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REVIEW ARTICLE

Current directions in tau research: Highlights from Tau 2020

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Abstract

Studies supporting a strong association between tau deposition and neuronal loss, neurodegeneration, and cognitive decline have heightened the allure of tau and tau-related mechanisms as therapeutic targets. In February 2020, leading tau experts from around the world convened for the first-ever Tau2020 Global Conference in Washington, DC, co-organized and cosponsored by the Rainwater Charitable Foundation, the Alzheimer's Association, and CurePSP. Representing academia, industry, government, and the philanthropic sector, presenters and attendees discussed recent advances and current directions in tau research. The meeting provided a unique opportunity to move tau research forward by fostering global partnerships among academia, industry, and other stakeholders and by providing support for new drug discovery programs, groundbreaking research, and emerging tau researchers. The meeting also provided an opportunity for experts to present critical research-advancing tools and insights that are now rapidly accelerating the pace of tau research.

KEYWORDS
Alzheimer's, biomarkers, neurodegeneration, tau, therapeutics

1 | TAU STRUCTURE AND BIOLOGY

The earliest discoveries regarding the structure and biology of assembled tau protein occurred in the context of Alzheimer's disease (AD) research and accumulated slowly over many decades. Nearly 60 years passed between the detection, by Alois Alzheimer, of intracellular neurofibrillary tangles (NFTs) in the brains of AD patients[1] and the subsequent discovery that NFTs contain paired helical filaments (PHFs).[2,3] Another two decades passed before researchers determined that the microtubule-associated protein tau[4] is an integral component of PHFs.[5–8] This series of discoveries became a foundation for further exploration of tau's structural diversity and wide range of functions and behavior in both physiologic and pathologic states. It is now clear that the highly flexible structure of this natively disordered protein allows it to participate in numerous signaling pathways and engage in a surprising number of physiological functions.[9,10] Yet, under pathologic conditions, tau monomers undergo conformational changes that lead to the development of abnormal filamentous inclusions, which in turn cause the degeneration of neurons and glial cells and result in a range of neurodegenerative diseases now collectively known as tauopathies.[11–14]

Tau protein is in the central and peripheral nervous systems in a variety of intracellular compartments as well as in extracellular locations, including the interstitial fluid and cerebrospinal fluid (CSF). It is most abundant in neuronal axons, where it plays a role in promoting the polymerization, assembly, and stability of microtubules, which are essential for axonal transport as well as for maintaining the structural integrity of neurons.[4,11,15–17] Tau is a member of the microtubule-associated protein (MAP) family, and it is encoded by a single gene, *MAPT*, which is located on human chromosome 17q21.31. Alternative messenger RNA (mRNA) splicing of exons from *MAPT* results in the expression of six different isoforms of tau protein in the human brain.[18] Each isoform comprises four parts: an N-terminal domain, which may play a role in regulating distance between microtubules; a proline-rich domain that plays a role in cell signaling and interactions with protein kinases and WW domain-containing proteins, with growing evidence that WW domain-containing proteins bind at the proline-rich domain; a microtubule-binding domain; and a C-terminal domain, which may be involved in the regulation of microtubule polymerization.[9,14,19] The isoforms differ at their N-terminals, coded by exons 2 and 3, and in their microtubule-binding regions, coded by exon 10. Alternative splicing of N-terminal exons 2 and 3 results in the addition of a 29-amino-acid sequence (1N), a less commonly expressed replication with a total of 58 amino acids (2N), or an absence of additional amino acids (0N). In the microtubule-binding compartment, the inclusion or exclusion of exon 10 results in

isoforms with four repeated microtubule-binding domains (4R) or with three microtubule-binding domains (3R), respectively. In the healthy adult human brain, 3R and 4R isoforms tend to be equally expressed, with few exceptions.[18,20] Tauopathies can be divided into three groups based on the isoforms present in their filamentous inclusions: 3R+4R tauopathies, 3R tauopathies, and 4R tauopathies (see Table 1).

1.1 | Diversity of tau filament conformers

The first structural analyses of PHF domains,[5,7,23] which established a foundation for discovering relationships between tau structure and function, revealed that when full-length tau assembles into filaments, the repeats form the filament core, and the N-terminal and C-terminal domains form the "fuzzy coat." The discovery that the core repeats of tau filaments also bind to microtubules led to an early hypothesis that an important physiologic function of tau (microtubule assembly) and tau's assembly into pathologic filaments may be mutually exclusive events.[21] Newer research involving the use of cryo-electron microscopy (cryo-EM) is revealing an astonishing diversity of tau filament structures among individuals with AD, Pick's disease, chronic traumatic encephalopathy (CTE), and corticobasal degeneration (CBD).[24–28] These differences exist between diseases; tau filament structures are the same for different individuals with the same disease. Such findings support the hypothesis that distinct conformers of filamentous tau may ultimately help explain not only the specific neuropathological lesions or types of tau inclusions associated with each tauopathy, but also distinct patterns of tau accumulation, progression of disease, and variations in clinical presentations among individuals with tauopathies.

Structural analyses of other proteinopathies will likely provide similar insights. Indeed, at Tau 2020, while accepting the $250,000 Rainwater Prize for outstanding innovation in neurodegenerative research, Michel Goedert described for the first time high-resolution cryo-EM structures of α-synuclein filaments from the human brain, which may ultimately provide important information about multiple-system atrophy (MSA). These filaments were from putamen of five individuals with MSA, a synucleinopathy that affects both nerve cells and glial cells, chiefly oligodendrocytes. The structures obtained by his team and that of Sjors Scheres differ from those determined by researchers using α-synuclein filaments assembled from recombinant proteins.[29] Because Goedert and Scheres previously had shown that the structures of tau filaments from the human brain differ from those of filaments assembled from full-length recombinant tau upon induction of aggregation with heparin,[27,30] it follows that filaments formed from recombinant proteins may not be ideal for structure-based drug design and related experiments. Findings from research by Goedert and Schweighauser et al.[29] may contribute to the development of specific imaging ligands for synucleinopathies, a major unmet clinical need.

An increasingly important area of tau research involves a deeper examination of how and why the morphologies of tau inclusions that characterize various tauopathies vary dramatically, even when their constituent tau fibrils contain the same isoforms. For example, although 4R tau is found in the tau inclusions of progressive supranuclear palsy (PSP), CBD, and argyrophilic grain disease (AGD),[31] CBD is characterized by the formation of "astrocytic plaques" (tau filaments in a corona-like arrangement in astrocytes), PSP by "tufted astrocytes" (long, thin radial processes in astrocytes), and AGD by argyrophilic granular inclusions in neuronal dendrites.[9,31–33] A better understanding of disease-specific tau structures will be instrumental for the development of tau imaging ligands that recognize disease-specific tau filaments for diagnostic and clinical testing in primary tauopathies. Further scrutiny of posttranslational modifications and other processes that result in a wide range of inclusions unique to specific tauopathies will likely have important implications for the development of new treatments.

HIGHLIGHTS

- In February 2020, leading tau experts convened for the Tau2020 Global Conference.
- Recent advances span tau biology, propagation, biomarkers, and therapeutics.
- Cryo-electron microscopy studies have revealed the diversity of tau filament structures.
- Tau positron emission tomography tracers allow in vivo visualization of tau deposition in the human brain.
- Therapeutic approaches aim to prevent the production, aggregation, spread, or deposition of pathologic tau.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors report the updates and advances in tau research presented at the Tau2020 Global Conference.
2. **Interpretation**: Significant advances spanning tau biology, propagation, biomarkers, and therapeutics are contributing to our understanding of tauopathies.
3. **Future directions**: At Tau 2020, the tau research community demonstrated an enthusiastic commitment to advancing the development of anti-tau therapeutics, necessary new imaging agents and biomarkers, and the critical tools that will be needed to facilitate anti-tau drug development. Tau2022 will provide a further update on progress, including on the potential of tau and tau-related mechanisms as therapeutic targets.

