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Tau biomarkers for neurodegenerative diseases: Current state and perspectives

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A B S T R A C T

Neurodegenerative diseases, particularly tauopathies, pose significant global health challenges, especially in aging populations. Tauopathies are characterized by progressive neuronal damage and intracellular deposits of hyperphosphorylated tau. Early and accurate diagnosis is hindered by overlapping clinical features and reliance on post-mortem analyses, emphasizing the need for reliable in vivo biomarkers to improve early diagnosis and management. Advances in tau biomarkers and imaging have facilitated targeted Alzheimer's disease therapies, but progress for other tauopathies remains inadequate. Future diagnostic frameworks should integrate multiple biomarkers across different tissues within specific **timelines**. However, challenges such as co-pathologies and limited understanding of pathogenic mechanisms remain significant obstacles. Emerging ultrasensitive technologies, including seeding amplification assays and minimally invasive sources of biomarkers like skin biopsy, hold promise for biomarker discovery. Here, we present the current clinical classification of tau proteinopathies, the challenges that are posed by the actual diagnostic criteria, followed by the most recent advancements in tau biomarker technologies.

1. Introduction

Neurodegenerative diseases pose a significant health challenge globally, particularly in aging populations. Among them, tauopathies, characterized by progressive neuronal damage and intracytoplasmic filamentous deposits of hyperphosphorylated, tau are the most prevalent [1]. Accurate and early diagnosis remains elusive due to overlapping clinical phenotypes and reliance on post-mortem neuropathological analysis. The clinical overlap among neurodegenerative diseases underscores the relevance of specific and reliable in vivo biomarkers to enable precise, early diagnosis and improve patient management. In fact, early detection is crucial, as clinical diagnosis often occurs after substantial neurodegeneration, limiting therapeutic efficacy of potentially effective drugs. Diagnostic tools, such as brain PET imaging and measurements of phosphorylated and total tau in cerebrospinal fluid (CSF) and plasma, have advanced Alzheimer's disease (AD) diagnostics but remain inadequate for the majority of other tauopathies. These include primary tauopathies such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and other neuropathologically well-defined diseases in which the clinical presentation is often an unreliable predictor of the underlying neuropathological diagnosis. This is due to the overlap of many signs and symptoms, such as parkinsonism with atypical features and cognitive-behavioral or language impairment, which further obscure the classical distinction between motor and cognitive syndromes in the movement disorders field. In addition, the individually low prevalence of many of these diseases further complicates their accurate characterization. The National Institute on Aging and Alzheimer's Association (NIA-AA) 2018 framework underscored the importance of biomarkers, prioritizing pathophysiological evidence over symptom-based diagnostics for AD: biomarkers are categorized using the amyloid-tau-neurodegeneration (A-T-N) system [2]. This includes amyloid PET imaging (A), phosphorylated tau biomarkers (T), and neurodegeneration markers (N) such as structural MRI, FDG-PET, and neurofilament light chain measure in CSF or blood. These tools are pivotal for diagnosis, disease staging, prognosis, and treatment monitoring. Similar paradigms based on biological markers such as alpha-synuclein detection in CSF or tissues, presence of neurodegeneration and genetic variants (SynNeurGe research diagnostic

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criteria) [3], and a biological staging system termed the neuronal α-synuclein disease integrated staging system (NSD-ISS) have now been proposed also for Parkinson's disease and dementia with Lewy bodies [4]. However, no biologically based staging systems using tau protein biomarkers are currently available for primary tauopathies or other secondary tauopathies.

In this review, we aim to present the current clinical classification of tau proteinopathies, the challenges that are posed by the actual diagnostic criteria, followed by the most recent advancements in the field of tau biomarker technologies.

2. Tau protein

Tau is a microtubule-binding protein coded by MAPT gene and widely distributed in both central (CNS) and peripheral nervous systems (PNS). The adult human brain presents mainly six Tau isoforms arising from the different combinations of the alternative splicing of exons 2, 3, and 10 (0N3R, 1N3R, 2N3R, 0N4R, 1N4R, 2N4R). In physiological conditions, the 3R and 4R isoforms are equally represented, while 0N, 1N, and 2N isoforms are expressed as 37 %, 54 %, and 9 % of total Tau [5]. Other variants deriving from the alternative splicing of exons 4A and 6 and intron 12 can be found in CNS and, more frequently, in PNS [6]. The balance of different isoforms is strictly linked to brain health and function. For example, the imbalance between 4R and 3R isoforms is strongly associated with tauopathies [7], which are indeed classified based on the predominant neuropathological isoform in brain. In addition, recent studies observed a decrease in the ratio between the isoform containing intron 12 and total tau in AD patients' brains, while the isoform containing exon 6 was found to be less prone to aggregation, suggesting a pathogenic role for these isoforms [6,8].

Tau protein presents four main functional domains: (1) the N-terminal acts as a stabilizer and spacer for microtubules and is involved in signal transduction [6,7,9]; (2) the proline-rich domain regulates tau phosphorylation and participates in signal transduction [6]; (3) the microtubule-binding region is essential for microtubule assembly, stabilization, and axonal transport [6]; (4) and the C-terminal is crucial for tau folding and its ability to adopt multiple conformations [10,11].

