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Review

RNA-based therapeutics for Alzheimer's disease and related tauopathies: challenges and opportunities

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ABSTRACT

Tauopathies are neurodegenerative diseases characterized by pathological tau protein accumulation. Though therapies involving monoclonal antibodies and small-molecule inhibitors have progressed, they have so far failed in multiple clinical trials, underscoring the need for innovative molecular approaches. RNA-based therapies offer an alternative disease-modifying approach by being able to target tau at its molecular origin. Diverse modalities, such as mRNA, ASO, RNAi, and SSO, offer distinct promises. Though their challenges are equally diverse, they also share common problems. This review examines the nascent field of RNA therapeutics for tauopathies, outlining emerging modalities, translational barriers, molecular targets, clinical trials, and patent trends.

1. Complexity of tau biology poses unique therapeutic challenges

Tauopathies are a group of neurodegenerative diseases characterized by the pathological aggregation of the microtubule-associated protein tau (MAPT) [1,2]. This group includes Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), frontotemporal dementia (FTD), and chronic traumatic encephalopathy (CTE). While these disorders share the common feature of tau dysregulation, they differ in the predominant tau isoforms involved, patterns of aggregation, and affected brain regions, resulting in distinct clinical and pathological phenotypes [3,4]. Understanding these mechanistic differences is essential for developing effective disease-modifying therapies.

Despite decades of research and growing understanding of tau biology, effective treatments for tauopathies remain elusive. Most current therapeutic strategies focus on targeting abnormal tau protein through immunotherapies [5,6], small molecules [7], or inhibitors of tau-related post-translational modifications [8,9]. While these protein-directed approaches have shown promise in preclinical studies, they have largely failed to yield meaningful clinical benefit. Major challenges include poor blood-brain barrier (BBB) penetration [10], limited ability to efficiently clear intracellular tau aggregates [11], and unintended off-target effects [12]. Moreover, because changes in tau pathophysiology typically begin years before the onset of clinical symptoms, therapeutic interventions at symptomatic stages are often initiated too late to prevent irreversible neurodegeneration.

Monoclonal antibodies and small-molecule inhibitors directed at tau targets have so far failed to demonstrate consistent efficacy in clinical trials [13]. The complexity of tau biology arises from its existence as multiple splice variants that generate six distinct isoforms [14], each isoform undergoing extensive post-translational modifications. These include hyperphosphorylation [15], acetylation [16], glycosylation, glycation, methylation, ubiquitylation, sumoylation and truncation [17]. Together, these modifications dynamically regulate microtubule stability and intracellular signaling. Both normal and pathologic tau interact with a wide range of cellular pathways. These include roles in microtubule organization and stabilization [18], synaptic signaling and neuronal activity [19–21] and axonal maturation and elongation [22]. Tau also participates in RNA binding and stress granule dynamics [23], innate immune and cytokine signaling [24,25], and mitochondrial dynamics and bioenergetics [26]. In addition, it influences cell cycle progression [27] and proliferation [28,29]. Tau also propagates between neurons along functional networks, and intervening in this extracellular

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phase remains technically challenging [30,31]. These multiple layers of complexity make the development of protein-directed therapies particularly challenging. Achieving both specificity and safety remains a formidable scientific and clinical hurdle.

These challenges have prompted increasing interest in upstream approaches that target tau expression at the RNA level. In this context, RNA-based therapeutics have emerged as a promising alternative. These therapies intervene early in the pathological cascade by modulating *MAPT* gene expression or splicing at the RNA level. Antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), and RNA-targeting CRISPR systems offer the ability to selectively silence, edit, or splice RNA transcripts [32–34], thus reducing the production of pathogenic tau isoforms or correcting splicing errors implicated in tauopathies. These approaches may facilitate precision targeting of familial *MAPT* mutations or isoform imbalances unique to specific tauopathies. Recent advances in delivery platforms such as lipid nanoparticles and adeno-associated viruses (AAVs) have significantly improved the feasibility of delivering RNA therapies across the BBB to affected brain regions [32]. The growing preclinical and early clinical evidence supports advancing these technologies as disease-targeted therapies for tauopathies.

2. RNA-based modalities for tauopathy therapeutics are diverse

A variety of RNA therapeutic modalities are being explored for the treatment of tauopathies, each leveraging distinct mechanisms of action and delivery platforms optimized for central nervous system (CNS). Together, these approaches modulate tau expression or function through complementary molecular mechanisms.

Antisense oligonucleotides (ASOs) represent one of the most clinically advanced RNA-based strategies [59]. These short, synthetic single strands of nucleic acids bind *MAPT* pre-mRNA to modulate splicing or promote transcript degradation through RNase H-mediated cleavage [20]. ASOs are typically administered via intrathecal injection, enabling direct delivery into the cerebrospinal fluid (CSF), although intravenous routes are also under investigation with novel delivery enhancers [37]. A recent phase 1 study of BIB080 by Biogen/Ionis Pharmaceuticals provides proof of concept for ASO therapy, where intrathecal injection reduced CSF and plasma total tau and phospho-tau levels and reversed changes on tau-positron emission tomography [60].

