A New Perspective on Tau Pathology in Alzheimer's Disease: From Biomarkers to Therapeutic Targets - A Narrative Review

Norbert Jamrozik1# ORCID: 0009-0008-8118-2622, **Jakub Sokołowski1** ORCID: 0009-0000-6305-0601**, Michał Godek1** ORCID: 0009-0008-3694-0113, **Jan Polaczek-Kornecki1** ORCID: 0009-0001-8520-8163, **Kinga Cogiel2** ORCID: 0009-0000-6456-2887, **Robert Gdula3** ORCID: 0009-0004-3738-2388, **Karol Płaszewski4** ORCID: 0009-0004-3432-9792, **Julia Sokal5** ORCID: 0009-0002-5343-987X, **Szymon Szostek6** ORCID: 0009-0005-6013-0979,

1Independent Public Health Care Center in Myślenice, Szpitalna 2, 32-400 Myślenice, Poland

2Dr. B. Hager Multi-Specialist District Hospital in Tarnowskie Góry, Pyskowicka 47-51, 42-612 Tarnowskie Góry, Poland

3Integrated Public Voivodeship Hospital in Elbląg, ul. Królewiecka 146, 82 - 300 Elbląg, Poland

4Zagłębiów Clinical Hospital, Czeladź, Szpitalna 40, 41-250 Czeladź, Poland

5Dr. Jan Biziel University Hospital No. 2 in Bydgoszcz, Kornela Ujejskiego 75, 85-168 Bydgoszcz, Poland

6Szpital Murcki Sp. z o.o. Katowice, Silesian Voivodeship, Sokołowskiego 2, 40-749 Katowice, Poland

***Abstract*:** Alzheimer's disease (AD) is driven by the pathological accumulation of hyperphosphorylated tau and β-amyloid, with tau playing a central role in neuronal toxicity and cognitive decline. This review synthesizes recent advances in tau biology, its role as a biomarker, and emerging therapeutic strategies, drawing on literature published between 2015 and 2025. Plasma phosphorylated tau isoforms, particularly p-tau217 and p-tau231, demonstrate high diagnostic accuracy, predict disease progression, and correlate with early amyloidosis, while tau-PET tracers such as [^{18}F]flortaucipir, RO948, and [^{18}F]MK-6240 offer sensitive, stage-specific detection strongly linked to cognitive decline. Anti-amyloid antibodies like lecanemab and donanemab indirectly reduce tau pathology and slow disease progression, but direct tau-targeted therapies remain in early clinical trials, with some promising phase 2 results yet to gain approval. Together, advances in tau biomarkers and therapeutics highlight tau's critical role in AD pathogenesis and underscore the need for harmonized platforms, diverse validation studies, and combination strategies integrating amyloid- and tau-directed approaches to improve diagnosis, monitoring, and treatment.

***Keywords*:** Alzheimer's disease, tau protein, phosphorylated tau, p-tau217, p-tau231, tau PET, tau ASO, RNAi tau, anti-tau antibody, lecanemab, donanemab, AT(N) model

MATERIALS AND METHODS

A comprehensive literature search was conducted in PubMed covering the period from January 2015 to March 2025 using combinations of the following keywords: Alzheimer's disease, tau protein, phosphorylated tau, p-tau181, p-tau217, p-tau231, tau-PET, AT(N) framework, tau antisense oligonucleotides, RNAi tau, anti-tau antibody, disease-modifying therapy. Additional relevant publications were identified through cross-referencing bibliographies of retrieved articles and consulting major conference proceedings (AAIC, CTAD, AD/PD). Eligible sources included primary research papers, preclinical studies, randomized controlled trials (phases I–III), meta-analyses, systematic and narrative reviews, and regulatory approval documents issued by the FDA and EMA. No language restrictions were applied. Studies were

included if they reported on tau structure, post-translational modifications, aggregation mechanisms, biomarker performance in cerebrospinal fluid, plasma, or neuroimaging, or therapeutic outcomes of tau- or amyloid-modifying interventions. Data extraction focused on study design, cohort characteristics, biomarker assay platforms, imaging modalities, diagnostic accuracy metrics (sensitivity, specificity, AUC), longitudinal predictive validity, therapeutic efficacy endpoints (cognitive scales, biomarker modulation), and safety outcomes. Findings partially were qualitatively synthesized and mapped onto the AT(N) biomarker framework to facilitate comparison across modalities and therapeutic strategies

INTRODUCTION

Tau protein is a low molecular weight (~55–62 kDa) structural protein that belongs to the family of microtubule-associated proteins (MAPs). It is characterized by a highly flexible and partially disordered structure (*IDP - intrinsically disordered protein*), which enables dynamic interactions with microtubules and other cytoskeletal components [1]. Tau is encoded by the *MAPT* (*microtubule-associated protein tau*) gene, located on chromosome 17q21.31. This gene comprises 16 exons, with alternative splicing giving rise to multiple tau isoforms [2]. The protein exhibits an elongated conformation and contains domains enriched in serine/threonine motifs that are subject to extensive phosphorylation. Alternative splicing of *MAPT* mRNA results in six major tau isoforms expressed in the adult human brain, which differ in the number of microtubule-binding repeats (3R or 4R tau) and in the presence of N-terminal inserts [3].

Tau protein consists of several key structural segments:

N-terminal domain (NTD) – This region of the protein does not directly bind microtubules but serves modulatory and interactive functions, engaging with organelles (e.g., mitochondria) and membrane-associated proteins. The NTD is enriched in negatively charged residues, allowing it to participate in the allosteric regulation of microtubule binding. It also contains motifs responsible for interactions with SH3 domain-containing proteins (e.g., the Fyn kinase),

suggesting a role in neuronal signal transduction [1].

