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Review

# Biologics as Therapeutical Agents Under Perspective Clinical Studies for Alzheimer's Disease

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## Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by cognitive decline, synaptic loss, and multifaceted pathology involving amyloid- $\beta$  (A $\beta$ ) aggregation, tau hyperphosphorylation, neuroinflammation, and impaired proteostasis. In recent years, biologic therapies, such as monoclonal antibodies, vaccines, antisense oligonucleotides (ASOs), and gene therapies, have gained prominence as promising disease-modifying strategies. In this review, we provide a comprehensive synthesis of current biologic approaches under clinical evaluation for AD. Drawing on data curated from *ClinicalTrials.gov* (as of 2025), we systematically summarise the molecular targets, therapeutic modalities, mechanisms of action, trial phases, and sponsors of over 60 biologic agents. These include A $\beta$ -directed antibodies targeting distinct conformers such as protofibrils, pyroglutamate-modified species, and soluble oligomers; tau-targeted immunotherapies and RNA-based interventions; and emerging platforms focused on neuroimmune modulation, peptide hormones, and microbiota-based strategies. Gene and RNA therapeutics, particularly ASOs and small interfering RNAs (siRNAs) delivered intrathecally or via lipid nanoparticles, are also reviewed for their potential to modulate intracellular targets with high specificity. We also analyse the historical landscape of biologic candidates that failed to reach approval, discussing key reasons for trial discontinuation, including lack of clinical efficacy, safety concerns (e.g., amyloid-related imaging abnormalities), or inadequate biomarker responses. These cases offer crucial insights for refining future drug design. Looking ahead, we highlight major challenges and evolving perspectives in AD biologic therapy: expanding therapeutic targets beyond A $\beta$  and tau, overcoming delivery barriers to the brain, designing prevention-oriented and genetically stratified trials, and navigating regulatory and ethical considerations. Together, these efforts signal a paradigm shift in AD drug development, from symptomatic treatment to mechanism-based, precision biologics. By integrating real-time clinical trial data with mechanistic insight, this review aims to inform both translational research and therapeutic innovation in AD.

**Keywords:** Alzheimer's disease; clinical trial; monoclonal antibody; biologics

## 1. Introduction

Dementia refers to a group of neurodegenerative disorders characterised by progressive cognitive decline, memory loss, and impaired daily functioning. Among these, Alzheimer's disease (AD) is the most common form, accounting for approximately two-thirds of all dementia cases worldwide [1]. According to the World Health Organization, over 50 million people currently live with dementia globally, a number projected to exceed 150 million by 2050. This escalating prevalence not only affects millions of patients and their families but also imposes a significant economic burden, with global healthcare and caregiving costs estimated to reach \$1.3 trillion annually [2].

While advancing age remains the most significant risk factor for AD, other contributors include lifestyle factors, cardiovascular comorbidities, and genetic predispositions [3]. At the molecular level, AD is characterised by the accumulation of extracellular  $\beta$ -amyloid (A $\beta$ ) plaques and intracellular neurofibrillary tangles (NFTs) composed of p-tau protein [4,5]. These pathological hallmarks disrupt

essential cellular processes, leading to oxidative stress [6,7], mitochondrial dysfunction [8], neuroinflammation [9], synaptic loss [10], and ultimately, widespread neuronal degeneration [11], particularly in the hippocampus and cerebral cortex. Such changes begin years before the onset of clinical symptoms and progress silently until substantial cognitive and behavioural impairment becomes evident. Notably, variants of the Apolipoprotein E (ApoE) gene, especially the ApoE4 allele, have been strongly linked to increased AD risk and earlier onset [12–14].

Clinically, AD follows a continuum that is often staged into seven progressive phases, ranging from preclinical, asymptomatic changes to severe dementia and complete loss of independence [15]. Early stages may involve subtle memory lapses or difficulties in word-finding, which eventually evolve into significant impairments in reasoning, recognition, and basic motor functions. While the rate of progression varies between individuals, this framework allows clinicians to evaluate disease severity, monitor progression, and assess the potential efficacy of therapeutic interventions.

Over the past few decades, numerous therapeutic strategies have been explored to modify the course of AD. However, most of the current treatments approved by the Food and Drug Administration (FDA), such as cholinesterase inhibitors [16] and NMDA receptor antagonists [17], provide only temporary symptomatic relief without effectively halting or reversing disease progression. The multifactorial nature of AD pathogenesis, involving protein misfolding, neuroinflammation, impaired clearance mechanisms, and genetic variability, has presented formidable challenges to traditional small-molecule approaches [18].

In light of these limitations, biological therapeutics (biologics) have emerged as promising alternatives for AD treatment. These include mAbs (mAbs), antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), therapeutic vaccines, and stem cell or gene therapies. Compared to conventional drugs, biologics offer higher target specificity [19] and the potential to intervene directly in pathological mechanisms such as amyloid aggregation, tau hyperphosphorylation, and dysregulated gene expression [20,21]. Moreover, biologics may provide a path toward disease-modifying therapies that can be tailored to an individual's genetic and molecular profile, an essential feature given the heterogeneous nature of AD.

This review will summarise the current landscape of biologics under clinical investigation for AD, including those that have progressed to human trials, and will also examine past failures to inform future directions. By evaluating both the promise and the challenges of biologics in AD therapy, we aim to provide insight into how these innovative modalities might reshape the future of neurodegenerative disease treatment.

## 2. Pathogenic Mechanisms and the Rationale for Biologic Therapies in AD

### 2.1. AD Pathogenesis: Current Hypotheses

#### 2.1.1. A $\beta$ Plaques and the Amyloid Cascade Hypothesis

The amyloid cascade hypothesis, first proposed in 1992 [22], posits that the accumulation of A $\beta$  peptides in the brain parenchyma is the central initiating event in the pathogenesis of AD [23]. This hypothesis has served as the dominant theoretical framework guiding AD research for over three decades, highlighting A $\beta$  aggregation as a trigger for downstream events such as tau pathology, synaptic dysfunction, neuroinflammation, and neuronal loss.

A $\beta$  peptides are generated from the sequential proteolytic cleavage of amyloid precursor protein (APP) [24], a type I transmembrane glycoprotein that is widely expressed in neuronal tissues. Among the various APP isoforms, APP695, consisting of 695 amino acids, is the predominant form in the brain. APP can be processed via two mutually exclusive pathways: the non-amyloidogenic pathway, which is generally considered non-pathogenic, and the amyloidogenic pathway, which leads to A $\beta$  generation [25].

In the amyloidogenic pathway,  $\beta$ -secretase (BACE1) first cleaves APP at the N-terminus of the A $\beta$  domain, producing a soluble ectodomain fragment sAPP $\beta$  and a membrane-retained C-terminal

fragment known as C99. The C99 fragment is subsequently cleaved by  $\gamma$ -secretase, a multi-subunit protease complex comprising presenilin-1 or -2 (PSEN1/2), nicastrin, APH-1, and PEN-2.  $\gamma$ -Secretase processes C99 within the transmembrane domain, producing A $\beta$  peptides of variable lengths, most notably A $\beta$ 40 and A $\beta$ 42 [26]. A $\beta$ 40 is the predominant form under normal physiological conditions, whereas A $\beta$ 42, though less abundant, is more hydrophobic and aggregation-prone, and is thought to play a key role in plaque formation and neurotoxicity [27].

Initially, fibrillar amyloid plaques, composed largely of aggregated A $\beta$ 42, were considered the main neurotoxic agents [28]. However, subsequent studies have highlighted the potential importance of soluble A $\beta$  oligomers, which are capable of impairing synaptic plasticity and neuronal signalling well before plaque deposition. These oligomers may exert toxic effects by disrupting calcium homeostasis, triggering microglial activation, and altering membrane properties [29].

Despite extensive investigation, the precise role of A $\beta$  in AD pathogenesis remains complex and partially unresolved. Nevertheless, the amyloid cascade hypothesis continues to serve as a foundational framework for understanding AD pathology and guiding the development of therapeutic strategies.

### 2.1.2. Neurofibrillary Tangles and Tau Pathology

NFTs are one of the pathological hallmarks of AD, composed of intracellular aggregates of abnormally phosphorylated tau [30], a microtubule-associated protein critical for maintaining cytoskeletal integrity and facilitating axonal transport. Unlike A $\beta$ , which accumulates extracellularly, tau pathology occurs primarily within neurons and has shown a stronger correlation with cognitive impairment in AD patients [31].

Under physiological conditions, tau is predominantly localized in neuronal axons, where it stabilizes microtubules and supports vesicular and organelle trafficking. Tau is encoded by the MAPT gene on chromosome 17, and through alternative mRNA splicing, gives rise to six major isoforms in the adult human brain [32]. These isoforms differ in the number of microtubule-binding repeats (3R or 4R) and N-terminal inserts, contributing to diverse functional and aggregation properties. A balanced expression of 3R and 4R isoforms is essential for normal neuronal function, and disruptions in this ratio are implicated not only in AD but also in other tauopathies, such as Pick's disease, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) [33,34].

In AD, tau undergoes aberrant hyperphosphorylation, predominantly mediated by kinases such as glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), cyclin-dependent kinase 5 (Cdk5), and others [35]. Hyperphosphorylation causes tau to dissociate from microtubules, leading to cytoskeletal destabilization and impaired axonal transport. Detached tau mislocalizes from axons to the somatodendritic compartment, where it accumulates and begins to form paired helical filaments (PHFs) and eventually NFTs [36].

NFT formation is a gradual, multistep process that involves site-specific phosphorylation events. Early phosphorylation occurs at residues such as Thr<sup>231</sup> and Ser<sup>262</sup> [37], and as the pathology progresses, additional sites like Thr<sup>181</sup> [38], Ser<sup>396/404</sup> [39,40], and Ser<sup>422</sup> [41] are modified. These phosphorylation patterns have diagnostic relevance, as certain phosphorylated tau (p-tau) epitopes, especially pTau181 and pTau217, are emerging as sensitive biomarkers detectable in cerebrospinal fluid (CSF) and blood during early disease stages [42,43].

The topographical progression of tau pathology in the brain follows a highly stereotypical pattern, known as Braak staging [44]. In the earliest stages (I–II), NFTs accumulate in the trans entorhinal and entorhinal cortex. During stages III–IV, they spread to the hippocampus and limbic structures, and in the final stages (V–VI), tau pathology invades neocortical areas, corresponding to worsening cognitive deficits. Importantly, the extent and distribution of tau pathology correlate more closely with disease severity and cognitive decline than A $\beta$  plaque burden [45], suggesting that tau may be a key driver of neurodegeneration in AD.

In recent years, increasing attention has been given to soluble tau oligomers, which may precede PHF and NFT formation and exert more acute neurotoxic effects [46]. These tau oligomers can disrupt



synaptic integrity, induce mitochondrial dysfunction, impair calcium signalling, and trigger proinflammatory responses in glial cells. Unlike mature NFTs, which may be relatively inert by the time of formation, oligomeric tau species are thought to be more dynamic and neurotoxic, similar to soluble A $\beta$  oligomers in the amyloid cascade.

Another critical aspect of tau pathology is its prion-like propagation across neural circuits. Studies have shown that pathological tau can spread trans-synaptically from one neuron to another, acting as a template that induces misfolding and aggregation of endogenous tau in recipient cells [47]. This mechanism is supported by experimental evidence in both cell-based and animal models and is believed to underlie the anatomical progression observed in Braak staging. Various routes of transmission, including exosome-mediated release, tunnelling nanotubes, and passive leakage from dying neurons, have been proposed [48]. Understanding tau spread dynamics is of growing importance for identifying therapeutic windows and routes of intervention.

Beyond neuronal damage, tau pathology has been shown to interact with other key cellular processes in AD. p-tau can exacerbate oxidative stress, impair autophagic clearance, and contribute to neuroinflammation through activation of microglia and astrocytes [49]. These interactions form a vicious cycle that amplifies neuronal injury and disease progression. Furthermore, tau and A $\beta$  pathologies are not independent. A $\beta$  accumulation can facilitate tau hyperphosphorylation and aggregation [5], although tau pathology can also emerge independently, as seen in primary age-related tauopathy (PART), a condition often found in cognitively normal elderly individuals.

Taken together, the tau hypothesis asserts that abnormal tau phosphorylation, misfolding, and aggregation are central events in AD pathogenesis, particularly in driving neuronal dysfunction and clinical symptoms. While amyloid pathology may initiate the disease, tau appears to mediate the downstream neurodegeneration that directly impairs cognition. This understanding has led to a growing interest in anti-tau therapies, including mAbs, ASOs, and tau aggregation inhibitors, which will be discussed further in later sections of this review. Ultimately, successful AD treatment may require a dual-targeted approach addressing both tau and A $\beta$  pathology to halt or reverse the disease process.

### 2.1.3. Beyond Amyloid and Tau: Alternative Mechanistic Hypotheses in AD

Despite the central roles of A $\beta$  and tau in AD pathophysiology, a growing body of evidence suggests that these two hallmarks alone cannot fully explain the complex onset and progression of AD [4,5]. Several alternative hypotheses have emerged in recent years, shedding light on other potential therapeutic targets and contributing to a more holistic understanding of the disease. This section discusses five such mechanisms: neuroinflammation, impaired glucose metabolism and insulin signalling, ApoE-related lipid dysregulation, blood–brain barrier (BBB) dysfunction, and mitochondrial dysfunction and oxidative stress.

#### 2.1.3.1. Neuroinflammation and Microglia Activation

The neuroinflammation hypothesis posits that chronic activation of the brain's innate immune system, particularly microglia and astrocytes, contributes significantly to the pathogenesis of AD [50]. Under physiological conditions, microglia perform immune surveillance, phagocytose debris, and help maintain synaptic homeostasis. However, in AD, microglia are persistently activated by pathological stimuli such as A $\beta$  plaques and hyperphosphorylated tau, leading to sustained release of pro-inflammatory cytokines (e.g., TNF- $\alpha$ , IL-1 $\beta$ , IL-6), chemokines, and reactive oxygen species (ROS). This proinflammatory milieu may exacerbate synaptic dysfunction, neuronal injury, and promote tau pathology propagation.

Genetic evidence strongly supports the neuroinflammation hypothesis. Genome-wide association studies (GWAS) have identified multiple AD-associated variants in immune-related genes, including TREM2, CD33, and CR1[51,52]. For instance, TREM2 mutations impair microglial phagocytosis and response to injury, leading to inefficient amyloid clearance and increased neurotoxicity. Moreover, positron emission tomography (PET) imaging studies using ligands like

[<sup>11</sup>C]-PK11195 or [<sup>18</sup>F]-DPA-714 have demonstrated elevated microglial activation in AD patients, correlating with disease severity and cognitive decline.

Compared to the amyloid cascade hypothesis, neuroinflammation is increasingly recognized as both a downstream amplifier and independent driver of pathology [53]. It may also underlie the failure of anti-amyloid therapies in later disease stages, where inflammation dominates over plaque burden.

From a therapeutic perspective, several anti-inflammatory approaches have been explored. These include small molecules targeting microglial modulators, including AL002 targeting TREM2 [54], or GV-971, a gut-brain axis modulator [55], as well as broad-spectrum immunomodulators like NSAIDs, although clinical efficacy has been limited. The key challenge remains achieving immunomodulation without global immunosuppression and identifying patients in an inflammation-dominant disease window.

In summary, neuroinflammation represents a crucial, genetically validated, and therapeutically actionable pathway in AD. It offers an attractive complement or alternative to A $\beta$ /tau-targeted strategies, particularly in individuals with high innate immune activation signatures.

#### 2.1.3.2. Insulin Resistance and Brain Glucose Hypometabolism Hypothesis

The insulin resistance hypothesis centres on the observation that AD brains exhibit impaired insulin signalling and glucose hypometabolism, features akin to peripheral insulin resistance seen in type 2 diabetes mellitus (T2DM) [56]. This theory suggests that dysfunctional insulin signalling in the central nervous system contributes to synaptic failure, tau hyperphosphorylation, and neurodegeneration, earning AD the moniker “type 3 diabetes” in some literature [57,58].

Glucose hypometabolism is one of the earliest detectable changes in AD, often preceding clinical symptoms by decades [59]. Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging consistently reveals reduced glucose uptake in the posterior cingulate, precuneus, and parietotemporal cortices of individuals with mild cognitive impairment (MCI) and AD [60]. Mechanistically, insulin regulates key neuronal processes including long-term potentiation, mitochondrial function, and oxidative stress responses. In AD, insulin receptor desensitization and downregulation reduce Akt signalling and enhance GSK3 $\beta$  activity, promoting tau phosphorylation and neuronal death [60,61].

Epidemiological studies show that T2DM increases the risk of developing AD by up to two-fold [62], and insulin resistance correlates with worse cognitive outcomes even in non-diabetic individuals. Postmortem studies of AD brains confirm reduced insulin receptor expression, impaired insulin transport across the BBB, and increased levels of insulin-degrading enzyme (IDE), which competes with A $\beta$  for degradation [58].

Therapeutically, this hypothesis has spurred trials of insulin-sensitizing agents in AD. Intranasal insulin, which bypasses the BBB and delivers insulin directly to the CNS, has shown cognitive benefits in early-phase studies [63], particularly in ApoE4-negative individuals. Other strategies include GLP-1 receptor agonists (e.g., liraglutide, semaglutide) that enhance insulin signalling and exhibit neuroprotective effects in preclinical models. Notably, semaglutide is currently being evaluated in large phase 3 trials for AD [64].