1.2 | Posttranslational modifications and noncanonical functions of tau

The classification of tau as a microtubule binding protein and the nearly exclusive focus on its role in promoting the assembly of axonal microtubules during early decades of research likely delayed the

TABLE 1 3R+4R, 3R, and 4R tauopathies

3R+4R tauopathies	3R tauopathies	4R tauopathies
Alzheimer's disease	Pick's disease	Argyrophilic grain disease
Amyotrophic lateral sclerosis/Parkinsonism–dementia complex	Familial frontotemporal dementia and Parkinsonism (some *MAPT* mutations, such as G272V and Q336R)	Corticobasal degeneration
Anti-IgLON5-related tauopathy		Guadeloupean Parkinsonism
Caribbean Parkinsonism		Globular glial tauopathy
Chronic traumatic encephalopathy		Huntington's disease
Diffuse neurofibrillary tangles with calcification		Progressive supranuclear palsy
Down syndrome		SLC9a-related Parkinsonism
Familial British dementia		Tau astrogliopathy
Familial Danish dementia		Familial frontotemporal dementia and Parkinsonism (some *MAPT* mutations, such as P301L and P301S, all known intronic mutations, and many coding region mutations in exon 10)
Niemann-Pick disease, type C		
Non-Guamanian motor neuron disease with neurofibrillary tangles		
Postencephalitic Parkinsonism		
Primary age-related tauopathy		
Progressive ataxia and palatal tremor		
Tangle-only dementia		
Familial frontotemporal dementia and Parkinsonism (some *MAPT* mutations, such as V337M and R406W)		

Notes: In some 3R+4R tauopathies, including Alzheimer's disease and chronic traumatic encephalopathy, all six isoforms can be found in disease filaments. In other tauopathies, only some isoforms are present in tau filaments.[21,22.]

investigation of other potential biologic functions that may be attributed to tau.[34] A deeper exploration of not only the structure and distribution of tau, but also its subcellular locations, post-translational modifications, and tauopathy-specific clusters of tau isoforms has begun to improve our understanding of atypical or noncanonical functions of tau protein, as well as the role of tau in neurodegeneration.[10,14,34]

Tau undergoes many posttranslational modifications in both physiologic and pathologic states, including phosphorylation, acetylation, methylation, ubiquitination, and truncation.[13,14,35] In research to date, the greatest focus has been on the role of abnormal hyperphosphorylation of tau in tau-mediated disease.[10] Tau phosphorylation has mainly been explored through the use of phosphorylation-dependent anti-tau antibodies (AD2, AT180, AT8, CP13, PHF1), some of them (AT100, Alz-50, MC1) recognizing specifically pathologic tau species.[36–41] A wide variety of stressors, including ischemia and trauma, can lead to tau phosphorylation in the brain.[42,43] More recently, a high-sodium diet has been found to trigger specific immune activation that results in tau phosphorylation in the brain and subsequent cognitive impairment.[44] Other posttranslational modifications, such as acetylation and ubiquitination, have also been shown to contribute either directly or indirectly to events that lead to neurodegeneration.[45] Recent research examining the role of ubiquitination in CBD, for example, suggests that posttranslational modifications of tau may play a role in the structural diversity of various tau strains.[24] Other posttranslational modifications appear to influence the stability of intracellular and extracellular tau under physiologic conditions, and a closer examination of these is leading to new insights regarding the impact of tau pathology.

We have recently gained greater insight into the effects of tau on and in the nucleus.[46,47] Physiologic tau is present in the nucleus, where it binds AT-rich satellite DNA and protects DNA from peroxidation-induced DNA damage.[48] Consistent with a role in maintaining genomic architecture, physiologic forms of tau co-localize with nucleoli[49] and pericentromeric heterochromatin, and tau knockout mice have reduced levels of proteins and histone modifications that maintain constitutive heterochromatin.[50] Pathologic forms of tau in the cytoplasm also negatively affect nuclear function through their effects on the actin cytoskeleton and microtubule dynamics. In *Drosophila* and induced pluripotent stem cell (iPSC)-derived neuron models of tauopathy, the effects of tau on actin and microtubules cause the nuclear envelope to involute and the nucleoskeleton to weaken.[51,52] In neuronal nuclei from *post mortem* human brain tissue of patients with AD, invaginations of the nuclear envelope contain filamentous actin and disease-associated phosphorylated tau.[51] Pathogenic forms of cytoplasmic tau are reported to affect nuclear pore localization, function, and nucleocytoplasmic trafficking;[52,53] induce widespread

decondensation of constitutive heterochromatin;[54] promote DNA damage;[55,56] alter RNA stability and RNA export;[57–59] promote ribosome instability;[60] and activate transposable elements.[61,62]

A wide range of additional novel physiologic roles for tau are currently under investigation, including its roles in enabling long labile domains;[63] modulating insulin signaling;[64] regulating myelination;[10,65,66] and regulating learning, memory, and synaptic plasticity.[67] Further examination of these roles will likely have important implications for drug development and will likely improve our ability to discriminate between physiologic and pathologic tau. An important goal moving forward will be to determine which posttranslational modifications play a direct role in triggering tau aggregation in neurodegenerative disease. For example, although hyperphosphorylation of tau can interfere with its role in microtubule assembly,[68] whether hyperphosphorylation of tau triggers human aggregation of tau has yet to be proven.[21] Meanwhile, evidence is emerging that even within a single entity such as AD, different posttranslational modifications lead to different patterns of tau uptake, which in turn affect the rate of progression of clinical disease.[69] Given the "drugability" of enzymes that affect posttranslational modifications and the structural and functional cross-talk between these, deciphering the posttranslational modification code of tau will create opportunities for drug development.[68,70]

2 | PHENOTYPIC AND GENETIC DIVERSITY OF TAUOPATHIES

Without genetic information, imaging, or other biomarkers, the ability to diagnose a specific tauopathy and predict disease course can be exceedingly difficult, because tauopathies frequently have overlapping signs and symptoms.[9,71] Indeed, many tauopathies still can be confirmed only at autopsy. Comprehensive neurologic and neuropsychologic evaluations aid in the recognition of clinical syndromes, and based on these evaluations alone, clinicians often can establish cognitive profiles that enable them to select from among competing clinical syndromes.[46,71] Increasingly, imaging studies and other biomarkers are being used to confirm clinical findings.[72] Imaging studies, together with *post mortem* studies, also have contributed enormously to understanding the underlying causes of specific symptoms by strengthening the link between unique clusters of symptoms associated with distinct tauopathies and corresponding anatomic regions of the brain vulnerable to a given disease.[72,73] In AD, for example, the early symptoms of impaired episodic memory correspond to tau burden in the medial lobe,[72] visual agnosia corresponds to tau burden in regions of the visual cortex (Brodmann areas 18 and 37),[74,75] and ideomotor and dressing apraxia correspond to the accumulation of tau aggregates in the anterior cingulate cortex.[76]

Some of the phenotypic variability among tauopathies, as well as an increased risk for some of them, can be traced to genetic mutations that promote specific tauopathies, to modifier genes, or to other anomalies in genomic architecture. Efforts to sort tauopathies genetically began with the discovery that dominantly inherited mutations in *MAPT* were associated with a form of frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17).[77–79] Because FTDP-17, now considered a familial subtype of frontotemporal lobar degeneration with tau pathology (FTLD-tau),[80] is associated with tau inclusions in neurons and glial cells but not with amyloidopathy, this discovery provided the earliest evidence that tau aggregates alone could lead to neurodegeneration and dementia.