Proline-rich region (PRR) – Located between the N-terminal domain and the microtubule-binding domain, the PRR is abundant in serine and threonine residues, making it a primary site of phosphorylation by kinases such as GSK3β and CDK5. The PRR also mediates tau's interactions with actin filaments and influences cytoskeletal stability in neurons [4,5].

Microtubule-binding domain (MTBD) – Comprising three (3R) or four (4R) repeat motifs (R1–R4), this domain is directly responsible for binding to and stabilizing microtubules. Mutations and phosphorylation within the MTBD are associated with cytoskeletal dysfunction and the aggregation of tau into neurofibrillary tangles (*NFTs)* [1,6].

C-terminal domain (CTD) – Although less well characterized, the CTD is believed to play a role in maintaining tau's extended conformation and mediating intramolecular interactions that influence its propensity to oligomerize. The CTD may also modulate electrostatic interactions and aggregation dynamics [1,6].

Under physiological conditions, tau protein stabilizes microtubules, which are key components of the cytoskeleton responsible for axoplasmic transport. Tau binding to microtubules enhances their stability and facilitates the proper distribution of cellular organelles, synaptic vesicles, and growth factors along axons [7]. According to recent meta-analyses and systematic reviews, tau also plays a crucial role in regulating various aspects of neuronal function, including presynaptic domain organization, synaptic plasticity, oxidative stress response, signal transduction, and DNA damage response. Studies in murine models have demonstrated that tau participates in the regulation of synaptic vesicle transport and the localization of presynaptic proteins, thereby affecting neurotransmission efficiency and the precision of neuronal signaling [8]. The absence of functional tau leads to disorganization of active zones in axon terminals, potentially disrupting synaptic homeostasis. In terms of synaptic plasticity, particularly with respect to spatial memory, tau has been shown to be essential for long-term potentiation (LTP). This is largely mediated through interactions with kinases and phosphatases, as well as its influence on the reorganization of the actin cytoskeleton. Mice with *MAPT* gene deletion (encoding tau) exhibit deficits in spatial orientation and working memory, as confirmed by behavioral tests such as the Morris Water Maze and Y-maze tasks [9]. Tau thus appears to be critical for the formation and stabilization of synaptic connections in the hippocampus, and consequently for the integration of memory traces. Additionally, tau is involved in the cellular response to oxidative stress and in DNA damage repair mechanisms. Under stress conditions, tau translocates to the nucleus, where it exhibits affinity for damaged DNA and acts as a protective factor against genomic degradation [10]. This phenomenon has also been observed in neurons exposed to H_2O_2, where tau appears to mitigate apoptosis induced by oxidative damage. Another important functional aspect of tau is its role in regulating the activity of kinases such as GSK-3β, CDK5, and Fyn, which are involved in glutamatergic receptor-mediated signal transduction (e.g., NMDA receptors). Tau facilitates the localization of Fyn kinase to the postsynaptic membrane, where it modulates phosphorylation of the NR2B subunit of the NMDA receptor, thereby influencing neuronal sensitivity to excitotoxicity [11]. The absence of tau disrupts these processes, leading to dysregulation of calcium signaling and weakened neuroprotective responses.

Phosphorylation of tau is a natural and reversible regulatory mechanism that modulates its affinity for microtubules. Under physiological conditions, tau is phosphorylated at a limited number of sites (approximately 2–3 phosphate groups per molecule), primarily by kinases such as GSK3β, CDK5, MARK, and CK1 [9,12]. This process is tightly regulated by phosphatases, most notably protein phosphatase 2A (PP2A), which accounts for more than 70% of tau dephosphorylation activity [13]. Maintaining the balance between kinase and phosphatase activity is essential for proper tau function.In Alzheimer's disease pathogenesis, this balance is disrupted due to kinase hyperactivity and phosphatase inhibition—factors often driven by

oxidative stress and mitochondrial dysfunction. As a result, tau undergoes hyperphos phorylation, leading to its detachment from microtubules, self-aggregation, and the formation of pathological structures known as neurofibrillary tangles (NFTs). These aggregates represent a key pathogenic hallmark of the disease [14,15].

Tau protein is encoded by the *MAPT* gene and undergoes alternative splicing, resulting in six isoforms that differ in the number of microtubule-binding repeat domains—either three repeats (3R) or four repeats (4R) [9]. These isoforms are critically involved in microtubule stabilization and the regulation of neuronal cytoskeletal dynamics. 3R tau isoforms contain three microtubule-binding repeats and exhibit a lower capacity to stabilize microtubules compared to the 4R isoforms, which include an additional fourth repeat. This structural difference underlies their functional specificity in neurons—4R isoforms are more efficient at stabilizing microtubules, which is essential for maintaining proper intracellular transport [16]. The balance between 3R and 4R tau isoforms is crucial for neuronal homeostasis. In the healthy adult human brain, the ratio of 3R to 4R tau isoforms is approximately 1:1, ensuring optimal tau function [17]. Disruption of this balance—such as an overrepresentation of either 3R or 4R isoforms—is associated with the pathogenesis of various tauopathies. For example, Pick's disease is characterized by a predominance of 3R isoforms, whereas tauopathies such as progressive supranuclear palsy and corticobasal degeneration are associated with an excess of 4R isoforms [9,17]. Dysregulation of tau isoform expression promotes pathological aggregation and the formation of neurofibrillary tangles, which impair cytoskeletal stability and neuronal function. Moreover, different tau isoforms display distinct affinities for kinases and phosphatases, which affects their phosphorylation status and susceptibility to pathological post-translational modifications [16].

