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Understanding Tau pathology: Insights from animal models

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ABSTRACT

Tauopathies represent a class of neurodegenerative diseases (NDs), including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), Pick's disease (PiD), and corticobasal degeneration (CBD), defined by intracellular accumulation of misfolded and hyperphosphorylated tau protein. The pathogenic cascade involves hyperphosphorylation, conformational changes, and aggregation into neurofibrillary tangles (NFTs), which are spatially and functionally linked to neuronal dysfunction, synaptic loss, and progressive cognitive and motor decline. To elucidate tau-mediated mechanisms, diverse transgenic rodent models expressing wild-type or mutant forms of human TAU have been generated. Although these models have advanced understanding of tau aggregation and propagation, tau-targeting therapies have failed to produce clinical benefits, raising concerns about the precise mechanism underlying tauopathies and the fidelity of animal models in evaluating therapeutic targets. This review systematically examines the neuropathological and behavioral phenotypes across established rodent and non-human primate (NHP) tauopathy models, highlighting mechanistic insights into tau-driven pathology. The advantages, limitations, and translational barriers of each model are critically evaluated to inform the development of more predictive preclinical platforms for therapeutic discovery.

Keywords: Tauopathy; Mouse model; Monkey model; Pathogenesis; Non-human primates

INTRODUCTION

Tau, a microtubule-associated protein highly enriched in neurons, plays a pivotal role in microtubule stabilization, axon transportation, and synapse integrity. Aberrant tau accumulation defines a heterogeneous spectrum of neurodegenerative diseases (NDs), collectively termed tauopathies, which include Alzheimer's disease (AD), progressive supranuclear palsy (PSP), Pick's disease (PiD), corticobasal degeneration (CBD), and sporadic frontotemporal dementia (FTD). These disorders differ in affected brain region and tau mutation pattern. Current therapeutic strategies primarily aim to suppress tau expression, prevent pathological aggregation, or facilitate clearance (Honig et al., 2018). Among immunotherapeutic approaches, monoclonal antibodies such as RF6100 have been developed to sequester tau oligomers and mitigate neurotoxicity (Ayalon et al., 2021). LY3303560 and E2814, which selectively target misfolded extracellular tau aggregates or microtubule-binding domains, have demonstrated acceptable safety profiles and preliminary efficacy in phase II trials (Müller-Thomsen et al., 2020; Roberts et al., 2020). Soluble tau assembly (STA)-targeting antibodies, against phosphorylated tau (p-tau) (Ser262/Ser356), serve as early cerebrospinal fluid (CSF) biomarkers associated with neurofibrillary tangle (NFT) formation (Islam et al., 2025). In AD and FTD, an imbalance between 3R and 4R isoforms, along with tau hyperphosphorylation, triggers toxic oligomerization, synaptic impairment, axonal transport derangement, neuronal death, and prion-like brain-wide propagation linked to early cognitive decline (Chang et al., 2021; Cummings et al., 2023). Despite the generation of dozens of tau transgenic mouse models incorporating various tau mutants and promoters, translation to clinical benefit remains elusive. Fundamental interspecies differences hinder the ability of murine models to fully recapitulate human tauopathy. In particular, filament ultrastructure, post-translational modifications (PTMs), isoform

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expression patterns, and the pathogenesis and transmission pathways of tau pathology in mouse models diverge markedly from those in human brains (Van Der Hoven et al., 2020). Moreover, mice lack complex behavioral domains such as language processing and emotional regulation, limiting their utility for modeling cognitive and psychiatric symptoms (Atri, 2019; Pagonabarraga et al., 2024). In contrast, certain aged non-human primates (NHPs) spontaneously develop tauopathy (Schultz et al., 2000) and exhibit closer neuroanatomical and molecular homology to humans. Recent advancements in the establishment of NHP models have further illuminated the cellular and circuit-level impacts of tau misfolding, bridging gaps between rodent studies and human clinical research. This review examines the genomic structure and expression profile of the tau gene, synthesizes current mechanistic understanding of tau-driven neurodegeneration, compares phenotypic and molecular features across rodent and NHP models, and discusses their relative advantages, limitations, and future potential in modeling tauopathies.

EXPRESSION AND STRUCTURE OF TAU

Microtubule-associated protein tau (*MAPT*), first identified in 1975, is ubiquitously expressed in neurons (Weingarten et al., 1975) and a cytoskeletal regulator critical for microtubule stabilization, axonal transport, and synaptic maintenance. Disruption of tau homeostasis has profound neurobiological consequences: *MAPT* knockout in mice results in impaired synaptic structure and microtubule stability (Harada et al., 1994), while overexpression induces pathological aggregation, transcellular propagation, and neuronal death (Ramsden et al., 2005). Structurally, tau is composed of four distinct regions, including the N-terminal region, proline-rich region (PRR), microtubule-binding domain (MBD), and C-terminal region (Guo et al., 2017). The *MAPT* gene, located on chromosome 17q21 (Neve et al., 1986), contains at least 16 exons (Figure 1A) and undergoes complex alternative splicing to generate six major isoforms in the adult human brain: 0N3R, 0N4R, 1N3R, 1N4R, 2N3R, and 2N4R (Figure 1B), ranging from 352 to 441 amino acids (Ayers et al., 2018). These isoforms differ in the presence of N-terminal inserts (encoded by exons 2 and 3) and microtubule-binding repeats (determined by inclusion or exclusion of exon 10). Interestingly, isoform expression and function differ across species and developmental stages. Fetal murine neurons predominantly express the 0N3R isoform, which promotes growth cone dynamics but exhibits low microtubule affinity (Waheed et al., 2023). In contrast, adult mice express only 4R isoforms, reflecting exon 10 splicing that enhances microtubule stability (Verwilst et al., 2018). In primates, all six isoforms are co-expressed, with a tightly regulated 1:1 ratio of 3R to 4R, although the distribution of N-terminal isoforms remains variable (Capano et al., 2022). Notably, perturbation of the 3R:4R balance is a hallmark of multiple tauopathies (Hong et al., 1998). In AD, aberrant splicing and isoform imbalance favor hyperphosphorylation, NFT formation, and β-sheet conversion (Hasegawa et al., 2014). In 4R-predominant disorders such as PSP and CBD, exon 10 splicing defects increase 4R tau deposition, triggering brainstem and cortical degeneration via microtubule transport collapse and inflammation (Koga et al., 2022). Conversely, 3R-dominant tauopathies involve selective exon 10 splicing inhibition, promoting 3R tau aggregation and mitochondrial dysfunction (Jin et al., 2021). These isoform-specific imbalances are closely associated with phosphorylation-dependent tau aggregation and the formation of cytotoxic tangles, contributing to the progressive neurodegeneration observed across the tauopathy spectrum.

