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published in
The Lancet Neurology
2022

DOI (link to publisher)
10.1016/S1474-4422(22)00168-5

document version
Publisher's PDF, also known as Version of record

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Article 25fa Dutch Copyright Act

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citation for published version (APA)
Ossenkoppele, R., van der Kant, R., & Hansson, O. (2022). Tau biomarkers in Alzheimer's disease: towards implementation in clinical practice and trials. *The Lancet Neurology*, *21*(8), 726-734. https://doi.org/10.1016/S1474-4422(22)00168-5

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Tau biomarkers in Alzheimer's disease: towards implementation in clinical practice and trials

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Lancet Neurol 2022; 21: 726–34

Published Online
May 25, 2022
https://doi.org/10.1016/S1474-4422(22)00168-5

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Summary

Background **Deposition of tau aggregates is a pathological hallmark of Alzheimer's disease that is closely linked both spatially and temporally to emergence of neurodegeneration and manifestation of clinical symptoms. There is an urgent need for accurate PET, CSF, and plasma biomarkers of tau pathology to improve the diagnostic process in clinical practice and the selection of participants and monitoring of treatment effects in trials.**

Recent developments **Innovative second-generation tau-PET tracers with high affinity and selectivity to tau pathology in Alzheimer's disease have enabled detection of tau pathology in medial temporal lobe subregions that are affected in the earliest disease stages. Furthermore, novel but common tau spreading subtypes have been discovered using tau-PET, suggesting much greater interindividual differences in the distribution of tau pathology across the brain than previously assumed. In the CSF biomarker field, novel phosphorylated tau (p-tau) assays have been introduced that better reflect tau tangle load than established CSF biomarkers of tau pathology. The advent of cost-effective and accessible blood-based biomarkers for tau pathophysiology (ie, p-tau181, p-tau217, and p-tau231) might transform the Alzheimer's disease field, as these biomarkers correlate with post-mortem Alzheimer's disease pathology, differentiate Alzheimer's disease from other types of dementia, and predict future progression from normal cognition and mild cognitive impairment to Alzheimer's disease. In controlled investigational settings, improvements in tau-PET and biofluid p-tau markers have led to earlier disease detection, more accurate diagnostic methods, and refinement of prognosis. The anti-tau therapy landscape is rapidly evolving, with multiple ongoing phase 1 and 2 trials of post-translational modification of tau, tau immunotherapy, tau aggregation inhibitors, and targeting production of tau and reduction of intracellular tau levels. Neuroimaging and biofluid tau markers hold potential for optimising such clinical trials by augmenting participant selection, providing evidence of target engagement, and monitoring treatment efficacy.**

Where next? **Major challenges to overcome are the high cost of tau-PET, partial sensitivity to detect early-stage Alzheimer's disease pathology, and off-target tracer binding. Prospective validation studies of biofluid p-tau markers are needed, and assay-related preanalytical and analytical factors need further refinement. Future studies should focus on demonstrating the diagnostic and prognostic accuracy of tau biomarkers—blood-based markers in particular—in non-tertiary settings, such as primary care, which is characterised by a diverse population with medical comorbidities. Large-scale head-to-head studies are needed across different stages of Alzheimer's disease to determine which tau biomarker is optimal in various clinical scenarios, such as early diagnosis, differential diagnosis, and prognosis, and for aspects of clinical trial design, such as proving target engagement, optimising participant selection, and refining monitoring of treatment effects.**

Introduction

Alzheimer's disease is a gradually progressive neurodegenerative disorder characterised by widespread deposition of amyloid β plaques in early stages, followed by aggregation of tau in the neocortex, neurodegeneration, cognitive decline, and ultimately dementia.[1,2] Within this complex pathological interplay of amyloid β, tau, neuroinflammation, and other factors, the aggregation of tau is key in the development of clinical Alzheimer's disease in view of the substantial neurotoxic effects of the protein.[3] A large post-mortem burden of tau tangles is strongly associated with decreased cognitive function.[4] In-vitro studies have shown that tau pathology can induce synaptic loss and decrease the function of neural networks,[5] and human neuroimaging studies have demonstrated that when and where tau pathology occurs corresponds to both onset[6] and type[7] of cognitive deficits. Tau pathology is, thus, closely linked both spatially and temporally to emergence of neurodegeneration and manifestation of clinical symptoms. Hence, accurate biomarkers of tau pathology offer great opportunities to improve diagnosis and prognostication in clinical practice and trial designs.

The protein tau is encoded by the *MAPT* gene, which is localised at chromosome 17q21. Tau is predominantly expressed in neurons and has an important role in tubulin polymerisation and stabilisation of microtubules, which, in turn, are integrated parts of the cytoskeleton that support intracellular transport. However, hyperphosphorylation of tau in Alzheimer's disease initiates the conformational change from natively unfolded tau into paired helical filament tau inclusions and neurofibrillary tangles. Currently, several in-vivo biomarkers are available that reflect different aspects of neurofibrillary tangle development,[8] including soluble phosphorylated tau (p-tau) levels measured at multiple phosphorylation sites in human CSF and in plasma,[2,9] and tau-PET tracers that enable visualisation and quantification of insoluble cerebral tau aggregates.[10] The advent of blood-based

biomarkers of p-tau has substantially changed the Alzheimer's disease landscape, suddenly making available a non-invasive, cost-effective, and scalable tau biomarker.