Genetic mutations can alter tau sequence, reducing its affinity for microtubules and increasing its tendency for aggregation [12,13], or can alter tau splicing, changing the ratio between the different isoforms and influencing axonal transport [14]. Among post-translational modifications, tau can undergo phosphorylation, acetylation, ubiquitination, methylation, oxidation, SUMOylation, O-GlcNAcylation, and N-glycosylation; these modifications, if not finely regulated, can alter its conformation, interaction with other proteins, and cellular localization [15,16].

Pathological detached tau undergoes aggregation cascade in a process that spans from oligomers to big aggregates, similar to other proteins linked to neurodegenerative diseases like alpha-synuclein and amyloid beta precursor protein. Aggregates of tau generate paired helical filaments or straight filaments, which form neurofibrillary tangles (NFTs) in neuronal body and neuropil threads in axons [17,18]. These big aggregates correlate with neurodegeneration and cognitive decline, albeit they seem to be less toxic than smaller oligomers and may play a protective role [19]. Finally, pathogenic tau is able to induce conformational conversion of monomers and propagate in the nervous system through specific spatiotemporal pathways (seeding) [20,21].

It has been recently shown that different tauopathies are characterized by diverse tau conformers or 'strains' that associate with different filaments ultrastucture [22]. Protein conformers may determine the susceptibility of cell type to pathology and the spatial distribution of tau deposits [23]. For example, PSP is characterized by globose 4R phosphorylated NFTs in the subthalamic nucleus, basal ganglia, and brainstem, but also tufted astrocytes in the neocortex, neostriatum, and midbrain tectum, and oligodendroglial coiled bodies in the basal telencephalon, diencephalon, brain stem, and cerebellum. On the other hand, CBD shows neuronal and glial inclusions in the neocortex and neostriatum, but its peculiarities are the presence of astrocytic plaques, a different kind of tau aggregates compared to tufted astrocytes, and the extensive thread-like cell processes affecting both grey and white matter [24,25].

3. Clinical spectrum in tauopathies

Under the neuropathological term of tauopathies, we group diseases consistently defined by tau protein inclusions in the brain, where tau pathology at the cellular level correlates with both neurodegeneration and clinical manifestations of disease. Primary tauopathies are those where tau is the main or the only pathological protein, as opposed to secondary tauopathies in which tau pathology is associated with additional pathogenic proteins like Aβ in AD. Another way to classify tauopathies is based on the predominant tau isoforms at the neuropathological level, along with the genetically determined or sporadic origin of each condition [1]. Clinically, a few syndromes are highly predictive of a neuropathologically defined tauopathy, while others may be nonspecific, with less certain clinico-pathological correlations and with significant overlap in signs and symptoms with other neurodegenerative diseases. As a consequence, the correct diagnosis of tauopathies in living subjects may also be challenging for specialists and may hinder the possibility to deliver the proper management for each disease.

3.1. Sporadic tauopathies

3.1.1. 3R/4R tauopathies

Sporadic tauopathies are the most frequent group, with AD, characterized by 3R+4R tau isoforms, being the most prevalent. Neuropathologically, AD is associated also with the extracellular deposition of Aβ protein, and it is the most common cause of dementia in the general population. The clinical spectrum of AD can range from subjective memory complaints to mild cognitive impairment (MCI) or dementia. However, in addition to the classic form of AD, there are other clinically important variants, such as the corticobasal syndrome (CBS). CBS can be clinically divided into subtypes, including the classic variant of CBS, the frontal-behavioral-spatial (FBS) variant, non-fluent agrammatic primary progressive aphasia (nfa-PPA), and the PSP-like syndrome (PSPS) [26]. Patients with CBS due to AD often exhibit prominent visuospatial impairments with aphasic features and are associated with a pattern of posterior cortical atrophy, frequently asymmetrical and primarily involving the precuneus and posterior cingulate cortex on MRI. Although CBS-AD typically presents with an earlier onset and a slower clinical progression compared to CBS caused by CBD, clinical data are insufficient to reliably distinguish between these underlying etiologies, making the use of biomarkers essential [27].

Another entity to consider in the differential diagnosis of AD is primary age-related tauopathy (PART). PART is a primary tauopathy (3R+4R) not associated with amyloid protein, characterized by the accumulation of phosphorylated tau neurofibrillary tangles in limbic regions. It manifests mainly as amnestic cognitive impairment, and progression to dementia is significantly slower in PART than in AD. While AD progressively affects most cognitive domains, PART tends to preserve executive functions, visuospatial abilities, and language for a longer period [28,29].

3.1.2. 4R tauopathies

Sporadic primary 4R tauopathies, including PSP and CBD, represent a wide phenotypic spectrum ranging from atypical parkinsonian syndromes to frontotemporal dementia. Current diagnostic criteria define varying degrees of probability for these entities, ranging from "possible PSP" or "possible CBD," which are less specific but cover a broader phenotypic spectrum, to "probable PSP" or "probable CBD," which are more specific for the neuropathological diagnosis [26,30]. However,

Table 1
Current findings from biomarkers studies in sporadic tauopathies.

