Narrative Review Article

Can A Synergistic Therapy Be Administered Against Both Aβ and Tau Aggregates in Alzheimer's Disease?

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and behavioral changes, and is pathologically defined by the accumulation of amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the brain. The amyloid cascade and tau hypotheses describe complementary mechanisms contributing to disease progression, yet current therapies have historically focused on targeting Aβ alone, with limited clinical success. These outcomes highlight the need for more comprehensive treatment approaches that address multiple pathogenic pathways. This review examines current evidence on Aβ and tau pathology, evaluates therapeutic strategies targeting each pathway, and assesses the scientific feasibility, challenges, and limitations of synergistic dual-target approaches in Alzheimer's disease. Genetic risk factors, including apolipoprotein E APOE4 polymorphism, transgenic mouse models, approved and experimental immunotherapies, and emerging biomarkers such as phosphorylated tau-217 (p-tau217) are discussed. While recent anti-amyloid monoclonal antibodies have shown modest clinical benefit, the interaction between Aβ and tau pathology suggests that combination therapy may offer improved disease progression. However, there are still several mechanistic, pathological, and safety challenges. Further research is required to determine whether dual-target therapies can be translated into effective and safe treatment for Alzheimer's disease.

Keywords: Alzheimer's disease; amyloid-β; tau, amyloid cascade hypothesis; tau hypothesis; APOE; genetic linkage; mouse models; immunotherapy; biomarkers; synergistic therapy

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and is characterized by progressive deterioration of memory, cognition, and behavior. Clinical symptoms include memory loss, impaired reasoning, communication difficulties, and personality changes. Pathologically, AD is associated with deposition of amyloid plaques and hyperphosphorylation of tau into neurofibrillary tangles in the brain (1). AD predominantly affects older adults, with prevalence increasing sharply after the age of 65 (2). As of 2024, 6.9 million Americans have AD, representing nearly 11% of the population aged 65 and older, and this number is projected to double by the year 2050 due to population aging (2). Although recent therapies have received regulatory approval, no curative treatment currently exists, and disease-modifying effects remain modest (3). Diagnosis of AD remains challenging, particularly in the early stages of the disease. Clinical evaluation and cognitive testing are commonly used but lack sensitivity. Additional diagnostic tools include brain imaging, cerebrospinal fluid (CSF)

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analysis, and assessment of family history; however, no single biomarker is sufficient to definitively diagnose AD across all disease stages (4). These diagnostic limitations complicate early intervention, when treatments are most likely to be effective.

Despite decades of research, therapeutic approaches targeting alone have yielded limited clinical benefit, prompting increasing interest in alternative or complementary approaches. Increasing evidence suggests that amyloid-β and tau pathologies interact during disease progression, potentially amplifying neurodegeneration. However, the feasibility and efficacy of therapeutics simultaneously targeting both Aβ and tau remain incompletely understood. The review evaluates current evidence on AB and tau pathology, examines therapeutic strategies targeting each pathway, and assesses the scientific rationale, challenges, and future potential of synergistic dual-target approaches for Alzheimer's disease.

GENETIC RISK FACTORS IN ALZHEIMER'S DISEASE: APOLIPOPROTEIN E (APOE) POLYMORPHISM

A major genetic risk factor for Alzheimer's disease is polymorphism in the Apolipoprotein E (APOE) gene, which plays a key role in Aβ metabolism polymorphism. There are three isoforms of APOE: APOE2, APOE3, and APOE4. Individuals carrying the APOE4 allele have a significantly increased risk of developing AD, with homozygous carriers exhibiting the highest susceptibility (4). In contrast, APOE2 is considered protective, while APOE3 is neutral (5).

In approximately 95% of late-onset Alzheimer's disease (LOAD) cases, it is assumed that the cause involves both environmental and genetic factors, whereas early-onset Alzheimer's disease (EOAD), is more frequently associated with highly penetrant genetic mutations (6). Most cases of AD do not follow Mendelian inheritance patterns. However, a small subset of EOAD cases exhibit autosomal dominant inheritance due to mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1) or presenilin 2 (PSEN2) genes (Figure 1).