Mechanisms of Hyperphosphorylation and Loss of Microtubule Function

Under physiological conditions, tau stabilizes neuronal microtubules by regulating their polymerization and supporting axoplasmic transport. This function is dependent on tightly controlled phosphorylation, which enables the dynamic interaction of tau with microtubules. In Alzheimer's disease (AD), however, tau undergoes hyperphosphorylation, leading to functional impairment and neuronal toxicity [9,18,19]. Tau hyperphosphorylation involves the excessive addition of phosphate groups to serine and threonine residues—over 80 potential phosphorylation sites have been identified. This process results from an imbalance between kinase and phosphatase activities. A key mechanism involves aberrant activation of several kinases, including glycogen synthase kinase 3 beta (GSK-3β), which plays a major role in phosphorylating multiple tau epitopes, particularly in the context of AD. Cyclin-dependent kinase 5 (CDK5), when aberrantly activated by the p25 cofactor instead of the physiological p35, exhibits neurotoxic activity. Other kinases such as microtubule affinity-regulating kinase (MARK) and dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) contribute to the destabilization of tau–microtubule interactions. A second contributing factor is excessive inhibition of phosphatases, especially protein phosphatase 2A (PP2A), which accounts for the majority of tau dephosphorylation under normal conditions. In AD, PP2A

activity is reduced due to oxidative stress, aberrant methylation, and other pathological changes, leading to the accumulation of phosphorylated tau. Oxidative stress and neuroinflammation further exacerbate this process [9,20,21]. As a consequence of hyperphosphorylation, tau dissociates from microtubules, resulting in microtubule destabilization. This disrupts axonal transport, impeding the delivery of mitochondria, synaptic proteins, and organelles to synapses. Ultimately, the cytoskeletal architecture of neurons becomes compromised, leading to microtubule degradation. Hyperphosphorylated tau also exhibits a strong propensity to oligomerize and form pathological aggregates known as neurofibrillary tangles (NFTs), which are characteristic of tauopathies. These aggregates impair synaptic function, promote neurodegeneration, and disrupt neuronal signaling [9,19]. Moreover, tau aggregates may act in a prion-like manner, propagating pathology from neuron to neuron [22], and can activate microglia and the immune system, further amplifying neurodegenerative processes [23].

Formation and Role of Neurofibrillary Tangles (NFTs)

Neurofibrillary tangles (NFTs) are one of the two major pathological hallmarks of Alzheimer's disease and other tauopathies. They consist of intracellular deposits of abnormally modified tau protein, primarily accumulating in neurons of the hippocampus and cerebral cortex. Neuropathological and neuroimaging studies have clearly demonstrated that the extent of tau aggregation and its spread—both in oligomeric form and as NFTs—correlates more strongly with the progression of neurodegeneration, synapse loss, and cognitive deficits than the presence of β-amyloid plaques. This makes tau a key target for both diagnostic efforts and the development of therapeutic strategies [24]. The formation of NFTs begins with disturbances in the post-translational regulation of tau. Hyperphosphorylated tau loses its affinity for microtubules, detaching and accumulating in the cytoplasm of neurons. Additional modifications—including acetylation, glycosylation, ubiquitination, and proteolysis (e.g., by caspases)—further destabilize tau's conformation, promoting the formation of aggregation-prone species. These aberrant tau molecules assemble into oligomers, which are considered highly neurotoxic. Their presence disrupts calcium homeostasis, mitochondrial function, and membrane integrity. Eventually, tau oligomers further aggregate into fibrous structures—straight filaments and paired helical filaments (PHFs)—which form the core of NFTs [9,25,26,27]. Immunohistochemical and electron microscopy studies reveal that NFTs are composed of twisted filaments accumulating in neuronal cell bodies and dendrites. These structures display strong autofluorescence and are identifiable using histopathological stains such as Bielschowsky silver or AT8 immunolabeling [28]. Progressive NFT formation leads to cytoskeletal disruption, microtubule loss, and impairment of axonal transport. Neurons burdened by toxic tau aggregates enter a dystrophic state and ultimately undergo apoptosis [9,29]. Moreover, pathological tau possesses the ability to spread between cells in a prion-like manner, contributing to the anatomically ordered progression of neurodegeneration, as described by Braak staging. Initially, pathological changes occur in the medial temporal lobe and then spread to other cortical areas as the disease advances. This cell-to-cell transmission mimics the propagation seen in classical prion diseases, such as the spread of PrP^Sc in

Creutzfeldt–Jakob disease. Pathological tau species can be released into the extracellular space through active mechanisms (e.g., exosomes) or passively, as a result of cell lysis. These aggregates can then be taken up by healthy neurons through endocytosis, phagocytosis, or receptor-mediated processes. Once inside the cytoplasm, pathological tau acts as a "seed," inducing conformational changes in endogenous, physiological tau to convert it into additional pathological forms—a mechanism known as "templated misfolding." This process contributes to the gradual and topographically organized spread of tau pathology, consistent with the classical Braak staging observed in Alzheimer's disease. This phenomenon supports the prion-like model of pathology propagation and helps explain the clinical progression of tau-related neurodegenerative diseases, even when they originate from initially localized foci of degeneration [22,30,31].