MicroRNAs (miRNAs) function as endogenous post-transcriptional regulators [61] of gene expression and can be harnessed therapeutically to modulate networks of tau-related pathways [62]. By binding to complementary sequences in target messenger RNAs (mRNAs), miRNAs suppress translation or promote degradation, thereby offering a broader post-transcriptional control [63]. For therapeutic applications, miRNA mimics or inhibitors can be delivered via viral vectors or nanoparticle-based systems [39]. This enables sustained modulation of tau expression and its upstream or downstream regulatory targets. mRNA-based therapies offer a complementary strategy aimed at restoring or enhancing the production of protective proteins involved in tau regulation [64]. These exogenous mRNAs are typically encapsulated in lipid nanoparticles for intravenous delivery [43,44], enabling systemic administration and potential CNS uptake, especially when coupled with targeting ligands or other delivery enhancers to cross the BBB. mRNA-based therapies allow for gain-of-function interventions by encoding tau modulators or neuroprotective factors, representing a flexible and transient platform for restoring homeostatic pathways in tauopathies.

Small Interfering RNAs (siRNAs) silence *MAPT* mRNA through RNA-induced silencing complex (RISC)-mediated degradation [65–68] thereby reducing tau protein expression. Typically delivered via intrathecal or intravenous routes, often with lipid nanoparticles, siRNAs offer high specificity, strong gene expression knockdown efficiency, and durable gene silencing. However, challenges include delivery optimization, BBB penetration, and off-target effects [48]. A recent Phase 1 clinical trial for LY3954068, a *MAPT*-targeting siRNA by Eli Lilly & Co, is currently being evaluated for early AD patients. Despite delivery and safety hurdles, siRNAs continue to advance toward clinical development for tauopathies.

Ribozymes and DNAzymes, though less clinically advanced, provide a highly specific catalytic approach [49,50], thereby directly reducing tau protein synthesis. These catalytic nucleic acids are designed to recognize and cleave defined RNA motifs within the *MAPT* transcript, and can be administered intrathecally or intravenously, often in combination with delivery vehicles to enhance stability and cellular uptake. While early in development, these catalytic modalities establish the feasibility of direct transcript cleavage as a precision strategy for tau reduction.

RNA aptamers are short, structured RNAs that bind tau or tau-associated proteins with high affinity to block aggregation [53,54,69]. Typically delivered via intravenous or intranasal routes [55], aptamers offer reversible binding and target selectivity [54]. However, they have limited intracellular activity and face delivery challenges [55]. While still in preclinical stages, they represent a promising class of extracellular tau aggregation inhibitors.

Each RNA modality offers distinct advantages and challenges in the context of tauopathies as shown in Table 1. ASOs provide high specificity with clinically validated delivery methods; miRNAs offer network-level modulation but require precise control to avoid unintended effects. While miRNA-based approaches primarily suppress pathogenic gene expression, mRNA therapies support gain-of-function applications; ribozymes and DNAzymes facilitate direct transcript cleavage; siRNAs offer potent and durable gene silencing; and RNA aptamers act extracellularly to block aggregation. Selecting the optimal RNA modality involves balancing target specificity, delivery feasibility, therapeutic durability, and alignment with the underlying pathological mechanism of each tauopathies.

3. RNA-based therapeutics can target tau directly or indirectly

The therapeutic potential of RNA-based technologies in tauopathies hinges on both the choice of molecular targets as well as the modality used. These targets can be broadly classified into those that directly modulate tau protein and its aggregates, and those that indirectly influence tau pathology by acting on upstream regulators such as kinases and phosphatases (Table 2). Each approach offers unique mechanisms and therapeutic implications that vary depending on disease context, stage of progression, and the predominant isoform involved. Table 2 provides a comprehensive landscape of potential RNA-based approaches to tau therapeutics. The sections below focus on a subset of high-priority targets, specifically those with the most robust preclinical validation for RNA-based intervention, such as MAPT, GSK3β, and protein phosphatase 2A (PP2A), which are currently being prioritized for clinical and preclinical development.

Directly targeting tau remains the most specific therapeutic strategy. RNA therapeutics such as ASOs and siRNAs can be designed to reduce total tau expression by degrading *MAPT* transcripts or modulating splicing patterns. This approach may be particularly useful in cases where tau overexpression or isoform imbalance contributes directly to neurotoxicity, such as in frontotemporal dementia with *MAPT* mutations. Splice-switching ASOs can be tailored to suppress 4R tau [70], depending on the disease subtype. Direct tau targeting may reduce the core pathological substrate early in the disease cascade, potentially slowing progression if administered before there is extensive neurodegeneration.

Targeting kinases represents an indirect but powerful means of modulating tau pathology. Multiple kinases, such as glycogen synthase kinase 3 beta (GSK3β), cyclin-dependent kinase 5 (CDK5), and MAPK family members, phosphorylate tau at sites that promote aggregation and misfolding. RNA therapeutics can be deployed to downregulate these kinases or inhibit their expression in neurons. This approach

Table 1
Comparison of different RNA therapeutic modalities for tauopathies.

RNA Modality for tauopathies	Mechanism of action for tauopathies	Delivery method in the CNS	Delivery vehicles	Key features	Limitations
ASOs	Binds pre-mRNA to modulate splicing or induce degradation [20]	Intrathecal, Intravenous [35]	Naked oligonucleotides, conjugates, nanoparticles [32]	High specificity, reversible, dose-dependent effects [36]	Requires repeated dosing, limited BBB penetration [37]
miRNA	Post-transcriptional regulation of multiple targets [38]	Intranasal, Intravenous	Viral vectors (AAVs), nanoparticles [39]	Can target multiple pathways simultaneously [40]	Unintended gene silencing, delivery challenges [41]
mRNA	Delivers synthetic mRNA for protein expression [42]	Intrathecal, Intravenous	Lipid nanoparticles (LNPs) [43, 44]	Enables protein replacement or modification [42]	Short half-life, immune response [45]
siRNA	Binds and degrades target mRNA via RISC [46]	Intrathecal, Intravenous [32]	LNPs	Strong knockdown efficiency, long-lasting effects [47]	Requires optimized delivery, off-target effects [48]
Ribozymes & DNAzymes	Cleaves tau mRNA to reduce expression [49,50]	Intrathecal, Intravenous [51]	Viral vectors (AAVs), nanoparticles, conjugated oligonucleotides	High specificity, catalytic activity [48]	Delivery, stability in vivo [52]
RNA Aptamers	Binds tau or related targets to block aggregation [53,54]	Intranasal, Intravenous [55]	Covalent conjugation, nanoparticles, LNPs [56,57]	High specificity, reversible binding [54]	Nuclease degradation, limited BBB penetration, off-target binding [58]