Disease	Tau isoforms	Clinical syndrome	Imaging	Matrix	Biomarkers	
					ImmunoCapture Assays	Seeding Amplification Assays
AD	3R/4R (+Aβ)	**Classic:** Predominant episodic memory impairment. **Others:** Logopenic variant, posterior cortical atrophy, CBS, dysexecutive variant [98].	Binding in medial temporal lobe, posterior cingulate, and temporo-parietal areas (AV1451, THK5351, THK5317, PBB3, MK-6240, RO-948) [55].	Brain Tissue	Total Tau [99,100] pT231 [99,101,102] pT181 [100–102] pT217 [102]	K18CFh [88,94] K19CFh [87,89,94] K12CFh [137] Full-length tau [138,139]
				CSF	pT181 [103–110] pT217 [111–114] pT231 [105] Total Tau [108–110,115] N224 [116]	K18CFh [88,94] K19CFh [87,94]
				Plasma	pT181 [70,103,104,117–126] pT217 [111,113,114,127–129] pT231 [130]	/
				Skin	Total Tau [131]	K18CFh [92] K19CFh [92]
				Olfactory mucosa	Total Tau [132] pT181 [132]	K18CFh [94] K19CFh [94]
				Saliva	Total Tau [133–136] pT181 [74,103,133–136]	/
PSP	3R/4Rtau	**RS:** early postural instability and falls, vertical supranuclear gaze palsy, axial rigidity. **P:** asymmetric onset and may be some levodopa responsiveness. **PGF:** early and progressive gait freezing within 3 years of onset. **SL:** nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech. **F:** apathy, impulsivity, and/or dysexecutive syndrome with behavioral dysfunction. **CBS:** combination of asymmetric apraxia, cortical sensory loss, dystonia, myoclonus, alien hand/limb, rigidity, and bradykinesia. **PI:** early and prominent postural instability with falls. **OM:** predominant slow vertical saccades, supranuclear gaze palsy, square wave jerks, and/or eyelid apraxia [30].	Binding in basal ganglia, midbrain, and other subcortical nuclei (AV1451, PBB3, THK5351, MK-6240, RO-948) [55].	Brain Tissue	Total tau [140]	K18CFh [88,94] K19CFh [87,89,94] K12CFh [137] Full-length tau [138,139]
				CSF	pT181 [104,141] pT217 [142] N224 [116]	K18CFh [88]
				Plasma	pT181 [104,117,118,120–122] pT231 [130]	/
				Skin	Total Tau [77]	K18CFh [91–93] K19CFh [91–93]
				Olfactory mucosa	/	K18CFh [94] K19CFh [94]
CBD	4R	**CBS:** combination of asymmetric apraxia, cortical sensory loss, dystonia, myoclonus, alien hand/limb, rigidity, and bradykinesia.	Binding in primary motor cortex, basal ganglia, and frontal cortex (AV1451, PBB3, THK5351, MK-6240, RO-948) [55].	Brain Tissue	/	K18CFh [88]

(*continued on next page*)

Table 1 (*continued*)

Disease	Tau isoforms	Clinical syndrome	Imaging	Matrix	Biomarkers	
					ImmunoCapture Assays	Seeding Amplification Assays
		FBS: prominent behavioral or personality changes (apathy, disinhibition), executive dysfunction, and/or visuospatial deficits. **Nfa-PPA:** nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech. **PSPS:** axial or symmetric rigidity or bradykinesia, early falls, postural instability, supranuclear gaze palsy, and/or decreased velocity of vertical saccades [26].				K19CFh [87,89]
				CSF	pT181 [104]	K18CFh [88]
					pT217 [142]	
				Plasma	pT181 [104,120]	/
				Skin	Total Tau [77]	K18CFh [91–93]
						K19CFh [91–93]
				Olfactory mucosa	/	K18CFh [94]
						K19CFh [94]
AGD	4R	Possible association with dementia and psychiatric disturbances, while some studies have not demonstrated such associations [143].	/	Brain tissue	/	K12CFh [137]
						K19CFh [89]
				Plasma	pT181 [120]	/
GGT	4R	**Type I:** bvFTD and/or primary progressive aphasia **Type II:** PSP syndrome and/or CBS. **Type III:** parkinsonism, dementia, and lower motor neuron involvement [36].	/	/	/	/
Pick's disease	3R	bvFTD, primary progressive aphasia, parkinsonism with CBS [38].	Binding in frontal and temporal cortex. Weaker binding than AD with 3R/4R tracers due to 3R predominance (AV1451) [144,145].	Brain Tissue	/	K19CFh [87,89]
						K18CFh [88]
						K12CFh [137]
						Full-length tau [138]
				Skin	/	K18CFh [92]
						K19CFh [92]
IgLON5	3R/4R	REM and non-REM sleep disorders, sleep apnea, stridor, bulbar dysfunction, ocular motor abnormalities, autonomic symptoms, parkinsonism, cerebellar ataxia, and/or chorea [51].	Increased tau binding in the brainstem, particularly the pons and dorsal medulla. Uptake also in the cerebellum. Tau accumulation increased over time in the medulla (PI-2620) [146].	/	/	/

Table 2
Current findings from biomarkers studies in genetic tauopathies.