Regardless of whether the genetic risk is polygenic, as in LOAD, or mendelian, as in familial EOAD, these alterations ultimately converge on dysregulation of Aβ production or clearance. APP is a transmembrane protein that undergoes cleavage by the β-secretase and γ-secratase complex. β-secretase cleavage produces a soluble extracellular fragment (sAPPβ) and a membrane-bound fragment (C99), which is subsequently cleaved by γ-secretase to generate aggregation-prone Aβ peptides and the APP intracellular domain (7). Mutations in PSEN1 and PSEN2, which encode components of the γ-secratase complex, can shift cleavage toward increased production of the pathogenic Aβ40-42 species, thereby promoting plaque formation and neurotoxicity (4, 6).

Although multiple genetic and environmental factors contribute to LOAD, APOE remains the strongest genetic determinant of risk. Individuals homozygous for APOE4 exhibit a lifetime Alzheimer's disease risk of approximately 40-50% by ages 70-85 (Figure 2) (4). In addition to its effects on amyloid pathology, APOE4 has been implicated in tau-mediated degeneration. Mouse models expressing human APOE4 alleles demonstrate higher levels of tau pathology and neurodegeneration compared to non-carriers, particularly in the presence of amyloid APP mutations. Specifically, transgenic models with the Swedish (KM670/671NL), Arctic (E693G), and Dutch (E693Q) APP mutations show increased Aβ fibril formation, further supporting the link between genetic risk factors and amyloid pathology (Table 1) (8).

MOLECULAR PATHOLOGY OF ALZHEIMER'S DISEASE

Amyloid-β (Aβ) pathology represents one of the two defining molecular hallmarks of Alzheimer's disease.

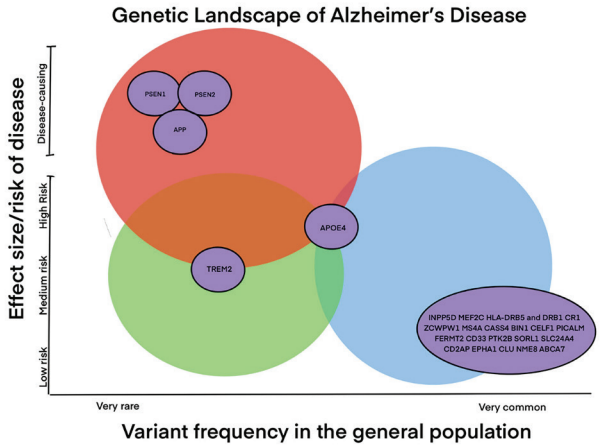

Figure 1. Allele frequency and risk of disease in humans. *The blue region shows variants that are rare and disease-causing and contain the PSEN1 and 2 and APP mutations. The green region shows alleles with low frequency that are high risk, and the red region shows common variants with little effect (28).*

