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## REVIEW ARTICLE

# A framework for translating tauopathy therapeutics: Drug discovery to clinical trials

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**Abstract**

The tauopathies are defined by pathological tau protein aggregates within a spectrum of clinically heterogeneous neurodegenerative diseases. The primary tauopathies meet the definition of rare diseases in the United States. There is no approved treatment for primary tauopathies. In this context, designing the most efficient development programs to translate promising targets and treatments from preclinical studies to early-phase clinical trials is vital. In September 2022, the Rainwater Charitable Foundation convened an international expert workshop focused on the translation of tauopathy therapeutics through early-phase trials. Our report on the workshop recommends a framework for principled drug development and a companion lexicon to facilitate communication focusing on reproducibility and achieving common elements. Topics include the selection of targets, drugs, biomarkers, participants, and study designs. The maturation of pharmacodynamic biomarkers to demonstrate target engagement and surrogate disease biomarkers is a crucial unmet need.

**KEYWORDS**

biomarkers, development, early-phase clinical trials, preclinical, tauopathy, therapeutics

**Highlights**

- Experts provided a framework to translate therapeutics (discovery to clinical trials).
- Experts focused on the “5 Rights” (target, drug, biomarker, participants, trial).

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- Current research on frontotemporal degeneration, progressive supranuclear palsy, and corticobasal syndrome therapeutics includes 32 trials (37% on biologics)
- Tau therapeutics are being tested in Alzheimer's disease; primary tauopathies have a large unmet need.

## 1 | INTRODUCTION

### 1.1 | Tau and tauopathies

Research in the mid-1980s demonstrated that tau is the major protein in neurofibrillary tangles, one of the pathological hallmarks of Alzheimer's disease (AD).<sup>1,2</sup> Subsequent research determined that tau aggregates are the primary pathological feature of a spectrum of clinically heterogeneous neurodegenerative diseases collectively referred to as tauopathies.<sup>3</sup> Primary tauopathies, with tau as the predominant pathological component, include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease, frontotemporal lobar degeneration (FTLD) due to mutations in the gene encoding microtubule-associated protein tau (MAPT), globular glial tauopathy (GGT), age-related tau astroglialopathy (ARTAG), primary age-related tauopathy (PART), and argyrophilic grain disease (AGD).<sup>4</sup> Secondary tauopathies in which tau aggregation is believed to occur in response to other pathological proteins or events include AD, Parkinson's disease, dementia with Lewy bodies (DLB), and chronic traumatic encephalopathy (CTE).<sup>4,5</sup>

Globally, > 55.2 million people have dementia; the annual incidence is  $\approx$  7 million new cases. By 2050, prevalence will increase to 139 million people worldwide.<sup>6</sup> AD accounts for 60% to 70% of all cases of dementia.<sup>7</sup> In the United States,  $\approx$  11% of people aged  $\geq$  65 years have AD dementia; 33% of those aged  $\geq$  85 years have AD dementia.<sup>8</sup> Prevalence estimates of the primary tauopathies are complicated by widespread misdiagnosis and a lack of specific diagnostic biomarkers. FTLD has been estimated to account for 2.6% of all-cause dementia.<sup>7,9</sup> In epidemiological studies in Olmsted County, Minnesota, the prevalence rates of PSP and corticobasal syndrome (CBS) were estimated to be comparable ( $\approx$  11/100,000).<sup>10</sup> Owing to the small number of cases studied to date, the incidence of CTE is currently unknown.<sup>11</sup> These estimates of the primary tauopathies conform to the definition of rare diseases with < 200,000 people affected with any of these disorders in the United States.<sup>12</sup>

In recent years, important advances have been made in the development of tools and identification of cellular pathways for diagnostic and therapeutic targeting of tau pathology. The mediators of pathogenic tau-induced neuronal dysfunction and death are being elucidated through studies of transcriptomics, including the disruption of nuclear and genomic architecture. The development of positron emission tomography (PET)-based tau imaging has transformed in vivo visualization of tau pathology in AD, and the tracking of its pathological spread in this disease. Important advances in

biologics include early-phase clinical trials testing tau-targeting antisense oligonucleotides (ASOs) to reduce tau production<sup>13</sup> as well as tau-based immunotherapy with monoclonal antibodies (mAbs) targeting the extracellular spread of tau.<sup>14</sup> The development of small molecules for tauopathy has been directed at reducing its production, decreasing its deposition, and enhancing its clearance through autophagy and proteostasis as well as inhibiting the posttranslational modification of tau that is associated with a pro-aggregating state.

In September 2022, the Rainwater Charitable Foundation, one of the largest independent primary tauopathy research funders with > \$140 M invested since 2009, convened and sponsored a workshop focused on a framework for translating tauopathy therapeutics from drug discovery to preclinical development to early-phase clinical trials. This initiative brought together a group of 35 leading preclinical and clinical research experts across neurodegenerative diseases, and more specifically in the tauopathies. Participants included 16 academic faculty, nine industry, and 10 charitable non-profit organizations. The workshop had four objectives: (1) to develop a framework and companion lexicon for the translation of therapeutics from late preclinical development studies to early, proof-of-concept (PoC) clinical trials in primary tauopathies; (2) to share knowledge to foster an environment for capturing the state of the art across different phases of therapeutic development; (3) to identify key questions to be addressed for progress in future therapeutic development of the tauopathies; and (4) to publish the workshop proceedings to share the framework and findings with the broader research community. These workshop objectives align with those from the Alzheimer's Disease-Related Dementias Summit in 2022.<sup>15</sup>

### 1.2 | The lexicon for tauopathy therapeutic development

Across the spectrum of neurodegenerative diseases, there have been several initiatives to develop a common lexicon to facilitate clinical drug development.<sup>16-20</sup> At this workshop, participants considered these existing frameworks across the neurodegenerative disease spectrum and applied them to tauopathy research. Table 1 provides the lexicon for tauopathies that was developed and advanced through this workshop. It refines study-related terms and differentiates types of biomarkers that are critical to the successful translation of medicines from preclinical development through early-phase clinical trials to the goal of achieving PoC.

### 1.3 | Proposed framework to clinical PoC

The workshop focused its framework from drug discovery to the milestone of PoC. It leveraged the *Rights of Precision Drug Development* of Cummings, Feldman, and Scheltens, with adaptation and application to tauopathy therapeutics.<sup>21</sup> Milestones for PoC within this framework include establishing a favorable profile of pharmaceutical properties including safety and tolerability, pharmacokinetics (PK)/pharmacodynamics (PD), blood–brain barrier (BBB) penetration, maximum tolerated dose (or equivalent), and dose(s) to be tested. Early phase 2a studies include safety and tolerability, dose range, and biomarker measures. Preliminary clinical effects, including directional trajectories, effect sizes, and consistency across measures, are ascertained without anticipating statistically significant drug–placebo differences at this stage in these small preliminary trials. Phase 2b studies provide fundamental data for clinical PoC, as they provide a broader assessment of safety, tolerability, impact on target engagement biomarkers; biological effects on other disease biomarkers; and estimates of clinical effect sizes, including those that would be potentially clinically important and likely to be pursued in later-stage registrational trials. Clinical PoC can be considered having been reached when there is a weight of converging evidence of dose, target engagement, PK/PD, biological effects, safety, and tolerability, as well as sufficient clinical evidence to support a decision to proceed to larger scale phase 3 confirmatory registrational trials. The demonstration of clinical efficacy in later stage trials is a prerequisite for full target validation.

## 2 | LANDSCAPE OVERVIEW

With the clinical workshop goal to focus on primary tauopathies, a search in Global Data on January 12, 2024, identified 30 planned or ongoing phase 1 through 3 interventional studies of either frontotemporal degeneration (FTD), PSP, and/or CBD. An abbreviated list of trials is provided in Table 2, including 15 studies in PSP, 17 studies in FTD, and three studies in CBD. Across these diseases, the therapeutic targets and treatments are broad and diverse.

Various approaches are being investigated with 20 small molecules across a diverse range of targets. There are four mAb programs, three gene therapy programs, and one program each of an ASO, cell therapy, fusion protein, synthetic peptide, and vaccine. Three of the programs include participants with PSP and CBD, and three different programs include both PSP and FTD participants. Of the PSP trials, only one is in phase 3, Amylyx's Relyvrio,<sup>22</sup> which is approved for usage in amyotrophic lateral sclerosis (ALS) patients. For the PSP trials, safety and tolerability is the most common primary clinical outcome of interest. There is a phase 3 trial for FTD testing an mAb from Alektor called latozinemab. The majority of the agents being evaluated in FTD trials do not directly target tau biology. Instead, their mechanisms of action include targeting progranulin delivery or activation and sortilin inhibition, among others. The Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center's Frontotemporal Lobar Degenera-

### RESEARCH IN CONTEXT

- 1. Systematic review:** There has not been an approved drug treatment for primary tauopathies. As they are rare diseases, it is vitally important to design studies to move with optimum efficiency from preclinical studies to early-phase clinical trials.
- 2. Interpretation:** A principled approach to drug development for the tauopathies is recommended using the framework of the "5 Rights" including target, drug, biomarker, participant, and design. A companion lexicon can facilitate communication, with a focus on reproducibility and common elements.
- 3. Future directions:** Academic and industry partnerships are fundamental to moving through bottlenecks and accelerating the translation of discoveries from academic labs (bench or basic research) into drug development programs for tauopathies. More timely data and sample sharing will support the necessary development of more robust disease modeling and simulation as well as back-translation from failed trials to inform future corrections. The maturation of pharmacodynamic biomarkers that can demonstrate target engagement and act as surrogate disease biomarkers is a crucial unmet need.

tion Module Sum of Boxes<sup>23</sup> is the most common composite clinical outcome. Of the studies that include biomarker outcomes, volumetric magnetic resonance imaging (MRI) and neurofilament light chains (NfL) in plasma or cerebrospinal fluid (CSF) are the most common biomarkers collected. Within the FTD trials, three trials are investigating agents directed at behavioral symptoms of FTD and are applicable to tauopathies. The Neuropsychiatric Inventory is the most common outcome in behavioral trials.<sup>24</sup>

### 2.1 | Applying lessons learned from related fields of neurodegenerative research

Many of the research challenges of tauopathies are similar to the other neurodegenerative diseases, particularly those diseases that share underlying tau pathophysiology in AD, Parkinson's disease, and ALS. Lessons learned from translational and later stage failed or negative trials in these diseases are relevant to planning future early-phase tauopathy trials.

In AD, the therapeutic road to the successful development of amyloid-lowering therapeutics has been long, complex, and informative. The regulatory approval of anti-amyloid-lowering mAbs, including aducanumab<sup>25</sup> and lecanemab,<sup>26</sup> and the promising phase 3 study results of donanemab<sup>27</sup> validate amyloid beta (A $\beta$ ) as a therapeutic target for AD drug development with the convincing demonstration

**TABLE 1** Proposed lexicon.

Term	Definition
Disease-monitoring biomarker	Can be applied serially and used to detect a change in the severity of disease; may be used for PoP or PoC
Disease-prognosis biomarker	Can forecast the rate of change associated with disease pathophysiology or natural history
Downstream biomarker	Response indicating an indirect impact on disease pathophysiology downstream to its initial site of action and target engagement
Drug repositioning	Developing a therapeutic for an indication other than for what it was originally intended, with prioritization during development and before approval
Drug repurposing	Application of established drug compounds to new therapeutic indications
In silico	Use of informatics (e.g., epidemiology, data mining) to identify novel compounds or for repurposing an existing compound
Patient selection	Defines the inclusion criteria that can use biomarkers to define or enrich a study population
Pharmacodynamic pathway biomarker	Pharmacodynamic biological response in a person linked to a pathway that is directly influenced by an intervention
Pharmacodynamic response biomarker	Biological response in a person linked to an intervention or exposure
Preclinical development	Phase of development that includes model systems in multiple species, including transgenics, knock-in models, and human-derived iPSCs
Preclinical disease stage	A clinical designation for human staging of disease that includes cognitively and behaviorally unimpaired individuals at risk of developing a tauopathy based on the presence of a known causal genetic mutation or disease-state biomarkers. Alternatively referred to as asymptomatic, at risk, or presymptomatic
Proof of principle	Achieved when a <i>biomarker</i> response indicates that a directed intervention has modified the known or suspected pathology of a tauopathy
Proof of concept	Achieved when an intervention has produced a <i>clinical response</i> that may be predictive of efficacy in patients with a tauopathy
Proof of mechanism	Evidence that a molecular target has been engaged and has affected the biology of target cells in a non-clinical model (aka TE)
Safety biomarker	Biomarker which can monitor the toxicity and/or safety of a drug through evaluation of risk
Stratification	Defines the approach to allocation of participants in a study population using biomarkers or other features (e.g., disease stage, severity, site, country) and allowing for a balance of factors identified as critical for a treatment response
Target engagement	A biomarker response that indicates the intervention reached its site of action and has sufficiently engaged its intended target
Target product profile	Describes the intended use, patient population, and other distinctive characteristics including efficacy and safety
TE biomarker	Biological response directly reflective of the intended target
Translational biomarker	Can be deployed in preclinical studies and then advanced to clinical trials, serving as a PD or TE measure
Treatment-predictive biomarker	Can predict the nature and/or extent of a response to treatment

Abbreviations: iPSCs, induced pluripotent stem cells; PD, pharmacodynamic; PoC, proof of concept; PoP, proof of principle; TE, target engagement.

that anti-amyloid mAbs remove A $\beta$  plaque, an effect that is associated with slowing of clinical decline. The slowing (25%–35%) across clinical outcome measures over 18 months in these phase 3 trials supports the amyloid hypothesis, as does definitive evidence of amyloid clearance on PET and reductions of phosphorylated tau (p-tau) and other fluid biomarkers. The potential for augmenting treatment response in AD with combinatorial therapies directed at tauopathy and neuroinflammation and their interaction is an appealing strategy.

At the same time, the failure or negative results of multiple preceding A $\beta$ -targeted late-stage AD trials are likely due to several factors that could be addressed in earlier phases of development,<sup>19,28</sup> including inconclusive definition of the target, insufficient evidence of target

engagement,<sup>29,30</sup> inclusion of patients who did not have A $\beta$  pathology, having non-A $\beta$  comorbid pathologies driving their clinical progression, and testing at an overly advanced stage of disease. For these failed A $\beta$ -targeted therapies, setting clinical PoC in phase 2 as a checkpoint before advancing to phase 3 trials would have required a better understanding of the range of doses for target engagement, the extent of pharmacodynamic response with A $\beta$  lowering, and the risk–benefit of the higher doses that were eventually required for clinical efficacy.

