Recent advances in immunotherapy targeting amyloid-beta and tauopathies in Alzheimer's disease

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From the Contents

Abstract

Alzheimer's disease, a devastating neurodegenerative disorder, is characterized by progressive cognitive decline, primarily due to amyloid-beta protein deposition and tau protein phosphorylation. Effectively reducing the cytotoxicity of amyloid-beta42 aggregates and tau oligomers may help slow the progression of Alzheimer's disease. Conventional drugs, such as donepezil, can only alleviate symptoms and are not able to prevent the underlying pathological processes or cognitive decline. Currently, active and passive immunotherapies targeting amyloid-beta and tau have shown some efficacy in mice with asymptomatic Alzheimer's disease and other transgenic animal models, attracting considerable attention. However, the clinical application of these immunotherapies demonstrated only limited efficacy before the discovery of lecanemab and donanemab. This review first discusses the advancements in the pathogenesis of Alzheimer's disease and active and passive immunotherapies targeting amyloid-beta and tau proteins. Furthermore, it reviews the advantages and disadvantages of various immunotherapies and considers their future prospects. Although some antibodies have shown promise in patients with mild Alzheimer's disease, substantial clinical data are still lacking to validate their effectiveness in individuals with moderate Alzheimer's disease.

Key Words: Alzheimer's disease; amyloid deposits; amyloid-beta; antibody; cognitive dysfunction; dementia; immunotherapy; oligomer; preventive immunization; tau hyperphosphorylation

Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive memory dysfunction, cognitive deficiency, changes in temperament and behavior, and even alterations in the ability to live daily (Srivastava et al., 2021). AD is divided into two types based on the cause: familial and sporadic. Genetic mutations cause familial AD, a rare early-onset disease characterized by defective genes coding amyloid precursor protein (APP), presenilin 1, and presenilin 2. Futhermore, sporadic AD accounts for > 90% of AD cases. Sporadic AD typically manifests later in life, typically after the age of 65 years, and is not inherited. In contrast, patients with familial AD develop symptoms before the age of 65 years.

AD has a complex pathogenesis (**Figure 1** and **Table 1**). The US Food and Drug Administration approved memantine in 2003 for the treatment of moderate-to-severe AD. GV-971, a widely used clinical drug, primarily targets the brain-gut axis by regulating the gut flora to suppress neuroinflammation. However, these drugs only alleviate symptoms and do not prevent pathological changes or cognitive deterioration (Yang et al., 2024).

To combat AD effectively, finding early biomarkers and new therapeutic targets is essential for the early identification and appropriate treatment of the disease (Gandy and Heppner, 2013; Long and Holtzman, 2019). Therefore, immunotherapy has attracted increasing attention. Active immunization enhances the patient's immune system to produce antibodies that combat disease-associated pathogens or molecules. Conversely, passive immune vaccination, which involves exogenous administration of antibodies targeting disease-associated antigens, can help mitigate the disease's progression (Parrocha and Nowick, 2023). Currently, the main goal of vaccines and immunotherapies targeting AD is to reduce the aggregation of disease-related peptides and proteins during the disease's development and progression (Gerson and Kayed, 2016). Amyloid-beta (Aβ) and tau proteins play a crucial role in the pathogenesis of AD (Abyadeh et al., 2024; Ye et al., 2024). Aβ aggregates in the brain to form fibers and plaques, while tau hyperphosphorylation leads to the formation of neurofibrillary tangles. In recent years, many clinical trials on antibodies, including lecanemab and donanemab, have yielded promising results, raising expectations that these therapies could revolutionize the traditional treatment of AD (**Figure 2**).

This review lists currently approved and ongoing clinical trials of Aβ and tau active and passive immunotherapy for AD. We discuss the pathogenesis of AD with respective therapeutic effects from different therapies and discuss their potential economic benefits and prospects for immunotherapy.

Search Strategy

We searched the literature on immunotherapy strategies for AD using the PubMed database for the past 20 years using the keywords Alzheimer's disease, immunotherapy, Aβ, tau, and improvement of cognitive impairment. Most of the literature selected was from 2014 to the present.

Pathophysiology of Alzheimer's Disease

Typically, AD manifests as extracellular Aβ deposits and intracellular neurofibrillary tangles, which are formed by excessive tau phosphorylation, leading to abnormal synaptic function and neuronal damage (Guo et al., 2020; Agustini et al., 2025; Long et al., 2025). The amyloid cascade hypothesis, proposed by Hardy and Higgins (1992), has been the main hypothesis about the pathogenesis of AD in recent years (Zhang et al., 2021). It suggests that APP is produced through protein cleavage, resulting in the aggregation of insoluble Aβ fragments, which act as an initiating factor in AD pathology. The imbalance between Aβ production and further clearance causes disease progression, including tau phosphorylation and neurofibrillary

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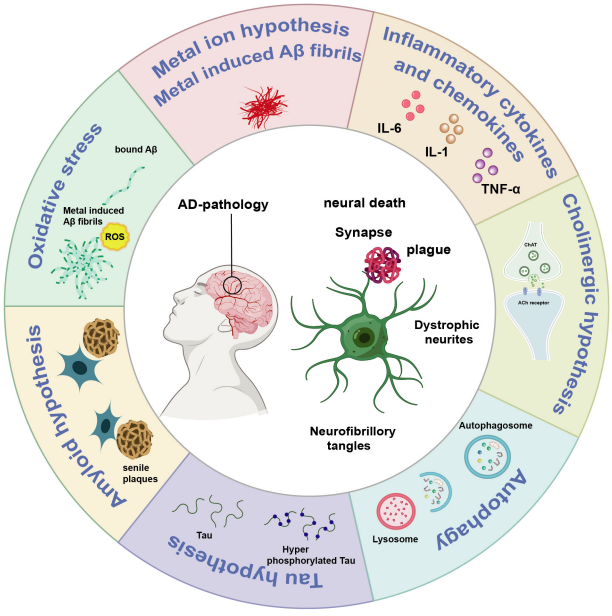

Figure 1 | The relative mechanism of AD.
The pathogenesis of AD includes amyloid hypothesis, tau hypothesis, oxidative stress, metal ion hypothesis, inflammatory cytokines and chemokines, cholinergic hypothesis, and autophagy. All of these may contribute to amyloid plaque, synapse dysfunction and neural death. AD: Alzheimer's disease; Aβ: amyloid-beta; IL-6: interleukin-6; ROS: reactive oxygen species; TNF-α: tumor necrosis factor.

Table 1 | Comparison of different therapeutic strategies of clinical stages and outcome

Target	Naturopathy	Mechanism of action	Trial phase	Effect and development
Aβ	Active immunotherapy	Vaccine, to elicit antibody response against Aβ	Reached phase II/III trial	Amilomotide induced adverse reaction of aseptic meningoencephalitis
	Passive immunotherapy	Combine with amyloid plaques and accelerate Aβ clearance	Many mAbs reached completed phase III trials	Aducanumab, Lecanemab and donanemab cleared amyloid plaques and slowed cognitive decline, accompanied with ARIA
	β-Secretase and γ-secretase inhibitors	Inhibit Aβ production	Completed phase III trial	No effects on cognitive decline and amyloid deposit clearance
Tau	Active immunotherapy	Vaccine, to elicit antibody response against tau	Phase II trial completed	Clinical benefits need to be further confirmed
	Passive immunotherapy	Block tau aggregation, seeding and spreading	The first generation completed phase II. The second generation is in Phase I/II trials	The first generation of mAbs targeting N-terminal region of tau failed. Clinical benefits of the second generation mAbs targeting tau mid-region or phosphorylated tau need to be further confirmed
Microglia modulator	Phagocytic microglia alleviate neuroinflammation	Modulate the action of microglia	APP/PS1 mice (preclinical)	Rescue of cognitive impairment and behavioral disfunction
		STAT3 inhibitor	5×FAD mice (preclinical)	Prevent learning and memory impairment
	Alleviate neurotoxicity	Cakcineurin/NFAT inhibitor	Phase II trial on MCI to AD	Not yet recruitig
Astrocyte modulator	Inhibit neurotoxicity	P38 MAPK inhibitor	hTau mice (preclinical)	Improve the spatial learning
	MRS2179	P2Y1R inhibitor	APP/PS1 mice (preclinical)	Disturb insulin metabolism
Insulin resistance	Intranasal insulin therapy	Give additional insulin	Phase II trial on MCI to moderate AD	Modulation by APOE4 genotype
	Relieve senile plaque	Metformin	Phase II trial on MCI to early	Reduction in recall ability
Anti-inflammation	Sodium oligomannate	Target brain-gut axis	Phase III clinical trials	Alleviate CNS inflammation
Improve microvascular status	Modulate neuroinflammation	Tyrosine kinase inhibitor	Phase II clinical trials	Reduce Aβ deposit and brain volume
AChE inhibitor	Inhibit cholinesterase	Cholinesterase inhibitors	Completed phase III trials	Delay the progression of AD
NMDA receptor antagonist	NMDA receptor antagonist	Regulate glutamate activity	Completed phase III trials	Improve cognitive decline

AChE: Acetylcholinesterase; AD: Alzheimer's disease; APOE4: apolipoprotein E4; APP: amyloid precursor protein; Aβ: amyloid-beta; CNS: central nervous system; FAD: familial AD; mAbs: monoclonal antibodies; MAPK: mitogen-activated protein kinase; MCI: mild cognitive impairment; NFAT: nuclear factor of activated T cells; NMDA: N-methyl-D-aspartate; P2Y1R: P2Y1 receptor; PS1: presenilin-1; STAT3: signal transducer and activator of transcription 3.

tangle formation. These abnormalities decrease synaptic function and lead to neuronal loss, which, in turn, results in cerebral atrophy, particularly in the intertemporal lobe, and the loss of memory function (Willbold et al., 2021; Jorfi et al., 2023). However, the mechanism of action between amyloid plaques and neurofibrillary tangles remains unclear, but it can be illustrated by three possible hypotheses. **Figure 3A** demonstrates the amyloidogenic and non-amyloidogenic APP-processing pathways. In the non-amyloidosis pathway, α-secretase cleaves APP into soluble APPα and C-terminal fragment C83/carboxyl-terminal fragment α. In the amyloidosis pathway, APP is cleaved into BACE1 by β-secretase to produce extracellular soluble APPβ and C-terminal fragment C99/carboxyl-terminal fragment β. Subsequently, C99/carboxyl-terminal fragment β is cleaved by γ-secretase to produce Aβ and carboxyl-terminal fragment γ-anti-inflammatory compounds (Goate, 2006). Aβ peptides spontaneously aggregate into oligomers, which are currently considered the most toxic structures. These oligomers form fibrils, which then aggregate into amyloid plaques (Zhao et al., 2020; Hu et al., 2025). AD is similar to Parkinson's disease since the main pathological changes in Aβ and tau proteins show Parkinson-like properties. There is a high-affinity bond between Aβ oligomers, cellular prion proteins, and pathologic tau (Crestini et al., 2022). These proteins can self-replicate, leading to the misfolding of normal protein pairs, further excessive protein accumulation, and brain damage, thus promoting disease progression. Although we clearly understand the major pathophysiology of AD, researchers are still exploring the exact roles of these proteins in disease progression. Whether the accumulation of beta plaques and tau proteins is a cause or result of AD remains unclear. However, clearing Aβ protein deposits in the brain is still the most recognized treatment approach for improving AD (Perneczky et al., 2024). Hence, further investigating the pathogenesis and mechanism of AD is crucial (Wisniewski and Goñi, 2014; Monteiro et al., 2023).