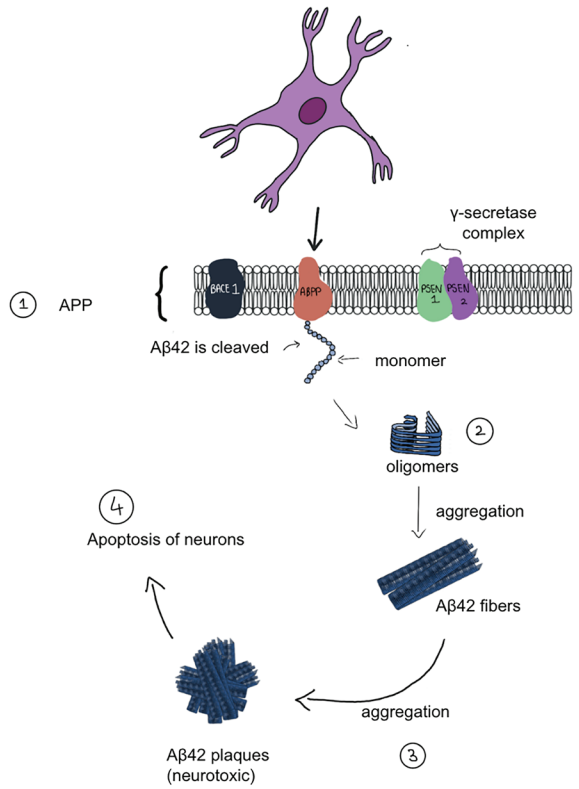

Figure 2. Amyloid cascade hypothesis. *(1) Depiction of the APP complex with a BACE1 and PSEN1 and 2 γ-secretase complex that cleaves APP to form Aβ42 monomers. (2) The monomers aggregate to form oligomers. (3) The oligomers aggregate further to form plaques. (4) The resulting plaques are neurotoxic and lead to the apoptosis of neurons.*

Amyloid-β originates from the cleavage of the amyloid precursor protein (APP), making APP processing a key step in the development of amyloid pathology. The APP gene is located on chromosome 21 and undergoes sequential cleavage by β-secretase and γ-secretase to generate Aβ peptides consisting of 36–43 amino acids (9). Although the physiological function of Aβ remains incompletely understood, its accumulation is strongly associated with neurodegeneration. Under normal conditions, Aβ is cleared from the brain through enzymatic and nonenzymatic pathways. Nonenzymatic pathways include microglial phagocytosis, interstitial fluid drainage, and transport across the blood-brain barrier via receptors such as low-density lipoprotein receptor-related protein-1 (LRP-1) (10, 11). Through this pathway, Aβ binds to LRP1 on endothelial cells in the blood-brain barrier and is transported into the bloodstream (4). When these clearance mechanisms are impaired, Aβ accumulates within the brain, promoting aggregation and plaque formation (4). In experimental models, disruption of LRP1 function at the blood–brain barrier reduces Aβ clearance into the circulation, resulting in increased accumulation of Aβ plaques within the brain (11) (Figure 2).

The amyloid cascade hypothesis proposes that once Aβ accumulates in the brain, its hydrophobic properties cause its monomers to aggregate. These aggregated monomers then progress to form β-sheets containing oligomers and fibrils, which in turn form plaques. In addition to plaque deposition, Aβ oligomers themselves

Table 1. Mouse Model Mutations. *Column 1 shows the name of the given mutation, column 2 shows the position of the mutation, column 3 shows the effect of the mutation on the production of Aβ aggregation and the Aβ40/Aβ42 ratio, and column 4 shows the model of the mouse used (4).*

Name	Mutation	Effect on Ab	Model Mouse
Swedish	KM670/671NL	Increased total amount of AB, unchanged amount of AB42/AB40 ratio	Tg2576, APP23, J20, TgCRND8, APPswe/PSEN1dE9, 5xFAD, A7, NL-G-F
Arctic	E693G	Arctic Aβ40 forms protofibrils at an increased propensity and faster rate	NL-G-F
Dutch	E693Q	Dutch Aβ increases aggregation rates and fibril formation	—
Austrian	T714I	Increased Aβ42/Aβ40	A7
Florida	I716V	Increased Aβ42(43)/Aβ40	5xFAD
Iberian	I716F	Increased Aβ42/Aβ40 ratio	NL-G-F
Indiana	V717F	Increased Aβ42/Aβ40	PDAPP. J20. TgCRND8
London	V717I	Increased Aβ42/ABβ0	5xFAD

are thought to be neurotoxic and capable of disrupting synaptic function, contributing to early neuronal dysfunction in Alzheimer's disease (4) (Figure 2).