ASO = Antisense Oligonucleotide; miRNA = microRNA; mRNA = Messenger RNA; siRNA = small interfering RNA.

Table 2
Comparison of targets of RNA therapeutics.

Potential tau-based targets	Examples
Directly Targeting Tau	Full length tau (2N4R, 2N3R, 1N4R, 1N3R, 0N4R, 0N3R); Truncated tau (MTBR, PHF6, 3R, 4R); MAPT transcripts
Targeting Tau Aggregates	PHFs, SFs, NFTs, Neuropil threads, tau oligomers, tau pretangles, tau spherulites, coiled bodies, tufted astrocytes, astrocytic plaques, globose tangles, pick bodies, argyrophilic grains, grain-like inclusions, flame-shaped tangles, mature tangles, ghost tangles
Targeting Kinases	c-Abl, AMPK, BRSK, CaMKII, CDK5, CK1, CK2, PKA, DYRK1A, Fyn, GSK-3, JNK, LRRK2, Met, MARK, MSK1, p35/41, p42/p44, ERKs1/2, p38MAPK, p70S6 kinase, Phosphorylase kinase, PKB/AKT, PKC, PKN, PSK1/TAOK2, PSK2/TAOK1, Rho kinase, RSK1/2, SAPK1γ, SAPK2a, SAPK2b, SAPK3, SAPK4, SGK1, SRPK2, Syk, TTBK1/2
Targeting Phosphatases	PP1, PP2A, PP2B or Calcineurin, PP2C, DUSPs, PP5, PTEN, TNAP

MTBR = Microtubule-Binding Repeat; PHF6 = Paired Helical Filament 6 Motif (VQIVYK); PHFs = Paired Helical Filaments; SFs = Straight Filaments; NFTs = Neurofibrillary Tangles; AMPK = AMP-Activated Protein Kinase; BRSK = BR Serine/Threonine Kinase; CaMKII = Calcium/Calmodulin-Dependent Protein Kinase II; CDK5 = Cyclin-Dependent Kinase 5; CK1 = Casein Kinase 1; CK2 = Casein Kinase 2; PKA = Protein Kinase A; DYRK1A = Dual-Specificity Tyrosine-Regulated Kinase 1A; Fyn = Fyn Proto-Oncogene, Src Family Tyrosine Kinase; GSK-3 = Glycogen Synthase Kinase 3 (α and β isoforms); JNK = c-Jun N-Terminal Kinase; LRRK2 = Leucine-Rich Repeat Kinase 2; Met = Hepatocyte Growth Factor Receptor (c-Met Tyrosine Kinase); MARK = Microtubule Affinity-Regulating Kinase; MSK1 = Mitogen- and Stress-Activated Kinase 1; p35/p41 = CDK5 Activator Proteins p35 and p41; p42/p44 = Extracellular Signal-Regulated Kinases 1 and 2 (ERK1/2); p38MAPK = p38 Mitogen-Activated Protein Kinase; p70S6 Kinase = 70 kDa Ribosomal Protein S6 Kinase; Phosphorylase Kinase = Glycogen Phosphorylase Kinase; PKB/AKT = Protein Kinase B (AKT); PKC = Protein Kinase C; PKN = Protein Kinase N; PSK1/TAOK2 = Thousand-and-One Amino Acid Kinase 2; PSK2/TAOK1 = Thousand-and-One Amino Acid Kinase 1; Rho Kinase = Rho-Associated Coiled-Coil–Containing Kinase (ROCK1/2); RSK1/2 = Ribosomal S6 Kinase 1 and 2; SAPK1γ = Stress-Activated Protein Kinase 1 Gamma (JNK3); SAPK2a = Stress-Activated Protein Kinase 2 Alpha (p38α); SAPK2b = Stress-Activated Protein Kinase 2 Beta (p38β); SAPK3 = Stress-Activated Protein Kinase 3 (p38γ); SAPK4 = Stress-Activated Protein Kinase 4 (p38δ); SGK1 = Serum/Glucocorticoid-Regulated Kinase 1; SRPK2 = Serine/Arginine Protein Kinase 2; Syk = Spleen Tyrosine Kinase; TTBK1/2 = Tau Tubulin Kinase 1 and 2; PP1 = Protein Phosphatase 1; PP2A = Protein Phosphatase 2A; PP2B = Protein Phosphatase 2B (Calcineurin); PP2C = Protein Phosphatase 2C; DUSPs = Dual-Specificity Phosphatases; PP5 = Protein Phosphatase 5; PTEN = Phosphatase and Tensin Homolog; TNAP = Tissue-Nonspecific Alkaline Phosphatase.

reduces pathological tau phosphorylation. For example, siRNAs or miRNA mimics can selectively silence kinase transcripts, while mRNA-based delivery of dominant-negative kinase regulators is also under investigation. Indirect modulation through kinase inhibition may affect multiple tau species and downstream toxic signaling pathways., However, vigilance for off-target effects is required, given the pleiotropic roles of kinases in cellular function [71].