Correlation Between Tau Deposits and Clinical Symptoms in Alzheimer's Disease

The progressive accumulation of pathological tau follows the Braak staging system, which describes the anatomical progression of tauopathy. Initially, tau deposits are confined to the medial temporal lobe—particularly the hippocampus, parahippocampal gyrus, and entorhinal cortex—which clinically manifests as episodic memory impairment. As the tau pathology spreads to limbic and association cortices, patients begin to experience disorientation, language deficits, apraxia, and impaired executive functioning [32]. The clinical presentation closely reflects the topographical distribution of tau deposits, as demonstrated by positron emission tomography (PET) using tau-binding ligands (e.g., flortaucipir). In patients clinically diagnosed with Alzheimer's-type dementia, extensive tau deposition is observed in the temporal, parietal, and frontal cortices. In contrast to β-amyloid plaques—which can also be present in cognitively unimpaired individuals—tau deposits exhibit a strong quantitative and qualitative correlation with cognitive decline. Studies have shown that higher flortaucipir uptake in cortical regions is strongly associated with lower cognitive test scores, such as the Mini-Mental State Examination (MMSE), and with more extensive gray matter atrophy, suggesting that tau PET more accurately reflects disease severity than fluid biomarkers such as cerebrospinal phosphorylated tau (p-tau) [33]. Moreover, meta-analyses of fluid biomarkers indicate that concentrations of phosphorylated tau isoforms (p-tau181, p-tau217, p-tau231) in cerebrospinal fluid and plasma correlate with disease stage and can predict the conversion from mild cognitive impairment (MCI) to overt dementia [34]. Tau, rather than β-amyloid, is believed to be directly responsible for neuronal damage, primarily through disruption of axonal transport, loss of cytoskeletal integrity, and induction of neuroinflammatory responses. Additionally, the anatomically gradient-like progression of tauopathy is associated with distinct clinical phenotypes. For instance, in the logopenic variant of primary progressive aphasia (PPA) associated with Alzheimer's disease, tau accumulation predominates in the left temporal lobe. In contrast, in tau-related frontotemporal dementia (FTD-tau), deposits are predominantly found in the frontal lobes and anterior temporal regions [9,35]. According to current knowledge, tau aggregation represents not only a biomarker of disease progression but also a direct mediator of neurotoxicity. The presence of tau pathology, as evidenced by tau PET imaging and elevated p-tau concentrations in cerebrospinal fluid, now forms one of the diagnostic criteria for the so-called biological diagnosis of Alzheimer's disease, according to

the AT(N) classification proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA) [34].

Tau Pathology in Related Disorders (PSP, CBD, CTE)

Tau protein, a key structural component of the neuronal cytoskeleton, undergoes pathological modifications not only in Alzheimer's disease (AD) but also in other primary tauopathies, including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and chronic traumatic encephalopathy (CTE). Each of these disease entities is characterized by a specific clinical phenotype and a unique histopathological profile of tau deposits [9,36]. In Alzheimer's disease, tau pathology consists of a mixture of isoforms containing three and four microtubule-binding repeats (3R/4R tau) [37]. Deposits predominantly form paired helical filaments (PHFs), which accumulate intracellularly in the form of neurofibrillary tangles (NFTs), primarily in the temporal cortex and hippocampus [9]. In progressive supranuclear palsy (PSP), tau pathology is dominated by 4R-tau. Aggregates of tau protein accumulate in neurons, astrocytes, and oligodendrocytes, with characteristic tufted astrocytes and granular oligodendroglial inclusions. These deposits are particularly abundant in brainstem structures (basal ganglia, substantia nigra, vestibular nuclei), thalamus, and prefrontal cortex, accounting for clinical features such as vertical gaze palsy, axial rigidity, and postural instability [38]. Corticobasal degeneration (CBD) is also a 4R tauopathy, but differs from PSP in terms of the morphology and distribution of tau aggregates. Astrocytic plaques and neuronal cytoplasmic inclusions are typical of CBD. The pathology primarily affects the frontoparietal cortex and basal ganglia, leading to clinical symptoms such as apraxia, dystonia, asymmetric parkinsonism, and cognitive impairment. Unlike PSP, CBD shows greater involvement of cortical neurons and motor pathways [39]. Chronic traumatic encephalopathy (CTE), in contrast, is an acquired tauopathy associated with repetitive head trauma, often seen in contact sport athletes. CTE features a mixture of 3R and 4R tau isoforms, but the deposits are perivascular and concentrated in the depths of cortical sulci. A pathognomonic hallmark is the irregular, focal deposition of tau in neurons and astrocytes, particularly in cortical layers II and III. Clinically, CTE is characterized by behavioral disturbances, impulsivity, depression, and progressive cognitive decline [40,41]. Although all these tauopathies share the presence of pathologically modified tau, they differ significantly in the dominant isoforms, the types of affected cells, the morphology of aggregates, and their anatomical distribution. These distinctions are essential for neuropathological differentiation and also inform the development of molecular biomarkers and targeted therapeutic strategies.