INFLUENCE OF TAU ISOFORM IMBALANCE ON PATHOGENESIS

Imbalance between 3R and 4R tau isoforms has emerged as a critical but underexplored contributor to tauopathy pathogenesis. While tauopathy brains frequently exhibit altered isoform proportions, the causal relationship between this imbalance and disease progression remains incompletely defined. Assessing isoform-specific toxicity in mouse models presents a challenge as adult mice express only 4R. To address this limitation, the humanized tau (hTau) mouse model was developed, in which endogenous *MAPT* is knocked out and replaced with full-length wild-type human *MAPT* (Andorfer et al., 2003). Using antisense oligonucleotides (ASOs) to modulate exon 10 splicing in hTau mice, Schoch et al. (2016) showed that increasing 4R tau levels enhanced hyperphosphorylation and seizure severity, whereas reducing 4R tau improved behavioral performance, implicating isoform imbalance in tau-mediated pathology. Subsequent investigations revealed that elevated 4R tau preferentially accumulated in astrocytes and induced pan-reactive gliosis and neuronal damage following forced 3R-to-4R splicing modification (Ezerskiy et al., 2022). This ASO-based approach altered exon 10 inclusion without affecting total tau expression, further supporting the pathogenic role of 4R tau excess in disease progression (Schoch et al., 2016). Modulating 4R tau levels represents a promising therapeutic approach for tau-related pathologies. Espíndola et al. (2018) employed a trans-splicing strategy in a mouse model of tauopathy to modulate the 3R:4R tau ratio in the prefrontal cortex, which significantly reduced p-tau accumulation and improved neuronal function. These findings demonstrate that rebalancing tau isoform expression offers a viable therapeutic entry point for halting or reversing tau-driven deterioration. Subsequent investigations revealed that elevated 4R tau preferentially accumulated in astrocytes and induced pan-reactive gliosis and neuronal damage following forced 3R-to-4R splicing modification (Ezerskiy et al., 2022). This ASO-based approach altered exon 10 inclusion without affecting total tau expression, further supporting the pathogenic role of 4R tau excess in disease progression (Schoch et al., 2016). In a recent study, overexpression of hTau in the hippocampus of middle-aged rhesus monkeys produced a primate model that closely mirrored AD-like pathology, with widespread cortical accumulation of 3R/4R tau, extensive hyperphosphorylation, impaired Aβ clearance, neuron loss, and cognitive decline (Jiang et al., 2024). Viral-mediated bilateral delivery of hTau induced both isoform imbalance and tau overexpression, reinforcing their combined contribution to the molecular and cellular hallmarks of disease. Collectively, these models establish that disruption of 3R:4R tau equilibrium, together with elevated tau burden, plays a central role in initiating and amplifying tauopathy, offering critical mechanistic insight into disease onset and progression.

Moreover, an imbalanced 3R:4R ratio may directly promote pathological p-tau through isoform-specific structural vulnerabilities. The presence of an additional microtubule-binding repeat (R2) in 4R tau exposes key phosphorylation sites, including S262 and S356, enhancing susceptibility to kinases like GSK-3β and accelerating β-sheet conformational shifts and oligomerization kinetics (Moore et al., 2023; Zhou

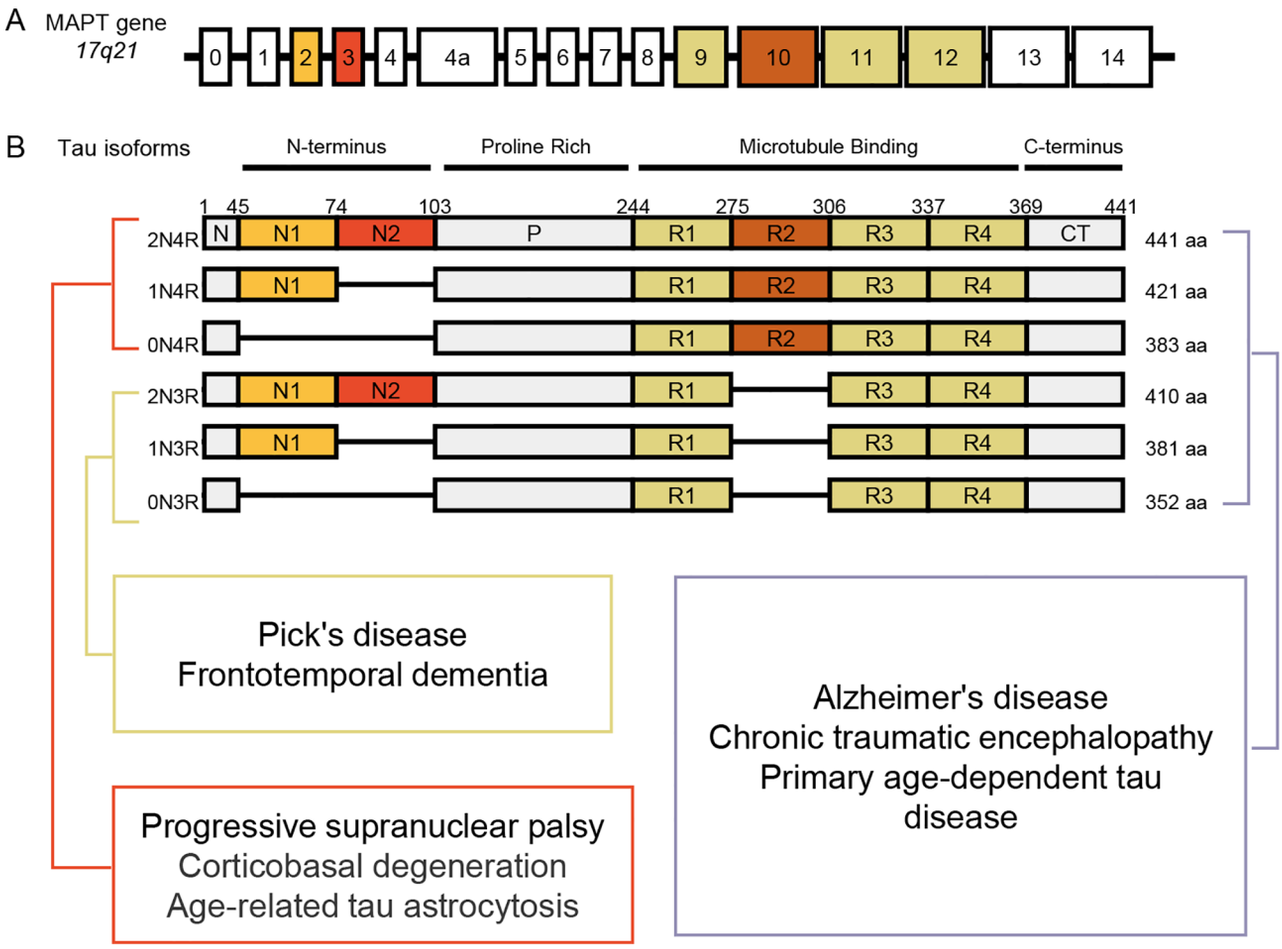


Figure 1 Schematic representation of human MAPT gene structure

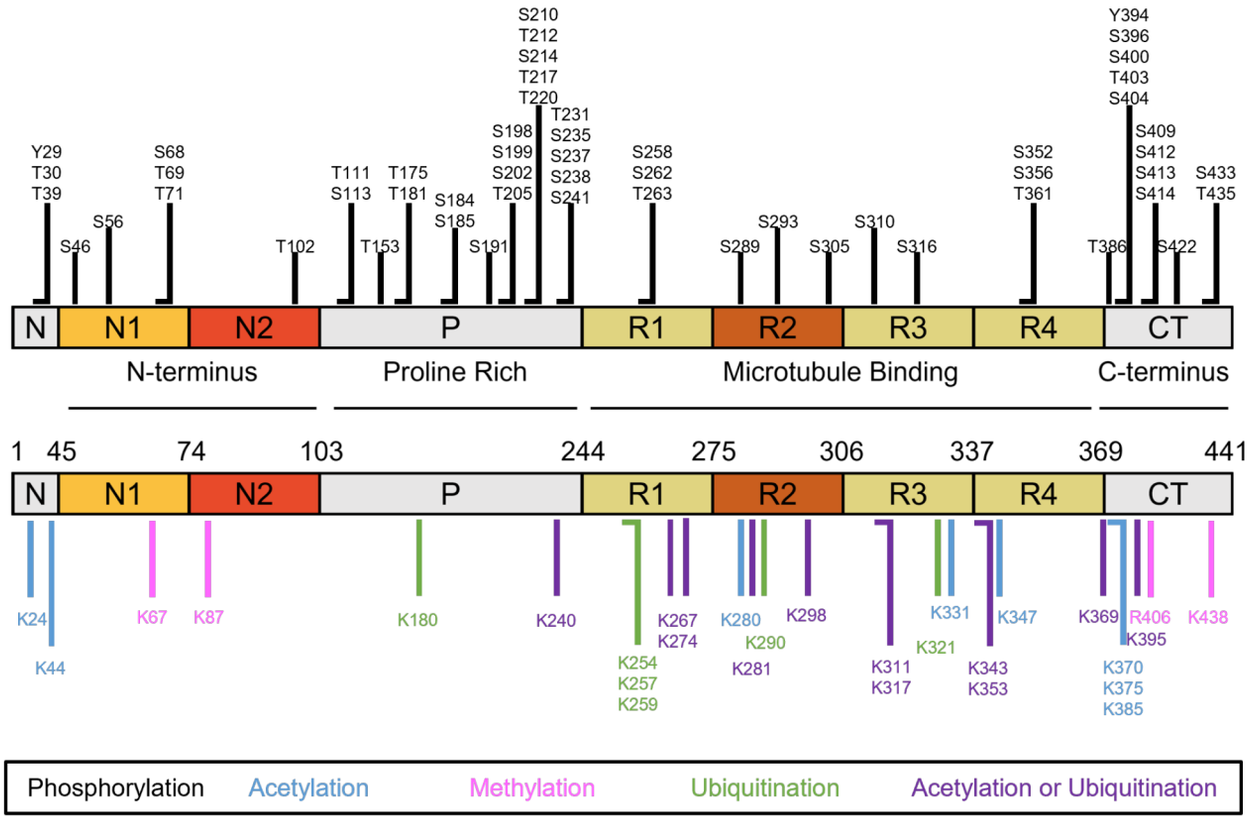
A: *MAPT* gene, located on chromosome 17q21, is composed of at least 16 exons. B: Alternative splicing of exons 2, 3, and 10 in *MAPT* pre-mRNA generates six isoforms. These give rise to different subtypes of tauopathy.

