Fetal Tau Bias in iPSC -Derived Neurons, MAPT Mutant Mouse Models and Molecular Mechanisms Assessment for Integrative Analysis of Tau Pathology

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ABSTRACT

Tauopathies, such as Alzheimer's disease and Frontotemporal Dementia, are caused by complex interactions between tau isoform imbalance, MAPT mutations, and harmful post-translational modifications. Despite significant breakthroughs, current human cellular models may not accurately reflect adult tau biology, limiting mechanistic knowledge and therapeutic translation. In this review, we draw on new knowledge from stem cell platforms, MAPT mutant mice models, and multi-omics investigations to identify important gaps and stakes in modeling tau pathology. Recent efforts using CRISPR-engineered human stem cell lines, NGN3-induced i3 neurons, and patient-derived iPSCs show great promise, but they consistently retain a fetal-like predominance of 3-repeat (3R) tau, limiting the ability to recapitulate adult 3R/4R tau ratios and age-associated tauopathy phenotypes. Organoid and multi-cell co-culture methods (such as RenVM and tri-cellular constructions) boost microenvironmental complexity, but are limited by developmental immaturity and variable tau isoform flipping. Complementary MAPT knock-in and transgenic mice models (e.g., P301L, P301S, V337M, S320F) provide robust in vivo mechanisms for tau misfolding, seeding, and propagation, while also revealing species-specific compensatory processes that differ from human neurodegeneration. At the molecular level, mass spectrometry based phosphoproteomics has revealed a coordinated network of tau post-translational modifications; phosphorylation, acetylation, and ubiquitination that converge on proline-rich and C-terminal regions to cause tau detachment from microtubules and aggregate. These findings highlight the necessity for integrated models that can capture both isoform regulation and combinatorial PTM landscapes. Together, these findings highlight a key translational gap that most human model systems fail to reach adult tau maturation, as animal models cannot fully mimic human-specific tau biology. We propose a paradigm that integrates sophisticated stem cell engineering, MAPT mutation-aligned mice models, and multi-omics profiling to create next-generation platforms for understanding tauopathy processes and accelerating therapeutics development.

Keywords: Tauopathy, Alzheimer’s disease, Frontotemporal Dementia, MAPT mutations, induced pluripotent stem cells (iPSCs), tau phosphorylation

INTRODUCTION

Alzheimer's disease (AD) and similar tauopathies are distinguished by aberrant aggregation of the microtubule-associated protein tau, which impairs neuronal function and causes neurodegeneration. While classic conceptions of AD emphasize the amyloid-β (Aβ) cascade, emerging evidence reveals a more complicated interplay between Aβ and tau disorders, suggesting that tau may actively contribute to disease progression, rather than just following amyloid. For instance, in a recently created APP^NL-G-

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F/MAPT^P301S double-knockin mice, researchers found that β-amyloid buildup increases tau pathology, inflammation, and neurodegeneration. This supports a synergistic paradigm where Aβ promotes tau misfolding and aggregation [1,2]. This model emphasizes the importance of combining amyloid and tau pathology in vivo to more accurately mimic human AD. Despite breakthroughs in animal models, applying findings from these systems to human disease remains difficult. A detailed mass-spectrometry-based comparison of tau post-translational modifications (PTMs) revealed that commonly used tauopathy mouse models (such as the P301S and P301L mutant lines) mimic early phosphorylation events in human disease but fail to reflect late-stage modifications, such as ubiquitination and acetylation, which are common in advanced Alzheimer's [3]. This gap highlights the critical need for models that better reproduce the entire spectrum of tau disease. Another dimension of tauopathies confuses the scenario even more. Human MAPT knock-in mouse models, which bear combinations of pathogenic mutations (such as P301S; Int10+3; S320F), show age-dependent tau buildup, behavioral impairments, and brain region-specific susceptibility [4]. These animal models, which closely reproduce human tau isoform ratios (3R/4R), provide an effective tool for investigating how individual mutations influence disease pathways in vivo.

