

# Emerging Diagnostic and Therapeutic Strategies for Tauopathies

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## Abstract

**Purpose of Review** Tauopathies represent a spectrum of incurable and progressive age-associated neurodegenerative diseases that currently are diagnosed definitively only at autopsy. Few clinical diagnoses, such as classic Richardson's syndrome of progressive supranuclear palsy, are specific for underlying tauopathy and no clinical syndrome is fully sensitive to reliably identify all forms of clinically manifest tauopathy. Thus, a major unmet need for the development and implementation of tau-targeted therapies is precise antemortem diagnosis. This article reviews new and emerging diagnostic therapies for tauopathies including novel imaging techniques and biomarkers and also reviews recent tau therapeutics.

**Recent Findings** Building evidence from animal and cell models suggests that prion-like misfolding and propagation of pathogenic tau proteins between brain cells are central to the neurodegenerative process. These rapidly growing developments build rationale and motivation for the development of therapeutics targeting this mechanism through altering phosphorylation and other post-translational modifications of the tau protein, blocking aggregation and spread using small molecular compounds or immunotherapy and reducing or silencing expression of the *MAPT* tau gene.

**Summary** New clinical criteria, CSF, MRI, and PET biomarkers will aid in identifying tauopathies earlier and more accurately which will aid in selection for new clinical trials which focus on a variety of agents including immunotherapy and gene silencing.

**Keywords** Tauopathy · Progressive supranuclear palsy · Alzheimer's disease · Immunotherapy · Gene therapy · Tau-PET

## Introduction

Tau is a highly soluble microtubule-associated protein which modulates stability of axonal cytoskeleton and is encoded by the *MAPT* gene on chromosome 17q21.3 consisting of 16 exons. Due to alternate splicing of E2, E3, and E10, six tau isoforms exist in human brain tissue that are defined by the presence or absence of E10 (the second microtubule-binding domain): three tau isoforms that contain three repeated binding domains (i.e., 3R tau) and the three tau isoforms containing E10 with four repeated binding domains (i.e., 4R tau). In the normal human brain, there exists a relative equal balance in the ratio of 3R:4R tau isoforms [1]. Tauopathies are a class of age-associated neurodegenerative diseases that are characterized by the presence of abnormal accumulations of pathogenic tau in neurons and/or glia. These disorders can be further classified by the relative balance of 3R and 4R tau isoforms found in pathological inclusions and morphological/ultrastructural features of inclusions.

Alzheimer's disease (AD) is defined by the presence of both amyloid-beta plaques and tau neurofibrillary tangles (NFTs) [2], which consist of relatively equal proportions of 3R and 4R tau isoforms in paired helical filaments [3••]. While NFTs in AD correlate most closely with clinical symptoms

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[4], the precise relationship between amyloidosis, NFTs, and cognitive dysfunction are currently unclear. As such, AD can be considered a mixed tauopathy due to the consistent findings of both tau NFTs and amyloid plaques. A distinct neuropathological entity, primary age-related tauopathy (PART), has been recently proposed to distinguish the pathological findings of NFT pathology found in relative or absolute absence of amyloid plaque pathology [5]. These individuals are usually older and may have mild or no clear cognitive impairment during life, with corresponding tau pathology found restricted to the medial-temporal lobe. Others claim that PART is within the spectrum of the AD due to the lack of biochemical differences between AD and PART NFTs and universal findings of medial temporal lobe NFTs in AD [6]. Further research is needed to help support or refute the distinction of PART from AD. Finally, moderate to severe comorbid AD NFT tau and amyloid-beta plaque pathology is common (~50%) in Lewy body disorders (LBD) [7] and NFTs confer a strong effect on prognosis and timing of the expression of dementia [8]. Thus, tau-directed therapies may likely impact not only primary tauopathies but also potentially mixed tauopathies such as AD and LBD patients with AD copathology. This review will focus on primary tauopathies, which are considered part of the frontotemporal lobar degeneration (FTLD) spectrum (i.e., FTLD-Tau) [9••], as these patients have a monoproteinopathy which is advantageous for testing tau-directed therapeutics [10].

