

Advancing the battle against Alzheimer's Disease: A focus on targeting tau pathology by antisense oligonucleotide

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Alzheimer's disease (AD), the most prevalent form of dementia, is an escalating public health concern that is receiving increasing attention. It is estimated that over 55 million individuals worldwide are affected by dementia, primarily due to AD, and this figure is projected to 139 million in 2050. The fundamental mechanism underlying AD remains elusive. The two primary pathological features of AD are the accumulation of Amyloid- β ($A\beta$) plaques and hyperphosphorylated tau (p-tau) protein, which form neurofibrillary tangles. However, current therapeutic options for AD predominantly focus on

symptom management. Aducanumab and Leqembi, approved by the U.S. Food and Drug Administration (FDA) for AD, are the two disease-modifying drugs targeting aggregated forms of $A\beta$, following the 2003 approval of memantine. Nonetheless, ongoing debates persist regarding their efficacy and safety, such as the occurrence of amyloid-related imaging abnormalities (ARIA) subsequent to administration.¹ Therefore, there is a pressing need for additional treatments that can modify the disease, with the aim of preventing or mitigating its progression.

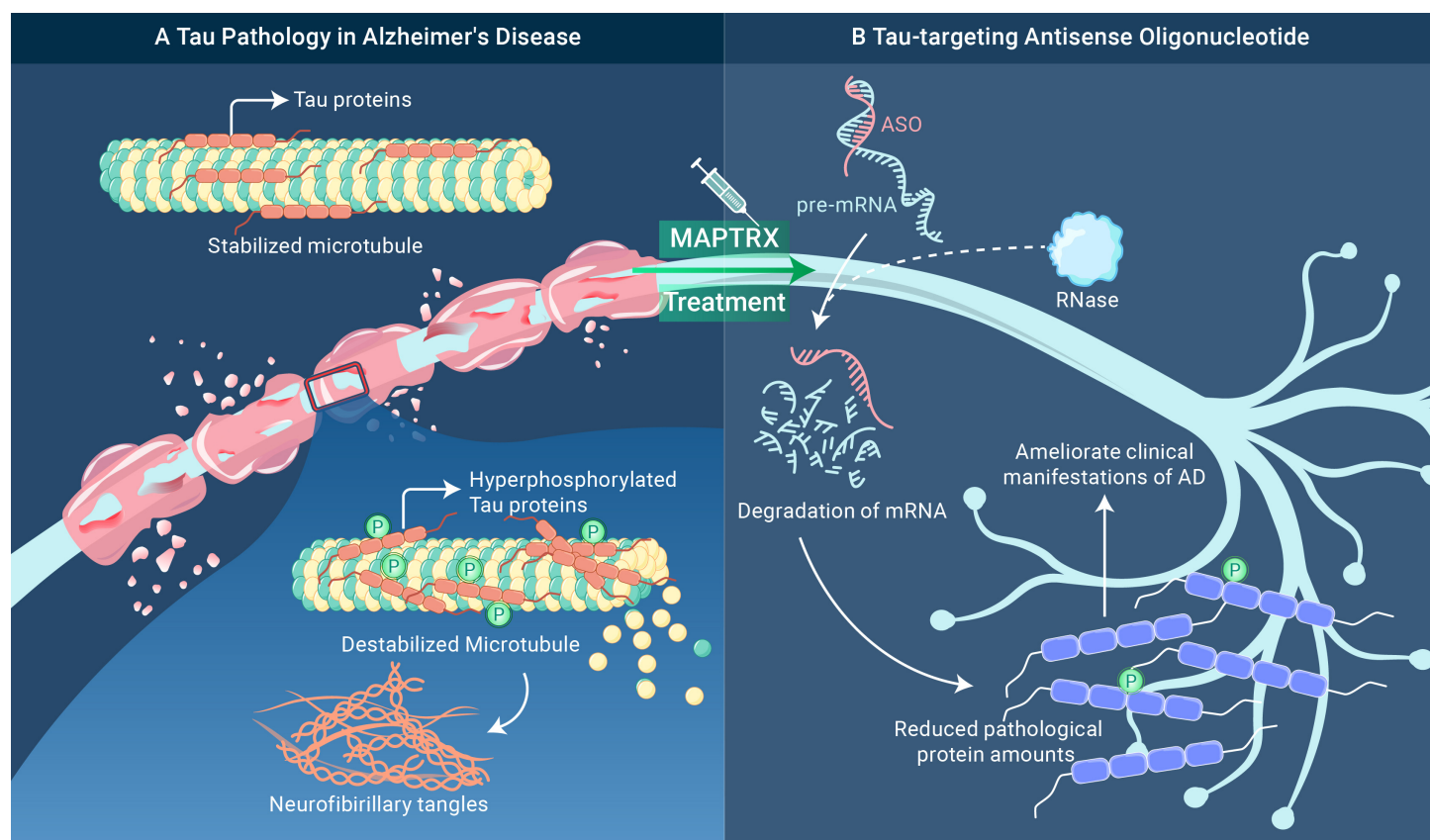


Figure 1. Tau pathology in Alzheimer's Disease (AD) and targeting of tau pathology by antisense oligonucleotide (A) Under physiological conditions, tau proteins are involved in the formation of microtubule. In AD, the hyperphosphorylated tau proteins affect microtubule stability and form neurofibrillary tangles, which ultimately lead to neuronal damage. (B) MAPTRX is a new antisense oligonucleotide (ASO) targeting the MAPT pre-mRNA. It causes mRNA degradation by RNase H1 and reduces both tau and hyperphosphorylated tau protein amounts. It has been verified to ameliorate clinical symptoms in AD patients.