Targeting phosphatases, particularly PP2A, offers another approach to tau regulation [72]. PP2A is the principal phosphatase responsible for dephosphorylating tau, and its reduced activity has been implicated in multiple tauopathies. Enhancing phosphatase activity through RNA therapeutics could restore the balance of tau phosphorylation, reducing the accumulation of hyperphosphorylated, aggregation-prone tau species [73]. RNA-based strategies in this domain include upregulation of catalytic or regulatory subunits of PP2A using mRNA constructs, or inhibition of negative regulators of phosphatase activity. Compared to kinase inhibition, phosphatase activation may offer a more targeted and stabilizing influence on tau homeostasis, although treatment delivery and target specificity remain key challenges.

These diverse targeting strategies reflect the growing recognition that tau pathology is multifactorial and requires tailored intervention points. While direct tau reduction may offer the most specific path forward, targeting kinases and phosphatases may provide possible alternative routes that address tau's post-translational landscape. The optimal therapeutic strategy may ultimately involve combinatorial targeting or sequential intervention based on disease stage and molecular subtype.

4. Multiple challenges and possibilities exist in RNA-based therapeutics for tauopathies

While RNA-based therapeutics have the potential to treat tauopathies, their successful translation from bench to bedside is met with a series of formidable challenges, as shown in Table 3. These barriers span biological, technological, and clinical domains, requiring multidisciplinary innovation to achieve safe, effective, and scalable therapies.

A primary challenge lies in efficient delivery to the CNS. The BBB poses a significant obstacle to systemic administration of RNA therapeutics [32]. Even when delivered intrathecally, distribution may be uneven, limiting drug exposure to deeper brain structures. Potential solutions include engineering peptide shuttles (e.g., transferrin receptor ligands) for receptor-mediated transcytosis [75] and refining lipid nanoparticle formulations [32,76]. Additional strategies include intrathecal administration [32], (as in BIIB080 ASO trials), intraventricular delivery from implanted subcutaneous reservoirs, and using AAV

Table 3
Major challenges in RNA therapeutics for tauopathies.

Challenge	Description	Potential Solutions
BBB Penetration	Efficient delivery of RNA therapeutics to the brain is difficult due to the restrictive nature of the BBB [32].	– Use of intrathecal/ intraventricular administration (e.g., BIIB080 ASO trials) [32]. – Development of nanoparticle-based delivery systems (e.g., lipid nanoparticles, exosomes) [32,74]. – Utilization of transferrin receptor-mediated transcytosis (TfR-targeting peptides) [75].
RNA Stability & Degradation	RNA molecules are prone to rapid degradation by nucleases in circulation [32,76].	– Chemical modifications (e.g., 2′-O-methyl, phosphorothioate linkages) [32,76]. – Use of LNAs for stability [74,77,78]. – Encapsulation in protective delivery systems (e.g., PEGylated nanoparticles) [32,74].
Off-Target Effects & Immunogenicity	Unintended gene silencing and immune activation can lead to adverse effects [74,79].	– In silico screening and high-throughput screening for specificity [80,81]. – Modifications to avoid immune recognition (e.g., incorporating modified uridines) [74,79].
Long-Term Efficacy & Safety	Sustained suppression of tau requires repeated dosing, which may pose toxicity risks [82].	– Sustained-release formulations to reduce dosing frequency [82]. – Optimized dosing schedules based on pharmacokinetic (PK) studies [83]. – Monitoring of CSF biomarkers (tau reduction, NfL levels) for treatment response [84].
Heterogeneity of Tau Isoforms	Different tauopathies involve distinct 3R/4R tau ratios, making a universal approach difficult [85,86].	– Development of isoform-specific RNA therapeutics (e.g., ASOs or siRNAs selectively targeting 4R tau) [87]. – Combination therapies targeting multiple tau isoforms [88].
Scalability & Manufacturing	Large-scale production of RNA therapeutics remains costly and complex [89].	– Improved biomanufacturing techniques for large-scale production [89]. – Use of enzymatic RNA synthesis (avoiding chemical synthesis limitations) [90].
Regulatory Hurdles & Clinical Translation	Limited clinical precedence for RNA-based tau-targeting therapies slows regulatory approval [91].	Accelerated approval pathways for rare neurodegenerative diseases [92]. – Comprehensive long-term follow-ups to assess safety and efficacy [92,93]. – Engagement with regulatory bodies (FDA, EMA) for early guidance [93].

BBB = Blood–Brain Barrier; RNA = Ribonucleic Acid; ASO = Antisense Oligonucleotide; GalNAc = N-Acetylgalactosamine; NfL = Neurofilament Light Chain; siRNA = Small Interfering RNA; LNAs = Locked Nucleic Acids; FDA = U.S. Food and Drug Administration; EMA = European Medicines Agency.

vectors with enhanced CNS tropism [94]. Studies are also exploring possible use of focused ultrasound to transiently open the BBB in targeted regions [95].

Beyond overcoming anatomical barriers such as the BBB, achieving precise cellular targeting within the CNS represents an additional layer of complexity. Since tau pathology and RNA delivery requirements vary across neuronal and glial populations, cell-type-specific strategies are essential. Emerging approaches include engineering viral capsids for specific tropism [96] or utilizing lipid-based and conjugate-based systems that can actively target specific cell types through cell surface modifications [97]. Such strategies should improve therapeutic precision and optimize efficacy across the heterogeneous cellular landscape of tauopathies.