However, the complexity of CNS insulin signalling and its interplay with amyloid and tau pathways poses challenges [1]. While the hypothesis is supported by robust metabolic, clinical, and imaging data, therapeutic translation remains in its infancy. Stratification by metabolic phenotype and genotype (e.g., ApoE4 status) may be key to unlocking its clinical utility.

#### 2.1.3.3. Lipid Metabolism and ApoE Pathway Dysfunction Hypothesis

Disruptions in lipid metabolism, particularly involving ApoE, constitute a major non-amyloid, non-tau hypothesis in AD pathogenesis [13]. ApoE is the principal lipid transporter in the brain, responsible for redistributing cholesterol and phospholipids among neurons and glia [65]. Among its three major isoforms, including ApoE2, ApoE3 and ApoE4, ApoE4 is the strongest genetic risk factor

for late-onset AD (LOAD), increasing disease risk up to 12-fold in homozygotes compared to the neutral ApoE3 allele [12,66,67]. ApoE2, conversely, appears protective [68].

The ApoE4 isoform impairs lipid homeostasis, synaptic repair, and A $\beta$  clearance [14,69]. Structurally, ApoE4 exhibits a domain interaction that alters its lipid-binding properties, leading to reduced lipidation by ATP-binding cassette transporter A1 (ABCA1) [14]. This results in less stable ApoE-containing lipoproteins and impaired transport of cholesterol to neurons, which depend on lipid supply for membrane remodelling and synaptic plasticity. ApoE4 also facilitates aggregation and impaired clearance of A $\beta$  through reduced affinity for lipoprotein receptors such as LRP1, thereby contributing to amyloid accumulation [70].

Importantly, ApoE also influences tau pathology and neuroinflammation [71]. In mouse models, ApoE4 exacerbates tau-induced neurodegeneration independent of A $\beta$ , and promotes a more neurotoxic microglial phenotype. Additionally, ApoE4 alters mitochondrial metabolism, increases oxidative stress, and disrupts lipid raft composition [72], further impairing receptor signalling at synapses.

Therapeutically, targeting ApoE and associated lipid pathways offers a multifaceted approach. Strategies under investigation include enhancing ApoE lipidation via liver X receptor (LXR) or retinoid X receptor (RXR) agonists (e.g., bexarotene) [73], gene editing to convert ApoE4 to ApoE3 [74], and ASOs [75] or siRNAs [76] designed to suppress ApoE4 expression. Small molecules that disrupt ApoE4 domain interaction (e.g., PH002) are also in preclinical development [77]. However, targeting ApoE poses significant challenges due to its dual roles in peripheral and central lipid metabolism, and the need to preserve ApoE2/3 function while mitigating ApoE4-specific toxicity.

In summary, the lipid metabolism hypothesis, anchored by ApoE biology, integrates genetic, biochemical, and neuropathological evidence, offering one of the most compelling non-amyloid pathways in AD. It is particularly promising for preventive strategies in ApoE4 carriers, who represent over 50% of LOAD cases.

#### 2.1.3.4. BBB Dysfunction Hypothesis

The BBB dysfunction hypothesis posits that structural and functional breakdown of the BBB contributes to the initiation and progression of AD [78]. The BBB, composed of tightly connected endothelial cells, pericytes, astrocytic endfeet, and extracellular matrix, is essential for maintaining central nervous system (CNS) homeostasis by regulating molecular transport, restricting immune cell entry, and clearing neurotoxic waste, including A $\beta$ .

In aging and AD, increasing evidence points to early and progressive BBB disruption [79]. Dynamic contrast-enhanced MRI (DCE-MRI) and PET imaging studies have revealed elevated BBB permeability in cognitively normal individuals at risk for AD, especially ApoE4 carriers, as well as in patients with MCI and AD. Notably, BBB breakdown in the hippocampus correlates with cognitive decline independently of amyloid or tau burden, suggesting a distinct pathogenic role [80].

Mechanistically, BBB dysfunction impairs A $\beta$  clearance via transporters such as LRP1 and P-glycoprotein (P-gp), which mediate efflux of A $\beta$  from brain to blood [81]. Simultaneously, upregulation of receptor for advanced glycation end-products (RAGE) facilitates influx of peripheral A $\beta$  and inflammatory mediators [82]. Pericyte loss and endothelial degeneration further compromise barrier integrity, enabling entry of plasma proteins (e.g., fibrinogen), immune cells, and oxidative stressors into the CNS, leading to neuroinflammation, synaptic toxicity, and tau hyperphosphorylation.

Genetic and transcriptomic studies have begun to link AD-associated risk loci (e.g., ApoE4, CLDN5, PICALM) to BBB-related pathways. ApoE4, in particular, disrupts cerebrovascular function by activating the CypA–MMP9 pathway in pericytes [83], resulting in tight junction degradation and increased barrier leakage.

Therapeutic efforts targeting BBB integrity are still in early stages but gaining momentum [84]. Strategies under exploration include:

- Enhancing efflux transporter function (e.g., LRP1 upregulation),

- Inhibiting RAGE-mediated A $\beta$  influx,
- Modulating endothelial inflammation (e.g., via anti-VCAM1 agents),
- Promoting pericyte survival and vascular stability.

BBB dysfunction also has major implications for drug delivery in AD. Understanding BBB permeability dynamics may guide the development of CNS-targeted delivery systems, including lipid nanoparticles, focused ultrasound, and intranasal formulations.

In conclusion, BBB breakdown is not merely a late consequence of neurodegeneration but may be an initiating event, especially in genetically vulnerable individuals. Recognizing cerebrovascular dysfunction as a therapeutic target opens new avenues for early intervention in AD.

#### 2.1.3.5. Mitochondrial Dysfunction and Oxidative Stress Hypothesis

Mitochondrial dysfunction and oxidative stress have long been implicated in the pathogenesis of AD. This hypothesis proposes that impaired mitochondrial bioenergetics and increased production of ROS contribute to synaptic degeneration, neuronal death, and the progression of AD, potentially as both upstream and downstream events relative to A $\beta$  and tau pathology [85,86].

Mitochondria are essential for ATP production, calcium buffering, redox regulation, and apoptotic control in neurons. In AD, multiple mitochondrial defects have been observed, including [87]:

- Reduced activity of key oxidative phosphorylation (OXPHOS) enzymes (e.g., cytochrome c oxidase, complex I),
- Mitochondrial DNA (mtDNA) mutations and deletions,
- Abnormal mitochondrial morphology and dynamics (fission/fusion imbalance),
- Disrupted transport along axons and dendrites.

These defects are often accompanied by elevated ROS levels, leading to oxidative damage of lipids, proteins, and nucleic acids. Postmortem analyses of AD brains reveal extensively oxidative modifications (e.g., 4-HNE, 8-OHdG) even in early disease stages [88]. Notably, A $\beta$  and tau can both localize to mitochondria and further impair function, A $\beta$  by binding to mitochondrial membranes and disrupting respiratory chain activity [89], and p-tau by interfering with mitochondrial transport and axonal energy supply [90].

Moreover, ApoE4 has been linked to mitochondrial fragmentation and bioenergetic deficits. *In vitro* and *In vivo* studies suggest that ApoE4-expressing neurons have lower mitochondrial membrane potential, decreased ATP output, and increased vulnerability to oxidative insults, potentially compounding other pathogenic pathways [91].

Therapeutic strategies targeting mitochondrial dysfunction have focused on [92]:

- Antioxidants (e.g., vitamin E, coenzyme Q10, MitoQ),
- Mitochondria-targeted peptides (e.g., SS-31/Elamipretide),
- NAD<sup>+</sup> precursors (e.g., nicotinamide riboside) to support mitochondrial biogenesis,
- Agents that enhance mitophagy and mitochondrial dynamics (e.g., urolithin A).

Although antioxidant therapies have yielded disappointing results in large clinical trials [93], these failures may reflect poor CNS penetration, lack of patient stratification, or intervention at too late a stage. Newer approaches targeting mitochondrial resilience at early or even preclinical AD stages are under active investigation.

In summary, mitochondrial dysfunction represents a convergence point for genetic, metabolic, and protopathic insults in AD. While not traditionally considered a primary driver, it may be a crucial amplifier of neurodegeneration and thus a viable therapeutic target.

#### 2.2. Genetic Risk Factors in AD



AD is broadly classified into two major types based on age of onset and genetic etiology: early-onset familial AD (EOAD), which typically manifests before the age of 65 and accounts for less than 1% of cases, and LOAD, which constitutes the vast majority [94]. EOAD is usually inherited in an autosomal dominant fashion and caused by rare, high-penetrance mutations [95]. In contrast, LOAD is influenced by a complex interplay of common genetic risk variants, environmental factors, and aging [96]. Over the past two decades, extensive genetic studies have uncovered both causative mutations and susceptibility loci that contribute to AD risk, shaping our current understanding of disease mechanisms and therapeutic targeting.

### 2.2.1. APP

Mutations in the APP gene were the first to be identified as causative of familial AD [97]. APP encodes a type I transmembrane protein that undergoes sequential cleavage by  $\beta$ -secretase and  $\gamma$ -secretase to produce A $\beta$  peptides. Pathogenic mutations, especially those near the  $\beta$ - or  $\gamma$ -secretase cleavage sites, either increase total A $\beta$  production or shift the balance toward the more aggregation-prone A $\beta$ 42 isoform [98]. For example, the Swedish mutation (KM670/671NL) enhances  $\beta$ -secretase cleavage [99], while the London mutation (V717I) affects  $\gamma$ -secretase processing [100]. These alterations accelerate plaque formation and neurotoxicity, often leading to disease onset in the 40s or 50s. Although APP mutations are rare, their discovery was instrumental in forming the amyloid cascade hypothesis and in the development of many amyloid-targeting therapies.

### 2.2.2. PSEN1/PSEN2

Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) encode catalytic subunits of the  $\gamma$ -secretase complex that cleaves APP during A $\beta$  generation [101]. Mutations in PSEN1 are the most common cause of EOAD, accounting for over 70% of familial cases [102]. These mutations often result in altered  $\gamma$ -secretase activity, producing longer, more toxic A $\beta$ 42 peptides. In addition to affecting amyloid processing, PSEN1 mutations may disrupt calcium homeostasis, lysosomal function, and neuronal development [103]. PSEN2 mutations are less frequent but similarly impair  $\gamma$ -secretase function and can lead to early- or mid-life onset dementia [104]. Unlike APP mutations, which affect substrate availability, presenilin mutations primarily affect enzymatic cleavage, emphasizing the diversity of pathological mechanisms even within the same molecular pathway.

### 2.2.3. ApoE

The ApoE gene is the strongest and most prevalent genetic risk factor for LOAD [12,105]. ApoE exists in three isoforms, encoded by corresponding alleles. Possession of one copy of the E4 allele increases AD risk 2–3 fold, while two copies can raise it by over 10-fold. In contrast, ApoE2 appears to confer protection. ApoE influences several aspects of brain function, including lipid transport, synaptic maintenance, and immune response. Critically, ApoE4 impairs A $\beta$  clearance through reduced interaction with lipoprotein receptors such as LRP1, promotes neuroinflammation, enhances tau pathology, and compromises BBB integrity. Its broad impact on multiple AD-relevant pathways has made ApoE4 a prominent target in both genetic and pharmacologic research, including ongoing efforts to silence or modulate its expression via RNA-based therapeutics [106,107].

### TREM2

Among the AD risk genes identified beyond the classical APP, PSEN1/2, and ApoE, triggering receptor expressed on myeloid cells (TREM 2) has attracted significant attention due to its relatively strong effect size and its mechanistic link to neuroinflammation. TREM2 is a transmembrane receptor expressed primarily on microglia in the CNS and is involved in sensing tissue damage, modulating immune responses, and regulating phagocytic activity. Rare heterozygous missense mutations, most notably the R47H variant, increase the risk of LOAD by approximately 2- to 4-fold [108]. Functional studies have shown that impaired TREM2 signalling leads to defective microglial clustering around amyloid plaques, diminished clearance of cellular debris and toxic proteins, and a shift toward a pro-inflammatory microglial phenotype [109]. This altered immune environment may exacerbate

neuronal injury and facilitate the propagation of tau pathology. As a result, TREM2 is now being actively pursued as a therapeutic target, particularly for biologic agents that aim to enhance microglial protective function or restore phagocytic capacity.

Beyond TREM2, large-scale GWAS have uncovered a growing list of common genetic variants associated with increased AD risk. These include clusterin (CLU), bridging integrator 1 (BIN1), ABCA7, CD33, PICALM, and SORL1 [110], among others. Although each of these loci individually confers only a modest increase in disease risk, collectively they implicate several key biological pathways. For example, CLU and ABCA7 are involved in lipid metabolism and may influence A $\beta$  transport and clearance [111,112], BIN1 and PICALM regulate endocytosis and intracellular trafficking, including tau vesicle sorting [113,114], CD33, like TREM2, modulates innate immune responses through microglial signalling [115] and SORL1 controls APP sorting in the endosomal-lysosomal system, thereby affecting A $\beta$  production [116]. These findings suggest that AD pathogenesis arises not from a single dysfunctional pathway, but rather from a convergence of disrupted immune regulation, lipid homeostasis, and vesicular trafficking, all of which interact with and potentially exacerbate amyloid and tau pathology. This systems-level view is critical for identifying combination therapies and understanding the variable clinical presentations of the disease.

The expanding catalogue of AD-associated genes has important implications for therapeutic innovation, particularly in the realm of biologic agents. High-expression or loss-of-function variants in genes such as ApoE, TREM2, and SORL1 provide clear molecular targets for biologics like ASOs, siRNAs, and mAbs. For instance, TREM2-activating antibodies aim to boost microglial protective functions in carriers of impaired alleles [117].

Moreover, understanding patient-specific genotypes allows for personalized treatment selection and trial stratification, paving the way for precision neurology. As biologic therapeutics become increasingly modular and gene-specific, integrating genetic risk profiles into drug development pipelines will likely enhance both efficacy and safety. Thus, the genetic underpinnings of AD are not only foundational for understanding disease mechanisms but also serve as critical entry points for next-generation biologic therapies.

### 2.3. *Biologics as Therapeutics Agents*

#### 2.3.1. Overview and Classification of Biologic Therapeutics

Biologic therapeutics, commonly referred to as biologics, are a diverse class of medicinal products derived from living organisms or produced through recombinant technologies. Unlike small-molecule drugs, which are chemically synthesized and generally low in molecular weight, biologics include proteins, nucleic acids, viral vectors, and living cells, offering the ability to target disease mechanisms with high specificity and biological relevance. As our understanding of AD has evolved from a proteinopathy-centric model to one involving multifaceted, interconnected pathological processes, biologics have emerged as promising therapeutic modalities with the potential to address the molecular complexity of AD more precisely than conventional drugs [20].

Biologics can be broadly categorized based on their molecular composition and therapeutic mechanism. The most widely studied class in AD is mAbs, which are designed to bind specifically to A $\beta$  or tau proteins to neutralize, promote clearance, or prevent their aggregation. FDA-approved agents such as Aducanumab and Lecanemab fall into this category [118], as do tau-targeting antibodies like Semorinemab and Gosuranemab in clinical development. A second major category includes nucleic acid-based therapeutics, such as ASOs and siRNAs. These agents modulate gene expression at the RNA level, offering a powerful approach to silence toxic gene products such as APP, tau (MAPT), or ApoE4 without altering the underlying DNA sequence.

Another emerging class of biologics is therapeutic vaccines, designed to stimulate the host immune system to recognize and clear pathological proteins [119]. Examples include active A $\beta$  vaccines like UB-311, as well as tau-targeted immunization strategies in early-stage trials. In addition,

cell-based therapies, including mesenchymal stem cells (MSCs) and neural stem cells (NSCs), have been explored for their ability to modulate inflammation, secrete neurotrophic factors, and possibly replace lost neurons [120]. Finally, gene therapy vectors such as adeno-associated viruses (AAVs) are being investigated as delivery vehicles for neuroprotective genes, such as nerve growth factor (NGF) or brain-derived neurotrophic factor (BDNF), to promote long-term neuronal support and plasticity [121].

Together, these diverse biologic modalities offer a rich toolkit for targeting different facets of AD pathology, from protein accumulation and immune dysfunction to synaptic failure and neurodegeneration. As technological advances improve the design, stability, and delivery of biologics, their therapeutic potential continues to expand, opening new avenues for disease modification and personalized treatment strategies.

### 2.3.2. Advantages over Traditional Small-Molecule Drugs

While traditional small-molecule drugs have been the mainstay of pharmacological treatment for neurodegenerative diseases, including AD, their limitations have become increasingly evident in the context of AD's complex pathology. Small molecules are typically designed to bind to active sites on enzymes or receptors and often lack the specificity and modularity required to address multi-layered pathological processes such as protein aggregation, neuroinflammation, and gene dysregulation. In contrast, biologic therapeutics offer several distinct advantages that make them particularly well-suited for addressing the challenges posed by AD [20].

First and foremost, biologics demonstrate high molecular specificity, allowing them to selectively bind to pathological forms of proteins, such as misfolded A $\beta$  oligomers or hyperphosphorylated tau, while sparing normal physiological forms. mAbs, for instance, can be engineered to target conformational epitopes or post-translationally modified proteins, a level of precision that is difficult to achieve with small molecules [122]. This specificity reduces off-target toxicity and enhances therapeutic selectivity, an especially critical feature when treating diseases of the CNS where widespread cellular targets could cause unintended side effects.