Gene	Tau isoforms	Clinical syndrome	Imaging	Matrix	Biomarkers	
					ImmunoCapture Assays	Seeding Amplification Assays
MAPT	3R, 4R, 3R/4R	**bvFTD**, parkinsonism, **PSP syndrome**, **CBS syndrome**, amnestic syndrome, depending on mutation [147–149].	Weak binding with 3R/4R tracer (AV-1451) for N279K and P301L mutations (4R predominant). Strong binding similar to AD in one R406W mutation case (3R/4R). Other cases with prominent uptake in hippocampus, temporal, and frontal lobes (AV-1451) [150].	Plasma	pT181 [122] Total Tau [73]	/
PSEN1	3R/4R	**AD**. Very early onset, mean 43.6 years. Associated with myoclonus, epileptic seizures, spastic paraparesis, and extrapyramidal signs. 16 % of cases with atypical cognitive presentation (behavioral/executive dysfunction, language impairment) [40,151].	Uptake similar to sporadic AD; in some cases, posterior predominance over medial temporal regions (AV-1451) [152,153].	Olfactory mucosa Plasma	/ pT217 [113,154] pT181 [154,155]	K18CFh [94] K19CFh [94] /
PSEN2	3R/4R	**AD**. Variable age of onset (45–88 years). Episodic memory impairment. Atypical cases include FTD and parkinsonism [40,151].	Uptake similar to sporadic AD; in some cases, posterior predominance over medial temporal regions (AV-1451) [152,153].	Plasma	pT181 [154] pT217 [154]	/
APP	3R/4R	**AD**. Early onset, mean 50.4 years. Predominant episodic memory impairment. Frequently associated with myoclonus and epileptic seizures [151].	Different uptake compared to sporadic AD. Early uptake in precuneus and posterior cingulate (AV-1451) [152].	Plasma	pT181 [154,155] pT217 [154]	/
Trisomy 21	3R/4R (+Aβ)	**AD**. Early onset, mean 51 years. Predominant episodic memory impairment. Early functional decline with high prevalence of epilepsy (75 %) [156].	Widespread cortical tau uptake with a typical AD regional distribution (AV-1451) [156].	CSF	pT181 [157]	/
APOE4/APOE4	3R/4R	**AD**. Early onset, mean 65 years, later than PSEN1, PSEN2, APP, or DSAD. Predominant episodic memory impairment; rapid progression from MCI to dementia [42].	Sporadic AD pattern. APOE4 homozygotes exhibit higher levels of tau accumulation at earlier stages compared to APOE3 homozygotes (AV-1451) [42].	/	/	/
PRNP	3R/4R, (+PrP)	**Genetic Creutzfeld-Jakob disease**: dementia, myoclonus, visual and cerebellar symptoms, pyramidal and/or extrapyramidal symptoms. **Gerstmann-Sträussler-Scheinker**: progressive cerebellar ataxia, cognitive impairment, sensory symptoms, pyramidal and/or extrapyramidal signs. **Fatal familial insomnia**: sleep disturbances, dementia, ataxia, psychiatric and/or autonomic symptoms [158,159].	Neocortical uptake with AD-like pattern (AV-1451) [160].	/	/	/
ITM2B	3R/4R, (+ABri, Adan)	**Familial Danish dementia**: cataracts, hearing loss, cerebellar ataxia, psychiatric symptoms, and dementia [44]. **Familial British dementia**: spastic paraparesis, cerebellar ataxia, stroke-like episodes, seizures, psychiatric symptoms and/or dementia [43].	/	/	/	/
HTT	4R	**Huntington's Disease**: chorea, parkinsonism, dystonia, ataxia, psychiatric symptoms and/or dementia [49].	/	Brain tissue Plasma Skin	Conformational Tau (Alz-50) [161] Total Tau [162] Total Tau [80]	/

AD: Alzheimer disease; PSP: progressive supranuclear palsy; CBS: corticobasal syndrome; DSAD: Down syndrome associated Alzheimer disease; MAPT: microtubule-associated protein tau; PSEN: presenilin; APP: amyloid-beta precursor protein; APOE: apolipoprotein E; PRNP: prion protein; ITM2B: integral membrane protein 2B; HTT: huntingtin.

particularly in CBS, neuropathological correlation remains low, as other diseases can present with the same syndrome. Some series have found that up to 32 % of CBS cases correspond to neuropathological diagnoses of PSP, while 30 % are attributable to AD [31]. As previously mentioned, CBS due to AD does not have discriminative clinical features compared to CBS not due to AD, but differentiation can be made based on atrophy patterns (frontal and subcortical predominance in non-AD CBS vs. posterior predominance in CBS-AD) and, more importantly, by using AD biomarkers such as pTau217 [27]. On the other hand, due to the clinico-pathological overlap between CBS and PSP and the lack of biomarkers with sufficient discriminatory capacity between the two entities, there is an ongoing debate about whether they should be considered separate clinical syndromes or grouped into a single clinical entity [32,33]. Finally, the category of "probable 4R-tauopathy" was established to group the clinical syndromes of PSP and CBD into a group that encompasses all possible phenotypes [30]. This category allows for the inclusion of cases with shared clinical features between CBS and PSP in which a tauopathy etiology is suspected, aiming to achieve better clinico-pathological correlation rather than focusing on differential clinical syndromes. However, this approach may also limit the possibility to develop targeted therapy for single diseases.

There are other primary sporadic 4R tauopathies with less well-defined clinical syndromes compared to those previously mentioned and also without available biomarkers for reliable in vivo diagnosis.

Among them, Argyrophilic Grain Disease (AGD) stands out as an age-related tauopathy characterized by the accumulation of argyrophilic grains with tau inclusions, initially in the limbic system and subsequently progressing to neocortical structures. AGD frequently coexists with granular fuzzy astrocytes, a form of age-related tau astrogliopathy (ARTAG). Both alterations are often found in limbic structures [34,35].