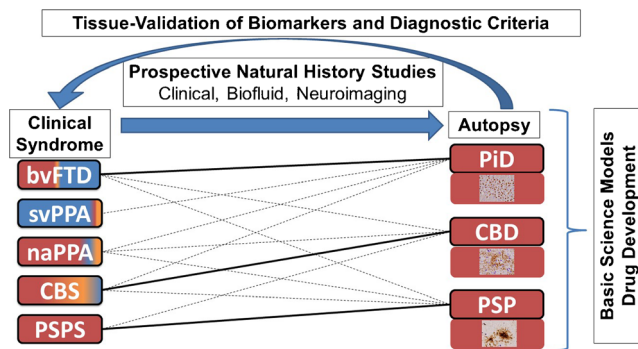
Three main strands of evidence suggest that the pathological process of tau accumulation within brain cells and propagation between cells is central to disease pathogenesis. First, pathological findings of tau pathology is the hallmark of these disorders and “gold-standard” for diagnosis, and regional topography of tau pathology in the CNS correlates well with clinical symptoms [4, 11, 12]. Second, patients with familial forms of tauopathy possess pathogenic mutations in the *MAPT* tau gene (FTDP-17); many of which correspond to accelerated fibrillization of tau and/or loss of microtubule binding function in vitro [13] demonstrating that altered tau function can contribute to disease pathogenesis. Finally, many recent animal- and cell-model studies find transmission of both recombinant tau and pathogenic tau-derived from brain homogenates of human tauopathy patients which can propagate from cell-to-cell in anatomically connected networks [14•, 15, 16]. These studies parallel the landmark human staging studies by Braak and Braak, which find sequential patterns of progressive cortical NFT pathology from serial cross-sectional AD autopsies [17] and provide compelling evidence that alteration of the tau protein alone is sufficient to recapitulate human disease. Further, studies using injections of brain extracts from various human tauopathies give rise to distinct morphologies of tau pathology in murine models that are similar to the features of tau pathology from human source tissue [18, 19]. In addition, inoculation with recombinant tau protein

can cause distinct morphologies of endogenous tau aggregations in cell models of disease and these specific aggregation types, when injected into transgenic mice, developed different regional patterns of tau pathology [20, 21]. These innovative studies suggest that there may be distinct strains of pathogenic tau that correspond to the various clinical and pathological forms of tauopathies. These strain-like properties are similar to those seen in spongiform encephalopathies; however, a clear distinction remains in that prions are infectious proteinaceous particles [22] and there is currently no evidence to suggest that tauopathies can be spread between humans or non-human primates [23]. These distinctions aside, the prion-like mechanism of tauopathy aggregation and spread is an attractive target for therapeutic development as it is likely the most proximal cause of neurodegeneration. Transmission models show minimal neuronal toxicity associated with exogenously induced tangles [14•, 15, 16, 18], and transgenic animals may show signs of degeneration prior to tau inclusion formation [24], suggesting that the toxic species of tau may be prefibrillar tau (i.e., soluble monomers, oligomers) rather than tangles themselves [25•]. It is likely that loss of tau microtubule stabilizing function contributes as well through compromised axonal transport and resultant altered cellular metabolism [26]. Other downstream mechanisms including impaired protein degradation pathways, oxidative stress, and inflammation likely contribute in the neurodegenerative process, and targeting these systems alone or in combination with tau-directed therapies may be advantageous as well.

This review highlights the clinicopathological heterogeneity of tauopathies, followed by an overview of the state of the science in diagnostic biomarkers and emerging therapeutic strategies to slow or halt tau-mediated neurodegeneration.