Amyloid-Beta Immunotherapy for Alzheimer's Disease

Amyloid-beta active immunotherapy

In recent years, a number of active and passive immunotherapies targeting Aβ have progressed from preclinical studies on AD mouse models to human clinical trials (Loeffler, 2013). However, to date, none of the testing methods have shown notable clinical efficacy until the successful clinical outcomes of lecanemab and donanemab (Sims et al., 2023; van Dyck et al., 2023). Therefore, whether the amyloid theory of Aβ represents the main pathogenesis of AD, being worthy of further study, is doubtful. Active immunotherapy is more dependent on the patient's own cellular and humoral immune function, being able to produce endogenous antibodies for a long time with fewer injections and lower medical costs. After obtaining promising results in animal trials, immunotherapy can also be tested in clinical trials, suggesting that immunotherapy targeting Aβ is beneficial for the brain (Wisniewski and Goñi, 2014). The administration of the anti-Aβ peptide vaccine to subjects aims to induce a regulated autoimmune response. Therefore, intolerant vaccines could cause an inadequate immune response or

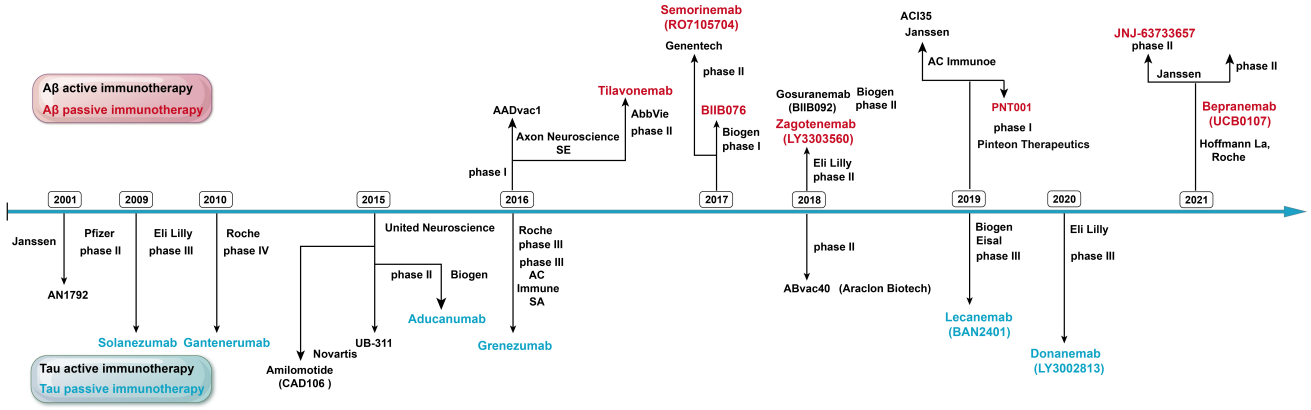

Figure 2 | **The chronology and important milestones of immunotherapy of AD.**
AD: Alzheimer's disease; Aβ: amyloid-beta.

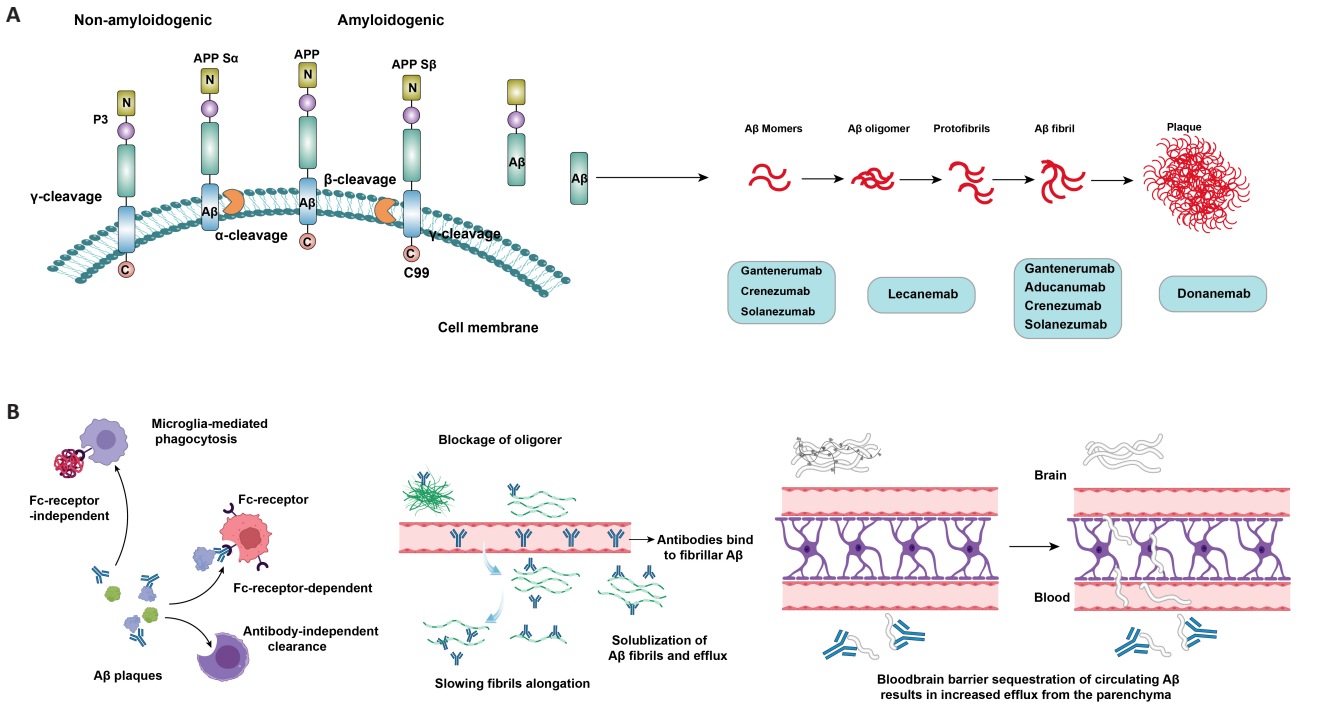

Figure 3 | **The amyloid hypothesis and immunotherapy mechanism based on Aβ.**
(A) There are two main ways of amyloid plaque formation: amyloidosis and non-amyloid processing. In the non-amyloid pathway, APP is cleaved by α-secretase, exposing the soluble amino terminal and C-terminal fragment (C83) of APP, which is subsequently cleaved by γ-secretase to produce the extracellular fragment p3 and the AICD. In the amyloid pathway, β-secretase cleaved APP to produce soluble amyloid precursor protein β- and C-terminal fragment (C99). Gamma-secretory enzymes then further shear C99 to release amyloid-beta and AICD. In the amyloid-producing pathway, APP mainly leads to the aggregation of cytotoxic oligomers and the formation of insoluble Aβ-fiber through the release of Aβ, which is easy to self-aggregation. Different antibodies target different forms of Aβ. Current passive immunotherapy antibodies act on different forms of Aβ targets. (B) The mechanism of Aβ immunotherapy. Antibody-mediated decomposition acts on Aβ plaques, and Aβ binds to its antibodies, preventing it from continuing to lengthen the fibers and blocking the formation of oligomers. The Fc segment mediated endocytosis of microglia can activate microglia to engulf and decompose plaques. In addition, peripheral antibodies bind to free Aβ, creating a concentration gradient of Aβ in the peripheral and central nervous systems, causing Aβ to move out of the brain along the concentration difference. APP: Amyloid precursor protein; Aβ: amyloid-beta; AICD: amyloid precursor protein intracellular domain; Fc: functional connectivity.

potentially trigger harmful autoimmune reactions (Aljassabi et al., 2024). **Table 2** provides some active trials on Aβ immunotherapy.

AN1792

In 1999, Schenk and ELAN Pharmaceutical Company demonstrated in *in vivo* experiments in transgenic mouse models that active immunization with full Aβ peptide combined with an adjuvant could effectively reduce amyloid plaque deposition, but the experiment was halted due to the adverse reaction of aseptic meningoencephalitis in immunized patients (Orgogozo et al., 2003) caused by the specific T cell-mediated pro-inflammatory responses to Aβ, which are induced by the application of the full peptide (Marciani, 2015). More importantly, autopsy results from patients treated with AN1792 showed significant Aβ plaque clearance, neuronal apoptosis, and a reduction in plaque-associated astrocytic clusters in the cortex and hippocampus. In summary, Gilman et al. (2005) clearly concluded that minimizing adverse immune inflammatory responses is important to enhance the effectiveness of immunotherapy with vaccines. However, some significant conclusions can be drawn from these experiments. Song et al. (2020) validated that the vaccine is effective in clearing amyloid deposits, with sustained slightly lower titers of anti-AN1792 antibodies being beneficial to delaying cognitive decline. Consequently, they developed second-generation vaccines with different epitopes, mainly B-cell fragments, to minimize the T-cell-related inflammatory response.

Amilomotide (CAD106)

The second-generation vaccines were created without removing the T-cell-related epitope required to produce a specific T-cell-associated response. CAD106 comprises multiple copies of $A\beta_{1-6}$ coupled to a virus-like particle derived from the bacteriophage Qβ (Wiessner et al., 2011). A phase I trial of CAD106 revealed that many patients

Table 2 | **Trials for Aβ active immunotherapy to treat Alzheimer's disease**

Drug	Aβ target	Company	Clinical phase	Status	Reduce Aβ burden	Slow cognitive	ARIA-E occurrence
AN1792	Aggregated $Aβ_{1–42}$, QS21, and Polysorbate80	ELAN, USA	Phase II	Halted	+	–	High
CAD106	$Aβ_{1–6}$/ Bacteriophage Qβ	Novartis, Basel, Switzerland	Phase I	Terminated	+	–	High
ABVac40	$Aβ_{33–40}$/KHL	AraclonBiotech, Barcelona, Spain	Phase I	Concluded in 2022	+	–	Low
ACC-001	$Aβ_{1–6}$-QS21	Janssen/Pfizer, France	Phase II	Not reported, finishing	+	–	Low
UB311	$Aβ_{1–14}$-targeting peptides as B-cell epitopes	United Neuroscience, Taiwan, China	Phase II	Terminated	+	–	Low
ACI-24	β-Sheet conformation of Aβ peptide	AC Immune, Phoenix, AZ, USA	Phase I/IIa	Not reported	+	–	Low
AD02	$Aβ_{1–6}$/mimetic KLH	Affiris AG, Vienna, Austria	Phase II ongoing	No detailed outcomes	+	+	Moderate
V-950	Aβ amino-terminal	Merck and Co.	Phase I (discontinued)	Unpublished	+	–	High

ARIA-E: Amyloid-related imaging abnormalities with edema; Aβ: amyloid-beta; KHL: keyhole limpet hemocyanin.

produce immunoglobulins containing more anti-Aβ IgM than anti-Aβ IgG (Winblad et al., 2012). Active immunotherapy with CAD106 showed benefits in delaying Aβ deposition and reducing the occurrence of adverse reactions (Bachmann et al., 2019; Riviere et al., 2024). However, as the first vaccine to enter phase II/III clinical trials, CAD106 treatment led to unpredictable variations in memory and changes in the brain volume and mass compared to the control group, ultimately halting further development of CAD-106 (Farlow et al., 2015; Vandenberghe et al., 2017).

ACI-24

ACI-24 is derived from the $Aβ_{1–12}$ fragment, which is anchored to liposomes by tetrapalmitoyl lysine and then anchored to the liposomes using a polyethylene glycol spacer at each end. In preclinical trials on transgenic mice, the vaccine successfully reduced Aβ levels and improved cognitive function. ACI-24 is currently undergoing phase II clinical trials to further test its safety, immunogenicity, and tolerability in patients with mild AD. Despite the original schedule for the phase II clinical trial to conclude in 2024, researchers canceled it in 2021 to enhance the vaccine formulation (Rafii et al., 2022; Rudan Njavro et al., 2022).

UB311

UB311 is an active immune vaccine consisting of two synthetic $Aβ_{1–14}$ peptides that bind to different helper T-cell peptide epitopes to induce antibodies against the N-terminal $Aβ_{1–14}$, minimizing the occurrence of adverse reactions (Ryan and Grundman, 2009). In a phase I trial of patients with mild-to-moderate AD, an Aβ antibody response rather than an inflammatory response was generated, demonstrating the safety and tolerability of the vaccine (Reiss et al., 2021). A phase IIa trial showed a 100% response rate after UB-311 immunization, which has strong targeted immunogenicity, and improved cognitive function in patients with early mild AD (Wang et al., 2017). However, this clinical trial did not include a placebo group. Instead, it compared the increase from baseline in the Alzheimer's Disease Assessment Scale scores of a subgroup of mild AD patients (Mini-Mental State Examination score ≥ 20) with a subgroup of patients with moderate AD. However, the small sample size and uncertain effects on behavior might limit its findings. Since the Neuropsychiatric Inventory scores in each group were low at baseline, identifying a further decline in scores was difficult (Yu et al., 2023). An allocation error halted another phase II trial, with injection site pain emerging as the most common adverse event associated with these treatments (Song et al., 2022).