In this Rapid Review, we provide an update on neuroimaging (PET) and biofluid (CSF and plasma) biomarkers of tau pathology in Alzheimer's disease, and discuss whether and how these tau biomarkers can support the clinical diagnostic and prognostic process. We also describe the anti-tau drug development pipeline and discuss whether and how tau biomarkers can improve clinical trials of tau-targeting agents.

Biomarkers of tau pathology in Alzheimer's disease

Tau-PET

Tau-PET tracers to measure insoluble tau aggregates that are formed in Alzheimer's disease were introduced in the mid-2010s, and the first tau-PET tracer, [^{18}F] flortaucipir, was approved for clinical use by the US Food and Drug Administration (FDA) in May, 2020. Two important developments in tau-PET research since 2020 include the possibility to visualise and quantify the earliest tau pathological changes in medial temporal lobe substructures, and the discovery of novel but common PET-based tau spreading subtypes.

First, informed by the neuropathological literature, two 2021 PET studies identified Brodmann area 35, the perirhinal cortex, as the earliest brain region affected by tau pathology in cognitively unimpaired individuals (figure 1).[11,12] Tau load in Brodmann area 35 was associated with reduced functional connectivity to the medial prefrontal cortex and subtle worse memory performance,[11,13] possibly representing an early tau-related mechanism in Alzheimer's disease. Future studies to further investigate this mechanism will possibly benefit from the 2021 introduction of a three-dimensional map of neurofibrillary tangle pathology constructed using ex-vivo MRI and histological imaging,[14] and from the advent of novel second-generation tau-PET tracers such as [^{18}F]MK6240, [^{18}F]RO948, and [^{18}F]PI2620, which bind with higher affinity and selectivity to tau pathology than does [^{18}F] flortaucipir, particularly in hippocampal regions.

Second, PET studies conducted in 2021 have contributed to the improved understanding of heterogeneity in spatial tau-PET patterns. On the basis of neuropathological findings, the distribution of neurofibrillary tangle pathology was initially considered to follow a spreading pattern from transentorhinal and entorhinal regions (Braak I–II), to limbic regions (Braak III–IV), and to neocortical regions (Braak V–VI). A 2021 study that used an unbiased machine-learning algorithm demonstrated the presence of various PET-based tau spreading subtypes within the typical, memory-predominant, clinical spectrum of Alzheimer's disease, including limbic (33%), medial temporal lobe sparing (17%), posterior (31%), and left temporal (19%) subtypes.[15] All these tau spreading subtypes were associated with distinct clinical presentations and cognitive trajectories. This observation goes against the notion of fixed spreading patterns and instead suggests clear interindividual variability in the spreading patterns of tau pathology across the brain.

CSF-based tau biomarkers

It has been possible to detect p-tau isoforms in CSF since the mid-1990s, and these biomarkers are assumed to reflect the increased production, phosphorylation, and secretion of tau in the brain.[16] Although CSF p-tau is widely used as a diagnostic biomarker in clinical practice nowadays, substantial improvements have been made in at least three different aspects of research (table).

First, over the past three decades, tau phosphorylated at threonine 181 (p-tau181) has been the predominant tau biomarker measured in CSF, but p-tau assays produced from 2020 onwards have yielded novel insights into the early changes of tau metabolism. For example, in individuals with autosomal dominant Alzheimer's disease, CSF p-tau217 levels start to increase at the time of amyloid β plaque formation, measured with amyloid-PET, while p-tau205 levels rise at the first signs of neuronal dysfunction, measured with [^{18}F] fluorodeoxyglucose (FDG)-PET.[18] Another study showed that CSF p-tau217 and p-tau231 could differentiate amyloid β-positive from amyloid β-negative individuals at the preclinical stage of Alzheimer's disease.[19]

Second, CSF p-tau217 performed somewhat better than did CSF p-tau181 in distinguishing Alzheimer's disease from other neurodegenerative disorders in observational studies, and it correlated more strongly to baseline and longitudinal tau-PET measures.[17,30] These findings suggest that CSF p-tau217 might provide the best diagnostic performance during the course of Alzheimer's disease compared with p-tau181, p-tau231, and other p-tau isoforms.