During the same decade, evidence emerged that pathologic tau associated with AD was more strongly correlated with disease progression, cognitive decline, and neuropathologic severity than amyloidopathy, and in turn that amyloidopathy was necessary but not sufficient to explain AD.[81] Subsequent PSP studies helped to confirm not only links between specific *MAPT* mutations and various tauopathies, but also that pathologic tau can be a direct cause of neurodegeneration.[78]

Neurodegenerative diseases in which tau is known to play a primary role, or primary tauopathies, include FTLD-tau, Pick's disease, PSP, CBD, AGD, and CTE. In contrast, so-called secondary tauopathies are those in which pathogenic tau formation develops in response to other pathogenic proteins or pathologic events.[9] Amyloid beta (Aβ) and α-synuclein, both of which have been reviewed extensively, are two examples of pathogenic proteins that have been regarded as stimulators of tau, resulting in the secondary tauopathies of AD and Lewy body dementia, respectively. It is important to note that no known pathogenic mutations in *MAPT* cause neuropathologically defined AD or other secondary tauopathies. Other secondary tauopathies include Niemann-Pick disease type C, Down syndrome, subacute sclerosing panencephalitis, and myotonic dystrophy. Although these differ significantly with regard to clinical manifestations, several secondary tauopathies have some common underlying causes, such as impaired endosomal–lysosomal trafficking, and also have in common that they may be preventable.

To date, more than 50 *MAPT* mutations have been associated with neurodegenerative disease. These mutations are believed to play a role in enhancing tau aggregation, disrupting tau protein structure, and/or interfering with the mRNA splicing of *MAPT* exons. *MAPT* mutations concentrated in exons 9 to 12 are believed to account for approximately 5% of cases of FTLD-tau.[21] Currently, there are no known correlations between *MAPT* mutations and posttranslational modifications of tau.[21]

In addition to direct mutations in the *MAPT* gene, different haplotypes of *MAPT* also have been implicated in the development of primary tauopathies. Two major haplotypes, H1 and H2, can be traced to an ancestral inversion of a large DNA fragment at 17q21.31, which encompasses *MAPT* and a number of other genes.[82,83] Inheritance of the H1 haplotype is associated with an increased risk for PSP, CBD, Parkinson's disease (PD), AGD, and amyotrophic lateral sclerosis (ALS),[21] but is not associated with Pick's disease.[84–86] In contrast, inheritance of the H2 haplotype is believed to confer protection against PSP, CBD, PD, and ALS.[87] The mechanism by which the H2 haplotype confers protection remains unclear; however, some evidence suggests that this haplotype is associated with increased inclusion of exon 3.[88] Newer research is examining the complexities of subhaplotypes and their contribution to risks for specific phenotypes.

Some evidence suggests that subhaplotypes of H1 result in differential risks for some disorders.[85,88,89]

Subhaplotypes of the 17q locus have distinctly different associations for PD and PSP. Subhaplotype H1c specifically seems to associate with PSP but not with PD. Early evidence suggests that in iPSC-derived neurons and microglia from H1c haplotype families, chromatin is in an open state near single nucleotide polymorphisms that associate with PSP; however, this is not the case in iPSC-derived astrocytes. Conversely, three other subhaplotypes (H1.1–H1.3) appear to associate with PD through expression of the astrocytic marker LRRC37A, with some variants being protective, and others increasing risk for PD.[90]

2.1 | Role of genetics in research-advancing tools and insights

A major goal in tau research is to determine the intricate steps by which mutations lead to tau aggregation and accumulation, and in turn to neurodegeneration and neuronal and glial cell death. Mouse and other animal models have proven inadequate for the study of tauopathies, largely because counterparts of human tauopathies do not exist in these models and because human tauopathies are difficult to mimic in these models. For example, although 3R and 4R isoforms are equally expressed in normal adult human brains, the expression of isoforms as well as the range of isoforms in animal brains differ dramatically.[91–93]

Because the inability to adequately capture the complexity of human *MAPT* mutations in animal models represents a significant barrier to the study of human tauopathies, researchers in the field are turning to the use of iPSCs. A recent project co-led by Celeste Karch, Alison Goate, and Sally Temple, involving the collection of fibroblasts, iPSCs, and neural precursor cells from individuals with a range of primary tauopathies, already has become an important tool for tau researchers. This team of researchers generated their collection from 140 individuals with *MAPT* mutations or risk variants, PSP, CBD, and normal cognition. They successfully generated 31 iPSC lines from *MAPT* mutation carriers, noncarrier family members, and autopsy-confirmed PSP patients and 33 genome-engineered iPSCs that were corrected or mutagenized. Together, the team developed a unique resource comprising fibroblasts, iPSCs, and neural progenitor cells coupled with comprehensive clinical histories that can be accessed by the scientific community for disease modeling and the development of novel therapeutics for tauopathies.[94]

One goal of current research is to identify gene variants that may play a role in the progression of various tauopathies. Recent research conducted by Edwin Jabbari and Huw Morris led to the discovery that a gene variant close to *LRRK2*, which is also associated with PD, likely plays a significant role in PSP progression.[95] The team conducted a genome-wide association study (GWAS) of 1001 people comprising one clinical cohort (individuals from the Progressive Supranuclear Palsy-Cortico-Basal Syndrome-Multiple System Atrophy, or PROSPECT, study in the United Kingdom) and one *post mortem* cohort (samples from brain banks in the United States, United Kingdom, and Germany) with the goal of discovering genetic variants that might influence progression of PSP and also might represent drug targets. They demonstrated that variation at the *LRRK2* locus determines the length of survival in individuals with PSP, from the onset of motor symptoms until death, likely through the regulation of gene expression. Their work suggests that modulation of proteostasis and neuroinflammation by *LRRK2* inhibitors might possibly have a therapeutic role in both PSP and PD.

Findings from recent studies that aim to identify potentially protective mutations in AD and other tauopathies also may eventually become a valuable tool for other researchers in the field. Families with autosomal dominant mutations, for example, provide a unique opportunity to study disease progression from preclinical to clinical stages, because carriers of these mutations are genetically determined to develop dementia. These families also may help develop new and more sensitive measures for early detection and help test the implementation of early interventions in clinical trials. Recent research led by Yakeel T. Quiroz at Harvard Medical School reported associations among amyloid and tau deposits using positron emission tomography (PET) imaging and episodic memory measures in cognitively unimpaired carriers of presenilin 1 (*PSEN1*) E280A mutation, several decades before clinical onset.[96,97] They also reported on the first case from the *PSEN1* E280A kindred who developed mild cognitive impairment (MCI) in her 70s, three decades after the estimated age of clinical onset for this kindred. When the patient was examined in the study by Quiroz et al.,[96] she had early MCI and very high brain amyloid, but limited tau tangle and neurodegenerative measurements. Genetic analysis revealed that she had two copies of the apolipoprotein E (*APOE*) ε3 Christchurch (R136S) mutation, suggesting that this genetic variant is protective by reducing tau pathology and neurodegeneration in the presence of high amyloid pathology.[98] Future longitudinal studies of these populations will be needed to further characterize the biomarker trajectory of specific genetic mutations. Much likely will be learned from "escapees" of autosomal dominant mutations—those who remain unimpaired at older ages. Quiroz et al.[96] are also characterizing newly identified Colombian families with *MAPT* mutations leading to frontotemporal dementia (FTD). They plan to extend their studies to include more families with early-onset dementia.

