced BBB penetration and targeting of cryptic epitopes that are inaccessible to whole antibodies. In addition, sdAbs are stable and easier to produce in large quantities than whole antibodies. Preclinical testing of scFvs and sdAbs in cell and animal models has shown that they can prevent the formation of tau polymers, act as imaging agents and reduce tau pathology[215,252,254,323,348,403–409]. One potential complicating factor for using unmodified antibody fragments as long-term therapies is that they can have a half-life in the order of hours, compared with 1–3 weeks for whole antibodies. However, we have observed fluorescent signal from tau scFvs and sdAbs in the brains of tauopathy mice several days after injection[215,407]. Thus, with a sufficient quantity of target to bind, antibody fragments seem to be retained in tissue. Moreover, scFvs and sdAbs can be delivered as gene therapies, which have been shown to reduce polymerization and clear tau in vivo[253,254,404,408,410]. Antibody fragment gene therapy is also supported by results from other neurodegenerative disease models[410–414].

Modified immunotherapy

Tau antibodies and antibody fragments can be incorporated into molecular complexes to promote targeted tau degradation through the proteasome or the endosomal–lysosomal system. Whole IgGs and antibody fragments have been used as the binding agents for extracellular, surface-bound or intracellular targets (Fig. 4). Although no modified,

multivalent sdAbs have yet been used to target tau in clinical trials, some have been tested for the treatment of cancer, as well as infectious and autoimmune diseases[415,416].

Targeted protein degradation via the ubiquitin–proteasome system.—scFvs and sdAbs can be modified to enhance target ubiquitination and proteasomal clearance. Gallardo et al. developed anti-tau scFv chimaeras by fusing scFvs to ubiquitin at either Lys48 or Lys63, which directs proteins to the proteasome or lysosome, respectively[389]. Both scFvs reduced intracellular tau levels in culture but only the proteasome-targeting scFv was effective in vivo.

Proteolysis-targeting chimaeras (PROTACs) are hetero-bivalent complexes comprised of a target binder (small molecule or antibody), a short linker and an E3 ligase-recruiting molecule. The complex brings the target protein and ubiquitination machinery into close proximity, leading to polyubiquitination and proteasome-mediated degradation of the protein. Small-molecule-based and peptide-based PROTACs have been shown to degrade tau in cultured cells[384–388]. In mouse models of AD and tauopathy, a tau-targeting PROTAC reduced t-tau and p-tau levels, preserved dendritic arborization and improved cognitive performance[384,388]. Several studies have successfully incorporated sdAbs as the target binding portion of the PROTAC to rapidly degrade a range of proteins[381–383].

A third strategy fuses the PEST (Proline (P), Glutamic Acid (E) / or Aspartic Acid (D), Serine (S), and Threonine (T)) proteasome-targeting motif to the antibody fragment of interest. This modification enhanced the efficacy of an anti-huntingtin scFv in transgenic mice[390]. sdAbs fused to the same PEST motif prevented α-synuclein-induced toxicity in cultured cells and reduced α-synuclein pathology in vivo[379,380].

Targeted protein degradation via the endosomal–lysosomal system.—Cell-surface lysosome-targeting receptors (LTRs) such as the cation-independent mannose-6-phosphate receptor (CI-M6PR) have been reported to facilitate transport of proteins to lysosomes[417]. CI-M6PR shuttles cargo to pre-lysosomal compartments, where the cargo dissociates and progresses to the lysosome while the receptor is recycled. CI-M6PR has been targeted to treat lysosomal storage disorders[418] and is highly expressed in neurons[419–421]. Tau-targeting antibodies could be modified to bind to CI-M6PR to enhance tau clearance.

So-called sweeping antibodies have a modified pH-sensitive variable domain that releases the target protein into acidic compartments to be digested, and the unbound antibody is recycled back to the cell surface[391]. The constant domain of the antibody can be modified to enhance Fc binding, which protects it from being degraded and enhances cellular uptake of the antibody–protein complexes. This approach could enhance the ability of tau antibodies to clear tau from the extracellular space through microglial phagocytosis.

Lysosome-targeting chimaeras (LYTACs) consist of an antibody or small molecule fused to a synthetic mannose-6-phosphonate glycopeptide that acts as an LTR ligand. The LYTAC molecule can simultaneously bind to a membrane-bound or extracellular target protein and the LTR. Once the antibody–target complex has been endocytosed, the target protein is released and the LYTAC is recycled back to the cell surface[392,393].