Third, a mass spectrometry study investigated the role of the microtubule binding region (MTBR) domain. Amounts in CSF of MTBR-tau varieties—such as MTBR-tau243, MTBR-tau299, or MTBR-tau354—are promising biomarkers to stage Alzheimer's disease and monitor target engagement in clinical trials.[20]

Blood-based tau biomarkers

The emergence of cost-effective and accessible blood-based soluble p-tau biomarkers—namely, p-tau181, p-tau217, and p-tau231—represents a potential transformation for diagnostic and prognostic procedures and for clinical trial design in Alzheimer's disease (table).[2] Increased amounts of p-tau biomarkers in plasma correspond strongly to the density of both amyloid β plaques and tau tangles, measured either in post-mortem brain tissue[22,24,31–33] or in vivo using PET.[21–24,31,32,34] The correlation between plasma p-tau biomarkers and amyloid β plaques could either indicate very early tau pathological changes or represent early physiological reactions to amyloid β plaques that are not directly related to tau tangle pathology.[20,32,35] Furthermore, plasma p-tau levels

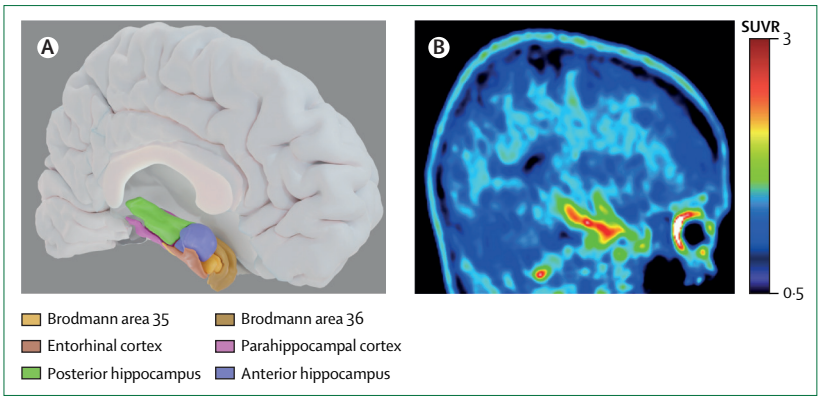

Figure 1: **Tau PET signal in the medial temporal lobe**
Schematic overview of important medial temporal structures (A) and a tau-PET scan using [^{18}F]RO948 in a woman aged 60–70 years with subjective cognitive decline, an *APOE* ε3/ε4 genotype, and a mini-mental state examination (MMSE) score of 29 (B). The tau-PET pattern indicates a significant tau load in the medial temporal lobe, whereas the neocortex is relatively spared. Since the medial temporal lobe is among the earliest affected brain regions in Alzheimer's disease and shows a tight association with memory performance, this figure demonstrates the potential of tau-PET to study the early manifestation of tau aggregates in Alzheimer's disease for research purposes or selection of participants. SUVR=standard uptake value ratio.

progressively rise when approaching the estimated age of symptom onset—predicted by parental age at onset—in familial forms of Alzheimer's disease,[24,36] and with advancing disease severity of Alzheimer's disease in people with Down syndrome.[27] Down syndrome involves trisomy of chromosome 21, on which the *APP* gene is located. Accordingly, p-tau levels change over time in amyloid β-positive cognitively unimpaired individuals, whereas they remain relatively stable in amyloid β-negative cognitively unimpaired individuals.[37–39]

The great potential for clinical use of plasma p-tau measures has been demonstrated by multiple studies showing excellent discriminative accuracy for the differential diagnosis of Alzheimer's disease versus non-Alzheimer's disease primary tauopathies (eg, progressive supranuclear palsy or corticobasal degeneration) or other non-Alzheimer's disease neurodegenerative disorders (eg, dementia with Lewy bodies or behavioural variant frontotemporal dementia).[22–24,31,40] Furthermore, plasma p-tau combined with brief cognitive testing and *APOE* genotyping predicted with high accuracy the development of future Alzheimer's disease in individuals with subjective cognitive decline and mild cognitive impairment.[29] Importantly, many of the aforementioned findings could be replicated in an ethnically more diverse population.[28] Finally, although some p-tau measures can be considered interchangeable,[26,41,42] p-tau217 might have slightly favourable properties in terms of its dynamic range, ability to predict tau-PET-positivity, and diagnostic performance in symptomatic individuals compared with other p-tau biomarkers,[21–24,28,31,32,40,43] but further research is needed to establish this observation.