Although Parkinson's disease is not considered a primary tauopathy, there is pathological tau aggregation and deposition in  $\approx$  50% of brains in affected patients, with evidence for cell-to-cell spread and interaction with  $\alpha$ -synucleinopathy.<sup>5</sup> The  $\alpha$ -synuclein ( $\alpha$ -syn)

**TABLE 2** Current therapeutic trials for PSP, CBD, and FTD (as of January 12, 2024)<sup>a</sup>.

Drug name	Company name	Development stage	Disease	Molecule type	Mechanism of action	Clinical trial details
Latozinemab	Alector Inc	Phase 3	FTD	Monoclonal antibody	Sortilin inhibitor	NCT06111014
Sodium phenylbutyrate + taurursodiol (AMX0035, Relyvrio, Albrioza)	Amylyx Pharmaceuticals Inc	Phase 3	PSP	Small molecule	Apoptosis regulator BAX inhibitor	NCT06122662
AZP-2006	AlzProtect SAS	Phase 2	PSP	Small molecule	Prosaposin-progranulin complex regulation	NCT04008355
Apilimod mesylate (LAM-002A)	OrphAI Therapeutics Inc	Phase 2	FTD	Small molecule	1-phosphatidylinositol-3-phosphate-5-kinase (PIKFYVE) inhibitor	NCT05483322
ASN-90	Grupo Ferrer Internacional SA	Phase 2	PSP	Small molecule	Protein O-GlcNAcase inhibitor	No active PSP trial found (to be initiated)
AVB-101	AviadoBio Ltd	Phase 2	FTD	Gene therapy	Progranulin activator	NCT06064890
Censavudine	Transposon Therapeutics Inc	Phase 2	FTD, PSP	Small molecule	Reverse transcriptase inhibitor	NCT04993755
Deulinoleate ethyl (R001)	Retrotope Inc	Phase 2	PSP	Small molecule	Downregulates oxidative stress. It protects cells from damage, mediated through lipid peroxidation	NCT04937530
Fasudil (BRAVYL)	Woolsey Pharmaceuticals Inc	Phase 2	PSP, CBD	Small molecule	Rho kinase inhibitor	NCT04734379
Hydromethylthionine mesylate (LMTX)	TauRx Therapeutics Ltd	Phase 2	PSP	Small molecule	MAPT inhibitor; TAR DNA-binding protein-43 inhibitor	No active PSP trial found (to be planned based on results in AD)
Oxytocin (Syntocinon)	Phoenixus AG	Phase 2	FTD	Synthetic peptide	Oxytocin receptor agonist	NCT03260920
PBFT-02	Passage Bio Inc	Phase 2	FTD	Gene therapy	Progranulin activator	NCT04747431
Rotigotine ER	UCB SA	Phase 2	FTD	Small molecule	Dopamine receptor agonist	NCT04937452
Tertomotide (GV1001, Riavax)	GemVax & Kael Co Ltd	Phase 2	PSP	Subunit vaccine	Telomerase reverse transcriptase added MOA: Gonadotropin releasing hormone receptor (GNRHR) agonist	NCT05819658
DNL593	Denali Therapeutics Inc	Phase 2	FTD	Fusion protein	Progranulin replacement	NCT05262023
PR-006	Prevail Therapeutics Inc	Phase 2	FTD	Gene therapy	Non-replicating recombinant adeno-associated virus serotype 9 (AAV9) to deliver codon-optimized DNA encoding wild-type progranulin	NCT04408625
Bepranemab (UCB0107)	UCB SA	Phase 1 Phase 1	PSP	Monoclonal antibody	Microtubule associated protein tau inhibitor	NCT04658199

(Continues)

TABLE 2 (Continued)

Drug name	Company name	Development stage	Disease	Molecule type	Mechanism of action	Clinical trial details
TPI-287	Cortice Biosciences Inc	Phase 1 <sup>(b)</sup> (see comment under clinical trials)	PSP, CBD	Small molecule	Tubulin inhibitor	NCT02133846 (completed in 2019)
AHT-434	Alterity Therapeutics Ltd	Phase 1	PSP, CBD	Small molecule	A-syn inhibitor	In phase 2 for multiple system atrophy (NCT05109091). No specific phase 1 trial found for PSP in Australia
AL-101	Alector Inc	Phase 1	FTD	Monoclonal antibody	Sortilin inhibitor	NCT04111666 (obtained fast track designation for FTD in 2020)
ANAVEX-371	Anavex Life Sciences Corp	Phase 1	FTD	Small molecule	Muscarinic acetylcholine receptor M1 agonist; Sigma non-opioid intracellular receptor-1 agonist	NCT04442945 (obtained orphan drug designation for FTD in 2016)
APNmAb-005	Aprinoia Therapeutics Inc	Phase 1	FTD, PSP	Monoclonal antibody	Microtubule associated protein tau inhibitor	NCT05344989
Buntanetap tartrate (Posiphen)	Annovis Bio Inc	Phase 1	FTD	Small molecule	A-syn inhibitor; A $\beta$ A4 protein inhibitor; MAPT inhibitor	No specific clinical trial found for FTD (except in pipeline on company website)
NAS-150	New Amsterdam Sciences Inc	Phase 1	PSP	Small molecule	NADPH oxidase 4 inhibitor	No active phase 1 trial found (in planning on company website)
NIO-752	Novartis AG	Phase 1	PSP	Antisense oligonucleotide	MAPT inhibitor	NCT04539041
NP-001	Neuvivo Inc	Phase 1	FTD	Small molecule	Purified form of sodium chlorite, which targets immune system macrophages	Listed by company as being in phase 1 but no clinical trial was found
ET-STEM	Samsung Medical Center	Phase 1	FTD	Cell therapy		NCT05315661
TQS-168	Tranquis Therapeutics Inc	Phase 1	FTD	Small molecule	Peroxisome proliferator activated receptor gamma coactivator 1 alpha modulator	The company announced completion of phase 1 in 2022. Exploratory development ongoing in FTD
VES-001	Vesper Bio ApS	Phase 1	FTD	Small molecule	Sortilin inhibitor	No clinical trial found but company announced dose to first volunteer in phase 1 study in Dec 2023
OLX-07010	Oligomerix inc	IND/CTA filed	PSP	Small molecule	Microtubule associated protein tau inhibitor	In phase 1 for PSP

Abbreviations: A $\beta$ , amyloid beta; AD, Alzheimer's disease; CBD, corticobasal degeneration; FTD, frontotemporal degeneration; MAPT, microtubule-associated protein tau; NADPH, nicotinamide adenine dinucleotide phosphate; PSP, progressive supranuclear palsy.

<sup>a</sup>Source: Main source Global Data.

<sup>b</sup>See comment under clinical trials.



hypothesis of Parkinson's disease is based on the discovery that Lewy body inclusions contain aggregates of  $\alpha$ -syn in patients with familial Parkinson's disease.<sup>31</sup> In a consensus white paper proposing a roadmap for Parkinson's disease to achieve PoC in clinical trials targeting  $\alpha$ -syn, Merchant et al. applied lessons from both AD clinical trials and previous Parkinson's disease trials.<sup>19</sup> This Alpha-Synuclein Working Group focused on the need to target early disease stages, establish target engagement and other biological measures of therapeutic response that are critical for the interpretation of study results, enrich trials with participants with demonstrated evidence of target pathology, identify clinical endpoints with greater sensitivity to demonstrate slowing of disease progression, and target multiple mechanisms for meaningful impact. The authors followed the five types of biomarker-based evidence (i.e., diagnostic, monitoring, response, predictive, prognostic)<sup>32</sup> and, by doing so, developed a lexicon of terms to be used as part of their roadmap. To date, in clinical trials with  $\alpha$ -syn-targeted mAbs in Parkinson's disease, including prasinezumab<sup>33</sup> and cinpanemab,<sup>34</sup>  $\alpha$ -syn has been negative. The informative results of the failed amyloid antibody trials in AD may help clinicians understand where the hurdles exist in dosing, target engagement, or biological effects in Parkinson's disease. Indeed, recent biomarker data released from the cinpanemab trial may offer insight into some of these hurdles.<sup>35</sup>

Among neurodegenerative diseases, ALS has recently seen significant therapeutic progress resulting from innovative drug development approaches. In a recent review, some of the above-mentioned AD and Parkinson's disease therapeutic development challenges were addressed in the context of ALS, including how recent molecular discoveries, progress in the development of therapeutics (i.e., biomarkers, drug repurposing strategies, and high-throughput drug screening), and new trial designs have been facilitated by improvements in patient-reported outcome measures.<sup>36</sup> Existing obstacles in ALS in moving promising therapeutics to the clinic have included the lack of large-scale research infrastructure to conduct clinical trials with the close follow-up needed.<sup>37</sup> The extent of disease heterogeneity and the lack of proven biomarkers and clinical outcomes have been hampering; however, genetic signatures have helped inform individual course and treatment response, with precision medicine focus and with programs around disease mutations. Within the goal of rapidly identifying novel treatments, biomarkers, and trial endpoints, new approaches to early-phase clinical trials have been developed.<sup>38</sup> The Healey ALS Platform Trial is a novel and informative approach using an adaptive platform design, with a master protocol allowing for the concurrent testing of multiple investigational products.<sup>38</sup> Platform trials like Healey ALS hold the potential to accelerate trials and drug development and are now being planned for the assessment of tau therapeutics.<sup>39</sup> They also create an opportunity for many patients to participate in clinical trials more easily.<sup>40</sup>

The recent regulatory approvals of the ASO Tofersen (QALSODY, Biogen) for persons with autosomal dominantly inherited superoxide dismutase 1 mutation causing ALS provides an example of a targeted success for tailored, precision-based RNA treatment approaches that might also aptly inform trials for those with tau mutations.<sup>41,42</sup> The approval pathway for Tofersen was accelerated based on biomarker

effects on NFL as a surrogate biomarker that was considered reasonably likely to predict clinical benefit. This approach might be available for use in tau therapeutic programs if key biomarker changes can be convincingly linked to clinical outcomes.

Other disorders with tau pathology are emerging and may gain more attention as their tau pathophysiology is better understood. For instance, the results of myotonic dystrophy (DM) studies may inform the development of tau therapeutics. DM is characterized by a toxic RNA gain-of-function mechanism that disrupts RNA processing, localization, and translation.<sup>43</sup> Adult-onset forms of DM have a congenital delay and progressive decline.<sup>44</sup> Some patients with DM types 1 and 2 show intracellular tau aggregates in the brain.<sup>45,46</sup> Another disorder displaying tau pathology includes tuberous sclerosis complex (TSC). TSC is an amyloid-independent tauopathy associated with elevated phosphorylated 3R/4R tau aggregation.<sup>47</sup> TSC is a neurodevelopmental disorder associated with mutations in the *TSC1* and *TSC2* genes, leading to the growth of benign masses in several organ systems and, often, to behavioral, cognitive, and psychiatric difficulties.<sup>48,49</sup> ARTAG is a recently described 4R tauopathy.<sup>50</sup> ARTAG presents with astrocytic tau pathology and predominantly affects the elderly. ARTAG is believed to be distinct from PART, which involves mostly neuronal tau pathology. Finally, there are copathologies, including transactivation response DNA-binding protein 43 kDa (TDP-43) and tau.<sup>51</sup> The comorbid tau and TDP-43 pathology may be synergistic with their neurotoxicity, and mixed pathology may be associated with severe AD outcomes.<sup>52</sup> Many of the tau therapeutics in development or the clinic today may be useful for these disorders in addition to the more traditionally known tauopathies.<sup>53</sup>

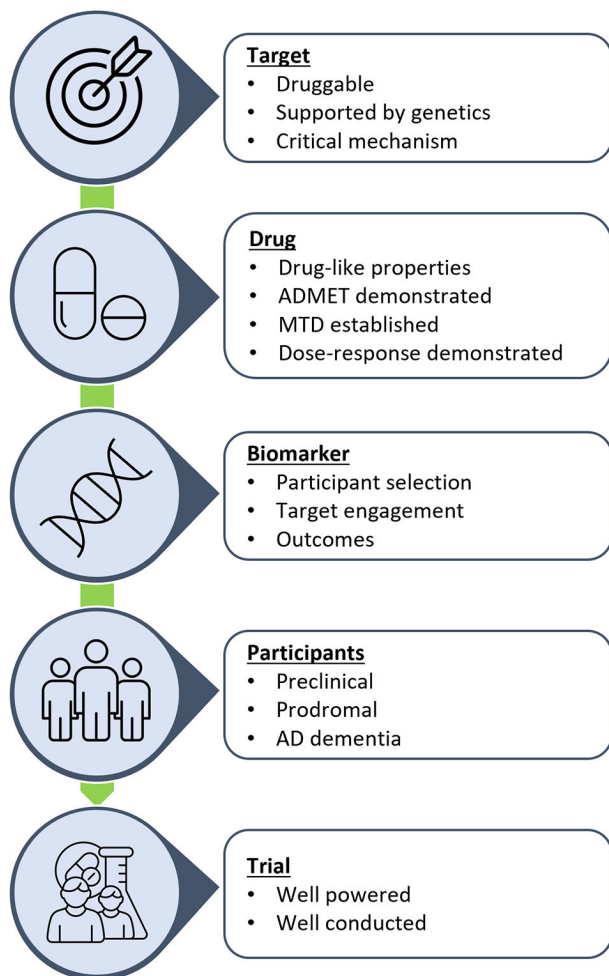
### 3 | THE 5 RIGHTS OF AD DRUG DEVELOPMENT: APPLIED TO TAUOPATHIES

Given the low success rates of clinical trials across neurodegenerative diseases including AD, Parkinson's disease, and ALS, coupled with the rare incidence of primary tauopathies, particular attention at this workshop focused on considerations around the most efficient and adaptive approaches to early-phase drug development. To this end, this workshop adapted the five "rights" of precision drug development for AD<sup>21</sup> with application to the other tauopathies. The framework includes the right target, right drug, right biomarker, right participants, and right trials (Figure 1).

#### 3.1 | The right target

The right "target" for tauopathy ideally includes those: (1) with a direct linkage to dysfunction in the disease, (2) are genetically causative, or (3) are associated with biomarker changes through the disease course. For tauopathies, this can include the production of tau species through effects on transcription and translation; cell-to-cell pathological spread via transsynaptic propagation, microtubule stabilization, and clearance, either intracellularly through autophagy and proteostasis; or





**FIGURE 1** Five “rights” of precision drug development for Alzheimer’s disease.<sup>18,21</sup> AD, Alzheimer’s disease; ADMET, absorption, distribution, metabolism, excretion, toxicology; MTD, maximum tolerated dose.

through active or passive immunomodulation.<sup>54</sup> Furthermore, there are identifiable targets that can prevent tau’s pathological posttranslational modification by acetylation, phosphorylation, O-GlcNAcylation, nitration, ubiquitination, and SUMOylation, leading to its misfolding and aggregation.<sup>55</sup> This approach in development and target validation in drug discovery follows the therapeutic hypothesis based on genetic, human pathologic, and model data. Denali Therapeutics refers to genetically verified drug targets as *degenogenes*, which by analogy are similar to oncogenes that have served as targets for oncology drug development.<sup>56</sup> An alternative approach is to use proteomic, lipidomic, or metabolomic approaches to identify new targets, relying on CSF and other biospecimen samples being drawn from natural history studies.

To identify the right target, the criteria and process for preclinical studies in preparation for early clinical drug nomination must be established. The target identification process can follow genetic causes of disease, and the biochemical pathways altered as a result (e.g., from post-mortem tissue). The genes and proteins in these pathways, as well

as the consequential pathophysiology resulting from these alterations (e.g., neurofibrillary tangles), become the targets. Model systems have been valuable for studying these altered disease processes and identifying tractable targets with the potential for modulation provided that a suitable agent (e.g., the right drug) can be identified. Major caveats to identifying the right target for tauopathies include limited availability of patient data from genetically affected pedigrees, access to ante-mortem and post-mortem tissues, and the lack of well-validated model systems that recapitulate the underlying biology and heterogeneity of disease for each specific tauopathy.

The workshop identified challenges and still unresolved issues in preclinical development and modeling of tauopathies. There is a clear need for better translational models that recapitulate human disease with which to advance target validation. This recommendation was born of the widespread recognition that all the tauopathy models to date have strengths and limitations, and it is unlikely that any one of the currently available models can capture all aspects of the clinical diseases. Rather, each model is used with appropriate awareness of its limitations and is selected based on the hypothesis that is being evaluated, and that is best matched to the mechanism of action of the drug being tested. Given these limitations, the workshop recognized that it is important to design a “fit-for-purpose” study with selected models to appropriately evaluate aspects of the disease that the model can represent.<sup>57,58</sup> The currently available murine tauopathy disease models do not generate human-relevant neurodegeneration, nor do they capture disease heterogeneity.<sup>59</sup> To increase the relevance, such models can be humanized by “knocking-in” a human gene to replace the mouse homologue rather than depending on protein-overproducing transgenic models. For tauopathies in particular, there is an unmet need presently for mouse models that are specific to unique tauopathies, and that can facilitate mechanistic studies for testing compound activity.