Antibody-based PROTACs (AbTACs) are antibody derivatives that promote lysosomal degradation. One arm of the engineered bispecific AbTAC antibody binds to an extracellular or membrane target and the other arm binds to a membrane-bound E3 ligase such as ring finger protein 43. As proof of concept, an AbTAC targeting programmed death ligand 1 successfully promoted lysosomal targeting and clearance of the protein[397].

Targeted protein degradation via the autophagy–lysosomal pathway.—The autophagy targeting chimaera (AUTAC) complex is composed of a cGMP-based degradation tag, a linker and a small molecule or antibody to bind to the target[394,395]. The use of a cGMP derivative was based on findings that 8-nitro-cGMP promoted Lys63 polyubiquitination and, thus, clearance through the autophagy–lysosomal system[396]. This method was successfully used to promote the autophagic degradation of mitochondria in human fibroblasts[395].

AUTOTACs, a second type of autophagy-targeting chimaera, are bidirectional complexes consisting of a module that interacts with the autophagy cargo receptor p62/SQSTM1 and a portion that binds the target[399]. This arrangement creates a link between the target and p62, leading to the oligomerization and activation of p62 and, in turn, target degradation by the autophagy–lysosome pathway. Using a modified 4-phenylbutyric acid molecular chaperone as a tau binder, AUTOTACs have successfully targeted misfolded tau in cells and tauopathy mice.

The tauopathy-homing and autophagy-activating nanoassembly (THN) has a magnetic mesoporous silica nanoparticle core embedded with PEGylated cerium oxide bound to the AT8 tau antibody[401]. AT8 binds to p-tau202/205 and cerium oxide promotes autophagy[400]. In cultured cells, THN particles colocalized with autophagosomes and promoted clearance of tau, and in a tauopathy rat model, THN particles were internalized by neurons and bound to pathological tau[401]. The treated animals showed amelioration of cognitive deficits.

Enhancing tau dephosphorylation.—Dephosphorylation-targeting chimaeras (DEPTACs) contain a tau-binding portion connected to a PP2A recruiter via a linker, with an added motif to increase cellular uptake[402]. This arrangement brings tau in close proximity to PP2A, thereby facilitating dephosphorylation. In tauopathy mice, treatment with a β-tubulin peptide-based DEPTAC lowered pathological tau levels while improving memory and microtubule assembly and increasing dendritic spine density. This approach would also avoid the dephosphorylation of unrelated proteins that could result if PP2A was targeted globally.

Conclusions

In our previous Review on tau-targeting therapies[1], we stated that the outcomes of pending trials would provide a clearer picture of the landscape of these therapies. Some therapies that showed promise in preclinical testing have failed to translate into benefits for patients. Other drugs have advanced to or within trials. Of the non-immunotherapy approaches, sodium selenate, lithium chloride and some OGA inhibitors have ongoing clinical trials, but many

others have either failed or not advanced. In addition, several candidates completed clinical trials but no results were released.

Among the recent clinical trials that were reported, ASOs produced promising results, safely reducing CSF tau levels below baseline in patients with mild AD[123]. Other measures, such as clinical presentation and brain volume, were not significantly different between the placebo and treatment groups; however, this study was relatively short (23 weeks) and had a small number of participants, with safety and pharmacokinetics being the principal endpoints. A larger multi-year phase II study is underway, with a focus on cognitive outcomes, the results are eagerly awaited.

The failure of some anti-tau antibodies might be attributed to several factors, including the choice of epitope, the study population and the mechanism of action, as well as limited information on how the properties of humanized antibodies relate to the mouse prototypes. Many studies have focused on N-terminal-tau-targeting antibodies that act extracellularly, despite the fact that over 99% of tau is intracellular and few N-terminal tau fragments are found in the extracellular space. In addition, these antibodies were trialed in patients with primary tauopathy even though extracellular tau levels are not increased in these individuals. Multiple groups, including ours, have highlighted the unsuitability of the N-terminus of tau as a therapeutic target[325,339,422–424]. The C-terminus of tau might also be an inappropriate target for extracellular antibodies.

The microtubule-binding region and C-terminus of tau are appealing targets for intracellular antibodies, as these regions make up the core of tau polymers. The efficacy of targeting specific phospho-epitopes might depend on the disease stage. Further development of peripheral and imaging biomarkers to identify the disease stage before treatment could allow antibody treatments to be tailored to the pathology of individual patients.