ABvac40

ABvac40 comprises the C terminal of Aβ40, which is coupled to keyhole limpet hemocyanin and repeated several times to induce a stronger immune response (Rudan Njavro et al., 2022). In a phase I clinical trial, about 11 of 12 immunized patients developed Aβ antibodies, and no amyloid-related imaging abnormalities, including cerebral edema, microhemorrhage, or other pathological symptoms of the inflammatory response, were observed. Lacosta et al. (2018) are expected to complete the ABvac40 II trial in December 2022 to further measure its safety and immune response. Phase II clinical trials are expected to be completed in 2024 and discontinued in 2021 as they continue to optimize the protocol for improving the vaccine design.

Other vaccines

ACC-001 is an experimental therapeutic vaccine targeting segments 1–7 of the N-terminal of Aβ and is still being evaluated to take advantage of the most immunogenic effects without an inflammatory response (van Dyck et al., 2016). AC-001 with or without QS-21 adjuvant had no adverse effects at the injection site and had an acceptable safety profile in all patients treated with mild-to-moderate AD. All groups generated high antibody titers, with the AC001 + QS-21 group generating the highest titers.

AV-1959D is a DNA vaccine targeting the N-terminal epitope of Aβ. Its immunogenicity and therapeutic efficacy were demonstrated in a transgenic mouse model and rabbit and non-human primate models (Aljassabi et al., 2024).

Amyloid-β passive immunotherapy

The method of passive immunization involves injecting *in vitro*-synthesized antibodies directly into the body. Passive immunotherapy has been widely used to effectively avoid T cell-dependent inflammation. Humanized monoclonal immunoglobulin can produce high antibody titer and clear Aβ protein, but adverse reactions, such as vasogenic edema or cerebral amyloid angioedema, may also occur (Vander Zanden and Chi, 2020). The Th1 response may be associated with immune-induced encephalitis. Animal model studies also showed that cloning Aβ-specific antibodies can effectively delay AD progression without the T-cell involvement; consequently, clinical trials of passive immunotherapy in AD subjects were successfully conducted (Foroutan et al., 2019; Janssens et al., 2021; Gnoth et al., 2022). Nevertheless, passive immunotherapy showed mixed results with transgenic mouse animal studies and clinical trials, confirming that anti-Aβ antibodies can significantly reduce Aβ levels and improve cognitive function (Wisniewski and Goñi, 2015; Wang et al., 2016; Weekman et al., 2016). Monoclonal antibodies have significant advantages in therapeutic drug development due to their high homogeneity and specificity to a single epitope; thus, producing large amounts of antibodies for passive immunotherapy is more reasonable (Lipman et al., 2005). However, the preparation of monoclonal antibodies requires more time and economic investment. Passive immune antibodies are costly and time-consuming, as well as have a high affinity for target antigens, and exhibit high sensitivity even when detecting small amounts of proteins (Waldmann, 2019). Nevertheless, the ability to recognize diverse epitopes greatly increases the possibility of cross-reactivity. So far, passive anti-Aβ antibodies are the most investigated drug to enter phase III clinical trials, such as solanezumab, lecanemab, aducanumab, and crenezumab (Dai et al., 2022). **Table 3** shows Aβ antibodies currently used in clinical development.

Bapineuzumab

Back in the early 20th century, the first study of bapineuzumab, an anti-Aβ antibody, entered phase III clinical trials. It mainly binds to the N terminal of Aβ, effectively clearing Aβ plaques in the brain without inducing an inflammatory response. Bapineuzumab was effective in early clinical trials, but subsequent trials failed due to inadequate doses and patient selection (Vandenberghe et al., 2016). Biomarker results confirmed that barperizumab may reduce Aβ accumulation and downstream tau phosphorylation; otherwise, neither trial showed a benefit of bapineuzumab in terms of clinical efficacy (Salloway et al., 2014). Positron emission tomography (PET) for apolipoprotein E4 (ApoE4) confirmed that bapineuzumab had a positive effect on the brain amyloid of Pittsburgh Compound B while demonstrating little effect on nanoparticles (Sperling et al., 2012; Liu et al., 2015). During

Table 3 | **Trials for Aβ passive immunotherapy to treat AD**

Antibody	Epitope location	Immunization strategy	Aβ isotype	Company	Last completed trial (Phase)	Status	ARIA
Bapineuzumab (AAB-01, 3D6)	1–5	$Aβ_{1–5}$ conjugated to immunoglobulin	Humanized IgG1	Janssen/Pfizer, Peoria, AZ, USA	Phase II	No clinical improvement	Moderate
LY2062430, m266	16–26	$Aβ_{13–28}$	Humanized IgG1	Eli Lilly, Tucson, AZ, USA	Phase III	No improvement, halted	Slight
Ponezumab (PF04360365)	30–40	$Aβ_{40}$	Humanized IgG2a	Janssen/Pfizer	Phase I/II	–	Low
Crenezumab (MABT5102a, RG7412)	13–24	Liposome anchored peptides	Humanized IgG4	Roche/Genentech, Armenia, Colombia	Phase II/III	No clinical improvement	Low
Gantenerumab (RO4909832, RG1450)	2–11, 18–27	human combinatorial antibody libraries	Humanized IgG1	Roche, Atlantis, FL, USA	Phase III	In autosomal dominant AD	No
Donanemab (N3pG, LY3002813)	3–7	Aβ pE3–42	Humanized IgG1	Eli Lilly	Phase III	Early AD	Low
Aducanumab (BIIB037)	3–7	B-cell librariesfrom healthy elderly	Humanized IgG1	Neurimmune/ Eisai/Biogen, Japan/Birmingham, AL, USA	Phase III	Early AD	High
BAN-2401 (Lecanemab, mAb158)	1–16	Protofibrils of E22G mutant Aβ	Humanized IgG1	Biogen/Eisai/Bioarctic	NCT01230853 (I, IIb)	Early or Mild AD	Low
MEDI-1814	29–42	Human combinatorial antibody libraries	Humanized IgG1	AstraZeneca/ medimmune	NCT02036645 (I)	mild to moderate AD	No

AD: Alzheimer's disease; Aβ: amyloid-beta.

the trial, certain disorders were associated with amyloid-associated vasogenic edema and intracerebral microhemorrhages (Salloway et al., 2009).

Aducanumab

Aducanumab (BIIB037) is a novel disease-modifying anti-Aβ human monoclonal antibody developed for AD. Aducanumab mainly binds to the N terminal of Aβ with high affinity and selectively targets Aβ aggregates, including not only insoluble fibrils but also soluble oligomers (Song et al., 2022). Patients with mild AD in clinical phase I studies receiving monthly intravenous aducanumab had reduced temporal brain Aβ in a dose-dependent approach after 1 year and reduced Mini-Mental State Examination and Clinical Dementia Rating Scale-Sum of Boxes to varying degrees (Sevigny et al., 2016). However, the results of the two phase III trials (EMERGE and ENGAGE) were different and had nothing to do with the efficiency of aducanumab (Vaz et al., 2022). In 2022, two randomized phase III trials, comprising 1638 participants in EMERGE and 1647 participants in ENGAGE, reported the efficacy and safety of aducanumab injections in 3285 patients (Budd Haeberlein et al., 2022). The multicenter, double-blind phase III trial involving 1795 patients with early-stage AD showed that aducanumab significantly reduced Aβ deposition in the cortex and hippocampus in AD compared with placebo, effectively delaying cognitive decline in early AD patients (Salloway et al., 2022). However, all clinical trials reported dose-dependent amyloid-associated imaging abnormalities and other adverse reactions, with common symptoms such as edema, headache, dizziness, falls, and brain microhemorrhages (Wojtunik-Kulesza et al., 2023). Although the relationship between Aβ and tau remains controversial, aducanumab has been shown to reduce tau phosphorylation, providing a theoretical basis for the combined treatment of AD with anti-tau and anti-amyloid drugs (Rubin, 2021). Nevertheless, the US Food and Drug Administration approved the clinical use of aducanumab in June 2021 with the "accelerated approval" route rather than a standard approval. It promised to report the results of its "post-market" trials by 2030 as a condition for further elucidating the impact of the drug on cognition (Franklin, 2021).

Lecanemab

Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody capable of binding multiple forms of Aβ, oligomers, and insoluble fibrils and specifically targeting soluble Aβ aggregates. The phase I clinical trial on lecanemab tested the safety, tolerability, and pharmacokinetics of antibody administration at different increasing doses. Lecanemab was well tolerated without cases of amyloid-related imaging abnormalities such as edema (Logovinsky et al., 2016). Subsequently, a large phase II trial, aiming to better clear Aβ-soluble oligomers and protofibrils, was conducted. The results of the clinical trial showed significant changes, such as reduced amyloid plaques and improved cognitive decline, at 18 months after treatment rather than 12 months (Volloch and Rits-Volloch, 2023). In late September 2022, Eisai and Biogen announced that their antibody, lecanemab, achieved favorable results in a phase III clinical trial (Swanson et al., 2021). Multiple studies confirmed that lecanemab does not reduce Aβ deposition in AD and effectively delays cognitive dysfunction (Vander Zanden and Chi, 2020; McDade et al., 2022). Currently, lecanemab is successfully registered as the most promising antibody for treating AD and preventing its progression. Another ongoing phase III trial, AHEAD 3–45, aims to evaluate the efficacy and safety of lecanemab in preclinical AD patients by examining baseline changes in the preclinical AD cognitive complex 5 scores at 216 weeks of treatment and is expected to be completed in 2027 (Vitek et al., 2023). The US Food and Drug Administration approved lecanemab through the accelerated approval route.

Donanemab

Donanemab (LY3002813) is a humanized monoclonal IgG1 antibody that recognizes the Aβ pyroglutamate N-terminal epitope of amyloid plaques (Cao et al., 2022). Phase I trial results showed that donanemab was well-tolerated and could effectively reduce Aβ deposition. In the phase II trial, donanemab slightly reduced the overall AD score scale in early AD patients, marking a decline in cognitive dysfunction (Mintun et al., 2021). The clinical trial administered 700 mg denosumab intravenously to control and experimental patients for 4-week intervals, followed by an additional dose of 1400 mg for 72 weeks. Using the Integrated AD Rating Scale as the primary endpoint event, donanemab was superior to the placebo. After donanemab immunization, amyloid plaque levels were decreased, and 67.8% of patients were Aβ-negative (Sims et al., 2023). Two phase III studies on preclinical AD were initiated to further verify the safety and effectiveness of donanemab (Shcherbinin et al., 2022; Marković et al., 2023). Patients with early symptomatic AD treated with donanemab revealed reductions in Aβ and tau, as demonstrated by the combined Alzheimer's Disease Rating Scale and Clinical Dementia Rating Box and psychometric test results. The progression of clinical symptoms and cognitive impairment were delayed and reduced by 35% and 36%, respectively (Gueorguieva et al., 2023). Furthermore, 2.5% and 9.6% of patients 2.5% and 9.6% of patients showed improvement in clinical symptoms and cognitive dysfunction after treatment with donanemab (Kurkinen, 2023). Currently, another phase III clinical trial (NCT03367403), Trailblazer-Alz3, is underway and will enroll 3300 patients with preclinical AD to further evaluate the safety and efficacy of donanemab.