The major challenge of recapitulating human tauopathies is finding a suitable model system that fully outlines the complex tau splicing in human brains.<sup>60,61</sup> For instance, rodent brains express neither the six isoforms of tau proteins found in adult humans nor the distinct patterns of 4-repeat (4R tau) in a number of the human primary tauopathies (CBD, PSP, AGD, GGT, and many of the *MAPT* mutations), nor the 3-repeat (3R) in others (Pick’s disease), nor the 4R/3R (AD tauopathy, PART, CTE).<sup>62–64</sup> Studies also showed that the presence of murine tau protein interferes with human tau protein aggregation and toxicity, whereas forced expression of wild-type human 4R tau is highly toxic to murine neurons.<sup>65,66</sup>

Human neuronal cell models could provide a more relevant in vitro system to recapitulate tauopathy in human brain-like conditions, including tau splicing. With recent advances in the inducible pluripotent stem cell (iPSC) and direct conversion technologies, human neurons with AD and tauopathy-inducing mutations can be generated and maintained in standard cell culture conditions.<sup>67–70</sup> These cellular models enable the characterization of the early stages of tauopathy in human neurons and the influence of AD and human *MAPT* mutations.<sup>67–72</sup> However, most human iPSC-derived neural culture models display the fetal tau-splicing pattern with predominantly 3R isoforms but lacking 4R, which is critical for recapitulating robust tau

pathology.<sup>61,73,74</sup> Intronic mutations altering 3R/4R tau splicing also induce tauopathy in humans.<sup>60,74</sup> Missense mutations causing tauopathy are concentrated in exon 10 of the tau gene, included only in the 4R tau isoform.<sup>60</sup> Therefore, insufficient expression of 4R tau in the iPSC-derived neuronal models makes it challenging to use these mutations for disease modeling. Furthermore, due to the *in vitro* nature of iPSCs, they also lack the micro-environment and cell–cell interactions that are critical to recapitulating human tauopathies.<sup>61,75,76</sup> Indeed, iPSC-derived neurons have failed to produce robust tauopathy, including aggregation of hyperphosphorylated tau species and tau-induced neurodegeneration.

Multiple technologies are being developed to address the shortcomings of insufficient 4R tau expression and to recapitulate robust tauopathy in human cellular models. Three-dimensional (3D) culture conditions accelerate 4R tau generation and, thereby, tauopathy in human neural cell cultures.<sup>77–82</sup> Choi et al. have shown that A $\beta$  accumulation in a 3D extracellular matrix is sufficient to induce robust tauopathy in human neural cells.<sup>77</sup> In this study, 3D-differentiated human fetal neural progenitor cells expressed an equimolar ratio of 4R and 3R tau isoforms, similar to those found in human adult brains.<sup>77</sup> Human iPSC-derived neurons, differentiated in the 3D matrix, also showed elevated 4R tau expression, although it took longer to display adult brain-like tau pathology.<sup>79,80</sup> Finally, brain organoid models required even more extended maturation (9–18 months) to exhibit elevated 4R tau expression, and the expression level is lower than in the iPSC-derived neurons in 3D culture systems.<sup>83,84</sup> The issue of slow maturation can be addressed to some degree through induced/transdifferentiated human neurons, which display more mature neuronal phenotypes and preserve disease-associated phenotypes in standard two-dimensional (2D) culture conditions, especially compared to iPSC-derived neurons.<sup>68</sup> When induced by mitochondrial RNAs, transdifferentiated human neurons consistently expressed high levels of 4R-related tau pathology comparable to human brains.<sup>85</sup> Adding a tauopathy mutation in the same model increases the 4R-to-3R tau ratio and promotes seed-competent insoluble tau species.<sup>85</sup> Exogenous tau seeds, recombinant or patient derived, have also been used to accelerate tau pathology in iPSC-derived human neurons.<sup>86–89</sup>

Although progress has been made, triggering *in vitro* full-blown tau pathology model systems remains challenging, as they lack the aging component observed in human brains. Direct conversion/transdifferentiation could mimic patient cells' age or stress conditions. Also, the biology in play is driven by the genetics of the donor. Furthermore, this technology depends on a supply of primary cells with low proliferative capacity, limiting the technology's generalized use for drug screening and validation. Recently, studies have demonstrated the critical role of microglia and peripheral immune cells in regulating brain tauopathy,<sup>90–92</sup> which has not yet been fully integrated into most human cellular tauopathy models but represents an emerging model area. Despite the challenges, new human cellular models of tauopathy provide an attractive platform to screen and validate drug candidates in human brain-like conditions and can complement current rodent and non-human primate

tauopathy models, potentially bridging the rodent-to-human translational gap.<sup>93</sup>

Beyond the models themselves, the workshop addressed the need for rigorous, reproducible non-clinical studies and initiatives to confirm findings and create a commonality of approach with replication. The Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD),<sup>94</sup> a consortium funded by the National Institute on Aging in 2016, represents such an effort to improve translation from animal models to humans.<sup>94</sup> MODEL-AD has generated > 50 new mouse models that recapitulate genetic risk for late-onset AD (LOAD) that are available to both non-profit and for-profit institutions, without any licensing restrictions.<sup>95</sup> The program has completed basic phenotypic analysis on > 30 of these models with comprehensive phenotyping including disease trajectories at the pathological, transcriptomic, proteomic, and functional levels on > 15 models.<sup>95</sup> Its aims include to (1) develop, characterize, and distribute the next generation of animal models of AD—with a focus on LOAD—based on human data; (2) establish and implement guidelines for rigorous preclinical testing in LOAD models with standards comparable to human clinical trials; and (3) provide a resource for standardized therapeutic efficacy testing of preclinical drug candidates that prioritizes translational biochemical and physiological endpoints over behavioral measures (e.g., mouse cognitive tests) using best practices.<sup>96</sup>

As part of the MODEL-AD consortium, the Preclinical Testing Core established a rigorous screening strategy with “Go/No-Go” decision points that permit unbiased assessments of potential therapeutic agents in the mouse models characterized by the consortium.<sup>96</sup> Based on the available funds, the Preclinical Testing Core can evaluate up to two compounds per year, through a program that selects compounds nominated by investigators from the greater research community: Screening the Optimal Pharmaceutical for Alzheimer's Disease (STOP-AD).<sup>97</sup> Upon selection, each compound is matched to an appropriate mouse model using a precision medicine-like approach (e.g., Right Patient) to ensure the target is expressed in the animal model within the stage of disease that is analogous to the interventional strategy of the anticipated clinical trial. For these studies, the selected outcome measures in the non-clinical trials are prioritized for those that are most translational from mouse models to humans. More specifically, the initial screen evaluates drug stability, formulation, and PK to confirm appreciable brain exposure and *in vivo* target engagement in the disease model at the disease-relevant ages. The findings from these initial steps allow for early identification and correction of drug formulation issues before advancing the drug to longer term, resource-intensive studies. Then, PD and predictive PK/PD modeling determine the dose regimen for long-term studies. The secondary screen evaluates target engagement and disease-modifying activity using non-invasive PET/computed tomography. If the compound meets the “Go” criteria for these endpoints, functional activity on behavioral endpoints is evaluated with a focus on identifying a therapeutic window and de-risking for the potential for side effects. The post-treatment analysis includes the evaluation of changes in proteomic and transcriptomic signatures after drug treatment. Importantly, the

STOP-AD program has developed an evaluation framework that can allow side-by-side comparisons of therapeutic candidates offering a common measure of their potential to be successful.<sup>97</sup> Studies have protocols that adhere to clear quantification within “Go/No-Go” decision guidelines and are conducted according to the Animal Research: Reporting of In Vivo Experiments guidelines.<sup>98,99</sup> The standards and measures are defined, including an a priori inclusion and exclusion criterion, and the clarity with which the proof of principle (PoP) and/or PoC are described facilitates the decision-making process. This resource is open to the greater research community, including for the screening of tauopathy-targeted compounds.

### 3.2 | The right drug

The right “drug” for tauopathy can be defined by a selectivity profile that includes a high affinity for its intended target, with low affinity for other off-target effects; a demonstrated ability to modify the intended disease biology; with good adsorption and bioavailability achieving a potentially effective dose in the central nervous system (CNS), including BBB permeability and a favorable therapeutic index (i.e., the predicted therapeutic dose is well below the no-observed-adverse-effect level). The important properties of drugs being selected for testing in tauopathies include having activity in the in vivo brain exposure that is relevant to in vitro data. This includes relevant free, unbound exposure in the brain after administration of acceptable doses. As drugs are selected and tested in early-phase trials, a well-characterized dose response in vivo, as reflected by robust PK/PD relationships, preferably with a clinically translatable biomarker, comprises key elements to be established. Characterizing the relationships among exposures in the brain, CSF, and plasma facilitates human studies and dose selection. If these relationships are 1:1:1, the move to the clinic can be made with greater confidence. By contrast, if there is a “brain penalty,” it must be anticipated in the dosing regimen. Establishing a sufficiently understood PK across the range of modalities of tauopathy drugs in development represents one of the complexities of finding the right drug. To identify the right drug, the workshop endorsed prespecifying criteria within the preclinical development for moving a compound into clinical development.

Tau may theoretically be a better AD therapeutic target than A $\beta$  because, unlike the weaker relationship of brain A $\beta$  plaque burden and cognition, the extent of insoluble tau pathology predicts both the onset of clinical symptoms of AD as well as the pattern of clinical decline.<sup>100–104</sup> Insoluble tau deposition measured by tau PET strongly correlates with the onset of clinical symptoms in autosomal dominant AD,<sup>102</sup> and temporal lobe tau PET uptake predicts the cortical spread of tau pathology,<sup>105</sup> brain atrophy,<sup>106</sup> and subsequent clinical decline in sporadic AD.<sup>103</sup> Moreover, the severity and type of symptoms in AD closely reflect the distribution of insoluble tau in the brain, suggesting that interventions reducing tau have the potential to produce large clinical effects.<sup>107–110</sup>

Clinical trials of early tau therapies, including biologics with first-generation N-terminal anti-tau mAbs, tilavonemab

(ABBV-8E12),<sup>111–113</sup> gosuranemab,<sup>114,115</sup> zagotenemab, and semorinemab<sup>116–118</sup> have failed to demonstrate consistent clinical benefits in AD and/or other tauopathies.<sup>119–121</sup> A trial of semorinemab in mild-to-moderate AD stands apart, having reported a  $\approx$  40% reduction in the rate of decline on the Alzheimer's Disease Assessment Scale-Cognitive Composite co-primary endpoint, but not on other endpoints, resulting in a lack of converging evidence and questions around the potential reproducibility of the findings.<sup>122</sup> By contrast, in prodromal-mild AD, semorinemab did not demonstrate clinical benefit, with modestly reduced CSF p-tau181 levels by  $\approx$  15% (mean of all doses). This effect was less than the  $\approx$  25% reductions reported for patients who responded to high-dose aducanumab or lecanemab, possibly explaining the lack of clinical effect in this population.<sup>25,123</sup> Although all four of these first-generation anti-tau mAbs had evidence of target engagement of N-terminal tau fragments in CSF,<sup>116,120,124,125</sup> none reported PD effects on insoluble aggregated tau.<sup>119,123</sup> Their lack of efficacy may have been due to the targeting of the N-terminal tau fragments, which may be non-pathogenic and may have diverted the necessary target engagement of mid- and C-terminal regions. Second-generation anti-tau mAbs and an active vaccine<sup>126</sup> that target the mid-domain microtubule-binding region (MTBR) and C-terminal regions have now entered clinical trials.<sup>127,128</sup> For current immunotherapies, including anti-tau mAbs, only a very low proportion ( $\approx$  0.1%) crosses the BBB and has brain uptake.<sup>129</sup> Research efforts are actively studying how to improve brain bioavailability through the enhancement of endogenous transport systems including receptor-mediated transcytosis, with ligand-receptor complexes, examples of which include transferrin receptors, low-density lipoprotein 1, or nanoparticles.<sup>130</sup> Alternative approaches include molecules with heavy-chain-only antibodies<sup>129</sup> to improve delivery.

A range of tau-targeted small-molecule therapeutic programs span phases 1 and 2 in trials of both primary and secondary tauopathies. None have reached full clinical PoC to date.<sup>131</sup> These include compounds that alter posttranslational modification of tau with acetylation inhibition (i.e., salsalate<sup>132</sup>), aggregation inhibition with methylene blue,<sup>133,134</sup> methylthionium, leuco-methylthionium (LMTM; i.e., Trx0237),<sup>135</sup> microtubule stabilization with davenutide, epothilone D, a macrolide, as well as taxane derivative abeteotaxane (i.e., TPI 287).<sup>121,131</sup> An array of glycoside hydrolase O-GlcNAcase inhibitors, which block the formation of neurotoxic tau aggregates by increasing the glycosylation of tau and lowering propensity to aggregate, are currently being tested in clinical trials, including ASN 120290 in PSP, LY3372689 in AD, and ASN 51 in AD and Parkinson's disease.<sup>136–138</sup> Kinase inhibitors, including glycogen synthase kinase 3 beta, a serine-threonine enzyme with the medications tideglusib, valproate, lithium, Fyn kinase of the Src family with saracatinib, and Abl tyrosine kinase with nilotinib have been through early-phase trials.<sup>139,140</sup>

The recent phase 1 results with the intrathecally delivered anti-MAPT ASO MAPTRx (ISIS 814907/BIB080) in AD achieved a dose-responsive reduction in CSF total tau, p-tau 181, and the ratio of total tau/A $\beta$ 42.<sup>13</sup> For the highest dose group of 60 mg every 4 weeks, a mean change of  $\approx$  60% in total tau was achieved supporting sufficient target engagement and advancement to phase 2.<sup>13</sup> Also, in a small number

of patients, tau PET demonstrated a drug–placebo difference with less insoluble tau in patients on active therapy by Week 25 and a reduction of insoluble tau below baseline after 100 weeks of exposure.<sup>141</sup> The molecule is now being tested in a phase 2 trial. A similar mechanism of action by NIO752, an intrathecal anti-MAPT ASO is being tested in phase 1 trials for AD and PSP.

Outcomes like these, combined with the learnings from failed anti-A $\beta$  and anti-tau mAb clinical trials and a growing tauopathy therapeutic landscape,<sup>53</sup> directed a consensus in the workshop that any new therapies being developed for tauopathies should demonstrate PD effects on validated tau biomarkers (tau PET and/or mid-domain MTBR sites for aggregated tau) or tau-related targets including neuroinflammation or neurodegeneration before moving forward to large clinical efficacy studies.

The number of ongoing clinical trials of disease-modifying therapies for AD has not increased significantly since 2012.<sup>27</sup> In 2018, the number of ongoing AD clinical trials was 40 times less than the number of ongoing trials in oncology.<sup>28</sup> In a recent evidence-based review and Delphi consensus, Ballard et al. proposed alternative, lower-risk approaches for new drug development in AD using drug repositioning and repurposing.<sup>28</sup> These approaches can expand drug development opportunities and accelerate the timelines for new treatments for AD and primary tauopathies. An advantage of drug repurposing is the known safety and tolerability profile of the candidate compound. Treatment-related safety risks for tauopathies in early-phase human trials can benefit from data and safety monitoring board oversight to identify and mitigate any safety and tolerability signals that arise. The designation of any potential adverse events of special interest that follow preclinical toxicology or phase 1 trials can help provide a focused evaluation of new compounds for early significant signals. With repositioned and repurposed drugs, the time and cost involved in progressing the candidate compound to clinical trials are reduced significantly. Additionally, costs associated with formulation optimization, manufacturing development, and drug–drug interaction studies have already been absorbed by the originating pharmaceutical companies. Thus, this could become a complementary and accessible route to drug development for tauopathy therapeutics by academic institutions, government agencies, and not-for-profit organizations. Such a pipeline can be further sourced from 3D human neural glial triculture drug screening,<sup>142</sup> in silico predictive modeling with the use of transcriptomic databases and computational modeling,<sup>143</sup> and through systematic reviews and Delphi panels, which rank potential candidates according to defined desirable features.<sup>144,145</sup>

However, repurposing and repositioning medicines is not without its challenges. Repurposing can involve medicines that were not optimized for CNS diseases and for which little is known about the CNS properties of the medicines, including the dosing needed to achieve target engagement.<sup>143</sup> If their CNS properties are poor or not optimized, reformulation of prodrugs or even new chemical entities may be needed.<sup>146</sup> Phase 1 dose-finding studies in healthy volunteers may be needed if the dose or age of the proposed population differs substantially from those of the original indication. Some current efforts use the process of “back-translating,” which validates selected models

by testing compounds that already have clinical data (e.g., levetiracetam) or for which there are large pharmacoepidemiology databases to investigate the effects of long-term exposure on AD risk and course.<sup>147,148</sup> Back-translation will become more feasible as clinically validated treatments such as the amyloid-lowering mAbs set benchmarks for comparisons. For repurposing a molecule, there must be a demonstration that the desired effect is mediated by a cognate target of the molecule, effective exposure in the brain, and exposures for efficacy that are within the limits of the investigational new drug (IND) application toxicology studies for the original indication. Some molecules have metabolites, and some of these may be active. Thus, it is important to account for these when conducting clinical trials for a new indication. Additionally, there can be regulatory complexities to address. For example, repurposed or repositioned drugs may have less (or non-existent) intellectual property–limiting patent life, which can then make it difficult to incentivize investment for registrational trials.