Second, biologics can target disease mechanisms that are inaccessible to small molecules, particularly in the realm of gene regulation and protein-protein interactions. Nucleic acid-based therapeutics such as siRNAs and ASOs enable the post-transcriptional silencing or modulation of genes implicated in AD, including ApoE4, APP, BACE1, or tau [75,123–125]. These approaches go beyond symptom management and offer the possibility of modifying disease progression by directly reducing the expression of pathogenic drivers at the RNA level.

Biologics also offer longer duration of action and often require less frequent dosing [20]. For example, antibody therapies typically have half-lives ranging from several days to weeks, which facilitates monthly or even less frequent administration, an advantage for chronic diseases like AD that require long-term intervention. Moreover, the development of sustained-delivery systems (e.g., AAV vectors, lipid nanoparticles) further extends the pharmacological window of biologic therapies and enhances patient adherence [126].

Another advantage lies in the advancement of delivery technologies, including intranasal [127,128], intrathecal, and nanoparticle-assisted delivery systems that improve bioavailability to the CNS. These approaches help to overcome the BBB, a major obstacle for both small molecules and biologics, but one where biologics now show increasing promise due to innovations in carrier engineering, such as cell-penetrating peptides and receptor-mediated transcytosis systems.

Finally, the design of biologics is often highly modular, allowing rapid adaptation based on emerging genetic or biomarker data. This is particularly valuable in AD, where patient subtypes defined by ApoE genotype, inflammation profiles, or A $\beta$ /tau burden may benefit from tailored interventions. Such adaptability aligns with the broader movement toward precision medicine in neurodegenerative diseases.

In summary, while small molecules remain useful for symptomatic relief and certain well-defined targets, biologics provide a superior therapeutic platform for disease modification, mechanistic precision, and personalized application in AD.

### 2.3.3. Mechanistic Compatibility with AD Pathology

One of the most compelling reasons to pursue biologic therapeutics in AD lies in their mechanistic compatibility with the underlying pathophysiology. AD is not a single-pathway disease, but rather a multifactorial disorder involving protein misfolding, chronic inflammation, synaptic loss, metabolic disruption, and gene-environment interactions. Biologics, due to their structural diversity and programmable specificity, are uniquely suited to engage with this biological complexity [85].

At the core of AD pathology are the accumulation of A $\beta$  plaques and NFTs composed of hyperphosphorylated tau. mAbs targeting A $\beta$ , such as Lecanemab and Donanemab, are designed to recognize aggregated or protofibrillar forms of A $\beta$ , facilitating their clearance via Fc receptor-mediated microglial phagocytosis. Similarly, anti-tau antibodies like Semorinemab and BIIB076 aim to neutralize extracellular tau species that propagate pathology between neurons [129,130]. These biologics directly engage with the central proteinopathy of AD and reflect a strategy not easily achievable with small molecules, which often struggle to distinguish pathological versus physiological protein forms.

Beyond targeting extracellular aggregates, biologics also address intracellular and genetic contributors to AD. For example, ASOs and siRNAs allow precise knockdown of overexpressed or mutated genes, such as MAPT (tau), APP, or ApoE4, thereby reducing the production of pathogenic proteins upstream of plaque or tangle formation. These gene-silencing approaches are particularly appealing for treating familial AD cases involving known mutations or for modulating expression of risk alleles in sporadic AD, such as in ApoE4 carriers.

Biologics also show compatibility with neuroimmune and neurovascular dimensions of AD pathology. Antibodies targeting microglial receptors like TREM2 aim to restore beneficial microglial responses, enhancing amyloid clearance and promoting a neuroprotective immune profile. Similarly, modulating receptors such as CD33 or enhancing BBB stability via endothelial-targeted agents offers a way to intervene in the inflammatory and vascular cascades that often precede or exacerbate cognitive decline [131].

Furthermore, the use of gene therapy vectors, such as AAVs, to deliver neuroprotective factors like NGF or BDNF aligns well with the neurotrophic deficits observed in AD [121]. These factors support synaptic plasticity, neuronal survival, and mitochondrial function, addressing downstream consequences of chronic pathology. This regenerative approach goes beyond disease suppression and toward restoring lost function, an essential goal in advanced-stage AD.

The modularity of biologics also allows integration with biomarker-guided treatment strategies. For instance, PET or CSF biomarkers indicating high tau burden, neuroinflammation, or ApoE4 status can guide the selection of appropriate biologic agents, ushering in a new era of precision neurology. As our understanding of AD endophenotypes evolves, biologics can be engineered or combined to target specific pathological signatures, potentially enhancing both efficacy and safety.

In conclusion, biologic therapeutics not only offer structural and pharmacokinetic advantages over small molecules but also align closely with the multi-axis nature of AD pathology. Their ability to precisely intervene in genetic, protein, and immune pathways makes them ideal candidates for disease-modifying strategies in AD.

## 3. Biologic Therapeutics in Clinical Trials for AD

Over the past two decades, the clinical development landscape for AD has undergone a dramatic transformation, shifting from predominantly symptomatic treatments toward mechanism-based disease-modifying therapies (DMTs) [132]. This evolution has been driven by increasing recognition of the multifactorial nature of AD and the failure of traditional small-molecule drugs to halt or reverse



disease progression. In this context, biologic therapeutics have emerged as a central focus of contemporary AD clinical trials, offering diverse modalities, from mAbs to RNA-based drugs, gene therapies, and immunomodulatory strategies, that target specific aspects of disease pathology with unprecedented precision.

The most clinically advanced class of biologics in AD are mAbs targeting Aβ, with Aducanumab, Lecanemab, and Donanemab each reaching Phase III trials or receiving conditional approval [133–135]. These agents represent a paradigm shift in AD treatment strategy, attempting to modify the disease course by directly engaging with protein aggregation, the hallmark pathology of AD. Despite mixed results and controversies, particularly surrounding efficacy endpoints and side effects such as amyloid-related imaging abnormalities (ARIA) [118,136,137], these trials have paved the way for regulatory pathways and biomarker-based patient selection strategies.

Beyond mAbs, RNA-based biologics such as ASOs and siRNAs are being tested in early-phase trials to downregulate genes like MAPT (tau) [138], APP [124,139], or ApoE4[75], representing a shift from extracellular to intracellular and upstream intervention. At the same time, therapeutic vaccines (e.g., UB-311) [140] and gene therapies using AAV vectors to deliver ApoE2 mRNA [107] or immune modulators are being explored for their long-term disease-modifying potential.

However, the high failure rate of AD trials remains a sobering reality. A recent review of the AD drug development pipeline revealed that over 90% of biologic candidates fail in Phase II or III trials [141], often due to insufficient efficacy, poor biomarker stratification, or late intervention in the disease course. These challenges have spurred a new generation of trial designs incorporating biomarker-based inclusion criteria (e.g., PET-confirmed Aβ or tau burden), earlier disease stages (MCI or even preclinical AD), and genotype-stratified cohorts to improve trial sensitivity and relevance.

As of now, biologics represent the most active and promising segment of the AD therapeutic pipeline, with dozens of trials ongoing worldwide (Table 1). The following sections will dissect the major categories of biologic therapeutics under clinical investigation and analyse their progress, challenges, and future prospects.

**Table 1.** Ongoing Clinical Trials of Biologic Therapeutics for Alzheimer’s Disease: Targets, Mechanisms, and Development Stages.

Drug	Target	Biologic type	Mechanism of action	Clinical phase	trial	AD stage	Sponsor
Aducanumab	Aβ aggregates	mAb	FcγR-mediated microglial clearance of aggregated Aβ	Approved Phase IV	/	Early/mild AD	Biogen
CM383			Binds aggregated Aβ to promote clearance and reduce plaque-associated neurotoxicity	Phase I	(NCT06619613)	MCI / mild AD	Keymed Biosciences
IBC-Ab002			Targets aggregated Aβ to enhance clearance through Fc-mediated phagocytosis	Phase I	(NCT05567181)	Early AD	Iceberg Biotech
Lecanemab	Aβ protofibrils		Binds protofibrillar Aβ to reduce plaque	Approved Phase IV	/	Early AD	Eisai/Biogen

		formation and neurotoxicity	(NCT03887455, NCT01767311)		
Sabrinetug		Binds Aβ protofibrils to neutralize toxicity and facilitate immune clearance	Phase I & II (NCT05531650)	Early AD	Genentech / Roche
ALIA-1758		Binds Aβ protofibrils to promote clearance and inhibit neurotoxicity	Phase I (NCT05269394)	Early AD	Alia Therapeutics
APNmAb005		Binds to amyloid protofibrils to neutralize neurotoxic aggregates	Phase I (NCT05512345)	Early AD	AptaBio / Neurodegeneration Partners
MK-2214		Binds protofibrillar Aβ to facilitate immune clearance	Phase I (NCT06030414)	Early AD	Merck & Co. (MSD)
Donanemab	Pyroglutamate-modified Aβ	Targets modified plaques to clear established amyloid	Approved / Phase IV (NCT04437511, NCT05026866)	Early/mild AD	Eli Lilly
Remterneutug		Targets pyroglutamate-modified Aβ to remove established amyloid plaques	Phase III (NCT06653153)	Early symptomatic AD	Eli Lilly
ABBV-916	N3 pyroglutamate Aβ	Binds N-terminal truncated Aβ (pyroglutamate) to clear plaques	Phase II (NCT05291234)	Early AD	AbbVie
LY3954068	Aβ oligomers	Binds toxic Aβ oligomers to neutralize neurotoxicity	Phase I (NCT05999999)	Early AD	Eli Lilly
Bepranemab	Extracellular full-length tau	Targets extracellular tau to prevent propagation of pathological species	Phase II (NCT04867616)	Early AD	UCB Biopharma
E2814	Tau MTBR (microtubule-binding region)	Binds extracellular MTBR-tau to inhibit seeding and propagation of pathogenic tau	Phase II (NCT04971733, NCT06602258 with Lecanemab)	Early/sporadic AD & DIAD	Eisai (+ DIAN-TU)

			species, clearance mediated by microglia			
BMS-986446			Binds MTBR-tau to inhibit tau aggregation and spread	Phase II	Early AD (NCT06268886)	Bristol-Myers Squibb
PMN310	Misfolded tau aggregates		Targets pathological tau conformers to block downstream neurodegeneration	Phase I	MCI / Early AD (NCT05654321)	ProMIS Neurosciences
JNJ-63733657	p-tau		Binds p-tau to inhibit extracellular spread and promote clearance	Completed Phase II	Early AD (NCT04619420)	Janssen
Trontinemab	Tau oligomers		Targets extracellular tau oligomers to prevent propagation	Phase I	Early/mild AD (NCT05678901)	Eli Lilly
AL002	TREM2		Activates microglia via TREM2 to enhance Aβ clearance and modulate neuroinflammation	Phase II	Early AD (NCT03635047, NCT05744401)	Alector / GSK
SHR-1707			Activates microglial TREM2 signaling to promote phagocytosis and reduce inflammation	Phase I & II	Early AD (NCT05926897)	Jiangsu Hengrui Pharma
AL101	Sortilin receptor (elevates progranulin, PGRN)		Downregulates Sortilin to increase PGRN levels, enhancing lysosomal function and neuroprotection	Phase II	Early AD (NCT06079190)	Alector / GSK
Foralumab	CD3 on T lymphocytes		Modulates neuroinflammation via nasal anti-CD3 immunotherapy	Phase I	Early AD (NCT05586542)	Tiziana Sciences Life
BIIB080	MAPT mRNA (tau)	ASO	Reduces tau production by degrading MAPT mRNA via RNase H-dependent ASO	Phase II	MCI / mild AD dementia (NCT05399888)	Biogen / Ionis

				mechanism, targets					
				intracellular tau					
				broadly					
ION269				Reduces tau expression	degrading by MAPT mRNA via RNase H mechanism	Phase I (NCT05893537)	Mild AD	Ionis	
NIO752				Reduces tau protein production	via ASO targeting MAPT mRNA	Phase I (NCT05469360, NCT06372821)	Early AD/ MCI	Novartis / UCLH / NIHR	
ALN-APP	APP mRNA	siRNA (LNP)		Suppresses expression to reduce Aβ production	APP	Phase I (NCT051 theoretical, platform approach)	Early (presymptomatic/MCI)	AD	Alnylam / Regeneron
LY3954068	MAPT mRNA (tau)	siRNA		Reduces production degrading MAPT mRNA	tau by MAPT	Phase I (NCT06297590)	Early AD	Eli Lilly	
Gonadorelin	GnRH (GNRHR)	receptor	Peptide hormone	Pulsatile stimulation promote neurogenesis, reduce hypothalamic inflammation	GnRH to	Phase II/III (NCT04390646)	Early Onset AD (Down syndrome)	N. Pitteloud et al.	
Leuprolide			Hormonal analog	Modulates hormones potentially slow neurodegeneration in postmenopausal women	sex to	Phase II ( NCT03649724)	MCI / mild AD	Weill Cornell / NIH-supported trial	
Insulin	CNS receptor	insulin	Peptide hormone	Improves glucose metabolism and cognition via central insulin signalling	brain	Phase II/III (NCT01767909, NCT05089656)	MCI / mild AD	Wake Forest / NIH	
Semaglutide	GLP-1 receptor		Peptide agonist	Modulates signalling, neuroinflammation, promotes neuroprotection	insulin reduces	Phase III (NCT04777396, NCT04777409)	Early AD	Novo Nordisk, Eli Lilly	



CpG1018	Aβ antigen (adjuvant only)	TLR9 agonist adjuvant	Enhances immune response to co-administered Aβ vaccine antigens via TLR9 activation	Phase I (NCT04524351)	Mild AD	Vaxxinity / Dynavax
AV-1959D	Aβ1–11 epitope	DNA Vaccine	Induces polyclonal antibodies against Aβ to clear plaques	Phase I (NCT05642429)	Early AD	Capo Therapeutics / IMM
ACI-24.060	Aβ oligomers & pyroglutamate Aβ	Active immunization (vaccine)	Induces polyclonal antibodies targeting pathogenic Aβ species, promoting immune-mediated clearance	Phase II (NCT05462106)	Prodromal AD & Down syndrome	AC Immune
ALZ-101	Aβ1–42 peptide		Elicits antibodies against Aβ1–42 to promote clearance	Phase I/II (NCT05399888)	Early AD	Alzinova AB
ACI-35	p-tau		Elicits antibodies against phosphorylated tau epitopes to inhibit intracellular aggregation	Phase I/IIa (no NCT listed)	MCI / mild AD	AC Immune / Janssen
BCG Vaccine	Trained innate immunity (macrophages)	Live attenuated vaccine	Boosts innate immune surveillance to mitigate neuroinflammation	Phase I/II (NCT05124171)	Early AD	University of Queensland / NIH <sup>1</sup>
Aldesleukin	IL-2 receptor on Tregs	Recombinant cytokine	Low-dose IL-2 selectively expands regulatory T cells to reduce neuroinflammation	Phase IIa (NCT06268886)	Early AD	Phase IIa (NCT06268886)
Sargramostim	Granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor		Stimulates innate immune cells to enhance Aβ clearance and neuroprotection	Phase II (NCT04902703)	Mild-to-moderate AD	Partner Therapeutics / CU Anschutz
ExPlas	Plasma factors	Plasma exchange biologic	Transfuses young plasma components to support neuronal health	Phase IIa (NCT05006716)	Mild AD to moderate	Alkahest / Grifols
Recombinant Human	Circulating Aβ	Plasma protein infusion	Alters peripheral Aβ dynamics to	Phase IIb (NCT04140176)	Mild to moderate AD	Grifols

Serum Albumin			promote central Aβ clearance						
XPro1595	Soluble TNFα	Dominant-negative TNF biologic	Inhibits TNFα to reduce neuroinflammation and synaptic loss	soluble	Phase II (NCT03943264)	Mild AD	INmune Bio		
ADEL-Y01	TGF-β1 pathway	Stem cell-derived biologic	Adipose-derived stem cell secretome modulates neuroinflammation and synaptic repair		Phase II (NCT05531526)	Mild to moderate AD	Anterogen Medipost	/	
Lomecel-B	MSC-secreted immunomodulatory and neurovascular factors	Allogeneic MSC therapy	Anti-inflammatory, pro-vascular, tissue repair, immunomodulatory, and low immunogenicity		Phase IIa (NCT05233774)	Mild AD	Longeveron		
Probiotics	Gut microbiota	Microbial consortia / dietary	Modulates gut-brain axis to reduce systemic inflammation and improve cognitive function		Phase II (NCT05325179)	MCI	Wake Forest		

3.1. Clinical Trial Phase and NCT Identifiers Were Obtained from ClinicalTrials.gov .3.1. Passive Immunotherapy: mAbs Against Aβ and tau

mAbs targeting Aβ or tau represent the most clinically advanced class of biologics for AD. These passive immunotherapies have yielded both landmark approvals and high-profile failures, reflecting the critical influence of antigen selectivity, target aggregation state, and disease stage at administration.