## Clinicopathological Complexity of Tauopathies

Primary tauopathies (FTLD-Tau) are both clinically and pathologically diverse. Figure 1 depicts the main clinicopathological associations of FTLD-Tau within the clinical spectrum of frontotemporal dementia (FTD). One major challenge to accurate diagnosis is that patients may present with either cognitive and/or motor symptoms that may be encountered at either memory or movement disorder clinic. Cognitive and motor impairment can cause additive disability and many patients require coordinated care across neurological disciplines. The main diagnostic considerations are other age-associated neurodegenerative diseases including forms of FTLD with TDP-43 or fused-in-sarcoma proteinopathy (i.e., FTLD-TDP, FTLD-FUS), AD, or LBD. Since there is no clinically available test to diagnose FTLD-Tau antemortem, it is important to exclude potentially treatable causes of “rapid-progressive dementia” in those patients with “red-flag” symptoms of acute



**Fig. 1** The importance of autopsy confirmation in improvement of diagnosis and treatment of tauopathies. *Figure* depicts clinicopathological associations of the three main FTLD-Tau neuropathologies found at autopsy with clinical syndromes. *Solid lines* represent the strongest associations (i.e., PiD with bvFTD, CBD with CBS, and PSP with PSPS) and *dashed lines* represent less frequent associations. *Color shading* of clinical phenotype boxes depict the relative frequencies of neuropathologies found at autopsy in each syndrome (*red* FTLD-Tau, *blue* FTLD-TDP, *yellow* AD) and *photomicrographs* in each neuropathology box depict characteristic inclusion morphologies (*PiD* Pick bodies, *CBD* astrocytic plaque, *PSP* tufted astrocyte). Schematic illustrates how detailed multimodal evaluations of patients with longitudinal clinical, biofluid, and neuroimaging assessments followed to autopsy can improve existing clinical criteria for detection of FTLD-Tau and differentiation from other neurodegenerative diseases and provide tissue validation for biomarkers obtained during life. Autopsy tissues also provide critical source of human-derived pathogenic tau species for use in animal/cell models of disease and therapeutic response to accelerate the development of disease modifying therapies. *naPPA* non-fluent agrammatic variant of primary progressive aphasia, *svPPA* semantic variant of primary progressive aphasia

onset, rapid progression, or atypical features such as seizure [27]. Below, we characterize the main classes of FTLD-Tau.

### Picks Disease (3R Tauopathy)

Pick’s disease (PiD) is the sole 3R predominant tauopathy [9•]. Neuropathological findings often include severe gross atrophy of the frontotemporal lobes and corresponding tau-positive intracellular inclusions. The morphological features include prominent round tau-positive “Pick bodies” in neurons with often severe neuron loss and diffuse neuropil threads and variable amounts of glial tau pathology in ramified astrocytes and oligodendrocytes [11]. Reactivity to C-terminal truncation epitopes [28] and the amyloid-binding dye, thioflavin-S [29], thought to be markers of mature tau inclusions of AD [30], is present in a subset of PiD tau pathology [11].

Clinically, PiD is most commonly associated with behavioral-variant FTD [31] (bvFTD), a disorder of social cognition previously referred to as *Pick’s disease*, but can be also seen in patients with clinical corticobasal syndrome [32] (CBS) or variants of primary progressive aphasia [33] (PPA) [34•]. Due to this clinical heterogeneity and high frequency of FTLD-TDP (~50–60%) in bvFTD [34•], current

nomenclature reserves the term *Pick’s disease* for the pathological findings above [9•].

### Progressive Supranuclear Palsy (4R Tauopathy)

Progressive supranuclear palsy (PSP) has pathological features of tau-positive glial inclusions in the form of “tufted astrocytes” in gray matter and “coiled-bodies” in oligodendrocytes in white matter, along with neuronal tangles [35]. The most severe pathology is usually seen in subcortical regions including the midbrain, pons, dentate nucleus of the cerebellum, and subthalamic nucleus, where large tau-reactive “globose” tangles may be found. Tau pathology in PSP is near exclusively of the 4R tau isoform type [35] and is reactive to acetylation at K280 [30] but lacks reactivity to mature tau markers including C-terminal truncation epitopes [28] and thioflavin-S [29]. A 900-kb inversion in *MAPT* has led to two haplotypes of polymorphisms in high linkage disequilibrium, H1 and H2 [36]. The H1 haplotype is a risk factor for PSP, and a recent genome-wide association study (GWAS) of autopsy-confirmed PSP identified several other polymorphisms that may increase risk of PSP tauopathy [37].