In recent years, researchers have increasingly focused on tau pathology as a significant pathological alteration in the development and progression of AD. Tau related pathology is characterized by the accumulation of p-tau protein, which is believed to be responsible for the formation of neurofibrillary tangles. It has been documented that there are multiple pathways by which p-tau can accumulate, leading to synaptic dysfunction and memory deficits. In comparison to $A\beta$ pathology, tau pathology exhibits a stronger correlation with synaptic damage, neuron death, and cognitive decline in both AD patients and animal models. PET, CSF, and plasma biomarkers of tau pathology have been widely employed to enhance the AD diagnostic process in

clinical practice.

Furthermore, tau pathology is not only a consequence of $A\beta$, but in certain situations, it can also be a driving factor for $A\beta$ production.² Preclinical studies conducted on animal models have demonstrated that reducing tau protein levels in the brain can alleviate synaptic abnormalities and cognitive decline caused by $A\beta$ pathology. Likewise, clinical evidence underscores the crucial role of tau pathology in the onset and progression of AD. A recent publication in Nature Medicine reported a second late-onset familial AD patient within the largest autosomal dominant inherited AD family that encompasses over 1,200 carriers of the *PSEN1* E280A mutation. This patient

exhibited a delay in disease onset of over 30 years, compared to the anticipated age of onset.³ Similar to the first reported late-onset familial AD patient in the same family in 2019, this fortunate patient displayed significantly reduced levels of phosphorylated tau protein in comparison to other carriers of the same mutation within the family.⁴ Further investigations revealed that the diminished p-tau levels in these two familial AD patients were attributed to the presence of distinct protective genetic variations, namely the *APOE3* R136S mutation and *RELN* H3447R mutation, respectively. The two fortunate familial AD patients still have high A β pathology, demonstrating that tau pathology has a considerable effect on the development of cognitive impairment in AD. These findings underscore the potential of targeting tau pathology in AD to substantially delay disease onset.

Targeting tau protein represents a promising avenue for combating AD and engenders hope among the general public. A recent study titled "Tau-targeting antisense oligonucleotide MAPTRx in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial" presents exciting outcomes from the initial application of gene silencing therapy for AD (Figure 1).⁵ The study evaluated the safety, pharmacokinetics, and targeting efficacy of intrathecally administered tau-targeting antisense oligonucleotide (ASO) in 46 patients with mild AD. The results indicated good tolerability of the drug, with both the treatment and placebo groups experiencing mild to moderate adverse effects, while no severe adverse events were observed in the treatment group. In the two treatment groups receiving the highest ASO doses (60 mg and 115 mg), there was a reduction of over 50% in total tau protein and p-tau protein levels in the cerebrospinal fluid after 24 weeks. This development is truly exciting in the field of neurodegenerative diseases, following the FDA's approval of ASO therapy for the treatment of Amyotrophic Lateral Sclerosis in April of this year. Future investigations should consider evaluating the potential impact of reducing tau protein levels on ameliorating clinical manifestations in AD patients. Furthermore, it is imperative to carefully examine the long-term safety implications of this approach, as tau protein serves functional roles in the human body.

Currently, many new small molecules that can selectively promote tau removal and alleviate cognitive impairment in animal models have been reported by researchers. Furthermore, more than thirteen drugs targeting tau are in clinical trials. All of them are disease-modifying biologics and small molecules. Most of them are in Phase 1 and Phase 2 trials. Among them, TRX0237, a second-generation tau protein aggregation inhibitor, is in Phase 3 trials. It is being investigated for its potential to slow the progression of mild to moderate AD.

Addressing the complexity of tau pathology through the inhibition of tau

aggregation, the enhancement of tau clearance, and the prevention of the spread of tau pathology by pharmacological agents or gene therapies, it is hoped that effective treatments can be developed to modify the disease. Nevertheless, further research is necessary to comprehend the mechanisms of tau dysfunction leading to the development and progression of AD, and to develop safe and effective drugs that can overcome the obstacles encountered in clinical practice.

In the context of AD, a condition that profoundly affects families worldwide, even the slightest advancements are cause for great enthusiasm. For instance, a mere 10-year delay in disease onset would hold tremendous implications for the majority of AD patients who experience its onset during their later stages of life. By specifically addressing the tau pathology, it undoubtedly fosters new hope in conquering this enduring affliction.

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DECLARATION OF INTERESTS

The authors declare no competing interests.