The Journal of Prevention of Alzheimer's Disease 13 (2026) 100626

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Editorial

Beyond target engagement: RNA therapeutics and the neuroimmune challenge in tauopathies

ARTICLE INFO

Keywords:
Alzheimer's disease
Tauopathies
RNA therapeutics
Neuroimmunology
Precision medicine

ABSTRACT

Recent advances in RNA-based therapeutics have generated considerable interest as a strategy for targeting tau pathology in Alzheimer's disease and related tauopathies. In their review, Rajbanshi and colleagues provide a comprehensive overview of emerging RNA therapeutic modalities, translational challenges, and ongoing clinical development efforts. This commentary discusses the promise of RNA-based approaches within the broader context of contemporary neurodegeneration research, highlighting the persistent disconnect between molecular target engagement and meaningful clinical benefit. Emerging evidence suggests that successful disease modification may require consideration of neuroimmune dysfunction, biological heterogeneity, and disease stage in addition to molecular pathology. The future success of RNA therapeutics will likely depend not only on achieving precise modulation of tau biology but also on translating these advances into sustained cognitive and functional benefit for patients.

Alzheimer's disease and related tauopathies have entered an era of increasingly sophisticated molecular therapeutics. Advances in biomarker development, molecular imaging, and target identification have enabled the development of interventions capable of engaging key pathological processes with unprecedented precision. Yet despite decades of progress and a growing understanding of tau biology, meaningful clinical benefits have remained difficult to achieve. Multiple tau-directed monoclonal antibodies and small-molecule therapies have demonstrated promising preclinical results and, in some cases, evidence of target engagement in humans, but these advances have not consistently translated into durable improvements in cognition or function. This persistent disconnect between molecular success and clinical efficacy has emerged as one of the central challenges in contemporary neurodegeneration research.

Against this backdrop, RNA-based therapeutics represent a notable shift in strategy. Rather than targeting aggregated tau protein after pathology has become established, these approaches intervene upstream at the transcript level through mechanisms including antisense oligonucleotides, small interfering RNAs, and splice-modulating therapies. By enabling selective modulation of MAPT expression, correction of pathogenic splicing patterns, and potentially isoform-specific intervention, RNA therapeutics offer a degree of precision that has been difficult to achieve with conventional protein-directed approaches. In their timely review, Rajbanshi and colleagues provide a comprehensive overview of the emerging RNA therapeutic landscape for tauopathies, synthesizing advances in molecular modalities, therapeutic targets, clinical development, and translational challenges [1]. Importantly, the review extends beyond molecular mechanisms to examine clinical development pathways, intellectual property trends, and emerging translational challenges, providing a multidimensional perspective on the future of RNA therapeutics.

A major strength of this review is its recognition that RNA therapeutics are not a singular technology, but rather a diverse and rapidly evolving set of molecular platforms with distinct mechanisms, advantages, and translational considerations. Rajbanshi and colleagues provide a comprehensive overview of antisense oligonucleotides, small interfering RNAs, microRNAs, messenger RNA-based approaches, aptamers, and catalytic nucleic acid technologies, illustrating how each modality may be leveraged to address different aspects of tau biology. Beyond cataloging these approaches, the authors thoughtfully address many of the practical challenges that will determine their clinical success, including blood-brain barrier penetration, target specificity, tau isoform heterogeneity, long-term safety, and scalable delivery strategies. The review also provides valuable discussion of ongoing clinical programs, emerging biomarker frameworks, and the evolving intellectual property landscape, collectively illustrating the field's progression from theoretical promise toward a clinically actionable therapeutic pipeline. Particularly noteworthy is its emphasis on precision medicine, highlighting opportunities for biomarker-guided and potentially isoform-specific interventions tailored to the biological heterogeneity of tauopathies.

Even as RNA therapeutics move closer to clinical implementation, an important translational question remains. Across neurodegenerative disease research, therapeutic development has become increasingly successful at demonstrating molecular target engagement, including reductions in cerebrospinal fluid tau concentrations, improvements in imaging biomarkers, and modulation of disease-associated pathways. For example, early clinical studies of the antisense oligonucleotide BIIB080 demonstrated reductions in CSF total tau and phosphorylated tau alongside favorable biomarker changes [1]. However, the broader

https://doi.org/10.1016/j.tjpad.2026.100626
Received 6 June 2026; Accepted 8 June 2026
Available online 15 June 2026

experience with tau-directed and other neurodegenerative therapeutics suggests that biomarker improvement alone does not necessarily translate into meaningful cognitive or functional benefit [2]. This distinction between surrogate markers of target engagement and clinically meaningful measures of disease modification represents one of the central challenges facing contemporary Alzheimer's disease therapeutics.