While the Steele Richardson Olszewski syndrome is the most recognized PSP clinical syndrome (i.e., PSPS) [38], PSP can present initially as pure parkinsonism (PSP-P), CBS, bvFTD, a non-fluent-agrammatic form of PPA (naPPA), pure akinesia with freezing of gait, and other more rare presentations such as cerebellar disorder [39, 40]. PSP-P in particular may be mistaken for idiopathic Parkinson’s disease early on in the course as there can be no clear clinical distinguishing features and at least 20–40% have been reported in certain series to be levodopa responsive [41–43]. The variety of clinical presentations in part reflect different distribution of the tau pathology within the brain [12, 44]. Finally, it is not uncommon for these clinical syndromes to overlap during the course of illness, where patients with naPPA language disorder eventually develop cardinal features of PSPS (oculomotor dysfunction and axial rigidity) or PSPS patients developing slow hesitant speech consistent with naPPA.

The NINDS/SPSP clinical criteria [38] requires a progressive a syndrome of supranuclear gaze palsy and slowed vertical saccades with falls within the first year to make a diagnosis of probable PSPS. These criteria are highly specific for PSP tauopathy but often lack sensitivity and over-represent the Richardson phenotype [45]. As such, updated clinical criteria for PSPS were developed in 2016 to expand the detection of PSP pathology in the context of these other clinical presentations and improve sensitivity [46]. These resultant criteria provide three levels of certainty based on the strength of association of four main classes of clinical features predictive of PSP tauopathy from large autopsy series [47], which allow for identifying patients with high specificity for clinical trials or

increased sensitivity for use in epidemiological studies or efforts for early detection [46].

### Corticobasal Degeneration (4R Tauopathy)

The main neuropathological findings of corticobasal degeneration (CBD) include diffuse tau-positive threads that are glial in origin and resemble plaques (i.e., astrocytic plaques) along with often severe white matter coiled bodies and threads, tau-positive ballooned neurons, and neuronal tangles [35]. Severe pathology is often in peri-rolandic cortical regions and subcortical structures in the basal ganglia and brainstem [30]. CBD tauopathy does not react to thioflavin-S [29] or C-terminal truncation antibodies [28] but is acetylated at lysine 280 [30]. Interestingly, CBD shares several genetic risk factors, including the H1 *MAPT* haplotype, with PSP [48] suggesting shared mechanisms of disease.

CBD is most commonly associated with an asymmetric frontoparietal syndrome often with lateralized extrapyramidal symptoms (i.e., CBS); however, clinical CBS is only shown to have underlying CBD tauopathy in about 50% of cases, while other neurodegenerative diseases associated with this syndrome include AD, PSP, and FTLT-DTP [49–51]. As such, the term CBD is now used to refer to this specific 4R tauopathy, while CBS distinguishes the clinical syndrome associated with this varied pathology. Clinical criteria for CBS have been developed to improve the diagnostic accuracy for CBD tauopathy [32], but initial replication suggests poor specificity and sensitivity [52]. Ongoing replication and refinement of criteria together with emerging biomarkers of tauopathy will improve diagnostic accuracy for CBD and other tauopathies (Fig. 1).

### Other Tauopathies

Less common tauopathies include other 4R tau predominant findings of argyrophilic grain-like inclusions largely constrained to limbic regions (i.e., argyrophilic grain disease, AGD) [53], globular glial tau inclusions (GGT) [54], and aging-related tau astroglial pathology (ARTAG) [55]. GGT has been described in rare cases of clinical FTD, sometimes with concurrent motor neuron disease, while AGD and ARTAG may be found in cognitively normal aged individuals and the clinical significance is currently unclear. AGD with neocortical involvement can be associated with neuropsychiatric or FTD symptoms.

### Biomarkers for Tauopathies

There is currently no established clinical test that can reliably identify FTLT-Tau antemortem and autopsy-confirmed studies are rare. Due to the complex clinicopathological

associations of FTLT-Tau pathology, study of living patients with PSPS provides an opportunity for biomarker development due to the high predictive value for underlying tauopathy which can be further validated in other forms of tauopathy confirmed at autopsy (Fig. 1).