TAU PROTEIN AS A BIOMARKER IN ALZHEIMER'S DISEASE

Tau in Cerebrospinal Fluid: t-tau and p-tau

Tau protein in cerebrospinal fluid (CSF) serves as a key biomarker for the diagnosis and monitoring of Alzheimer's disease (AD) and other neurodegenerative conditions. Two main variants are distinguished: total tau (t-tau), which reflects nonspecific neuronal degeneration,

and phosphorylated tau (p-tau), which is a more specific indicator of AD-related tau pathology. The measurement of t-tau and p-tau in CSF is performed using immunoenzymatic assays such as ELISA on samples obtained through lumbar puncture. This procedure is a standard part of neurodegenerative diagnostics and allows for precise quantification of biomarker concentrations. T-tau is not exclusive to AD—elevated levels are also observed in other neurodegenerative states as well as in acute brain injuries. In the AT(N) classification system, t-tau is categorized as a marker of neurodegeneration ("N") [42]. For p-tau, certain phosphorylation epitopes are of key significance: p-tau181, p-tau217, and p-tau231. Among these, p-tau181 is one of the most extensively studied. Its levels in CSF are significantly elevated in AD patients compared to cognitively normal individuals, confirming its diagnostic value. A meta-analysis showed that p-tau181 levels in CSF are on average 1.88 times higher in AD patients than in healthy individuals (95% CI: 1.79–1.97) [43]. More recent studies suggest that p-tau217 shows better specificity and stronger correlation with both amyloid and tau deposition as well as with clinical symptoms. Research has shown that CSF p-tau217 levels are on average 3.49 times higher in AD patients than in healthy controls (95% CI: 2.02–6.03) [44]. P-tau231, in turn, appears earlier than other isoforms and may be useful in identifying the very early stages of the disease [45,46]. Increasing attention is also being paid to less common variants such as p-tau205, which shows a strong correlation with tau-PET imaging findings and with the extent of pathology according to Braak staging [47]. All of these biomarkers constitute a crucial component of modern AD diagnostics, supporting both disease differentiation and assessment of disease progression.

Tau Biomarkers in Serum and Plasma (p-tau181, p-tau217, p-tau231)

Phosphorylated tau isoforms can also be detected in plasma and serum. These allow for the non-invasive identification of neurodegenerative changes characteristic of Alzheimer's disease (AD), and their concentrations correlate with the presence of amyloid β (Aβ) plaques and pathologically modified tau in the brain, as confirmed by PET imaging and neuropathological correlation. Among the biomarkers mentioned, p-tau217 demonstrates the highest diagnostic value—both in identifying prodromal stages of AD and in distinguishing AD from other dementias. Studies have shown that plasma p-tau217 levels strongly correlate with the presence of both Aβ plaques and neurofibrillary tangles (NFTs), achieving an area under the curve (AUC) of up to 0.96 in distinguishing AD patients from healthy controls, surpassing the diagnostic accuracy of p-tau181 and p-tau231. Furthermore, p-tau217 increases earlier in the disease course than other forms, making it a useful indicator of very early pathological changes [34]. P-tau181 also remains an important diagnostic and prognostic marker. Its rise in plasma is specific to Alzheimer's disease and is observed even before full-blown dementia symptoms appear. Although its specificity and sensitivity are lower than those of p-tau217, it is still valuable when combined with other biomarkers, such as the plasma Aβ42/40 ratio, especially in high-risk populations [48]. P-tau231, on the other hand, may serve as a very early marker of tauopathy associated with AD, showing elevated levels before significant clinical and structural changes occur. It is believed that p-tau231 reflects early tau phosphorylation induced by

amyloid deposition in the cortex, potentially marking the transition from the preclinical to the prodromal stage of the disease [49].

On May 16, 2025, the U.S. Food and Drug Administration (FDA) approved the first blood test to aid in the diagnosis of Alzheimer's disease. Developed by Fujirebio Diagnostics, the test—called Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio—measures the levels of two proteins in blood plasma: phosphorylated tau at position 217 (pTau217) and β-amyloid 1-42. The calculated ratio of these biomarkers correlates with the presence of amyloid plaques in the brain, a hallmark of AD pathology. The test was approved for use in adults aged 55 and older who show cognitive symptoms suggestive of Alzheimer's disease. In a clinical study involving 499 patients with cognitive impairment, the test demonstrated 91.7% positive agreement and 97.3% negative agreement compared with PET scans or cerebrospinal fluid testing. This approval marks a major step toward more accessible and less invasive diagnostics for Alzheimer's disease.

Tau PET – Imaging Tau Pathology in the Living Brain

Tau PET imaging, which uses radiolabeled ligands that selectively bind to pathological forms of the tau protein, represents one of the most significant advancements in Alzheimer's disease (AD) diagnostics in recent years. This technique enables in vivo visualization of hyperphosphorylated tau aggregates, particularly in the form of neurofibrillary tangles (NFTs). In contrast to amyloid PET, tau PET provides not only the presence of pathology but also its topography and intensity, which correlates more closely with a patient's clinical condition and the progression of neurodegeneration. Studies using tracers such as [18F]flortaucipir, [18F]MK-6240, and [18F]RO-948 have shown that tau accumulation follows the Braak staging scheme—beginning in the medial temporal lobe structures like the hippocampus and entorhinal cortex, then spreading to the temporal, parietal, and frontal cortices. The presence of tau deposits in specific brain regions correlates with the type and severity of clinical symptoms, and their extent can serve as a predictor of progression from mild cognitive impairment (MCI) to full-blown dementia. A meta-analysis by Ossenkoppele et al. (2021) demonstrated that tau PET has a high specificity (>90%) for AD, effectively distinguishing it from other dementias such as dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD), making it a valuable differential diagnostic tool [50]. Tau PET plays a crucial role not only in diagnosis but also in research on disease mechanisms and monitoring treatment efficacy. Tau PET results correlate well with p-tau181 and p-tau217 levels in cerebrospinal fluid and plasma, confirming the consistency between imaging and fluid biomarkers [51]. In clinical trials, tau PET is used to identify individuals in preclinical or prodromal stages of AD who exhibit both amyloid positivity (confirmed via PET or CSF) and region-specific tau deposition. The combination of these biomarkers significantly improves the predictive accuracy for progression to dementia [52]. Despite its high diagnostic value, tau PET has limitations. These include variability in ligand affinity and off-target binding in certain brain regions, as well as reduced efficacy in detecting 4R tauopathies like progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), where tau aggregate structures differ from those in AD. Additionally, the

limited availability of this technology and its high cost currently restrict its use primarily to academic centers and clinical research settings.