Tau biomarkers in clinical practice

Regarding early detection of tau tangle pathology, tau-PET has shown limited sensitivity,[44] with only 5–10% of amyloid β-positive cognitively unimpaired individuals and 50–67% of amyloid β-positive individuals with mild cognitive impairment showing suprathreshold tau-PET signal in neocortical regions.[45–48] By contrast, both CSF and plasma p-tau markers show elevations already in early disease stages.[19,22–24,28,29,31,35,37,43] Thus, biofluid markers seem superior to PET-based tau biomarkers for detecting early pathological changes in Alzheimer's disease. However, several challenges need to be addressed before large-scale clinical implementation, particularly for plasma p-tau. These challenges include assay-related factors (ie, specificity and selectivity), preanalytical factors (ie, methodology, sample handling, and storage), and analytical factors (ie, internal and external quality control, development of reference material, and reference methods against which to calibrate the assays).[49] For the differential diagnosis of Alzheimer's disease versus other neurodegenerative disorders, tau-PET has shown excellent discriminative accuracy, with a sensitivity and specificity of more than 90%.[45,47] In our opinion, we consider tau-PET the best first biomarker investigation for the differential diagnosis of dementia syndromes, for which Alzheimer's disease is among the suspected causes. Our belief is further supported by the regional information provided by tau-PET, which enhances its diagnostic specificity.[44] Future studies will have to determine whether this advantage outweighs practical considerations, including exposure to radiation, costs, and limited accessibility—and methodological issues such as off-target binding to basal ganglia, choroid plexus, substantia nigra, meninges, and skull,[50] as well as the fact that tau-PET is currently only approved for clinical use in the USA. In the past 5 years, several observational and longitudinal studies have shown that increased tau-PET signal at baseline is a strong predictor of cognitive decline over time,[51–53] particularly in the preclinical and amyloid+ mild cognitive impairment stages of Alzheimer's disease.[52] Head-to-head comparisons between biofluid and neuroimaging biomarkers of tau pathology are needed to establish the optimal prognostic tau biomarker.

Anti-tau drug development

Another area of promise for tau biomarkers is their potential role in development of tau-targeting therapeutics. The first generation of tau-targeting interventions focused on either reversing post-translation modifications that might drive the aggregation of tau, such as hyperphosphorylation, or on preventing the aggregation event directly. Examples of such approaches include administration of nicotinamide to reduce tau phosphorylation, and use of curcumin, which binds to β-sheet structures such as neurofibrillary tangles, to prevent protein aggregation. Strategies that target post-translation modifications or aggregation of tau have been extensively reviewed elsewhere.[54,55]

Two fast-developing clinical strategies are tau immunotherapy and targeting the production of tau.

	Year	Participants	Population	Phosphorylation site	Main finding	Importance
CSF biomarkers						
Janelidze et al[17]	2020	226	Cognitively unimpaired, MCI, sporadic AD, non-AD	181, 217	Compared with p-tau181, p-tau217 showed greater longitudinal increases and correlated better with CSF and PET measures of amyloid β and tau	Suggests that p-tau217 might be more useful than p-tau181 in the diagnostic work-up of AD
Barthélemy et al[18]	2020	370	Autosomal dominant AD, non-carriers	181, 202, 205, 217	p-tau217 and p-tau181 increase approximately 2 decades before presence of aggregated tau pathology, while p-tau205 increases closer to symptom onset	Different soluble CSF p-tau species are associated with distinct AD related processes
Suárez-Calvet et al[19]	2020	381	Cognitively unimpaired	181, 217, 231	CSF p-tau181, p-tau217, and p-tau231 levels are increased in the context of subtle amyloid β elevations	Early changes in neuronal tau metabolism can be detected with CSF p-tau assays
Horie et al[20]	2021	163	Cognitively unimpaired, MCI, sporadic AD, non-AD	243, 299, 354	MTBR species of tau correlated with tau-PET and cognition	MTBR-tau species in CSF could serve as biomarkers to stage AD and monitor target engagement in clinical trials
Plasma biomarkers						
Janelidze et al[21]	2020	526	Cognitively unimpaired, MCI, sporadic AD, non-AD	181	p-tau181 increased from cognitively unimpaired to MCI to AD and distinguished AD from non-AD dementia	Demonstrates potential of plasma p-tau181 as a non-invasive diagnostic and prognostic biomarker of AD
Thijssen et al[22]	2020	362	Cognitively unimpaired, MCI, sporadic AD, FTLD	181	High discriminative accuracy of p-tau181 for AD versus FTLD	Demonstrates potential of plasma p-tau181 for the differential diagnosis AD versus FTLD
Karikari et al[23]	2020	1131	Cognitively unimpaired, MCI, sporadic AD, non-AD	181	High discriminative accuracy of p-tau181 for AD versus non-AD neurodegenerative disorders	Demonstrates potential of plasma p-tau181 for the differential diagnosis AD versus non-AD
Palmqvist et al[24]	2020	1402	Cognitively unimpaired, MCI, sporadic AD, non-AD, and autosomal dominant AD	217	High discriminative accuracy of p-tau217 for AD versus non-AD neurodegenerative disorders	Plasma p-tau217 outperformed MRI and other plasma biomarkers and was comparable to key CSF and PET measures
Barthélemy et al[25]	2020	126	Cognitively unimpaired, MCI, sporadic AD	181, 217	Higher accuracy for detecting increased CSF amyloid β levels for p-tau217 compared with p-tau181	Plasma p-tau217 might be a more specific marker for detecting amyloidosis at both symptomatic and asymptomatic stages of AD
Mielke et al[26]	2021	200	Cognitively unimpaired, MCI	181, 217, 231	Subtle differences across plasma p-tau species and platforms	Suggests some degree of interchangeability across plasma p-tau measures
Lleo et al[27]	2021	410	Cognitively unimpaired, adults with Down Syndrome	181	High separation between asymptomatic and symptomatic adults with Down Syndrome	Demonstrates potential of plasma p-tau181 in Down Syndrome where the clinical diagnosis of AD is challenging due to intellectual disability
Brickman et al[28]	2021	413	Controls, AD	181, 217	Increased p-tau181 and p-tau217 in autopsy confirmed and clinical AD	Replication of previous studies in an ethnically more diverse population
Palmqvist et al[29]	2021	883	Subjective cognitive decline, MCI	181, 217	The combination of plasma p-tau217, cognition, and *APOE* genotype predicted future AD-type dementia with high accuracy	Algorithms that include plasma p-tau may improve the prognosis in preclinical and mild cognitive impairment with amyloid+ stages of AD