Solanezumab

Solanezumab (LY2062430) is a humanized monoclonal antibody that recognizes the mid-domain of $Aβ_{13–28}$ to accelerate Aβ clearance (Doody et al., 2014). Early in the disease, this toxic fragment aggregates into amyloid plaques before protein deposits turn into fibrillar deposits. Solanezumab was the first anti-Aβ antibody tested in a phase III trial (NCT00904683), which ultimately failed. We designed a phase II trial to assess the safety of solanezumab over 12 weeks in mild-to-moderate AD and healthy volunteers. The data showed that the doses of 400 mg per week were well-tolerated, while patients with $Aβ_{42}$-negative cerebrospinal fluid showed dose dependence, indicating that $Aβ_{42}$ could be removed from the plaque (Farlow et al., 2012). Consequently, the phase III trial of solanezumab

in mild-to-moderate AD patients was performed. However, the results were unsatisfactory due to no improvement in cognitive impairment (Fiala et al., 2018). A subsequent statistical analysis of several clinical trials in patients with mild-to-moderate AD suggested that cognitive impairment did not improve after immunotherapy (Fiala et al., 2018). The ongoing phase III trial of solanezumab (NCT02008357), which is exploring its effect on amyloid plaques in the brain, demonstrated that Aβ levels were decreased compared to placebo in preclinical AD patients treated for up to 240 weeks, while cognitive impairment was not improved (Sperling et al., 2023).

Gantenerumab

Gantenerumab (RO4909832) is a human IgG1 monoclonal antibody that exhibits a high affinity for binding to agglomerated Aβ and promotes Aβ clearance through Fc receptor-mediated phagocytosis (Bohrmann et al., 2012). Regardless of the presence of the ApoE4 allele, the initial phase 3 trial utilized gantenerumab at a target dose of 1020 mg/month in a 9-month regimen with 510 mg subcutaneously injected every 2 weeks for 116 weeks. Unfortunately, gantenerumab failed to meet the primary endpoint of the clinical total dementia score, which was to slow cognitive decline for 116 weeks, in a subsequent phase III trial (Ostrowitzki et al., 2017). Using gantenerumab in patients with early AD decreased the amyloid plaque load at 116 weeks compared to the placebo group, but a slower clinical decline was still observed (Bateman et al., 2023). After injecting gantenerumab, cerebrospinal fluid biomarkers remained altered and increased, including phosphorylated tau181, total tau protein, and neurogranin. In summary, the efficacy of gantenerumab in delaying the progression of AD was low. Additionally, two open-label, multicenter phase III trials (NCT04339413 and NCT04374253) are ongoing to evaluate the safety and efficacy of gantenerumab long-term dosing (Klein et al., 2019). Studies are projected to continue until 2026.

Crenezumab

Crenezumab (MABT5102A) is a fully humanized anti-Aβ IgG4 monoclonal antibody that targets the mid-domains of $A\beta_{1-40}$ and $A\beta_{1-42}$, which are oligomeric and aggregated fibrillary forms of amyloid plaques (Loureiro et al., 2020). In phase I trials, the antibody exhibited a good safety profile without adverse effects, such as vasogenic edema and microhemorrhage (Adolfsson et al., 2012). Subcutaneously injected crenezumab reduced oligomer levels in the cerebrospinal fluid of most patients in the phase II trials, while PET amyloid load did not change (Pegueroles et al., 2021), nor did cognitive function improve (Yang et al., 2019). Phase III trials of CREAD and CREAD2 were initiated in 2016 and 2017, respectively, to better evaluate the efficacy and safety of crenezumab in patients with early AD. However, due to inconclusive efficacy, both studies failed to reduce clinical symptoms decline in patients with early AD, leading to their termination after the mid-stage. These trials showed no significant changes in AD biomarkers, indicating that CREAD is unlikely to meet its primary endpoint even if no new safety signals are found (Ostrowitzki et al., 2022).

Tau Immunotherapy for Alzheimer's Disease

Amyloid plaques formed by Aβ protein aggregation and neurofibrillary tangles (Monteiro et al., 2023), which consist of tau protein, are the two main pathological features of AD. Tau is a cytoplasmic protein stabilizing microtubules by binding to tubulin during normal microtubule polymerization (Parrocha and Nowick, 2023). Tau hyperphosphorylation reduces its stability and affinity for microtubules, resulting in microtubule disintegration, self-aggregation of separated molecules, misfolding into tau oligomers, and aggregation into neurofibrillary tangles. These non-physiological forms of tau can cause various related pathological events, including decreased axonal transport function, altered synaptic structure and function, mitochondrial dysfunction, activation of different protein reactions, and misfolded protein degradation (Kopeikina et al., 2012). Moreover, developing therapies targeting Aβ and tau can more effectively delay the progression of AD. These therapies include active immunotherapy with vaccines and monoclonal antibody, which have been investigated in multiple studies. However, identifying the epitopes that produce tau-specific therapeutic antibodies remains challenging (Ashton et al., 2022). The expansion of tau pathology is thought to spread between neurons; thus, extracellular tau could be a target for AD drug development (Gu et al., 2013). Although only 0.1%–0.3% of antibodies can cross the blood–brain barrier (BBB), only a small fraction of tau antibodies against Ser 396/404 enters neurons via clathrin-dependent Fcγ receptor endocytosis (Ji and Sigurdsson, 2021). **Figure 4** demonstrates the proposed mechanism of immunization targeting tau. Therefore, a key factor in tau immunotherapy development is the availability of sufficient tau antibodies to reach and enter neurons. Accordingly, several active immune studies targeting phosphorylated tau peptides demonstrated the possibility of modulating tau pathophysiological changes in AD mouse models (Boutajangout et al., 2010). **Table 4** displays preclinical studies focusing on tau peptide vaccine therapy.

Tau active immunotherapies

ACI-35

ACI-35 is a liposome vaccine containing 16 amino acids located at sites 393–408 of the human tau protein sequence, phosphorylated at S396 and S404 residues. In tau P301L–transgenic and other wild-type mice, ACI-35 induced a specific polyclonal antibody response to p-tau production (Theunis et al., 2013). In December 2013, a phase Ib study testing ACI-35 in 24 patients with mild-to-moderate AD was initiated and concluded in June 2017 (Theunis et al., 2017). A weak immune response to the vaccine was achieved even using a booster shot (Parrocha and Nowick, 2023). Another phase Ib/IIa clinical trial, beginning in August 2019, showed high titers of specific antibodies against phosphorylated tau and aggregated tau. However, the trial was not presented on ClinicalTrials.gov or other clinical registration centers because details were not available at submission (Panza et al., 2016).

AADvac1

AADvac1 is an active vaccine, representing a synthetic peptide derived from the 294–305 amino acids of the tau sequence, coupled to keyhole limpet hemocyanin with aluminum hydroxide as an adjuvant. Additionally, it is the first clinically developed vaccine specifically targeting tau protein. Transgenic mice treated with AADvac1 showed reduced nuclear factor degeneration and improved neurobehavioral deficits (Anand and Sabbagh, 2015). Phase I clinical trial showed that AADvac1 treatment produced IgG antibodies against tau peptides in mild-to-moderate elderly AD patients with high heterogeneity (Hung and Fu, 2017). Several clinical trials confirmed that AADvac1 was safe and well-tolerated, although it did not prevent cognitive decline (Novak et al., 2018b, 2021; Cullen et al., 2024). A preclinical test on AADvac1 showed cortical atrophy and increased ventricle volume in mice treated with AADvac1 compared to controls, causing a widespread concern (Novak et al., 2017). A phase II clinical trial of AADvac1 was successfully conducted and ended in 2019 to further evaluate its safety, efficacy, and tolerability of long-term use in patients, showing no significant improvement in cognitive function.

Tau passive immunotherapy

Semorinemab

Semorinemab (RO7105705) is a humanized IgG4 monoclonal antibody that recognizes 6–23 amino acids of tau protein and simultaneously binds to different tau forms, including monomers and oligomers. After semorinemab treatment, tau in the brains of human tau P301L–transgenic mice was significantly reduced (Ayalon et al., 2021). The second phase of the trial, in which nearly three-quarters of patients were APOE4 carriers, did not achieve changes in the cognitive status of the mice. There are currently no reports of phase III trials on ClinicalTrials.gov. A phase II randomized controlled study on patients with mild-to-moderate AD was conducted to further test the safety and efficacy of semorinemab (Teng et al., 2022). However, semorinemab did not achieve the expected effect of the first phase II trial of TAURIEL (NCT03289143). Although the AD Assessment Scale evaluation found that semorinemab had a significant effect on cognition, this effect did not provide significant outcomes or benefits (Monteiro et al., 2023). Consequently, the trial will be converted to an open trial until October 2023 to further explore and validate the effects of semorinemab on primary and secondary endpoint events.

JNJ-63733657

JNJ-63733657 (Janssen) is a humanized IgG1 monoclonal antibody that can effectively bind to tau microtubules and prevent further tau aggregation. In December 2017, a phase I trial was launched to evaluate the safety and tolerability of this monoclonal antibody, primarily by testing healthy volunteers and patients with mild AD. JNJ-63733657 inhibited the seed-spreading ability of tau, effectively preventing its spread in P301L mouse models (Bijttebier et al., 2021). This phase II clinical trial started in January 2021 and is expected to end in 2025.

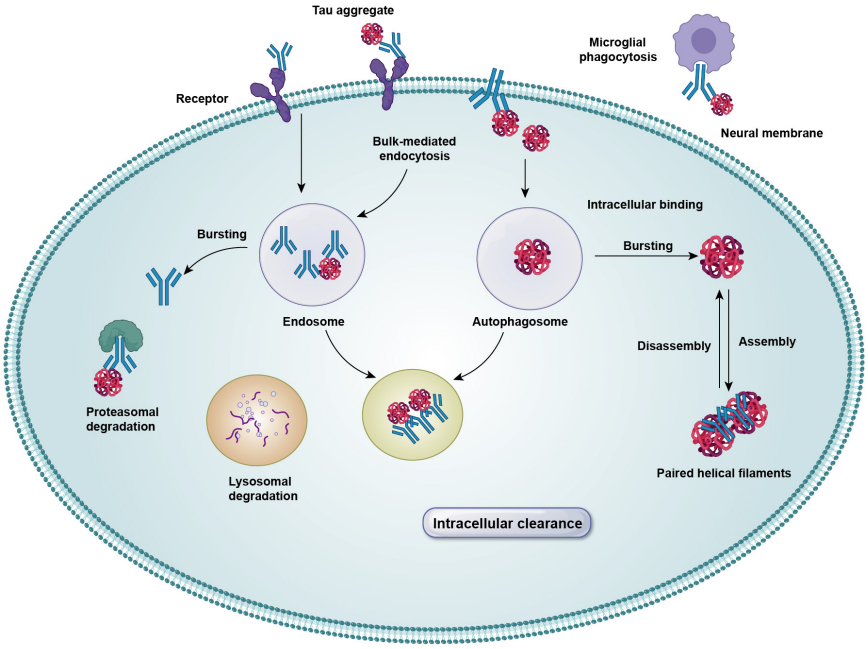

Figure 4 | **The proposed mechanism of anti-tau antibodies.**
Antibodies can bind to tau proteins both inside and outside the cell. Residual pathological tau is present in neurons and astrocytes. After neuronal apoptosis, these tau tangles mainly accumulate outside the cell. tau antibodies cannot be stably taken up within neurons, and they mainly work in extracellular organelles. Among them, antibodies mainly attract tau to aggregate, interfere with their further aggregation, induce microglia to phagocytose them, and prevent tau from spreading within neurons. Other antibodies can be easily detected within neurons by binding to tau proteins via the endoplasmic reticulum lysosomal system, promoting their depolymerization, or by the E3 ubiquitin-protein ligase TRIM21 binding site. TRIM21: Tripartite-motif protein 21.