### Structural Neuroimaging

Neuroimaging techniques using structural magnetic resonance imaging (MRI) of gray matter and diffusion tensor imaging (DTI) of white matter within the context of autopsy-confirmed clinical FTD find some regional differences between subtypes of FTLT-Tau and FTLT-TDP [56]. In one study, diagnostic accuracy to differentiate FTLT-Tau from FTLT-TDP using DTI measurements of cortical white matter degeneration showed high diagnostic accuracy validated by post-mortem measure of white matter degeneration in these patients [57]. In a series of clinical CBS, anatomic dissociation of gray and white matter pathology was seen between patients with AD and CBD pathology [58], suggesting that MRI/DTI measurements may also be useful to distinguish FTLT-Tau from atypical forms of AD. PSP has been well-described to be associated with midbrain atrophy that can be appreciated on standard structural MRI as the “hummingbird sign” [59], “morning glory sign” [60], or “Mickey Mouse sign” [61]. In one study of 48 pathologically confirmed cases of PSP or synucleinopathy, 16/22 (72.7%) of PSP cases were able to be correctly identified by radiologist reviewing conventional MRI, and the presence of a hummingbird sign or morning glory sign was 100% specific but was 68.4% sensitive [62]. A variety of ratios of brainstem structures have been reported to aid in distinguishing PSP from other forms of parkinsonism and from controls; these measures have been associated with a range of sensitivity and specificity [63–68].

### Molecular Imaging

Several radioligands specific for tau pathology have been recently developed [69–71] to detect and track progression of tau pathology in living patients. [<sup>18</sup>F]AV1451 has most extensively studied and there is a strong signal associated with AD tauopathy that recapitulates Braak tangle staging [72]; however, autoradiographic studies suggest that there may be mild or negligible binding to FTLT-Tau [73, 74]. As aforementioned, tau pathology in AD and FTLT-Tau have different biochemical and conformational properties which could contribute. Some studies have shown the ability to discriminate PSPS patients from controls and from patients with AD [26, 75, 76]; however, evidence for potential off-target binding in melanin-containing cells has been described in regions susceptible to PSP tauopathy [74] (i.e., substantia nigra, basal ganglia) which could influence interpretation. Emerging autopsy studies provide good correlation with topography of

FTLD-Tau pathology post-mortem and antemortem [ $^{18}\text{F}$ ]AV1451 signal [26, 77], suggesting potential utility in FTLD-Tau but further study with tissue validation for this and other tracers is needed.

### Biofluid

Cerebrospinal fluid (CSF) analysis may be another avenue for biomarker development in tauopathies. The largest body of data for CSF biomarkers exists for AD-related measures of total and phosphorylated forms of tau (t-tau, p-tau) and amyloid-beta ( $\text{A}\beta_{1-42}$ ) protein. The AD CSF signature of elevated CSF tau and decreased  $\text{A}\beta_{1-42}$  can differentiate AD from controls [78] and may help distinguish atypical forms of AD pathology associated with clinical FTD from those with underlying FTLD-Tau pathology [79]. Further, CSF p-tau levels directly correlate with the burden of post-mortem tau pathology in FTLD [80], and low CSF p-tau levels or the ratio of p-tau to t-tau may accurately distinguish FTLD-TDP from FTLD-Tau [81–83]. Measurements of other forms of tau, including specific isoforms or modifications [84–86], and novel analytes are an area of study needed to help provide FTLD-Tau specific markers for use in diagnostics and trial endpoints.

### Therapeutic Strategies Targeting Pathological Tau

At this time, treatment of tauopathies is largely supportive [87–92] and disease modification remains a primary and unmet goal. Symptomatic therapies often consist of off-label uses of medicines focused on specific clinical features (e.g., psychiatric medications for behavioral changes in clinical FTD) but data is lacking [93]. Due to the poor specificity of most clinical diagnoses associated with FTLD-Tau (Fig. 1), current clinical trials focus on PSPS or AD. Previous disease-modulating trials using riluzole and coenzyme q10 in PSP failed to show long-term benefit [94–96]. Drug development efforts targeting tau currently focus on several broad strategies including inhibiting tau post-translational modifications and aggregation, immunotherapy, stabilizing microtubules, or reducing overall levels of tau protein synthesis (Table 1).