CRISPR-Cas9, a technology that enables researchers to edit parts of the genome by altering its DNA sequence, may prove to be another remarkably useful tool in tau research. At Tau 2020, Patrick Hsu received the Rainwater Charitable Foundation's innovative early career scientist award for his work involving the correction of *MAPT* mutations using CRISPR editing to repair defective tau splicing in neurons. Using a novel RNA-targeting CRISPR system that would no longer induce permanent, and at times unwanted, changes to the genetic code, he successfully targeted *MAPT* RNA to correct splicing imbalances and reduced pathologic tau isoforms in neuronal models of FTD.[99]

3 | TAU PROPAGATION AND HYPOTHETICAL MECHANISMS OF CELL DEATH

The sequential emergence of tau pathology in different areas of the brain, which has been shown to occur in disease-specific, stereotypical patterns in several tauopathies, has been attributed to the vulnerability

or susceptibility of various regions of the brain to a particular disease process.[100] Alongside theories of regional vulnerability, more recent experimental evidence has suggested that propagation might occur in a prion-like manner, whereby abnormal tau seeds are templated and transferred from donor cells to recipient cells.[31,101–103] Although a growing number of newer studies have supported the latter hypothesis, several steps in this hypothesized process remain unclear.[31] Indeed, as yet, tau pathology has not been proven to have several prion-specific characteristics, which include not only cell-to-cell transmission but also infectious transmission from one tissue to another and transmission between organisms.[22,31,104] A better understanding of the events that lead to the formation of tau filaments and insoluble tau aggregates, as well as the detailed events that trigger tau seeding, templated aggregation, and release and uptake in neuronal cells, will be necessary to solve the problems posed by various theoretical mechanisms of tau propagation.[22,31]

Numerous studies have demonstrated evidence of tau-induced seeding, or the induction of aggregation by abnormal tau,[105–108] and some of these also have shown evidence of templated aggregation.[105,109,110] Yet, these studies have so far involved only experimental models, in most cases involving the injection of human brain homogenates into transgenic mice, or the treatment of cultured cells with similar brain extracts. To date, there is limited evidence of templated seeding activity in tau aggregates obtained from individuals with tauopathies, although some researchers have used sophisticated biosensor assays to detect tau seeds in brain homogenates and CSF of individuals with AD and Pick's disease that appear to be capable of inducing aggregation.[111–114]

3.1 | Tau secretion and uptake

Substantial evidence suggests that tau is secreted under normal physiologic conditions,[115] and that tau exists outside cells in the absence of tau pathology or cell death.[116–118] However, whether this physiologic secretion of tau plays any role in the propagation of tau pathology is unknown. Under normal conditions, most tau is secreted in a free, monomeric form, and its release may be mediated by vesicles such as exosomes and ectosomes. This process is known to be regulated by neuronal activity and sleep–wake cycles and may suggest an as yet poorly understood physiologic function of tau.[31,119–121] Transcellular transfer of tau has been demonstrated in cultured cells and in mice,[108,118,122] but the degree to which processes observed in these studies reflect the transfer of pathologic tau in the human brain is yet to be determined. Research examining the mechanisms that might regulate the uptake of tau into cells, and the mechanisms by which tau release and subsequent uptake of tau leads to neuronal damage, has been limited. The role of extracellular vesicles in tau transfer has been recently highlighted.[123] A few studies have demonstrated that tau can bind to receptors on cells, such as heparan sulfate proteoglycans (HSPGs), amyloid precursor protein,[124–126] and low-density lipoprotein receptor-related protein (LRP),[127] and subsequently may gain entry into the cells by means of receptor-mediated endocytosis. Some studies also have shown that tau may trigger damage in receiving neuronal cells by activating signal transduction pathways that lead to Ca^{2+} release.[128]

Recent research elucidated how tau proteins can be taken up in cultured human neurons by binding to the LRP1 on the surface of these cells and demonstrated that LRP1 controls the endocytosis of tau as well as its subsequent spread.[127] After knocking out various cell-surface receptors, these researchers discovered that H4 neuroglioma cells and iPSC-derived neurons without LRP1 receptors were unable to endocytose tau in the form of oligomers or monomers and partially prevented fibril uptake. In contrast, knocking out other members of the low-density lipoprotein receptor family, including LRP1 homologs, did not interfere with tau uptake. Previous research indicating that HSPGs played a role in mediating tau uptake showed that some tau still can gain access to neuronal cells even after HSPGs are knocked out.[126] HSPGs are a common low-affinity, high-capacity binding site for LRP ligands, and it will be important to investigate how they may interact, which may indicate that they bind tau in a cooperative manner. The finding that LRP1 is a key regulator of tau spread in the brain suggests that it is a potential target for the treatment of diseases involving tau spread and aggregation.[127] More research will be required to determine the detailed mechanisms by which LRP1 binds to tau.

3.2 | Potential mechanisms of toxicity and cell death

It is generally assumed that the propagation of tau leads directly to neuronal toxicity, the dysfunction of neuronal networks, and the death of neuronal and glial cells.[31] However, the specific events and mechanisms underlying such toxicity and cell death, and the degree to which distinct pathologic tau species may use different mechanisms, remain unclear. Potential modes of toxicity explored to date have included the disruption of axonal transport and various synaptic defects.[31] However, some studies have shown a lack of neurodegeneration despite demonstrated propagation of tau aggregates.[129] Thus, how exactly propagation of pathologic tau is related to cell death has remained an unanswered question.

Brelstaff et al. recently reported that neurons containing tau inclusions, when under stress, signal nearby phagocytes to engulf and dispose of these neurons while they are still alive.[130] The authors examined living neurons with tau inclusions from P301S-tau mice, which released phosphatidylserine that in turn signaled cocultured phagocytes (BV2 cells and microglia) to identify them and begin the process of phagocytosis. The neurons induced activated microglia to secrete the opsonin milk-fat-globule EGF-factor-8 (MFGE8) and nitric oxide (NO) to facilitate engulfment. The authors noted that neurons with tau inclusions can be rescued when secretion of MFGE8 and NO is prevented. Brelstaff et al. also noted that these neurons, with tau inclusions, are among a long list of cells that undergo phagocytosis while still alive as part of a homeostatic mechanism aimed at regulating cell populations.[130] The finding that phagocytosis of live neurons containing tau inclusions occurs may have implications for the development of

anti-tau therapeutics. For example, a method for preventing phagocytosis may preserve neurons for treatments that inhibit tau aggregation and toxicity.

3.3 | Reconciling propagation theories

There is a growing consensus that the spread of tau pathology in the brain can be attributed to both the selective vulnerability of various neuronal populations to pathologic processes[131–134] and to the spread of tau pathology by means of a prion-like mechanism.[31,100,135–141] Although these were initially regarded as competing theories, recent findings suggest that these theories are not incompatible. Structural and functional connectivity studies assessing brain connectivity and networks have been used to predict how tau will spread, and some studies have shown that tau spreads throughout brain networks, in areas where functionally strong and spatially short connections increase the likelihood of tau seeding and spread.[138,142] Recent multimodal neuroimaging studies have shown that future tau accumulation and neurodegeneration in AD could be predicted by taking into account the specific connectivity of the epicenter (i.e., the region where the pathology starts)[143] and that the best prediction is achieved with a combination of baseline tau levels, functional connectivity, and distance between brain regions.[140] Tau spreading is assumed to be an active process along connected brain regions rather than the result of passive diffusion.

4 | TAU IMAGING

During the past decade, the in vivo visualization of tau deposition in the human brain has been made possible by the development of a number of selective tau PET tracers, which are currently in different stages of development.[144–148] Although tau PET imaging is beginning to be used in clinical trials, most tracers are still simultaneously undergoing validation. Because tau PET imaging has the potential to facilitate accurate diagnoses of tauopathies, assess disease severity and progression, evaluate the efficacy of potential anti-tau treatments, and improve the selection of clinical trial participants, it has become an area of particularly intensive investigation during the past 5 years.