Immunotherapies and non-immunotherapy candidates face several common challenges. Both antibodies and small molecules must cross the BBB and enter neurons. Studies must also be long enough for the clinical benefits of the therapies to become apparent. Moreover, the choice of outcome measures must be carefully considered.

The failed immunotherapy candidates highlight the need for more research into how to select and optimize antibodies. We have long argued that to maximize efficacy, antibodies should be able to target both intracellular and extracellular pathological tau. Our group and others have demonstrated the importance of neuronal uptake of antibodies, and data on the role of TRIM21 further supports intracellular mechanisms[182–184,194,209,211,212,214,227,348,425]. Antigen binding, charge and cellular uptake can all be altered by changing constant domains — either swapping between murine IgGs or from murine to human — even if the variable region remains the same[182,348]. Following humanization, antibodies must be thoroughly re-evaluated, which is feasible in culture models but difficult in vivo owing to a lack of suitable human-like animal models.

Combination trials of therapies targeting both tau and Aβ should become more common in the near future. However, such approaches might not be applicable to all patients; for example, individuals who carry the apolipoprotein E ε4 have an increased risk of

amyloid-related imaging abnormalities after treatment with lecanemab or donanemab. We also expect modified antibody approaches, as well as antibody-based gene therapies and/or gene-editing strategies, to enter trials. Advances in tau biomarkers should enable suitable patient populations to be identified at earlier stages of the disease, thereby increasing the likelihood of a positive outcome.

Progress in the field of tau-targeting therapies has not been as rapid as we had hoped. However, the intracellular location, size and complexity of tau makes it a more challenging target than Aβ, and it took nearly 40 years from the discovery of Aβ to an approved therapy (which, notably, is an antibody). We believe that it is time for tau-targeting therapies to receive a similar degree of support to their Aβ-targeting counterparts. Watching large companies with extensive resources periodically scale back their research into therapies for neurodegeneration has been worrying, but is understandable to some extent in view of the difficulty and high cost of these studies. As always, more basic research is needed, both to test potential therapies, and to explore the pathological mechanisms of AD and other tauopathies, which will help us to determine how best to optimize existing candidates and to identify new targets for intervention.

Supplementary Material

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Key points

Therapies targeting expression, post-translational modifications, aggregation and clearance of tau have advanced to human testing. These have been largely safe and well tolerated.

Clinical efficacy of tau targeting therapies has yet to be established and some trials have failed. However, multiple trials are ongoing and new candidates continue to enter trials.

Antisense oligonucleotides have recently shown promising results in human testing in reducing tau expression. Larger studies will determine whether this translates into clinical benefits.

Most of the ongoing trials are immunotherapies. These can target tau intra- and/or extracellularly, but targeting tau only extracellularly is less likely to be effective.

Choice of epitope, antibody subclass and its charge, patient population, and mechanism of action must all be carefully considered when selecting antibodies and vaccines for clinical trials. Ideally, antibodies should be thoroughly retested after humanization, as this process may alter their properties.