Table 4 | **Clinical trials of tau immunotherapy for AD**

Antibody	Company	Isotype	Mode of action	Target population	Clinical phase
BIIB076 (6C5)	Biogen, Hallandale Beach, FL, USA	IgG1	Reduction in tau transfer	Healthy controls patients with mild AD	I/II
ABBV 8E12 (HJ8.5)	AbbVie, Phoenix, AZ, USA	IgG4	Reduction in tau pathology	Patients with PSP AD	I/II
Zagotenemab (MC1)	Lilly, Phoenix, AZ, USA	IgG	Reduction in tau pathology	Patients with mild/ early AD	I/II
RG7345 (anti pS422)	Roche, Basel, Switzerland	N/A	Reduction in tau pathology	Healthy controls, discontinued	I
UCB0107 (antibody-UCB)	Biopharma, Fresno, CA, USA	IgG4	Reduction in uptake, cell transfer and seeding	Healthy controls	I
AADvac1	Axon Neuroscience, Salzburg, Austria	IgG	Target pathological tau	Patients with AD	I

AD: Alzheimer's disease; PSP: progressive supranuclear palsy.

Gosuranemab

Gosuranemab is a humanized IgG4 that targets the N-terminal end of extracellular tau isoforms (Dominy et al., 2019). The phase I trial confirmed that BIIB092 was safe and well-tolerated without serious adverse reactions in the low and medium dose groups but with an incidence of side effects of 8% in the highest dose group. The antibody reduces tau aggregation by binding to the N-terminal tau protein, with its titers maintaining a certain level for a relatively long time. Antibodies did not reduce AD biomarkers, such as total tau and plasma tau phosphorylated at residue 181 (Boxer et al., 2019). A phase II clinical trial enrolled 528 subjects with mild AD who tested positive for Aβ-PET from November 2017 to 2020 (Qureshi et al., 2018). Another phase II trial of gosuranemab in patients with early AD was discontinued due to the lack of evidence of improved cognitive impairment after comparing experimental and placebo groups (Dam et al., 2021).

Zagotenemab (LY3303560)

Zagotenemab is a humanized IgG1 that generates antibodies against a specific tau conformational epitope, thereby forming neurofibrillary structures at the N-terminus of amino acids 7–9. The conformational epitope to which the antibody specifically binds is located in the N-terminal region of tau (Roberts et al., 2020). The main epitopes identified are not continuous and are primarily related to the severity of AD and the abnormal conformation of the main pathological structure of tau. To date, zagotenemab has successfully completed two phase I trials in healthy participants and patients with AD (Novak et al., 2018a; Willis et al., 2023). The phase 2 trial enrolled 285 patients with cognitive impairment for at least 6 months and run until August 2021. Eli Lilly announced the discontinuation of the zagotenemab clinical trial in October 2021 due to inadequate control and analysis of endpoint events (Gerson and Kayed, 2016).

Bepranemab

Preclinical trials of UCB0107, a tau antibody developed by UCB Biopharma that targets 235–246 amino acids in the proline region, showed that bepranemab could effectively prevent the accumulation and spread of pathological tau; additionally, it can inhibit tau fibrosis at 100% using the antibody concentration of 300 nM (Novak et al., 2018a). In a preclinical study, bepranemab demonstrated its effectiveness in mouse models of tau by stimulating the cell defense against misfolded tau, altering isomer binding site of tau, or reducing tau expression (Truong et al., 2021). It is currently being evaluated in a phase II clinical trial for AD, which is expected to be accomplished in 2025 (Panza et al., 2023).

Tilavonemab

ABBV-8E12 is a humanized IgG4 monoclonal antibody targeting tau amino acids 25–30, which represent the aggregated pathologic extracellular form of tau (Kfoury et al., 2012). Initial studies showed that the ABBV-8E12 monoclonal antibody can reduce and prevent the spread of neurofibrillary tangles in the brains of P301S tau transgenic mice (West et al., 2017). Unlike some other tau antibodies, the antibody does not require uptake into neurons. In mouse models, the antibody could block the seeding and uptake of tau by primary neurons in cell-based tau sensor trials (Albert et al., 2019; Koga et al., 2021). A double-blind, placebo-controlled phase I study tested a single dose of tilavonemab and found it to be safe and well-tolerated with no clinical adverse events. A subsequent interim analysis of phase II data found no significant benefit in the experimental group, and AbbVie discontinued tilavonemab development in 2021 (Florian et al., 2023).

Challenges and Perspectives of Immunotherapy for Alzheimer's Disease

The main pathological changes of AD are those related to Aβ and tau proteins (Wang et al., 2024). While AD vaccine development has focused on Aβ, recent research have shown that tau proteins can bind to and work in concert with Aβ (Mashal et al., 2022). A study found that a small peptidergic compound P021 can promote nerve regeneration, enhance synaptic plasticity, and mitigate neurodegeneration, including tau and Aβ pathological changes in 3Tg-AD transgenic AD mouse models (Baazaoui and Iqbal, 2017).

Current evidence shows that therapies targeting Aβ and tau have been effective. Although many preclinical studies reported that passive and active immunotherapy is successful in clearing Aβ deposition, it does not improve cognitive function. **Table 5** shows the advantages and disadvantages of active and passive immunotherapy. Moreover, the interaction between Aβ and tau proteins suggests that combination therapy may be more beneficial, especially since early initiation of

Table 5 | **Summary of the advantages and disadvantages of the active and passive immunotherapies**

	Advantages	Disadvantages
Active immunotherapy	Natural immune response suitable for long term therapy	Development of tolerance to be avoided
	Persistent antibody titers for longer duration	Use of adjuvant to avoid inflammation by T-cell infiltration
	Lower cost and low antibody dose	Generation of antibody responses in older patients
	Peak titers gradually reached, reduced risk of adverse effects	Replies on the patient's own immune response, not suitable for subjects with impaired immune system
Passive immunotherapy	mAbs have high specificity for recognizing targets to avoid inhibiting other substrates	Short-lived, frequent doses, high costs and may induce anti-antibody response
	Appropriate and effective for the elder people	High incidents of hypersensitivity reaction
	Can select different subtypes of IgG upon diseases	Cause an imbalance in the immune system
	Rapid initiation of protection (hours to days)	Not proper for prophylactic purposes

therapy is critical to slowing or preventing AD (Lemere, 2013). Hence, even clearing amyloid accumulation cannot reverse cognitive impairment once neuronal damage has occurred (Vander Zanden and Chi, 2020). Therefore, adjusting the direction of diagnosis and treatment to early detection of AD before symptoms appear and maximizing the preservation of its function before neuronal loss is crucial to delay cognitive decline.

In this review, we discuss the current comparison of the most advanced active and passive immunotherapies for Aβ and tau, which, theoretically, may slow or stop the progression of brain pathology in patients with AD. Aβ is a transmembrane protein of the amyloid precursor, while tau is microtubulin, a brain-specific protein specifically enriched in axons. These two proteins can interact, inducing synaptic dysfunction and the decline of neuronal function. Targeting any protein has its advantages and disadvantages. Selective targeting of amyloid significantly reduces the risk of vasogenic edema and other complications. A major advantage of tau protein immunization is that targeting neuron-specific proteins may simultaneously impair its normal physiological function. Therefore, targeting both pathologies simultaneously might have greater therapeutic potential than targeting each protein individually. Aβ activates the immune system, triggers tau phosphorylation, and promotes the formation of neurofibrillary tangles. Recent studies have shown that Aβ and tau pathology share a common upstream trigger inducing synaptic dysfunction together. Currently, it is generally believed that Aβ is the "trigger" for AD, whereas tau is the "bullet" driving AD (Bloom, 2014). Aβ interacts with tau primarily by acting on the C-terminus of the hsp70-interacting protein, as Aβ deposition decreases protein expression at the hsp70C-terminus, elevating tau levels (Lyon and Milligan, 2019). The common hallmark of neurodegenerative diseases is neuroinflammation, with Aβ and tau proteins are mainly associated with neuroinflammation, which further leads to the development of AD (Alawieyah Syed Mortadza et al., 2018). In recent years, animal and clinical trials have confirmed that Aβ immunotherapy reduces Aβ and tau levels simultaneously. Similarly, tau immunotherapy reduces Aβ levels. Therefore, the researchers hypothesized that combination of the two proteins would be a better therapy and prevention strategy in early AD patients (Busche and Hyman, 2020). Additionally, several clinical trials tested other main molecules, such as triggering receptors expressed on myeloid cell 2, tumor necrosis factor-α, and CD38 (Ewers et al., 2019). Advancements in single-cell sequencing and transcriptome sequencing have identified an increasing number of molecules as potential targets for immunotherapy (Park et al., 2023).

The US Food and Drug Administration approved aducanumab in 2021 (Dunn et al., 2021) and lecanemab via the accelerated approval pathway in 2023 (van Dyck et al., 2023) since these antibodies decreased early-stage amyloid deposits and mildly delayed cognitive decline based on cognitive function tests. Rather than simply improving disease symptoms, these treatments target the processes underlying the pathogenesis of AD to slow its progression and improve prognosis (Vogt et al., 2023). However, the approval of aducanumab and lecanemab antibodies raises the possibility that neurodegenerative diseases, such as AD, can be prevented or slowed down by promoting Aβ clearance and decreasing its deposition. However, this development brings us one step closer to a complete cure for AD.

Immunotherapy is currently the most advanced treatment strategy for AD, but there are still some issues requiring more attention. The safest and most reasonable approach to overcome the potential shortcomings of immunotherapy would be to target only toxic molecules without causing an associated inflammatory response. In recent years, vaccine development has focused on targeting the most toxic Aβ oligomers. The dendritic cells stimulated by Aβ oligomer act as natural adjuvants to effectively avoid autoimmune T lymphocyte responses. Currently, monoclonal antibodies can be administered to patients systemically (intravenously, intramuscularly, or subcutaneously), but it is unclear how many antibodies can cross the BBB and bind to Aβ peptide in the brain. The effective enhancement of the BBB passage rate will become a new challenge for future vaccine therapy (Meredith et al., 2015). Only about 0.1% of monoclonal antibodies can cross the BBB, with the liver or kidneys metabolizing the rest, according to a previous study (Yu and Watts, 2013). The efficiency of BBB penetration by antibodies varied in several clinical trials, being influenced by many factors. The BBB penetration will be the greatest limitation of immunotherapy developed to date. Therefore, methods to enhance the efficiency of delivering vaccines or antibodies are needed to ensure their passage through the BBB; thus, peripherally injected antibody drugs could adequately enter the brain. Some bioengineering and delivery techniques could help to solve this problem. Due to the excellent biocompatibility, biodegradability, and low toxicity of nanotechnology, it can help carry different types of therapeutic molecules through the BBB, which has greatly improved conventional AD treatments (Carradori et al., 2018). Hence, new techniques for generating antibodies in the brain are crucial for AD immunotherapy.

Antibodies can cross the BBB through endocytosis and travel through epithelial cells by binding to the transferrin receptor (Tolar et al., 2020). Therefore, Roche developed a derivative of gantenerumab that improved its BBB passage rate 8-fold by binding to a Fab fragment of the transferrin receptor. A novel, nasally administered, PEI-coupled R8-Aβ_{25-35} peptide significantly reduced Aβ deposition and improved memory deficits in APP/PS1 AD mouse models. However, repeated intranasal administration can cause irreversible damage due to the sensitivity and limited area of the nasal mucosa (Correa et al., 2023). Full-length DNA Aβ_{1-42} immunization delivered by electroporation has the potential to be used in clinical trials since electroporation can promote antibody binding rates to a greater extent by adjusting the parameters of the electrical impulses without producing an inflammatory response (Rosenberg et al., 2018).

Aβ and tau oligomers continuously spread outside the cell through promoter-like replication mechanisms, becoming the most toxic structural forms of Aβ and tau proteins. Targeting only Aβ or tau oligomers is therapeutically advantageous because it does not affect the normal physiological function of these proteins (Mielke et al., 2021). There is increasing evidence that the most toxic fragment of AD is a soluble Aβ oligomer, which is closely correlated with clinical symptoms (Ghosh et al., 2023). The toxic Aβ oligomer is phagocytized by microglia, processed, and integrated to form dense Aβ plaque deposits with relatively low neurotoxicity (Portelius et al., 2010). Tau oligomers, which are highly toxic, can promote the diffusion of endogenous tau with abnormal conformation in mice (Lewis and Dickson, 2016). Oligomers with > 10 than ten tau molecules are currently considered the most toxic and seed-dispersive. More different hyperphosphorylated tau epitopes should be explored to improve tau vaccines.