Tau's molecular toxicity is caused by more than merely aggregation. Pathological tau experiences a network of post-translational modifications (PTMs), including phosphorylation, acetylation, and ubiquitination, all of which impact its structure and interactions. A recent review revealed how such alterations impair tau's microtubule-stabilizing function, disrupt axonal transport, and activate neuroinflammatory pathways [5]. Furthermore, mass-spectrometry validation in animal models demonstrated that phosphorylation in the proline-rich and C-terminal domains is a prominent early cause of aggregation [3]. Despite these developments, human cellular models of tauopathy continue to be a significant challenge. Induced pluripotent stem cell (iPSC)-derived neurons and organoids are commonly employed to research tau, however they frequently retain fetal-like 3R tau isoforms, failing to fully replicate the adult 3R/4R tau equilibrium found in the human brain. This immaturity restricts their usefulness in simulating adult-onset tauopathies and testing treatments.

To address these constraints, researchers are increasingly using multimodal platforms, including as CRISPR-engineered human neurons, patient-derived iPSCs, and sophisticated in vivo models, to capture the genetic and metabolic complexity of tauopathies. Such collaboration may be critical for closing the translational gap. Only by better simulating adult-like tau biology can the field create next-generation therapeutics that effectively target disease-causing tau pathologies. In this review, we summarize recent achievements in stem cell modeling, MAPT-mutant mice lines, tau PTM mapping, and amyloid-tau interactions, and propose a unified paradigm for future tauopathy research. A conceptual overview of the primary biological and technology elements influencing tau pathology modelling is depicted in figure 1.

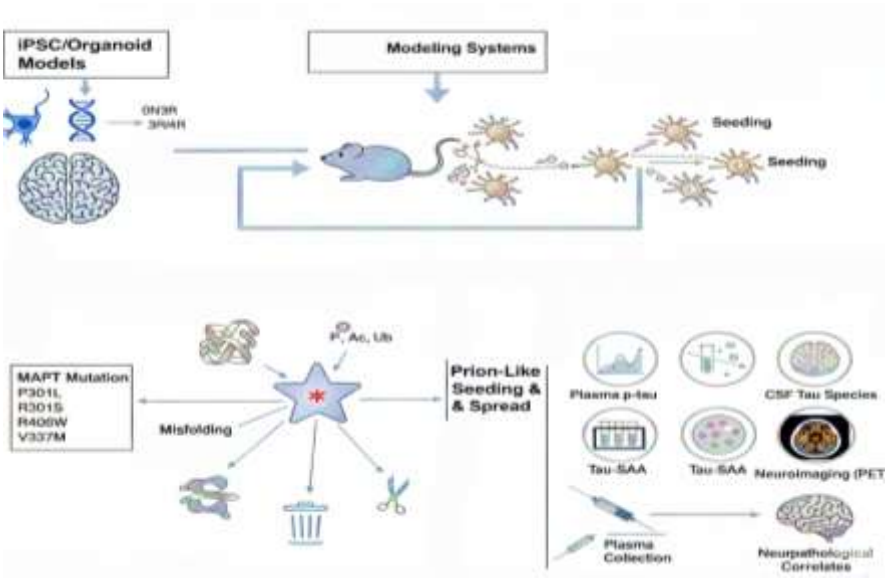

Figure 1. The significant aspects influencing tau research, such as fetal tau bias in iPSC-derived neurons, organoid maturation restrictions, MAPT mutant mice models, post-translational modification complexity, prion seeding & clearance, and biomarker frameworks. Together, these components illustrate the multifaceted difficulty of adequately modeling human tauopathy.

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Stem-Cell Models of Tauopathy