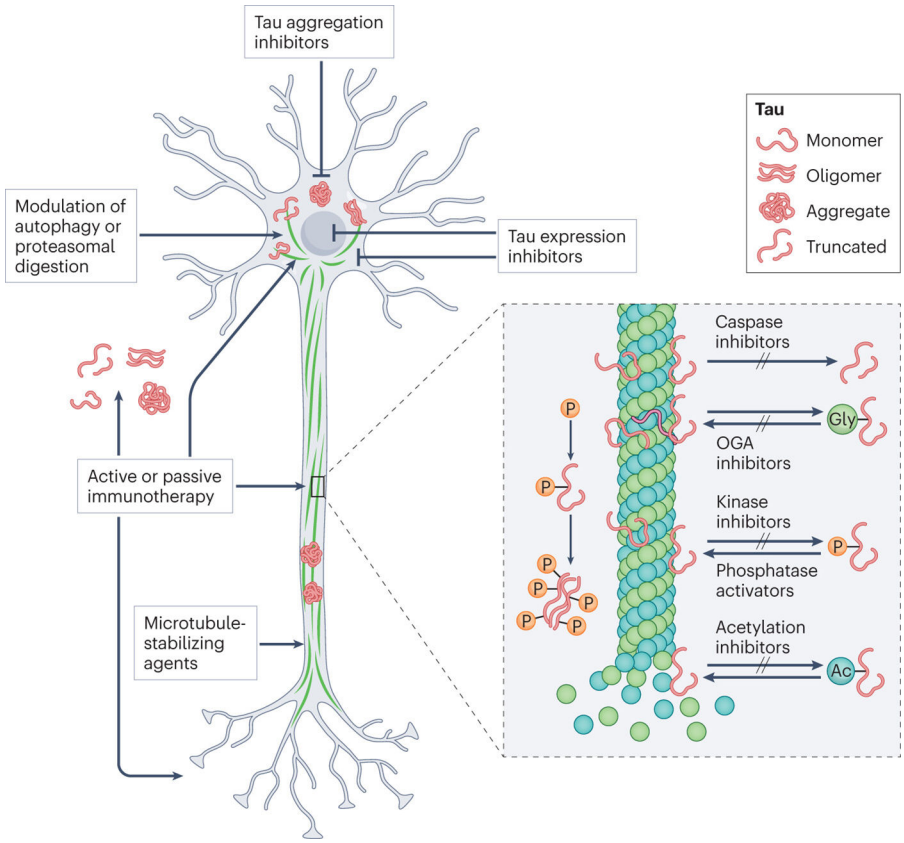

Figure 1 |. Tau-related therapeutic targets.

The figure shows the various tau-targeting approaches that are in preclinical or clinical development for the treatment of Alzheimer disease and primary tauopathies. Antisense oligonucleotides can be used to reduce tau expression. Inhibitors of tau aggregation include curcumin and the methylene blue derivative LMTX. Microtubule stabilizers such as TPI-287 and NAP can be used to compensate for loss of the normal microtubule-stabilizing function of tau. Clearance of pathological tau can be enhanced using modulators of autophagy or proteasomal degradation. Active and passive immunotherapies use antibodies to target pathological tau intracellularly or extracellularly and promote its degradation and clearance. Pathological tau is characterized by extensive post-translational modifications, including hyperphosphorylation, acetylation, truncation. Glycosylation can be protective or detrimental. The inset shows various inhibitors that target the enzymes involved in these modifications. Ac, acetyl group, Gly, glycosyl group; OGA, *O*-GlcNAcase; P, phosphate. Adapted from ref.[1]

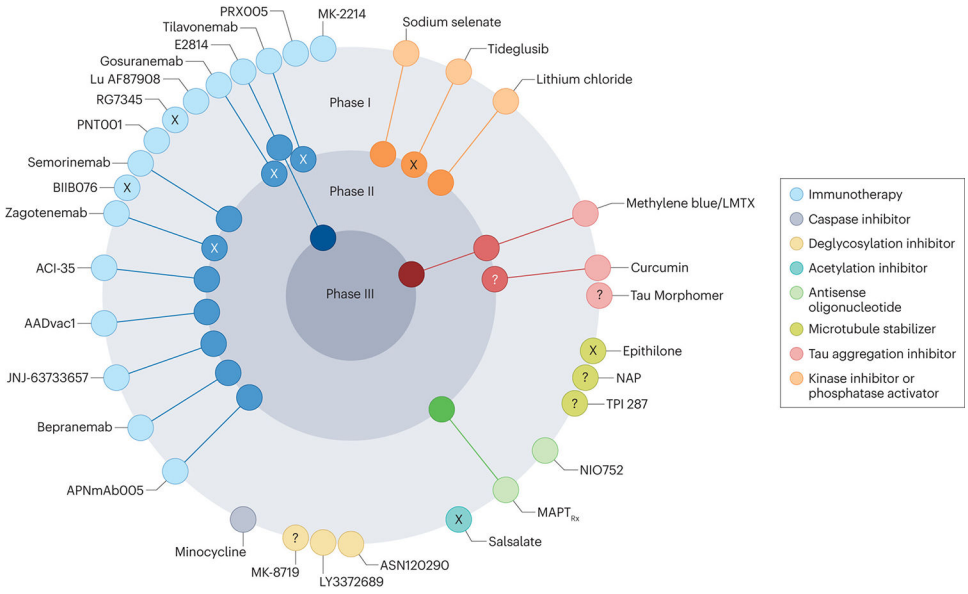

Figure 2 |. Current status of clinical trials of tau-targeting drugs.