Therapeutic efforts targeting the formation of Aβ aggregates have included β-secretase (BACE1) inhibitors, which have been shown to reduce Aβ levels in cerebrospinal fluid by approximately 90% (12). However, despite successfully lowering the amyloid burden, these inhibitors did not slow cognitive decline in clinical trials and were associated with adverse effects, thereby limiting their use (12). The aggregation of another protein, tau, represents a second, equally important contributor to Alzheimer's disease progression. Tau is a microtubule-associated protein responsible for binding to and stabilizing microtubules within neuronal axons, supporting axonal structure, and intracellular transport (15). In AD, tau undergoes post-translational modifications, most notably hyperphosphorylation, which causes it to dissociate from microtubules and aggregate into neurofibrillary tangles (13). Loss of stabilization from tau binding interferes with axonal transport, limiting the movement of proteins and organelles needed for synaptic function and ultimately affecting neuronal survival (13). Tau phosphorylation is regulated by the balance of kinase and phosphatase activity, and disruption of this balance can drive excessive tau phosphorylation and microtubule destabilization.

Although hyperphosphorylation is the most commonly observed modification in Alzheimer's disease, tau aggregation can also be influenced by acetylation, truncation, and glycosylation (13). Aggregated tau takes on multiple structural forms, including soluble oligomers, straight filaments, twisted ribbons, and paired helical filaments. In neurons containing neurofibrillary tangles (NFTs), these structural and biochemical changes are associated with measurable cytoskeletal abnormalities, such as reduced microtubule number and length, altered tubulin expression, and increased tubulin acetylation, all of which disrupt normal cytoskeletal organization and contribute to neuronal dysfunction (13) (Figure 3).

THERAPEUTIC STRATEGIES TARGETING AMYLOID-B AND TAU

Monoclonal antibodies targeting amyloid-β (Aβ) represent the most advanced disease-modifying therapies currently available for Alzheimer's disease (AD). Several antibodies, including aducanumab, lecanemab, and gantenerumab, have been developed to bind distinct Aβ species and promote amyloid clearance.

The binding properties of aducanumab, lecanemab, and gantenerumab have been evaluated using experimental models carrying the Arctic APP mutation, which promotes accelerated formation of Aβ40 protofibrils. Antibody affinity for Aβ monomers, oligomers, and protofibrils was measured using enzyme-linked immunosorbent assays (ELISA), a standard method for quantifying antibody–antigen interactions. Gantenerumab demonstrated the highest affinity for Aβ monomers, with an IC50 of 2.6 μM, whereas lecanemab exhibited the strongest binding to both small and large protofibrils, with an IC50 of approximately 0.8 nM. In contrast, aducanumab showed substantially weaker binding, with IC50 values exceeding 80 nM for small protofibrils and 22 nM for large protofibrils (14).

Further comparisons revealed that gantenerumab binds more strongly to large protofibrils than small protofibrils, while lecanemab exhibited approximately threefold greater affinity than gantenerumab for small protofibrils and over 100-fold greater affinity than aducanumab (14). Both lecanemab and gantenerumab exhibited similar binding affinities for Aβ oligomers, whereas aducanumab showed minimal binding within the concentration range tested. For smaller oligomeric species, such as dimers and trimers, gantenerumab demonstrated approximately tenfold stronger binding than lecanemab (14).

The FDA has approved two anti-Aβ monoclonal

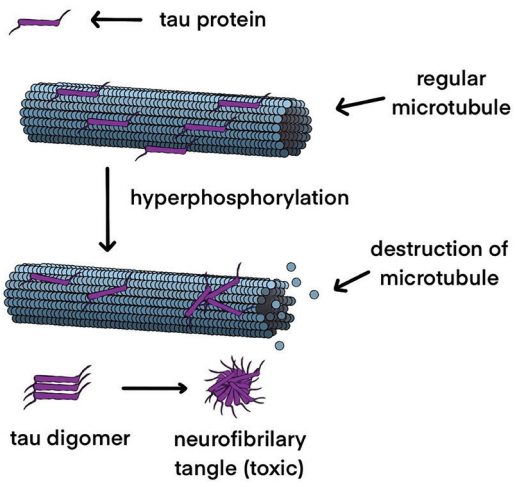

Figure 3. Tau hypothesis. *The first image is a regular microtubule, which is held together by the tau protein. The second image shows a microtubule with hyperphosphorylated tau and the formation of toxic neurofibrillary tangles.*