Studies are presented in chronological order of publication, and all represent observational studies. Studies were selected on the basis of novelty, importance, and timing. AD=Alzheimer's disease, FTLD=frontotemporal lobar degeneration, MCI=mild cognitive impairment, MTBR=microtubule binding region.

Table: **Selection of relevant studies measuring p-tau levels in CSF or in plasma**

Currently, a diverse set of anti-tau targeting strategies are in the drug-development pipeline for Alzheimer's disease (figure 2). Tau biomarkers have played a part in the clinical development of these therapies.

Tau immunotherapies

Tau immunotherapy strategies are designed to neutralise tau through antibody binding, with the goal of blocking the propagation of tau across neurons to prevent large-scale aggregation. Most tau immunotherapies currently in development target the N-terminal or MTBR domain. Several N-terminal targeting immunotherapies, such as semorinemab and gonsuranemab, and MTBR-targeting immunotherapies, such as Aadvac1 and zagotenemab, are currently undergoing or have completed phase 2 clinical trials (figure 2), and have been shown to reduce CSF p-tau levels.[56–59] However, none of these trials has shown significant reductions in tau-PET signal, and only one trial using semorinemab in individuals with mild-to-moderate Alzheimer's disease demonstrated slowing of decline on a primary cognitive endpoint.[60] However, no effect was observed on other primary and secondary outcome