At the time of writing, the most active field is tau immunotherapy, with two active vaccines (AADvac1 and ACI-35) and nine antibodies (APNmAb005, E2814, JNJ-63733657, Lu AF87908, MK-2214, PNT001, PRX005, semorinemab and bepranemab) in ongoing clinical trials. 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 sometimes difficult to determine, ? reflects uncertainty about the current status of trials. Adapted from ref.[1].

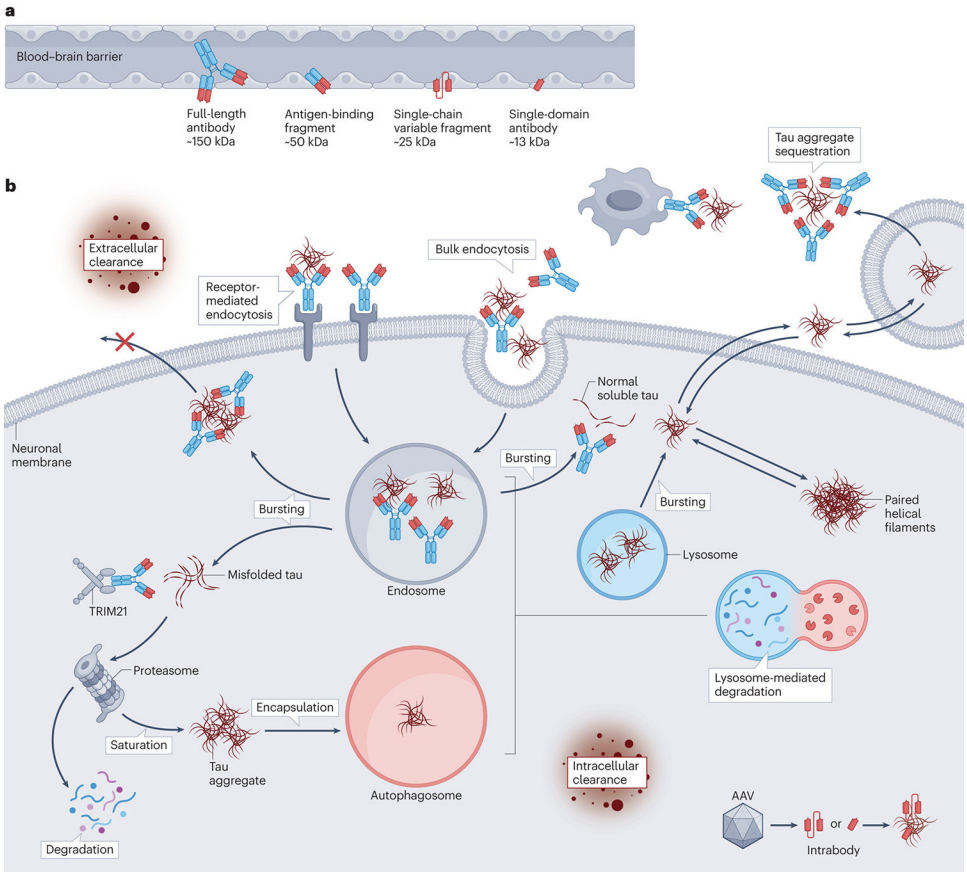

Figure 3 |. Proposed modes of action of anti-tau antibodies.

a | Tau antibodies can consist of whole IgGs (~150 kDa) antibody fragments such as antigen-binding fragments (50 kDa), single-chain variable fragments (~25 kDa), and single-domain antibodies (~13 kDa). **b** | Antibodies might target tau intracellularly or extracellularly, and should ideally act in both compartments to maximize efficacy. Extracellularly, antibodies could sequester tau aggregates, prevent tau aggregation, promote microglial phagocytosis of tau–antibody complexes and/or facilitate removal of tau to the periphery. These mechanisms would all reduce the spread of tau between neurons and subsequent pathological seeding. Antibodies, with or without tau, can also be internalized by neurons through either receptor-mediated or bulk endocytosis. Inside the neuron, these antibodies can bind to tau aggregates within the endosomal–lysosomal system. There, they can promote disassembly of tau aggregates, allowing greater access for lysosomal enzymes. Formation of tau–antibody complexes within the endosomal–lysosomal system might also prevent tau from disrupting endosomal membranes and escaping back into the cytosol, thereby aiding complete tau degradation. Some antibodies might also enter the cytosol, where they can sequester misfolded tau or promote proteasomal clearance through tripartite motif containing 21 (TRIM21) binding, thereby enhancing clearance and preventing tau secretion. Antibodies bound to larger tau aggregates could be cleared via the autophagosome. Antibody fragments, either administered or encoded by adeno-associated virus (AAV) vectors, also have therapeutic potential. Astrocytic tau pathology

can presumably be targeted using the same mechanisms of action, although experimental confirmation is required.