3.1.1. Anti-Aβ mAbs

Early-generation antibodies such as Solanezumab and Bapineuzumab were designed based on distinct pathogenic assumptions about Aβ toxicity. Solanezumab binds to monomeric Aβ in the brain interstitial fluid, aiming to sequester soluble peptides and prevent oligomer formation [142]. However, multiple large trials (e.g., EXPEDITION, DIAN-TU) showed no meaningful reduction in amyloid burden or cognitive benefit. In contrast, Bapineuzumab and Gantenerumab targeted fibrillar Aβ within plaques and achieved some plaque clearance but failed to show clinical efficacy and induced high rates of ARIA, especially cerebral edema (ARIA-E) and microhemorrhages (ARIA-H) [143,144].

The recent approvals of Lecanemab and Donanemab mark a shift toward antibodies targeting more toxic Aβ intermediates, such as protofibrils and pyroglutamate-modified Aβ species [134]. Both drugs demonstrated significant reductions in amyloid PET signal and modest slowing of cognitive decline (~27–35%) in early-stage AD populations (CDR 0.5) [145]. Notably, their trials (CLARITY-AD, TRAILBLAZER-ALZ 2) incorporated rigorous biomarker screening and early disease-stage enrolment, addressing past failures where treatment began too late.

Despite these advances, key limitations remain. ARIA incidence remains substantial, particularly in ApoE4 homozygotes [146], and intravenous dosing with frequent MRI monitoring presents logistical and cost-related challenges. Moreover, the clinical benefits are statistically significant but arguably clinically modest, raising questions about long-term real-world value [147].

Mechanistically, these results reaffirm A $\beta$  as a therapeutically tractable but temporally limited target, most effective in preclinical or prodromal stages, and unlikely to reverse downstream pathology once tau and neurodegeneration are established. As such, anti-A $\beta$  antibodies may serve best as early-intervention tools, perhaps in combination with tau- or inflammation-targeted therapies.

### 3.1.2. Anti-tau mAbs

Tau-targeted immunotherapy has emerged as a key strategy in AD, driven by the observation that tau pathology correlates more closely with cognitive impairment than A $\beta$  deposition [148]. Therapeutic approaches have focused on either passive immunization using mAbs or active immunization through vaccines, aiming to neutralize pathogenic tau species and halt their propagation.

mAbs against tau, such as Semorinemab, Gosuranemab, Zagotenemab, and Tilavonemab, were designed to bind extracellular forms of tau and thereby prevent its “prion-like” spread between neurons [149]. While this concept is supported by experimental models, clinical trials have yielded disappointing results. In a Phase 2 trial, Semorinemab failed to produce cognitive benefits in moderate AD, despite lowering plasma tau levels [150]. Similarly, Gosuranemab, Zagotenemab and Tilaconemab showed no significant effect on either biomarkers or cognition in placebo-controlled studies [151,152].

Several factors may explain these failures. First, the extracellular tau pool represents only a fraction of total pathogenic tau, and antibodies have limited access to the cytosol, where toxic aggregates accumulate. Second, tau pathology is often already widespread at the time of clinical diagnosis, limiting the potential for antibodies to block propagation. Finally, tau exists in multiple conformational and phosphorylation states, and current antibodies may lack sufficient selectivity or affinity for the most toxic forms.

### 3.2. Active Immunotherapy: Vaccines Targeting A $\beta$ and tau

Active immunotherapy, or therapeutic vaccination, represents a distinct subclass of biologics that seeks to stimulate the body's own immune system to recognize and neutralize pathological proteins involved in AD, primarily A $\beta$  and tau. Unlike mAbs that require repeated administration, vaccines may offer longer-lasting effects, lower cost, and improved accessibility, making them particularly attractive for population-wide or preventive strategies.

The earliest efforts at A $\beta$  vaccination, such as AN1792, were halted due to meningoencephalitis in a subset of participants, attributed to off-target T cell activation [153]. This outcome underscored the need for safer epitope design and T cell-independent formulations. More recent vaccine candidates, most notably UB-311, have addressed these concerns through rational antigen engineering [140].

UB-311, a synthetic peptide vaccine designed to elicit polyclonal antibodies against oligomeric A $\beta$ , utilizes helper T-cell epitopes to boost B-cell responses while minimizing pro-inflammatory risk [140]. In a Phase 2a trial, UB-311 was well-tolerated and generated sustained A $\beta$ -specific antibody titers. [154] Although the study was not powered for clinical efficacy, it showed promising trends toward cognitive stabilization and reduced neuropsychiatric symptoms. UB-311 has since advanced to Phase 2b, representing one of the most clinically mature A $\beta$  vaccine candidates to date.

On the tau side, several active immunization strategies are in development. ACI-35 is a liposome-based vaccine targeting p-tau epitopes, designed to induce conformationally selective antibody responses [149,155]. Phase 1b/2a data show robust immunogenicity, with no major safety signals [156]. Another candidate, AADvac1, elicits antibodies against truncated, misfolded tau forms

implicated in early tangle formation. Though AADvac1 completed a Phase 2 trial without meeting primary endpoints [157,158], exploratory analyses suggested a potential cognitive benefit in biomarker-positive subgroups.

Despite these advances, challenges remain. One major concern is the limited ability of antibodies, endogenous or exogenous, to penetrate neurons and access intracellular tau aggregates, which may limit efficacy in symptomatic AD. Additionally, heterogeneity in patient immune responses, the need for booster dosing, and delayed onset of action present practical hurdles. Immunotherapies against tau have thus far not replicated the relative success of anti-A $\beta$  antibodies, and their failure to improve clinical outcomes suggests the need to reconsider both the target (e.g., intracellular vs extracellular tau) and the delivery mechanism. While immunotherapy remains an active area of investigation, future progress may depend on combining tau-targeted agents with upstream disease-modifying strategies or transitioning to transcript-level interventions better suited to modulate intracellular tau burden.

Nevertheless, the scalability and preventive potential of vaccines continue to drive interest. In contrast to mAb therapy, which is expensive and logistically demanding, vaccines could be deployed in preclinical or at-risk populations, including ApoE4 carriers or individuals with biomarker evidence of early pathology. As such, therapeutic vaccination represents a promising, if still evolving, strategy for AD modification, particularly as an adjunct to other biologics or in preventive contexts.

### 3.3. RNA Therapeutics and Gene-Modifying Approaches: Redefining Targets at the Transcript Level

The past decade has seen a growing shift from protein-directed therapies toward transcript-level interventions in AD. RNA-based therapeutics, including ASOs, siRNAs, and emerging gene therapies, offer the ability to modulate pathogenic gene expression upstream of protein accumulation. These biologics present distinct advantages in accessing intracellular targets and achieving allele- or isoform-specific regulation, especially for diseases with well-defined genetic risk factors.

One of the most advanced RNA therapeutics in AD is BIIB080 (IONIS MAPTRx), an ASO targeting MAPT mRNA, designed to reduce production of all tau isoforms [159]. Administered intrathecally, BIIB080 achieved dose-dependent, sustained reductions in CSF total and p-tau in a Phase 1b study, without significant adverse events [160]. This intracellular mechanism may overcome the limitations observed with extracellular tau antibodies. A Phase 2 trial is currently ongoing, and BIIB080 represents a promising proof of concept for transcript-level tau modulation.

Other RNA-based drugs are targeting amyloidogenic pathways. ALN-APP, an investigational siRNA delivered via lipid nanoparticles (LNPs), aims to suppress APP expression and thereby reduce A $\beta$  production [161]. It has entered early-phase clinical trials and highlights the growing interest in hepatic or intrathecal RNA delivery systems that circumvent the BBB. Preclinical siRNA and shRNA candidates are also being developed against targets such as BACE1, PSEN1, and ApoE4, often using modified nanoparticles, cell-penetrating peptides, or viral vectors for brain delivery.

Perhaps most notably, the AAV-based gene therapy LX1001 is under clinical investigation for the upregulating of ApoE2 expression in AD patients [107]. ApoE4 remains the strongest genetic risk factor for LOAD, and LX1001 introduces an ApoE2 plasmid to adjust the ratio of ApoE2 and ApoE4 via AAV delivery. This therapy has completed a Phase 2 trial, representing a landmark effort to intervene at the genetic level in sporadic AD. Promising results have been reported, including reductions in key biomarkers such as plasma pTau181 and pTau217.

Gene therapy in AD also includes neuroprotective strategies. NT-501, an encapsulated cell implant engineered to secrete ciliary neurotrophic factor (CNTF), is in clinical evaluation for preserving neuronal function [162]. While cell-based delivery bypasses immune barriers and allows long-term release, issues of surgical implantation, host responses, and limited distribution remain challenges.

Despite their promise, RNA and gene therapies face significant hurdles, including delivery efficiency, long-term safety, immune activation, and cost. Nonetheless, these approaches may enable



precision treatment for genetically defined subpopulations (e.g., ApoE4 homozygotes), multi-target regulation, and early-stage intervention before irreversible pathology occurs. As delivery systems improve and companion diagnostics evolve, transcript- and gene-level biologics are poised to reshape the landscape of AD drug development (Table 2).

**Table 2.** Discontinued or Failed Biologic Therapeutics in Alzheimer’s Disease: Clinical Trial Phases, Targets, and Reasons for Termination.

Drug	Target	Biologic type	Mechanism of action	Clinical trial phase (at failure)	Reason for failure / outcome	Sponsor
Gantenerumab	Fibrillar Aβ	mAb	Clears fibrillar Aβ via microglial activation	Phase III (GRADUATE 1: NCT03444870, GRADUATE 2: NCT03443973)	Despite significant plaque reduction, no cognitive benefit was observed in interim analyses, leading to early termination.	Roche
Bapineuzumab			Targets Aβ via Fc-mediated phagocytosis	Phase III (Studies 301/302: NCT00667810, NCT00667824)	Failed to meet primary cognitive and function endpoints in ApoE4 carriers & non-carriers, incidence of ARIA, all trials subsequently discontinued	Janssen/Pfizer
Solanezumab	Soluble Aβ		Enhances peripheral clearance of soluble Aβ	Phase III (EXPEDITION 1–3: NCT01767311, NCT02008357, A4: NCT02008357)	Failed to meet primary cognitive endpoints in mild-to-moderate and preclinical AD, subgroup analyses showed only marginal trends without statistical power.	Eli Lilly
Ponezumab			Peripheral sink effect, targets Aβ to enhance systemic clearance	Phase II (NCT00945672)	No cognitive or biomarker benefit in mild-to-moderate AD patients	Prizer
Crenezumab	Aβ oligomers		Binds oligomeric Aβ, reduced Fc effector	Binds oligomeric Aβ, reduced effector activity (IgG4)	Terminated after futility analyses revealed no significant clinical benefit in	Genentech/Roche

			activity (IgG4)			prodromal/mild AD, also failed in the Alzheimer's Prevention Initiative (API) for autosomal dominant AD.	
RG7345	Aggregated Aβ		Anti-Aβ monoclonal antibody	Phase I (NCT01224106)	I	Trial completed with no follow-up, development not continued	Roche / Genentech
GSK933776			Binds plaque-forming Aβ to lower CNS Aβ without ARIA	Phase I (NCT00459550, NCT01424436)	I	Engaged target and altered Aβ levels, but no subsequent efficacy trials, likely discontinued	GSK
Gosuranemab	Extracellular N-terminal tau		Binds N-terminal tau to block cell-to-cell propagation	Phase II (TANGO: NCT03352557)	II	Trial failed to demonstrate clinical benefit despite target engagement, program discontinued.	Biogen
Semorinemab			Targets N-terminal tau to inhibit spreading of pathology	Phase II (Tauriel: NCT03289143, Lauriet: NCT03828747)		No significant slowing of cognitive or functional decline observed in mild-to-moderate AD patients.	Genentech
AN1792 Vaccine	Full-length Aβ <sub>1-42</sub>	Peptide vaccine	Induces polyclonal anti-Aβ antibody response	Phase II (NCT00021723)	II	Induced meningoencephalitis in ~5% of participants due to autoimmune T-cell response, program halted for safety reasons.	Elan/Wyeth
ACC-001	Aβ <sub>1-7</sub> peptide (with QS-21 adjuvant)		Vaccine targeting Aβ <sub>1-7</sub> with QS-21 adjuvant	Phase II (NCT01284387)	II	Terminated due to injection-site reactions and lack of efficacy	Janssen / Pfizer
ABvac40	C-terminal Aβ <sub>40</sub> epitope		Induces antibodies targeting Aβ <sub>40</sub> to	Phase II (NCT02927237)	II	Phase II results unpublished, program status	Araclon Biotech

			prevent aggregation			unclear, likely discontinued		
UB-311	Aβ1–14 (soluble and aggregated forms)		Induces Th2-skewed anti-Aβ antibody response	Phase (NCT04055376)	Ila	Trial completed, no publicly reported efficacy outcomes since 2021	United Biomedical Inc.	
AADvac1	Truncated pathological tau		Induces antibodies against misfolded tau protein	Phase (NCT02579252)	II	No significant slowing of cognitive decline, biomarker changes modest, development halted or stalled	AXON Neuroscience	
BIIB092 (Tilavonemab)	N-terminal extracellular tau		Binds extracellular tau to block seeding and spread	Phase (NCT03352557)	II	Failed to slow decline despite tau binding, development discontinued	Biogen	
RO7105705			Blocks tau propagation in extracellular space	Phase (NCT03828747)	II	Modest biomarker changes but failed to slow clinical progression	Genentech	
Lu AF20513	Multi-epitope Aβ	DNA vaccine	Targets multiple Aβ epitopes	Phase (NCT01519363)	I	Study completed with no publication or further clinical development	Lundbeck	
CAD106	Aβ1–6	Active vaccine	Induces Aβ antibodies while avoiding T-cell response	Phase (NCT02565511)	II/III	Did not meet cognitive endpoints in patients with prodromal AD	Novartis	
Octagam IVIG	Polyvalent antibodies	IV immunoglobulin therapy	Hypothesized to clear Aβ/Opsonize for immune-mediated clearance	Phase (NCT01561053)	III	Failed to meet cognitive or functional endpoints in mild-to-moderate AD	Baxter / Baxalta	

3.4. Clinical Trial Phase and NCT Identifiers Were Obtained from ClinicalTrials.gov .3.4. Failure and Lessons Learned from Biologic Trials

The landscape of biologic therapeutics for AD is littered with high-profile failures, many of which have profoundly influenced how the field now designs and interprets clinical trials. Despite elegant mechanisms, favourable preclinical data, and even target engagement in humans, many biologic agents have failed to demonstrate clinical benefit. These outcomes demand not only technical reassessment, but a broader reflection on disease biology and therapeutic timing.

Among the most notable disappointments was solanezumab, a mAb designed to bind soluble monomeric A $\beta$ , thereby sequestering it before oligomerization and plaque formation. The mechanistic rationale was elegant: prevent the cascade before it begins. In practice, however, trials including EXPEDITION and DIAN-TU showed that although solanezumab increased peripheral A $\beta$  clearance, it had minimal impact on brain amyloid burden, and no measurable effect on cognition or function [163]. This disconnect between peripheral pharmacodynamics and central pathology raised a critical concern—was the target itself insufficient, or had the intervention simply come too late?

Crenezumab, another antibody with higher affinity for oligomeric A $\beta$ , was expected to overcome the limitations of solanezumab. Yet, in both sporadic and genetically determined AD cohorts (including the landmark Colombian PSEN1 mutation carriers), Crenezumab failed to slow cognitive decline. Post hoc analyses suggested that by the time symptoms manifest, even in familial AD, removing extracellular A $\beta$  may no longer suffice, particularly if tau and neurodegeneration have already gained momentum [164].

The same theme emerged in anti-tau trials. Semorinemab, Gosuranemab, and Zagotenemab all showed some evidence of target engagement, reducing extracellular tau levels in CSF or plasma but failed to produce clinical improvements in cognition or function. While antibodies can neutralize extracellular tau, the most toxic tau species likely reside intracellularly, where antibodies have limited access. These trials raised an uncomfortable but essential question: Can immunotherapy succeed if the pathogenic process has already shifted from seeding to irreversible neuronal loss?

Equal importance was the realization that biomarker changes do not always translate to clinical benefit. Several agents showed amyloid clearance or tau reduction on PET or CSF assays, yet patients continued to decline [165]. This decoupling implies that molecular pathology may be necessary but not sufficient to drive the clinical syndrome, or that damage becomes self-sustaining beyond a critical threshold.

Across these failures, a few common themes have emerged. First, many trials enrolled patients in mild-to-moderate stages of AD, too late for disease-modifying interventions to reverse established damage. Second, early biologics often lacked precise stratification tools, resulting in heterogeneous trial populations, some of whom may not have had active amyloid or tau pathology. Third, the field's reliance on traditional cognitive endpoints may have underestimated subtle, early effects better captured by biomarkers.

Crucially, these failures have reshaped how we now approach clinical trials. Biomarker-confirmed inclusion is now standard [166]. Trials increasingly enrol prodromal or preclinical patients. Outcomes integrate imaging, fluid biomarkers, and cognitive composites. And perhaps most importantly, biologics are no longer tested in isolation, they are being paired with more nuanced diagnostics and, increasingly, with complementary therapeutics targeting inflammation, synaptic function, or metabolic resilience.

In retrospect, these failures were not in vain. They clarified the limits of certain targets, exposed the need for earlier intervention, and forced the field to recalibrate its expectations and designs. The modest success of agents like Lecanemab and Donanemab is built on these hard-earned lessons, and points to a more mature, biologically grounded era of drug development in AD.