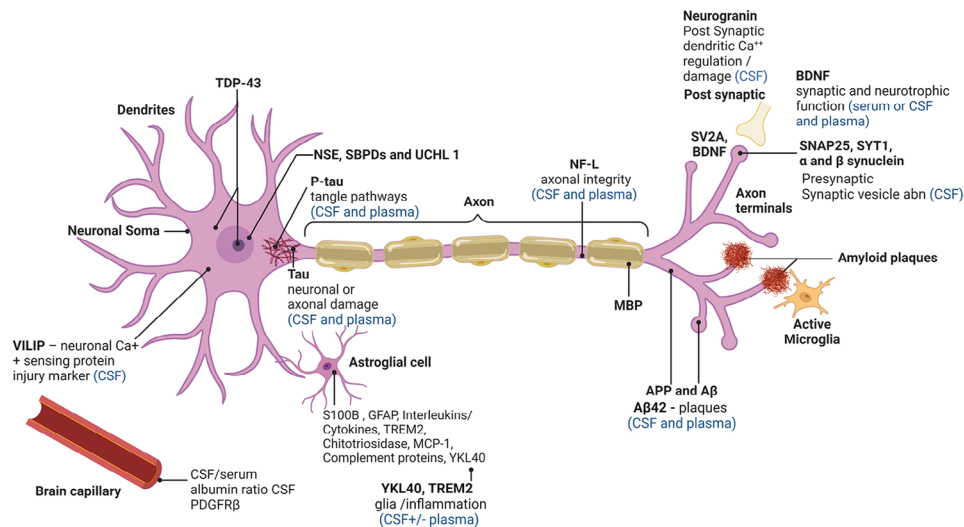
### 3.3 | The right biomarker

The right “biomarkers” for tauopathy trials are selected across a range of uses that make each “fit for purpose” in development, including diagnosis and inclusion, PD evaluation of target engagement, monitoring of treatment response, and predictive and prognostic modeling.<sup>32</sup> Currently, the tau biomarkers available for use in primary tauopathies and those for secondary tauopathy associated with AD differ significantly. Whereas excellent progress has been realized in AD-related tau biomarkers, there remains a significant unmet need in the tau canonical biomarkers for the primary tauopathies. The development of tau biomarkers specific to primary tauopathies was recognized in the workshop as being one of the most pressing gaps in this area of therapeutic research.

Through the anti-amyloid mAb development in AD, much has been learned about the utility of amyloid and tau biomarkers.<sup>149</sup> Figure 2 is a schematic showing a mapping of fluid biomarkers of potential relevance in tauopathy therapeutic trials. Diagnostically, amyloid PET and CSF measures of A $\beta$ 42, ratio of A $\beta$ 42/40, p-tau181, and p-tau217, in various permutations have reached broad acceptance and validation as identifying in vivo amyloid pathology.<sup>150</sup> After a substudy within the bapineuzumab phase 3 clinical trials, it was recognized that 21.4% of participants for these anti-amyloid mAb trials were amyloid-negative with PET standard uptake value ratios below the diagnostic threshold. Thus, there was a trial paradigm shift to require biomarker confirmation for anti-amyloid mAb clinical trials.<sup>151</sup> This improved diagnostic accuracy of participants with target pathology addressed a critical factor in the progress of anti-amyloid mAbs in clinical trials by eliminating this significant trial design liability.

The PD effects of aducanumab and lecanemab decisively lowering aggregated amyloid on PET scanning served to support the initial US Food and Drug Administration (FDA) accelerated approval because the medications were successfully targeting the fundamental pathophysiology of the disease with a reasonable likelihood of predicting clinical benefit for patients.<sup>25,152</sup> Subsequently, for lecanemab, full





**FIGURE 2** Biomarkers of potential interest in tauopathies. A $\beta$ , amyloid beta; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; MCP-1, monocyte chemoattractant protein-1; NF-L, neurofilament light; NSE, neuron-specific enolase; PDGFR $\beta$ , platelet-derived growth factor receptor  $\beta$ ; S100B, S100 calcium-binding protein B; SBPD, spectrin breakdown products; SNAP 25, synaptosomal-associated protein 25 kDa; SV2A, synaptic vesicle glycoprotein 2A; SYT 1, synaptotagmin 1; TDP-43, transactive response DNA-binding protein 43 kDa; TREM2, triggering receptor expressed on myeloid cells 2; UCHL1, ubiquitin C-terminal hydrolase 1; VILIP, visinin-like protein; YKL-40, chitinase-like protein based on 3 N-terminal amino acids tyrosine (Y), lysine (K) and leucine (L) + molecular mass of 40 kDa 14.

regulatory approval followed based on converging clinical evidence.<sup>26</sup> Other biomarker effects with lecanemab treatment included significant changes of plasma measures of glial fibrillary acid protein, p-tau181, and A $\beta$ 42/40 at 6 months, providing the potential for early readout of biomarkers that might predict later clinical response.

Increased p-tau concentrations in biofluids largely reflect A $\beta$  pathology-induced tau phosphorylation and secretion.<sup>153</sup> By contrast, there are no ideal or clinically validated tau fluid biomarkers or imaging tracers for diagnosis, PD monitoring, or disease monitoring in the primary tauopathies. Fluorodeoxyglucose PET is currently the functional imaging biomarker modality that is widely available for use as an outcome measure in primary tauopathies. Fluorodeoxyglucose PET findings of hypometabolism differ across the 4R tauopathy disorders, with some phenotypic patterns being appreciable.<sup>154</sup> Tau PET biomarkers have the potential to inform target engagement and infer drug effects; however, ligands are needed for 4R tauopathies and use outside of AD. The patterns of tau PET with <sup>18</sup>F-flortaucipir may also have some phenotypic utility; however, the degree of uptake does not correlate well with the extent of tauopathy and is unlikely to be sufficient for pharmacodynamic effects in the primary tauopathies. Second-generation tau PET ligands, including [<sup>18</sup>F]PI-2620, and [<sup>18</sup>F]PM-PBB3 (also known as [<sup>18</sup>F]APN-1607 and [<sup>18</sup>F]Florzolotau) primary tauopathies are being actively explored as 4R tau biomarkers with variable results in non-AD tauopathies.<sup>155,156</sup> Overall, current data indicate that better 3R- and 4R-tau PET ligands are needed to support clinical development. For other imaging biomarkers, structural MRI is a commonly used and robust modality to measure longitudinal changes in brain atrophy. Its measurement can run in parallel with clinical effects; however, its signal-to-noise ratio can be low, and the directionality of treatment

effects is often uncertain. Similarly, across types of biomarkers, treatment effects may not be concordant or follow expected directions. Thus, predictions made in designing trials with different treatments may not always be correct, and development plans are best updated with preliminary data.

Recently, there has been potentially transformative tau biomarker discovery research that has identified tau MTBR isoforms that can distinguish primary tauopathies as well as tangle-specific sites in AD.<sup>157,158</sup> Using an immunoprecipitation and mass spectrometry approach, Horie et al. reported on 4R isoform-specific tau species from MTBR-tau275 and MTBR-tau282 that provide the first biomarkers that may significantly aid in the diagnosis of primary tauopathies and, in turn, in the facilitation of clinical trials and monitoring treatment response for these disorders.<sup>157</sup> Another tau fragment, ending at amino acid 368, has a similar potential.<sup>159</sup> Furthermore, abnormalities in the MTBR residue 243 (MTBR-tau243) have been reported to be specific for insoluble tau aggregate pathology, reflecting cortical tangle pathology in AD.<sup>158</sup> When measured in CSF, MTBR-tau243 is identified as a potential surrogate measure that can track the extent of this pathology.<sup>158</sup> When coupled with an assay for p-tau205, the combination improves the prediction of both tau PET positivity and Mini-Mental State Examination scores.<sup>158</sup> These MTBR tau biomarkers differ from the soluble p-tau measures of 181, 231, and 217, which reflect the presence of amyloid pathology and amyloid PET correlations more so than insoluble tau tangle pathology and tau PET.<sup>158</sup> Confirmatory and further validation studies are anticipated. New insights from cryo-electron microscopy studies may also lead to the development of potential new CSF tau biomarkers derived from microtubule-binding domain peptides.<sup>160,161</sup>

Outside tau biomarkers, NfL may be applicable for specific contexts of use, as it is sensitive to neuronal axonal damage/degeneration and has the potential to track disease progress and response to treatment.<sup>41</sup> Plasma levels of NfL have been reported to correlate with the severity of post-mortem tangle pathology and neurodegeneration.<sup>162</sup> However, NfL lacks specificity across the tauopathies<sup>163</sup> and is elevated across a spectrum of neurologic and neurodegenerative diseases.<sup>164,165</sup> NfL may perform best as a biomarker of disease course in natural history studies and for prognostic segregation of treatment response as an enrollment enrichment tool in clinical trials, but may also have utility as a PD biomarker, as seen in clinical trials in ALS, multiple sclerosis, and spinal muscular atrophy.<sup>166</sup>

The availability of more and better biomarkers will continue to advance drug development at all stages, including preclinical/non-clinical and clinical stages of development. There is a need to carefully consider the context of use for biomarkers, as the evidentiary burden of supportive data will be different for safety, diagnostic, risk, prognostic, predictive, PD, and monitoring biomarkers.<sup>167</sup> Importantly, a biomarker need not be fully qualified by regulators to be used in a clinical trial and generate high-value data. One goal in biomarker development is to have real-world evidence to be sufficiently qualified to be included in the evidentiary package.

A useful resource for biomarker development is the FDA's BEST (Biomarkers, EndpointS, and other Tools) Resource.<sup>32</sup> The BEST Resource was developed by the FDA–National Institutes of Health Joint Leadership Council to provide harmonization of terms used in translational science and medical product development. There is an emphasis on endpoints and aims, to capture distinctions between biomarkers and clinical assessments and to describe their specific roles in biomedical research, clinical practice, medical product development, and in the regulation of products by the FDA.

### 3.4 | The right participants

The phenotypic spectrum of tauopathies crosses diverse clinical features, presentations, and variable symptomatic progression rates through the disease course. This heterogeneity complicates the identification of the right participants at the most appropriate stage of the disease to evaluate novel tauopathy treatments. Through genetic testing for highly penetrant autosomal dominant *MAPT* mutations, it is possible to identify disease carriers in their preclinical phase of the disease. Staged development is needed to eventually design preventative clinical trials in such individuals. Initial efficacy on target PD and biological biomarkers can be followed by longer term studies of clinical efficacy and comparisons to modeled synthetic control groups or historical comparison groups such that trials can then be designed to test prevention/delay of disease onset in carriers in the preclinical phase of the disease.

Following the informative example of the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU), interventions can be undertaken within a platform trial design that compares multiple

early interventions with a prespecified biomarker interim analysis (stage gate) to proceed to longer term trials.<sup>168</sup> The ALLFTD<sup>169</sup> and GENFI<sup>170</sup> studies have successfully enrolled the largest numbers of families affected by genetic forms of *MAPT* mutation-FTD as well as sporadic disease and have followed them in the largest international longitudinal observational natural history studies.<sup>171,172</sup> They have also come together in the FTD Prevention Initiative,<sup>173</sup> in which they are combining data for the organization of prevention clinical trials, and developing disease progression models and simulations.<sup>174</sup> For rare neurogenetic diseases, the FDA has indicated its interest in such innovative approaches to create disease progression models that could support clinical endpoints, enrollment criteria, and evaluation of changes in natural history from experimental treatment intervention.<sup>175</sup>

For sporadic disease, there has been considerable interest in characterizing distinct phenotypes of 4R tauopathies including PSP with subtypes of Richardson's syndrome<sup>176</sup> and subtyping of CBS.<sup>177</sup> However, there remain inherent limitations. In PSP, the confirmation of diagnosis can take many years as the multisystem manifestations develop, and in usual care settings, misdiagnosis with Parkinson's disease is frequent. This delay leads to difficulties in identifying the right patient to enroll in clinical trials at an early stage. The sequence and speed at which symptoms progress can be highly variable, and the point of intervention may be very important. With the recent example of the anti-amyloid mAb donanemab, it is evident that intervention in sporadic AD associated with less tau burden is more clinically efficacious than intervention at later stages of disease when greater tau pathology is present.<sup>27,178</sup> This sheds important light on the right patient tied to the right stage of disease and the right intervention from preclinical symptoms through the dementia stages.

There are also important patient factors for clinical trials that span dementia stages. The provisions for obtaining patient consent and advance planning for research are important, given that capacity will typically be lost in the course of the tauopathies, and intentions must be made clear to legally authorized representatives. Best practices for patient and caregiver engagement and communication can help consolidate interest in research and clinical trial participation and encourage brain donation on passing. Even at the early stages of the disease, anosognosia and metacognitive impairment in self-awareness and self-monitoring can occur in FTD, particularly behavioral variant FTD. The effects of being unaware of symptoms or impairment can limit directly reported symptoms and treatment effects.<sup>179,180</sup> Questionnaires and patient-reported assessments need to be interpreted accordingly. It is important to shape inclusion criteria with consideration given to patient comorbidities and their concomitant medications, to increase enrollment and representativeness of patient populations.

Trial participation and retention is a key challenge for the rare disease primary tauopathies. FTD Disorders Registry data showed travel burden as the single largest factor discouraging individuals from participating in clinical trials. Workshop participants discussed the importance of reducing the costs of study-related travel and costs by remote participation using digital health technologies (DHTs). DHTs, which are more widely available post-COVID, can be further leveraged

to better understand the patient experience, particularly as they can be administered and monitored at home, potentially improving the feasibility of trial participation and retention by reducing the number of required trips to the clinic.<sup>181</sup> At-home use of DHTs also provides an opportunity to parse between good- and bad-day assessments, some of which can be disease related. An elevated level of variability may reflect a primary mechanism of a patient's disease progression. In theory, increasing the frequency of at-home assessments could increase the power of the study and reduce the number of needed participants.

Historically, the patient's perspective has been included only in later-stage clinical development in relationship to marketing strategies, yet these perspectives can be addressed more inclusively earlier and diversely throughout the clinical drug development process. A participant's and family's risk tolerance can be surveyed in advance of a research program involving CSF-administered biologic or gene therapy, particularly to consider the acceptability of potential drug delivery mechanisms and toxicity. This would be useful in evaluating any assumptions about the therapeutic intervention with a more formal understanding of the end user's perspective. Including patient feedback early in the process can help with the optimization of consent forms; increase patient retention, especially for pathologies such as PSP, which can progress quickly during a trial; and reduce study-related travel burden. From the FDA's perspective, patient and caregiver engagement should be conducted systematically (i.e., via Patient-Focused Drug Development program<sup>182</sup>) to ensure the prespecified primary and secondary endpoints of a clinical trial are clearly and formally correlated with quality-of-life measures. Many of these points are yet to be elucidated in rare neurological disorders.