In addition to delivery and cellular targeting, maintaining RNA integrity in biological environments remains a critical issue. RNA molecules are inherently unstable and prone to rapid degradation by nucleases in blood and extracellular fluids, which limits their therapeutic efficacy [32,76]. Chemical modifications such as 2′-O-methyl and phosphorothioate linkages can enhance nuclease resistance. Locked nucleic acids (LNAs) provide further stability through constrained sugar chemistry [77,78] and encapsulating RNA in PEGylated or lipid-based nanoparticles protects it from enzymatic degradation during delivery [74].

Closely tied to delivery and stability are the risks of off-target effects and immunogenicity [74,79]. These risks represent additional challenges, particularly for repeat dosing in chronic diseases. Synthetic RNA can activate innate immune responses via toll-like receptors (TLRs), leading to inflammation or adverse events. Chemical modifications to RNA backbones (e.g., 2′-O-methoxyethyl, phosphorothioate linkages), screening with *in silico* and in vitro off-target prediction tools [98,80,81] may help improve safety profiles.

Achieving sustained tau suppression and a durable therapeutic response often requires repeated dosing, raising concerns about long-term toxicity and patient compliance [82]. Innovations such as sustained-release formulations or depot-based delivery systems are being developed to extend drug exposure [99]. Furthermore, monitoring CSF biomarkers, including phosphorylated tau (p-tau) and neurofilament light chain (NfL), can help tailor treatment schedules and evaluate long-term safety [84].

Another important consideration is the molecular heterogeneity of tauopathies [85,100]. Distinct disorders within the tauopathy spectrum are defined by variable ratios of 3-repeat (3R) and 4-repeat (4R) tau isoforms, with some diseases dominated by 3R (such as Pick's disease), others by 4R (such as PSP and CBD), and still others exhibiting mixed 3R/4R profiles. This diversity complicates the design of RNA therapeutics that can address all relevant pathologies, and isoform-specific strategies may be needed. ASOs or siRNAs targeting 4R tau [70] can be customized to offer molecular precision for treatment of each tauopathy subtype.

Beyond scientific hurdles, scalable manufacturing remains a major practical challenge. The large-scale production of RNA therapeutics remains a significant bottleneck due to cost, complexity, and stringent quality control [89]. There is a need for improved biomanufacturing processes to support clinical and commercial demands. Enzymatic synthesis of RNA, as opposed to traditional chemical synthesis, offers a promising alternative for scalable, cost-effective production while maintaining high purity and yield [90].

Finally, the path to regulatory approval for RNA-based therapies in tauopathies remains nascent, with few clinical precedents to guide development. A major challenge is the lack of long-term safety data, which complicates regulatory assessment. To overcome regulatory hurdles, developers are increasingly utilizing accelerated approval pathways for rare neurodegenerative diseases [92] and engaging with regulatory agencies early in the development process [93] to align on trial design and biomarker strategy.

Comprehensive long-term follow-up studies and the establishment of robust, disease-relevant biomarkers will be critical for successful clinical translation. Measuring target engagement, dose response, and clinical efficacy is challenging in tauopathies, especially in presymptomatic or slowly progressive forms, where conventional clinical measures lack sensitivity and drug-placebo differences in the period of a clinical trial are modest. To improve trial efficiency and accelerate development timelines, a combination of fluid biomarkers, tau PET imaging, and

emerging digital cognitive assessments may offer more responsive measures of therapeutic impact.

5. Clinical translation of RNA therapeutics for tauopathies is still nascent

The translation of RNA therapeutics into clinical trials for tauopathies marks a significant step toward disease-modifying interventions. These clinical programs target tau pathology either directly, by reducing or modifying *MAPT* expression, or indirectly, by modulating upstream regulators such as kinases and phosphatases involved in tau phosphorylation. Several therapeutic candidates are currently in various phases of clinical development as of April 2026, which are illustrated in Table 4, reflecting the diversity of RNA modalities and the evolving understanding of tau biology.

One of the most advanced candidates is BIIB080 (IONIS-MAPT Rx), a gapmer developed by Ionis Pharmaceuticals in collaboration with Biogen [IONIS press release] [101]. This agent directly targets the *MAPT* mRNA, reducing total tau protein production. BIIB080 is delivered intrathecally and has completed Phase 1b studies in patients with early AD, demonstrating dose-dependent tau lowering in CSF and good tolerability [102]. The trial's success has paved the way for Phase 2 [NCT05399888] development, with recruitment underway for broader efficacy assessment.

LY3954068 is a siRNA candidate developed by Eli Lilly that also targets *MAPT* mRNA to reduce tau expression. Unlike ASOs, siRNAs utilize the RISC for mRNA degradation, offering a complementary mechanistic approach. LY3954068 is currently being evaluated in a Phase 1 clinical trial [NCT06297590] enrolling individuals with early symptomatic AD. The study is focused on assessing safety, pharmacokinetics, and target engagement, with administration via intrathecal injection. This trial represents one of the first attempts to translate siRNA technology to target tau in humans, with an estimated primary completion date of February 2027. If successful, it could open the door for broader RNAi-based strategies in neurodegenerative diseases.