Thus, tau hyperphosphorylation can be restructured, inducing large tau oligomers to propagate in a "prion-like" manner (Dujardin and Hyman, 2019). To sum up, separate mechanisms of different forms, isomers, and epitopes of Aβ and tau should be emphasized in AD immunotherapy. Additionally, > 80 potential phosphorylation sites exist on serine, threonine, and tyrosine residues of tau, presenting a great challenge for screening for biologically relevant antigens (Cao et al., 2019). Studying the binding sites of antigens can increase the understanding of molecular biological mechanisms in AD and help develop more effective immunotherapy strategies (van Dyck, 2018). Diagnosis and intervention in the early, pre-symptomatic stages of AD are considered a more effective strategy. PET scans and cerebrospinal

fluid analysis are used to detect amyloid deposits for intervention before severe clinical symptoms occur. Aβ appears earlier than tau in the progression of AD; thus, Aβ immunotherapy is more beneficial for early AD. A phase 3 clinical trial of bapineuzumab achieved promising results, with PET scans showing a significant reduction in Aβ deposition after 18 months of antibody treatment compared to placebo. This finding provides a new direction for early diagnosis and treatment. However, the lack of accurate biomarkers or precise cognitive scales of AD complicate the establishment of early diagnosis. However, an increasing number of APOE4 testing is expected in the future (Choo et al., 2022).

Active immunotherapy is influenced by many factors, including immune deficiency in the elderly, the immune response to their own proteins, and the application of certain adjuvants that can enhance the immune effect. A method to produce safe and high-titer antibodies for the elderly and immunocompromised population may be helpful for AD vaccines. Furthermore, improved sensitivity of biomarkers, including imaging biomarkers that can precede the occurrence of Aβ deposition and early cognitive function screening for AD, could provide better direction for clinical trials.

Conclusions and Future Perspectives

We are confident that we will soon overcome the obstacle of immunotherapy for AD. Effectively reducing the cytotoxicity of $A\beta_{42}$ aggregates and tau oligomers greatly significant for delaying disease progression and promoting the adjustment of immunotherapy strategies for AD. Previous reports showed that several proteins work together in the pathogenesis of AD. The pathophysiology of AD dictates that combination therapy may be more beneficial. The combination of > 2 drugs targeting multiple pathways can produce synergistic effects and achieve better therapeutic results than using a single drug. Therefore, developing combined therapy against both pathogenic proteins is the main direction for future treatment. Drug cocktails for the treatment of acquired immune deficiency syndrome are a typical example of successful drug recombination. Despite promising results in patients with early AD, aducanumab, lecanemab, and donanemab still require a significant amount of clinical data to track efficacy in patients with intermediate AD. Thus far, only the US Food and Drug Administration approved the use of lecanemab and aducanumab. As the clinical application of lecanemab and aducanumab expands, the side effects, including amyloid-associated imaging abnormalities with cerebral microhemorrhages, superficial siderosis, and vasogenic edema, become increasingly evident. Due to the diversified antibody characteristics, active and passive immunotherapy can also have negative effects. However, efforts are still made to reduce tau and α-syn levels to a greater extent by adjusting the dose of anti-Aβ antibody and improving the immune method to avoid adverse reactions. Furthermore, targeting the most toxic molecules without interfering with their normal physiological functions could be the most reasonable and safe approach. As dendritic cells are a natural adjuvant and considered to play a key role in the toxicity of oligomers, targeting mutant Aβ oligomers may avoid triggering an autoimmune T-cell response. Therefore, stimulating a dendritic cell vaccine could be a promising approach for AD immunotherapy.

Recent animal studies have shown that many antigenic epitopes of tau protein are highly toxic. Hence, targeting them can improve cognitive function, which may be a better therapeutic prospect at present and can be used as a biomarker for AD to help establish early diagnosis. Sensitive biomarkers will be combined to help treat AD more effectively. For example, the combination of passive immune antibodies and drugs targeting biomarkers can promote the phagocytic activity of microglia and astrocytes, potentially improving the clearance of Aβ and tau pathologies. This approach is worth further exploration. A comparative analysis with previous major AD treatments would further reinforce the novelty and significance of the proposed innovations. In the future, we will be able to thoroughly compare the recent therapies for AD one by one.

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References

Abyadeh M, Gupta V, Paulo JA, Mahmoudabad AG, Shadfar S, Mirshahvaladi S, Gupta V, Nguyen CTO, Finkelstein DI, You Y, Haynes PA, Salekdeh GH, Graham SL, Mirzaei M (2024) Amyloid-beta and tau protein beyond Alzheimer's disease. Neural Regen Res 19:1262-1276.
Adolfsson O, et al. (2012) An effector-reduced anti-β-amyloid (Aβ) antibody with unique aβ binding properties promotes neuroprotection and glial engulfment of Aβ. J Neurosci 32:9677-9689.
Agustini D, Sabloak R, Hasan S, Umar PT (2025) The role of fusion proteins as biomarkers and therapeutic agents for Alzheimer's disease: A narrative review. NeuroMarkers 2:100041.
Alawieyah Syed Mortadza S, Sim JA, Neubrand VE, Jiang LH (2018) A critical role of TRPM2 channel in Aβ(42) -induced microglial activation and generation of tumor necrosis factor-α. Glia 66:562-575.
Albert M, Mairet-Coello G, Danis C, Lieger S, Caillierez R, Carrier S, Skrobala E, Landrieu I, Michel A, Schmitt M, Citron M, Downey P, Courade JP, Buée L, Colin M (2019) Prevention of tau seeding and propagation by immunotherapy with a central tau epitope antibody. Brain 142:1736-1750.
Aljassabi A, Zieneldien T, Kim J, Regmi D, Cao C (2024) Alzheimer's disease immunotherapy: current strategies and future prospects. J Alzheimers Dis 98:755-772.
Anand K, Sabbagh M (2015) Early investigational drugs targeting tau protein for the treatment of Alzheimer's disease. Expert Opin Investig Drugs 24:1355-1360.
Ashton NJ, et al. (2022) Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring. Nat Med 28:2555-2562.
Ayalon G, et al. (2021) Antibody semorinemab reduces tau pathology in a transgenic mouse model and engages tau in patients with Alzheimer's disease. Sci Transl Med 13:eabb2639.
Baazaoui N, Iqbal K (2017) Prevention of dendritic and synaptic deficits and cognitive impairment with a neurotrophic compound. Alzheimers Res Ther 9:45.
Bachmann MF, Jennings GT, Vogel M (2019) A vaccine against Alzheimer`s disease: anything left but faith? Expert Opin Biol Ther 19:73-78.
Bateman RJ, et al. (2023) Two phase 3 trials of Gantenerumab in early Alzheimer's disease. N Engl J Med 389:1862-1876.
Bijttebier S, Theunis C, Jahouh F, Martins DR, Verhemeldonck M, Grauwen K, Dillen L, Mercken M (2021) Development of immunoprecipitation - two-dimensional liquid chromatography- mass spectrometry methodology as biomarker read-out to quantify phosphorylated tau in cerebrospinal fluid from Alzheimer disease patients. J Chromatogr A 1651:462299.
Bloom GS (2014) Amyloid-β and tau: The trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol 71:505-508.
Bohrmann B, Baumann K, Benz J, Gerber F, Huber W, Knoflach F, Messer J, Oroszlan K, Rauchenberger R, Richter WF, Rothe C, Urban M, Bardroff M, Winter M, Nordstedt C, Loetscher H (2012) Gantenerumab: a novel human anti-Aβ antibody demonstrates sustained cerebral amyloid-β binding and elicits cell-mediated removal of human amyloid-β. J Alzheimers Dis 28:49-69.
Boutajangout A, Quartermain D, Sigurdsson EM (2010) Immunotherapy targeting pathological tau prevents cognitive decline in a new tangle mouse model. J Neurosci 30:16559-16566.
Boxer AL, et al. (2019) Safety of the tau-directed monoclonal antibody BIIB092 in progressive supranuclear palsy: A randomised, placebo-controlled, multiple ascending dose phase 1b trial. Lancet Neurol 18:549-558.
Budd Haeberlein S, et al. (2022) Two randomized phase 3 studies of Aducanumab in early Alzheimer's disease. J Prev Alzheimers Dis 9:197-210.
Busche MA, Hyman BT (2020) Synergy between amyloid-β and tau in Alzheimer's disease. Nat Neurosci 23:1183-1193.
Cao LL, Guan PP, Liang YY, Huang XS, Wang P (2019) Cyclooxygenase-2 is essential for mediating the effects of calcium ions on stimulating phosphorylation of tau at the sites of Ser 396 and Ser 404. J Alzheimers Dis 68:1095-1111.
Cao Y, Yu F, Lyu Y, Lu X (2022) Promising candidates from drug clinical trials: Implications for clinical treatment of Alzheimer's disease in China. Front Neurol 13:1034243.
Carradori D, Balducci C, Re F, Brambilla D, Le Droumaguet B, Flores O, Gaudin A, Mura S, Forloni G, Ordoñez-Gutierrez L, Wandosell F, Masserini M, Couvreur P, Nicolas J, Andrieux K (2018) Antibody-functionalized polymer nanoparticle leading to memory recovery in Alzheimer's disease-like transgenic mouse model. Nanomedicine 14:609-618.
Choo IH, Chong A, Chung JY, Ha JM, Choi YY, Kim H (2022) A single baseline amyloid positron emission tomography could be sufficient for predicting Alzheimer's disease conversion in mild cognitive impairment. Psychiatry Investig 19:394-400.
Correa D, Scheuber MI, Shan H, Weinmann OW, Baumgartner YA, Harten A, Wahl AS, Skaar KL, Schwab ME (2023) Intranasal delivery of full-length anti-Nogo-A antibody: A potential alternative route for therapeutic antibodies to central nervous system targets. Proc Natl Acad Sci U S A 120:e2200057120.
Crestini A, Santilli F, Martellucci S, Carbone E, Sorice M, Piscopo P, Mattei V (2022) Prions and neurodegenerative diseases: A focus on Alzheimer's disease. J Alzheimers Dis 85:503-518.
Cullen NC, Novak P, Tosun D, Kovacech B, Hanes J, Kontsekova E, Fresser M, Ropele S, Feldman HH, Schmidt R, Winblad B, Zilka N (2024) Efficacy assessment of an active tau immunotherapy in Alzheimer's disease patients with amyloid and tau pathology: A post hoc analysis of the "ADAMANT" randomised, placebo-controlled, double-blind, multi-centre, phase 2 clinical trial. EBioMedicine 99:104923.
Dai Y, Lei C, Zhang Z, Qi Y, Lao K, Gou X (2022) Amyloid-beta targeted therapeutic approaches for Alzheimer's disease: long road ahead. Curr Drug Targets 23:1040-1056.
Dam T, Boxer AL, Golbe LI, Höglinger GU, Morris HR, Litvan I, Lang AE, Corvol JC, Aiba I, Grundman M, Yang L, Tidemann-Miller B, Kupferman J, Harper K, Kamisoglu K, Wald MJ, Graham DL, Gedney L, O'Gorman J, Haeberlein SB (2021) Safety and efficacy of anti-tau monoclonal antibody gosuranemab in progressive supranuclear palsy: A phase 2, randomized, placebo-controlled trial. Nat Med 27:1451-1457.