The Association for Frontotemporal Degeneration generated a Voice of the Patient Report<sup>183</sup> as part of the FDA's Externally Led Patient-Focused Drug Development initiative. Using a combination of testimonials, polls, and a large survey executed in collaboration with the FTD Disorders Registry, the initiative documented insights from people living with FTD disorders, their care partners, and caregivers.<sup>183</sup> The meeting was designed to help the FDA understand the experiences and priorities of those affected by all FTD disorders, including PSP and CBS, and to use this knowledge to inform risk-benefit analyses of drug candidates and guide regulatory decisions throughout the drug development process. Meeting participants described their lived experience with FTD disorders, including their experiences seeking and receiving treatment as well as their priorities for the development of new therapies.<sup>183</sup> Overall, participants mentioned a broad spectrum of FTD symptoms and described the devastating impact of these symptoms on every aspect of their day-to-day lives. Participants expressed frustration and concern about the lack of effective therapies for symptom control and/or disease modification. Among those on medications, side effects were noted to be common and often exacerbated by inappropriate or off-label prescriptions. The vast majority of participants expressed an overwhelming desire to participate in research studies of new treatment options.<sup>183</sup> Further insights from people with lived experience of FTD disorders can be accessed through the FTD Disorders Registry, a direct-to-

participant registry available to researchers for data, collaboration, and recruitment support.

In a study conducted by UCB Biopharma SRL, patient interviews were conducted to obtain a better understanding of their "journey" with PSP.<sup>184</sup> Conceptually, interview questions addressed motor, non-motor, and constitutional symptoms and dysfunction as well as the effects of PSP on daily life. The results showed that the current clinical journey involves cycling through the health-care system, a delayed and terminal diagnosis, a lack of treatment, and rapid disease progression. The emotional journey was dominated by negative feelings, especially around diagnosis, with brief moments of positivity. To effectively address this, it was appreciated that patients, caregivers, and health-care providers should be mindful of taking the diagnostic journey together and that health-care providers communicate clearly what is known and unknown at specific time points as well as provide prognostic expectations, even if they are not optimistic. Education should be customized for all involved parties, and a coordinated effort is required from all stakeholders toward a common goal for better, more supportive care of people living with PSP and their caregivers. Recommendations included longer consultation times, closer collaboration among health-care providers and patient organizations, and more diversified support and education for patients and caregivers.

### 3.5 | The right trial

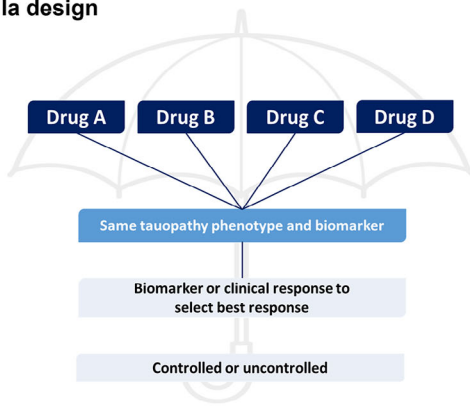
To identify the right trial, workshop participants discussed the options and considerations to optimize trial design for the rare disease primary tauopathies to advance to PoC. The workshop members agreed that fundamentally the right trial should demonstrate target engagement with a sensitive, validated biomarker that tracks to the mechanism of action and related biological impact on the disease. Confidence in dosing using sound PK and maximum tolerated dose and PD, where possible, serves to help bracket the dose range in early-phase trials with allometric dose scaling as applicable from preclinical/non-clinical models. Depending on the target population and the trial's primary and secondary outcomes, distinctive and different biomarkers may be required. Early-phase trials, while serving as learning opportunities, still benefit from having a predefined "Go/No-Go" matrix. The right trial should have a reliable algorithm for decision making, target engagement, and safety/tolerability, which may differ by tauopathy.

For the rare disease primary tauopathies, enrollment and sample sizes to achieve definitive clinical efficacy are likely to be a continuous challenge. Traditional designs, therefore, are not ideally suited to adapt to and learn from incoming trial data and will, in turn, be less than optimal. Fortunately, innovative design options with potential applicability for tauopathies are gaining familiarity and experience with researchers. Figure 3 shows the types of seamless designs with stage gates, basket and umbrella designs, and platform trials. Many of these have had their genesis in oncology trials. All of these have the potential to increase efficiency in early-phase trials.

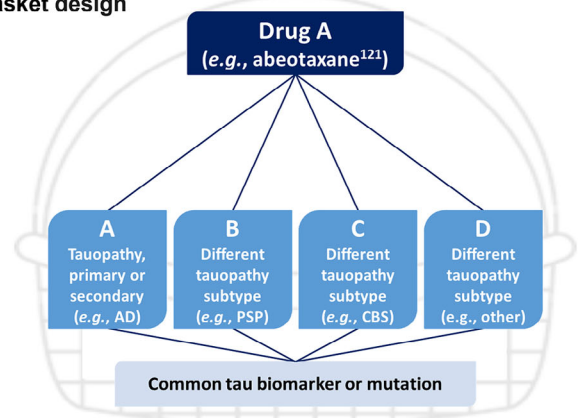
Several platform trial examples exist across neurodegenerative diseases, which serve as important points of reference. The Healey ALS



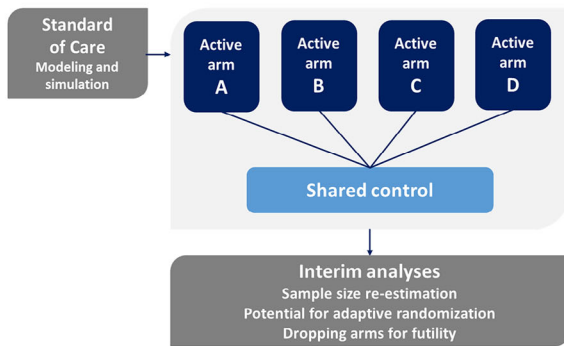
**Umbrella design**



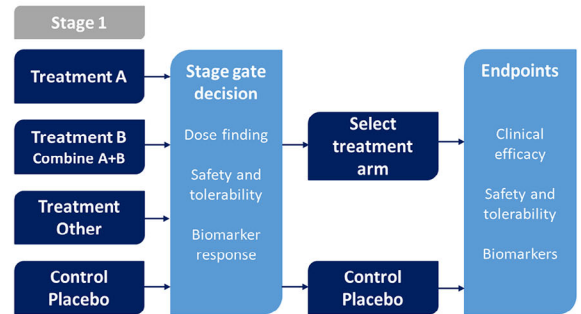
**Basket design**



**Open-platform trial**



**Seamless design**



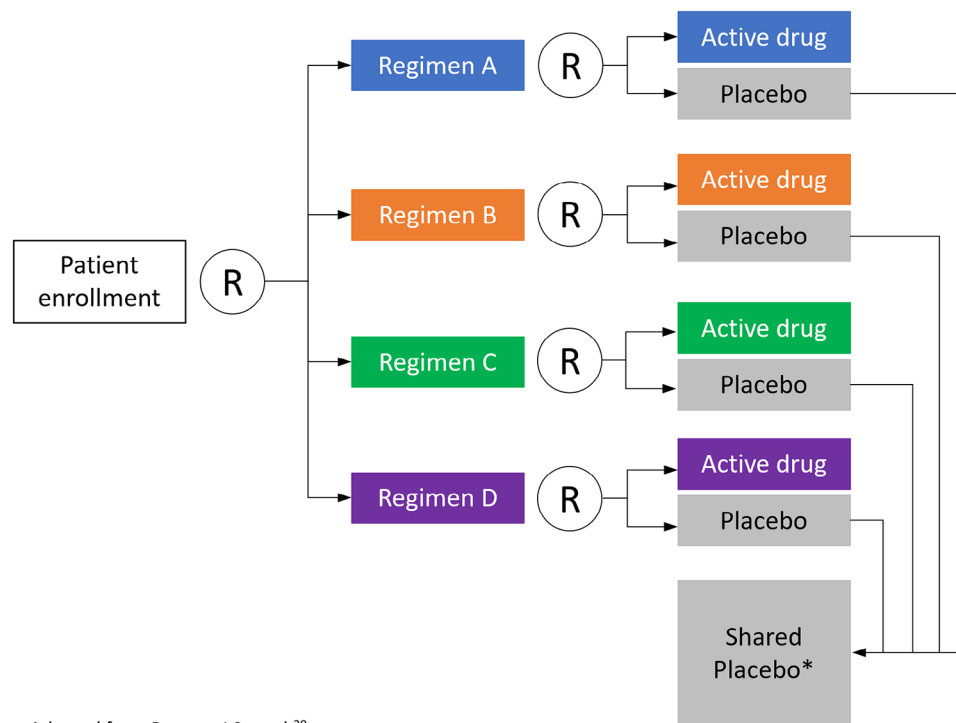
**FIGURE 3** Trial schema designs. AD, Alzheimer's disease; CBS, corticobasal syndrome; PSP, progressive supranuclear palsy.

Platform Trial is testing multiple compounds (regimens) concurrently in a perpetual open manner in ALS.<sup>38</sup> It has provisions for adding new treatments (regimens) as they are identified for testing on the platform as well as for dropping regimens when futility criteria are met. There is a shared control arm for all the active regimens enabling a higher randomization rate to active treatment of 3:1 active versus control within a given regimen. To achieve this type of open platform, there is an agreed-to master protocol and common rules for all regimens and a shared single trial infrastructure and resources.<sup>185</sup> There are provisions for outside borrowing of historical or synthetic data, allowing multiple sources of information to be used within the platform. This design allows for the incorporation of all information, adaptation to accumulating evidence, and use of powerful analytic methods, even in the absence of clear PD biomarkers for agents that may be studied. All of the adaptations are planned before the trial starts with well-defined criteria for adaptation clearly explained and key trial parameters specified (Figure 4).<sup>186</sup> Directed by Bayesian analyses, more patients can be adaptively randomized to better-performing interventions. By “playing the winners,” there can be seamless transformation to confirmatory later-stage trials. The strengths of this design come from the extensive modeling and simulation conducted before the trial launches around the natural history and disease progression, including the best endpoints and biomarkers for the phase of the disease being tested. The availability of natural history and patient-level data for clinical trial simulation is key to this design, as is the development of disease progression models.<sup>174,187</sup> One advantage of characterizing progression

rates is the ability to identify and differentiate rapid and slow disease progressors; a better understanding of rapid progression would help build confidence in pursuing PoP and PoC studies.

The challenges of this type of innovative design include the modeling and simulation needed upfront before the trial launches; the need for buy-in from diverse stakeholders, including the health authorities (FDA) and those who contribute their compounds; the understanding that it may not be conducive to all treatment modalities (e.g., gene therapies); and that power and type 1 error of a trial do not apply. The DIAN-TU provides another example of a platform trial that includes adaptive design and a disease progression model.<sup>188</sup> Within the context of autosomal dominant AD, the DIAN-TU has successfully investigated the anti-amyloid mAbs gantenerumab and solanezumab in those who were asymptomatic and mildly symptomatic, incorporating a seamless design in which the initial phase of biomarker outcome was used as the stage gate to the longer term clinical endpoints.<sup>189</sup> The DIAN-TU Tau NexGen,<sup>190</sup> a secondary prevention trial in asymptomatic mutation carriers, is now poised to demonstrate biological engagement of tau and/or combination-directed therapeutic drugs to significantly decrease insoluble tau as measured by tau PET, or soluble tau as measured in CSF and plasma, to reach PoC of potential clinical and cognitive benefit to support the transition to seamless phase 3 validation studies.

The urgency to develop more efficient clinical trial designs is growing for sporadic AD. With the approval of lecanemab, and possibly donanemab soon, it will be necessary to investigate the effects of other



Adapted from Paganoni S, et al.<sup>38</sup>

\*Shared infrastructure and Parent Protocol allow for sharing of placebo data.

**FIGURE 4** Participant flow in the Healey ALS Platform Trial. ALS, amyotrophic lateral sclerosis; R, randomization.

therapeutic modalities in combination with anti-amyloid therapies. The number of potential combinations and control conditions suggests that traditional parallel trial designs will be prohibitively expensive and time consuming. The new National Institutes of Health-funded AD Tau Platform Trial will be a phase 2, factorial design platform that will test at least two therapies alone or in combination with anti-amyloid therapies in early sporadic AD with a focus on tau biomarkers for demonstrating biological PoC<sup>191</sup> scheduled to begin in late 2024 or 2025.

Given the poor translatability of non-clinical models to human disease, it is uncertain which pathogenic mechanisms (and candidate therapies) may be related to which (if any) human disease. Increasingly, it is recognized that tau metabolism and likely pathogenic mechanisms vary in different tauopathies (e.g., AD and PSP). One approach to identifying the right participants (therapeutic indication) is to assess a tau therapy in multiple different tauopathies in parallel or successive clinical trials. In this paradigm, basket and umbrella trial designs (Figure 3) also offer some unique considerations for tauopathy therapeutic development.<sup>185</sup> Within a basket trial design, multiple tauopathy phenotypes, supported by biomarker evidence as likely being caused by underlying tau pathology, can be simultaneously treated with the same treatment. Outcomes of an early-phase basket trial can, in turn, then include safety, tolerability, and biomarkers with comparison across the clinical phenotypes to determine which phenotype represents the best one to pursue into further development.<sup>192</sup> In the example of such a tauopathy basket trial, the microtubule stabilizer abetotaxane was tested and showed differential safety, tolerability, and biomarker profiles when tested in AD, PSP, and CBS.<sup>121</sup> These results

enabled important comparative information to be identified early in development.<sup>121</sup> Alternatively, in an umbrella design,<sup>185</sup> multiple drugs can be used to treat the same tauopathy with biomarkers being used to identify which of the drugs emerges as the best drug to advance. For the primary tauopathies, one of the important rate-limiting factors with basket designs is the dependency on robust and specific tauopathy biomarkers that are fit for purpose. By analogy to ALS, much can be learned from rapid, inexpensive trials, even in the absence of specific biomarkers, if there is sufficient power to measure an effect on a clinical endpoint. In PSP-Richardson's syndrome, experience in mild-moderate disease with new, more powerful versions of the PSP rating scale suggests that such trials may now be feasible in this primary tauopathy.

Within-subject or single-case experimental designs provide an alternative design option that investigates change in individual patients as the unit of analysis rather than an aggregate change in a group of patients. This approach addresses the challenge of inherent heterogeneity by using the same individual during the pretreatment phase as the control condition. As applied in tauopathies, this n-of-1-based approach acquires a run-in period (with or without placebo) with frequent repeated biomarker measures to create an optimal pretreatment profile followed by crossover to an active period of treatment. Determinations are made on the treatment response of each participant with a defined response rate of individuals defined within the trial. It also serves as an initial evaluation of PK and target engagement. This approach provides for efficient and economical screening (i.e., "rapid fail") and early-stage "Go/No-Go" decisions, and

establishes foundational human data to formulate intellectual property and refine the design of subsequent phase 2 and 3 trials. This approach has been incorporated into more complex designs that have been used previously for behavioral interventions within the Sequential Multiple Assignment Randomized Trial (SMART).<sup>193</sup> Statistical approaches include repeated measures of visual, time series, or Bayesian change analyses. Generalizability is evaluated using an analytic or metanalytic combination of single case trials.

#### 4 | PARTNERSHIPS AND ACCELERANTS

In this workshop, bottlenecks were discussed, and considerations were then proposed for accelerating the translation of discoveries made in academic laboratories into the clinical pipeline. These academic laboratories may have a promising new compound but may lack the resources or drug discovery knowledge to move it forward. Academic, not-for-profit foundations, lay support organizations, and industry partnerships are seen as fundamental vehicles to accelerate the transition of discoveries from academic labs (i.e., bench or basic research) into industry-based drug development programs and successful early-phase clinical trials (i.e., clinical trials). The end goal for academic and industry researchers is the same: to increase the capacity for good, rigorous drug discovery and development, leading eventually to new treatments for patients. Once this is established, different stakeholders can use their strengths to optimize the development process. Academic researchers excel at understanding the target profile, clinical and biomarker measures, and clinical adoption. Pharmaceutical and biotech companies rigorously test and effectively commercialize the product. It is important to understand the bottlenecks and to partner with agencies and organizations (e.g., drug discovery institutes) that can provide resources to overcome these hurdles. Academic researchers should develop their intellectual property strategy as early as possible, and academic technology transfer offices should seek support from external consultants and attorneys to ensure protection that provides the basis for proprietary development and market readiness. Finally, as a shared priority for the research community, funders could consider supporting efforts to create more and better compound libraries and to improve immediate access to these valuable resources.