## 4. Future Perspectives and Challenges

### 4.1. Rethinking Therapeutic Targets Beyond Amyloid and tau

The long-standing focus on A $\beta$  and tau in AD research has produced both landmark advances and frustrating limitations. Recent approvals of anti-amyloid antibodies such as Lecanemab and Donanemab offer partial validation of the amyloid hypothesis, but their modest efficacy and safety concerns underscore a crucial reality: amyloid and tau alone may not fully account for disease initiation and progression, particularly in sporadic LOAD. As a result, a paradigm shift is underway, toward broader, multidimensional targets that capture the complexity of AD pathophysiology.



Among the most actively explored area is neuroinflammation, which is increasingly recognized not as a secondary response but as a driver of synaptic loss and neuronal dysfunction. Genetic studies have implicated immune-related genes such as TREM2, CD33, and INPP5D, all of which regulate microglial activation states. Therapeutic strategies aimed at modulating microglial phenotype, rather than simply suppressing inflammation, are gaining ground. For example, AL002 (a TREM2 agonist antibody) is currently in Phase 2 trials, aiming to enhance microglial phagocytosis and resilience in early-stage AD [54].

Another emerging area is vascular dysfunction and BBB breakdown. Evidence suggests that BBB leakage may precede and exacerbate amyloid deposition, tau propagation, and neuroinflammation. Agents such as anti-VCAM1 antibodies or small molecules targeting pericyte health aim to restore neurovascular integrity, potentially delaying disease onset or progression [167].

Metabolic and endocrine dysregulation, particularly insulin signalling impairment, also constitutes a promising therapeutic axis. The repurposing of GLP-1 receptor agonists, such as semaglutide [168], originally developed for diabetes, reflects this metabolic angle. These agents are now being evaluated in Phase 3 AD trials, supported by preclinical data demonstrating anti-inflammatory and neuroprotective effects independent of glycaemic control.

Lipid metabolism, especially involving ApoE, presents another compelling target. ApoE4, the strongest genetic risk factor for sporadic AD, affects synaptic plasticity, cholesterol transport, and glial function. Therapies aimed at reducing ApoE4 levels (e.g., LX1001) or enhancing ApoE2-like functions are being developed, including RNA-based strategies and receptor modulators. These efforts aim not just to lower risk, but to modify underlying pathobiology in genetically susceptible individuals.

Collectively, these emerging targets reflect a growing appreciation for AD as a multi-system disorder, involving immune, vascular, metabolic, and genetic factors. Future biologic therapies are likely to succeed not through monotherapy, but via strategic combinations that address multiple axes of disease vulnerability. To that end, mechanistically diverse biologics, and the diagnostics needed to guide their use, represent the next frontier in AD drug development.

#### *4.2. Overcoming Delivery Barriers to the Brain*

One of the most persistent obstacles in AD biologic development is the challenge of delivering large or complex molecules to the brain. Most biologics, such as mAbs and nucleic acids, face significant barriers in crossing the BBB, a highly selective interface that limits the entry of over 98% of potential CNS therapeutics [169]. As a result, many promising biologics fail not because of insufficient potency, but because they cannot reach their intended targets at therapeutic concentrations.

Currently approved anti-amyloid antibodies, such as Lecanemab and Donanemab, require regular intravenous administration, with systemic distribution and only a small fraction penetrating the CNS. This results in high treatment burdens, risk of peripheral side effects, and increased healthcare costs. Moreover, the need for intensive MRI monitoring, primarily to detect ARIA, underscores the delicate balance between efficacy and safety in CNS-targeted biologics.

To overcome these limitations, several innovative delivery strategies are under development. Among the most promising are LNP platforms, which have gained clinical validation in mRNA vaccine delivery. When tailored with cell-penetrating peptides (CPPs) or surface ligands that recognize brain endothelial receptors (e.g., transferrin or insulin receptor), LNPs may facilitate receptor-mediated transcytosis across the BBB. Furthermore, intranasal administration of nanoparticle-encapsulated therapeutics bypasses systemic circulation altogether, offering a non-invasive route to the brain via the olfactory and trigeminal pathways [124,139].

AAV vectors, widely used in gene therapy, offer another route for durable CNS delivery. While conventional systemic AAV administration often leads to hepatic sequestration and immune clearance, recent innovations in capsid engineering and direct intracerebroventricular (ICV) or

intrathecal injection (IV) have enhanced CNS tropism. However, concerns around immunogenicity, manufacturing cost, and limited dosing capacity remain.

Other emerging approaches include focused ultrasound (FUS) with microbubbles to transiently disrupt the BBB [170], exosome-based delivery systems, and biodegradable polymeric nanoparticles (PNPs). Each has shown promise in animal models, but translation to clinical-scale human application remains in early stages.

In essence, solving the delivery challenge is not merely a technical hurdle, it is a prerequisite for translating biological insight into therapeutic success. As more biologics target intracellular or gene-level mechanisms, delivery platforms will need to balance efficiency, safety, and patient acceptability. Ultimately, innovations in delivery may prove just as critical as target selection in shaping the future of AD therapy.

#### 4.3. Designing Trials for Prevention and Precision

The limited efficacy of many AD therapeutics, especially biologics, has increasingly been attributed not to the failure of mechanisms per se, but to late timing of intervention. By the time clinical symptoms emerge, neurodegeneration is often well underway, with widespread synaptic loss, glial dysfunction, and tau pathology. This has shifted the therapeutic paradigm toward early-stage or even pre-symptomatic intervention, ushering in a new era of prevention-oriented and precision-guided trial design.

A cornerstone of this shift is the use of biomarkers to detect preclinical disease [171]. Advanced imaging, like amyloid-PET and tau-PET, CSF biomarkers, including A $\beta$ 42/40 ratio and p-tau, and increasingly plasma biomarkers, such as p-tau181, p-tau217, neurofilament light chain (NfL), now enable the identification of individuals with pathological changes years before cognitive symptoms appear. These markers not only facilitate early diagnosis, but also allow for pathology-confirmed inclusion criteria, as exemplified by the CLARITY-AD and TRAILBLAZER-ALZ studies [172].

Genetic risk factors, particularly ApoE4 carrier status, are also being used to enrich trial populations most likely to benefit from specific interventions, or to stratify for adverse event risks such as ARIA. Trials like the AHEAD 3–45 and API Generation Study have embraced this genotype-based approach, enrolling cognitively normal individuals at elevated risk for AD. Meanwhile, gene-targeted biologics such as LX1001 specifically address genetically defined subgroups, highlighting the potential for genotype-guided therapy.

Innovations in trial design are equally important. Adaptive designs allow for real-time modification of trial parameters, such as dosage and patient subgroup allocation, based on interim data. Platform trials test multiple drugs in parallel within a shared infrastructure, improving efficiency and comparability. These flexible models may be particularly valuable for AD, where biological heterogeneity and slow progression demand long, costly studies.

Outcome measures are also evolving. In early-stage populations, conventional cognitive scales often lack sensitivity to subtle change. Composite endpoints that integrate biomarker shifts, digital cognitive assessments, and functional measures are being developed to more accurately capture early therapeutic effects. Moreover, fluid biomarkers are increasingly used as surrogate endpoints, potentially shortening trial durations and enabling earlier regulatory evaluation.

Together, these innovations signal a shift from the one-size-fits-all approach of earlier decades toward a personalized, stage-sensitive therapeutic model. By selecting the right patients, at the right time, and measuring the right outcomes, prevention- and precision-oriented trials hold the promise of transforming AD drug development, especially for biologics that may act most effectively before irreversible damage occurs.

#### 4.4. Ethical, Regulatory, and Access Considerations

As biologic therapies for AD move toward broader clinical use, ethical and practical challenges become increasingly prominent. High treatment costs, complex administration protocols, and biomarker-based eligibility raise concerns about equity and access. Intravenous antibodies like

Lecanemab require frequent infusions and MRI monitoring, limiting feasibility in many health systems. Gene and RNA therapies, such as LX1001 or BIIB080, pose additional hurdles in terms of regulatory oversight, long-term safety, and manufacturing complexity.

Efforts to intervene in the preclinical stage also introduce dilemmas. Early biomarker or genetic risk disclosure, particularly in asymptomatic individuals, can trigger psychological distress, discrimination risks, and challenges in informed consent [173]. Identifying who should be screened, and when, will require careful ethical and public health frameworks.

Moreover, as diagnostics and therapies become increasingly commercialized, regulators face the task of balancing innovation with transparency and affordability. Surrogate endpoints, like amyloid clearance, are gaining regulatory acceptance, but their relationship with long-term clinical outcomes remains under scrutiny.

In the long run, biologic progress must be matched by policy mechanisms that promote fair access, ensure safety monitoring, and support sustainable implementation. Without such frameworks, scientific advances may risk deepening, rather than alleviating, disparities in dementia care.

## References

1. P.T. Kamatham, R. Shukla, D.K. Khatri, L.K. Vora, Pathogenesis, diagnostics, and therapeutics for Alzheimer's disease: Breaking the memory barrier, *Ageing Res Rev*, 101 (2024) 102481.
2. E. Twiss, C. McPherson, D.F. Weaver, Global Diseases Deserve Global Solutions: Alzheimer's Disease, *Neurol Int*, 17 (2025).
3. 2024 Alzheimer's disease facts and figures, *Alzheimers Dement*, 20 (2024) 3708-3821.
4. W. Gulisano, D. Maugeri, M.A. Baltrons, M. Fà, A. Amato, A. Palmeri, L. D'Adamio, C. Grassi, D.P. Devanand, L.S. Honig, D. Puzzo, O. Arancio, Role of Amyloid- $\beta$  and Tau Proteins in Alzheimer's Disease: Confuting the Amyloid Cascade, *J Alzheimers Dis*, 64 (2018) S611-s631.
5. H. Zhang, W. Wei, M. Zhao, L. Ma, X. Jiang, H. Pei, Y. Cao, H. Li, Interaction between A $\beta$  and Tau in the Pathogenesis of Alzheimer's Disease, *Int J Biol Sci*, 17 (2021) 2181-2192.
6. M.C. Jurcău, F.L. Andronie-Cioara, A. Jurcău, F. Marcu, D.M. Țiț, N. Pașcalău, D.C. Nistor-Cseppentő, The Link between Oxidative Stress, Mitochondrial Dysfunction and Neuroinflammation in the Pathophysiology of Alzheimer's Disease: Therapeutic Implications and Future Perspectives, *Antioxidants (Basel)*, 11 (2022).
7. E. Tönnies, E. Trushina, Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease, *J Alzheimers Dis*, 57 (2017) 1105-1121.
8. T. Ashleigh, R.H. Swerdlow, M.F. Beal, The role of mitochondrial dysfunction in Alzheimer's disease pathogenesis, *Alzheimers Dement*, 19 (2023) 333-342.
9. W. Zhang, D. Xiao, Q. Mao, H. Xia, Role of neuroinflammation in neurodegeneration development, *Signal Transduct Target Ther*, 8 (2023) 267.
10. J. Subramanian, J.C. Savage, M. Tremblay, Synaptic Loss in Alzheimer's Disease: Mechanistic Insights Provided by Two-Photon in vivo Imaging of Transgenic Mouse Models, *Front Cell Neurosci*, 14 (2020) 592607.
11. G. Moya-Alvarado, N. Gershoni-Emek, E. Perlson, F.C. Bronfman, Neurodegeneration and Alzheimer's disease (AD). What Can Proteomics Tell Us About the Alzheimer's Brain?, *Mol Cell Proteomics*, 15 (2016) 409-425.
12. A.M. Di Battista, N.M. Heinsinger, G.W. Rebeck, Alzheimer's Disease Genetic Risk Factor APOE- $\epsilon$ 4 Also Affects Normal Brain Function, *Curr Alzheimer Res*, 13 (2016) 1200-1207.
13. C.C. Liu, C.C. Liu, T. Kanekiyo, H. Xu, G. Bu, Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy, *Nat Rev Neurol*, 9 (2013) 106-118.
14. A.C. Raulin, S.V. Doss, Z.A. Trottier, T.C. Ikezu, G. Bu, C.C. Liu, ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies, *Mol Neurodegener*, 17 (2022) 72.

15. O. Sheppard, M. Coleman, Alzheimer's Disease: Etiology, Neuropathology and Pathogenesis, in: X. Huang (Ed.) Alzheimer's Disease: Drug Discovery, Exon Publications Copyright: The Authors., Brisbane (AU), 2020.
16. G.T. Grossberg, Cholinesterase inhibitors for the treatment of Alzheimer's disease:: getting on and staying on, *Curr Ther Res Clin Exp*, 64 (2003) 216-235.
17. J. Liu, L. Chang, Y. Song, H. Li, Y. Wu, The Role of NMDA Receptors in Alzheimer's Disease, *Front Neurosci*, 13 (2019) 43.
18. D.M.A. Oliver, P.H. Reddy, Small molecules as therapeutic drugs for Alzheimer's disease, *Mol Cell Neurosci*, 96 (2019) 47-62.
19. G. Adami, K.G. Saag, R.D. Chapurlat, N. Guañabens, G. Haugeberg, W.F. Lems, R. Matijevic, N. Peel, D. Poddubnyy, P. Geusens, Balancing benefits and risks in the era of biologics, *Ther Adv Musculoskelet Dis*, 11 (2019) 1759720x19883973.
20. D.F. Weaver, Drug Design for Alzheimer's Disease: Biologics vs. Small Molecules, *Curr Alzheimer Res*, 20 (2024) 821-826.
21. J. Zhang, Y. Zhang, J. Wang, Y. Xia, J. Zhang, L. Chen, Recent advances in Alzheimer's disease: Mechanisms, clinical trials and new drug development strategies, *Signal Transduct Target Ther*, 9 (2024) 211.
22. J.A. Hardy, G.A. Higgins, Alzheimer's disease: the amyloid cascade hypothesis, *Science*, 256 (1992) 184-185.
23. R. Ricciarelli, E. Fedele, The Amyloid Cascade Hypothesis in Alzheimer's Disease: It's Time to Change Our Mind, *Curr Neuropharmacol*, 15 (2017) 926-935.
24. C. Zhang, A.J. Saunders, Therapeutic targeting of the alpha-secretase pathway to treat Alzheimer's disease, *Discov Med*, 7 (2007) 113-117.
25. V.W. Chow, M.P. Mattson, P.C. Wong, M. Gleichmann, An overview of APP processing enzymes and products, *Neuromolecular Med*, 12 (2010) 1-12.
26. S.L. Cole, R. Vassar, The Alzheimer's disease beta-secretase enzyme, BACE1, *Mol Neurodegener*, 2 (2007) 22.
27. D. Im, T.S. Choi, Distinctive contribution of two additional residues in protein aggregation of A $\beta$ 42 and A $\beta$ 40 isoforms, *BMB Rep*, 57 (2024) 263-272.
28. C. Song, T. Zhang, Y. Zhang, Conformational Essentials Responsible for Neurotoxicity of A $\beta$ 42 Aggregates Revealed by Antibodies against Oligomeric A $\beta$ 42, *Molecules*, 27 (2022).
29. Y. Zhang, H. Chen, R. Li, K. Sterling, W. Song, Amyloid  $\beta$ -based therapy for Alzheimer's disease: challenges, successes and future, *Signal Transduct Target Ther*, 8 (2023) 248.
30. A. Boutajangout, E.M. Sigurdsson, P.K. Krishnamurthy, Tau as a therapeutic target for Alzheimer's disease, *Curr Alzheimer Res*, 8 (2011) 666-677.
31. A. Boutajangout, J. Ingadottir, P. Davies, E.M. Sigurdsson, Passive immunization targeting pathological phospho-tau protein in a mouse model reduces functional decline and clears tau aggregates from the brain: Clearance of pathological tau by passive immunization, *Journal of neurochemistry*, 118 (2011) 658-667.
32. A.R. Chaudhary, F. Berger, C.L. Berger, A.G. Hendricks, Tau directs intracellular trafficking by regulating the forces exerted by kinesin and dynein teams, *Traffic*, 19 (2018) 111-121.
33. M.A. Utton, G.M. Gibb, I.D. Burdett, B.H. Anderton, A. Vandecandelaere, Functional differences of tau isoforms containing 3 or 4 C-terminal repeat regions and the influence of oxidative stress, *J Biol Chem*, 276 (2001) 34288-34297.
34. B.L. Goode, M. Chau, P.E. Denis, S.C. Feinstein, Structural and functional differences between 3-repeat and 4-repeat tau isoforms. Implications for normal tau function and the onset of neurodegenerative disease, *J Biol Chem*, 275 (2000) 38182-38189.
35. S. Jayapalan, J. Natarajan, The role of CDK5 and GSK3B kinases in hyperphosphorylation of microtubule associated protein tau (MAPT) in Alzheimer's disease, *Bioinformation*, 9 (2013) 1023-1030.
36. P. Rawat, U. Sehar, J. Bisht, A. Selman, J. Culberson, P.H. Reddy, Phosphorylated Tau in Alzheimer's Disease and Other Tauopathies, *Int J Mol Sci*, 23 (2022).
37. A.D. Alonso, J. Di Clerico, B. Li, C.P. Corbo, M.E. Alaniz, I. Grundke-Iqbal, K. Iqbal, Phosphorylation of tau at Thr212, Thr231, and Ser262 combined causes neurodegeneration, *J Biol Chem*, 285 (2010) 30851-30860.