NIO752 is another tau-targeting ASO developed by Novartis, which underwent a Phase 1 trial for PSP [NCT04539041] and is currently under investigation in a Phase 1b [NCT05469360] study for early AD. Similar to BIIB080, NIO752 is designed to bind *MAPT* mRNA and promote its degradation, reducing tau protein synthesis. The study is evaluating the agent's pharmacodynamics, safety, tolerability, and pharmacokinetics following intrathecal administration. While still in early clinical development, NIO752 represents an important addition to the expanding pipeline of RNA therapeutics for tauopathies. The estimated primary completion date is November 2027, and outcomes from this trial may inform subsequent dose selection and design for future efficacy studies.

While these individual programs underscore the progress of tau-targeted RNA therapeutics, they also highlight a broader therapeutic challenge: interventions focused on a single pathological cascade may have limited impact if upstream drivers of disease remain unaddressed. Consequently, combination approaches targeting both tau and amyloid-beta have been proposed to maximize disease-modifying potential. Emerging evidence suggests that RNA-based tau-targeting therapies could potentially be combined with amyloid-targeting strategies, such as monoclonal antibodies against Aβ, to achieve a more robust disease-modifying effect (simultaneous targeting of Aβ and tau pathologies has been proposed as a promising therapeutic strategy in AD [103]. Given that amyloid pathology often precedes tau aggregation, early intervention with amyloid-targeting agents followed by tau-directed RNA therapeutics may synergistically slow disease progression. Clinical trial designs could explore combinatorial or sequential approaches, informed by biomarker-driven staging of AD.

Building on these considerations, the timing of RNA-based tau interventions is likely critical for efficacy. Preclinical and early symptomatic stages may be most suitable, as RNA therapeutics aim to prevent the accumulation of pathogenic tau species before extensive neurodegeneration occurs. This concept is supported by experience in other neurological disorders, such as spinal muscular atrophy [104], where early administration of RNA-targeting therapies yields significantly greater functional outcomes compared to later-stage treatment.

Building on learning from these early trials, the continued advancement of RNA therapeutics targeting tau will depend on addressing key challenges related to delivery, specificity, and long-term safety. As more trials progress into later phases, the field will benefit from biomarker-guided dosing, clinical efficacy in diverse tauopathy populations, and the comparative advantages and challenges of different RNA modalities.

Table 4
Clinical trials underway as of April 2026 for RNA therapeutics in tauopathies.

Therapeutic agent	BIIB080 (IONIS-MAPTRx)	LY3954068	NIO752
Therapeutic modality	ASO	siRNA	ASO
Therapeutic target	MAPT transcript	MAPT transcript	MAPT transcript
Mechanism	ASO targeting MAPT mRNA to reduce tau production	siRNA targeting MAPT mRNA to reduce tau levels	ASO targeting MAPT mRNA to reduce tau production
Indication	Early Alzheimer's Disease	Early Alzheimer's Disease	Early Alzheimer's Disease
Phase	Phase 2 (CELIA Study)	Phase 1	Phase 1b
Status	Active (Primary readout expected Q2/Q3 2026)	Ongoing	Ongoing
Details	This study evaluates the safety and efficacy of BIIB080 in reducing tau protein levels. The trial is active, with an estimated completion date in May 2026 (Primary)/Jan 2029 (Full)	This study evaluates the safety of LY3954068. The trial is active, with an estimated completion date in Feb 2027	This study evaluates the pharmacodynamics, safety, tolerability, and pharmacokinetics of NIO752. The trial is active, with an estimated completion date in Nov 2027
Institutions owning the drugs	Biogen Inc./ Ionis Pharmaceuticals Inc.	Eli Lilly & Co.	Novartis Farma SpA

ASO = Antisense Oligonucleotide; MAPT = Microtubule-Associated Protein Tau.

6. The most highly cited patent relates to RNA drug delivery methods

The growing interest in RNA-based therapeutics for tauopathies is reflected in intellectual property filings by academic institutions, biotechnology companies, and biopharmaceutical companies, with RNA drug delivery being the most influential patent.

To systematically evaluate the intellectual property landscape surrounding RNA-based therapeutics targeting tauopathies, we conducted a structured patent search using the Lens.org platform. The search was limited to the claims or abstract section of patents to capture inventions with legally asserted therapeutic mechanisms. We used the following Boolean query: (claims:((RNA OR siRNA OR antisense OR ASO OR mRNA OR miRNA OR oligonucleotide) AND (tau OR MAPT) AND (Alzheimer* OR tauopathy* OR "frontotemporal dementia" OR PSP OR CBD))) OR abstract:((RNA OR siRNA OR antisense OR ASO OR mRNA OR miRNA OR oligonucleotide) AND (tau OR MAPT) AND (Alzheimer* OR tauopathy* OR "frontotemporal dementia" OR PSP OR CBD))). Filters were applied to include patents filed in the United States between

January 2000 and December 2024, with a legal status of granted or pending, and encompassing both active and expired patents. This query yielded 152 raw results in Lens.org (Supplementary Table S1) and 177 raw results in Google Patents (Supplementary Table S2), reflecting minor differences in indexing and metadata structures between platforms. Further downstream analysis was based only on the lens.org dataset, as it provided a more structured bibliometric data suitable for systematic analysis.

Analysis of relevant patents over time showed an upward trend in patent filings over time for RNA based therapeutics as shown in Fig. 1A. This reflects a broad and growing investment in RNA therapeutics, with a subset focus on tau-targeting strategies for neurodegenerative diseases.