Human pluripotent stem cell (PSC) based systems, such as induced pluripotent stem cell (iPSC)-derived neurons, CRISPR-engineered neuronal lines, and multicellular brain organoids, have emerged as critical tools for modeling tau's complex biology in Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD-tau). These platforms have a distinct advantage, they capture human-specific genetic settings while providing temporal control over tau expression, phosphorylation, and aggregation. Recent engineering breakthroughs have produced PSC-derived neurons capable of expressing elevated levels of 4-repeat (4R) tau, a key requirement for replicating adult tauopathies, and have shown that these cultures can support tau seeding, propagation, and conformational diversification under controlled conditions [6]. However, the developmental immaturity of most stem-cell-derived neural systems continues to be a major concern. Standard differentiation techniques produce neurons that mostly express 3-repeat (3R) tau, indicating a fetal or early postnatal phenotype rather than the mature tau landscape found in adult human cortex. This mismatch severely limits the ability to mimic diseases characterized by pathological 3R/4R tau imbalances, such as Alzheimer's disease, primary age-related tauopathy (PART), and various MAPT mutation-driven types of FTLD-tau. Despite ongoing efforts to manipulate tau isoform ratios through CRISPR-editing of MAPT splice-regulatory elements such as S305 and intron 10 mutations, the field is still refining methods for achieving stable, adult-like 4R tau expression without compromising neuronal viability or synaptic maturation [7,8]. Nonetheless, current PSC have proven invaluable for examining early tau post-translational modifications (PTMs), kinase-substrate interactions, and cell-intrinsic stress responses. Advanced phosphoproteomic techniques allow for the simultaneous assessment of wide PTM landscapes, including phosphorylation, ubiquitination, and acetylation, as well as their dynamic interplay during the early phases of tau misfolding [8]. Complementary seeding and biosensor assays have shown that human neurons can internalize exogenous pathological tau species, amplify disease-linked conformers, and spread them across neural networks, though the efficiency of these processes is highly dependent on isoform maturation status. These findings highlight the importance of multimodal validation, which involves cross-checking results in iPSC neurons with more mature humanized mouse models, long-term organoids, and ex-vivo tissue systems [9].

Stem-cell based platforms are altering the study of tau biology by linking molecular pathways to human genetics. However, their best application necessitates an understanding of critical constraints, including tau isoform immaturity, as well as deliberate integration with more mature in vivo systems. As differentiation methods, CRISPR designs, and phospho-multiomics technologies advance, PSC models will play an increasingly important role in mechanistic discovery, therapeutic screening, and individualized tauopathy modeling.

Amyloid-Tau Interactions

Emerging data suggests a synergistic link between amyloid-β (Aβ) and tau diseases. The two proteins appear to promote each other through molecular interactions, localized microenvironments, and network-level dissemination, rather than Aβ alone causing tau aggregation [10]. Recent molecular and computational investigations provide detailed insights into how Aβ and tau interact to allow pathological seeding. Tau's microtubule-binding repeats (R1-R4) have different affinities for different surfaces of Aβ fibrils. R1 and R3 preferentially bind the lateral surfaces, while R2 and R4 show higher affinity for the fibril elongation ends, promoting β-sheet formation and nucleation of tau aggregation [11,12]. Biochemical investigations show that certain areas of the Aβ core can bind to tau epitopes, speeding up the spread of tau species. In vivo, the Aβ plaque microenvironment promotes tau aggregation. When pathogenic tau seeds from AD brains are injected into amyloid-bearing mice, dystrophic neurites surrounding plaques rapidly aggregate, generating "neuritic-plaque tau" before neurofibrillary tangles (NFTs) emerge [11]. This phenomenon aligns with human imaging and connectivity studies, for instance, tau spreading in Alzheimer's disease correlates with regions of high local Aβ/tau interaction (e.g., inferior temporal gyrus), suggesting that anatomical connectivity and amyloid burden both influence tau propagations.

These molecular findings challenge the traditional amyloid cascade concept and propose a more integrated model where Aβ and tau work together rather than sequentially [13,14]. Recent evaluations suggest that targeting common epitopes or interaction interfaces may improve therapeutic outcomes compared to focusing

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solely on Aβ or tau [12]. The molecular interactions of Aβ and tau, especially cross-seeding interfaces, provide promise for drug discovery.