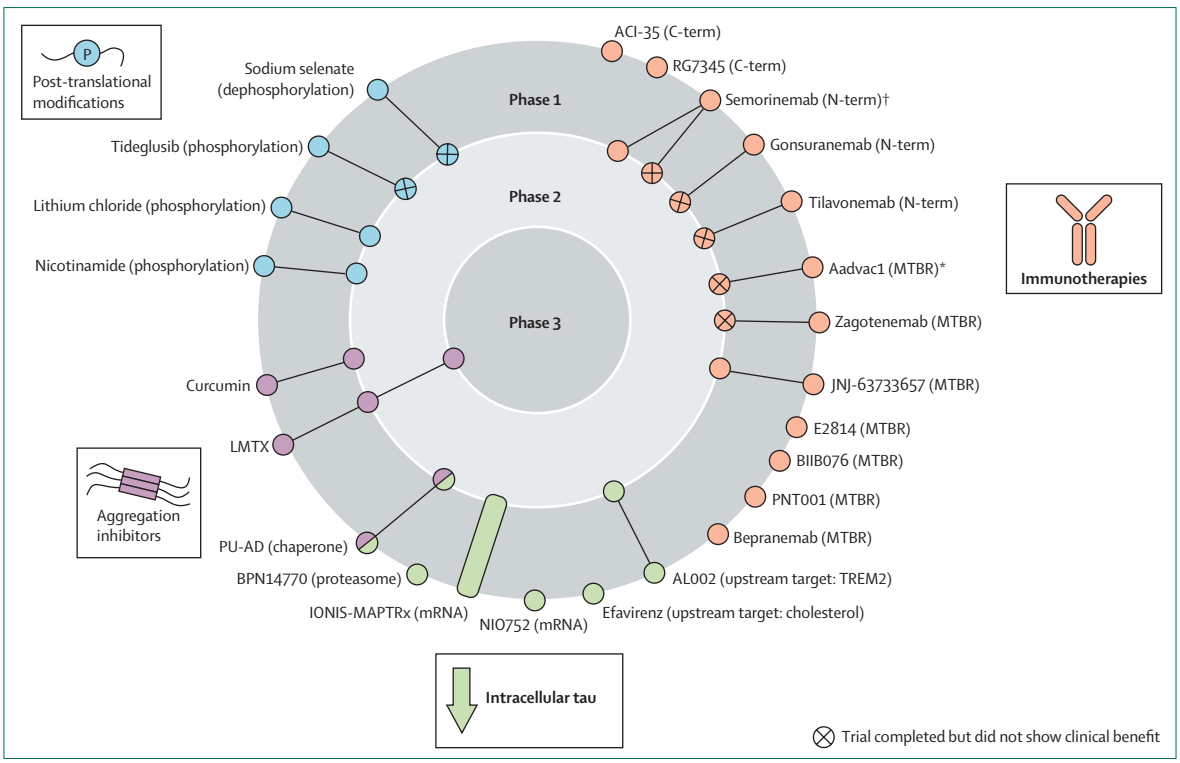

Figure 2: **Tau-targeting drug development pipeline and potential use of tau biomarkers in trials**
Proposed mode of actions for the different drugs are indicated, and for immunotherapies the antigen site on tau is indicated. Drugs that target other post-translational modifications of tau, such as acetylation and glycosylation, are currently being tested in trials for tauopathies other than Alzheimer's disease and are, therefore, not shown in this figure. *Post-hoc analysis identified subgroups of responders, but additional trials are required. †Phase 2 testing of semorinemab in individuals with amyloid+ mild cognitive impairment and early Alzheimer's disease yielded negative results, whereas another phase 2 study in individuals with moderate Alzheimer's disease showed slowing of decline on one of the two primary cognitive endpoints.

measures of cognition in this trial, and semorinemab was not effective in earlier stages of Alzheimer's disease, for example in amyloid+ individuals with mild cognitive impairment.[59] The absence of clear clinical and biological benefits of tau immunotherapies, to date, has several possible explanations. Although tau immunotherapy mainly targets extracellular tau to prevent the spread of tau, it probably does not directly target intracellular tau in neurons, where tau is thought to be most pathogenic.[3] Furthermore, the presumed mechanism of action for tau immunotherapy—ie, blocking the transfer of tau between cells—could be imperfect, either because tau might be transported in exosomes, or in tunnelling nanotubes where antibodies cannot bind to tau, or because the dwell time of extracellular tau in the synaptic cleft might be too short for antibodies to efficiently neutralise most of the tau seeds.[16,61]

Targeting production and degradation of intracellular tau

Targeting intracellular tau levels either by reducing tau production or by enhancing tau degradation might be a viable therapeutic strategy, as an alternative to immunotherapy. As a rationale for this approach, increased tau production has been reported in people with Alzheimer's disease, which correlated with the level of amyloid β plaques.[16]

Multiple strategies targeting intracellular tau are being pursued. A potential therapeutic approach, which has yielded clinical benefits in other proteinopathies and neurological diseases,[62] is the use of antisense oligonucleotides that prevent tau mRNA translation, thereby reducing tau production rates and overall levels of tau. After encouraging results in mice and cynomolgus monkeys,[63,64] the antisense oligonucleotide BIIB080 is in a combined phase 1–2 study for mild Alzheimer's disease (NCT03186989). The main goal of this study is to assess the safety and pharmacokinetic profile of the agent during a 13-week treatment period. Initial results have been encouraging, with strong reductions in CSF total-tau and p-tau, accompanied by good tolerability.[65] Another tau-targeting antisense oligonucleotide in development is NIO752 (NCT04539041) which has started clinical trials in progressive supranuclear palsy, but not yet in Alzheimer's disease. Besides antisense oligonucleotides, treatments based on small interfering ribonucleic acids (siRNAs) are also being developed for reducing tau production.

Another means to reduce intracellular tau is by enhancing tau degradation. An approach in early-stage development is proteolysis-targeting chimeras, in which small molecules bind tau and target it to achieve proteasomal degradation.[66,67] Overall proteasomal activation by