et al., 2022). Conversely, 3R tau preferentially undergoes lysine acetylation at K274 and K281, which impairs ubiquitin-proteasomal degradation and indirectly amplifies p-tau accumulation (Wesseling et al., 2020). While these observations suggest that 3R:4R imbalance directly modulates PTM landscapes, definitive evidence in human neurons remains limited. Future studies addressing this gap are essential to establish a mechanistic foundation for p-tau isoform-targeted precision therapeutics.

POST-TRANSLATIONAL MODIFICATIONS OF TAU

Tau undergoes extensive PTM, with at least 95 distinct PTM sites identified in AD brains, including acetylation (Cohen et al., 2011), glycosylation (Liu et al., 2002), ubiquitination, and proteolytic truncation (Cripps et al., 2006) (Figure 2). These modifications exhibit dynamic progression across disease stages: In early Braak stages I–III phosphorylation predominates within the PRR (e.g., T181, S231) and at C-terminal sites such as S396. As pathology advances to Braak IV–V stages, phosphorylation emerges within the MBD (e.g., S262/S263). By Braak stage VI, widespread accumulation of PTMs is observed, including acetylation (K353, K369) and ubiquitination (K259, K311) (Wesseling et al., 2020), constituting a complex pathological network. Crosstalk among PTMs occurs through steric hindrance, charge-based competition (e.g., K280 acetylation blocks S262 phosphorylation), and enzymatic feedback (GSK-3β-mediated phosphorylation suppresses HDAC6, elevating acetylation) (Brotzakis et al., 2021; Lovestone et al., 2015; Zhou et al., 2022). Site-specific phosphorylation events differentially regulate ubiquitination: phosphorylation at S396/S404 facilitates recruitment of the CHIP E3 ligase to promote tau degradation, whereas phosphorylation at T231 structurally masks ubiquitination motifs, with USP10 ubiquitination further stabilizing aggregates. (Ferrer et al., 2003; Liu et al., 2024; Wei et al., 2022). These modifications collectively influence tau solubility, microtubule binding, and aggregation propensity (Šimić et al., 2016). The crosstalk between PTMs limits monotherapies, necessitating multi-target strategies that address dynamic modification tracking, kinase selectivity, and blood-brain barrier (BBB) penetration.

Targeting tau PTMs has yielded both non-immunotherapeutic and immunotherapeutic strategies. Kinase inhibitors such as GSK-3β-targeting Tideglusib and CDK5-targeting Seliciclib were developed to reduce tau hyperphosphorylation, but both were discontinued during Phase III trials due to suboptimal efficacy and safety concerns (Lovestone et al., 2015; Zhao et al., 2024). PP2A activators (e.g., sodium selenate) demonstrated significant reductions in phosphorylated and insoluble tau in transgenic mice, yet failed to translate in clinical Phase I/Ib trials (NCT01494883) (Corcoran et al., 2010; Malpas et al., 2016). Enhancers of O-GlcNAcylation, such as MK-8719, similarly failed in Phase III



Phosphorylation | Acetylation | Methylation | Ubiquitination | Acetylation or Ubiquitination

Modification	3R	4R	3R : 4R	Sites
Phosphorylation	PiD	PSP/CBD/ARTAG	AD/FTD-Tau/CTE	Ser/Thr/Tyr
Acetylation	PiD	PSP/CBD/ARTAG	AD/FTD-Tau/CTE	Lys
Ubiquitination		PSP/CBD	AD/FTD-Tau/CTE	Lys
Methylation		ARTAG	AD/FTD-Tau/CTE	Lys

Figure 2 Post-translational modifications of *MAPT*

Phosphorylation (black), acetylation (blue), methylation (pink), ubiquitination (green), and shared acetylation or ubiquitination (purple) sites are indicated. Modifications implicated in tauopathy are enclosed in black boxes.

trials (NCT04088059) due to poor therapeutic benefit (Alhadidy et al., 2025). In contrast, passive immunotherapies involving anti-tau antibodies have advanced into late-stage clinical development, with multiple candidates in Phase II trials targeting distinct antigenic epitopes, including AADvac1 (targeting tau residues 294–305 in the PRR), ACI-35.030 (pS396/pS404), Gosuranemab (N-terminal), Tilavonemab (mid-domain), E2814 (MBD), and JNJ-63733657 (pS214) (Hickman et al., 2011; Novak et al., 2017). Concurrently, p-tau species in cerebrospinal fluid (CSF) and plasma—particularly T217 and T231—have been validated as early diagnostic biomarkers for tauopathy (Congdon et al., 2023), enabling preclinical identification of asymptomatic tau-positive individuals and offering a window for preventive intervention before overt neurodegeneration develops.

TAUOPATHIES AND TAU-ASSOCIATED NDs

Tauopathies represent a class of age-related NDs characterized by aberrant phosphorylation and pathological aggregation of tau (Wolfe, 2012). These conditions are broadly categorized as primary or secondary tauopathies based on whether tau pathology arises as a primary driver or a secondary consequence of other pathological processes (Imbimbo et al., 2022). Primary tauopathies, such as PSP, CBD, PiD, FTD, and FTDP-17 (Creekmore et al., 2024), are marked by the tau isoforms present and the extent of p-tau accumulation, often occurring independently of other protein pathologies (Lee et al., 2001). In PSP, NFTs composed predominantly of 4R tau appear in different brain regions, with neuronal and glial inclusions sharing immunohistochemical profiles with AD pathology (Matsusaka et al., 1998; Morris et al., 2002). These legions consist of tau-positive filamentous aggregates in neurons, oligodendrocytes, and astrocytes, accompanied by progressive neuronal loss and glial proliferation (Kouri et al., 2011). In contrast, PiD features argyrophilic tau-containing filamentous inclusions and pronounced degeneration within limbic

structures, including the hippocampus, entorhinal cortex (ERC), and amygdala (Guillozet-Bongaarts et al., 2007). Tau-immunoreactive neuronal inclusions and associated glial pathology are also prominent features, with insoluble tau aggregate mainly composed of 3R isoforms. Notably, phosphorylation at Ser262 is absent, suggesting isoform-specific heterogeneity in site-selective phosphorylation (Goedert et al., 1995).

Secondary tauopathies arise as downstream manifestations of other pathological processes (Lee et al., 2001). AD remains the most prevalent example, defined by the co-existence of NFTs and amyloid β (Aβ) plaque depositions. Aging-related tau astrogliopathy (ARTAG) comprises heterogeneous 4R tau accumulations within astrocytic subtypes, such as spiny astrocytes, thorn-shaped astrocytes (TSAs), and granular/fuzzy astrocytes (GFAs), distributed throughout subpial, subependymal, and perivascular regions of white and gray matter (Kovacs et al., 2016). TSAs, enriched in 4R p-tau, lack terminal truncation (Ferrer et al., 2003) and are immunoreactive to AT8 and 4R tau antibodies but not 3R-specific antibodies, with band detection in the sarcosine-insoluble fraction uniformly showing specific 4R bands. Chronic traumatic encephalopathy (CTE), a progressive disorder linked to repetitive mild traumatic brain injury (TBI), is characterized by deposition of NFTs and glial fibers in the neocortex (Costanza et al., 2011). Its tau inclusions comprise both 3R and 4R isoforms, with sparse deposits throughout the brain and spinal cord, neuronal loss in the hippocampus, and extensive extracellular tangles (Mckee et al., 2015).