4.1 | Imaging AD pathology

In AD research, PET imaging of Aβ plaques has significantly improved our understanding of spatial and temporal evolution of amyloid pathology, and also played an integral role in the discovery that Aβ is a necessary but not sufficient cause of AD-related cognitive decline.[149,150] The validation of currently available amyloid PET radiopharmaceuticals, which are highly sensitive and specific for the detection of Aβ, involved a rigorous process involving in vitro studies to ascertain binding affinity, selectivity, and pharmacokinetics. A critical final stage of amyloid PET validation involved a comparison of in vivo binding with *post mortem* neuropathology. In the field of tau research, a significant milestone was reached very recently when the results of the first such tau imaging study, which compared [^{18}F]flortaucipir (FTP) PET images to *post mortem* immunohistochemical tau pathology were published in April 2020.[151] Shortly after, on May 28, 2020, another major milestone was reached when the Food and Drug Administration approved Tauvid (FTP) as a radioactive diagnostic for PET imaging to estimate the aggregate density and distribution of NFTs—the first tau tracer approved for use in patients who are being evaluated for AD.

Fleisher et al. used FTP (previously referred to as AV1451 and T807) to obtain PET scans of 64 patients diagnosed with AD or non-AD dementia as well as individuals with normal cognition. Among individuals with dementia, only patients over the age of 50 who had a life expectancy of less than 6 months were enrolled, which resulted in a mean time between scan and autopsy of only 2.6 months.[151] Visual interpretation of FTP PET scans as consistent with an AD pattern predicted a Braak stage V or VI pathology with a high degree of sensitivity (ranging from 92.3% to 100.0%) and specificity (ranging from 52.0% to 92.0%) and strongly suggested that PET imaging with FTP could be used to determine the density and distribution of AD tau pathology and the presence of AD neuropathologic change necessary to support a neuropathologic diagnosis of AD. This study, whose results agree with those of several similar studies[152,153] has a number of important implications for clinical research. Most importantly, the study's results suggest that FTP may be a valuable tool for measuring the outcomes of anti-tau therapies for AD, determining whether anti-amyloid therapies can effectively reduce pathologic tau, and measuring disease stage and progression for the selection of clinical trial participants.[154]

Although tau PET may be useful for accurately assessing advanced stages of tau pathology, it has not yet been proven sensitive enough to accurately detect early pathology. For example, current tau PET tracers cannot accurately distinguish between Braak stage 0 (absence of tauopathy) and Braak stage 1 (early tauopathy in the entorhinal cortex in the medial temporal lobe).[152,153,155,156] Until very recently, researchers also have been unable to pinpoint the precise area in the brain where tau accumulation in AD first begins using tau PET imaging. However, Sanchez et al. recently reported findings that suggest that cortical tau pathology may begin in a region of the brain they call the "rhinal cortex"—a region defined anatomically using brain surface anatomy that is sampled during PET imaging.[157] The area comprises the anterior section of the collateral sulcus (rhinal sulcus) and separates the parahippocampal gyrus from the fusiform gyrus. Examining a cross-sectional and longitudinal tau PET of older individuals and healthy controls from the Harvard Aging Brain Study, the researchers found that tangles can begin to accumulate in this region prior to spread to neocortical areas in clinically normal adults. These detailed observations of subsequent spread of pathology, beginning with invasion of the temporal neocortex and precuneus, were used to develop new tau PET staging thresholds.[157]

As newer tau tracers for AD continue to undergo development, a key goal will be to continue to refine our understanding of the relationship between amyloid and tau during disease progression, using both amyloid PET and tau PET technology. A recent analysis of data from the

Harvard Aging Brain Study examined correlations among longitudinal changes in amyloid plaques, NFTs, and changes in cognition.[158] Findings from this analysis supported a hypothesized model of disease progression in which significant amyloid load leads to the accumulation of both amyloid plaques and NFTs, with the latter in turn driving cognitive decline. Based on their review,[158] concluded that clinically normal older individuals must reach a critical threshold of baseline amyloidosis prior to the acceleration of neocortical tau accumulation. They also concluded that amyloid and tau likely have a synergistic relationship, and found that in nearly all cases, clinical progression was associated with high levels of both amyloid and tau. One important goal in follow-up research involving larger populations will be to identify factors associated with relative resistance to tau accumulation, particularly among individuals with significant amyloid accumulation.

4.2 | Imaging non-AD tau pathology

The development of tau-specific PET ligands has made it possible to investigate the measurement of tau deposition not only in AD but also in a wide range of non-AD tauopathies, including PSP,[155,159–162] CBD,[155,163–166] and Pick's disease.[155] However, FTP and other currently available tau tracers, when used to image non-AD pathology, have generally demonstrated low-affinity binding, significant off-target binding, and other characteristics that have resulted in limited sensitivity and specificity.[165,167–169] These in vivo results converge with autoradiography studies that have shown absent-to-low binding of FTP to non-AD tauopathies.[170–172] Furthermore, FTP binding is also found in patients harboring tau-negative FTLD with TDP-43 inclusions (FTLD-TDP), limiting its utility for differentiating FTLD-tau from FTLD-TDP.[153] The utility of second-generation tau tracers in imaging non-AD has been variable. The radiotracers [^{18}F]R0948 and [^{18}F]MK6240 appear to be even more AD-specific than FTP.[173,174] Conversely, early in vitro and in vivo studies applying the ligands [^{18}F]PI-2620[175] and [^{18}F]PM-PBB3 (also known as [^{18}F]APN-1607)[176] have shown encouraging early results in a variety of non-AD tauopathies.[174,177–179] A new first-in-class 4R-tau radiotracer, [^{3}H]CBD-2115, was recently disclosed that has an attractive in vitro profile in human brain tissue homogenate binding assays, showing higher affinity (4.9 nM) for progressive supranuclear palsy specific 4R-tau deposits than [^{3}H]flortaucipir (45 nM) or [^{3}H]MK-6240 (> 50 nM). Although this tracer does not show sufficient blood–brain barrier (BBB) penetration for in vivo utility, its selectivity profile makes it an attractive departure point for optimization of brain penetration.[180] Nevertheless, the search continues for a better tracer for non-AD tauopathies, which must demonstrate ample BBB penetration, low toxicity, low nonspecific binding, and rapid uptake and clearance from the brain, without leaving radiolabeled metabolites in the brain.[150,181]

Although FTP has proven to be less useful for imaging non-AD tauopathies, because it is exceedingly selective for AD, it can be a useful for tool for differential diagnosis or accurate discrimination between AD and non-AD tauopathies.[182] As research geared toward the development of non-AD tau tracers continues, a key aim will be to achieve excellent PET imaging-to-autopsy correlations. A recently published study that illustrates this process was undertaken with the aim of developing an imaging biomarker for CTE. [^{18}F]flortaucipir was used to assess the correlation between in vivo FTP PET imaging of tau and *post mortem* brain tissue in an individual with CTE. In this patient, a White male former professional American football player with pathologically confirmed CTE, FTP PET findings during life showed only a modest correspondence with *post mortem* pathology and suggested that FTP may have limited utility as a tau biomarker in CTE.[183]

Because tau is a complex molecular imaging target, with heterogeneity in biochemistry and in the microstructure of tau aggregates, it is unlikely that a single tau PET tracer will be useful for capturing patterns of spread associated with different non-AD tauopathies. However, important collaborative efforts are currently under way to optimize the imaging of non-AD tauopathies, in part by taking advantage of the subtle differences in tau folding revealed by cryo-EM technology. The Tau Centers Without Walls, funded by a National Institute of Neurological Disorders and Stroke grant, is bringing together tau imaging experts who are dedicated to developing successful new tracers for non-AD tauopathies. In addition, the Rainwater Charitable Foundation has undertaken a two-pronged approach to the development of non-AD tauopathies tracers. First, it created the PIPETTE Consortium (Philanthropic Investments in Pet Tracers) in 2017 as a cofunding partnership with the Michael J. Fox Foundation to leverage efforts toward creation and optimization of specific α-synuclein and tau ligands. The partners hope to fund promising ligand tracer development at both for-profit and academic institutions that use best-practice structure-based and ligand-based medicinal chemistry optimization using available high-resolution cryo-EM structures of tau and α-synuclein. Second, through the Tau Consortium, it has convened a multidisciplinary team comprising experts in structural biology, computational chemistry, medicinal chemistry, and biophysics to tackle 4R-tau specific ligands. These efforts are expected to improve the efficiency of developing optimal ligands in part by using new computation methods that will likely reduce time to development.

