TAU-BASED THERAPEUTICS IN ALZHEIMER'S DISEASE: WHERE WE ARE AND WHAT LIES AHEAD

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Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative condition clinically defined by progressive memory loss and cognitive impairment. It currently affects over 47 million people worldwide, a figure projected to exceed 131 million by 2050. AD is the leading cause of dementia, accounting for approximately 60–80% of all diagnosed cases. Sporadic Alzheimer's disease, the most common form, occurs in 10–50% of individuals over the age of 65. Its development is influenced by a wide range of factors, including aging, lifestyle choices (such as diet, exercise, education, and cognitive activity), immune system decline, chronic inflammation, infections (both chronic and latent), vascular dysfunction, and sleep disturbances. Recent findings also suggest a possible link between gut microbiota, ischemic events, and AD pathogenesis.

The heritability of sporadic AD is notably high—estimated at 70–79% in twin studies—yet its underlying causes are largely multifactorial. The disease is believed to result from a complex interplay of genetic, environmental, vascular, and still-unknown contributors. One known genetic risk factor is the ε4 allele of the apolipoprotein E (APOE) gene, which is associated with increased susceptibility to sporadic AD. Nevertheless, a significant portion of the genetic risk remains unexplained. AD is currently the leading cause of acquired disability globally, affecting one in two women and one in three men. It is widely regarded as one of the major unsolved challenges in modern medicine due to its profound impact on families, society, and global healthcare systems. In 2010, the worldwide economic burden of dementia was estimated at USD 604 billion—a figure expected to rise dramatically unless effective interventions are developed.

From a neuropathological standpoint, AD is characterized by the extracellular accumulation of amyloid-β (Aβ) plaques and the intracellular formation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. These pathological changes are central to the postmortem diagnosis of the disease. The most neurotoxic forms of both amyloid and tau are believed to be their soluble oligomeric forms, which can propagate between neurons in a prion-like fashion. The underlying mechanisms driving plaque and tangle formation remain poorly understood but are generally attributed to abnormal protein misfolding and aggregation. These processes lead to widespread neuronal death and synaptic loss, resulting in brain atrophy. In fact, the brains of individuals with advanced AD may weigh up to one-third less than those of age-matched individuals without dementia.

Substances Preventing Tau Protein Post-Translational Changes

The strong association between tau protein hyperphosphorylation and the progression of Alzheimer's disease (AD) has led to the development of therapeutic strategies targeting tau-modifying enzymes, particularly protein kinases. Among them, glycogen synthase kinase-3 (GSK-3) has emerged as one of the most advanced clinical targets. Initial clinical trials explored

the use of lithium—a known GSK-3 inhibitor—in AD patients. However, the outcomes were inconclusive, possibly due to limited patient numbers, variability in responsiveness, and lithium's narrow therapeutic window.

Tideglusib (NP031112, NP-12), another GSK-3 inhibitor, has shown promise in preclinical models, where it reduced neuronal loss, gliosis, and tau phosphorylation while improving spatial memory in transgenic mice. In a phase IIa placebo-controlled, dose-escalation study involving 30 AD patients treated for five months, Tideglusib was found to be safe and showed favorable, though statistically non-significant, cognitive trends. A larger phase IIb trial involving 308 patients across 55 European centers also confirmed the safety profile of Tideglusib, but no significant clinical benefit was observed.

Another kinase of interest is Fyn tyrosine kinase, which contributes to tau phosphorylation at the N-terminal region and is also implicated in amyloid-related signaling. Saracatinib (AZD0530), a Fyn inhibitor, improved memory performance in AD mouse models and was shown to be safe and well tolerated in a phase I clinical trial. A multicenter phase IIa trial evaluating Saracatinib in 159 AD patients is currently ongoing.

Substances That Prevent Microtubule Destabilization by Amyloid

Research has shown that amyloid oligomers contribute to microtubule destabilization and impair axonal transport by activating the phosphatase calcineurin, particularly in tau-deficient mouse models. These findings suggest that microtubule destabilization may be a critical mechanism underlying neurodegeneration in Alzheimer's disease.

Epothilone D (BMS-241027), a small-molecule microtubule stabilizer capable of crossing the blood–brain barrier, demonstrated promising results in preclinical models. In a transgenic mouse model of tauopathy, Epothilone D enhanced axonal microtubule density and led to improved cognitive performance, although it did not significantly alter tau pathology. The compound progressed to a phase I, double-blind, randomized, placebo-controlled, multicenter clinical trial (NCT01492374) aimed at evaluating its safety and tolerability in AD patients. However, no results from this trial have been published, and further development of the drug for Alzheimer's treatment has been discontinued.

More recently, another small-molecule compound, abeotaxane (TPI-287), was investigated in a phase I clinical study (NCT02133846) to assess its safety and tolerability in AD patients. The treatment involved intravenous administration every three weeks over a nine-week period, with an optional extension phase of three months under open-label conditions. Unfortunately, the drug was poorly tolerated in individuals with Alzheimer's disease, and no significant improvements were observed in exploratory cognitive outcome measures. As a result, abeotaxane did not advance beyond the early trial phase.