Multiple lines of evidence now indicate that tauopathy can intersect with other disease modalities (Creekmore et al., 2024; Lantero-Rodriguez et al., 2024). Co-localization of tau with α-synuclein has been detected in the brains of patients with Parkinson's disease (PD) (Arima et al., 1999), with a significant correlation between tau levels in CSF and clinical manifestations (Hu et al., 2010). Genome-wide association studies (GWAS) have identified *MAPT* as a genetic risk factor for PD, implicating tau in disease susceptibility and progression (Edwards et al., 2010; Pan et al., 2021). In AD, approximately 57% of cases exhibit co-aggregation of TAR DNA binding protein-43 (TDP-43) (Davidson et al., 2011), a hallmark of an overlapping pathology spectrum. The co-occurrence of tau and TDP-43 aggregates in aged human brains has been repeatedly observed, yet it remains unclear whether these two pathologies develop independently or concurrently (Smith et al., 2018). Mechanistically, cytoplasmic accumulation of TDP-43 inhibits mitochondrial complexes, disrupting microtubule binding and axonal transport and thereby exacerbating mitochondrial and endoplasmic reticulum (ER) stress (Laclair et al., 2016). Loss of nuclear TDP-43 also dysregulates tau exon 10 splicing and increases 4R tau, thereby facilitating NFT formation (Estades Ayuso et al., 2023). In TBI models, TDP-43 mislocalization and hyperphosphorylated tau co-contribute to neuronal death, with genetic susceptibility (e.g., *C9orf72* mutations) exacerbating tau-induced TDP-43 aggregation (Lai et al., 2024). TDP-43 pathology enhances p-tau accumulation and facilitates seeding activity, worsening tau-mediated neurotoxicity and cell death (Tomé et al., 2023). ND progression is frequently driven by the co-accumulation of multiple pathogenic proteins, which—despite distinct identities—often originate under similar pathological conditions and thus may also exhibit similarities in their underlying mechanisms of deterioration.

ANIMAL MODELS OF TAUOPATHY

Rodents remain the most widely utilized laboratory models due to their amenability to genetic engineering, rapid breeding cycles, and low maintenance requirements (Wang et al., 2024). NHPs, however, offer distinct experimental advantages owing to their close genetic similarity to humans. Beyond the capacity to recapitulate human-like tau isoform expression, NHPs display neuroanatomical features—such as cellular composition, cortical organization, and glial diversity—that more closely resemble those of the human brain than rodent systems (Chen & Zhang, 2022; Pan et al., 2024). These differences are critical for modeling tauopathy, particularly in capturing the spatiotemporal dynamics of tau post-translational modifications. In the human brain, tau pathology progresses through a staged accumulation of phosphorylation, followed by enhanced acetylation and ubiquitination at late disease stages. Rodent models incompletely recapitulate this sequential PTM landscape, often lacking robust late-stage modifications (Oshima et al., 2024). Moreover, tau propagation in mouse brains typically occurs over a narrow temporal window and affects limited brain regions, whereas in humans, tau pathology disseminates over decades through complex neuronal circuits shaped by evolving microenvironmental conditions. NHPs exhibit propagation patterns that more closely approximate this physiological trajectory, highlighting their translational relevance for mechanistic research.

Researchers have developed various models of tauopathy in recent years, including naturally occurring, genetically modified, and chemically induced systems. Rodent models, though widely used, face intrinsic limitations in recapitulating human tauopathies. Fundamental interspecies differences in synaptic architecture, neuronal subtype composition, and glial-mediated neuroinflammatory responses impair the fidelity of rodent models in capturing disease-relevant features (Arnsten et al., 2019). Adult mice exclusively express the 4R tau isoform, lacking the balanced 3R/4R expression observed in humans (Waheed et al., 2023). Transgenic mouse lines carrying mutations such as P301S or P301L often overexpress human tau to non-physiological levels, resulting in aberrant subcellular localization and artificial aggregation patterns (Ramsden et al., 2005). Furthermore, the short lifespan of rodents accelerates pathological manifestations. While PS19 mice recapitulate tau phosphorylation and early aggregation, they fail to develop mature NFTs characteristic of human tauopathies (Yukawa et al., 2023). Similarly, SHR24 rats require exogenous seeding to induce tau pathology, reflecting an absence of endogenous aggregation cascades, diverging from the decadal progression of human disease (Valachova et al., 2018). In contrast, NHP models offer superior anatomical and molecular fidelity. Intracerebral administration of mutant human tau into the ERC of rhesus monkey induces progressive pathology that faithfully replicates human-like pathological propagation patterns, neuroinflammatory cascades, and region-specific neuronal loss (Beckman et al., 2024; Jiang et al., 2024), establishing a physiologically relevant platform for studying tau-mediated neurodegenerative cascades.

Rodent models of tauopathy (rTg4510, JNPL3, pR5, PS19, Tau58/2, SHR24, and SHR72)

Over 50 pathogenic mutations in the *MAPT* locus have been identified in patients with FTD with parkinsonism linked to chromosome 17 (FTDP-17), predominantly clustered within the MBD of tau. Transgenic mouse models carrying exon 10

mutations (e.g., P301L/P301S) have been instrumental in recapitulating core pathological features of tauopathy, including tau hyperphosphorylation, oligomer formation, and NFT accumulation. These models exhibit diverse neurodegenerative phenotypes such as cognitive deficits, motor dysfunction, and neuroinflammation. In addition to exon 10, mutations in exons 9 (G272V), 11 (V337M), and 13 (R406W) have been introduced to investigate mechanistic aspects of tau-mediated toxicity and to assess candidate therapeutics (Brandt et al., 2005; Poorkaj et al., 1998; Spillantini et al., 1998). The preferential use of rodent models stems from their rapid reproduction cycles and cost-effectiveness (Table 1).

The JNPL3 mouse model expresses the 0N4R isoform of human tau with the P301L mutation under the regulation of the murine prion promoter (MoPrP), resulting in tau protein expression levels approximately double those of endogenous tau in hemizygous mice. Neuropathological manifestations primarily occur in the spinal cord and brainstem, characterized by progressive motor deficits (Lewis et al., 2000). Early signs of motor impairment emerge by 4.5 months, with pronounced locomotor dysfunction evident by 10 months. Histological examination reveals extensive NFT deposition across the brainstem, basal ganglia, spinal cord, and cerebellum, reflecting an anatomical distribution similar to that observed in FTDP-17 patients (Lin et al., 2005; Sahara et al., 2014). Notably, this model uniquely demonstrates gait initiation failure (GIF), a phenotype relevant to motor-dominant tauopathies in humans (Jang et al., 2019), providing a valuable platform for investigating mechanisms of lower motor neuron vulnerability. However, the relative paucity of cortical pathology in JNPL3 mice limits its utility in modeling cortical tauopathies such as AD and FTD.