POTENTIAL THERAPEUTIC TARGETS RELATED TO TAU PROTEIN

Tau protein, a key player in the pathogenesis of Alzheimer's disease (AD), represents a promising therapeutic target. In the context of disease-modifying treatments, a variety of strategies have been developed in recent years aiming to limit tau hyperphosphorylation, aggregation, and neurotoxicity, as well as to promote its clearance from the central nervous system.

Anti-Tau Immunotherapy: Monoclonal Antibodies

Immunotherapy based on monoclonal antibodies targeting tau protein represents one of the most extensively studied therapeutic approaches in the treatment of Alzheimer's disease (AD), although its clinical efficacy remains limited so far. Antibodies such as gosuranemab, semorinemab, tilavonemab, and zagotenemab have been investigated in numerous randomized phase II and III clinical trials, with results reviewed in systematic reviews and meta-analyses. In a meta-analysis involving 2,193 patients with AD, semorinemab showed a statistically significant, though clinically modest, improvement in cognitive function as measured by the MMSE and ADAS-Cog scales (mean difference of 0.52–3.30 points). Tilavonemab, on the other hand, had the most favorable safety profile, with the lowest incidence of vascular complications such as ARIA-E and ARIA-H [53]. These findings are consistent with an earlier 2022 meta-analysis of 34 trials involving 5,549 patients, which showed no significant overall impact of anti-tau therapies on ADAS-Cog scores, apart from a minor improvement in the subgroup of agents targeting post-translational tau modifications [54]. A systematic review including both published and unpublished data from trials using anti-tau and anti-amyloid antibodies also reported limited efficacy of anti-tau interventions, highlighting the need for further research on mechanisms of action and optimal timing of intervention. The analysis also indicated that monoclonal antibodies may increase the risk of adverse events, such as amyloid-related imaging abnormalities (ARIA), underlining the importance of close patient monitoring during therapy [55]. Finally, 2025 data—although primarily focused on anti-amyloid antibodies (aducanumab, lecanemab, donanemab)—also confirmed that these treatments affect tau biomarkers in cerebrospinal fluid and plasma. This suggests that future therapeutic strategies may need to target both pathogenic pathways simultaneously [56].

Inhibitors of Tau-Phosphorylating Kinases

Immunotherapy based on inhibitors of kinases responsible for tau hyperphosphorylation—such as GSK-3β, CDK5, or Fyn—has been intensively studied in recent years, but results so far have

been disappointing. A 2022 meta-analysis of 34 randomized clinical trials (n = 5,549) evaluating various classes of anti-tau drugs, including kinase inhibitors (saracatinib, nilotinib, tideglusib), found no significant improvement in cognitive function as measured by the ADAS-Cog scale (mean difference MD = –0.77; 95% CI: –1.64 to 0.10). Only the subgroup of drugs targeting post-translational tau modifications showed a modest effect (MD = –0.80; 95% CI: –1.43 to –0.17) [54]. In a phase I/II trial of nilotinib, an Abl kinase inhibitor, conducted in AD patients, a reduction in tau levels in cerebrospinal fluid was observed; however, this did not translate into clinical improvements or changes in neurodegeneration biomarkers [57]. Saracatinib, a Fyn kinase inhibitor, showed promising preclinical data but failed to yield significant benefits in cognitive performance or tau-PET imaging in a phase II trial [58]. Despite encouraging biological rationale, the efficacy of tau-phosphorylating kinase inhibitors remains inconclusive and requires further, more targeted clinical investigations.

Modulators of Tau Aggregation and Clearance

Clinical trials investigating drugs that modulate tau aggregation and clearance represent a key area in the search for effective disease-modifying therapies for Alzheimer's disease (AD). Data from a systematic review and meta-analysis of 34 randomized controlled trials (RCTs) involving over 5,500 AD patients indicate that drugs directly targeting tau aggregation—particularly aggregation inhibitors such as hydromethylthionine mesylate (HMTM)—did not demonstrate statistically significant improvement in cognitive function in the general study population (mean difference in ADAS-Cog: –0.77; 95% CI: –1.64 to 0.10) [54]. Importantly, a subgroup of drugs acting on post-translational modifications of tau, such as phosphorylation and acetylation, showed a modest but statistically significant therapeutic effect (MD = –0.80; 95% CI: –1.43 to –0.17), suggesting a greater therapeutic potential of this class of compounds [54]. Further evidence supporting the clinical relevance of HMTM comes from the LUCIDITY phase III trial program, which demonstrated safety and stabilization of neurodegeneration biomarkers at a dosage of 16 mg/day [59]. According to available data and TauRx's 2023 press releases, prespecified analyses from the LUCIDITY trial revealed that 12 months of HMTM treatment at this dose led to a 93% reduction in serum neurofilament light chain (NfL) compared to baseline. Since NfL is considered a biomarker of axonal damage rate, this reduction may reflect a slowing of neurodegeneration in early-stage patients. This observation could have prognostic significance, particularly in the context of early therapeutic intervention. A parallel line of research focuses on multifunctional inhibitors designed to target both amyloid-β (Aβ) and tau aggregation. A 2021 structure–activity review presented several chemical compounds capable of interacting with β-sheet-rich regions, thereby modulating both key pathogenic pathways of AD. The authors emphasized that such dual-target approaches may help disrupt the pathological cascade earlier, potentially offering greater neuroprotection [60]. Overall, current analyses suggest that tau aggregation inhibitors do not produce a significant clinical effect in unselected AD populations. However, in specific subgroups—particularly those in early disease stages and with simultaneous effects on post-translational tau modifications—efficacy may be higher. Ongoing and upcoming trials are critical to identifying patients who may truly benefit from therapies targeting tau pathology.