38. S. Muraoka, W. Lin, K. Takamatsu-Yukawa, J. Hu, S. Ikezu, M.A. DeTure, D.W. Dickson, A. Emili, T. Ikezu, Enrichment of Phosphorylated Tau (Thr181) and Functionally Interacting Molecules in Chronic Traumatic Encephalopathy Brain-derived Extracellular Vesicles, *Aging Dis*, 12 (2021) 1376-1388.
39. G.T. Bramblett, M. Goedert, R. Jakes, S.E. Merrick, J.Q. Trojanowski, V.M. Lee, Abnormal tau phosphorylation at Ser396 in Alzheimer's disease recapitulates development and contributes to reduced microtubule binding, *Neuron*, 10 (1993) 1089-1099.
40. S.D. Yang, J.S. Song, J.S. Yu, S.G. Shiah, Protein kinase FA/GSK-3 phosphorylates tau on Ser235-Pro and Ser404-Pro that are abnormally phosphorylated in Alzheimer's disease brain, *J Neurochem*, 61 (1993) 1742-1747.
41. L. Troquier, R. Caillierez, S. Burnouf, F.J. Fernandez-Gomez, M.E. Grosjean, N. Zommer, N. Sergeant, S. Schraen-Maschke, D. Blum, L. Buee, Targeting phospho-Ser422 by active Tau Immunotherapy in the THYTau22 mouse model: a suitable therapeutic approach, *Curr Alzheimer Res*, 9 (2012) 397-405.
42. L. Yu, P.A. Boyle, S. Janelidze, V.A. Petyuk, T. Wang, D.A. Bennett, O. Hansson, J.A. Schneider, Plasma p-tau181 and p-tau217 in discriminating PART, AD and other key neuropathologies in older adults, *Acta Neuropathol*, 146 (2023) 1-11.
43. A.M. Brickman, J.J. Manly, L.S. Honig, D. Sanchez, D. Reyes-Dumeyer, R.A. Lantigua, P.J. Lao, Y. Stern, J.P. Vonsattel, A.F. Teich, D.C. Airey, N.K. Proctor, J.L. Dage, R. Mayeux, Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study, *Alzheimers Dement*, 17 (2021) 1353-1364.
44. F. St-Onge, M. Chapleau, J.C. Breitner, S. Villeneuve, A.P. Binette, Tau accumulation and its spatial progression across the Alzheimer's disease spectrum, *medRxiv*, (2023).
45. A. Bejanin, D.R. Schonhaut, R. La Joie, J.H. Kramer, S.L. Baker, N. Sosa, N. Ayakta, A. Cantwell, M. Janabi, M. Lauriola, J.P. O'Neil, M.L. Gorno-Tempini, Z.A. Miller, H.J. Rosen, B.L. Miller, W.J. Jagust, G.D. Rabinovici, Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease, *Brain*, 140 (2017) 3286-3300.
46. K.J. Kopeikina, B.T. Hyman, T.L. Spires-Jones, Soluble forms of tau are toxic in Alzheimer's disease, *Transl Neurosci*, 3 (2012) 223-233.
47. C.A. Brunello, M. Merezko, R.L. Uronen, H.J. Huttunen, Mechanisms of secretion and spreading of pathological tau protein, *Cell Mol Life Sci*, 77 (2020) 1721-1744.
48. G.S. Gibbons, V.M.Y. Lee, J.Q. Trojanowski, Mechanisms of Cell-to-Cell Transmission of Pathological Tau: A Review, *JAMA Neurol*, 76 (2019) 101-108.
49. Y. Chen, Y. Yu, Tau and neuroinflammation in Alzheimer's disease: interplay mechanisms and clinical translation, *J Neuroinflammation*, 20 (2023) 165.
50. J.W. Kinney, S.M. Bemiller, A.S. Murtishaw, A.M. Leisgang, A.M. Salazar, B.T. Lamb, Inflammation as a central mechanism in Alzheimer's disease, *Alzheimers Dement (N Y)*, 4 (2018) 575-590.
51. G. Tosto, C. Reitz, Genome-wide association studies in Alzheimer's disease: a review, *Curr Neurol Neurosci Rep*, 13 (2013) 381.
52. C. Bellenguez, F. Küçükali, I.E. Jansen, L. Kleindam, S. Moreno-Grau, N. Amin, A.C. Naj, R. Campos-Martin, B. Grenier-Boley, V. Andrade, P.A. Holmans, A. Boland, V. Damotte, S.J. van der Lee, M.R. Costa, T. Kuulasmaa, Q. Yang, I. de Rojas, J.C. Bis, A. Yaqub, I. Prokic, J. Chapuis, S. Ahmad, V. Giedraitis, D. Aarsland, P. Garcia-Gonzalez, C. Abdelnour, E. Alarcón-Martín, D. Alcolea, M. Alegret, I. Alvarez, V. Álvarez, N.J. Armstrong, A. Tsolaki, C. Antúnez, I. Appollonio, M. Arcaro, S. Archetti, A.A. Pastor, B. Arosio, L. Athanasiu, H. Bailly, N. Banaj, M. Baquero, S. Barral, A. Beiser, A.B. Pastor, J.E. Below, P. Benček, L. Benussi, C. Berr, C. Besse, V. Bessi, G. Binetti, A. Bizarro, R. Blesa, M. Boada, E. Boerwinkle, B. Borroni, S. Boschi, P. Bossù, G. Bräthen, J. Bressler, C. Bresner, H. Brodaty, K.J. Brookes, L.I. Brusco, D. Buiza-Rueda, K. Bürger, V. Burholt, W.S. Bush, M. Calero, L.B. Cantwell, G. Chene, J. Chung, M.L. Cuccaro, Á. Carracedo, R. Cecchetti, L. Cervera-Carles, C. Charbonnier, H.H. Chen, C. Chillotti, S. Ciccone, J. Claassen, C. Clark, E. Conti, A. Corma-Gómez, E. Costantini, C. Custodero, D. Daian, M.C. Dalmasso, A. Daniele, E. Dardiotis, J.F. Dartigues, P.P. de Deyn, K. de Paiva Lopes, L.D. de Witte, S. Debette, J. Deckert, T. Del Ser, N. Denning, A. DeStefano, M. Dichgans, J. Diehl-Schmid, M. Diez-Fairen, P.D. Rossi, S. Djurovic, E. Duron, E. Düzel, C. Dufouil, G. Eiriksdottir, S. Engelborghs, V. Escott-Price, A. Espinosa, M. Ewers, K.M. Faber, T. Fabrizio, S.F.



- Nielsen, D.W. Fardo, L. Farotti, C. Fenoglio, M. Fernández-Fuertes, R. Ferrari, C.B. Ferreira, E. Ferri, B. Fin, P. Fischer, T. Fladby, K. Fließbach, B. Fongang, M. Fornage, J. Fortea, T.M. Foroud, S. Fostinelli, N.C. Fox, E. Franco-Macías, M.J. Bullido, A. Frank-García, L. Froelich, B. Fulton-Howard, D. Galimberti, J.M. García-Alberca, P. García-González, S. Garcia-Madrone, G. Garcia-Ribas, R. Ghidoni, I. Giegling, G. Giorgio, A.M. Goate, O. Goldhardt, D. Gomez-Fonseca, A. González-Pérez, C. Graff, G. Grande, E. Green, T. Grimmer, E. Grünblatt, M. Grunin, V. Gudnason, T. Guetta-Baranes, A. Haapasalo, G. Hadjigeorgiou, J.L. Haines, K.L. Hamilton-Nelson, H. Hampel, O. Hanon, J. Hardy, A.M. Hartmann, L. Hausner, J. Harwood, S. Heilmann-Heimbach, S. Helisalmi, M.T. Heneka, I. Hernández, M.J. Herrmann, P. Hoffmann, C. Holmes, H. Holstege, R.H. Vilas, M. Hulsman, J. Humphrey, G.J. Biessels, X. Jian, C. Johansson, G.R. Jun, Y. Kastumata, J. Kauwe, P.G. Kehoe, L. Kilander, A.K. Ståhlbom, M. Kivipelto, A. Koivisto, J. Kornhuber, M.H. Kosmidis, W.A. Kukull, P.P. Kuksa, B.W. Kunkle, A.B. Kuzma, C. Lage, E.J. Laukka, L. Launer, A. Lauria, C.Y. Lee, J. Lehtisalo, O. Lerch, A. Lleó, W. Longstreth, Jr., O. Lopez, A.L. de Munain, S. Love, M. Löwemark, L. Luckcuck, K.L. Lunetta, Y. Ma, J. Macías, C.A. MacLeod, W. Maier, F. Mangialasche, M. Spallazzi, M. Marquí, R. Marshall, E.R. Martin, A.M. Montes, C.M. Rodríguez, C. Masullo, R. Mayeux, S. Mead, P. Mecocci, M. Medina, A. Meggy, S. Mehrabian, S. Mendoza, M. Menéndez-González, P. Mir, S. Moebus, M. Mol, L. Molina-Porcel, L. Montreal, L. Morelli, F. Moreno, K. Morgan, T. Mosley, M.M. Nöthen, C. Muchnik, S. Mukherjee, B. Nacmias, T. Ngandu, G. Nicolas, B.G. Nordestgaard, R. Olaso, A. Orellana, M. Orsini, G. Ortega, A. Padovani, C. Paolo, G. Papenberg, L. Parnetti, F. Pasquier, P. Pastor, G. Peloso, A. Pérez-Cordón, J. Pérez-Tur, P. Pericard, O. Peters, Y.A.L. Pijnenburg, J.A. Pineda, G. Piñol-Ripoll, C. Pisanu, T. Polak, J. Popp, D. Posthuma, J. Priller, R. Puerta, O. Quenez, I. Quintela, J.Q. Thomassen, A. Rábano, I. Rainero, F. Rajabli, I. Ramakers, L.M. Real, M.J.T. Reinders, C. Reitz, D. Reyes-Dumeyer, P. Ridge, S. Riedel-Heller, P. Riederer, N. Roberto, E. Rodriguez-Rodriguez, A. Rongve, I.R. Allende, M. Rosende-Roca, J.L. Royo, E. Rubino, D. Rujescu, M.E. Sáez, P. Sakka, I. Saltvedt, Á. Sanabria, M.B. Sánchez-Arjona, F. Sanchez-Garcia, P.S. Juan, R. Sánchez-Valle, S.B. Sando, C. Sarnowski, C.L. Satizabal, M. Scamosci, N. Scarmeas, E. Scarpini, P. Scheltens, N. Scherbaum, M. Scherer, M. Schmid, A. Schneider, J.M. Schott, G. Selbæk, D. Seripa, M. Serrano, J. Sha, A.A. Shadrin, O. Skrobot, S. Slifer, G.J.L. Snijders, H. Soininen, V. Solfrizzi, A. Solomon, Y. Song, S. Sorbi, O. Sotolongo-Grau, G. Spalletta, A. Spottke, A. Squassina, E. Stordal, J.P. Tartan, L. Tárraga, N. Tesí, A. Thalamuthu, T. Thomas, G. Tosto, L. Traykov, L. Tremolizzo, A. Tybjærg-Hansen, A. Uitterlinden, A. Ullgren, I. Ulstein, S. Valero, O. Valladares, C.V. Broeckhoven, J. Vance, B.N. Vardarajan, A. van der Lugt, J.V. Dongen, J. van Rooij, J. van Swieten, R. Vandenberghe, F. Verhey, J.S. Vidal, J. Vogelgsang, M. Vyhnalek, M. Wagner, D. Wallon, L.S. Wang, R. Wang, L. Weinhold, J. Wiltfang, G. Windle, B. Woods, M. Yannakoulia, H. Zare, Y. Zhao, X. Zhang, C. Zhu, M. Zulaica, L.A. Farrer, B.M. Psaty, M. Ghanbari, T. Raj, P. Sachdev, K. Mather, F. Jessen, M.A. Ikram, A. de Mendonça, J. Hort, M. Tsolaki, M.A. Pericak-Vance, P. Amouyel, J. Williams, R. Frikke-Schmidt, J. Clarimon, J.F. Deleuze, G. Rossi, S. Seshadri, O.A. Andreassen, M. Ingelsson, M. Hiltunen, K. Sleegers, G.D. Schellenberg, C.M. van Duijn, R. Sims, W.M. van der Flier, A. Ruiz, A. Ramirez, J.C. Lambert, New insights into the genetic etiology of Alzheimer's disease and related dementias, *Nat Genet*, 54 (2022) 412-436.
53. R.J. Boyd, D. Avramopoulos, L.L. Jantzie, A.S. McCallion, Neuroinflammation represents a common theme amongst genetic and environmental risk factors for Alzheimer and Parkinson diseases, *J Neuroinflammation*, 19 (2022) 223.
  54. H. Long, A. Simmons, A. Mayorga, B. Burgess, T. Nguyen, B. Budda, A. Rychkova, H. Rhinn, I. Tassi, M. Ward, F. Yeh, T. Schwabe, R. Paul, S. Kenkare-Mitra, A. Rosenthal, Preclinical and first-in-human evaluation of AL002, a novel TREM2 agonistic antibody for Alzheimer's disease, *Alzheimers Res Ther*, 16 (2024) 235.
  55. X. Yang, Z. Zhangyi, A. Yu, Q. Zhou, A. Xia, J. Qiu, M. Cai, X. Chu, L. Li, Z. Feng, Z. Luo, G. Sun, J. Zhang, M. Geng, S. Chen, Z. Xie, GV-971 attenuates the progression of neuromyelitis optica in murine models and reverses alterations in gut microbiota and associated peripheral abnormalities, *CNS Neurosci Ther*, 30 (2024) e14847.
  56. S.E. Arnold, Z. Arvanitakis, S.L. Macauley-Rambach, A.M. Koenig, H.-Y. Wang, R.S. Ahima, S. Craft, S. Gandy, C. Buettner, L.E. Stoeckel, D.M. Holtzman, D.M. Nathan, Brain insulin resistance in type 2 diabetes and Alzheimer disease: Concepts and conundrums, *Nature reviews. Neurology*, 14 (2018) 168-181.

57. M. Kciuk, W. Kruczkowska, J. Gałęzewska, K. Wanke, Ż. Kałuzińska-Kołat, M. Aleksandrowicz, R. Kontek, Alzheimer's Disease as Type 3 Diabetes: Understanding the Link and Implications, *Int J Mol Sci*, 25 (2024).
58. R. Kandimalla, V. Thirumala, P.H. Reddy, Is Alzheimer's disease a Type 3 Diabetes? A critical appraisal, *Biochim Biophys Acta Mol Basis Dis*, 1863 (2017) 1078-1089.
59. E. Blázquez, V. Hurtado-Carneiro, Y. LeBaut-Ayuso, E. Velázquez, L. García-García, F. Gómez-Oliver, J.M. Ruiz-Albusac, J. Ávila, M. Pozo, Significance of Brain Glucose Hypometabolism, Altered Insulin Signal Transduction, and Insulin Resistance in Several Neurological Diseases, *Front Endocrinol (Lausanne)*, 13 (2022) 873301.
60. D.S. Knopman, C.R. Jack, Jr., H.J. Wiste, E.S. Lundt, S.D. Weigand, P. Vemuri, V.J. Lowe, K. Kantarci, J.L. Gunter, M.L. Senjem, M.M. Mielke, R.O. Roberts, B.F. Boeve, R.C. Petersen, 18F-fluorodeoxyglucose positron emission tomography, aging, and apolipoprotein E genotype in cognitively normal persons, *Neurobiol Aging*, 35 (2014) 2096-2106.
61. A. Sędzikowska, L. Szablewski, Insulin and insulin resistance in alzheimer's disease, *International journal of molecular sciences*, 22 (2021) 9987.
62. S. Chatterjee, A. Mudher, Alzheimer's Disease and Type 2 Diabetes: A Critical Assessment of the Shared Pathological Traits, *Front Neurosci*, 12 (2018) 383.
63. C.Y.J. Wong, A. Baldelli, C.M. Hoyos, O. Tietz, H.X. Ong, D. Traini, Insulin Delivery to the Brain via the Nasal Route: Unraveling the Potential for Alzheimer's Disease Therapy, *Drug Deliv Transl Res*, 14 (2024) 1776-1793.
64. M. Sabbagh, C. Boschini, S. Cohen, M. Fugger, F. Jessen, S. Dandanell, S.D. Pedersen, L.R.S. Tarazona, V.R. Aroda, Safety considerations of semaglutide in the potential treatment of Alzheimer's disease: A pooled analysis of semaglutide in adults aged  $\geq 65$  years, *Alzheimers Dement (N Y)*, 11 (2025) e70076.
65. R.W. Mahley, Central Nervous System Lipoproteins: ApoE and Regulation of Cholesterol Metabolism, *Arterioscler Thromb Vasc Biol*, 36 (2016) 1305-1315.
66. E. Genin, D. Hannequin, D. Wallon, K. Sleegers, M. Hiltunen, O. Combarros, M.J. Bullido, S. Engelborghs, P. De Deyn, C. Berr, F. Pasquier, B. Dubois, G. Tognoni, N. Fiévet, N. Brouwers, K. Bettens, B. Arosio, E. Coto, M. Del Zompo, I. Mateo, J. Epelbaum, A. Frank-Garcia, S. Helisalmi, E. Porcellini, A. Pilotto, P. Forti, R. Ferri, E. Scarpini, G. Siciliano, V. Solfrizzi, S. Sorbi, G. Spalletta, F. Valdivieso, S. Vepsäläinen, V. Alvarez, P. Bosco, M. Mancuso, F. Panza, B. Nacmias, P. Boss, O. Hanon, P. Piccardi, G. Annoni, D. Seripa, D. Galimberti, F. Licastro, H. Soininen, J.F. Dartigues, M.I. Kambouh, C. Van Broeckhoven, J.C. Lambert, P. Amouyel, D. Campion, APOE and Alzheimer disease: A major gene with semi-dominant inheritance, *Molecular psychiatry*, 16 (2011) 903-907.
67. Y.A. Martens, N. Zhao, C.-C. Liu, T. Kanekiyo, A.J. Yang, A.M. Goate, D.M. Holtzman, G. Bu, ApoE Cascade Hypothesis in the pathogenesis of Alzheimer's disease and related dementias, *Neuron (Cambridge, Mass.)*, 110 (2022) 1304-1317.
68. Z. Li, F. Shue, N. Zhao, M. Shinohara, G. Bu, APOE2: protective mechanism and therapeutic implications for Alzheimer's disease, *Mol Neurodegener*, 15 (2020) 63.
69. Y.Y. Sun, Z. Wang, H.C. Huang, Roles of ApoE4 on the Pathogenesis in Alzheimer's Disease and the Potential Therapeutic Approaches, *Cell Mol Neurobiol*, 43 (2023) 3115-3136.
70. H.C. Hunsberger, P.D. Pinky, W. Smith, V. Suppiramaniam, M.N. Reed, The role of APOE4 in Alzheimer's disease: strategies for future therapeutic interventions, *Neuronal Signal*, 3 (2019) Ns20180203.
71. D. Dias, C.C. Portugal, J. Relvas, R. Socodato, From Genetics to Neuroinflammation: The Impact of ApoE4 on Microglial Function in Alzheimer's Disease, *Cells*, 14 (2025).
72. E. Schmukler, S. Solomon, S. Simonovitch, Y. Goldshmit, E. Wolfson, D.M. Michaelson, R. Pinkas-Kramarski, Altered mitochondrial dynamics and function in APOE4-expressing astrocytes, *Cell Death Dis*, 11 (2020) 578.
73. Y. Liang, S. Lin, T.P. Beyer, Y. Zhang, X. Wu, K.R. Bales, R.B. DeMattos, P.C. May, S.D. Li, X.C. Jiang, P.I. Eacho, G. Cao, S.M. Paul, A liver X receptor and retinoid X receptor heterodimer mediates apolipoprotein E expression, secretion and cholesterol homeostasis in astrocytes, *J Neurochem*, 88 (2004) 623-634.