### Tau Phosphorylation, Acetylation, and Aggregation

Under normal physiological conditions tau is phosphorylated at multiple residues [131], but in tauopathies, tau is hyperphosphorylated and phosphorylation at specific residues may contribute to loss of microtubule binding and promotion of aggregation [132]. Glycogen synthase kinase (GSK)-3 $\beta$  and CKD5 have kinase activity for tau and have been studied as potential targets for inhibition [133, 134]. Valproic acid is known to be GSK-3 $\beta$  inhibitor [135, 136], but a trial in PSP showed poor tolerability and failed to meet the primary

endpoint [98]. Similarly, lithium is also a GSK-3 $\beta$  inhibitor that decreased tau accumulations in mouse models [137, 138], but a trial in humans was halted because of poor tolerability (NCT00703677) and another in AD trial failed to reduce CSF p-tau in patients after a 10-week course [97]. CDK5 activity can be inhibited by the use of siRNA or thiazolidinediones [102, 129]; however, it is not clear if aberrant CDK5 activity can be selectively reduced without affecting normal activity [139]. Tideglusib is a thiazolidinedione class small molecule with GSK-3 $\beta$  inhibition activity that failed to show a significant change in clinical rating scales in a phase II trial in PSP; however, MRI measurements performed during the trial showed decreased occipital lobe atrophy in patients who received the drug [99, 100]. Tideglusib also failed a phase II trial in AD as well [101].

The tau protein also undergoes several post-translational modifications including acetylation, nitration, O-glc-NAC, and caspase-mediated cleavage which all are potential therapeutic targets [140, 141]. Acetylation at specific residues of tau at lysine 174 has shown to inhibit its degradation [142] and at lysine 280 accelerate fibrillization [143]. The non-steroidal anti-inflammatory compound, salsalate, has inhibitory activity on acetyl-transferase and ameliorated tau pathology in a murine model [144]. A phase I clinical trial for salsalate is in progress for PSPS.

Methylene blue is a compound shown to have anti-aggregant properties for not only tau [145] but also TDP-43 [146], making it an attractive candidate for clinical bvFTD, which has mixed underlying pathology (Fig. 1). The mechanism of action is currently unclear but some evidence suggests that it can oxidize cysteine residues of tau to maintain a monomeric state [147]. Methylene blue-derived compounds have been tested in a phase III trials for both AD and bvFTD but clinical endpoints were not reached.

### Microtubule-Stabilizing Agents

Microtubule stabilizing agents have been used in oncology to prevent aberrant cell division in solid tumors and have the potential to abrogate loss of microtubule-binding function in tauopathies. Initial studies in paclitaxel were affective in a tau murine model [148•] but may be limited by side effects from exposure to the peripheral nervous system at dosages that reach the CNS in humans; however, several later studies find related compounds with high blood brain barrier (BBB) permeability can ameliorate tau pathology and restore axonal transport in transgenic mouse models [103, 149–151], including the taxane derivative, TPI-287 [105], which is currently in a phase I trial for CBS/PSPS. The protective neuropeptide fragment, davunetide, has microtubule-stabilizing properties, among other potential mechanisms of action, and was recently studied in a large multicenter randomized placebo controlled stage IIb/III trial in over 300 patients with PSP but