5 | THE IMPORTANCE OF NEW BIOMARKERS FOR TAU

Optimizing the efficiency with which therapies for the treatment of tauopathies are developed will require new tau imaging agents and other novel biomarkers to more accurately assess target engagement, improve the selection of clinical trial participants, and precisely gauge the effects of treatment. Advances in our understanding of tau biology are being incorporated into the development of blood and CSF biomarkers that have the potential to improve measurements of tau, phosphorylated tau, and other markers of neurodegeneration.

Plasma tau phosphorylated at residue 181 (p-tau181) is a useful biomarker for AD and also has proven to be useful in distinguishing individuals with AD from healthy controls and from individuals with other tauopathies.[184,185] In two recent studies, p-tau181 was measured in 993 plasma samples. Plasma p-tau217 also was proven able

to discriminate between neurodegenerative diseases in 1402 persons from multiple cohorts, with performance close to that of CSF and PET markers.[186,187]

As anti-tau drug development continues, some novel biomarkers may well be developed in conjunction with treatments. At Tau 2020, Kristin Wildsmith discussed the simultaneous development of a tau PET tracer ([^{18}F]GTP1) and an anti-tau antibody drug (semorinemab; Genentech).[188] [^{18}F]GTP1 was studied in an AD natural history study to guide use of tau PET in ongoing therapeutic trials (i.e., trials underway by Genentech and Roche). Wildsmith is optimistic that [^{18}F]GTP1 will show that drugs are slowing the spread of tau. It is hoped that [^{18}F]GTP1 will provide proof of activity in the brain, by tracking the accumulation of tau pathology, and determine whether baseline tau burden predicts treatment response. In a cross-sectional population, the degree of [^{18}F]GTP1-specific binding increased with AD severity and could differentiate diagnostic cohorts.

[^{18}F]GTP1 may be a better staging tool than CSF p-tau181, and there are other novel CSF tau biomarkers, such as tau368[189] and CSF p-tau217 that may also outperform p-tau181.[186,190] Recent data published in July 2020 suggest that CSF results extend to plasma p-tau217.[187,191]

6 | APPROACHES TO TAU THERAPEUTICS

Current approaches to disease-modifying treatments for tauopathies involve the targeting of various forms of intracellular and/or extracellular tau to prevent the production, aggregation, spread, or deposition of pathologic tau. Although numerous strategies, including those involving the inhibition of various protein kinases, the inhibition of tau aggregation, the knockdown of the *MAPT* gene using antisense oligonucleotides (ASOs), and active and passive immunotherapies, have shown promise in animal models and other preclinical studies, anti-tau therapeutics have yet to progress beyond the early phases of clinical trials. During the past few years, important overarching goals of anti-tau drug development have included the aim to increase both the number and the efficiency of tau clinical trials, with an emphasis on novel trial design, and to accelerate the development of new biomarkers that can confirm target engagement, ensure appropriate selection and stratification of clinical trial participants, and provide accurate information regarding the reduction of tau burden or spread.[192]

To date, passive immunotherapy has been the dominant strategy for reducing pathologic forms of tau, mirroring the initial focus in anti-amyloid therapies in AD, with multiple compounds in phase 1 and 2 trials. Therapeutic antibodies aim to neutralize or eliminate extracellular tau to slow the progression of tau-mediated neuronal dysfunction and degeneration. Multiple targets are under investigation, ranging from pan-tau antibodies (targeting all six isoforms), to antibodies against specific conformations or unique species of tau. Anti-tau antibodies also differ with regard to their binding site on tau, whether to the N-terminus, the C-terminus, the microtubule binding region, or the proline-rich region.[193–196] Given the large size of the tau protein, many different epitopes could be targeted. How to identify the "best" epitope to target may become a critical issue, and the answer is not obvious. Different selection criteria can be proposed; for example, it might make sense to prioritize epitopes or conformations that clearly distinguish between pathologic and physiologic forms of tau.[69] An alternative approach has focused on identifying the antibody most capable of blocking tau spread by unbiased screening of tau antibodies in a quantitative in vitro assay attempting to model the uptake and seeding of human pathological tau. In this approach, N-terminally directed antibodies demonstrated surprisingly poor efficacy, whereas a mid-region antibody excelled.[197] These data were further supported by in vivo experiments.[198] Clinical trials of this antibody, bepranemab (UCB0107, UCB, Roche/Genentech), in both PSP and AD started early 2018. While clinical development of bepranemab in AD remain in process, plans to continue clinical testing in PSP have been halted.

Because conformational changes in the N-terminal of tau occur early in AD, this region has been the focus of several efforts to develop anti-tau antibodies for AD. The N-terminal fragment also has been a focus in AD because it has been shown to play a role in increasing Aβ production[199] and also to damage neurons by interfering with mitochondrial function and synaptic plasticity.[200] Although antibodies targeting the N-terminal region of tau have exhibited various degrees of efficacy in preclinical trials, there have been clinical trial failures in PSP. There are ongoing clinical trial efforts in AD.

In July 2019, after a preplanned interim futility analysis, AbbVie halted a phase 2 trial of ABBV-8E12, an anti-tau antibody that targets the N-terminal. A humanized IgG4 antibody, ABBV-8E12 recognizes an aggregated, extracellular form of pathologic tau that has been implicated in transneuronal propagation of tau pathology in cell-based and mouse models, and also is believed to account for the stereotypical progression of tau pathology in AD.[101,201] However, the antibody is still undergoing testing in a phase 2 trial of individuals with MCI and early dementia due to AD.

Later in 2019, a phase 2 study of another antibody that targets the N-terminus, gosuranemab (BIIB092; Biogen)[202] for PSP was discontinued. The primary endpoint, as measured by the PSP rating scale at week 52, proved not to be statistically significant, and the study did not demonstrate efficacy with regard to key clinical secondary endpoints. However, although Biogen discontinued development of gosuranemab for PSP and other primary tauopathies, a phase 2 study of gosuranemab for the treatment of MCI in individuals with AD or mild AD is ongoing.

The pan-tau monoclonal antibody semorinemab is currently in phase 2 trials in prodromal and mild AD (TAURIEL GN39763)[203] and in moderate AD (LAURIET GN40040)[204] after positive safety data from the phase 1 study. Although final results are expected in the third quarter of 2021, Roche and AC Immune have announced that TAURIEL did not meet its primary or secondary endpoints demonstrating no benefit over placebo.