Translational Perspectives

The molecular intricacy of tau-driven neurodegeneration has prompted a wide range of treatment methods, including passive immunotherapy and seed inhibition, as well as manipulation of extracellular clearance mechanisms. Success in preclinical models has been uneven, and new translational research highlights the importance of aligning therapeutic methods with the biology of tau proliferation, post-translational modification (PTM), and clearance. One intriguing therapeutic path is to directly target tau's seeding and self-propagation activity. Recent research has improved seed amplification assays (SAA) to find small compounds or antibodies that prevent tau aggregation. For example, a newly developed tau SAA platform exhibited the ability to detect physiological quantities of tau seeds in Alzheimer's brains while also identifying clinically approved drugs that drastically diminish seeding efficiency [15]. Because tau seeding is critical to disease dissemination, such tests offer a scalable and sensitive approach to identifying aggregation inhibitors with translational potential. Beyond intracellular pathways, the glymphatic clearance system has been identified as a regulator of tau disease. In a recent in vivo study, pharmacological suppression of aquaporin-4 (AQP4), a key component of the glymphatic system, greatly increased tau aggregation and propagation, worsening cognitive impairment in tau-seeded animal models [16]. These findings indicate that therapeutic augmentation of glymphatic function or avoidance of age-related decline could be a unique and underutilized method for mitigating tau distribution.

Therapeutic efforts must take into account the extensive network of tau PTMs and proteolytic fragments, both of which influence tau toxicity, aggregation, and cellular trafficking. Recent reviews have highlighted that certain truncated tau species generated by protease cleavage and aberrant phosphorylation or ubiquitination patterns significantly contribute to pathology, and suggest that inhibiting specific proteases, blocking fragment formation, or modulating PTM machinery are potential interventions [17]. However, accuracy is essential. Given the diversity of tau species, therapies will most likely need to distinguish between pathological and healthy isoforms or alterations. To translate preclinical achievements into human trials, robust biomarkers and patient classification are required. High-sensitivity assays are currently being used to detect phospho-tau in biofluids (e.g., plasma), which informs not just diagnosis but also treatment engagement [18, 19]. A recent review highlights that biomarker-led trial designs, such to those utilized in amyloid-targeting therapy, are critical for tau-directed therapeutics [20, 21]. Such trials should include biomarkers for seeding activity, PTM patterns, and clearance pathways to ensure precise target engagement and treatment efficacy monitoring.

While these therapy procedures are promising, there are still significant challenges. Tau exists in several conformational and PTM states. Therapies must selectively eliminate pathogenic species while preserving physiologically functioning tau. Preclinical achievements often come from overexpression or inoculation models. Translating these discoveries to clinical disease necessitates ensuring therapeutic efficacy in models that mimic adult tau biology, including isoform balance, PTM topography, and propagation dynamics. Combination treatments, such as seed inhibitors and glymphatic enhancers, may be more effective than monotherapies due to their dual involvement in intracellular seeding and extracellular clearance. Designing clinical trials with biomarker techniques, such as plasma p-tau, seeding assays, and neuroimaging, can speed the process from preclinical discovery to disease-modifying therapies.

DISCUSSION

Tau pathology is caused by a combination of internal molecular vulnerabilities (misfolding, aberrant PTMs, proteolytic cleavage, and poor proteostasis) and external modulators such amyloid-β (Aβ), inflammation, and lymphatic dysfunction. An increasing collection of research helps to refine how these factors interact across disease phases. Jiang et al. (2024) found that Aβ accumulation in APPNL-G-F/MAPTP301S mice leads to faster tau aggregation and neuritic plaque-associated seeding, indicating a clear relationship between amyloid burden and early amplification of tauopathy. He et al. previously demonstrated that Aβ plaques can increase tau-seeded disease, indicating an early amyloid-tau synergy. These findings highlight that amyloid and tau

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pathology are mutually accelerating processes, which is consistent with the cross-talk outlined by Avila et al. (Avila et al., 2025) and reviewed by Haut et al. (Haut et al., 2024).