#### 5 | CONCLUSION

The workshop identified important unmet needs in translational tau therapeutic research, including the need for high-fidelity models, model-to-human translation biomarkers, more target mechanisms, more validated biomarkers (e.g., PD, diagnostic, predictive, response monitoring, safety), and more rigorous definitions of acceptable outcomes for “Go/No-Go” decisions. More sensitive and tailored clinical outcomes, including digital biomarkers, are also tagged as important priority areas. When achieved and synthesized into comprehensive discovery and development programs, these advances will enable

accelerated identification of new therapeutic options for patients with tauopathies.

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Steven E. Arnold declares lecture honoraria from: Abbvie, Biogen, and Eisai; serving on advisory boards for: Allyx Therapeutics, Bob's Last Marathon, Cassava, Cortexyme, Sage Therapeutics, and vTv Therapeutics; consulting for: Athira, Boyle-Shaughnessy Law, Cognito Therapeutics, M3 Biotech, Orthogonal Neuroscience, and Risen Pharmaceutical Technology; and institutional research grant support from: Abbvie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Amylyx, Athira, Chromadex, Cycleron Therapeutics, EIP Pharma, Janssen/Johnson & Johnson, NIH, Novartis, Seer Biosciences, and vTv Therapeutics. Clive Ballard declares grants from Synexus, reMYND, and Novo Nordisk; consultancy fees from Tau Therapeutics, Acadia Pharmaceuticals, Johnson & Johnson, Suven Life Sciences, Sunovion, Exciva, Roche, AbbVie, Orion Pharma, BioExcel, AARP, and Lilly; and honoraria from Bristol Myers Squibb, Axome Therapeutics, Tau Therapeutics, and Biogen. Dirk Beher is a co-founder, employee, and shareholder of Asceneuron SA. Bradley F. Boeve received honorarium for SAB activities for the Tau Consortium; institutional research grant support from: Alector, Biogen, Transposon, Cognition Therapeutics, EIP Pharma, GE Healthcare; institutional NIH grant support from: P30 AG062677, U19 AG063911, R01 AG038791, U01 NS100620, U19 AG071754, U24 AG056270; institutional foundation support from: Lewy Body Dementia Association, American Brain Foundation; and institutional philanthropic support from: Mayo Clinic Dorothy and Harry T. Mangurian Jr. Lewy Body Dementia Program, the Little Family Foundation, Ted Turner Family Foundation. Adam L. Boxer received grant support from NIH U19AG063911, R01AG073482, R56AG075744, R01AG038791, RF1AG077557, R01AG071756, U01AG045390, Rainwater Charitable Foundation, Bluefield Project to Cure FTD, GHR Foundation, Alzheimer's Association, Association for Frontotemporal Degeneration, Alzheimer's Drug Discovery Foundation, UCSF Parkinson's Spectrum Disorders Center, University of California Cures AD Program; industry research support from: Biogen, Eisai, Regeneron; and did industry consulting for: AGTC, Alchemab, Alector, Amylyx, Arkuda, Arvinas, Arrowhead, Eli Lilly, Merck, Muna, Oscotec, Roche, Switch, Transposon, Wave. Jeffrey L. Cummings reports consulting for: Acadia, Alkahest, AlphaCognition, AriBio, Biogen, Cassava, Cerecin, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, GAP Innovations, Grifols, Janssen, Karuna, Lilly, Lundbeck, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Ono, Otsuka, PRODEO, Prothena, ReMYND, Resverlogix, Roche, Sage Therapeutics, SignantHealth, Suven, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies; and grant funding from: NIGMS grant P20GM109025, NINDS grant U01NS093334, NIA grant R01AG053798, NIA grant P20AG068053, NIA grant P30AG072959, NIA grant R35AG71476, Alzheimer's Disease Drug Discovery Foundation (ADDF), Ted and Maria Quirk Endowment, and the Joy Chambers-Grundy Endowment. Penny A. Dacks is an employee of AFTD. Kristophe Diaz is an employee of

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## REFERENCES

- Goedert M, Wischik CM, Crowther RA, Walker JE, Klug A. Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau. *Proc Natl Acad Sci U S A*. 1988;85(11):4051-4055. doi:10.1073/pnas.85.11.4051
- Wischik CM, Novak M, Thogersen HC, et al. Isolation of a fragment of tau derived from the core of the paired helical filament of Alzheimer disease. *Proc Natl Acad Sci U S A*. 1988;85(12):4506-4510. doi:10.1073/pnas.85.12.4506
- Orr ME, Sullivan AC, Frost B. A brief overview of tauopathy: causes, consequences, and therapeutic strategies. *Trends Pharmacol Sci*. 2017;38(7):637-648. doi:10.1016/j.tips.2017.03.011
- Boeve BF, Boxer AL, Kumfor F, Pijnenburg Y, Rohrer JD. Advances and controversies in frontotemporal dementia: diagnosis, biomarkers, and therapeutic considerations. *Lancet Neurol*. 2022;21(3):258-272. doi:10.1016/S1474-4422(21)00341-0
- Zhang X, Gao F, Wang D, et al. Tau pathology in Parkinson's disease. *Front Neurol*. 2018;9:809. doi:10.3389/fneur.2018.00809
- World Health Organization. Dementia. WHO. [https://www.who.int/health-topics/dementia#tab=tab\\_1](https://www.who.int/health-topics/dementia#tab=tab_1)
- Leroy M, Bertoux M, Skrobala E, et al. Characteristics and progression of patients with frontotemporal dementia in a regional memory clinic network. *Alzheimers Res Ther*. 2021;13(1):19. doi:10.1186/s13195-020-00753-9
- Alzheimer's Association. 2022 Alzheimer's Disease Facts and Figures. <https://www.alz.org/alzheimers-dementia/facts-figures>
- Turcano P, Stang CD, Mielke MM, et al. Incidence of frontotemporal disorders in Olmsted County: a population-based study. *Alzheimers Dement*. 2020;16(3):482-490. doi:10.1016/j.jalz.2019.08.199
- Coyle-Gilchrist IT, Dick KM, Patterson K, et al. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. *Neurology*. 2016;86(18):1736-1743. doi:10.1212/WNL.0000000000002638
- Smith DH, Johnson VE, Trojanowski JQ, Stewart W. Chronic traumatic encephalopathy—confusion and controversies. *Nat Rev Neurol*. 2019;15(3):179-183. doi:10.1038/s41582-018-0114-8
- U.S. Food and Drug Administration. *Rare Diseases: Common Issues in Drug Development Guidance for Industry*. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; 2019. <https://www.fda.gov/media/119739/download>
- Mummery CJ, Borjesson-Hanson A, Blackburn DJ, et al. Tau-targeting antisense oligonucleotide MAPT(Rx) in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. *Nat Med*. 2023;29(6):1437-1447. doi:10.1038/s41591-023-02326-3
- Plotkin SS, Cashman NR. Passive immunotherapies targeting Abeta and tau in Alzheimer's disease. *Neurobiol Dis*. 2020;144:105010. doi:10.1016/j.nbd.2020.105010
- National Institute of Neurological Disorders and Stroke. *ADRD Summit 2022 Report to the National Advisory Neurological Disorders and Stroke Council*. National Institutes of Health; 2022. <https://www.ninds.nih.gov/news-events/events/adrd-summit-2022>
- Boxer AL, Gold M, Feldman H, et al. New directions in clinical trials for frontotemporal lobar degeneration: methods and outcome measures. *Alzheimers Dement*. 2020;16(1):131-143. doi:10.1016/j.jalz.2019.06.4956
- Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol*. 2010;9(11):1118-1127. doi:10.1016/S1474-4422(10)70223-4
- Friedman LG, McKeehan N, Hara Y, et al. Value-generating exploratory trials in neurodegenerative dementias. *Neurology*. 2021;96(20):944-954. doi:10.1212/WNL.00000000000011774
- Merchant KM, Cedarbaum JM, Brundin P, et al. A proposed roadmap for parkinson's disease proof of concept clinical trials investigating

- compounds targeting alpha-synuclein. *J Parkinsons Dis.* 2019;9(1):31-61. doi:10.3233/JPD-181471
20. Nicholson KA, Cudkowicz ME, Berry JD. Clinical trial designs in amyotrophic lateral sclerosis: does one design fit all? *Neurotherapeutics.* 2015;12(2):376-383. doi:10.1007/s13311-015-0341-2
  21. Cummings J, Feldman HH, Scheltens P. The "rights" of precision drug development for Alzheimer's disease. *Alzheimers Res Ther.* 2019;11(1):76. doi:10.1186/s13195-019-0529-5
  22. Paganoni S, Hendrix S, Dickson SP, et al. Effect of sodium phenylbutyrate/taurursodiol on tracheostomy/ventilation-free survival and hospitalisation in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial. *J Neurol Neurosurg Psychiatry.* 2022;93(8):871-875. doi:10.1136/jnnp-2022-329024
  23. Miyagawa T, Brushaber D, Syrjanen J, et al. Use of the CDR(R) plus NACC FTLD in mild FTLD: data from the ARTFL/LEFFTDS consortium. *Alzheimers Dement.* 2020;16(1):79-90. doi:10.1016/j.jalz.2019.05.013
  24. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology.* 1994;44(12):2308-2314. doi:10.1212/wnl.44.12.2308
  25. Budd Haeblerlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *J Prev Alzheimers Dis.* 2022;9(2):197-210. doi:10.14283/jpad.2022.30
  26. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med.* 2023;388(1):9-21. doi:10.1056/NEJMoa2212948
  27. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: the TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA.* 2023;330(6):512-527. doi:10.1001/jama.2023.13239
  28. Ballard C, Aarsland D, Cummings J, et al. Drug repositioning and repurposing for Alzheimer disease. *Nat Rev Neurol.* 2020;16(12):661-673. doi:10.1038/s41582-020-0397-4
  29. Karran E, Hardy J. A critique of the drug discovery and phase 3 clinical programs targeting the amyloid hypothesis for Alzheimer disease. *Ann Neurol.* 2014;76(2):185-205. doi:10.1002/ana.24188
  30. Toyn JH, Ahljianian MK. Interpreting Alzheimer's disease clinical trials in light of the effects on amyloid-beta. *Alzheimers Res Ther.* 2014;6(2):14. doi:10.1186/alzrt244
  31. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science.* 1997;276(5321):2045-2047. doi:10.1126/science.276.5321.2045
  32. FDA-NIH Biomarker Working Group. *BEST (Biomarkers, EndpointS, and other Tools) Resource.* U.S. Food and Drug Administration and National Institutes of Health; 2016. <https://pubmed.ncbi.nlm.nih.gov/27010052/>
  33. Pagano G, Taylor KI, Anzures-Cabrera J, et al. Trial of Prasinezumab in Early-stage Parkinson's disease. *N Engl J Med.* 2022;387(5):421-432. doi:10.1056/NEJMoa2202867
  34. Lang AE, Siderowf AD, Macklin EA, et al. Trial of Cinpanemab in Early Parkinson's disease. *N Engl J Med.* 2022;387(5):408-420. doi:10.1056/NEJMoa2203395
  35. Hutchison RM, Fraser K, Yang M, et al. Cinpanemab in Early Parkinson Disease: evaluation of biomarker results from the phase 2 SPARK clinical trial. *Neurology.* 2024;102(5):e209137. doi:10.1212/WNL.0000000000209137
  36. Kiernan MC, Vucic S, Talbot K, et al. Improving clinical trial outcomes in amyotrophic lateral sclerosis. *Nat Rev Neurol.* 2021;17(2):104-118. doi:10.1038/s41582-020-00434-z
  37. van den Berg LH, Sorenson E, Gronseth G, et al. Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials. *Neurology.* 2019;92(14):e1610-e1623. doi:10.1212/WNL.0000000000007242
  38. Paganoni S, Berry JD, Quintana M, et al. Adaptive platform trials to transform amyotrophic lateral sclerosis therapy development. *Ann Neurol.* 2022;91(2):165-175. doi:10.1002/ana.26285
  39. Aisen PS, Bateman RJ, Carrillo M, et al. Platform trials to expedite drug development in Alzheimer's disease: a report from the EU/US CTAD Task Force. *J Prev Alzheimers Dis.* 2021;8(3):306-312. doi:10.14283/jpad.2021.21
  40. Bedlack RS, Pastula DM, Welsh E, Pulley D, Cudkowicz ME. Scrutinizing enrollment in ALS clinical trials: room for improvement? *Amyotroph Lateral Scler.* 2008;9(5):257-265. doi:10.1080/17482960802195913
  41. Miller TM, Cudkowicz ME, Genge A, et al. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. *N Engl J Med.* 2022;387(12):1099-1110. doi:10.1056/NEJMoa2204705
  42. Paganoni S, Macklin EA, Hendrix S, et al. Trial of sodium phenylbutyrate-aurursodiol for amyotrophic lateral sclerosis. *N Engl J Med.* 2020;383(10):919-930. doi:10.1056/NEJMoa1916945
  43. Thomas JD, Oliveira R, Sznajder LJ, Swanson MS. Myotonic dystrophy and developmental regulation of RNA processing. *Compr Physiol.* 2018;8(2):509-553. doi:10.1002/cphy.c170002
  44. De Serres-Berard T, Pierre M, Chahine M, Puymirat J. Deciphering the mechanisms underlying brain alterations and cognitive impairment in congenital myotonic dystrophy. *Neurobiol Dis.* 2021;160:105532. doi:10.1016/j.nbd.2021.105532
  45. Caillet-Boudin ML, Fernandez-Gomez FJ, Tran H, Dhaenens CM, Buee L, Sergeant N. Brain pathology in myotonic dystrophy: when tauopathy meets spliceopathy and RNAopathy. *Front Mol Neurosci.* 2014;6:57. doi:10.3389/fnmol.2013.00057
  46. Laforce RJ, Dallaire-Theroux C, Racine AM, et al. Tau positron emission tomography, cerebrospinal fluid and plasma biomarkers of neurodegeneration, and neurocognitive testing: an exploratory study of participants with myotonic dystrophy type 1. *J Neurol.* 2022;269(7):3579-3587. doi:10.1007/s00415-022-10970-x
  47. Liu AJ, Lusk JB, Ervin J, Burke J, O'Brien R, Wang SJ. Tuberous sclerosis complex is a novel, amyloid-independent tauopathy associated with elevated phosphorylated 3R/4R tau aggregation. *Acta Neuropathol Commun.* 2022;10(1):27. doi:10.1186/s40478-022-01330-x
  48. de Vries PJ, Whittemore VH, Leclézio L, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. *Pediatr Neurol.* 2015;52(1):25-35. doi:10.1016/j.pediatrneurol.2014.10.004
  49. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus G. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013;49(4):243-254. doi:10.1016/j.pediatrneurol.2013.08.001
  50. Kovacs GG, Ferrer I, Grinberg LT, et al. Aging-related tau astroglialopathy (ARTAG): harmonized evaluation strategy. *Acta Neuropathol.* 2016;131(1):87-102. doi:10.1007/s00401-015-1509-x
  51. Riku Y, Yoshida M, Iwasaki Y, Sobue G, Katsuno M, Ishigaki S. TDP-43 proteinopathy and tauopathy: do they have pathomechanistic links? *Int J Mol Sci.* 2022;23(24):15755. doi:10.3390/ijms232415755
  52. Tome SO, Tsaka G, Ronisz A, et al. TDP-43 pathology is associated with increased tau burdens and seeding. *Mol Neurodegener.* 2023;18(1):71. doi:10.1186/s13024-023-00653-0
  53. Cummings JL, Gonzalez MI, Pritchard MC, May PC, Toledo-Sherman LM, Harris GA. The therapeutic landscape of tauopathies: challenges and prospects. *Alzheimers Res Ther.* 2023;15(1):168. doi:10.1186/s13195-023-01321-7
  54. Li C, Gotz J. Tau-based therapies in neurodegeneration: opportunities and challenges. *Nat Rev Drug Discov.* 2017;16(12):863-883. doi:10.1038/nrd.2017.155
  55. Gerson JE, Castillo-Carranza DL, Kaye R. Advances in therapeutics for neurodegenerative tauopathies: moving toward the