This raises a fundamental question for the next generation of RNA-based interventions: is modulation of tau pathology alone sufficient to alter the trajectory of neurodegenerative disease? Several explanations merit consideration. Therapeutic intervention may occur after critical thresholds of neurodegeneration have already been crossed, when neuronal loss and network dysfunction have become only partially reversible. Conventional cognitive endpoints may fail to capture subtle but biologically meaningful changes occurring earlier in the disease course, potentially obscuring therapeutic effects during preclinical and prodromal stages. Alternatively, pathogenic processes initiated by tau accumulation may become increasingly self-sustaining over time, reducing the impact of subsequently lowering tau burden. Emerging frameworks further suggest that chronic neuroimmune dysfunction may evolve into an important driver of disease progression after symptom onset, such that successful suppression of pathogenic proteins may not fully reverse established inflammatory and neurodegenerative cascades [2]. Within this context, RNA therapeutics may ultimately encounter the same translational barrier faced by earlier tau-directed strategies if molecular target engagement proves insufficient to modify the broader biological systems that underlie clinical decline. Ultimately, patients experience neurodegenerative disease through changes in cognition, function, and quality of life rather than through changes in molecular biomarkers. Understanding these broader biological systems may be critical for overcoming the persistent disconnect between biomarker improvement and clinical efficacy.

Increasingly, Alzheimer's disease is being conceptualized not solely as a disorder of toxic protein accumulation, but as a systemic disease involving dynamic interactions among neurons, glia, and peripheral and central immune processes that evolve across the disease course [3]. Dysregulation of the immune system is now recognized as a cardinal feature of AD, and growing evidence suggests that communication between the peripheral and central immune compartments contributes to disease pathogenesis and progression [3]. Tau pathology exists within a broader biological context characterized by microglial and astrocytic activation, cytokine signaling, altered immune surveillance, and persistent inflammatory responses. Indeed, tau itself participates in innate immune and cytokine signaling pathways, underscoring the bidirectional relationship between protein pathology and neuroimmune dysfunction [1].

Recent frameworks propose that neuroimmune responses may evolve over the course of disease. Early glial activation may initially serve protective functions by facilitating clearance of pathological proteins and supporting tissue repair [2,3]. However, chronic exposure to pathogenic protein species may ultimately drive maladaptive immune states characterized by persistent inflammation, impaired resolution mechanisms, and reduced cellular resilience [2]. Within this framework, neurodegeneration is no longer viewed as a purely neuron-centric process but rather as a self-reinforcing network of pathological interactions that may persist even after the initiating molecular insult has been attenuated. This evolving perspective reflects a broader transformation in our understanding of brain immunity, in which the central nervous system is increasingly recognized as being in continuous communication with peripheral immune compartments rather than functioning as an immunologically isolated organ [4].

These considerations point toward a future in which the success of RNA therapeutics may depend as much on patient selection and treatment timing as on molecular target selection. The review appropriately emphasizes opportunities for precision intervention through isoform-specific targeting, biomarker-guided therapy, and increasingly sophisticated approaches to RNA delivery [1]. Indeed, accumulating evidence suggests that interventions targeting tau pathology may be most effective during presymptomatic or early biomarker-positive stages of disease, before extensive neurodegeneration and systems-level dysfunction become established [1,3]. This concept is reflected in the growing emphasis on biologically staged intervention and the use of fluid and imaging biomarkers to identify patients most likely to benefit from treatment [1].

At the same time, emerging work across dementia research highlights the importance of biological heterogeneity in shaping disease progression and therapeutic response. Genetic susceptibility, environmental exposures, resilience factors, and neuroimmune state may all influence how neurodegenerative processes unfold and how patients respond to intervention [5]. As a result, future therapeutic strategies may require a broader conception of precision medicine that extends beyond molecular targets alone to encompass the biological context in which pathology develops and progresses [5].

The review also highlights the potential value of combinatorial therapeutic approaches [1]. Rather than viewing tau as an isolated target, future interventions may increasingly integrate RNA-based tau suppression with amyloid-directed therapies, neuroimmune modulation, or other disease-modifying strategies. Such approaches reflect a broader shift occurring across neurodegeneration research: away from expectations of single-target rescue and toward the goal of network-level disease modification. In this framework, the future of RNA therapeutics may depend not only on molecular precision, but also on biologically staged intervention capable of addressing the complex and interconnected mechanisms that drive disease progression.

Rajbanshi and colleagues capture an important transition in the evolution of tau-directed therapeutics. By moving intervention upstream to the level of RNA, these approaches offer unprecedented opportunities for molecular specificity, therapeutic flexibility, and precision targeting of disease-relevant pathways. As the field progresses from preclinical promise to clinical implementation, RNA-based therapeutics are increasingly positioned as a potentially transformative strategy for Alzheimer's disease and related tauopathies.

At the same time, the challenges confronting RNA therapeutics are likely to extend beyond delivery platforms, target selection, and biomarker engagement. Durable clinical success will require a deeper understanding of disease timing, biological heterogeneity, and the complex neuroimmune processes that shape vulnerability, resilience, and progression. Future advances will depend not only on identifying increasingly sophisticated molecular interventions, but also on developing therapeutic frameworks capable of addressing the interconnected biological systems that underlie neurodegeneration.

RNA therapeutics may ultimately redefine the treatment landscape for tauopathies. Their success, however, will be measured not by their ability to modify molecular biomarkers alone, but by whether they can be translated into sustained cognitive and functional benefit for patients.

Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

No generative AI or AI-assisted technologies were used in the preparation of this manuscript.

CRediT authorship contribution statement

Elizabeth Anne Breen: Conceptualization, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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