**Table 1** Novel therapeutic approaches in tauopathies

Therapeutic class	Drug name	References	Trials
Kinase inhibitors (GSK-3b and CDK5)	Lithium	(Hampel et al., [97])	NCT00703677
	Valproic acid	(Leclair-Visonneau et al., [98])	NCT00385710
	Tideglusib	(Hoglinger et al., [99]; Tolosa et al., [100]; Lovestone et al., [101])	NCT01350362
	Thiazolidinedione	(Cho et al., [102])	–
Acetylation inhibitors	Salsalate	(Min et al., 2015)	NCT02422485
Microtubule stabilizers	Epothilone-D	(Zhang et al., [103])	–
	Davunetide	(Boxer et al., [104])	NCT01056965
	TPI-287	(Fitzgerald et al., [105])	NCT02133846
	Dicytostatin	(Makani et al., 2016)	–
Anti-aggregant	Methylene Blue	(O'Leary et al., 2010; Melis et al., 2015; Wischik et al., 2015)	NCT01626378 NCT01689246
Immunotherapy	Active immunization with phosphorylated tau fragments	(Asuni et al., [106•]; Boimel et al., [107]; Bi et al., [108]; Rozenstein-Tsalkovich et al., [109]; Theunis et al., [110]; Kontsekova et al., [111]; Selenica et al., [112]; Novak et al., [113])	NCT02579252 (AADVacc-1) ACI-35
	Passive immunization with monoclonal antibodies	(Boutajangout et al., [114•]; Chai et al., [115]; Collin et al., [116]; Walls et al., [117]; Lasagna-Reeves et al., [118]; Castillo-Carranza et al., [119]; Chai et al., [115]; d'Abramo et al., 2013; Ittner et al., [120]; Sankaranarayanan et al., [121]; Yanamandra et al., [122]; Yanamandra et al., [123])	NCT02294851, NC-T02281786, NCT02460094, NCT02494024, NCT02820896
Gene therapy	ASO	(Roberson et al., [124•]; Ittner et al., [125]; Roberson et al., [126]; Leroy et al., [127]; Peacey et al., [128])	–
	siRNA	(Piedrahita et al., [129]; Xu et al., [130])	–

unfortunately did improve symptoms [104]. Another trial is underway in CBS/PSPS (NCT01056965).

### Tau Immunotherapy

Tau immunotherapy has become an interest for therapeutic development due in part to the rapid advances in transmission studies of tauopathy. These data suggest that pathogenic species of tau can be accessible in the extracellular space and thereby more accessible for antibody-mediated degeneration [152•].

Active immunization with full length tau caused an inflammatory reaction in mice [153], but immunization using different types of tau fragments and a number of different adjuvants in mouse models has shown improved safety and efficacy in reducing tau pathology in transgenic animals [106•, 107–110, 112]. A recent phase I clinical trial using active immunization was recently completed showing favorable safety profile [113]. Passive immunization studies, which circumvent activation of the innate immune system, have also been an area of

intense research and find evidence for mild to moderate reduction of tau pathology and improvement in clinical phenotypes in some, but not all studies (for a recent comprehensive review please See [154•]). These studies include administration of monoclonal antibodies targeting a range of potential target epitopes including phospho-serine 396,404 [114•, 115], other phospho-epitopes [116, 117], oligomeric tau [118, 119], pathogenic conformations of tau [26, 115, 120, 121], or antibodies developed from an extracellular seeding assay [122, 123] to murine models of tauopathies.

There are several factors which could contribute to efficacy of tau immunotherapy. Only a fraction of circulating antibody can penetrate the BBB and safety and efficacy of repeated dosing of both passive and active immunization are unclear. Techniques to increase permeability such as focused ultrasound [26] or viral vector delivery [26] in murine models provide proof-of-concept for mechanisms to potentially improve CNS delivery of antibodies. The optimal epitope selection for antibody development is unclear as there are

uncertainties in the pathogenic species of tau that is neurotoxic. A disease-specific epitope intuitively would be desirable to avoid degradation of normal soluble tau [26]; however, some data exists for the therapeutic potential for reducing total tau levels in tauopathies. Tau antibodies have the ability to target extracellular or intracellular tau, largely depending on the isoelectric charge of the antibody. In theory, intracellular tau targeting may result in greater efficacy, but could potentially lead to more toxicity than using an acidic, negatively charged antibody capable of only targeting extracellular tau [155]. Presumably, targeting of tau in these separate compartments would stimulate clearance by both external microglia and internal lysosomal/endosomal pathway. Lastly, the optimal affinity of antibodies to promote tau clearance is uncertain. It is possible that high-affinity antibodies could help bind smaller tau aggregates but high affinity binding could also inhibit degradation or even promote aggregation [156].