- specific targeting of the most toxic tau species. *ACS Chem Neurosci*. 2014;5(9):752-769. doi:10.1021/cn500143n
56. Denali Therapeutics. Genetic pathway potential. <https://www.denalitherapeutics.com/science/pathway>
  57. ALZFORUM. Research Models. Accessed November 4, 2022. <https://www.alzforum.org/research-models/search?species=&diseases=&genes%5B%5D=33511&types=&keywords-entry=&keywords=tau#results>
  58. Sahara N, Yanai R. Limitations of human tau-expressing mouse models and novel approaches of mouse modeling for tauopathy. *Front Neurosci*. 2023;17:1149761. doi:10.3389/fnins.2023.1149761
  59. Chung DC, Roemer S, Petrucelli L, Dickson DW. Cellular and pathological heterogeneity of primary tauopathies. *Mol Neurodegener*. 2021;16(1):57. doi:10.1186/s13024-021-00476-x
  60. Liu F, Gong CX. Tau exon 10 alternative splicing and tauopathies. *Mol Neurodegener*. 2008;3:8. doi:10.1186/1750-1326-3-8
  61. Wray S. Modeling tau pathology in human stem cell derived neurons. *Brain Pathol*. 2017;27(4):525-529. doi:10.1111/bpa.12521
  62. Gotz J, Ittner LM. Animal models of Alzheimer's disease and frontotemporal dementia. *Nat Rev Neurosci*. 2008;9(7):532-544. doi:10.1038/nrn2420
  63. Irwin DJ. Tauopathies as clinicopathological entities. *Parkinsonism Relat Disord*. 2016;22(Suppl 1):S29-S33. doi:10.1016/j.parkreldis.2015.09.020
  64. Lee VM, Kenyon TK, Trojanowski JQ. Transgenic animal models of tauopathies. *Biochim Biophys Acta*. 2005;1739(2-3):251-259. doi:10.1016/j.bbadis.2004.06.014
  65. Ando K, Leroy K, Heraud C, et al. Accelerated human mutant tau aggregation by knocking out murine tau in a transgenic mouse model. *Am J Pathol*. 2011;178(2):803-816. doi:10.1016/j.ajpath.2010.10.034
  66. Wegmann S, Maury EA, Kirk MJ, et al. Removing endogenous tau does not prevent tau propagation yet reduces its neurotoxicity. *EMBO J*. 2015;34(24):3028-3041. doi:10.15252/embj.201592748
  67. Karch CM, Kao AW, Karydas A, et al. A comprehensive resource for induced pluripotent stem cells from patients with primary tauopathies. *Stem Cell Reports*. 2019;13(5):939-955. doi:10.1016/j.stemcr.2019.09.006
  68. Mertens J, Paquola ACM, Ku M, et al. Directly reprogrammed human neurons retain aging-associated transcriptomic signatures and reveal age-related nucleocytoplasmic defects. *Cell Stem Cell*. 2015;17(6):705-718. doi:10.1016/j.stem.2015.09.001
  69. Penney J, Ralvenius WT, Tsai LH. Modeling Alzheimer's disease with iPSC-derived brain cells. *Mol Psychiatry*. 2020;25(1):148-167. doi:10.1038/s41380-019-0468-3
  70. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663-676. doi:10.1016/j.cell.2006.07.024
  71. Kuhn R, Mahajan A, Canoll P, Hargus G. Human induced pluripotent stem cell models of frontotemporal dementia with tau pathology. *Front Cell Dev Biol*. 2021;9:766773. doi:10.3389/fcell.2021.766773
  72. Schoch KM, DeVos SL, Miller RL, et al. Increased 4R-tau induces pathological changes in a human-tau mouse model. *Neuron*. 2016;90(5):941-947. doi:10.1016/j.neuron.2016.04.042
  73. Iovino M, Agathou S, Gonzalez-Rueda A, et al. Early maturation and distinct tau pathology in induced pluripotent stem cell-derived neurons from patients with MAPT mutations. *Brain*. 2015;138(11):3345-3359. doi:10.1093/brain/awv222
  74. Sposito T, Preza E, Mahoney CJ, et al. Developmental regulation of tau splicing is disrupted in stem cell-derived neurons from frontotemporal dementia patients with the 10 + 16 splice-site mutation in MAPT. *Hum Mol Genet*. 2015;24(18):5260-5269. doi:10.1093/hmg/ddv246
  75. Israel MA, Yuan SH, Bardy C, et al. Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. *Nature*. 2012;482(7384):216-220. doi:10.1038/nature10821
  76. Moore S, Evans LD, Andersson T, et al. APP metabolism regulates tau proteostasis in human cerebral cortex neurons. *Cell Rep*. 2015;11(5):689-696. doi:10.1016/j.celrep.2015.03.068
  77. Choi SH, Kim YH, Hebisch M, et al. A three-dimensional human neural cell culture model of Alzheimer's disease. *Nature*. 2014;515(7526):274-278. doi:10.1038/nature13800
  78. Lin YT, Seo J, Gao F, et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-Derived brain cell types. *Neuron*. 2018;98(6):1141-1154.e7. doi:10.1016/j.neuron.2018.05.008
  79. Lomoio S, Pandey RS, Rouleau N, et al. 3D bioengineered neural tissue generated from patient-derived iPSCs mimics time-dependent phenotypes and transcriptional features of Alzheimer's disease. *Mol Psychiatry*. 2023;28(12):5390-5401. doi:10.1038/s41380-023-02147-3
  80. Miguel L, Rovelet-Lecrux A, Feyeux M, et al. Detection of all adult Tau isoforms in a 3D culture model of iPSC-derived neurons. *Stem Cell Res*. 2019;40:101541. doi:10.1016/j.scr.2019.101541
  81. Raja WK, Mungenast AE, Lin YT, et al. Self-organizing 3D human neural tissue derived from induced pluripotent stem cells recapitulate Alzheimer's disease phenotypes. *PLoS One*. 2016;11(9):e0161969. doi:10.1371/journal.pone.0161969
  82. Seidel D, Krinke D, Jahnke HG, et al. Induced tauopathy in a novel 3D-culture model mediates neurodegenerative processes: a real-time study on biochips. *PLoS One*. 2012;7(11):e49150. doi:10.1371/journal.pone.0049150
  83. Bowles KR, Silva MC, Whitney K, et al. ELAVL4, splicing, and glutamatergic dysfunction precede neuron loss in MAPT mutation cerebral organoids. *Cell*. 2021;184(17):4547-4563.e17. doi:10.1016/j.cell.2021.07.003
  84. Lovejoy C, Alatza A, Arber C, et al. Engineered cerebral organoids recapitulate adult Tau expression and disease-relevant changes in Tau splicing. *Research Square*. 2020. doi:10.21203/rs.3.rs-37620/v1
  85. Capano LS, Sato C, Ficulle E, et al. Recapitulation of endogenous 4R tau expression and formation of insoluble tau in directly reprogrammed human neurons. *Cell Stem Cell*. 2022;29(6):918-932.e8. doi:10.1016/j.stem.2022.04.018
  86. Oakley DH, Klickstein N, Commins C, et al. Continuous monitoring of tau-induced neurotoxicity in patient-derived iPSC-neurons. *J Neurosci*. 2021;41(19):4335-4348. doi:10.1523/JNEUROSCI.2590-20.2021
  87. Usenovic M, Niroomand S, Drolet RE, et al. Internalized tau oligomers cause neurodegeneration by inducing accumulation of pathogenic tau in human neurons derived from induced pluripotent stem cells. *J Neurosci*. 2015;35(42):14234-14250. doi:10.1523/JNEUROSCI.1523-15.2015
  88. Verheyen A, Diels A, Dijkmans J, et al. Using human iPSC-derived neurons to model TAU aggregation. *PLoS One*. 2015;10(12):e0146127. doi:10.1371/journal.pone.0146127
  89. Verheyen A, Diels A, Reumers J, et al. Genetically engineered iPSC-Derived FTDP-17 MAPT neurons display mutation-specific neurodegenerative and neurodevelopmental phenotypes. *Stem Cell Reports*. 2018;11(2):363-379. doi:10.1016/j.stemcr.2018.06.022
  90. Chen X, Firulyova M, Manis M, et al. Microglia-mediated T cell infiltration drives neurodegeneration in tauopathy. *Nature*. 2023;615(7953):668-677. doi:10.1038/s41586-023-05788-0
  91. Perea JR, Llorens-Martin M, Avila J, Bolos M. The role of microglia in the spread of tau: relevance for tauopathies. *Front Cell Neurosci*. 2018;12:172. doi:10.3389/fncel.2018.00172
  92. Shi Y, Manis M, Long J, et al. Microglia drive APOE-dependent neurodegeneration in a tauopathy mouse model. *J Exp Med*. 2019;216(11):2546-2561. doi:10.1084/jem.20190980
  93. Sukoff Rizzo SJ, Homanics G, Schaeffer DJ, et al. Bridging the rodent to human translational gap: marmosets as model systems for the study of Alzheimer's disease. *Alzheimers Dement (N Y)*. 2023;9(3):e12417. doi:10.1002/trc2.12417



94. MODEL-AD: Model Organism Development for Late Onset Alzheimer's Disease. Accessed November 4, 2022. <https://model-ad.org>
95. Oblak AL, Forner S, Territo PR, et al. Model organism development and evaluation for late-onset Alzheimer's disease: MODEL-AD. *Alzheimers Dement (N Y)*. 2020;6(1):e121110. doi:10.1002/trc2.12110
96. Sukoff Rizzo SJ, Masters A, Onos KD, et al. Improving preclinical to clinical translation in Alzheimer's disease research. *Alzheimers Dement (N Y)*. 2020;6(1):e12038. doi:10.1002/trc2.12038
97. Quinney SK, Muruges K, Oblak A, et al. STOP-AD portal: selecting the optimal pharmaceutical for preclinical drug testing in Alzheimer's disease. *Alzheimers Dement*. 2023;19(11):5289-5295. doi:10.1002/alz.13108
98. Percie du Sert N, Ahluwalia A, Alam S, et al. Reporting animal research: explanation and elaboration for the ARRIVE guidelines 2.0. *PLoS Biol*. 2020;18(7):e3000411. doi:10.1371/journal.pbio.3000411
99. Percie du Sert N, Hurst V, Ahluwalia A, et al. The ARRIVE guidelines 2.0: updated guidelines for reporting animal research. *PLoS Biol*. 2020;18(7):e3000410. doi:10.1371/journal.pbio.3000410
100. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239-259. doi:10.1007/BF00308809
101. Chang CW, Shao E, Ahluwalia L. Tau: enabler of diverse brain disorders and target of rapidly evolving therapeutic strategies. *Science*. 2021;371(6532):eabb8255. doi:10.1126/science.abb8255
102. Gordon BA, Blazey TM, Christensen J, et al. Tau PET in autosomal dominant Alzheimer's disease: relationship with cognition, dementia and other biomarkers. *Brain*. 2019;142(4):1063-1076. doi:10.1093/brain/awz019
103. Ossenkopp R, Smith R, Mattsson-Carlsson N, et al. Accuracy of tau positron emission tomography as a prognostic marker in preclinical and prodromal Alzheimer disease: a head-to-head comparison against amyloid positron emission tomography and magnetic resonance imaging. *JAMA Neurol*. 2021;78(8):961-971. doi:10.1001/jamaneurol.2021.1858
104. Vogel JW, Young AL, Oxtoby NP, et al. Four distinct trajectories of tau deposition identified in Alzheimer's disease. *Nat Med*. 2021;27(5):871-881. doi:10.1038/s41591-021-01309-6
105. Sanchez JS, Becker JA, Jacobs HIL, et al. The cortical origin and initial spread of medial temporal tauopathy in Alzheimer's disease assessed with positron emission tomography. *Sci Transl Med*. 2021;13(577):eabc0655. doi:10.1126/scitranslmed.abc0655
106. La Joie R, Visani AV, Baker SL, et al. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Sci Transl Med*. 2020;12(524):eaau5732. doi:10.1126/scitranslmed.aau5732
107. Boxer AL, Yu JT, Golbe LI, Litvan I, Lang AE, Hoglinger GU. Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. *Lancet Neurol*. 2017;16(7):552-563. doi:10.1016/S1474-4422(17)30157-6
108. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018
109. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577-1590. doi:10.1016/S0140-6736(20)32205-4
110. Wang Y, Mandelkow E. Tau in physiology and pathology. *Nat Rev Neurosci*. 2016;17(1):5-21. doi:10.1038/nrn.2015.1
111. Yanamandra K, Jiang H, Mahan TE, et al. Anti-tau antibody reduces insoluble tau and decreases brain atrophy. *Ann Clin Transl Neurol*. 2015;2(3):278-288. doi:10.1002/acn3.176
112. Yanamandra K, Kfoury N, Jiang H, et al. Anti-tau antibodies that block tau aggregate seeding in vitro markedly decrease pathology and improve cognition in vivo. *Neuron*. 2013;80(2):402-414. doi:10.1016/j.neuron.2013.07.046
113. Florian H, Wang D, Arnold SE, et al. Tilavonemab in early Alzheimer's disease: results from a phase 2, randomized, double-blind study. *Brain*. 2023;146(6):2275-2284. doi:10.1093/brain/awad024
114. Bright J, Hussain S, Dang V, et al. Human secreted tau increases amyloid-beta production. *Neurobiol Aging*. 2015;36(2):693-709. doi:10.1016/j.neurobiolaging.2014.09.007
115. Sopko R, Golonzhka O, Arndt J, et al. Characterization of tau binding by gosuranemab. *Neurobiol Dis*. 2020;146:105120. doi:10.1016/j.nbd.2020.105120
116. Ayalon G, Lee SH, Adolfsson O, et al. Antibody semorinab reduces tau pathology in a transgenic mouse model and engages tau in patients with Alzheimer's disease. *Sci Transl Med*. 2021;13(593):eabb2639. doi:10.1126/scitranslmed.abb2639
117. Lee SH, Le Pichon CE, Adolfsson O, et al. Antibody-mediated targeting of tau in vivo does not require effector function and microglial engagement. *Cell Rep*. 2016;16(6):1690-1700. doi:10.1016/j.celrep.2016.06.099
118. Teng E, Manser PT, Shah M, et al. The use of episodic memory tests for screening in clinical trials for early Alzheimer's disease: a comparison of the free and cued selective reminding test (FCSRT) and the repeatable battery for the assessment of neuropsychological status (RBANS). *J Prev Alzheimers Dis*. 2023;10(1):41-49. doi:10.14283/jpad.2022.101
119. Dam T, Boxer AL, Golbe LI, et al. Safety and efficacy of anti-tau monoclonal antibody gosuranemab in progressive supranuclear palsy: a phase 2, randomized, placebo-controlled trial. *Nat Med*. 2021;27(8):1451-1457. doi:10.1038/s41591-021-01455-x
120. Hoglinger GU, Litvan I, Mendonca N, et al. Safety and efficacy of tilavonemab in progressive supranuclear palsy: a phase 2, randomized, placebo-controlled trial. *Lancet Neurol*. 2021;20(3):182-192. doi:10.1016/S1474-4422(20)30489-0
121. Tsai RM, Miller Z, Koestler M, et al. Reactions to multiple ascending doses of the microtubule stabilizer TPI-287 in patients with Alzheimer disease, progressive supranuclear palsy, and corticobasal syndrome: a randomized clinical trial. *JAMA Neurol*. 2020;77(2):215-224. doi:10.1001/jamaneurol.2019.3812
122. Shugart J. First cognitive signal that tau immunotherapy works? ALZFORUM. 2021. Accessed September 2, 2021. <https://www.alzforum.org/news/research-news/first-cognitive-signal-tau-immunotherapy-works>
123. Teng E, Manser PT, Pickthorn K, et al. Safety and efficacy of semorinab in individuals with prodromal to mild Alzheimer disease: a randomized clinical trial. *JAMA Neurol*. 2022;79(8):758-767. doi:10.1001/jamaneurol.2022.1375
124. Boxer AL, Qureshi I, Ahljanian M, et al. Safety of the tau-directed monoclonal antibody BIIB092 in progressive supranuclear palsy: a randomised, placebo-controlled, multiple ascending dose phase 1b trial. *Lancet Neurol*. 2019;18(6):549-558. doi:10.1016/S1474-4422(19)30139-5
125. Kim B, Mikytuck B, Suh E, et al. Tau immunotherapy is associated with glial responses in FTLT-tau. *Acta Neuropathol*. 2021;142(2):243-257. doi:10.1007/s00401-021-02318-y
126. Novak P, Kovacech B, Katina S, et al. ADAMANT: a placebo-controlled randomized phase 2 study of AADvac1, an active immunotherapy against pathological tau in Alzheimer's disease. *Nat Aging*. 2021;1:521-534.
127. Courade JP, Angers R, Mairet-Coello G, et al. Epitope determines efficacy of therapeutic anti-Tau antibodies in a functional assay with human Alzheimer Tau. *Acta Neuropathol*. 2018;136(5):729-745. doi:10.1007/s00401-018-1911-2
128. Ji C, Sigurdsson EM. Current status of clinical trials on tau immunotherapies. *Drugs*. 2021;81(10):1135-1152. doi:10.1007/s40265-021-01546-6
129. Bhatt R, Ramos O. Blood-brain barrier permeable antibodies for Alzheimer's potential therapeutic and diagnostic applications.