Dominy SS, et al. (2019) Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv 5:eaau3333.
Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H, Mohs R, Alzheimer's Disease Cooperative Study Steering Committee, Solanezumab Study Group (2014) Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 370:311-321.
Dujardin S, Hyman BT (2019) Tau prion-like propagation: state of the art and current challenges. Adv Exp Med Biol 1184:305-325.
Dunn B, Stein P, Cavazzoni P (2021) Approval of Aducanumab for Alzheimer disease-the FDA's perspective. JAMA Intern Med 181:1276-1278.
Ewers M, Franzmeier N, Suárez-Calvet M, Morenas-Rodriguez E, Caballero MAA, Kleinberger G, Piccio L, Cruchaga C, Deming Y, Dichgans M, Trojanowski JQ, Shaw LM, Weiner MW, Haass C, Alzheimer's Disease Neuroimaging Initiative (2019) Increased soluble TREM2 in cerebrospinal fluid is associated with reduced cognitive and clinical decline in Alzheimer's disease. Sci Transl Med 11:eaav6221.
Farlow M, Arnold SE, van Dyck CH, Aisen PS, Snider BJ, Porsteinsson AP, Friedrich S, Dean RA, Gonzales C, Sethuraman G, DeMattos RB, Mohs R, Paul SM, Siemers ER (2012) Safety and biomarker effects of solanezumab in patients with Alzheimer's disease. Alzheimers Dement 8:261-271.
Farlow MR, Andreasen N, Riviere ME, Vostiar I, Vitaliti A, Sovago J, Caputo A, Winblad B, Graf A (2015) Long-term treatment with active Aβ immunotherapy with CAD106 in mild Alzheimer's disease. Alzheimers Res Ther 7:23.
Fiala M, Restrepo L, Pellegrini M (2018) Immunotherapy of mild cognitive impairment by ω-3 supplementation: why are amyloid-β antibodies and ω-3 not working in clinical trials? J Alzheimers Dis 62:1013-1022.
Florian H, Wang D, Arnold SE, Boada M, Guo Q, Jin Z, Zheng H, Fisseha N, Kalluri HV, Rendenbach-Mueller B, Budur K, Gold M (2023) Tilavonemab in early Alzheimer's disease: Results from a phase 2, randomized, double-blind study. Brain 146:2275-2284.
Foroutan N, Hopkins RB, Tarride JE, Florez ID, Levine M (2019) Safety and efficacy of active and passive immunotherapy in mild-to-moderate Alzheimer's disease: A systematic review and network meta-analysis. Clin Invest Med 42:E53-E65.
Franklin M (2021) ICER report on Alzheimer's disease: Implications from a patient perspective. J Manag Care Spec Pharm 27:1618-1620.
Gandy S, Heppner FL (2013) Microglia as dynamic and essential components of the amyloid hypothesis. Neuron 78:575-577.
Gerson J, Kayed R (2016) Therapeutic approaches targeting pathological tau aggregates. Curr Pharm Des 22:4028-4039.
Ghosh S, Ali R, Verma S (2023) Aβ-oligomers: A potential therapeutic target for Alzheimer's disease. Int J Biol Macromol 239:124231.
Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, Eisner L, Kirby L, Rovira MB, Forette F, Orgogozo JM (2005) Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology 64:1553-1562.
Gnoth K, Geissler S, Feldhaus J, Taudte N, Ilse V, Zürner S, Greiser S, Braumann UD, Rahfeld JU, Cynis H, Schilling S (2022) Evidence for enhanced efficacy of passive immunotherapy against beta-amyloid in CD33-negative 5xFAD mice. Biomolecules 12:399.
Goate A (2006) Segregation of a missense mutation in the amyloid beta-protein precursor gene with familial Alzheimer's disease. J Alzheimers Dis 9:341-347.
Gu J, Congdon EE, Sigurdsson EM (2013) Two novel Tau antibodies targeting the 396/404 region are primarily taken up by neurons and reduce Tau protein pathology. J Biol Chem 288:33081-33095.
Gueorguieva I, Willis BA, Chua L, Chow K, Ernest CS, Shcherbinin S, Ardayfio P, Mullins GR, Sims JR (2023) Donanemab population pharmacokinetics, amyloid plaque reduction, and safety in participants with Alzheimer's disease. Clin Pharmacol Ther 113:1258-1267.
Guo T, Zhang D, Zeng Y, Huang TY, Xu H, Zhao Y (2020) Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Mol Neurodegener 15:40.
Hardy JA, Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. Science 256:184-185.
Hu Z, Yang J, Zhang S, Li M, Zuo C, Mao C, Zhang Z, Tang M, Shi C, Xu Y (2025) AAV mediated carboxyl terminus of Hsp70 interacting protein overexpression mitigates the cognitive and pathological phenotypes of APP/PS1 mice. Neural Regen Res 20:253-264.
Hung SY, Fu WM (2017) Drug candidates in clinical trials for Alzheimer's disease. J Biomed Sci 24:47.
Janssens J, Hermans B, Vandermeeren M, Barale-Thomas E, Borgers M, Willems R, Meulders G, Wintmolders C, Van den Bulck D, Bottelbergs A, Ver Donck L, Larsen P, Moechars D, Edwards W, Mercken M, Van Broeck B (2021) Passive immunotherapy with a novel antibody against 3pE-modified Aβ demonstrates potential for enhanced efficacy and favorable safety in combination with BACE inhibitor treatment in plaque-depositing mice. Neurobiol Dis 154:105365.
Ji C, Sigurdsson EM (2021) Current status of clinical trials on tau immunotherapies. Drugs 81:1135-1152.
Jorfi M, Maaser-Hecker A, Tanzi RE (2023) The neuroimmune axis of Alzheimer's disease. Genome Med 15:6.
Kfoury N, Holmes BB, Jiang H, Holtzman DM, Diamond MI (2012) Trans-cellular propagation of Tau aggregation by fibrillar species. J Biol Chem 287:19440-19451.
Klein G, Delmar P, Voyle N, Rehal S, Hofmann C, Abi-Saab D, Andjelkovic M, Ristic S, Wang G, Bateman R, Kerchner GA, Baudler M, Fontoura P, Doody R (2019) Gantenerumab reduces amyloid-β plaques in patients with prodromal to moderate Alzheimer's disease: A PET substudy interim analysis. Alzheimers Res Ther 11:101.
Koga S, Dickson DW, Wszolek ZK (2021) Neuropathology of progressive supranuclear palsy after treatment with tilavonemab. Lancet Neurol 20:786-787.
Kopeikina KJ, Hyman BT, Spires-Jones TL (2012) Soluble forms of tau are toxic in Alzheimer's disease. Transl Neurosci 3:223-233.
Kurkinen M (2023) Donanemab: Not two without a third. Adv Clin Exp Med 32:1085-1087.
Lacosta AM, Pascual-Lucas M, Pesini P, Casabona D, Pérez-Grijalba V, Marcos-Campos I, Sarasa L, Canudas J, Badi H, Monleón I, San-José I, Munuera J, Rodríguez-Gómez O, Abdelnour C, Lafuente A, Buendía M, Boada M, Tárraga L, Ruiz A, Sarasa M (2018) Safety, tolerability and immunogenicity of an active anti-Aβ(40) vaccine (ABvac40) in patients with Alzheimer's disease: A randomised, double-blind, placebo-controlled, phase I trial. Alzheimers Res Ther 10:12.
Lemere CA (2013) Immunotherapy for Alzheimer's disease: Hoops and hurdles. Mol Neurodegener 8:36.
Lewis J, Dickson DW (2016) Propagation of tau pathology: Hypotheses, discoveries, and yet unresolved questions from experimental and human brain studies. Acta Neuropathol 131:27-48.
Lipman NS, Jackson LR, Trudel LJ, Weis-Garcia F (2005) Monoclonal versus polyclonal antibodies: Distinguishing characteristics, applications, and information resources. ILAR J 46:258-268.
Liu E, et al. (2015) Amyloid-β 11C-PiB-PET imaging results from 2 randomized bapineuzumab phase 3 AD trials. Neurology 85:692-700.
Loeffler DA (2013) Intravenous immunoglobulin and Alzheimer's disease: What now? J Neuroinflammation 10:70.
Logovinsky V, Satlin A, Lai R, Swanson C, Kaplow J, Osswald G, Basun H, Lannfelt L (2016) Safety and tolerability of BAN2401--A clinical study in Alzheimer's disease with a protofibril selective Aβ antibody. Alzheimers Res Ther 8:14.
Long JM, Holtzman DM (2019) Alzheimer disease: an update on pathobiology and treatment strategies. Cell 179:312-339.
Long Y, Liu J, Wang Y, Guo H, Cui G (2025) The complex effects of miR-146a in the pathogenesis of Alzheimer's disease. Neural Regen Res 20:1309-1323.
Loureiro JC, Pais MV, Stella F, Radanovic M, Teixeira AL, Forlenza OV, de Souza LC (2020) Passive antiamyloid immunotherapy for Alzheimer's disease. Curr Opin Psychiatry 33:284-291.
Lyon MS, Milligan C (2019) Extracellular heat shock proteins in neurodegenerative diseases: New perspectives. Neurosci Lett 711:134462.
Marciani DJ (2015) Alzheimer's disease vaccine development: A new strategy focusing on immune modulation. J Neuroimmunol 287:54-63.
Marković M, Milošević J, Wang W, Cao Y (2023) Passive immunotherapies targeting amyloid-β in Alzheimer's disease: A quantitative systems pharmacology perspective. Mol Pharmacol 105:1-13.
Mashal Y, Abdelhady H, Iyer AK (2022) Comparison of tau and amyloid-β targeted immunotherapy nanoparticles for Alzheimer's disease. Biomolecules 12:1001.
McDade E, Cummings JL, Dhadda S, Swanson CJ, Reyderman L, Kanekiyo M, Koyama A, Irizarry M, Kramer LD, Bateman RJ (2022) Lecanemab in patients with early Alzheimer's disease: Detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. Alzheimers Res Ther 14:191.
Meredith ME, Salameh TS, Banks WA (2015) Intranasal delivery of proteins and peptides in the treatment of neurodegenerative diseases. AAPS J 17:780-787.
Mielke MM, Frank RD, Dage JL, Jeromin A, Ashton NJ, Blennow K, Karikari TK, Vanmechelen E, Zetterberg H, Algeciras-Schimnich A, Knopman DS, Lowe V, Bu G, Vemuri P, Graff-Radford J, Jack CR, Jr., Petersen RC (2021) Comparison of plasma phosphorylated tau species with amyloid and tau positron emission tomography, neurodegeneration, vascular pathology, and cognitive outcomes. JAMA Neurol 78:1108-1117.
Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW, Shcherbinin S, Sparks J, Sims JR, Brys M, Apostolova LG, Salloway SP, Skovronsky DM (2021) Donanemab in early Alzheimer's disease. N Engl J Med 384:1691-1704.
Monteiro C, Toth B, Brunstein F, Bobbala A, Datta S, Ceniceros R, Sanabria Bohorquez SM, Anania VG, Wildsmith KR, Schauer SP, Lee J, Dolton MJ, Ramakrishnan V, Abramzon D, Teng E (2023) Randomized phase II study of the safety and efficacy of semorinemab in participants with mild-to-moderate Alzheimer disease: Lauriet. Neurology 101:e1391-e1401.
Novak P, et al. (2017) Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: A randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Neurol 16:123-134.
Novak P, Kontsekova E, Zilka N, Novak M (2018a) Ten years of tau-targeted immunotherapy: The path walked and the roads ahead. Front Neurosci 12:798.
Novak P, Schmidt R, Kontsekova E, Kovacech B, Smolek T, Katina S, Fialova L, Prcina M, Parrak V, Dal-Bianco P, Brunner M, Staffen W, Rainer M, Ondrus M, Ropele S, Smisek M, Sivak R, Zilka N, Winblad B, Novak M (2018b) FUNDAMANT: an interventional 72-week phase 1 follow-up study of AADvac1, an active immunotherapy against tau protein pathology in Alzheimer's disease. Alzheimers Res Ther 10:108.
Novak P, et al. (2021) ADAMANT: a placebo-controlled randomized phase 2 study of AADvac1, an active immunotherapy against pathological tau in Alzheimer's disease. Nat Aging 1:521-534.
Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C (2003) Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology 61:46-54.
Ostrowitzki S, Lasser RA, Dorflinger E, Scheltens P, Barkhof F, Nikolcheva T, Ashford E, Retout S, Hofmann C, Delmar P, Klein G, Andjelkovic M, Dubois B, Boada M, Blennow K, Santarelli L, Fontoura P, SCarlet RoAD Investigators (2017) A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimers Res Ther 9:95.
Ostrowitzki S, et al. (2022) Evaluating the safety and efficacy of Crenezumab vs placebo in adults with early Alzheimer disease: Two phase 3 randomized placebo-controlled trials. JAMA Neurol 79:1113-1121.
Panza F, Solfrizzi V, Seripa D, Imbimbo BP, Lozupone M, Santamato A, Tortelli R, Galizia I, Prete C, Daniele A, Pilotto A, Greco A, Logroscino G (2016) Tau-based therapeutics for Alzheimer's disease: Active and passive immunotherapy. Immunotherapy 8:1119-1134.
Panza F, Dibello V, Sardone R, Castellana F, Zupo R, Lampignano L, Bortone I, Stallone R, Cirillo N, Damiani C, Altamura M, Bellomo A, Daniele A, Solfrizzi V, Lozupone M (2023) Clinical development of passive tau-based immunotherapeutics for treating primary and secondary tauopathies. Expert Opin Investig Drugs 32:625-634.
Park H, Cho B, Kim H, Saito T, Saido TC, Won KJ, Kim J (2023) Single-cell RNA-sequencing identifies disease-associated oligodendrocytes in male APP NL-G-F and 5XFAD mice. Nat Commun 14:802.
Parrocha CMT, Nowick JS (2023) Current peptide vaccine and immunotherapy approaches against Alzheimer's disease. Peptide science (Hoboken, NJ) 115:e24289.
Pegueroles J, Montal V, Bejanin A, Vilaplana E, Aranha M, Santos-Santos MA, Alcolea D, Carrió I, Camacho V, Blesa R, Lleó A, Fortea J, Alzheimer Disease Neuroimaging Initiative, Australian Imaging BaLRG (2021) AMYQ: An index to standardize quantitative amyloid load across PET tracers. Alzheimers Dement 17:1499-1508.