Analysis of patent ownership at the institutional level highlights the diverse contributors to this space as shown in Fig. 1B Alector LLC holds approximately 23–24 patents in this domain. Ionis Pharmaceuticals Inc has an estimated 17–18 patents, and Biogen Ma INC, possesses around 14 patents. These three organizations collectively account for a substantial portion of the identified patents. Additional contributors include F. Hoffmann-La Roche AG, Ac Immune SA, Adimab LLC, Janssen Pharmaceuticals Inc., Bristol Myers Squibb Company, and Regeneron Pharmaceuticals Inc., among others. Several academic and research institutions such as Centre National De La Recherche Scientifique and Washington University each hold approximately 4 patents. Other academic contributors include Université De Montpellier, Institut Curie, and University of Zurich, each with around 2 patents.

To further characterize innovation within this domain, all retrieved U.S. patent documents were ranked by citation count from the lens.org dataset to identify influential patents (Table 5). The most frequently cited patents encompassed a range of technologies, including antisense oligonucleotide platforms, delivery systems, and biomarker-based targeting strategies. The ten most cited entries spanned a range of innovation types, from oligonucleotide therapeutics to biomarker-based targeting and delivery technologies. The most cited patent, Drug delivery product and methods received over 300 citations and is broadly classified under ASOs, suggesting foundational contributions to RNA delivery systems that may be applicable to CNS targets such as tau. Other highly cited patents included inventions from academic institutions such as the University of Rochester and the University of Zurich, which focused on evaluating brain-wide paravascular clearance pathways and generating disease-specific binding molecules, respectively, both conceptually relevant to tauopathy treatment. Additionally, patents from companies like Nanosomix and Rosetta Inpharmatics highlighted the integration of diagnostic biomarkers with RNA modulation platforms. Notably, while not all top-cited patents claimed tau or *MAPT* explicitly, their citation frequency underscores their enabling role in advancing RNA-based strategies for neurodegenerative disorders. These findings highlight the importance of foundational delivery, targeting, and diagnostic platforms in shaping the current landscape of tau-directed RNA therapeutics.

The overall patent landscape reflects a maturing and increasingly diversified field, with broad participation from industry and academia driving innovation across RNA modalities, delivery platforms, and tau-relevant targets, collectively highlighting the sustained advancement of RNA-based therapeutic research in tauopathies.

7. Shaping the future of RNA-based tauopathy therapeutics

As RNA therapeutics advance toward clinical application in tauopathies, they raise important regulatory considerations related to safety. Unlike small-molecule drugs, which follow well-established regulatory pathways, large-molecule therapeutics such as ASOs, siRNAs, and mRNA constructs face more extensive oversight under biologics or advanced therapy medicinal product (ATMP) regulations [105]. Because these agents act often directly within the CNS via intrathecal delivery, they require comprehensive evaluation of off-target effects, long-term safety, and pharmacokinetics [106]. Consequently, regulatory frameworks must evolve in parallel with scientific innovation to balance patient protection with timely therapeutic progress in tauopathies [107].

The future of RNA therapeutics in tauopathies is promising, with multiple classes of interventions affecting a variety of targets at various stages of development. Advances in delivery systems include lipid nanoparticles, receptor-mediated transport, and self-amplifying RNA constructs. These innovations are critical for BBB penetration, enabling both systemic and targeted administration and facilitating chronic therapeutic regimens. These innovations are poised to redefine gene-modifying interventions, positioning RNA-based therapies as a

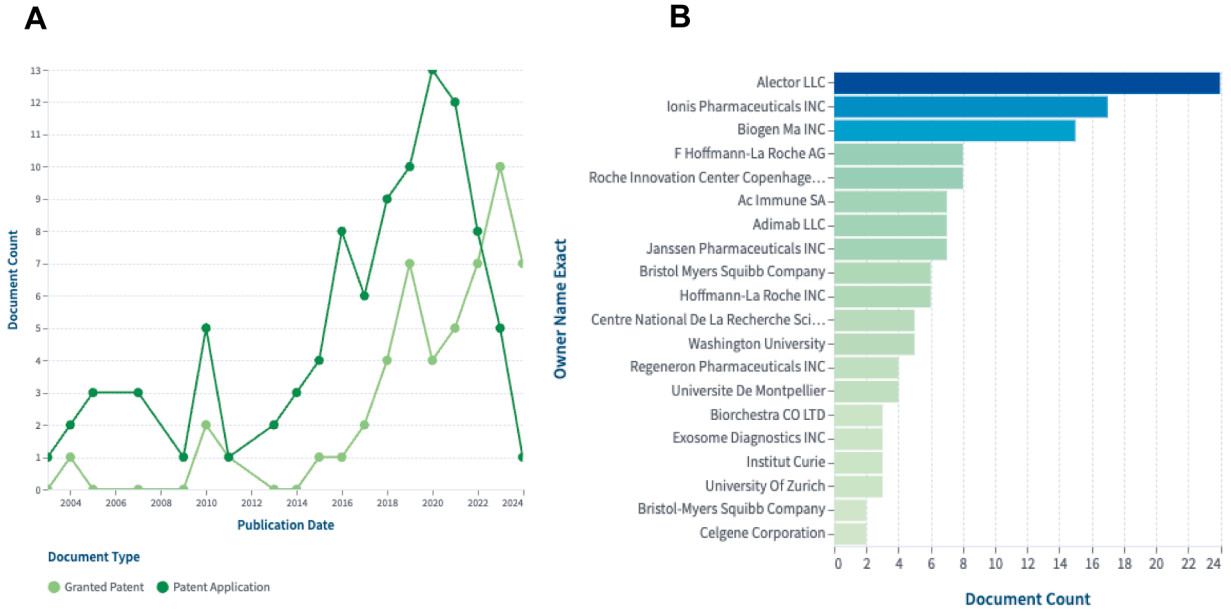


Fig. 1. Trends and distribution of patents related to RNA-based therapeutics for tauopathies. (A) Annual trend in the number of granted patents and active applications for RNA-based therapeutics targeting MAPT or tau-related mechanisms (2000–2024), based on Lens.org data. (B) Distribution of patent ownership among leading academic institutions, biotechnology companies, and pharmaceutical organizations engaged in tau-focused RNA drug development.