Gene Therapies and RNA Interference Targeting MAPT

Advances in molecular biology and targeted therapeutics have enabled the development of strategies aimed directly at suppressing the expression of the *MAPT* gene, which encodes the tau protein. In the context of Alzheimer's disease (AD)—a neurodegenerative disorder characterized by hyperphosphorylation, aggregation, and trans-synaptic spreading of tau—gene therapy and RNA interference (RNAi) represent innovative approaches to modulate pathogenic protein expression at the post-transcriptional level. The most advanced therapeutic strategies focus on the use of small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs), which bind to *MAPT* mRNA, leading to its degradation or translational repression. Preclinical studies using synthetic siRNAs conjugated with lipophilic C16 chains demonstrated effective reduction of *MAPT* mRNA and tau protein levels in the brains of non-human primates, with a sustained therapeutic effect lasting at least 16 weeks following a single intracerebral administration [61]. In another study conducted in P301S transgenic mice—a tauopathy model—a single siRNA administration resulted in over 80% reduction of *MAPT* mRNA and nearly 60% reduction in soluble tau, accompanied by approximately 97% decrease in tau aggregates and lowered serum levels of neurofilament light chain (NfL), suggesting attenuation of axonal degeneration [62]. Early clinical trials utilizing ASO-based therapies have also yielded promising results. In a randomized, placebo-controlled phase 1b trial involving BIIB080 (MAPTRx)—administered via intrathecal injection in patients with mild AD—dose-dependent reductions in CSF levels of phosphorylated tau (p-tau) and total tau (t-tau) were observed, without significant adverse events [63]. Additionally, ongoing research focuses on optimizing delivery systems and refining target site selection within the *MAPT* mRNA. A 2024 review in *Translational Neurodegeneration* emphasized the need for improved specificity and enhanced central nervous system (CNS) distribution of siRNA and ASO therapeutics [64].

Current Therapeutic Options in Alzheimer's Disease Treatment

In recent years, only two anti-Aβ monoclonal antibodies—lecanemab and donanemab—have demonstrated clinically meaningful slowing of Alzheimer's disease (AD) progression in phase III clinical trials. These antibodies target β-amyloid and are classified as disease-modifying therapies (DMTs), although they differ in epitope specificity and the pathological stage of amyloid they engage. Lecanemab (BAN2401) is an IgG1 monoclonal antibody that selectively binds to soluble Aβ protofibrils—intermediate aggregates between monomers and insoluble amyloid plaques. Its mechanism of action involves facilitating clearance of neurotoxic Aβ protofibrils via microglial phagocytosis, while also inhibiting further aggregation of Aβ and reducing its overall burden in the brain, as confirmed by decreased PET SUVr values within 6–12 months of treatment [65]. Donanemab (LY3002813) is an IgG1 monoclonal antibody that targets pyroglutamylated Aβ (Aβ pE3), a major component of mature amyloid plaques. It exhibits high affinity for fibrillar Aβ deposits while sparing soluble forms. Donanemab induces rapid plaque clearance through microglia-mediated immune mechanisms, including Fcγ receptor-dependent pathways. Efficacy in reducing amyloid burden has been observed via PET

imaging within 3–6 months of treatment initiation [66]. In the multicenter, randomized, placebo-controlled Clarity AD trial (n = 1,795), lecanemab administered over 18 months reduced cognitive decline by 27% compared to placebo, as measured by the Clinical Dementia Rating – Sum of Boxes (CDR-SB). Improvements were also observed in ADAS-Cog and ADCS-ADL scores, alongside a significant reduction in brain amyloid burden [65]. Comparable outcomes were reported in the TRAILBLAZER-ALZ 2 phase III trial (n = 1,736), where donanemab slowed disease progression by approximately 35%, particularly in patients with lower baseline tau pathology on PET imaging [66]. Among anti-Aβ antibodies evaluated in phase III trials, lecanemab and donanemab were the only agents to demonstrate both statistically and clinically significant effects. However, both are associated with a notable risk of amyloid-related imaging abnormalities (ARIA), occurring in approximately one-third of treated patients, necessitating regular neuroimaging monitoring. In contrast, solanezumab failed to demonstrate cognitive benefit in a preclinical population (A4 study), with 240-week follow-up confirming the lack of efficacy despite biomarker evidence of amyloid engagement [67]. Other investigational agents, such as buntanetap, have not yet been validated in peer-reviewed randomized controlled trials, limiting their current clinical relevance.

Lecanemab, marketed as Leqembi, received accelerated FDA approval on January 6, 2023, followed by traditional approval on July 6, 2023, based on phase III CLARITY-AD data demonstrating significant clinical benefit [68]. Donanemab, commercially known as Kisunla, was approved by the FDA on July 2, 2024 for the treatment of early-stage Alzheimer's disease, marking a major advancement in the pharmacological management of AD [69]. Both drugs are now available in the United States and other countries, including Japan, the United Kingdom, and South Korea, reflecting broad regulatory endorsement and representing a significant breakthrough in AD therapy.