The limited success to date in clinical trials testing passive immunotherapy directed at tau and amyloid targets offers some insight into several ways in which future anti-tau antibody trials might evolve. Determining sufficient dose and target engagement with pharmacodynamic and biologic effects of a tau-based therapy is likely to be critical. The development of passive immunotherapy for the amyloidopathy of

AD has underscored the need to have sufficient dosing. Several monoclonal antibodies, including aducanumab and gantenerumab, failed to show therapeutic effects until the need for sustained and larger doses was appreciated. The need to better identify the target pathology in those selected for inclusion in trials was underscored in the bapineuzumab phase 3 program, in which an a N-terminus directed beta amyloid monoclonal antibody was tested in trials with more than 2000 subjects and in which 21.4% of participants were Pittsburgh compound B PET negative for the target amyloidopathy prior to enrollment.[205] It is also important to recognize the value of being able to diagnose patients at an earlier stage of disease. The availability of neuroimaging of markers of amyloidopathy and tauopathy; CSF biomarkers; and, more recently, blood-based biomarkers of amyloid and tau offers critical new opportunities for meeting this goal. Another important aim will be to eliminate factors that might potentially confound trial findings, such as patients or clinical trial participants taking large numbers of medications simultaneously. A third important goal will be to improve outcome measures so they are tailored to different clinical phenotypes.

The heterogeneity among different tauopathies with regard to their biochemical composition, their capacities for seeding and propagation, their different morphologies (tau inclusions), and their tendency to reside in specific compartments of neuronal and glial cells strongly suggests that a single anti-tau immunotherapy is unlikely to be effective in the treatment of multiple tauopathies.[22,206]

Active tau vaccines, like passive anti-tau antibodies, target various regions of tau, including the C-terminus, the microtubule-binding domain, and the mid-region. In preclinical studies, many anti-tau vaccines developed to date have demonstrated the ability to reduce tau pathology,[207] and in animals, some of these have resulted in improved cognition or motor abilities. Only two active anti-tau vaccines have begun to be tested in clinical trials: the ACI-35 vaccine for AD (AC Immune SA, Janssen) and the AADvac1 vaccine for AD and nonfluent primary progressive aphasia (Axon Neuroscience SE). In April 2020, AADvac1 was reported in a phase 2 trial to slow neurodegeneration as measured by significant reduction in levels of plasma neurofilament light chain as well as levels of CSF tau and phosphorylated tau. Although initially ACI-35 demonstrated only a weak immune response during early clinical testing, recent data from a phase 1/2 study demonstrated very high levels of anti-tau antibody titers, levels unprecedented in the tau field, bringing hope that this enhanced immunogenicity approach will show therapeutic effects.

ASOs, whose safety and efficacy have been demonstrated in clinical trials in other therapeutic areas, are short, single-stranded, synthetic DNA-like molecules designed to target and degrade mRNA through the nuclear enzyme RNase H1, thereby reducing production of the subsequent protein.[208] Unlike immunotherapy, tau ASOs can target both intracellular and extracellular tau. However, due to their highly negative charge and inability to cross the BBB, ASOs must be administered intrathecally. Importantly, ASOs are highly selective, dose titratable, and reversible. The first ASO to directly target *MAPT* gene expression (ISIS814907/BIIB080), and in turn tau protein levels, was developed by Ionis Pharmaceuticals in collaboration with Timothy Miller at Washington University in St. Louis. In adult wild-type and human tau-transgenic mouse models, ASOs that targeted tau mRNA, resulting in decreased tau protein levels, have been shown to reduce toxin-induced seizures, neuronal loss, and neurofibrillary pathology. Importantly, human tau ASOs in tau-transgenic mice not only prevented additional tau pathology from forming, but reversed pre-existing neurofibrillary tangles and "seed-competent" tau species. Tau ASOs also have normalized behavioral phenotypes and lengthened survival in mice.[209] Infusion of tau ASO into the CSF of cynomolgus monkeys by an intrathecal bolus was shown to reduce tau mRNA across different brain regions, and CSF tau protein levels after ASO exposure directly correlated to hippocampal tau levels.[208] In partnership with Biogen, Ionis Pharmaceuticals is testing the MAPT-Rx ASO in a phase 1 clinical trial in mild AD. Enrollment for this study was completed in January 2020, and the MAPT-Rx ASO has been well tolerated thus far. Biogen recently licensed BIIB080 and will run all future clinical trials in AD and primary tauopathies.

It is critical that we learn lessons from the negative results in anti-amyloid trials of recent years. We must determine when (at what stage) to treat and how to diagnose early, using biomarkers to identify individuals at an earlier stage of disease. It will be essential to develop markers of patient variability in progression and to determine how much tau should be reduced to ensure safety and efficacy. It also will be important to validate outcome measures to enable robust measurement of biologic and cognitive change.

6.1 | Addressing challenges associated with current approaches to drug development

At Tau 2020, several presentations offered a glimpse of unique strategies currently being pursued in industry to address challenges associated with developing anti-tau therapies. Moving forward, innovative clinical trial designs will be needed to improve the efficiency with which high-quality evidence is obtained during the testing of new interventions. In the field of oncology, for example, master protocols designed with the goal of answering more clinical questions more efficiently and in less time have been successfully implemented.[210] One such master protocol, a basket study, was recently used for the first time in tau research to assess the safety, tolerability, and pharmacodynamics of the microtubule stabilizer TPI-287 in AD, PSP, and corticobasal syndrome (CBS).[211] The goal of a basket study is to examine a single targeted therapy in the context of multiple diseases or disease subtypes, defined by specific underlying molecular causes.[210,211] Although the clinical trial examining TPI-287 did not support further development of the intervention, it did demonstrate the potential value of conducting basket clinical trials to compare the effects of tau-directed therapies in AD, which is a secondary tauopathy, as well as in the primary tauopathies PSP and Aβ PET-negative CBS.[211]

One significant obstacle to treating neurodegenerative disorders has been the difficulty in crossing the BBB, which regulates the transfer of proteins, nutrients, and waste products to protect the brain from toxins, but can also restrict the entry of some drugs. Using the transferrin receptor (TfR), expressed by brain capillary endothelial cells, Denali Therapeutics has developed a large molecule platform—known

as the transport vehicle (TV)—that is capable of transporting a range of molecules over the BBB by binding the apical domain of TfR engineered into the Fc domain of an IgG and subsequently trancytosing through endothelial cells and into the interstitial space of the central nervous system (CNS).[212] Denali has demonstrated both utility and modularity of their TV platform to significantly increase brain levels of numerous types of cargo attached to this TV system, including enzymes,[213] proteins, antibody Fab arms (ATV; eg, ATV:Tau), and oligonucleotides (OTV). With this modularity built into the TV platform, Denali is exploring whether tau can be directly targeted using an ATV:Tau molecule that increases tau antibody levels in the brain and/or an OTV:Tau that delivers a tau-targeted oligonucleotide to the CNS via a systemic injection.

Arvinas is creating a new class of drugs that are capable of degrading pathogenic proteins, including tau. The company designs proteolysis-targeting chimera (PROTAC) degrader molecules, which are heterobifunctional, modular small molecules engineered to induce the degradation of disease-causing proteins by harnessing the ubiquitin-proteasome system.[214] PROTAC small molecules can target the source of pathologic intracellular tau; degrade it; and, in turn, impact the source of extracellular pathologic tau. They also can discriminate between wild-type and pathologic forms of tau. Arvinas's investigational therapeutic has the potential to ensure BBB penetration with oral administration. This approach has advantages over antibodies, which only block extracellular tau, and over current ASOs in the clinic, which so far do not appear capable of discriminating between normal and pathologic tau.

7 | LOOKING AHEAD

At Tau 2020, the tau research community demonstrated an enthusiastic commitment to advancing the development of anti-tau therapeutics, necessary new imaging agents and biomarkers, and the critical tools that will be needed to facilitate anti-tau drug development. The meeting was marked by a strong collaborative spirit and dedication to deepening our understanding of all aspects of tau biology and its relationship to a wide range of heterogeneous tauopathies.