Model Fidelity

Despite significant advances, no single experimental model accurately reproduces the whole intricacy of clinical tauopathies. Wenger et al. demonstrated that commonly used mice lines reproduce early but not late human pathology, limiting their translational power (Wenger et al., 2023). The key constraint remains throughout stem-cell-derived neurons, which continue to exhibit fetal-like tau expression patterns, specifically an underrepresentation of 4R tau isoforms, concealing late-stage conformational alterations important to Alzheimer's disease (Kühn et al., 2021; Baumann, 2024). Morito et al.'s recent humanized MAPT knock-in mice represent a significant step forward, allowing for physiological expression of human tau without overexpression artifacts. Representational depiction of tau accumulation can be observed through figure 2. Human iPSC systems have emerged as powerful platforms for detecting cell-intrinsic tau disease modifiers. Parra Bravo et al. discovered genetic regulators of tau propagation in a 4R-dominant iPSC model, showing novel modulators of transcellular dissemination (Parra Bravo et al., 2024). This complements Samelson et al.'s proteostasis-focused CRISPR screens, which identified ER-Golgi trafficking and lysosomal nodes as major regulators of tau turnover. These findings demonstrate that mature, adult-like human models with physiologic 3R/4R balance, intact splicing, and complicated PTM dynamics should remain the top goal for future tau research.

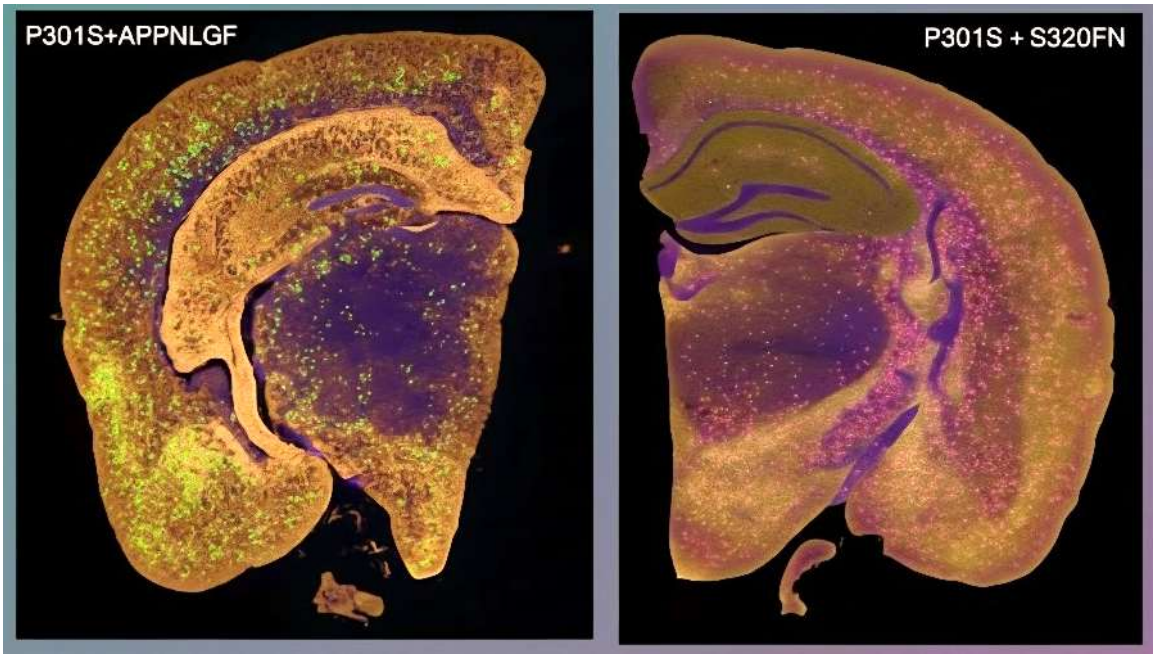

Figure 2. Diverse MAPT mutations and primary tauopathies cause varied geographic distributions of tau aggregates throughout the mice brain. These varying deposition and transmission patterns highlight the biological variety of tau species, as well as the necessity for model systems that incorporate regional vulnerability.

Mechanistic Layers

Tau toxicity cannot be linked to a particular molecular event. Instead, pathogenic conformer production is driven by certain combinations of PTMs (phosphorylation, acetylation, and ubiquitination), as well as protease-generated fragments. Yang et al. described how these PTM signatures interact to produce unique, highly seeding-competent tau species, while shortened fragments promote fibrillization and propagation (Yang et al., 2024). Song et al. (2023) found that tau microtubule-binding repeats interact differently with amyloid-β fibrils, indicating a structural foundation for amyloid-accelerated tau templating. These findings support Yan and Cook's assertion that mass spectrometry-based PTM mapping is crucial for validating mechanistic insights and improving model fidelity.