Integrated Approach: Tau + Amyloid + Neurodegeneration – The AT(N) Model

The AT(N) framework, developed by the National Institute on Aging–Alzheimer's Association, proposes the assessment of three core biochemical axes of Alzheimer's disease (AD) pathology: β-amyloid deposition (A), pathological tau (T), and neurodegeneration (N). This classification system allows for more accurate diagnosis and disease trajectory prediction. Recent studies involving individuals with Down syndrome utilized amyloid and tau PET imaging, in conjunction with hippocampal volume assessment via MRI, and demonstrated that tau positivity (T+) correlates more strongly with episodic memory deficits than amyloid positivity (A+) alone [70]. Furthermore, clinical validation of the AT(N) model has shown that neuroimaging modalities, particularly tau-PET and FDG-PET, offer the greatest specificity in diagnosis and prognosis. Notably, tau-PET showed a strong negative correlation with global cognitive decline, as measured by the MMSE ($r \approx -0.69$, $p = 0.014$) [71]. Expanding on this approach, fluid biomarker studies have indicated that the most diagnostically sensitive combinations include CSF A (Aβ42/40 ratio),

neuroimaging T (tau-PET), and neuroimaging N (FDG-PET–based neurodegeneration), yielding an AUC ≈ 1.00 in differentiating AD from healthy controls. For MCI, the optimal model comprised CSF A, CSF p-tau, and neuroimaging N, achieving an AUC ≈ 0.96 [72]. Plasma-based biomarkers are gaining increasing attention, particularly p-tau181, p-tau217, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP), which show good predictive accuracy for dementia conversion (AUCs ranging from 70% to 80%), although further validation is needed before clinical implementation [73]. Other analyses reveal that individuals classified as T+/N+ exhibit the fastest decline in memory and executive function, suggesting that AT(N) scenarios may serve as valuable tools for clinical monitoring and early intervention targeting [74]. Finally, the AT(N) model is evolving toward an expanded "ATN+X" framework, incorporating additional pathological domains such as inflammation (I), synaptic dysfunction (S), and vascular pathology (V). These extensions allow for increasingly precise patient stratification, which is essential for personalized treatment planning and the development of combination therapies.

Discussion

Despite significant advances in the development of tau biomarkers for the diagnosis and treatment of Alzheimer's disease (AD), their clinical implementation remains limited by several key constraints. One major issue is the high heterogeneity observed in meta-analyses, which stems from differences in study populations (e.g., MCI vs. AD), assay platforms (e.g., p-tau181, p-tau217, p-tau231), and detection technologies (e.g., Simoa, immunoassays). These discrepancies hinder interstudy comparability and compromise the definitive evaluation of diagnostic utility for individual biomarkers [75]. Additionally, many clinical studies are based on relatively small cohorts and often lack sufficient longitudinal follow-up, reducing statistical power and limiting the ability to assess the prognostic value of tau biomarkers in tracking disease progression [75]. In real-world clinical settings, the use of tau biomarkers faces multiple challenges: there is no widely accepted consensus on cut-off thresholds, testing frequency, or their impact on therapeutic decisions [76,77]. Moreover, the limited accessibility of tau-PET imaging and the moderately invasive nature of lumbar puncture restrict the application of tau-based biomarkers primarily to specialized academic centers [77]. In response to these limitations, substantial efforts are underway to develop less invasive approaches, such as plasma p-tau assays—especially p-tau217 and p-tau231—alongside complementary markers such as neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP). However, the specificity and robustness of these plasma biomarkers across ethnically and clinically diverse populations still require thorough validation [75,77]. Looking ahead, the future utility of tau biomarkers critically depends on large-scale, multicenter, long-term prospective studies, which are essential to their clinical validation and to defining their role as response indicators for emerging disease-modifying therapies (DMTs) [78]

CONCLUSIONS

Plasma assays for phosphorylated tau isoforms have emerged as highly sensitive and specific tools for Alzheimer's diagnosis and risk stratification, with early elevations detectable even before clinical symptoms appear. When combined with markers of neurodegeneration such as neurofilament light chain and glial fibrillary acidic protein, these fluid biomarkers further enhance diagnostic precision. In parallel, tau-PET imaging using tracers like flortaucipir and RO948 enables precise visualization of neurofibrillary pathology and correlates closely with cognitive decline. Clinically approved anti-amyloid antibodies not only clear amyloid plaques but also lower cerebrospinal fluid levels of phosphorylated tau and modestly slow disease progression. Direct tau-targeting strategies are now advancing: antisense oligonucleotides have demonstrated clear reductions in tau biomarkers without serious safety concerns, and RNA interference approaches show potent aggregate clearance and neuroprotective effects in early models. Monoclonal antibodies against tau, kinase inhibitors, and aggregation modulators continue to be refined, as efforts focus on optimizing target engagement and dosing to achieve meaningful clinical benefits.

Disclosure

Authors' Contributions Statement:
Conceptualization: Norbert Jamrozik
Data Curation: Jakub Sokołowski, Jan Polaczek-Kornecki, Robert Gdula
Formal Analysis: Julia Sokal, Robert Gdula
Investigation: Michał Godek, Kinga Cogiel
Administration: Szymon Szostek, Karol Płaszewski,
Resources: Julia Sokal
Software: Szymon Szostek, Michał Godek
Supervision: Karol Płaszewski, Kinga Cogiel
Validation: Jakub Sokołowski
Visualization: Szymon Szostek
Writing- Original Draft: Jan Polaczek-Kornecki
Writing- Review & Editing: Norbert Jamrozik

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