Two current human studies using an active immunization approach include one phase II trial by Axon Pharmaceuticals SE using tau fragment tau294–305 linked to keyhole limpet hemocyanin (KLH) with an alum adjuvant in patients with mild to moderate AD [111] (NCT02579252) and a phase I trial by AC Immune and Janssen using the phospho-serine 396,404 epitope with a liposomal adjuvant [110]. Passive immunization with a humanized monoclonal antibody targeting a disease specific phospho-epitope [116] was evaluated in a phase I study in 2015 but this was discontinued (NCT02281786). Passive immunization strategies currently in trials include a humanized monoclonal antibody specific for N-terminal extracellular fragments of tau in a phase II trial in PSPS patients (NCT02460094), a phase I trial in PSPS using a humanized antibody targeting extracellular tau aggregates [152•] (NCT02494024) and a phase I study of a tau-specific antibody thought to induce limited microglial activation in healthy controls (NCT02820896) (Table 1).

### Gene Therapy

Reducing levels of tau may be of therapeutic benefit by reducing toxic gain-of-function. Tau knockout mice have been reported to have a largely preserved function by several groups [157, 158], but others have reported a variety of symptoms including motor deficits and weakness [159], impaired contextual and cued fear in conditioning tasks [160], parkinsonism, and cognitive impairment [159, 161, 184]. Thus, the overall safety of long-term tau suppression is currently unclear but several preclinical studies suggest that this strategy can reduce tau-mediated neurodegeneration. Reducing tau levels can potentially be accomplished by inhibiting translation through the use of small interfering RNA fragments (siRNA) or antisense oligonucleotides (ASOs). Indeed, under normal conditions, microRNA species regulate tau translation through binding to the 3' untranslated region of tau mRNA

[162]. SiRNAs are being studied in vitro and in vivo in tau transgenic mice [130]. ASOs can be created that induce the destruction of the bound mRNA by recruiting RNaseH1 or that bind mRNA without causing it to be digested. Of these non-degrading ASOs, the total protein product can be decreased by preventing the 5' cap from forming [163] or by inducing alternative splicing if directed towards the appropriate splice site [164]. Reducing the total tau protein has been beneficial in transgenic mice overexpressing amyloid-beta [124–127]. In tauopathies, inducing alternative splicing with ASOs may be useful to decrease the amount of 4R tau in favor of 3R tau or vice versa as appropriate for specific diseases, and in vitro experiments have been carried out to this effect [128]. Drug delivery of these compounds continues to be a challenge [165]. Intrathecal injection and intraventricular injection have been used previously in other neurodegenerative diseases [166–169]. Tagging ASOs or siRNAs to lipid-based [170] and non-lipid [171, 172]-based vectors can aid in trafficking across the BBB. Viral vectors may be used as well for siRNA delivery, which have the advantage of being able to directly target the nucleus, and such an approach has been used in animal models of Huntington's disease and amyotrophic lateral sclerosis [173–175]. Intraparenchymal injections have been utilized in rat and non-human primate models of Huntington's disease to delivery these viral vectors [176, 177]. Other strategies to transiently increase BBB permeability have been investigated as well including a variety of different compounds and most recently focused ultrasound [178–182].

### Conclusion

Tauopathies are diverse clinicopathological entities that often require coordinated effort between cognitive and movement disorder specialists for accurate diagnosis and effective supportive care. One major obstacle for therapeutic development in tauopathies is the lack of an accurate biomarker to identify tauopathy and track disease progression. Indeed, current clinical trial outcomes largely rely on subjective cognitive or motor functional scales due to the lack of a validated prognostic marker. The high specificity of clinical PSPS and AD for tauopathy makes these patient populations eligible for many emerging biomarker and clinical trials targeting tau, while most other patients cannot currently participate due to the inability to accurately differentiate FTLD-Tau from FTLD-TDP associated with clinical bvFTD, PPA, and CBS. A rapid growth in recent basic science research on the mechanisms of tauopathy provides several avenues for potential therapeutic development of disease-modifying therapies. Coordinated efforts among patients, clinicians, and basic scientists in prospective natural history studies (Fig. 1), such as those currently ongoing in the USA (NCT02365922, NCT02372773,

NCT02966145) and Europe [183], along with tissue validation are needed to improve diagnostics and accelerate the development of therapeutics in tauopathies.

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#### Compliance with Ethical Standards

**Conflict of Interest** David Coughlin declares that he has no conflict of interest.

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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