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Therapeutic Pathways

Given the prion-like proliferation of pathogenic tau, seeding inhibition has emerged as a key treatment strategy. Gorski et al. recently developed the Tau Seed Amplification Assay (Tau-SAA), which is a sensitive and scalable technique for screening for seeding and transmission modifiers. Extracellular fluid dynamics also influence tau dispersion. Lopes et al. found that glymphatic inhibition significantly exacerbates tau propagation in mouse models, implying that improving glymphatic and interstitial clearance could provide considerable therapeutic synergy (Lopes et al., 2024). This is consistent with the larger notions of proteostasis and clearance pathways emphasized in tau-targeting techniques (Mohan Kumar & Talwar, 2025).

Biomarkers and Trial Design

Rapid advancements in fluid biomarkers have transformed the translational environment. Plasma phospho-tau species have shown good diagnostic and staging potential, and Gonzalez-Ortiz et al. confirmed their suitability for treatment trial applications. Therriault et al.'s recent comparisons of immunoassay- and mass spectrometry-derived p-tau levels underscore the importance of standardization and multi-platform techniques. Penny et al. underlined that future studies should use biomarker-anchored designs that incorporate p-tau measurements, Tau-SAA, and multimodal imaging to evaluate real-time target engagement and disease change (Penny et al., 2024).

Thus, it can be inferenced that current tauopathy models, which include rodent models, iPSC-derived neurons, and 3D organoids, jointly recreate many aspects of human tau biology. Wenger et al. demonstrated and Baumann confirmed that widely utilized models efficiently reproduce early-stage tau alterations but are limited in their ability to depict late-stage, adult human tau conformers. As a result, capturing the entire illness spectrum requires the integration of different complimentary systems, particularly human MAPT knock-in models (Morito et al., 2025). iPSC-derived neurons often retain fetal tau expression and do not achieve the physiological 3R/4R tau ratio found in adult human brains (Kühn et al., 2021). This immature splicing profile obscures important disease-relevant vulnerabilities in tau behavior, slowing mechanistic research and decreasing translational accuracy for drug testing. Accumulating data suggested that toxic tau species are caused by complicated combinations of post-translational modifications; phosphorylation, acetylation, and ubiquitination rather than single erroneous events. Yang et al. and Yan & Cook discovered that PTM "signatures," frequently accompanied by proteolytic truncation, stimulate the production of highly pathogenic conformers (Yang et al., 2024; Yan & Cook, 2023). This emphasizes the significance of combined PTM mapping with mass spectrometry. Humanized MAPT knock-in mice (Morito et al., 2025) and MAPT mutant models (Wenger et al., 2023) accurately replicate sequential tau misfolding, templating, and dissemination. These models have helped to discover genetic drivers of tau pathology and influence the creation of biomarker techniques for disease progression and treatment engagement (Gonzalez-Ortiz et al., 2023). To further tauopathy research, human stem-cell-derived models must attain adult-like tau splicing, isoform balance, PTM dynamics, and neuron-glia interactions. Parra Bravo et al. and Samelson et al. found that advances in iPSC engineering and CRISPR-based functional genomics can bring stem-cell systems closer to physiologic adult tau biology (Parra Bravo et al., 2024; Samelson et al., 2024).

CONCLUSION

Several high-priority objectives arise based on integrated knowledge from genetic investigations, human-model research, and tau propagation biology. To accurately simulate adult human tauopathy, human iPSC and organoid models must demonstrate consistent 3R/4R tau switching, mature splicing patterns, and age-equivalent PTM landscapes. Given the variety of tau species shown by PTM-mapping research, targeted therapeutics must distinguish hazardous conformers based on phosphorylation, truncation, or acetylation signals. Future therapeutics should combine seeding inhibition, clearance enhancement (including glymphatic modulation), and intracellular proteostasis support to address the numerous mechanistic levels of tau toxicity. Plasma p-tau isoforms, Tau Seed Amplification Assays, and mass-spectrometry-based signatures should be used in the initial phases of clinical trials to allow for real-time monitoring of target engagement and disease change. Emerging research shows that early amyloid disease increases tau aggregation. Dual-pathway treatments that address amyloid triggers and tau propagation may be required.