The rTg4510 mouse model utilizes a forebrain-specific CaMKIIα-driven tetracycline-controlled transactivator (tTA) system to overexpress human 0N4R tau harboring the P301L mutation, achieving expression levels approximately 13-fold higher than endogenous murine tau (Santacruz et al., 2005). This model exhibits a rapid, age-dependent progression of tau pathology that parallels key features of human neurodegeneration. Tau misfolding and pre-tangle conformers appear in cortical neurons by 2.5 months, followed by robust NFT formation by 4 months and substantial forebrain atrophy by 10 months (Ramsden et al., 2005). Behavioral deficits, particularly impairments in spatial learning and memory, exhibit

Table 1 Tau transgenic mouse models

Model	Isoform-mutations	Modification	Expression pattern	Tangles (months)	Gliosis (months)	Neuronal loss (months)	Synaptic loss (months)	Behavior/cognition (months)	References
rTg4510	0N4R-P301L	CaMKIIα transgenic	Spinal cord, brainstem, cerebellum	2.5	NA	5.5	8	2.5	Ramsden et al., 2005; Santacruz et al., 2005
JNPL3	0N4R-P301L	MoPrP transgenic	Cortex, hippocampus	4.5	10	10	NA	4.5	Jang et al., 2019; Lewis et al., 2000; Lin et al., 2005; Sahara et al., 2014
pR5	2N4R-P301L	MurineThy1.2 transgenic	Hippocampus, amygdala	6	3	NA	NA	NA	Bodea et al., 2017; Götz et al., 2001a; Hatch et al., 2017; Pennanen et al., 2006
PS19	1N4R-P301S	MoPrP.Xho transgenic	Hippocampus, brainstem, cortex	5	3	8	6	6	Takeuchi et al., 2011; Yoshiyama et al., 2007
Tau58/2	0N4R-P301S	MurineThy1.2 transgenic	Spinal cord, prefrontal cortex	3	NA	NA	NA	6	Kreilaus et al., 2021; Van Eersel et al., 2015
Tau G272V	hTau40-G272V	Murine prion protein (PrP)	Spinal cord oligodendrocytes and motor neurons	6	NA	NA	NA	NA	Götz et al., 2001a
Tau R406W	hTau40-R406W	CaMKIIα transgenic	Hippocampus (areas CA1, CA2), neocortex, amygdala, striatum, olfactory bulb	18	NA	NA	NA	16-23	Tatebayashi et al., 2002
Tau V377M	hTau40-V377W	PDGF transgenic	Hippocampus, cortex	11	NA	15	NA	11	Tanemura et al., 2001, 2002
Ala152Thr-Tau	hTau40-A152T	Murine Thy1.2 transgenic	Hippocampus, cortex, cerebellum, spinal motor neurons, basal ganglia	5	10	16	12	16	Sydow et al., 2016
hTau	Only hTau (knockout of endogenous mouse tau)		Hippocampus, neocortex, internal olfactory cortex, ventromedial hypothalamus, medial septal nucleus, basal ganglia	9	NA	NA	NA	NA	Andorfer et al., 2003

NA: Not available.

a temporal correlation with pathological progression, as demonstrated by performance decline in the Morris water maze. The accelerated tauopathy timeline renders this model suitable for preclinical therapeutic testing, including evaluation of compounds such as BSc3094, which reduce tau aggregation *in vivo* (Pickhardt et al., 2007). However, genomic artifacts introduced during transgenesis (e.g., *Fgf14* deletion) may compromise phenotype specificity, necessitating cautious interpretation of experimental results (Gamache et al., 2019). Transcriptomic profiling of hippocampal tissue from rTg4510 mice has revealed gene co-expression networks enriched in neurodegenerative signatures. Tyrosine kinase-binding protein (TYROBP) and CD68—markers of microglial activation—emerge as central nodes in these networks, implicating immune signaling cascades in tau-mediated degeneration. Notably, *TYROBP* encodes a co-receptor for *TREM2*, a known AD risk gene, and its expression trajectory in this model correlates with both aging and tau pathology (Wesseling et al., 2020).

The pR5 transgenic mouse model was engineered to express the 2N4R isoform of human tau bearing the P301L mutation under the control of the murine Thy1.2 promoter. This model exhibits a slow-developing tauopathy, with p-tau deposits detected in CA1 pyramidal neurons of the hippocampus as early as 3 months of age, followed by the onset of spatial memory deficits around 6 months, as measured by behavioral assays (Götz et al., 2001a; Hatch et al., 2017). Robust NFT pathology becomes prominent in basolateral amygdala by 18 months (Deters et al., 2008). Notably, this model exhibits moderate tauopathy severity without overt neurodegeneration (Götz et al., 2001a; Hatch et al., 2017), making it particularly suitable for studying early molecular events, including synaptic plasticity dysregulation, glial activation, and neuroinflammation. However, the extended timeline required for NFT formation (>18 months) imposes constraints on studying late-stage pathology and necessitates long-duration experimental designs (Bodea et al., 2017).

The PS19 mouse model expresses the 1N4R isoform of human tau carrying the P301S mutation under the control of the MoPrP, and exhibits a robust, temporally distinct pattern of tau-mediated neurodegeneration (Yoshiyama et al., 2007). Initial phenotypes include hippocampal synaptic dysfunction and microgliosis, with synaptic loss, impaired synaptic transmission, and axonal transport defects in hippocampal circuits by 3 months. By 6 months, widespread astrogliosis becomes evident in the hippocampus, amygdala, ERC, and brainstem, followed by a marked increase in microglial proliferation by 8 months. These glial activation events correlate temporally with NFT accumulation and astrocytic morphological changes (Takeuchi et al., 2011). Notably, insoluble tau aggregates display age-dependent accumulation, with NFT-like inclusions observed at 5 months using Gallyas silver staining. This model highlights a neuroinflammatory cascade, in which microglial activation precedes overt NFT formation (Yoshiyama et al., 2007). Mechanistic studies have implicated CCR5-mediated mTORC1 activation via PI3K-AKT-TSC2 signaling in autophagy inhibition and promotion of tau aggregation (Festa et al., 2023), establishing PS19 as a valuable platform for studying inflammation-pathology crosstalk However, the rapid disease progression and median survival of approximately 9 months limit its utility for modeling chronic tauopathy (Yoshiyama et al., 2007), though it remains well suited for short-term therapeutic intervention studies.

The Tau58/2 mouse model expresses the 0N4R isoform of human tau with the P301S mutation under the control of the murine Thy1.2 promoter and exhibits a regionally distinct trajectory of tau pathology. NFTs first emerge in the spinal cord and later spread to the prefrontal cortex, while the hippocampus remains relatively unaffected, resulting in delayed cognitive deficits. Motor impairments are more pronounced in males, with early onset at 6 months and overt locomotor dysfunction in both sexes by 10 months (Kreilaus et al., 2021). Between 3 and 10 months, tau pathology progressively expands to the cerebral cortex and brainstem, accompanied by gradual increases in phosphorylated and insoluble tau, with male mice displaying greater NFT burden than females (Van Eersel et al., 2015). This model is particularly suitable for exploring sex-specific mechanisms of tau toxicity. Additionally, electrophysiological analyses reveal neuronal hyperexcitability and abnormal long-term potentiation (LTP) in this model (Przybyla et al., 2020), making it valuable for probing tau-induced synaptic and circuit-level dysfunction. However, the lack of hippocampal involvement limits its relevance for studying core features of AD and related tauopathies affecting limbic circuits.

The Ala152Thr-Tau mouse model expresses human 2N4R tau carrying the A152T mutation under the murine Thy1.2 promoter. It recapitulates key pathological features reminiscent of AD and PSP, including widespread tau phosphorylation, aggregation, synaptic degeneration, and neuroinflammation across multiple brain regions such as the hippocampus, cortex, cerebellum, spinal motor neurons, and basal ganglia-associated structures. Cognitive decline emerges in parallel with neuroinflammatory activation and impaired autophagic flux, while proteasomal dysfunction appears to contribute to late-stage neuronal death. This model provides a robust platform for investigating tau-induced cellular toxicity and evaluating neuroprotective therapies (Sydow et al., 2016).

The hTau mouse model is generated by crossing human tau-expressing 8c mice with *MAPT*-knockout (*MAPT*-KO) mice. This model predominantly expresses 3R isoforms and spontaneously recapitulates early-stage AD-like tau pathology independent of Aβ. Its spatiotemporal distribution and molecular characteristics, including tau phosphorylation, conformational abnormalities, and paired helical filaments (PHFs), closely mirror human AD pathology. Ultrastructural analysis via transmission electron microscopy has revealed PHFs with high morphological fidelity to those observed in AD brains, supporting its relevance for studying tau pathogenesis and screening candidate therapeutics (Andorfer et al., 2003).