74. B. Teter, J. Campagna, C. Zhu, G.E. McCauley, P. Spilman, D.B. Kohn, V. John, Successful Gene Editing of Apolipoprotein E4 to E3 in Brain of Alzheimer Model Mice After a Single IV Dose of Synthetic Exosome-Delivered CRISPR, *bioRxiv*, (2024) 2024.2004.2023.590784.
75. A. Litvinchuk, T.V. Huynh, Y. Shi, R.J. Jackson, M.B. Finn, M. Manis, C.M. Francis, A.C. Tran, P.M. Sullivan, J.D. Ulrich, B.T. Hyman, T. Cole, D.M. Holtzman, Apolipoprotein E4 Reduction with Antisense Oligonucleotides Decreases Neurodegeneration in a Tauopathy Model, *Ann Neurol*, 89 (2021) 952-966.
76. C.M. Ferguson, S. Hildebrand, B. Godinho, J. Buchwald, D. Echeverria, A. Coles, A. Grigorenko, L. Vangjeli, J. Sousa, N. McHugh, M. Hassler, F. Santarelli, M.T. Heneka, E. Rogaev, A. Khvorova, Silencing Apoe with divalent-siRNAs improves amyloid burden and activates immune response pathways in Alzheimer's disease, *Alzheimers Dement*, 20 (2024) 2632-2652.
77. T. Williams, D.R. Borchelt, P. Chakrabarty, Therapeutic approaches targeting Apolipoprotein E function in Alzheimer's disease, *Molecular Neurodegeneration*, 15 (2020) 8.
78. A.E. Alkhalifa, N.F. Al-Ghraiyyah, J. Odum, J.G. Shunnarah, N. Austin, A. Kaddoumi, Blood-Brain Barrier Breakdown in Alzheimer's Disease: Mechanisms and Targeted Strategies, *Int J Mol Sci*, 24 (2023).
79. E.G. Knox, M.R. Aburto, G. Clarke, J.F. Cryan, C.M. O'Driscoll, The blood-brain barrier in aging and neurodegeneration, *Mol Psychiatry*, 27 (2022) 2659-2673.
80. A. Montagne, S.R. Barnes, M.D. Sweeney, M.R. Halliday, A.P. Sagare, Z. Zhao, A.W. Toga, R.E. Jacobs, C.Y. Liu, L. Amezcua, M.G. Harrington, H.C. Chui, M. Law, B.V. Zlokovic, Blood-brain barrier breakdown in the aging human hippocampus, *Neuron*, 85 (2015) 296-302.
81. D. Wang, F. Chen, Z. Han, Z. Yin, X. Ge, P. Lei, Relationship Between Amyloid- $\beta$  Deposition and Blood-Brain Barrier Dysfunction in Alzheimer's Disease, *Front Cell Neurosci*, 15 (2021) 695479.
82. J. Derk, M. MacLean, J. Juraneck, A.M. Schmidt, The Receptor for Advanced Glycation Endproducts (RAGE) and Mediation of Inflammatory Neurodegeneration, *J Alzheimers Dis Parkinsonism*, 8 (2018).
83. M.S. CHOI, APOE4 lead to neurovascular dysfunction & inflammation is an early change in Alzheimer's disease?, *Alzheimer's & Dementia*, 20 (2024) e095248.
84. J. Li, M. Zheng, O. Shimoni, W.A. Banks, A.I. Bush, J.R. Gamble, B. Shi, Development of Novel Therapeutics Targeting the Blood-Brain Barrier: From Barrier to Carrier, *Adv Sci (Weinh)*, 8 (2021) e2101090.
85. W. Wang, F. Zhao, X. Ma, G. Perry, X. Zhu, Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances, *Mol Neurodegener*, 15 (2020) 30.
86. A. Misrani, S. Tabassum, L. Yang, Mitochondrial Dysfunction and Oxidative Stress in Alzheimer's Disease, *Front Aging Neurosci*, 13 (2021) 617588.
87. Y. Zong, H. Li, P. Liao, L. Chen, Y. Pan, Y. Zheng, C. Zhang, D. Liu, M. Zheng, J. Gao, Mitochondrial dysfunction: mechanisms and advances in therapy, *Signal Transduction and Targeted Therapy*, 9 (2024) 124.
88. K. Li, T. Rashid, J. Li, N. Honnorat, A.B. Nirmala, E. Fadaee, D. Wang, S. Charisis, H. Liu, C. Franklin, M. Maybrier, H. Katragadda, L. Abazid, V. Ganapathy, V.L. Valaparla, P. Badugu, E. Vasquez, L. Solano, G. Clarke, G. Maestre, T. Richardson, J. Walker, P.T. Fox, K. Bieniek, S. Seshadri, M. Habes, Postmortem Brain Imaging in Alzheimer's Disease and Related Dementias: The South Texas Alzheimer's Disease Research Center Repository, *J Alzheimers Dis*, 96 (2023) 1267-1283.
89. L. Pagani, A. Eckert, Amyloid-Beta interaction with mitochondria, *Int J Alzheimers Dis*, 2011 (2011) 925050.
90. A. Eckert, R. Nisbet, A. Grimm, J. Götz, March separate, strike together--role of phosphorylated TAU in mitochondrial dysfunction in Alzheimer's disease, *Biochim Biophys Acta*, 1842 (2014) 1258-1266.
91. M. Pires, A.C. Rego, Apoe4 and Alzheimer's Disease Pathogenesis-Mitochondrial Deregulation and Targeted Therapeutic Strategies, *Int J Mol Sci*, 24 (2023).
92. J. Shi, Y. Yu, H. Yuan, Y. Li, Y. Xue, Mitochondrial dysfunction in AMI: mechanisms and therapeutic perspectives, *J Transl Med*, 23 (2025) 418.
93. M.A. Pappolla, R.N. Martins, B. Poeggeler, R.A. Omar, G. Perry, Oxidative Stress in Alzheimer's Disease: The Shortcomings of Antioxidant Therapies, *J Alzheimers Dis*, 101 (2024) S155-S178.
94. C.A. Valdez-Gaxiola, F. Rosales-Leycegui, A. Gaxiola-Rubio, J.M. Moreno-Ortiz, L.E. Figueroa, Early- and Late-Onset Alzheimer's Disease: Two Sides of the Same Coin?, *Diseases*, 12 (2024).

95. J. Hoogmartens, R. Cacace, C. Van Broeckhoven, Insight into the genetic etiology of Alzheimer's disease: A comprehensive review of the role of rare variants, *Alzheimers Dement (Amst)*, 13 (2021) e12155.
96. S.J. Virolainen, A. VonHandorf, K.C.M.F. Viel, M.T. Weirauch, L.C. Kottyan, Gene–environment interactions and their impact on human health, *Genes & Immunity*, 24 (2023) 1-11.
97. J.M. Ringman, G. Coppola, New genes and new insights from old genes: update on Alzheimer disease, *Continuum (Minneap Minn)*, 19 (2013) 358-371.
98. H. Hampel, J. Hardy, K. Blennow, C. Chen, G. Perry, S.H. Kim, V.L. Villemagne, P. Aisen, M. Vendruscolo, T. Iwatsubo, C.L. Masters, M. Cho, L. Lannfelt, J.L. Cummings, A. Vergallo, The Amyloid- $\beta$  Pathway in Alzheimer's Disease, *Mol Psychiatry*, 26 (2021) 5481-5503.
99. R. MacLeod, E.K. Hillert, R.T. Cameron, G.S. Baillie, The role and therapeutic targeting of  $\alpha$ -,  $\beta$ - and  $\gamma$ -secretase in Alzheimer's disease, *Future Sci OA*, 1 (2015) Fso11.
100. C.R. Muratore, H.C. Rice, P. Srikanth, D.G. Callahan, T. Shin, L.N. Benjamin, D.M. Walsh, D.J. Selkoe, T.L. Young-Pearse, The familial Alzheimer's disease APPV717I mutation alters APP processing and Tau expression in iPSC-derived neurons, *Hum Mol Genet*, 23 (2014) 3523-3536.
101. B. De Strooper, T. Iwatsubo, M.S. Wolfe, Presenilins and  $\gamma$ -secretase: structure, function, and role in Alzheimer Disease, *Cold Spring Harb Perspect Med*, 2 (2012) a006304.
102. M.H. Dai, H. Zheng, L.D. Zeng, Y. Zhang, The genes associated with early-onset Alzheimer's disease, *Oncotarget*, 9 (2018) 15132-15143.
103. J. Bagaria, E. Bagyinszky, S.S.A. An, Genetics, Functions, and Clinical Impact of Presenilin-1 (PSEN1) Gene, *Int J Mol Sci*, 23 (2022).
104. Y. Cai, S.S. An, S. Kim, Mutations in presenilin 2 and its implications in Alzheimer's disease and other dementia-associated disorders, *Clin Interv Aging*, 10 (2015) 1163-1172.
105. R. Fernandez-Calle, S.C. Konings, J. Frontinan-Rubio, J. Garcia-Revilla, L. Camprubi-Ferrer, M. Svensson, I. Martinson, A. Boza-Serrano, J. Luis Venero, H.M. Nielsen, G.K. Gouras, T. Deierborg, APOE in the bullseye of neurodegenerative diseases: impact of the APOE genotype in Alzheimer's disease pathology and brain diseases, *Molecular neurodegeneration*, 17 (2022) 1-62.
106. R.J. Jackson, M.S. Keiser, J.C. Meltzer, D.P. Fykstra, S.E. Dierksmeier, S. Hajizadeh, J. Kreuzer, R. Morris, A. Melloni, T. Nakajima, L. Tecedor, P.T. Ranum, E. Carrell, Y. Chen, M.A. Nishtar, D.M. Holtzman, W. Haas, B.L. Davidson, B.T. Hyman, APOE2 gene therapy reduces amyloid deposition and improves markers of neuroinflammation and neurodegeneration in a mouse model of Alzheimer disease, *Mol Ther*, 32 (2024) 1373-1386.
107. J.B. Rosenberg, M.G. Kaplitt, B.P. De, A. Chen, T. Flagiello, C. Salami, E. Pey, L.Z. Zhao, R.J.R. Arbona, S. Monette, J.P. Dyke, D.J. Balion, S.M. Kaminsky, D. Sondhi, G.A. Petsko, S.M. Paul, R.G. Crystal, AAVrh.10-Mediated APOE2 Central Nervous System Gene Therapy for APOE4-Associated Alzheimer's Disease, *Human Gene Therapy Clinical Development*, 29 (2018) 24-47.
108. R. Li, X. Wang, P. He, The most prevalent rare coding variants of TREM2 conferring risk of Alzheimer's disease: A systematic review and meta-analysis, *Exp Ther Med*, 21 (2021) 347.
109. M. Lin, J.X. Yu, W.X. Zhang, F.X. Lao, H.C. Huang, Roles of TREM2 in the Pathological Mechanism and the Therapeutic Strategies of Alzheimer's Disease, *J Prev Alzheimers Dis*, 11 (2024) 1682-1695.
110. B.W. Kunkle, B. Grenier-Boley, R. Sims, J.C. Bis, V. Damotte, A.C. Naj, S. van der Lee, S. Ahmad, H. Adams, D. Vojinovic, H. Comic, G. Roshchupkin, F. Rivadeneira, A. Uitterlinden, N. Amin, A. Ikram, C. Duijn, J. Lambert, M.A. Pericak-Vance, Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates A beta, tau, immunity and lipid processing, *Nature genetics*, 51 (2019) 414+.
111. S.C. Fang, L. Wang, M.T. Cheng, D. Xu, Z.P. Chen, J. Wang, W. Liao, Y. Li, C.Z. Zhou, W.T. Hou, Y. Chen, Structural insights into human ABCA7-mediated lipid transport, *Structure*, 33 (2025) 583-593.e585.
112. E.M. Foster, A. Dangla-Valls, S. Lovestone, E.M. Ribe, N.J. Buckley, Clusterin in Alzheimer's Disease: Mechanisms, Genetics, and Lessons From Other Pathologies, *Front Neurosci*, 13 (2019) 164.
113. P. Dourlen, D. Kilinc, I. Landrieu, J. Chapuis, J.C. Lambert, BIN1 and Alzheimer's disease: the tau connection, *Trends Neurosci*, 48 (2025) 349-361.
114. W. Xu, L. Tan, J.T. Yu, The Role of PICALM in Alzheimer's Disease, *Mol Neurobiol*, 52 (2015) 399-413.