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Tauopathies are a convergence site for a variety of chemical interactions that affect proteostasis, synaptic integrity, and neuron survival. Advances in human stem-cell systems, long-term brain organoids, multimodal imaging, and high-resolution proteomics have altered our ability to simulate early tau changes and understand the mechanisms that lead to phosphorylation, misfolding, and disease dissemination. At the same time, cross-species studies involving Drosophila, zebrafish, and humanized mouse models have helped us better understand conserved neurotoxic pathways and cell-type vulnerabilities. Together, these tools now enable researchers to investigate tau biology with unparalleled precision. Despite this progress, significant gaps persist. Current models are still unable to properly capture adult-like tau isoform balance, late-stage aggregation dynamics, and the chronic neuroinflammatory environment associated with human tauopathies. The geographical and temporal complexities of tau propagation, particularly the interaction of synaptic degeneration, membrane trafficking, and glial responses, are only partially understood. To bridge these gaps, diverse experimental systems must be integrated, more physiologically mature human models need to be developed, and quantitative frameworks for tracking tau conformational states across time be improved.

Looking ahead, the combination of stem-cell technology, nano-bioengineering, and artificial intelligence has the potential to produce predictive and translationally applicable platforms. These combined techniques may allow for earlier diagnosis of disease trajectories, more accurate testing of treatment candidates, and the creation of precision nanomedicines capable of modifying tau at the molecular and network levels. As the science works toward holistic models that account for tauopathy's molecular and systemic complexity, the prospects for major treatment breakthroughs improve. This review emphasizes the relevance of transdisciplinary, human-centered, and technology-enabled methods to understanding and, eventually, curing tau-driven neurodegeneration.

Ethics Statement

This study is a review of the literature and not an experiment involving human participants, personal data, or animals. Therefore, ethical approval of animal committee and informed consent were not required. Images and diagrams are of hypothetical nature, provided for representational and educational purposes only. All referred papers were analyzed and reported in compliance with established academic and ethical guidelines.

Conflict Of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

AK conceptualized the review theme, created the framework, conducted the literature review, combined mechanistic and model-based insights, and wrote the entire manuscript. RM contributed to sections on stem cell technologies, organoids, and molecular biotechnology frameworks. SK contributed to the synthesis of pharmacological and therapeutic views, as well as the refinement of mechanistic considerations. ApK supplied clinical interpretation, insights into translational applicability, and the matching of preclinical models with human disease characteristics. SS helped to shape the public-health conceptualization, contextual significance, and clarity of communication for broader scientific audiences. All authors evaluated the manuscript, made adjustments, and approved the final version.

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Abbreviations and acronyms

AD: Alzheimer's disease

Aβ: Amyloid-β

APP: Amyloid Precursor Protein

CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats

CNS: Central nervous system

CSF: Cerebrospinal Fluid

DLB: Dementia with Lewy Bodies

ER: Endoplasmic Reticulum

FTD: Frontotemporal Dementia

GFP: Green Fluorescent Protein

GWAS: Genome-Wide Association Study

iPSC: Induced Pluripotent Stem Cell

iPSC-Ns: iPSC-derived neurons

MAPT: Microtubule-Associated Protein Tau

MT: Microtubules

NGN3: Neurogenin-3

NFTs: Neurofibrillary Tangles

PD: Parkinson's disease

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PET: Positron Emission Tomography

PTM: Post-Translational Modification

RNA-seq: RNA Sequencing

SAA: Seed Amplification Assay

SD05N10: A modified mouse genetic background utilized in tau research

SPT: Single Particle Tracking

TBI: Traumatic Brain Injury

Tau-SAA: Tau Seed Amplification Assay

3R/4R: Tau isoforms with three or four repeats

UPR: Unfolded Protein Response

WT: Wild Type