The *MAPT*-KO mouse model, generated through targeted disruption of exon 1 of *MAPT* under endogenous promoter regulation, results in complete depletion of endogenous murine tau expression. Pathological manifestations are most pronounced in small-caliber axons, such as cerebellar parallel fibers, which exhibit reduced microtubule density, impaired cross-linking, and decreased cytoskeletal stability, while large-caliber axons remain largely unaffected due to compensatory up-regulation of microtubule-associated protein 1A (MAP1A). Developmental abnormalities emerge from embryonic day 14.5 (E14.5) through postnatal day 30 (P30), with the hallmark feature being disorganized microtubule architecture in cerebellar axons, despite the absence of overt neurodegeneration or behavioral deficits. This model highlights the indispensable role of tau in stabilizing microtubules within specific axonal populations, while compensatory mechanisms mediated by other microtubule-associated proteins may

obscure phenotypic severity. Owing to its lack of widespread neurodegenerative features, the *MAPT*-KO model exhibits utility for studying tau-dependent microtubule dynamics rather than tauopathy progression (Harada et al., 1994; Tucker et al., 2001).

Promoter-driven systems targeting tau expression to defined cell types have enabled the generation of region- and cell type-specific models. In one such model, the murine prion promoter combined with an autoregulatory transactivator loop drives high-level expression of G272V-mutant 2N4R tau in neurons and oligodendrocytes, effectively recapitulating glial tau pathology characteristic of PSP, CBD, and FTDP-17 (Götz et al., 2001b). Similarly, transgenic expression of R406W-mutant tau under control of the CaMKIIα promoter restricts pathology to forebrain neurons, resembling the tau pathology observed in AD (Tatebayashi et al., 2002). In another construct, the V377M tau mutation is selectively expressed in the hippocampus, with total hTau levels maintained at less than 10% of endogenous tau expression. Phosphorylated tau aggregates become detectable by 6 months (Tanemura et al., 2001, 2002), providing a model for localized, low expression tauopathy.

To better characterize the pathology of diseases such as AD, mouse models incorporating extracellular accumulation of Aβs and NFTs have been developed (Serrano-Pozo et al., 2011). Among these, the 3×Tg mouse model harbors familial AD-associated mutations in human *APP*, *PS1*, and *MAPT*. While these models closely mimic the clinicopathological manifestations of AD, they exhibit poor exogenous gene stability, making them challenging to generate and expensive to maintain (Boutajangout et al., 2002; Oddo et al., 2003).

Transgenic rat models have emerged as valuable tools for dissecting isoform-specific mechanisms underlying tau-mediated neurodegeneration. The SHR24 and SHR72 lines, developed by Norbert Zilka and colleagues, express human truncated tau (amino acids 151–391), corresponding to 3R and 4R isoforms, respectively (Valachova et al., 2018). In SHR24 rats, p-tau (AT8+) localizes to the hippocampus and ERC by 3–6 months. As pathology advances, NFTs propagate to the cortex and striatum by 9–12 months, accompanied by neuronal loss. While Filipcik et al. (2012) reported preserved neuronal populations in the neocortex, brainstem, and hippocampus of SHR24 rats, independent studies by Koson et al. (2008) and Mravec et al. (2016) identified significant neuronal loss in the motor cortex, indicating differential vulnerability of brain regions to tau pathology. SHR24 rats also exhibit progressive cortical degeneration, extensive spinal cord and brainstem tau pathology, and pronounced accumulation of NFTs in the motor cortex. This is accompanied by activation of microglia and astrocytes, up-regulation of proinflammatory factors (IL-6, TNF-α), and cognitive impairments such as memory deficits (Koson et al., 2008; Mravec et al., 2016). In contrast, SHR72 rats develop more aggressive pathology, with widespread tau aggregation in the brainstem, deep cerebellar nuclei, and spinal cord. This is also associated with a significantly reduced lifespan relative to SHR24 rats (Koson et al., 2008). Both models exhibit key histopathological hallmarks of human tauopathy, including argyrophilic inclusions, Congo red birefringence, and thioflavin S positivity (Zilka et al., 2006). Their divergent regional vulnerability and isoform-specific phenotypes provide a comparative framework for investigating the distinct contributions of 3R and 4R tau species to disease progression.

Recent advances in transgenic animal models have emphasized both refinement of established mouse lines and the development of novel rat mutation-based systems. Extensive characterization of traditional P301L/P301S mouse models, such as JNPL3 and rTg4510, has clarified their pathological phenotypes, temporal kinetics, and translational relevance. Notably, rTg4510 mice exhibit age-dependent tau accumulation and forebrain atrophy, mimicking key features of human neurodegeneration, while transcriptomic analyses have uncovered hippocampal gene expression networks linked to AD. Beyond exon 10 mutations, newly engineered models carrying *MAPT* mutations in exons 9, 11, and 13 expand the tools available for mechanistic dissection. Concurrent progress in rat model development, exemplified by the SHR24 and SHR72 lines expressing distinct tau isoforms, have enabled region-specific mapping of tau pathology and provided a platform for exploring isoform-dependent mechanisms of 3R and 4R tau. These advancements reflect a broader shift toward mechanistic precision in tauopathy research, with integrated multi-model approaches facilitating deeper study of the molecular underpinnings of tauopathy pathogenesis.

Non-human primate models of tauopathy

NHPs used in ND research primarily belong to the genus *Macaca*, including *Macaca mulatta* and *Macaca fascicularis* (Didier et al., 2016; Lane, 2000). These species exhibit highly conserved neuroanatomical circuitry, cognitive function, emotional expression, and motor coordination that closely resemble human physiology (Amiez et al., 2019; Van Essen et al., 2019; Ledoux, 2003; Phillips et al., 2014), highlighting the critical role of NHPs in biomedical research across neurodegenerative disorders, aging biology, and immune system dynamics (Table 1).

In contrast to wild-type rodents—where endogenous tau fails to form NFTs, likely due to limited sequence homology (88%) with human tau—tau expressed in NHPs shares over 98.5% homology in rhesus macaques and exceeds 99% in gorillas (Andorfer et al., 2003; Drummond & Wisniewski, 2017; Perez et al., 2013). Importantly, tau isoform expression patterns in primate brains closely parallel those in humans, with both 3R and 4R isoforms expressed in both species (Capano et al., 2022). Furthermore, cortical areas vulnerable to tau pathology in humans, such as the prefrontal cortex, exhibit similar structural susceptibilities in NHPs, including developmental hypoplasia and regional connectivity profiles linked to tau-related diseases like AD and FTLD (Petrides et al., 2012; Preuss, 1995). As such, NHPs serve as a crucial translational bridge between rodent models and human neuropathology, offering higher fidelity for modeling disease progression and therapeutic response.

Tu et al. (2023) generated the first transgenic tauopathy model in cynomolgus monkeys using lentiviral-mediated delivery of mutant human tau (0N4R-P301L) into pre-implantation monkey embryos (Table 2). The transgene, driven by a murine prion promoter and tagged with an N-terminal FLAG epitope, induced robust tau pathology by 39 months, including spinal cord Aβ oligomer accumulation, neurodegeneration, and decreased brain metabolic activity. Behavioral deficits were particularly pronounced between 38 and 42 months, characterized by a progressive decline in fine motor coordination. Histopathological examination revealed reduced neuronal density and reactive gliosis in the prefrontal cortex, striatum, hippocampus, and spinal cord, with the Tau1 monkey displaying the most severe pathology. The *MAPT* mutant monkey model exhibited pronounced motor deficits,

accompanied by a robust inflammatory response, indicating that the expression of mutant tau led to substantial behavioral and pathological impairments. Notably, endogenous Aβ oligomers accumulated selectively in the spinal cord of transgenic monkeys but not in other brain regions or in the AAV9-hTau (P301L) mouse model. This species- and region-specific induction of Aβ oligomers implicates human tau as a driver of endogenous amyloidogenic processes uniquely in NHPs (Figure 3). These findings provide the first evidence linking tau expression to endogenous Aβ formation in primate systems and uncover a complex pathological interaction between tau and amyloid pathways that is absent in rodent models. However, the mechanisms underlying this phenomenon require further investigation.