Another primary 4R tauopathy with a defined clinical syndrome, but currently impossible to diagnose in vivo due to overlap with more prevalent syndromes and the absence of reliable biomarkers, is Globular Glial Tauopathy (GGT). GGT is neuropathologically divided into several subtypes and clinically exhibits significant heterogeneity. Lower motor neuron involvement may be a frequent and distinguishing feature in certain subtypes. MRI markers, such as pronounced temporal lobe atrophy with preservation of the midbrain, can help differentiate GGT from PSP and CBD; however, there are currently no biomarkers available for a reliable in vivo diagnosis [36,37].

3.1.3. 3R tauopathies

Pick's disease is the only known primary 3R tauopathy and is currently considered a strictly neuropathological entity, as clinical antemortem diagnosis is not possible. This limitation arises from its clinical heterogeneity, overlap with other disorders, low prevalence, and lack of diagnostic biomarkers. Neuropathologically, it is characterized by frontal and temporal atrophy, with the presence of Pick bodies (argyrophilic 3R tau inclusions) and Pick cells (swollen neurons). Clinically, the most common presentations include the behavioral variant of frontotemporal dementia (bvFTD) and primary progressive aphasia, although motor phenotypes with CBS have also been reported [38].

3.2. Genetically determined tauopathies

Genetically determined primary tauopathies include those resulting from mutations in the *MAPT* gene, which follow an autosomal dominant inheritance pattern. Depending on the mutation, they can lead to the accumulation of different tau isoforms. The clinical phenotype of these patients ranges from bvFTD to parkinsonism, with clinical phenotypes resembling PSP and CBS [39].

Other genetically determined tauopathies associated with 3R+4R tau isoforms are linked to mutations in the amyloid precursor protein (APP) gene, the presenilin 1 and 2 genes (PSEN1 and PSEN2), trisomy 21, and homozygosity for APOE4 [40–42]. These are genetically determined forms of AD, and neuropathologically, they are invariably linked to Aβ protein deposition.

Additionally, rare genetic diseases involving the ITM2B gene, which interacts molecularly with APP, are associated with tauopathy (3R+4R) alongside ABri and ADan proteins. Known as familial British and familial Danish dementia, these conditions manifest with cognitive impairment, progressive spastic tetraparesis, and cerebellar ataxia starting around age 60. Neuroimaging typically reveals features consistent with cerebral amyloid angiopathy [43,44]. Finally, some hereditary prion diseases due to mutations in the PRPN gene (e.g., E200K and V203I) result in a 3R+4R tauopathy associated with the prion protein PrP. Clinically, these diseases can manifest with a combination of dementia, myoclonus, pyramidal and extrapyramidal symptoms, cerebellar ataxia, and/or visual disturbances. MRI diffusion abnormalities in the caudate and putamen can aid in the diagnosis [45,46].

3.3. Other secondary tauopathies

Among secondary tauopathies, we find other entities with tau co-pathology. Some of the most recently defined tauopathies, characterized by a distinctive clinical syndrome and biomarkers that allow for diagnostic confirmation, include Huntington's disease (HD). HD is a genetically determined condition caused by the expansion of the CAG trinucleotide repeat and manifests with motor disturbances (primarily chorea in early stages), as well as cognitive and neuropsychiatric symptoms [47–49]. Another disease recently classified in this category is anti-IgLON5-related tauopathy. Clinically, this condition is characterized by parasomnias in both REM and non-REM sleep, sleep apnea, stridor, bulbar dysfunction, and extrapyramidal symptoms. Biomarkers include the detection of IgG4 anti-IgLON5 antibodies in serum or CSF, along with specific HLA haplotypes. Neuropathologically, it is defined by subcortical neuronal deposits of 3R+4R tau with a rostro-caudal gradient, different from other tauopathies such as PSP, CBS, or ARTAG due to its distribution and the absence of significant glial involvement [50,51].

4. Tau-based imaging biomarkers

Tau PET imaging has emerged as a promising tool for detecting abnormal tau pathology in various neurodegenerative diseases, such as AD, PSP, and CBD. This imaging modality provides valuable insights into disease progression and regional tau deposition, supporting both diagnosis and disease monitoring (Tables 1–2).