Immunotherapy Against Tau Protein

Initial insights into immunotherapy for Alzheimer's disease (AD) emerged during investigations into whether the human β-amyloid peptide 1–42 could cross the blood–brain barrier. Despite the underwhelming outcomes of several late-stage clinical trials targeting amyloid-beta through immunotherapeutic strategies, interest in immunotherapy for neurodegenerative diseases—especially AD—remains strong. This approach is being actively explored as a promising method for clearing pathological proteins from the brain.

Recent experimental studies involving anti-tau immunotherapy in animal models have shown encouraging results, supporting its potential for the removal of toxic tau species in

tauopathies such as Alzheimer's disease. These strategies involve using antibodies to target and eliminate abnormal tau protein aggregates, with the aim of restoring or preserving neuronal function. The effectiveness of such therapies is closely linked to the selection of appropriate tau epitopes—regions of the protein that can be specifically recognized by the immune system.

Given that hyperphosphorylation of tau is believed to drive its aggregation and the formation of neurofibrillary tangles, various phosphorylated epitopes have been tested in preclinical models, many of which have produced beneficial outcomes. However, phosphorylation is not the only post-translational modification involved in tau aggregation. Other alterations—such as glycosylation, truncation, and ubiquitination—also play a role in the transformation of tau from a soluble protein into insoluble deposits. These insights have paved the way for a broad range of both active and passive immunotherapy strategies in the treatment of Alzheimer's disease.

Several immunotherapeutic approaches currently under investigation target different regions of the tau protein, not limited solely to phospho-epitopes. These trials represent a new generation of potential therapies that may intervene more effectively in the disease process.

One of the most notable developments in this field is AADvac-1, an active vaccine-based immunotherapy composed of a synthetic tau peptide sequence corresponding to amino acid residues 294–305 from a misfolded tau fragment. A phase I randomized, double-blind, placebo-controlled clinical trial involving 30 AD patients aged 50–85 assessed the safety and immunogenicity of AADvac-1. Participants received subcutaneous injections over a three-month period. The vaccine was well tolerated, with mostly mild or no adverse effects reported. Moreover, the generation of high anti-tau antibody titers indicated a robust immune response.

Future Perspectives

As highlighted throughout this chapter, the current status of tau-targeted therapies for Alzheimer's disease (AD) remains inconclusive. This uncertainty is largely due to the limited number of studies, inconsistent methodologies, and insufficient high-quality evidence. The field is still in its early stages, making it difficult to draw broad or definitive conclusions. Despite the urgent need for effective interventions, there has been little therapeutic advancement in AD over the past two decades. Existing medications provide only modest symptomatic relief, and many large-scale clinical trials—particularly those focused on amyloid—have failed to show clinical efficacy in phase III trials.

One reason for this lack of progress may be the prolonged dominance of the amyloid hypothesis, which has shaped most therapeutic strategies, often at the expense of exploring tau protein—the principal component of neurofibrillary tangles, which correlates more directly with the severity of dementia. Although research on tau has gained momentum in recent years, the quality of available data remains limited, and some studies have reported adverse effects without long-term safety data.

Several tau-targeting clinical trials have failed thus far, but these outcomes provide valuable lessons for future research. First, tau pathology primarily affects neurons intracellularly, indicating that future therapeutic strategies should be designed to penetrate cells and act within the neuronal environment. Second, as the field of immunotherapy continues to evolve, it is important to develop second- and third-generation tau-directed immunotherapies. Smaller antibody fragments, for instance, may offer better penetration into

the brain and neurons, increased flexibility in epitope targeting, and enhanced suitability for gene therapy applications compared to full-sized antibodies.

Third, recent efforts have focused on screening compounds that prevent tau seeding and spread. However, less attention has been given to identifying agents that inhibit the neurotoxicity of tau aggregates—an equally important goal that may not necessarily correlate with their aggregation or propagation properties. Ideally, future screening models should incorporate multiple functional endpoints in a unified assay system.

Fourth, the structural diversity of tau aggregates complicates the development of small-molecule aggregation inhibitors, though this variability may be less problematic for antibody-based therapies. Fifth, broader neurodegeneration-related targets—beyond amyloid and tau—should continue to be investigated, despite their inherent complexity. Sixth, there is a growing consensus that the timing of therapeutic intervention is critical. Future long-term clinical trials should prioritize early-stage intervention, particularly during the preclinical or prodromal phases of the disease. Finally, tau-targeted therapies may prove more beneficial in later stages of AD, as tau pathology is more closely correlated with cognitive decline than amyloid burden.

The data presented in this chapter—including the distribution and abundance of intra- and extracellular tau, the diversity of tau epitopes, and preliminary evidence that antibodies may differentially influence tau toxicity—point to important directions for future research. These findings suggest that specific immunotherapeutic strategies targeting distinct tau forms could be clinically meaningful.

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