antibody therapies: Aduhelm® (aducanumab), which was discontinued in 2024, and Leqembi® (lecanemab) in 2023. These therapies are indicated for patients with early symptomatic, amyloid-positive AD and aim to slow disease progression by reducing amyloid plaque burden. However, treatment is associated with adverse effects, most notably amyloid-related imaging abnormalities (ARIA), as well as headaches, infusion reactions, and increased fall risk (15). ARIA incidence is strongly influenced by APOE4 genotype, with rates of approximately 45% in APOE4 homozygotes, 19% in heterozygotes, and 13% in non-carriers treated with lecanemab (15). In addition to safety concerns, these therapies remain costly (approximately $5,300 per year) and are accessible only to a limited subset of patients meeting strict clinical criteria (16, 17).

Given the close association between tau pathology, neuronal dysfunction, and cognitive decline, tau-targeted therapeutic strategies have aimed to limit tau aggregation or promote its clearance. Early approaches examined modulation of post-translational modifications and microtubule stabilization, while more recent efforts have focused on generating immunotherapies designed to target aggregated or pathological tau species (18, 19). Two types of immunization therapies have been tested: active immunization and passive immunization. In active immunization, the vaccine elicits an immune response that enables the body to produce antibodies against tau. Examples include AADvac1 and ACI-35, which are based on synthetic segments of the tau protein and target specific regions involved in aggregation (18, 20). In contrast, passive immunization involves repeated administration of monoclonal antibodies, such as BIIB076 and BIIB092, which bind phosphorylated tau species that have dissociated from microtubules and formed aggregates (19). Although both approaches have been evaluated in preclinical and clinical studies, to date, no tau-targeted therapy has received regulatory approval, largely due to limited efficacy and challenges related to central nervous system penetration (19, 20). Despite strong correlations between tau pathology and cognitive decline, tau-targeted therapies have thus far failed to demonstrate meaningful clinical benefit, in contrast to the modest effects observed with anti-amyloid antibodies.

RATIONALE AND EVIDENCE FOR SYNERGISTIC DUAL-TARGET THERAPY

Increasing evidence indicates that amyloid-β and tau pathologies are mechanistically linked during Alzheimer's disease progression. Experimental and clinical studies suggest that amyloid accumulation promotes tau phosphorylation, aggregation, and spread, while tau pathology worsens the functional deficits associated with amyloid toxicity (4, 11, 18). These interactions differ across disease stages, with amyloid pathology appearing early in Alzheimer's disease and tau pathology correlating more closely with cognitive decline and disease severity (4, 21).

Preclinical studies using transgenic mouse models expressing both amyloid and tau pathology demonstrate accelerated neurodegeneration compared to models targeting either pathology alone, supporting the biological plausibility of a combined therapeutic strategy (8, 18). Despite this rationale, dual-target approaches remain largely unexplored in clinical settings.

Several challenges complicate the development of synergistic therapies, including increased risk of adverse effects—particularly amyloid-related imaging abnormalities (ARIA)—limitations imposed by blood–brain barrier penetration, incomplete understanding of Aβ–tau interactions, and difficulties in optimizing dosing regimens (4, 22). Nevertheless, it has been proposed that combining lower doses of amyloid- and tau-targeted therapies could mitigate toxicity while preserving therapeutic benefit, a hypothesis that warrants evaluation in controlled clinical trials (4, 18).

BIOMARKERS FOR MONITORING DISEASE AND THERAPEUTIC RESPONSE

Biomarkers play a central role in diagnosing Alzheimer's disease, distinguishing it from other neurodegenerative conditions, and monitoring changes in pathology over time. Cerebrospinal fluid (CSF) analysis and positron emission tomography (PET) imaging have traditionally been used to detect amyloid-β (Aβ) and tau pathology. In CSF, Alzheimer's disease is characterized by reduced Aβ42 or Aβ42/40 ratios and increased levels of phosphorylated tau species, including p-tau181 and p-tau217 (23). Amyloid PET imaging enables visualization of fibrillar Aβ plaques in the brain (24).