4.1. First-generation tau PET tracers

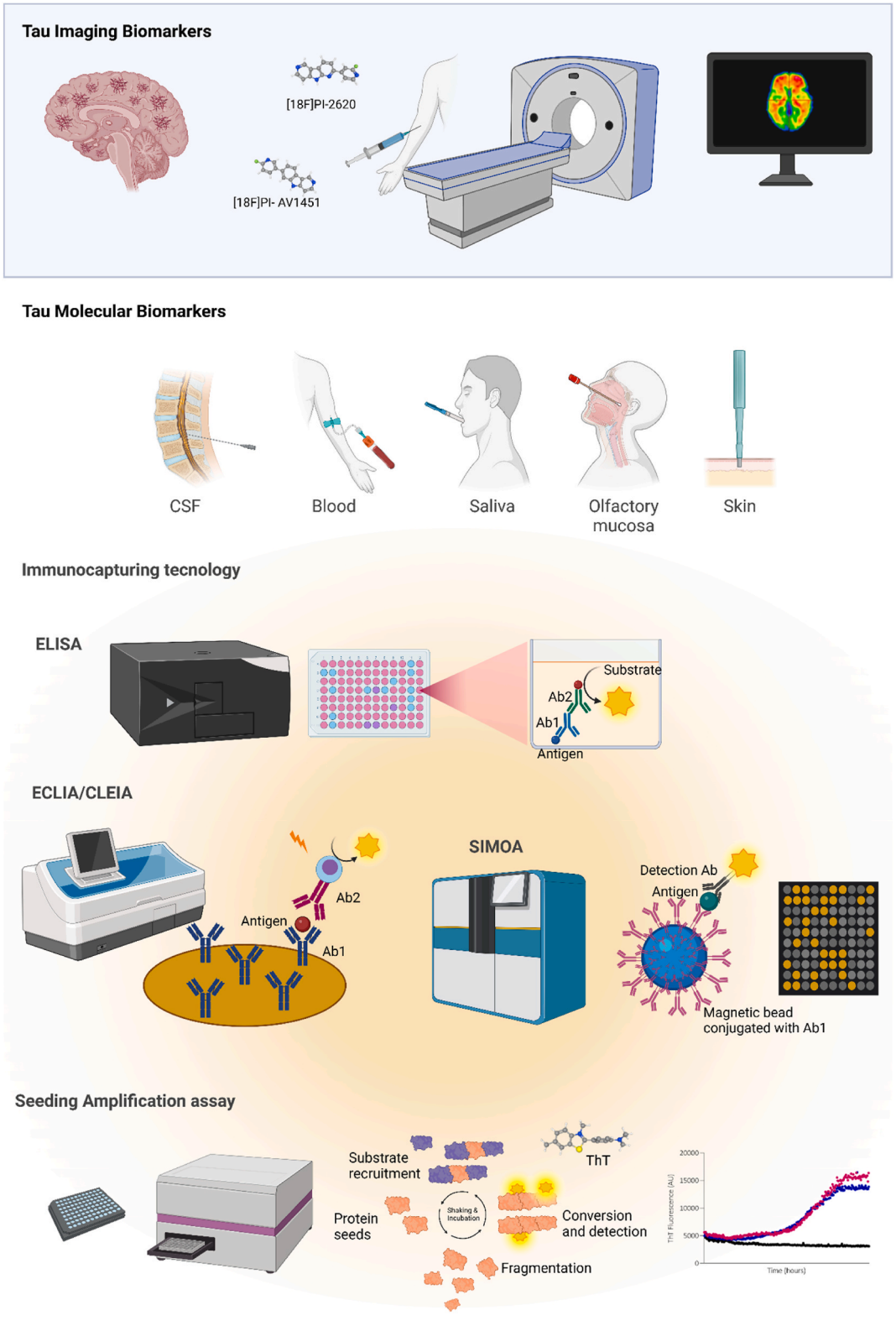
PET tracers targeting tau have undergone significant evolution over the years. First-generation ligands, such as [18F]AV1451 (or [18F] flortaucipir), faced notable limitations, including limited target affinity and off-target binding, particularly due to their affinity for non-tau-related structures like monoamine oxidase-B, which affects regions such as the basal ganglia [52]. When comparing AD and healthy elderly populations, tracer uptake was predominantly restricted to the medial temporal lobe in healthy subjects, consistent with neuropathological findings of PART in these individuals. In AD, however, uptake was more intense and extended to other temporo-parietal areas. In the various AD subtypes, tau deposits also appeared to follow expected neuropathological patterns. While medial temporal lobe retention was consistent, findings in other cortical areas were variable in healthy individuals [53]. Additionally, in longitudinal studies, tracer uptake did not always show a stepwise progression based on neuropathology, sometimes presenting uniform accumulation rates instead [54].

In primary sporadic 4R tauopathies such as PSP and CBD, some studies have demonstrated uptake patterns consistent with expected neuropathology. However, off-target binding is particularly problematic in these patients because regions like the basal ganglia and midbrain are heavily affected by this phenomenon [55]. For [18F]AV1451, longitudinal studies have shown progressive tracer uptake and correlations with functional measures in these diseases [56]. One major drawback of this tracer, however, is its low affinity for straight tau filaments, such as those found in PSP and CBD [55].

4.2. Second-generation tau PET tracers

To improve tracer specificity, second-generation tau PET tracers were developed. In AD, tracers such as [18F]MK6240, [18F]RO948, and [18F]PI-2620 demonstrated high specificity for 3R+4R tau in the frontal cortex, temporal cortex, and hippocampus in postmortem studies, correlating with typical regions of tau accumulation in advanced AD. Although, with lower binding site density, these tracers also showed some affinity in PSP [57].

Tracers such as [18F]PI-2620 and [18F]PM-PBB3 (also known as [18F]florzolotau) have shown greater affinity for 4R tau compared to first-generation tracers and overcome the issue of off-target binding that affected PSP and CBD patients. These tracers can identify affected regions such as the midbrain, basal ganglia, and primary motor cortex, and compared to first-generation tracers, they appear to better reflect subcortical-specific tau accumulation. This has led to improving the correlation between tracer uptake and motor clinical manifestations [58]. Studies with [18F]PI-2620 have shown significant uptake in the globus pallidus of PSP patients; however, uptake has also been observed



(caption on next page)