Complementing these findings, Beckman et al. (2021) developed a tauopathy model by delivering AAV vectors carrying P301L/S320F mutations of *MAPT* into the ERC of rhesus monkeys. NFTs were detectable by AT100 immunoreactivity within one month, with abnormal p-tau accumulation and hippocampal propagation evident 3 months later. Tau pathology continued to develop over time, mirroring human-like spreading dynamics. This model also identified myeloid cell triggering receptor 2 (*TREM2*)-positive microglia as key effectors of tau pathology, driving a shift toward reactive phenotypes and exacerbating neuroinflammation. More recently, Jiang et al. (2024) developed an AD-like tauopathy model through AAV9-mediated delivery of human 2N4R tau into the bilateral hippocampus of rhesus monkeys. This single-injection strategy induced all six hTau isoforms and triggered hallmark features of tauopathy within 2–3 months, including extensive accumulation of p-tau, hippocampal atrophy, and severe neural degeneration. Notably, astrocyte and microglial activation increased 2.5- to 4-fold and 2.5- to 3.5-fold, respectively, across the hippocampus. This model also recapitulated key aspects of amyloid pathology, including impaired Aβ clearance and enhanced accumulation, potentially mediated by tau-driven endosomal entrapment of APP/BACE or AQP4-mediated disruption of perivascular and glymphatic clearance mechanisms (Paspalas et al., 2018; Sadleir et al., 2016; Simon et al., 2022). Together, these NHP models represent a critical advancement in the field, offering a dynamic and biologically relevant framework for exploring tau pathogenesis, Aβ interactions, neuroinflammatory circuits, and therapeutic efficacy in a species with unparalleled proximity to

Table 2 Tau NHP models

Method	Isoform-Mutations	Tangles (months)	Gliosis (months)	Neuronal loss (months)	Aß oligomer (months)	Behavior/Cognition (months)	References
Lentiviral transduction	0N4R-P301L	37	37	37	37	38-42	Tu et al., 2023
AAV viral injection	2N4R-P301L	1.5	6	6	NA	NA	Jiang et al., 2024
AAV viral injection	0N4R-P301L/S320F	2	2	NA	NA	NA	Beckman et al., 2021

NA: Not available.

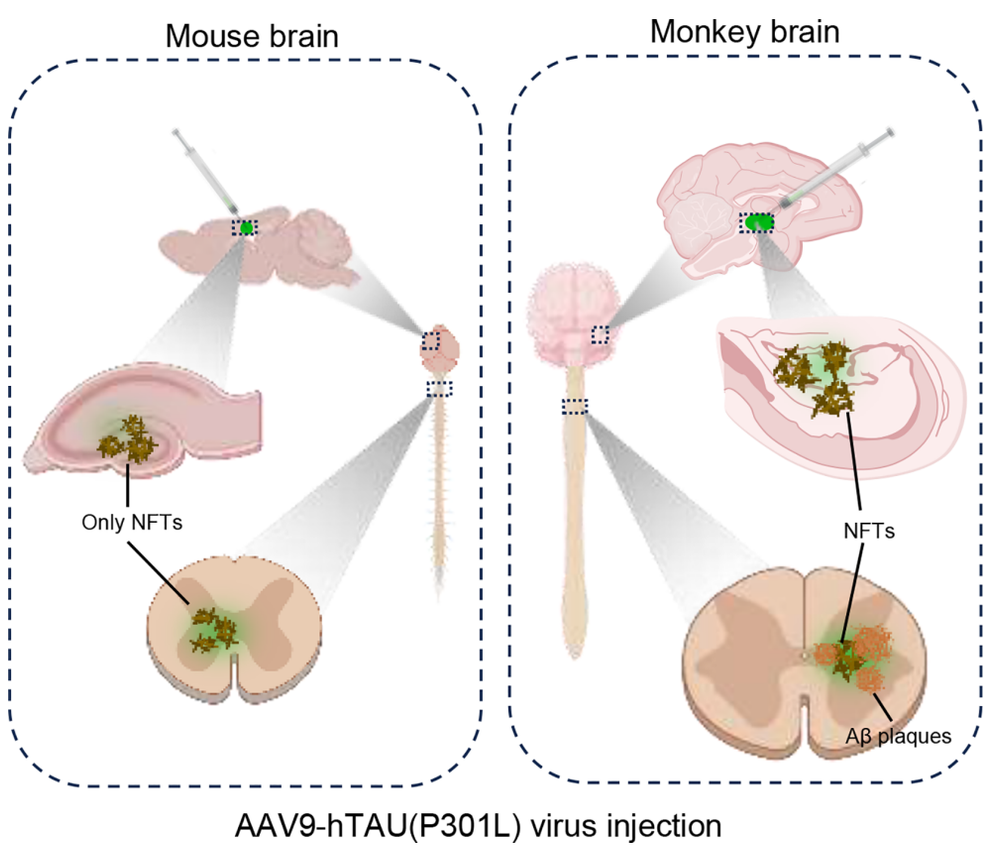


Figure 3 Generation of Aβ oligomers is species- and brain region-specific

Aβ aggregation is induced exclusively by the mutant hTau (P301L) expression in the spinal cord of monkeys, but not in the hippocampus. Green hexagon symbolizes AAV9-hTau (P301L) virus, which drives tau protein accumulation, while brown plaques represent resulting Aβ aggregates.

human disease biology.

Aging monkey models of tauopathy

Clinical diagnosis typically occurs at advanced disease stages, when significant neuropathology has already developed and is often accompanied by cognitive decline and behavioral disturbances. In contrast, the preclinical phase—spanning several decades—is characterized by progressive pathological accumulation without overt cognitive symptoms (Dubois et al., 2016; Van Der Kant et al., 2020). Aged rodents (mice >18 months; rats >24 months) generally exhibit age-dependent changes but fail to develop key AD-like features such as senile plaques or NFTs. In contrast, aged monkeys (>16 years) naturally develop early-stage AD-like pathology, including both amyloid plaques and NFTs (Freire-Cobo et al., 2021; Neils-Strunjas et al., 2006; Song et al., 2009), making them more suitable models for investigating the molecular and cellular mechanisms of brain aging.

Initial evidence from aged chimpanzee brains revealed tau-positive plaques and neurofibrillary filaments localized to neocortical regions (Rosen et al., 2008), indicating that age-related tauopathies in primates may proceed via mechanisms conserved with human disease. Aged rhesus monkeys (4.5–38 years) also develop AD-like tau pathology, including NFTs that progress spatiotemporally to Braak stage III, with p-tau emerging later in association cortices than in the ERC, recapitulating the hierarchical spread observed in human AD (Arnsten et al., 2019; Paspalas et al., 2018). Similar age-associated tau pathology has been observed in black-tailed monkeys (Frye et al., 2021), while common marmosets display progressive neurofibrillary changes, with p-tau detectable even in young individuals and within microglia (Rodriguez-Callejas et al., 2017). Aging African green-tailed monkeys exhibit AD-like transcriptional signatures in prefrontal and visual cortices, accompanied by spontaneous p-tau accumulation (Cramer et al., 2018). Among these species, the common marmoset is particularly advantageous due to its manageable size, complex brain architecture, and natural age-related aggregation of Aβ and p-tau (Perez-Cruz & Rodriguez-Callejas, 2023). Marmoset brains co-express 3R and 4R isoforms and exhibit aberrant tau hyperphosphorylation at AD-characteristic sites, independent of age, as validated by proteomic and transcriptomic analyses (Huhe et al., 2024). This non-transgenic primate model uniquely recapitulates core features of AD, providing a critical platform for mechanistic and therapeutic studies.

Naturally aged NHPs provide a biologically relevant platform for modeling tauopathy progression and elucidating its underlying mechanisms. The high sequence and structural homology between NHP and human tau, combined with comparable patterns of brain aging, position NHPs as superior models for tauopathy research. The transition from young adulthood (>5 years) to midlife (<15 years) in monkeys may represent a critical window during which age-related tau pathology accelerates, offering unique opportunities for longitudinal investigation.