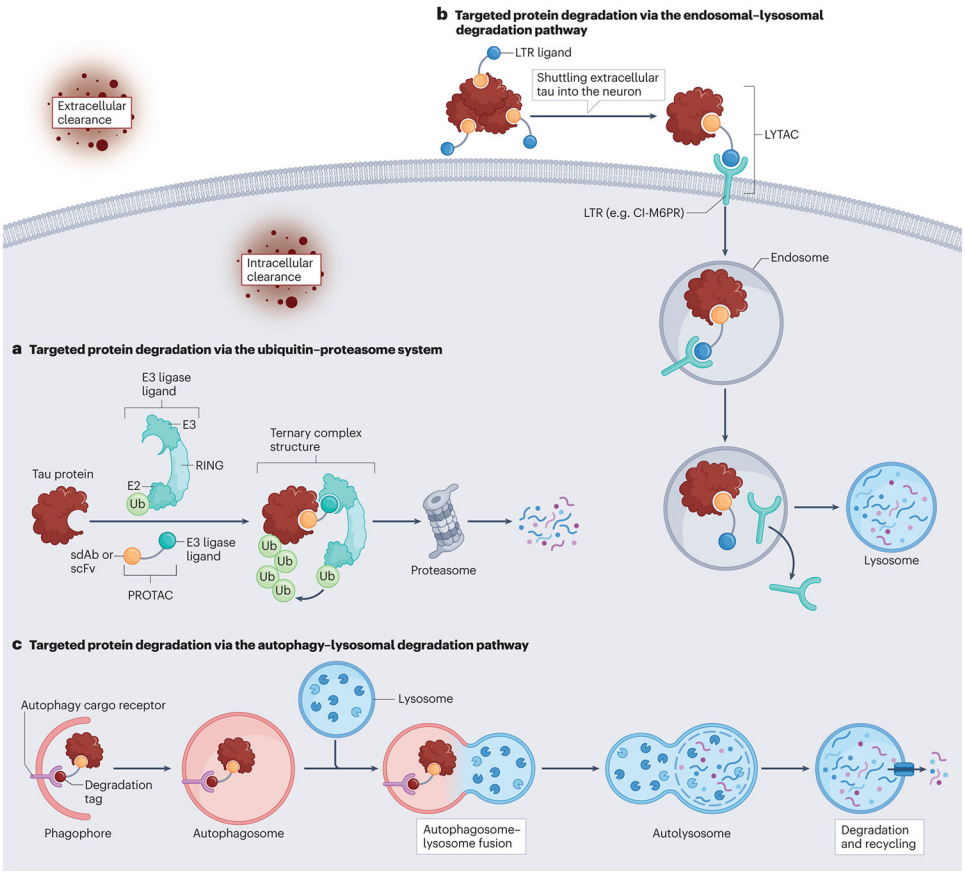

Figure 4 |. Modified immunotherapy strategies.

a | Targeted protein degradation via the ubiquitin–proteasome system. Proteolysis-targeting chimaeras (PROTACs) are hetero-bivalent complexes comprising a target binder (single-domain antibody (sdAb) or single-chain variable fragment (scFv)), a short linker and an E3 ligase-recruiting molecule. These complexes bring the target protein (in this case, tau) and E3 ligase into close proximity and trigger proteasome-based degradation. **b** | Targeted protein degradation via the endosomal–lysosomal degradation pathway. Lysosome-targeting chimaeras (LYTACs) are hetero-bivalent complexes are comprising a target binder (sdAb or scFv), a short linker and a ligand for the lysosome-targeting receptor (LTR). They shuttle extracellular tau into the neuron for degradation. **c** | Targeted protein degradation via the autophagy–lysosomal degradation pathway. Autophagy-targeting chimaeras are hetero-bivalent complexes comprising a target binder (sdAb, or scFv), a short linker and a degradation tag, which can enhance tau degradation through the autophagy–lysosomal degradation pathway. CI-M6PR, cation-independent mannose-6-phosphate receptor; RING, really interesting new gene; Ub, ubiquitin.