Fig. 1. Tau biomarkers
Abnormal Tau pathology in the brain can be detected and visualized by PET imaging. Tracers of the first- ([18F]PI-AV1451) and second-generation ([18F]PI-2620) provide insights into disease progression and regional tau deposition.
Pathological Tau can be detected in multiple biospecimens such as CSF, blood, saliva, olfactory mucosa, and skin. Several techniques have been developed for its detection. For ELISA, CLEIA/ECLIA, and SIMOA, the target antigen is linked by the capture (Ab1) and the detection (Ab2) antibody. Depending on the technique, Ab2 is conjugated to an enzyme [ELISA: horseradish peroxidase (HRP) reduces its substrate, 3,3′,5,5′-tetramethylbenzidine (TMB), inducing a colorimetric reaction], a luminescent marker [ECLIA/CLEIA: ruthenium or iridium that emit luminescence after electrochemical stimulation], or a fluorophore [SIMOA: fluorescence]. The signal obtained is proportional to the amount of the target protein in the sample. SAA takes advantage of the ability of misfolded proteins present in samples (seeds) to recruit and trigger conformational changes in the provided substrate (recombinant protein), to create fibril aggregates that can be detected and stained by ThT. The measure over time of ThT fluorescence describes the kinetics of aggregate formation.
The figure has been produced with bioRender software. The chemical structure of the compounds ([18F]PI-AV1451, [18F]PI-2620, and ThT) has been obtained from PubChem - National Center for Biotechnology Information (https://pubchem.ncbi.nlm.nih.gov/compound/Flortaucipir, 2-(2-(Fluoro-18F)-4-pyridinyl)-9H-pyrrolo(2,3-b:4,5-c')dipyridine | C15H9FN4 | CID 145722629 - PubChem, Thioflavin T | C17H19ClN2S | CID 16953 - PubChem).

in healthy controls, indicating limited specificity. Furthermore, *in vivo* uptake did not correlate well with levels found postmortem. While [18F]PI-2620 shows promise as a tracer for AD, [18F]PM-PBB3 is considered potentially more specific for 4R tauopathies [59]. In summary, the combination of second-generation tau PET tracers with other imaging techniques, such as amyloid PET or brain MRI, may provide additional value for diagnosis and decision-making in both AD and primary 4R tauopathies like PSP and CBD [60,61]. Recent postmortem and preclinical non-human studies suggest that the second-generation tracer [18F]OXD-2314 exhibits higher affinity for 4R tau compared to [18F]PI-2620 and [18F]PM-PBB3; however, clinical studies are needed to validate these findings [62].

In summary, tau PET appears to be a promising biomarker that may aid in identifying different primary tauopathies in vivo. However, further studies are needed to validate the results of new tracers and include longitudinal follow-ups to confirm their utility as potential diagnostic or monitoring biomarkers.

5. Tau-based molecular biomarkers

Tau protein measurement in biospecimens has emerged as a fundamental tool for the accurate diagnosis of AD, and several studies have shown abnormal tau findings in various neurodegenerative diseases (Tables 1–2).

5.1. Immunocapturing technology

Originally, tau protein quantification in cerebrospinal fluid (CSF) was performed by ELISA in patients with AD [63]. Since then, many studies have consistently demonstrated increased levels of total and phosphorylated tau species in AD versus healthy controls [64]. However, while CSF tau was associated with cognitive impairment, it didn't correlate as well with tau burden by PET or post-mortem brain studies [65,66]. An increase in CSF total tau was also demonstrated in brain traumatic injury [67] and other neurodegenerative diseases like Creutzfeldt-Jakob disease (CJD), whereas phosphorylated tau was not observed in these conditions [64]. These findings support the hypothesis that phosphorylated tau elevation in CSF is specific for AD, and it is not merely a reflection of neurodegeneration and release of cell content in CSF. Moreover, in primary tauopathies like FTD or PSP, levels of tau, including several phosphorylated species and N-terminal fragments (N224) that are enriched in neurofibrillary tangles, were not observed [68,69]. These results suggest that alternative processing and secretion of tau in the extracellular space may occur in these diseases. Chemiluminescence (CLEIA) and electrochemiluminescence (ECLIA) based fully-automated platforms for total and phosphorylated tau detection in CSF are currently used in clinical routines for AD diagnosis [70].

Lately, the rapid development of ultrasensitive immunoassays, like the single molecule array (Simoa), has largely increased the sensitivity and accuracy of tau detection in other biofluids like blood with obvious advantages for a less invasive and more extensible diagnostic tool. Similarly to CSF, phosphorylated tau species (pTau 181, pTau217 and pTau231, pTau205) were found to be increased in plasma of patients with AD early on in the disease course and correlated with the start of amyloid pathology in brain [71]. As far as concern other tauopathies, several studies have shown a non-specific increase of plasma total tau in FTD and DLB [72,73]; while, phosphorylated Tau was not increased in plasma of subjects with FTD, PSP, and CBS [64]. Of interest, plasmatic concentrations of pTau181 resulted strongly associated with Aβ-PET and CSF pTau181, independently from the diagnosis, suggesting that it could be a biomarker of AD-related pathology in other diseases [64].

Saliva is another biofluid that has been highly tested since the first detection of tau in 2011, however, no standardized and validated protocols for diagnostic salivary tau measurement have been approved so far. A study using CLEIA platform showed an increase of phosphorylated salivary tau in MCI and AD [74], while another one, using a similar technology, showed negative results and argued that low levels of tau in saliva and the absence of correlation with CSF values prevent saliva from being a valid alternative to CSF [75].