115. A. Griciuc, S. Patel, A.N. Federico, S.H. Choi, B.J. Innes, M.K. Oram, G. Cereghetti, D. McGinty, A. Anselmo, R.I. Sadreyev, S.E. Hickman, J. El Khoury, M. Colonna, R.E. Tanzi, TREM2 Acts Downstream of CD33 in Modulating Microglial Pathology in Alzheimer's Disease, *Neuron*, 103 (2019) 820-835.e827.
116. C. Hung, E. Tuck, V. Stubbs, S.J. van der Lee, C. Aalfs, R. van Spaendonk, P. Scheltens, J. Hardy, H. Holstege, F.J. Livesey, SORL1 deficiency in human excitatory neurons causes APP-dependent defects in the endolysosome-autophagy network, *Cell Rep*, 35 (2021) 109259.
117. K. Schlepckow, E. Morenas-Rodríguez, S. Hong, C. Haass, Stimulation of TREM2 with agonistic antibodies—an emerging therapeutic option for Alzheimer's disease, *Lancet Neurol*, 22 (2023) 1048-1060.
118. W. Wu, Y. Ji, Z. Wang, X. Wu, J. Li, F. Gu, Z. Chen, Z. Wang, The FDA-approved anti-amyloid- $\beta$  monoclonal antibodies for the treatment of Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials, *Eur J Med Res*, 28 (2023) 544.
119. R.J. Malonis, J.R. Lai, O. Vergnolle, Peptide-Based Vaccines: Current Progress and Future Challenges, *Chem Rev*, 120 (2020) 3210-3229.
120. R. Hernández, C. Jiménez-Luna, J. Perales-Adán, G. Perazzoli, C. Melguizo, J. Prados, Differentiation of Human Mesenchymal Stem Cells towards Neuronal Lineage: Clinical Trials in Nervous System Disorders, *Biomol Ther (Seoul)*, 28 (2020) 34-44.
121. A.P. Kells, D.M. Fong, M. Dragunow, M.J. During, D. Young, B. Connor, AAV-mediated gene delivery of BDNF or GDNF is neuroprotective in a model of Huntington disease, *Mol Ther*, 9 (2004) 682-688.
122. F. Ducancel, B.H. Muller, Molecular engineering of antibodies for therapeutic and diagnostic purposes, *MAbs*, 4 (2012) 445-457.
123. D. Alarcón-Arís, R. Pavia-Collado, L. Miquel-Rio, V. Coppola-Segovia, A. Ferrés-Coy, E. Ruiz-Bronchal, M. Galofré, V. Paz, L. Campa, R. Revilla, A. Montefeltro, J.H. Kordower, M. Vila, F. Artigas, A. Bortolozzi, Anti- $\alpha$ -synuclein ASO delivered to monoamine neurons prevents  $\alpha$ -synuclein accumulation in a Parkinson's disease-like mouse model and in monkeys, *EBioMedicine*, 59 (2020) 102944.
124. C. Sun, S. Sha, Y. Shan, X. Gao, L. Li, C. Xing, Z. Guo, H. Du, Intranasal Delivery of BACE1 siRNA and Berberine via Engineered Stem Cell Exosomes for the Treatment of Alzheimer's Disease, *Int J Nanomedicine*, 20 (2025) 5873-5891.
125. A.J. Hinrich, F.M. Jodelka, J.L. Chang, D. Brutman, A.M. Bruno, C.A. Briggs, B.D. James, G.E. Stutzmann, D.A. Bennett, S.A. Miller, F. Rigo, R.A. Marr, M.L. Hastings, Therapeutic correction of ApoER2 splicing in Alzheimer's disease mice using antisense oligonucleotides, *EMBO molecular medicine*, 8 (2016) 328-345.
126. A. Al Ayidh, M. Abbas, M. Parayangat, T. Ijyas, Advances in Nanomaterials for Targeted Drug Delivery: Emerging Trends and Future Prospects in Nanodrug Development, *Curr Cancer Drug Targets*, (2025).
127. B. Qi, Y. Yang, Y. Cheng, D. Sun, X. Wang, R. Khanna, W. Ju, Nasal delivery of a CRMP2-derived CBD3 adenovirus improves cognitive function and pathology in APP/PS1 transgenic mice, *Mol Brain*, 13 (2020) 58.
128. T.M. Ross, P.M. Martinez, J.C. Renner, R.G. Thorne, L.R. Hanson, W.H. Frey, 2nd, Intranasal administration of interferon beta bypasses the blood-brain barrier to target the central nervous system and cervical lymph nodes: a non-invasive treatment strategy for multiple sclerosis, *J Neuroimmunol*, 151 (2004) 66-77.
129. C. Ji, E.M. Sigurdsson, Current Status of Clinical Trials on Tau Immunotherapies, *Drugs*, 81 (2021) 1135-1152.
130. C. Song, J. Shi, P. Zhang, Y. Zhang, J. Xu, L. Zhao, R. Zhang, H. Wang, H. Chen, Immunotherapy for Alzheimer's disease: targeting  $\beta$ -amyloid and beyond, *Translational Neurodegeneration*, 11 (2022) 18.
131. M. Zhu, X. Tian, X. Han, Y. Ma, W. Fa, N. Wang, R. Liu, Y. Dong, Y. Ren, C. Liu, N. Tian, H. Zhang, L. Song, S. Tang, L. Cong, Y. Wang, T. Hou, C. Qiu, Y. Du, Synergistic associations of CD33 variants and hypertension with brain and cognitive aging among dementia-free older adults: A population-based study, *Alzheimers Dement*, 20 (2024) 7193-7204.
132. Q. Wang, S. Chen, J. Wang, H. Shang, X. Chen, Advancements in Pharmacological Treatment of Alzheimer's Disease: The Advent of Disease-Modifying Therapies (DMTs), *Brain Sci*, 14 (2024).
133. L.K. Huang, Y.C. Kuan, H.W. Lin, C.J. Hu, Clinical trials of new drugs for Alzheimer disease: a 2020-2023 update, *J Biomed Sci*, 30 (2023) 83.



134. T.B. Ameen, S.N. Kashif, S.M.I. Abbas, K. Babar, S.M.S. Ali, A. Raheem, Unraveling Alzheimer's: the promise of aducanumab, lecanemab, and donanemab, *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery*, 60 (2024) 72.
135. M. Jin, J.M. Noble, What's in It for Me? Contextualizing the Potential Clinical Impacts of Lecanemab, Donanemab, and Other Anti- $\beta$ -amyloid Monoclonal Antibodies in Early Alzheimer's Disease, *eNeuro*, 11 (2024).
136. M. Shi, F. Chu, F. Zhu, J. Zhu, Impact of Anti-amyloid- $\beta$  Monoclonal Antibodies on the Pathology and Clinical Profile of Alzheimer's Disease: A Focus on Aducanumab and Lecanemab, *Frontiers in aging neuroscience*, 14 (2022) 870517-870517.
137. L. Soderberg, M. Johannesson, P. Nygren, H. Laudon, F. Eriksson, G. Osswald, C. Moller, L. Lannfelt, Lecanemab, Aducanumab, and Gantenerumab - Binding Profiles to Different Forms of Amyloid-Beta Might Explain Efficacy and Side Effects in Clinical Trials for Alzheimer's Disease, *Neurotherapeutics*, (2022).
138. A. Easton, M.L. Jensen, C. Wang, P.H. Hagedorn, Y. Li, M. Weed, J.E. Meredith, V. Guss, K. Jones, M. Gill, C. Krause, J.M. Brown, L. Hunihan, J. Natale, A. Fernandes, Y. Lu, J. Polino, M. Bookbinder, G. Cadelina, Y. Benitex, R. Sane, J. Morrison, D. Drexler, S.E. Mercer, C. Bon, N.J. Pandya, R. Jagasia, T.H. Ou Yang, T. Distler, F. Grüniger, M. Meldgaard, M. Terrigno, J.E. Macor, C.F. Albright, J. Loy, A.M. Hoeg, R.E. Olson, A.M. Cacace, Identification and characterization of a MAPT-targeting locked nucleic acid antisense oligonucleotide therapeutic for tauopathies, *Mol Ther Nucleic Acids*, 29 (2022) 625-642.
139. X. Yang, W. Yang, X. Xia, T. Lei, Z. Yang, W. Jia, Y. Zhou, G. Cheng, H. Gao, Intranasal Delivery of BACE1 siRNA and Rapamycin by Dual Targets Modified Nanoparticles for Alzheimer's Disease Therapy, *Small*, 18 (2022) e2203182.
140. C.Y. Wang, P.N. Wang, M.J. Chiu, C.L. Finstad, F. Lin, S. Lynn, Y.H. Tai, X. De Fang, K. Zhao, C.H. Hung, Y. Tseng, W.J. Peng, J. Wang, C.C. Yu, B.S. Kuo, P.A. Frohna, UB-311, a novel UBith® amyloid  $\beta$  peptide vaccine for mild Alzheimer's disease, *Alzheimers Dement (N Y)*, 3 (2017) 262-272.
141. A. Mullard, Parsing clinical success rates, *Nature Reviews Drug Discovery*, 15 (2016) 447-447.
142. J. Zhao, R. Nussinov, B. Ma, Mechanisms of recognition of amyloid- $\beta$  ( $A\beta$ ) monomer, oligomer, and fibril by homologous antibodies, *J Biol Chem*, 292 (2017) 18325-18343.
143. L.A. Miles, G.A. Crespi, L. Doughty, M.W. Parker, Bapineuzumab captures the N-terminus of the Alzheimer's disease amyloid-beta peptide in a helical conformation, *Sci Rep*, 3 (2013) 1302.
144. R.J. Bateman, J. Cummings, S. Schobel, S. Salloway, B. Vellas, M. Boada, S.E. Black, K. Blennow, P. Fontoura, G. Klein, S.S. Assunção, J. Smith, R.S. Doody, Gantenerumab: an anti-amyloid monoclonal antibody with potential disease-modifying effects in early Alzheimer's disease, *Alzheimers Res Ther*, 14 (2022) 178.
145. P.F. Høilund-Carlsen, M.E. Revheim, T. Costa, K.P. Kepp, R.J. Castellani, G. Perry, A. Alavi, J.R. Barrio, FDG-PET versus Amyloid-PET Imaging for Diagnosis and Response Evaluation in Alzheimer's Disease: Benefits and Pitfalls, *Diagnostics (Basel)*, 13 (2023).
146. S. Teipel, Y. Tang, A. Khachaturian, Clinical efficacy of anti-amyloid antibodies in apolipoprotein E  $\epsilon$ 4 homozygotes: A Bayesian reanalysis of lecanemab and donanemab phase 3 results, *Alzheimers Dement (N Y)*, 11 (2025) e70083.
147. T. Daly, K.P. Kepp, B.P. Imbimbo, Are lecanemab and donanemab disease-modifying therapies?, *Alzheimers Dement*, 20 (2024) 6659-6661.
148. M.R. Brier, B. Gordon, K. Friedrichsen, J. McCarthy, A. Stern, J. Christensen, C. Owen, P. Aldea, Y. Su, J. Hassenstab, N.J. Cairns, D.M. Holtzman, A.M. Fagan, J.C. Morris, T.L. Benzinger, B.M. Ances, Tau and  $A\beta$  imaging, CSF measures, and cognition in Alzheimer's disease, *Sci Transl Med*, 8 (2016) 338ra366.
149. E.E. Congdon, C. Ji, A.M. Tetlow, Y. Jiang, E.M. Sigurdsson, Tau-targeting therapies for Alzheimer disease: current status and future directions, *Nat Rev Neurol*, 19 (2023) 715-736.
150. C. Monteiro, B. Toth, F. Brunstein, A. Bobbala, S. Datta, R. Cenicerros, S.M. Sanabria Bohorquez, V.G. Anania, K.R. Wildsmith, S.P. Schauer, J. Lee, M.J. Dolton, V. Ramakrishnan, D. Abramzon, E. Teng, Randomized Phase II Study of the Safety and Efficacy of Semorinemab in Participants With Mild-to-Moderate Alzheimer Disease: Lauriet, *Neurology*, 101 (2023) e1391-e1401.
151. B.P. Imbimbo, C. Balducci, S. Ippati, M. Watling, Initial failures of anti-tau antibodies in Alzheimer's disease are reminiscent of the amyloid- $\beta$  story, *Neural Regen Res*, 18 (2023) 117-118.

152. M. Shulman, J. Kong, J. O'Gorman, E. Ratti, R. Rajagovindan, L. Viollet, E. Huang, S. Sharma, A.M. Racine, J. Czerkowicz, D. Graham, Y. Li, H. Hering, S.B. Haeberlein, TANGO: a placebo-controlled randomized phase 2 study of efficacy and safety of the anti-tau monoclonal antibody gosuranemab in early Alzheimer's disease, *Nat Aging*, 3 (2023) 1591-1601.
153. C.A. Lemere, E. Masliah, Can Alzheimer disease be prevented by amyloid-beta immunotherapy?, *Nat Rev Neurol*, 6 (2010) 108-119.
154. H.J. Yu, S.P. Dickson, P.N. Wang, M.J. Chiu, C.C. Huang, C.C. Chang, H. Liu, S.B. Hendrix, J.C. Dodart, A. Verma, C.Y. Wang, J. Cummings, Safety, tolerability, immunogenicity, and efficacy of UB-311 in participants with mild Alzheimer's disease: a randomised, double-blind, placebo-controlled, phase 2a study, *EBioMedicine*, 94 (2023) 104665.
155. K. Shahpasand, A. Sepehri Shamloo, S.M. Nabavi, K. Ping Lu, X. Zhen Zhou, "Tau immunotherapy: Hopes and hindrances", *Hum Vaccin Immunother*, 14 (2018) 277-284.
156. L.A. Sandusky-Beltran, E.M. Sigurdsson, Tau immunotherapies: Lessons learned, current status and future considerations, *Neuropharmacology*, 175 (2020) 108104.
157. B. Kovacech, N.C. Cullen, P. Novak, J. Hanes, E. Kontsekova, S. Katina, V. Parrak, M. Fresser, J. Vanbrabant, H.H. Feldman, B. Winblad, E. Stoops, E. Vanmechelen, N. Zilka, Post hoc analysis of ADAMANT, a phase 2 clinical trial of active tau immunotherapy with AADvac1 in patients with Alzheimer's disease, positive for plasma p-tau217, *Alzheimers Res Ther*, 16 (2024) 254.
158. W. Islam, T. Niidome, T. Sawa, Enhanced Permeability and Retention Effect as a Ubiquitous and Epoch-Making Phenomenon for the Selective Drug Targeting of Solid Tumors, *J Pers Med*, 12 (2022).
159. C.J. Mummery, A. Börjesson-Hanson, D.J. Blackburn, E.G.B. Vijverberg, P.P. De Deyn, S. Ducharme, M. Jonsson, A. Schneider, J.O. Rinne, A.C. Ludolph, R. Bodenschatz, H. Kordasiewicz, E.E. Swayze, B. Fitzsimmons, L. Mignon, K.M. Moore, C. Yun, T. Baumann, D. Li, D.A. Norris, R. Crean, D.L. Graham, E. Huang, E. Ratti, C.F. Bennett, C. Junge, R.M. Lane, Tau-targeting antisense oligonucleotide MAPT(Rx) in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial, *Nat Med*, 29 (2023) 1437-1447.
160. A.L. Edwards, J.A. Collins, C. Junge, H. Kordasiewicz, L. Mignon, S. Wu, Y. Li, L. Lin, J. DuBois, R.M. Hutchison, N. Ziogas, M. Shulman, L. Martarello, D. Graham, R. Lane, S. Budd Haeberlein, J. Beaver, Exploratory Tau Biomarker Results From a Multiple Ascending-Dose Study of BIIB080 in Alzheimer Disease: A Randomized Clinical Trial, *JAMA Neurol*, 80 (2023) 1344-1352.
161. R. McCartan, O. Khorkova, C.H. Volmar, C. Wahlestedt, Nucleic acid-based therapeutics for the treatment of central nervous system disorders, *Front Genet*, 14 (2023) 1250276.
162. D.F. Emerich, C.G. Thanos, NT-501: an ophthalmic implant of polymer-encapsulated ciliary neurotrophic factor-producing cells, *Curr Opin Mol Ther*, 10 (2008) 506-515.
163. P.S. Aisen, J. Cummings, R. Doody, L. Kramer, S. Salloway, D.J. Selkoe, J. Sims, R.A. Sperling, B. Vellas, The Future of Anti-Amyloid Trials, *J Prev Alzheimers Dis*, 7 (2020) 146-151.
164. K. Yoshida, A. Moein, T. Bittner, S. Ostrowitzki, H. Lin, L. Honigberg, J.Y. Jin, A. Quartino, Pharmacokinetics and pharmacodynamic effect of crenezumab on plasma and cerebrospinal fluid beta-amyloid in patients with mild-to-moderate Alzheimer's disease, *Alzheimers Res Ther*, 12 (2020) 16.
165. J. Cummings, The Role of Biomarkers in Alzheimer's Disease Drug Development, *Adv Exp Med Biol*, 1118 (2019) 29-61.
166. O. Hansson, R.M. Edelmayer, A.L. Boxer, M.C. Carrillo, M.M. Mielke, G.D. Rabinovici, S. Salloway, R. Sperling, H. Zetterberg, C.E. Teunissen, The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease, *Alzheimer's & Dementia*, 18 (2022) 2669-2686.
167. Y. Reiss, S. Bauer, B. David, K. Devraj, E. Fidan, E. Hattingen, S. Liebner, N. Melzer, S.G. Meuth, F. Rosenow, T. Rüber, L.M. Willems, K.H. Plate, The neurovasculature as a target in temporal lobe epilepsy, *Brain Pathology*, 33 (2023) e13147.
168. J.L. Cummings, A. Atri, H.H. Feldman, O. Hansson, M. Sano, F.K. Knop, P. Johannsen, T. León, P. Scheltens, evoke and evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease, *Alzheimers Res Ther*, 17 (2025) 14.

169. D. Wu, Q. Chen, X. Chen, F. Han, Z. Chen, Y. Wang, The blood–brain barrier: Structure, regulation and drug delivery, *Signal Transduction and Targeted Therapy*, 8 (2023) 217.
170. K.T. Chen, K.C. Wei, H.L. Liu, Focused Ultrasound Combined with Microbubbles in Central Nervous System Applications, *Pharmaceutics*, 13 (2021).
171. J.R. Sims, J.A. Zimmer, C.D. Evans, M. Lu, P. Ardayfio, J. Sparks, A.M. Wessels, S. Shcherbinin, H. Wang, E.S. Monkul Nery, E.C. Collins, P. Solomon, S. Salloway, L.G. Apostolova, O. Hansson, C. Ritchie, D.A. Brooks, M. Mintun, D.M. Skovronsky, T.-A. Investigators, Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial, *JAMA*, 330 (2023) 512-527.
172. R. Tarawneh, V.S. Pankratz, The search for clarity regarding "clinically meaningful outcomes" in Alzheimer disease clinical trials: CLARITY-AD and Beyond, *Alzheimers Res Ther*, 16 (2024) 37.
173. J.L. Molinuevo, J. Cami, X. Carné, M.C. Carrillo, J. Georges, M.B. Isaac, Z. Khachaturian, S.Y. Kim, J.C. Morris, F. Pasquier, C. Ritchie, R. Sperling, J. Karlawish, Ethical challenges in preclinical Alzheimer's disease observational studies and trials: Results of the Barcelona summit, *Alzheimers Dement*, 12 (2016) 614-622.

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