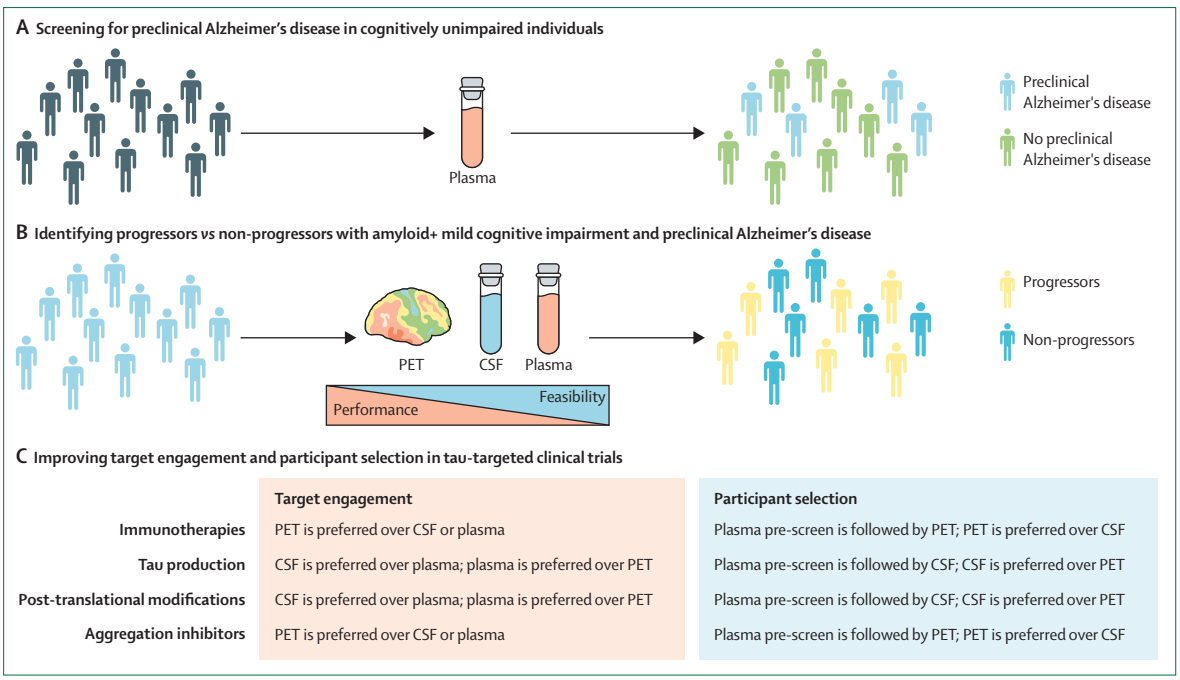

Figure 3: **The potential role of tau biomarkers in tau-targeting clinical trials**
The potential role of tau biomarkers in tau-targeted clinical trials regarding screening (A), identifying fast progressors (B), and improving target engagement and participant selection (C). Progressors=individuals who will show clinical progression of the disease in the coming years. Non-progressors=those whose disease will not progress. Note that the people coloured in light blue in (B) represent the people with preclinical Alzheimer's disease from (A). The balance between performance and feasibility indicates that tau PET is expected to provide the best performance for identifying progressors, whereas plasma biomarkers are expected to provide the highest faesibility. CSF biomarkers are an intermediary between PET and plasma biomarkers.

small molecules, for example using PDE4 inhibition,[68] has also been shown to reduce intracellular tau levels in preclinical models. Novel PDE4 inhibitors are being tested in phase 1 trials (NCT02840279).

Although the biological processes that drive tau accumulation in Alzheimer's disease remain largely unknown, genetic risk factors for Alzheimer's disease, and associated biological changes in cholesterol metabolism, immune function, and endocytosis, can directly contribute to tau accumulation.[69] Inhibiting these aberrant upstream processes might halt, or revert, intracellular tau accumulation. A phase 2 clinical study (INVOKE-2; NCT04592874) is ongoing to target one of these upstream processes, TREM2-dependent microglial activation, with the aim to evaluate the efficacy of the TREM2-activating antibody AL002 in early Alzheimer's disease. In human-induced pluripotent stem cell models of Alzheimer's disease, reducing brain cholesterol through the repurposed HIV drug efavirenz was shown to reduce intracellular p-tau accumulation[70] and improve cognitive function in tau-transgenic mice.[71] On the basis of these findings, a phase 1b trial with mid-to-high doses of efavirenz is currently ongoing for early Alzheimer's disease.[72]

These direct and indirect tau-targeting therapies illustrate the diverse portfolio of tau-targeting approaches. Moreover, they demonstrate that tau biomarkers are increasingly being incorporated into clinical trials of tau-targeting interventions.

Tau biomarkers to improve clinical trials

Tau biomarkers have the potential to optimise clinical trials of tau-targeting therapeutics by assessing target engagement. Additionally, tau biomarkers could help to augment participant selection, identify progressors versus non-progressors, and monitor treatment efficacy. Several points are important to consider with respect to use of tau biomarkers in clinical trials.

First, plasma p-tau biomarkers are cost-effective and scalable tools that might serve as a screening method to identify preclinical Alzheimer's disease among cognitively unimpaired individuals (figure 3). However, depending on the class of anti-tau treatment under study (due to different mechanisms of action), a positive blood-based biomarker result should be confirmed using tau-PET or CSF p-tau. Simulations of clinical trials have shown that this screening approach is likely to be cost-effective, as the required sample size for showing clinical benefit[73] or reductions in tau-PET accumulation[74,75] could be decreased by 60–70%. Another approach to participant selection might be to use the capability of tau-PET to reveal the distribution of tau pathology across the entire brain and only select those individuals with early-stage tau pathology. For example, in a 2021 phase 2 clinical trial of a monoclonal antibody against amyloid β (donanemab), individuals with high tau load were excluded, and findings showed that efficacy was highest in the tertile of participants with the lowest tau-PET retention.[76]

Second, given the relatively slow evolution of Alzheimer's disease from preclinical and amyloid+ mild cognitive impairment stages, it will be important to identify individuals whose disease will progress in the coming years (progressors) versus those who will remain stable (non-progressors). This process will ensure clinical trials are enriched with progressors, not only to shorten their duration but also to reduce the required sample size to detect effects of a drug on clinical outcomes. Both increased tau-PET signal and plasma or CSF p-tau concentrations have been associated with faster cognitive decline over time.[18,29,33,38,52,53] A key aspect in selecting the optimal tau biomarker for this approach is the balance between biomarker performance and feasibility. In terms of performance, such as the ability to accurately predict short-term cognitive decline, current published work suggests a slight advantage of tau-PET over the biofluid tau biomarkers, whereas blood-based biomarkers and CSF markers are more cost-effective and time-effective compared with tau-PET (figure 3).[2]