Skin is highly innervated by sensory and autonomic nerves, in which axons are enriched in microtubules and tau [15]. Indeed, recent studies have analyzed Tau isoforms in skin nerves of patients with PSP, CBD, PD, MSA, AD, and HD. Higher levels of total tau measured by ELISA were observed in skin lysates of primary tauopathies and HD compared to healthy subjects and synucleinopathies. Further, it correlated to clinical variables alongside genetic and neuroimaging biomarkers in HD. Since skin biopsy is minimally invasive and allows the detection of other biological markers, such as alpha-synuclein in PD and other synucleinopathies, it is a promising source of multiple biomarkers for neurodegenerative diseases [76–83].

5.2. Seeding amplification assays

Seeding amplification assays (SAA), Real-Time Quaking Induced Conversion assay (RT-QuIC), and protein misfolding cyclic amplification (PMCA), are alternative ultrasensitive assays initially developed for prion protein detection [84]. SAA are now extended to neurodegenerative diseases for detection of minimal amount of misfolded proteins called seeds in CSF and other peripheral tissues (e.g., blood, skin, and olfactory mucosa) [85,86]. Biological samples are incubated with the substrates and subjected to alternative cycles of shaking and incubation, while thioflavin-T enables monitoring of amyloid fibrils formation, which results from the aggregation of the substrate. Tau-SAA was first developed for 3R-Tau detection in post-mortem brains and CSF of patients with Pick's Disease [87] and then expanded to study 3R/4R and 4R [88,89] pathologies, like AD and PSP-CBD, respectively. These assays are based on fragments of recombinant tau (tauK18 for detection of tau 4R and tauK19 for detection of tau 3R) that have been specifically modified (tauK18CFh and K19CFh) to increase sensitivity and specificity of the assay. It is conceivable that a panel of tau RT-QuIC assays for 3R, 4R, and 3R/4R could support in future discrimination of several tauopathies [90].

Of particular interest is the application of SAA to skin tissue. A skin Tau-SAA study exploring 4R and 3R isoforms detection in two

anatomical sites, cervical area and distal leg, showed a greater sensitivity of 4R-SAA in cervical area for PSP and CBD [91]. These results were confirmed by other studies, which analyzed both autoptic and living skin biopsies in PSP CBD and AD [92,93].

Since olfactory dysfunction is a common symptom of several neurodegenerative diseases, Tau-SAA analysis of olfactory mucosa might be a promising tool, and it has shown good sensitivity for PSP and CBD patients [94]. However, olfactory mucosa collection might be invasive and burdened by complications such as bleeding or infection and might miss the olfactory epithelium, containing the pathology [95], while alternative less invasive techniques such as nasal brushing require otorhinolaryngologists [96].

The complexity and high content of proteins in blood make this biofluid less suitable for SAA; for example, it has been reported to contain inhibitors for RT-QuIC assay in samples from CJD [97]. At the moment, there are no available studies on Tau-RT-QuIC directly in blood for AD or other tauopathies. It is conceivable that other minimally invasive tissues, such as skin or saliva, may be among the best options for RT-QuIC and PMCA assays.

6. Conclusions and future perspective

In conclusion, tauopathies encompass a broad spectrum of clinico-pathological entities that, nonetheless, cannot currently be diagnosed in vivo with sufficient reliability due to the absence of specific biomarkers, except for AD and known genetic causes. The research field in peripheral biomarkers detection in neurodegenerative disorders is highly active and currently expanding, highlighting the importance and the urgency of adding novel biomarkers for the management of these diseases (Fig. 1). Tau biomarkers, in association with imaging progress, have significantly contributed to the biomarker-guided targeted therapies in AD. By contrast, the research of biomarkers for other tauopathies and Lewy bodies diseases has just started, and huge, conjunct efforts from the scientific community are required. It is now possible to envision that for each disease, a combination of several markers, in different tissues in a precise time frame, will tremendously increase our capacity to diagnose correctly patients with overlapping clinical phenotypes. Future research should focus on integrating multimodal biomarkers and combining molecular, imaging, and biomarkers from different tissues to improve diagnostic precision and patient stratification. Additionally, longitudinal biomarker assessments over time could offer critical insights into disease progression and treatment response, further advancing personalized therapeutic approaches in tauopathies and other neurodegenerative disorders. Still, many challenges are on the horizon, such as the frequent occurrence of co-pathologies, especially in aging population, which might complicate the possibility to correctly stratify patients, and the limited knowledge of pathophysiological processes, especially in a spatio-temporal frame for most of the diseases. Based on the successful development in AD, the discovery of novel biomarkers in tauopathies and other neurodegenerative diseases will require a tiered process, starting from autopsy-confirmed cases, moving to CSF, blood, and peripheral tissues. Thanks to the continuous development of increasingly sensitive technologies and access to informative and minimally invasive tissues, like skin biopsy, novel promising biomarkers are emerging for neurodegenerative diseases. These results, together with the progress already reached for tau biomarkers in CSF and plasma for AD, will hopefully leverage the chances to deliver the urgently needed, accurate biomarkers for the diagnosis and treatment of patients with tauopathies.

CRediT authorship contribution statement

Elena Vacchi: Writing – review & editing, Writing – original draft. **Iñigo Ruiz-Barrio:** Writing – review & editing, Writing – original draft. **Giorgia Melli:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of competing interest

The authors declare no competing interests.

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