CONCLUSIONS

Recent advances in tauopathy research have illuminated molecular mechanisms underpinning disease progression and catalyzed the development of increasingly sophisticated animal models, with NHPs emerging as pivotal systems for translational neuroscience. While murine models remain indispensable in preclinical research due to their rapid generation and cost efficiency, they exhibit critical limitations in capturing the complexity of human tauopathies. Despite effectively recapitulating early-stage features such as hyperphosphorylated tau and mild cognitive deficits (Davidowitz et al., 2023; Valachova et al., 2018), they inadequately reflect advanced human-specific PTMs, including ubiquitination and acetylation, and fail to model progressive neurodegeneration within complex neural networks. Therapeutic interventions that reduce p-tau in rodents often lack clinical translatability, constrained by interspecies metabolic heterogeneity and compensatory signaling pathways in the human central nervous system. Furthermore, overexpression of mutant tau in these models induces gain-of-function phenotypes without replicating hallmark NFT formation or substantive neuronal loss—limitations attributed to species-specific tau resistance and truncated rodent lifespans. The absence of endogenous 3R tau further restricts modeling of PiD or AD-related 3R/4R isoform imbalances central to certain NDs. Although genome-edited mice expressing all six human tau isoforms enable propagation studies, they remain insufficient for investigating Aβ-tau crosstalk critical to AD pathogenesis (Han et al., 2025; Hosokawa et al., 2022) (Figure 4).

In contrast, NHPs offer superior neuroanatomical and molecular homology, including spontaneous age-related co-aggregation of Aβ and tau (Huhe et al., 2024; Jiang et al., 2024). Endogenous expression of all six tau isoforms, together with conserved AD-like phosphorylation profiles, permits modeling of disease-relevant tauopathies without reliance on transgenic manipulation (Perez-Cruz & Rodriguez-Callejas, 2023). Recent NHP studies have revealed rapid hippocampal atrophy and motor deficits upon mutant tau overexpression, mirroring late-stage AD pathology within weeks (Jiang et al., 2024; Tu et al., 2023). These models provide valuable insight into tau-induced neurodegeneration and its intersection with Aβ pathology, which appears region- and species-specific. However, ethical considerations, extended maturation periods, and technical bottlenecks in germline editing constrain widespread adoption. Advances in viral vector systems, including chemogenetic tools and retrograde circuit tracers, will facilitate propagation dynamics and therapeutic modulation. Notably, pioneering work by Chen et al. (2023) has demonstrated the therapeutic potential of chemogenetic striatal modulation in NHP models of PD—a strategy adaptable to tauopathy research. Emphasis should also be placed on recapitulating non-motor symptoms by establishing refined behavioral assessment systems and emotional evaluation scales to enhance clinical phenotype relevance.

Integration of organoid models with organ-on-a-chip microfluidic systems offers a promising direction to better recapitulate the physiological microenvironment and monitor pathological progression in real time (Mitrofanova et al., 2024). CRISPR-engineered induced pluripotent stem cell (iPSC)-derived organoids could enhance disease-specific modeling (Parra Bravo et al., 2024) by incorporating patient-derived mutations, such as P301S *MAPT*, to study isoform-specific aggregation mechanisms. Standardized protocols for long-term culture and vascularization are also critical for improving organoid maturity, as demonstrated in bioengineered “mini-colon” systems.

Future convergence of gene-editing technology, organoid platforms, and multi-omics profiling is expected to bridge translational gaps between model systems and human disease, offering a robust framework for the precise treatment of

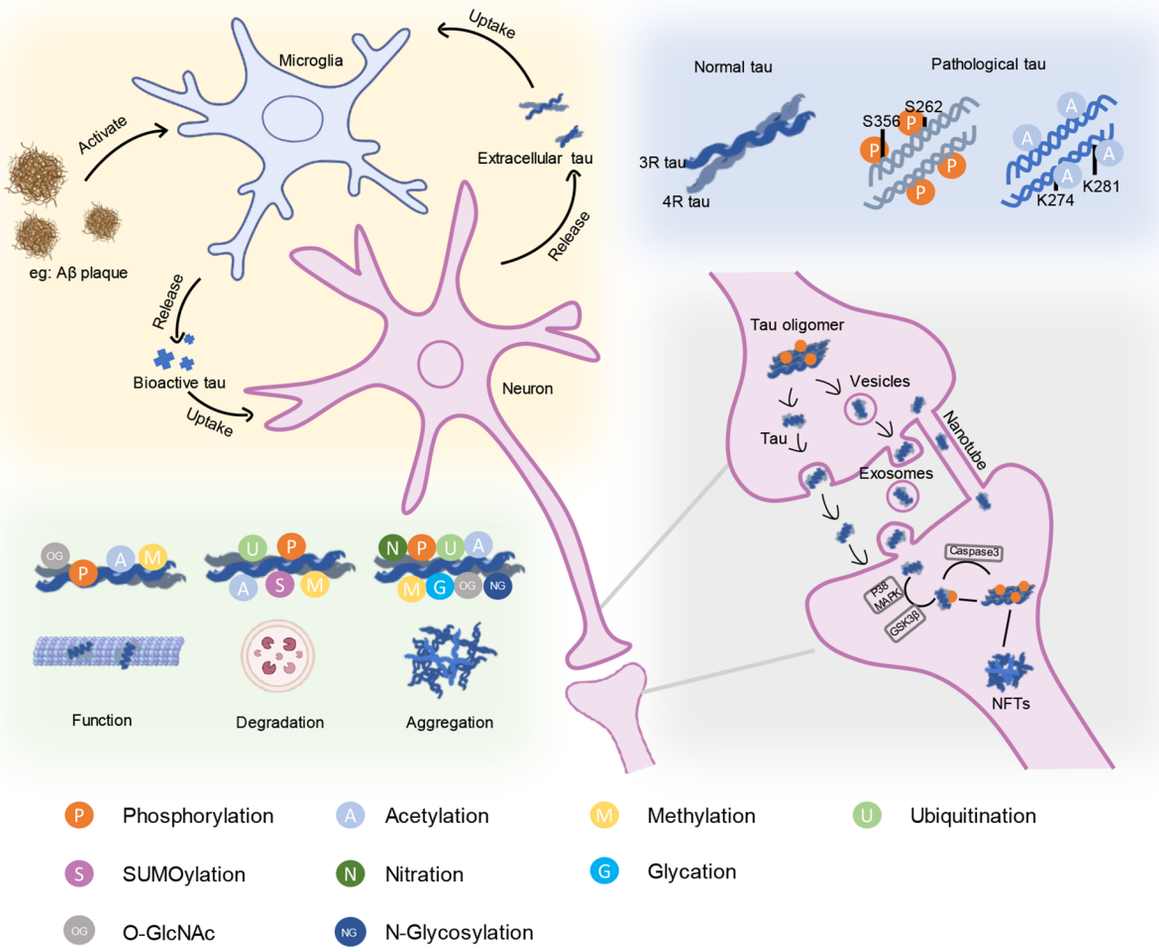


Figure 4 Schematic representation of key aspects of tau pathology

Illustrated processes include: the influence of other pathologies (e.g., Aβ plaques) on tau aggregation; isoform imbalance-driven pathological modification by 3R and 4R tau; site-specific post-translational modifications (PTMs) regulating tau function, degradation, and aggregation; and mechanisms underlying trans-synaptic propagation of tau.

tauopathies. Identification of key molecular events within temporally defined intervention windows may guide the development of targeted strategies to halt or reverse tau-driven neurodegeneration.

COMPETING INTERESTS

The authors declare that they have no competing interests

AUTHORS' CONTRIBUTIONS

D.J.H. and X.Y.G.: Conceived the idea for this review. H.Z., M.T.P., and Y.X.L.: Drafted the manuscript. H.Z. and M.T.P.: Constructed figures and tables. D.J.H., X.Y.G., and X.J.L.: Revised the manuscript. All authors read and approved the final version of the manuscript.

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