Third, tau biomarkers can be used to show target engagement and monitor the effects of anti-tau treatments during a clinical trial. Drugs altering the production or post-translational modification of tau target the very early stages of tau pathophysiology. Since tau-PET is established for measuring the forms of tau in later stages of development, insoluble tau aggregates,[44] biofluid markers would be preferred for early-stage research of tau. CSF p-tau is probably superior to the more peripheral plasma p-tau markers because it more closely reflects brain processes. By contrast, tau-PET is possibly the optimal marker in trials of aggregation inhibitors and most types of immunotherapies. For example, some immunotherapies can clear tau from both CSF and the parenchyma. Thus, reduced tau-PET signal, measuring pathological changes in the brain directly, will probably show stronger correspondence with treatment efficacy than will reduced amounts in CSF of p-tau, which are a more distant measure of brain pathology.[8] Another important feature of tau-PET is that it shows a gradual increase in tau levels from the early stages of Alzheimer's disease until the advanced stages,[77] by contrast with biofluid (particularly CSF) N-terminal and p-tau markers that tend to plateau relatively early in the disease course.[9,39,78–80] This gradual increase observed on PET yields an advantage when monitoring treatment effects.

Search strategy and selection criteria

We searched PubMed and Embase from June 1, 2019, to April 1, 2022, for publications on tau biomarkers in Alzheimer's disease and anti-tau clinical trials, using the terms "Tau-PET", "p-tau", "CSF", "plasma", "Alzheimer", "dementia", "mild cognitive impairment", "controls", "cognitively normal", and "clinical trial". Only articles in English were reviewed. The final reference list was generated on the basis of originality and relevance to the scope of this Rapid Review.

Conclusions and future directions

The advent of cost-effective and accessible blood-based biomarkers for tau pathology represents a substantial transformation in the field of Alzheimer's disease research. These markers have been shown to correlate with post-mortem tau pathology, differentiate Alzheimer's disease from other types of dementia, and track disease progression over time. Relevant developments in the tau-PET field since 2020 include detection of tau pathology in medial temporal lobe subregions that are affected in early Alzheimer's disease, and the discovery of novel but common PET-based tau spreading subtypes. There are several challenges for moving towards implementation of these biomarkers in clinical practice and trials. These include high costs, limited accessibility, restricted sen-Ωsitivity to detect early-stage Alzheimer's disease pathology, and off-target binding (for tau-PET biomarkers), and stability, reliability, and prospective validation (for biofluid tau biomarkers). Nevertheless, these biofluid and neuro-imaging tau markers hold great potential for improving diagnosis and prognostication in Alzheimer's disease, and for optimising clinical trials by providing evidence of target engagement, augmenting trial participant selection, and accurately tracking treatment effects over time.

Future studies must address current knowledge gaps. For blood-based biomarkers, diagnostic and prognostic performance should be assessed in less well controlled settings, such as non-tertiary hospitals and primary care, in which access to additional diagnostic testing (eg, extensive cognitive assessment or biomarkers) is scant. The patient population seeking medical attention at local primary care units differs greatly from people treated at specialised memory clinics, in terms of diversity (ie, ethnicity, socioeconomic status, and age), medical comorbidities (ie, vascular pathology, coronary heart disease, and other proteinopathies), and a lower prevalence of neurodegenerative conditions. All these factors affect the accuracy of prediction models. It will also be important for future prospective studies to be undertaken utilising consecutive measurements, reflecting real-world clinical practice, rather than following the approach of academic studies, in which samples are analysed in a single batch with only minor variations in study protocols, storage, and transfer of samples. Furthermore, future head-to-head studies are crucial to determine which tau biomarker is most appropriate in each of the clinical scenarios, such as early diagnosis, differential diagnosis, and prognosis, and across different stages of Alzheimer's disease. Tau biomarkers should also be compared against biomarkers of amyloid β and neurodegeneration, such as structural MRI or neurofilament light chain in CSF or plasma. Multiple aspects of Alzheimer's disease pathophysiology can be measured from a single sample of CSF or plasma, and the most parsimonious combination of biomarkers

needs to be established to generate the optimal diagnostic or prognostic algorithm, with a focus on individualised diagnostics and prognostics. This future step would improve personalised medicine for individuals with Alzheimer's disease. Finally, although substantial progress has been made, more research is needed to inform tau-targeted clinical trial design.

Contributors

All authors contributed to literature review, interpretation of the literature, and writing of the report.

Declaration of interests

OH has acquired research support for Lund University from Avid Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy and speaker fees from Roche, Genentech, Siemens, Biogen, Alzpath, and Cerveau. RO and RVDK declare no competing interests.

Acknowledgments

We thank Olof Strandberg (Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden) and David Berron (German Center for Neurodegenerative Diseases, Magdeburg, Germany) for their contributions to figure 1, and Randall Bateman (Department of Neurology, Washington University, St. Louis, MO, USA) for intellectual input on the manuscript.

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