Table 5
Key patents in RNA therapeutics for tauopathies, extracted from lens.org database.

Patent citation count	Patent number	Publication Date	Owners	Title
314	US 86969304 A	12/22/05	University of Massachusetts (2008–03–10)	Drug delivery product and methods
54	US 201414769396 A	1/7/16	The research foundation for the State University of New York (2015–08–19); University of Rochester (2015–08–19)	Methods for evaluating brain-wide paravascular pathway for waste clearance function and methods for treating neurodegenerative disorders based thereon
41	US 201414522585 A	4/30/15	Nanosomix Inc. (2016–03–30)	Biomarkers and diagnostic methods for Alzheimer's disease and other neurodegenerative disorders
36	US 55892804 A	8/9/07	Rosetta Inpharmatics LLC (2007–01–26); Merck Sharp & Dohme LLC (2022–04–07); Merck Sharp & Dohme Corp (2009–11–02)	Computer systems and methods for identifying surrogate markers
33	US 52203108 A	8/12/10	University of Zurich (2009–12–18)	Method of Providing Disease-Specific Binding Molecules and Targets
33	US 201113066590 A	11/24/15	Nlife therapeutics S.L (2014–11–24); Micure Therapeutics Ltd. (2019–06–18); Palomo Limited (2021–07–01)	Compositions and methods for selective delivery of oligonucleotide molecules to specific neuron types
28	US 201314387853 A	10/1/15	Ionis Pharmaceuticals Inc. (2015–12–18); Biogen MA Inc. (2020–01–14); Washington University (2018–11–28)	Methods for modulating tau expression for reducing seizure and modifying a neurodegenerative syndrome
28	US 73343708 A	11/25/10	New York University (2014–08–20); Neurimmune Therapeutics AG(2010–07–05); Neurimmune Holding AG (2010–10–21)	Method of providing patient specific immune response in amyloidoses and protein aggregation disorders
28	US 201414906047 A	5/26/16	Ionis Pharmaceuticals Inc. (2015–12–18); Biogen MA Inc. (2020–01–14)	Compositions for modulating Tau expression
24	US 201716463062 A	9/12/19	Alector LLC (2017–03–15)	Anti-SIRP-Alpha Antibodies and Methods of Use Thereof
21	US 29323007 A	07/09/09	SYLENTIS S.A.U (2008–10–17)	Treatment of CNS Conditions

cornerstone of precision neurotherapeutics for complex neurodegenerative disorders.

Successful clinical translation will depend on integrating advanced biomarkers and stratified trial designs to enable personalized treatment strategies. Significant hurdles include long-term safety, durability, immunogenicity, and the challenge of treating mixed or co-pathological phenotypes where tauopathies frequently overlap with other proteinopathies including TDP-43 [108]. Preclinical studies in relevant animal and organoid models have provided encouraging proof of concept, but more comprehensive investigations are needed to evaluate long-term efficacy, off-target effects, and cell-type specificity [37,109].

Despite these challenges, RNA therapeutics represent an increasingly viable strategy for addressing the complex pathophysiology of tauopathies. RNA-based modalities act upstream of tau aggregation. These include ASOs, siRNAs, miRNAs, ribozymes, and mRNA therapies. Together, they offer the opportunity to modulate gene expression, correct splicing and regulate key pathways involved in tau production and phosphorylation. Ongoing clinical trials targeting *MAPT* and its regulators, coupled with an expanding patent landscape and progress in CNS-targeted delivery systems, are accelerating clinical translation.

Ultimately, continued innovation and clinical validation will determine the impact of these interventions. Through collaborative research, RNA-based therapeutics have the potential to deliver true disease-modifying benefits and alter the natural course of tauopathies, including AD, FTD, CBD, PSP, and CTE.

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Data availability statement

The data supporting the findings of this study are derived from publicly available sources. Patent data were obtained from Lens.org and Google Patents, and the datasets generated and analyzed during the current study are available in the supplementary Tables S1 and S2.

Table S1. RNA therapeutics-related raw patents filed in the United States, as retrieved from Lens.org. Table S1 is available at doi.org/10.6084/m9.figshare.30632585

Table S2. RNA therapeutics-related raw patents filed in the United States, as retrieved from Google Patents. Table S2 is available at doi.org/10.6084/m9.figshare.30639245

Ethical statement

This article does not contain any studies involving human participants or animals performed by any of the authors. Informed consent not applicable.

Studies on human and/or animal statement

This article does not contain any original studies with human participants or animals performed by any of the authors.

Informed consent

Not Applicable

Approval and registration number

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Declaration of the use of generative AI

The authors use generative AI for language editing to enhance clarity and readability. After using these tools, the author reviewed and revised the text as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Binita Rajbanshi: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Conceptualization. **Ilaria Brentari:** Writing – review & editing, Visualization, Writing – original draft. **Michela Alessandra Denti:** Writing – review & editing. **Jeffrey L. Cummings:** Writing – review & editing. **Anuj Guruacharya:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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