Despite their diagnostic value, both CSF analysis and PET imaging have significant limitations. CSF collection requires lumbar puncture, an invasive procedure associated with procedural risks and patient discomfort (25). PET imaging requires intravenous injection of radiotracers, exposing patients to ionizing radiation and potential short-term side effects such as headache, dizziness, and discomfort, in addition to high cost

and limited accessibility (26). These constraints limit their feasibility for widespread screening or repeated monitoring. As a result, blood-based biomarkers have gained increasing attention as more accessible alternatives. However, detecting Alzheimer's-related proteins in blood presents unique challenges, as target proteins such as Aβ and phosphorylated tau are present at much lower concentrations than in CSF and are highly diluted in plasma (21). As a result, conventional immunoassays lack sufficient sensitivity for reliable detection.

Recent advances in ultrasensitive detection technologies have addressed this limitation. Among blood-based biomarkers, phosphorylated tau at threonine 217 (p-tau217) has shown a strong ability to distinguish Alzheimer's disease from other neurodegenerative disorders, with performance comparable to established CSF and PET measures (27). To achieve the sensitivity required for detecting Alzheimer 's-related proteins in blood, single-molecule array (Simoa®) assays developed by Quanterix are commonly used. The Simoa bead-based assay employs paramagnetic particles ("beads") coated with antibodies that bind target proteins such as Aβ or p-tau217 (Figure 4). A second, fluorescently labeled detection antibody is then added, allowing formation of an immunocomplex. The beads are subsequently loaded into a Simoa® disc containing approximately 200,000 microwells, each designed to isolate a single bead. This compartmentalization enables detection of individual protein molecules, allowing reliable measurement of Aβ and p-tau species even at very low concentrations (28).

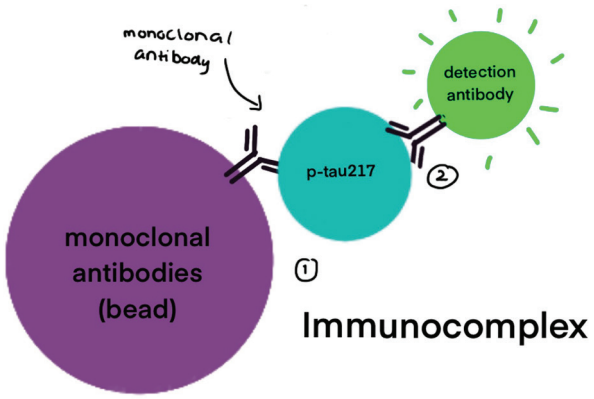

Figure 4. Simoa® bead immunoassay. *The purple circle depicts the "bead" used in the Simoa assay with a p-tau217 bound to it. Bound to the complex is a detection antibody to make sure the results can be observed.*

Together, these developments suggest that blood-based biomarkers could provide a more accessible way to identify Alzheimer's disease pathology and to track biological changes during treatment, including in future studies of combined therapeutic approaches.

CONCLUSION

Alzheimer's disease involves multiple interacting pathogenic pathways, making it unlikely that a single-target therapy will fully address disease progression. Although current treatments focus largely on amyloid clearance and provide modest clinical benefit, their limitations highlight the need for broader approaches that reflect the complexity of the disease. Thus, therapies targeting both amyloid-β and tau may better reflect the biology of the disease, particularly if applied early in disease progression.

Nevertheless, substantial challenges remain. Safety concerns, including treatment-related adverse effects, pharmacological barriers such as blood–brain barrier penetration, and gaps in understanding how amyloid and tau interact, all complicate the development of dual-target therapies. Continued preclinical work, improved use of biomarkers to guide treatment decisions, and carefully designed clinical trials will be necessary to determine whether combined therapeutic strategies can translate into clear clinical benefit for patients with Alzheimer's disease.

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CONFLICT OF INTEREST

The author(s) declare that there are no conflicts of interest regarding the publication of this article.

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