Table 1|

Advantages and disadvantages tau-targeting therapies

Drug type	Advantages	Disadvantages
Antisense oligonucleotides	Lowering total tau levels might lead to dissociation of aggregates and reduce pathology Specifically targets tau Safe and well tolerated in human testing Reduces CSF tau levels below baseline in humans	Also reduces levels of non-pathological tau, which might have unforeseen consequences Tau knockdown or knockout produces cognitive and motor deficits in some animal models
Phosphatase activators	Dephosphorylation increases tau–microtubule binding and makes tau less prone to aggregation PP2A is responsible for most tau dephosphorylation	PP2A is also involved in metabolism, gene expression, signal transduction, apoptosis and cell cycle entry, so global inhibition might have off-target effects In mild-to-moderate AD, PP2A inhibition does not reduce AD biomarker levels in CSF
Kinase inhibitors	Reduced phosphorylation increases tau–microtubule binding and makes tau less prone to aggregation The kinase inhibitor lithium is already approved for humans and is widely used for other conditions	The targeted kinases are involved in other signalling pathways; for example, GSK3β affects metabolism, autophagy, DNA repair and apoptosis, so global inhibition might have off-target effects Long-term lithium use has serious adverse effects Low doses of lithium produced no change in GSK3β activity
Acetylation inhibitors	Reduced acetylation increases tau–microtubule binding, regulates phosphorylation and promotes tau cleavage, making tau less prone to aggregation The acetylation inhibitor salsalate reduceds acetylated and total tau levels, prevents hippocampal atrophy and improves memory in tauopathy mice, and is safe and well tolerated in humans	Inhibiting acetylation will affect various molecules with unknown consequences Salsalate failed to improve cognition, prevent reductions in volumetric imaging and reduce AD biomarker levels in CSF in humans Salsalate is not tau-specific
Deglycosylation inhibitors	*O*-glcNAcylation of tau is protective and prevents phosphorylation and aggregation OGA inhibitors showed good brain penetration and safety in clinical trials	OGA inhibitors does not just target tau; they are involved in metabolic and signalling functions The biological relevance of *O*-glcNAcylation to other proteins is unknown
Caspase inhibitors	Blocking tau truncation promotes its binding to microtubules, thereby inhibiting tau aggregation and toxicity and resulting in improved function of synapses and organelles	The targeted caspases do not just cleave tau; for example, caspase 1 is involved in cytokine activation and apoptosis and caspase 3 affects tissue regeneration and differentiation as well as apoptosis The caspase inhibitor minocycline produces adverse effects, particularly with long-term treatment
Tau aggregation inhibitors	Overall, reduced tau aggregation diminishes tau toxicity Small molecules might be easier and cheaper to synthesize than antibodies Medicinal chemistry can be used to modify tau binding and brain uptake	Small-molecule tau aggregation inhibitors with efficacy in culture often show toxicity and/or lack of blood–brain barrier permeation in vivo These compounds typically bind to β-sheets that are found in various proteins, including normal ones To some extent, tau aggregation might be a defence mechanism to prevent toxicity of smaller aggregates such as oligomers
Microtubule stabilizers	Stabilizing microtubules improves axonal transport and supports the maintenance of neuronal processes and dendritic spines	Microtubule stabilizers have primarily been used for cancer treatment and have a narrow therapeutic window and substantial toxicity The microtubule stabilizer TPI-287 was poorly tolerated in human testing and was shown to worsen dementia symptoms; its brain penetrance could not be confirmed
Active immunotherapy	Specifically targets tau Active immunotherapy is more cost-effective and longer lasting than passive immunotherapy Inducing a polyclonal response in patients might further improve efficacy	Possible adverse immune responses, which could be irreversible Antibodies generated might not target optimal epitopes
Passive immunotherapy	Specifically targets tau Antibodies can be designed to target specific pathological epitopes, and treatment can potentially be tailored to disease stage Antibodies or antibody fragments can be further modified to enhance clearance Adverse effects are likely to be reversible because the antibodies will be cleared if treatment is stopped	Possible adverse immune response Choice of epitope is important, as not all epitopes are present at any given time Optimal efficacy requires both extracellular and intracellular clearance Humanization might change antibody properties

AD, Alzheimer disease; CSF, cerebrospinal fluid; GSK3β, glycogen synthase kinase 3β; OGA, *O*-GlcNAcase;PP2A, protein phosphatase 2A.