Representatives of various public, private, and academic entities conveyed their blueprints for moving forward. The National Institute on Aging (NIA), for example, has expressed a commitment to pursuing a diversified pharmacologic and nonpharmacologic portfolio of dementia treatments, with a significant portion of their budget devoted to research and related development of treatments for tauopathies and other dementias.

During the past year, the NIA awarded a $73-million grant over 5 years toward the establishment of the Target Enablement to Accelerate Therapy Development for Alzheimer's Disease (TREAT-AD) Drug Discovery Center, which will be devoted to researching the tau protein and other targets. The Discovery Center will be led by Allan Levey of Emory University, Atlanta; Lara Mangravite of Sage Bionetworks; and Aled Edwards, of the Structural Genomics Consortium. These research teams and others will leverage the data and results from the Accelerating Medicines Partnership–Alzheimer's Disease program and develop a series of new therapeutic hypotheses centered on tau, among other prioritized novel targets. TREAT-AD will develop target-enabling tools, including high-quality antibodies and chemical probes, and will openly disseminate all data, methods, and reagents to all interested academic and/or commercial investigators to accelerate validation of novel drug targets and to seed new drug-discovery efforts.

Moving forward, an important focus will be supporting tau-focused drug discovery efforts as well as early-career researchers. Toward this aim, the Rainwater Charitable Foundation and the Alzheimer's Association have partnered to fund emerging drug discovery programs as part of their Tau Pipeline Enabling Program. These 2-year awards go to drug-discovery teams at private and academic organizations in the United States and European Union. A total of $7 million has been granted in the 2 years of this partnership to 13 therapeutic programs.[215] Additionally, the Tau Consortium funds a large portfolio of therapeutic programs focusing on diverse tau targeting mechanisms and modalities (small molecules, antibodies, intrabodies, PROTACS, and ASOs) and provides integrated drug discovery expertise and resources through partnerships with drug discovery institutes and contract research organizations.[216] Importantly, academic drug discovery teams are guided by drug discovery and intellectual property consultants to ensure development of robust data with forward movement into clinical development.

The NIA is also funding many new and early-career awards, including those for non-AD investigators interested in AD research, while the National Institute of Neurological Disorders and Stroke has established a new multidisciplinary Centers Without Walls for research on tau, with a primary focus on data sharing and open science.

A second global tau conference is planned for 2022. As with Tau 2020, the goal of the upcoming Tau 2022 conference will be to provide a forum for academic, industry, philanthropic, and government stakeholders to share new developments in tau research while encouraging enhanced collaboration and alignment regarding remaining challenges in the field. It is hoped that Tau 2022 will continue to attract new talent and funding to the field, while fostering greater awareness of the need for this important research.

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CONFLICTS OF INTEREST

CES is a full-time employee of the Alzheimer's Association and, in the past 36 months, reports consultation fees from Jazz Pharmaceuticals and support for attending meetings and/or travel to the AAIC Satellite Symposium Sydney (2019) and Society for the Study of Ingestive Behavior (SSIB) Annual Meeting (2019). CES reports an unpaid role as a trustee of Dementia Adventure (2018–2020). HS is a full-time employee of the Alzheimer's Association and, in the past 36 months,

reports grants or contracts received from the National Institutes on Aging at NIH and unpaid roles as Chair, Health Research Alliance Programmatic Chair, CDMRP, Alzheimer's. DB is an employee of Asceneuron SA and, in the past 36 months, reports grants or contracts received from the Alzheimer's Drug Discovery Foundation (ADDF; USD 2.2 M in 02/2021 paid to Asceneuron SA) and reimbursements for his travel and meeting expenses as an employee by Asceneuron SA. He is holder of stock, stock options, and founder warrants of Asceneuron SA as founder, employee, and board director. AB in the past 36 months: reports grants or contracts received from NIH, Bluefield Project, Rainwater Charitable Foundation, Biogen, Eisai, Regeneron, Woolsey paid to institution; onsulting, lectures, presentations, speakers bureaus, manuscript writing, or educational events fees from Arvinas, Arkuda, AZTherapies, GSK, ACTG, Lundbeck, Oligomerix, Ono, Regeneron, Roche, Samumed, Stealth, Third Rock, Transposon, Wave, UCB, Peerview, UCLA all paid to AB; he serves on Scientific Advisory Board: Alector, Arvinas, Arkuda, AZTherapies; holds stock options: Alector, Arvinas, Arkuda, AZTherapies; has unfunded biomarker collaborations with Eli Lilly, Novartis, Biogen, LMI all to institution. PB is an unpaid board member of Stroke Onward, a non-profit organization, and is a very minor shareholder of Posit Science. JPB, in the past 36 months, reports grants or contracts received from Belgian National Fund for Research (FNRS) paid to Universite Libre dd Bruxelles, and received support for attending meetings and/or travel to Tau2020 Global Conference February 12–13, 2020, Washington, D.C. LB, in the past 36 months, reports grants or contracts received from French National Research Agency Fondation Recherche Medicale LabEx DISTALZ made to his institution; support for attending meetings and/or travel for the ADPD meeting Tau 2020-Rainwater Charitable Foundation; patents: WO2020193520 method of treatment of tauopathy disorders by targeting new tau species, WO2020120644 New anti-tau single domain antibody, WO2018178078 New tau species. AC is a full-time employee of Arvinas and, in the past 36 months, had patents planned, issued, or pending for WO2016126995A1 - Tau antisense oligomers and uses thereof; is a FSHD Society TACT member; and held stock or stock options in Arvinas. In the past 36 months, GC has received research support from the European Union's Horizon 2020 research and innovation programme (grant agreement number 667696), Inserm, Fondation d'entreprise MMA des Entrepreneurs du Futur, Fondation Alzheimer, Programme Hospitalier de Recherche Clinique, Region Normandie, Association France Alzheimer et maladies apparentees, Fondation Vaincre Alzheimer and Fondation Recherche Alzheimer (all to Inserm); reports personal fees from Fondation d'entreprise MMA des Entrepreneurs du Futur; and reports consultation fees from Fondation d'entreprise MMA des Entrepreneurs du Futur. M Citron is a full-time employee of UCB and, in the past 36 months. reports conference travel funded by UCB and employee stock/stock options in UCB, a biopharmaceutical company engaged in Tau drug development. SDV is a full-time employee and shareholder in Denali Therapeutics Inc. and reports, in the past 36 months, patents planned, issued, or pending for methods for modulating tau expression for reducing seizure and modifying a neurodegenerative syndrome. US20200032257A1, tau modulators and methods and compositions for delivery thereof. US20180153921A1 and methods for treating and monitoring progranulin-associated disorders WO2020081575A1. HF has received in last 36 months grant funding to UCSD from Biohaven Pharmaceuticals, Annovis (QR Pharma), AC Immune, Vivoryon (Probiodrug), and LuMind Foundation; reports fees for service agreements through UCSD for consulting with Novo Nordisk, Merck Pharmaceuticals, Samus Therapeutics, Arkuda Therapeutics, Samumed, and Axon Neurosciences (no personal funds received, all funds to UCSD); reports personal payment received for patent: Feldman HH (filed November 26, 2008). 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LTS has patents in prosecutions from previous employer the CHDI Foundation where LTS worked on a different role to their current role—these patents are owned by the CHDI Foundation, a non-for-profit organization developing therapeutics for patients suffering from Huntington's Disease (https://patents.justia.com/inventor/leticia-m-toledo-sherman); is an employee of the Rainwater Charitable Foundation, a non-profit research organization. SW, in the past 36 months, reports consulting fees from Pfizer, and reports leadership or fiduciary roles in board, society, committee, or advocacy groups for Atalanta, Eikonizo, RBNC, Sironax, Aratome, Denali, TargetALS, Mending Minds with no payment received, part of the job; reports stock or stock options from Denali. 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