- Alzheimers Dement.* 2023;19(S7)(Drug Development):e061328. doi:10.1002/alz.061328
130. Zhao P, Zhang N, An Z. Engineering antibody and protein therapeutics to cross the blood-brain barrier. *Antib Ther.* 2022;5(4):311-331.
  131. VandeVrede L, Boxer AL, Polydoro M. Targeting tau: clinical trials and novel therapeutic approaches. *Neurosci Lett.* 2020;731:1349-19. doi:10.1016/j.neulet.2020.134919
  132. Soeda Y, Takashima A. New insights into drug discovery targeting tau protein. *Front Mol Neurosci.* 2020;13:590896. doi:10.3389/fnmol.2020.590896
  133. Schirmer RH, Adler H, Pickhardt M, Mandelkow E. Lest we forget you - methylene blue.... *Neurobiol Aging.* 2011;32(12):2325.e7-16. doi:10.1016/j.neurobiolaging.2010.12.012
  134. Wischik CM, Edwards PC, Lai RY, Roth M, Harrington CR. Selective inhibition of Alzheimer disease-like tau aggregation by phenothiazines. *Proc Natl Acad Sci U S A.* 1996;93(20):11213-11218. doi:10.1073/pnas.93.20.11213
  135. Wischik CM, Benthall P, Gauthier S, Miller S, Kook K, Scheltemer BO. Oral tau aggregation inhibitor for Alzheimer's disease: design, progress and basis for selection of the 16 mg/day dose in a phase 3, randomized, placebo-controlled trial of hydromethylthionine mesylate. *J Prev Alzheimers Dis.* 2022;9(4):780-790. doi:10.14283/jpad.2022.63
  136. Ryan JM, Quattropiani A, Abd-Elaziz K, et al. O1-12-05: phase 1 study in healthy volunteers of the O-GlcNAcase inhibitor ASN120290 as a novel therapy for progressive supranuclear palsy and related tauopathies. *Alzheimers Dement.* 2018;14(7S\_Part\_4):251.
  137. Wang X, Li W, Marcus J, et al. MK-8719, a novel and selective O-GlcNAcase inhibitor that reduces the formation of pathological tau and ameliorates neurodegeneration in a mouse model of tauopathy. *J Pharmacol Exp Ther.* 2020;374(2):252-263. doi:10.1124/jpet.120.266122
  138. Park J, Kim DY, Hwang GS, Han IO. Repeated sleep deprivation decreases the flux into hexosamine biosynthetic pathway/O-GlcNAc cycling and aggravates Alzheimer's disease neuropathology in adult zebrafish. *J Neuroinflammation.* 2023;20(1):257. doi:10.1186/s12974-023-02944-1
  139. Piscopo P, Crestini A, Carbone E, et al. A systematic review on drugs for synaptic plasticity in the treatment of dementia. *Ageing Res Rev.* 2022;81:101726. doi:10.1016/j.arr.2022.101726
  140. Yadikar H, Torres I, Aiello G, et al. Screening of tau protein kinase inhibitors in a tauopathy-relevant cell-based model of tau hyperphosphorylation and oligomerization. *PLoS One.* 2020;15(7):e0224952. doi:10.1371/journal.pone.0224952
  141. Edwards AL, Collins JA, Junge C, et al. Exploratory tau biomarker results from a multiple ascending-dose study of BIIB080 in Alzheimer disease: a randomized clinical trial. *JAMA Neurol.* 2023;80(12):1344-1352. doi:10.1001/jamaneurol.2023.3861
  142. Park J, Wetzel I, Marriott I, et al. A 3D human triculture system modeling neurodegeneration and neuroinflammation in Alzheimer's disease. *Nat Neurosci.* 2018;21(7):941-951. doi:10.1038/s41593-018-0175-4
  143. Taubes A, Nova P, Zalocusky KA, et al. Experimental and real-world evidence supporting the computational repurposing of bumetanide for APOE4-related Alzheimer's disease. *Nat Aging.* 2021;1(10):932-947. doi:10.1038/s43587-021-00122-7
  144. Cunniffe N, Vuong KA, Ainslie D, et al. Systematic approach to selecting licensed drugs for repurposing in the treatment of progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2021;92(3):295-302. doi:10.1136/jnnp-2020-324286
  145. O'Brien JT, Chouliaras L, Sultana J, Taylor JP, Ballard C, Group RS. RENEWAL: REpurposing study to find NEW compounds with Activity for Lewy body dementia-an international Delphi consensus. *Alzheimers Res Ther.* 2022;14(1):169. doi:10.1186/s13195-022-01103-7
  146. Boyarko B, Podvin S, Greenberg B, et al. Evaluation of bumetanide as a potential therapeutic agent for Alzheimer's disease. *Front Pharmacol.* 2023;14:1190402. doi:10.3389/fphar.2023.1190402
  147. Desai RJ, Varma VR, Gerhard T, et al. Comparative risk of Alzheimer Disease and related dementia among medicare beneficiaries with rheumatoid arthritis treated with targeted disease-modifying antirheumatic agents. *JAMA Netw Open.* 2022;5(4):e226567. doi:10.1001/jamanetworkopen.2022.6567
  148. Varma VR, Desai RJ, Navakkode S, et al. Hydroxychloroquine lowers Alzheimer's disease and related dementias risk and rescues molecular phenotypes related to Alzheimer's disease. *Mol Psychiatry.* 2023;28(3):1312-1326. doi:10.1038/s41380-022-01912-0
  149. FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approach. 2023. Accessed July 6, 2023. <https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval>
  150. Dumas A, Destrebecq F, Esposito G, Suchonova D, Steen Frederiksen K. Rethinking the detection and diagnosis of Alzheimer's disease: outcomes of a European Brain Council project. *Aging Brain.* 2023;4:100093. doi:10.1016/j.nbas.2023.100093
  151. Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med.* 2014;370(4):322-333. doi:10.1056/NEJMoa1304839
  152. FDA's Decision to Approve New Treatment for Alzheimer's Disease. U.S. Food & Drug Administration; 2021. Accessed June 7, 2021. <https://www.fda.gov/drugs/our-perspective/fdas-decision-approve-new-treatment-alzheimers-disease>
  153. Karikari TK, Ashton NJ, Brinkmalm G, et al. Blood phospho-tau in Alzheimer disease: analysis, interpretation, and clinical utility. *Nat Rev Neurol.* 2022;18(7):400-418. doi:10.1038/s41582-022-00665-2
  154. Stamelou M, Respondek G, Giagkou N, Whitwell JL, Kovacs GG, Hoglinger GU. Evolving concepts in progressive supranuclear palsy and other 4-repeat tauopathies. *Nat Rev Neurol.* 2021;17(10):601-620. doi:10.1038/s41582-021-00541-5
  155. Bischof GN, Brendel M, Barthel H, et al. Improved tau PET SUVR quantification in 4-repeat tau phenotypes with [(18)F]PI-2620. *J Nucl Med.* 2024;65(6):952-955. doi:10.2967/jnumed.123.265930
  156. Volter F, Beyer L, Eckenweber F, et al. Assessment of perfusion deficit with early phases of [(18)F]PI-2620 tau-PET versus [(18)F]flutemetamol-amyloid-PET recordings. *Eur J Nucl Med Mol Imaging.* 2023;50(5):1384-1394. doi:10.1007/s00259-022-06087-y
  157. Horie K, Barthelemy NR, Spina S, et al. CSF tau microtubule-binding region identifies pathological changes in primary tauopathies. *Nat Med.* 2022;28(12):2547-2554. doi:10.1038/s41591-022-02075-9
  158. Horie K, Salvado G, Barthelemy NR, et al. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. *Nat Med.* 2023;29(8):1954-1963. doi:10.1038/s41591-023-02443-z
  159. Blennow K, Chen C, Cicognola C, et al. Cerebrospinal fluid tau fragment correlates with tau PET: a candidate biomarker for tangle pathology. *Brain.* 2020;143(2):650-660. doi:10.1093/brain/awz346
  160. Fitzpatrick AWP, Falcon B, He S, et al. Cryo-EM structures of tau filaments from Alzheimer's disease. *Nature.* 2017;547(7662):185-190. doi:10.1038/nature23002
  161. Shi Y, Zhang W, Yang Y, et al. Structure-based classification of tauopathies. *Nature.* 2021;598(7880):359-363. doi:10.1038/s41586-021-03911-7
  162. Ashton NJ, Leuzy A, Lim YM, et al. Increased plasma neurofilament light chain concentration correlates with severity of post-mortem neurofibrillary tangle pathology and neurodegeneration. *Acta Neuropathol Commun.* 2019;7(1):5. doi:10.1186/s40478-018-0649-3
  163. Bacioglu M, Maia LF, Preische O, et al. Neurofilament light chain in blood and CSF as marker of disease progression in mouse models and

- in neurodegenerative diseases. *Neuron*. 2016;91(2):494-496. doi:10.1016/j.neuron.2016.07.007
164. Bridel C, van Wieringen WN, Zetterberg H, et al. Diagnostic value of cerebrospinal fluid neurofilament light protein in neurology: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76(9):1035-1048. doi:10.1001/jamaneurol.2019.1534
  165. Meeter LHH, Vijverberg EG, Del Campo M, et al. Clinical value of neurofilament and phospho-tau/tau ratio in the frontotemporal dementia spectrum. *Neurology*. 2018;90(14):e1231-e1239. doi:10.1212/WNL.0000000000005261
  166. Zetterberg H, Teunissen C, van Swieten J, et al. The role of neurofilament light in genetic frontotemporal lobar degeneration. *Brain Commun*. 2023;5(1):fcac310. doi:10.1093/braincomms/fcac310
  167. U.S. Food and Drug Administration. Biomarker Qualification Program. Context of Use. 2021. <https://www.fda.gov/drugs/biomarker-qualification-program/context-use>
  168. Mills SM, Mallmann J, Santacruz AM, et al. Preclinical trials in autosomal dominant AD: implementation of the DIAN-TU trial. *Rev Neurol (Paris)*. 2013;169(10):737-743. doi:10.1016/j.neurol.2013.07.017
  169. The ALLFTD Research Study. The ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration Study. <https://www.allftd.org/>
  170. GENFI: Genetic FTD Initiative. <https://www.genfi.org/>
  171. Bovee B, Bove J, Brannelly P, et al. The longitudinal evaluation of familial frontotemporal dementia subjects protocol: framework and methodology. *Alzheimers Dement*. 2020;16(1):22-36. doi:10.1016/j.jalz.2019.06.4947
  172. Rohrer JD, Nicholas JM, Cash DM, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol*. 2015;14(3):253-262. doi:10.1016/S1474-4422(14)70324-2
  173. FTD Preventive Initiative. Boxer Lab, University of California San Francisco. 2023. <https://boxerlab.ucsf.edu/study/fpi>
  174. Staffaroni AM, Quintana M, Wendelberger B, et al. Temporal order of clinical and biomarker changes in familial frontotemporal dementia. *Nat Med*. 2022;28(10):2194-2206. doi:10.1038/s41591-022-01942-9
  175. U.S. Food and Drug Administration. *Human Gene Therapy for Neurodegenerative Diseases: Guidance for Industry*. Center for Biologics Evaluation and Research; 2022. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-neurodegenerative-diseases>
  176. Kowalska A, Jamrozik Z, Kwiecinski H. Progressive supranuclear palsy – parkinsonian disorder with tau pathology. *Folia Neuropathol*. 2004;42(2):119-123.
  177. Jellinger KA. Pathomechanisms of cognitive and behavioral impairment in corticobasal degeneration. *J Neural Transm (Vienna)*. 2023. doi:10.1007/s00702-023-02691-w
  178. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in Early Alzheimer's Disease. *N Engl J Med*. 2021;384(18):1691-1704. doi:10.1056/NEJMoa2100708
  179. Eslinger PJ, Dennis K, Moore P, Antani S, Hauck R, Grossman M. Metacognitive deficits in frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 2005;76(12):1630-1635. doi:10.1136/jnnp.2004.053157
  180. Rosen HJ. Anosognosia in neurodegenerative disease. *Neurocase*. 2011;17(3):231-241. doi:10.1080/13554794.2010.522588
  181. Taylor JC, Heuer HW, Clark AL, et al. Feasibility and acceptability of remote smartphone cognitive testing in frontotemporal dementia research. *Alzheimers Dement (Amst)*. 2023;15(2):e12423. doi:10.1002/dad2.12423
  182. U.S. Food and Drug Administration. *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments*. Center for Drug Evaluation and Research; 2022. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome>
  183. Dodge S, Dacks P, Niehoff D, et al. *Frontotemporal Degeneration (FTD): A Voice of the Patient Report*. The Association for Frontotemporal Degeneration; 2021:1-75.
  184. Respondek G, Breslow D, Amirghiasvand C, et al. The lived experiences of people with progressive supranuclear palsy and their caregivers. *Neurol Ther*. 2023;12(1):229-247. doi:10.1007/s40120-022-00420-1
  185. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med*. 2017;377(1):62-70. doi:10.1056/NEJMra1510062
  186. U.S. Food and Drug Administration. Center for Biologics Evaluation and Research, Center for Drug Evaluation Research. *Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry*. Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research; 2019. FDA-2018-D-3124. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry>
  187. Wang G, Berry S, Xiong C, et al. A novel cognitive disease progression model for clinical trials in autosomal-dominant Alzheimer's disease. *Stat Med*. 2018;37(21):3047-3055. doi:10.1002/sim.7811
  188. Bateman RJ, Benzinger TL, Berry S, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: adaptive design and disease progression model. *Alzheimers Dement*. 2017;13(1):8-19. doi:10.1016/j.jalz.2016.07.005
  189. Salloway S, Farlow M, McDade E, et al. A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease. *Nat Med*. 2021;27(7):1187-1196. doi:10.1038/s41591-021-01369-8
  190. Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. *A Study of Potential Disease Modifying Treatments in Individuals With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation (DIAN-TU) (DIAN-TU)*. National Library of Medicine, National Center for Biotechnology Information. <https://clinicaltrials.gov/study/NCT05269394>
  191. Boxer AL, Sperling R. Accelerating Alzheimer's therapeutic development: the past and future of clinical trials. *Cell*. 2023;186(22):4757-4772. doi:10.1016/j.cell.2023.09.023
  192. Cummings J, Montes A, Kamboj S, Cacho JF. The role of basket trials in drug development for neurodegenerative disorders. *Alzheimers Res Ther*. 2022;14(1):73. doi:10.1186/s13195-022-01015-6
  193. Almirall D, Nahum-Shani I, Sherwood NE, Murphy SA. Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research. *Transl Behav Med*. 2014;4(3):260-274. doi:10.1007/s13142-014-0265-0

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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