Perneczky R, Dom G, Chan A, Falkai P, Bassetti C (2024) Anti-amyloid antibody treatments for Alzheimer's disease. Eur J Neurol 31:e16049.
Portelius E, Bogdanovic N, Gustavsson MK, Volkmann I, Brinkmalm G, Zetterberg H, Winblad B, Blennow K (2010) Mass spectrometric characterization of brain amyloid beta isoform signatures in familial and sporadic Alzheimer's disease. Acta Neuropathol 120:185-193.
Qureshi IA, Tirucherai G, Ahlijanian MK, Kolaitis G, Bechtold C, Grundman M (2018) A randomized, single ascending dose study of intravenous BIIB092 in healthy participants. Alzheimers Dement (N Y) 4:746-755.
Rafii MS, et al. (2022) Safety, tolerability, and immunogenicity of the ACI-24 vaccine in adults with down syndrome: A phase 1b randomized clinical trial. JAMA Neurol 79:565-574.
Reiss AB, Montufar N, DeLeon J, Pinkhasov A, Gomolin IH, Glass AD, Arain HA, Stecker MM (2021) Alzheimer disease clinical trials targeting amyloid: lessons learned from success in mice and failure in humans. Neurologist 26:52-61.
Riviere ME, Langbaum JB, Turner RS, Rinne JO, Sui Y, Cazorla P, Ricart J, Meneses K, Caputo A, Tariot PN, Reiman EM, Graf A (2024) Effects of the active amyloid beta immunotherapy CAD106 on PET measurements of amyloid plaque deposition in cognitively unimpaired APOE ε4 homozygotes. Alzheimers Dement 20:1839-1850.
Roberts M, et al. (2020) Pre-clinical characterisation of E2814, a high-affinity antibody targeting the microtubule-binding repeat domain of tau for passive immunotherapy in Alzheimer's disease. Acta Neuropathol Commun 8:13.
Rosenberg RN, Fu M, Lambracht-Washington D (2018) Intradermal active full-length DNA Aβ42 immunization via electroporation leads to high anti-Aβ antibody levels in wild-type mice. J Neuroimmunol 322:15-25.
Rubin R (2021) Recently approved Alzheimer drug raises questions that might never be answered. JAMA 326:469-472.
Rudan Njavro J, Vukicevic M, Fiorini E, Dinkel L, Müller SA, Berghofer A, Bordier C, Kozlov S, Halle A, Buschmann K, Capell A, Giudici C, Willem M, Feederle R, Lichtenthaler SF, Babolin C, Montanari P, Pfeifer A, Kosco-Vilbois M, Tahirovic S (2022) Beneficial effect of ACI-24 vaccination on Aβ plaque pathology and microglial phenotypes in an amyloidosis mouse model. Cells 12:79.
Ryan JM, Grundman M (2009) Anti-amyloid-beta immunotherapy in Alzheimer's disease: ACC-001 clinical trials are ongoing. J Alzheimers Dis 17:243.
Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, Sabbagh M, Honig LS, Doody R, van Dyck CH, Mulnard R, Barakos J, Gregg KM, Liu E, Lieberburg I, Schenk D, Black R, Grundman M, Bapineuzumab 201 Clinical Trial Investigators (2009) A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 73:2061-2070.
Salloway S, et al. (2014) Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 370:322-333.
Salloway S, Chalkias S, Barkhof F, Burkett P, Barakos J, Purcell D, Suhy J, Forrestal F, Tian Y, Umans K, Wang G, Singhal P, Budd Haeberlein S, Smirnakis K (2022) Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating Aducanumab in patients with early Alzheimer disease. JAMA Neurol 79:13-21.
Sevigny J, et al. (2016) The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 537:50-56.
Shcherbinin S, Evans CD, Lu M, Andersen SW, Pontecorvo MJ, Willis BA, Gueorguieva I, Hauck PM, Brooks DA, Mintun MA, Sims JR (2022) Association of amyloid reduction after Donanemab treatment with tau pathology and clinical outcomes: The TRAILBLAZER-ALZ randomized clinical trial. JAMA Neurol 79:1015-1024.
Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, Collins EC, Solomon P, Salloway S, Apostolova LG, Hansson O, Ritchie C, Brooks DA, Mintun M, Skovronsky DM, TRAILBLAZER-ALZ 2 Investigators (2023) Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA 330:512-527.
Song C, Shi J, Zhang P, Zhang Y, Xu J, Zhao L, Zhang R, Wang H, Chen H (2022) Immunotherapy for Alzheimer's disease: Targeting β-amyloid and beyond. Transl Neurodegener 11:18.
Song G, Yang H, Shen N, Pham P, Brown B, Lin X, Hong Y, Sinu P, Cai J, Li X, Leon M, Gordon MN, Morgan D, Zhang S, Cao C (2020) An immunomodulatory therapeutic vaccine targeting oligomeric amyloid-β. J Alzheimers Dis 77:1639-1653.
Sperling R, Salloway S, Brooks DJ, Tampieri D, Barakos J, Fox NC, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Lieberburg I, Arrighi HM, Morris KA, Lu Y, Liu E, Gregg KM, Brashear HR, Kinney GG, Black R, Grundman M (2012) Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. Lancet Neurol 11:241-249.
Sperling RA, Donohue MC, Raman R, Rafii MS, Johnson K, Masters CL, van Dyck CH, Iwatsubo T, Marshall GA, Yaari R, Mancini M, Holdridge KC, Case M, Sims JR, Aisen PS (2023) Trial of Solanezumab in preclinical Alzheimer's disease. N Engl J Med 389:1096-1107.
Srivastava S, Ahmad R, Khare SK (2021) Alzheimer's disease and its treatment by different approaches: A review. Eur J Med Chem 216:113320.
Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, Lannfelt L, Bradley H, Rabe M, Koyama A, Reyderman L, Berry DA, Berry S, Gordon R, Kramer LD, Cummings JL (2021) A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther 13:80.
Teng E, Manser PT, Pickthorn K, Brunstein F, Blendstrup M, Sanabria Bohorquez S, Wildsmith KR, Toth B, Dolton M, Ramakrishnan V, Bobbala A, Sikkes SAM, Ward M, Fuji RN, Kerchner GA (2022) Safety and efficacy of semorinemab in individuals with prodromal to mild Alzheimer disease: a randomized clinical trial. JAMA Neurol 79:758-767.
Theunis C, Crespo-Biel N, Gafner V, Pihlgren M, López-Deber MP, Reis P, Hickman DT, Adolfsson O, Chuard N, Ndao DM, Borghgraef P, Devijver H, Van Leuven F, Pfeifer A, Muhs A (2013) Efficacy and safety of a liposome-based vaccine against protein Tau, assessed in tau.P301L mice that model tauopathy. PLoS One 8:e72301.
Theunis C, Adolfsson O, Crespo-Biel N, Piorkowska K, Pihlgren M, Hickman DT, Gafner V, Borghgraef P, Devijver H, Pfeifer A, Van Leuven F, Muhs A (2017) Novel phospho-tau monoclonal antibody generated using a liposomal vaccine, with enhanced recognition of a conformational tauopathy epitope. J Alzheimers Dis 56:585-599.
Tolar M, Abushakra S, Sabbagh M (2020) The path forward in Alzheimer's disease therapeutics: Reevaluating the amyloid cascade hypothesis. Alzheimers Dement 16:1553-1560.
Truong DJ, et al. (2021) Non-invasive and high-throughput interrogation of exon-specific isoform expression. Nat Cell Biol 23:652-663.
van Dyck CH, Sadowsky C, Le Prince Leterme G, Booth K, Peng Y, Marek K, Ketter N, Liu E, Wyman BT, Jackson N, Slomkowski M, Ryan JM (2016) Vanutide cridificar (ACC-001) and QS-21 adjuvant in individuals with early Alzheimer's disease: Amyloid imaging positron emission tomography and safety results from a phase 2 study. J Prev Alzheimers Dis 3:75-84.
van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T (2023) Lecanemab in early Alzheimer's disease. N Engl J Med 388:9-21.
Vandenberghe R, et al. (2016) Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. Alzheimers Res Ther 8:18.
Vandenberghe R, Riviere ME, Caputo A, Sovago J, Maguire RP, Farlow M, Marotta G, Sanchez-Valle R, Scheltens P, Ryan JM, Graf A (2017) Active Aβ immunotherapy CAD106 in Alzheimer's disease: A phase 2b study. Alzheimers Dement (N Y) 3:10-22.
Vander Zanden CM, Chi EY (2020) Passive immunotherapies targeting amyloid beta and tau oligomers in Alzheimer's disease. J Pharm Sci 109:68-73.
Vaz M, Silva V, Monteiro C, Silvestre S (2022) Role of Aducanumab in the treatment of Alzheimer's disease: challenges and opportunities. Clin Interv Aging 17:797-810.
Vitek GE, Decourt B, Sabbagh MN (2023) Lecanemab (BAN2401): An anti-beta-amyloid monoclonal antibody for the treatment of Alzheimer disease. Expert Opin Investig Drugs 32:89-94.
Vogt AS, Jennings GT, Mohsen MO, Vogel M, Bachmann MF (2023) Alzheimer's disease: A brief history of immunotherapies targeting amyloid β. Int J Mol Sci 24:3895.
Volloch V, Rits-Volloch S (2023) Effect of Lecanemab in early Alzheimer's disease: mechanistic interpretation in the amyloid cascade hypothesis 2.0 perspective. J Alzheimers Dis 93:1277-1284.
Waldmann H (2019) Human monoclonal antibodies: the benefits of humanization. Methods Mol Biol 1904:1-10.
Wang CY, Wang PN, Chiu MJ, Finstad CL, Lin F, Lynn S, Tai YH, De Fang X, Zhao K, Hung CH, Tseng Y, Peng WJ, Wang J, Yu CC, Kuo BS, Frohna PA (2017) UB-311, a novel UBITh(®) amyloid β peptide vaccine for mild Alzheimer's disease. Alzheimers Dement (N Y) 3:262-272.
Wang HC, Yu YZ, Liu S, Zhao M, Xu Q (2016) Peripherally administered sera antibodies recognizing amyloid-β oligomers mitigate Alzheimer's disease-like pathology and cognitive decline in aged 3× Tg-AD mice. Vaccine 34:1758-1766.
Wang L, Lu D, Wang X, Wang Z, Li W, Chen G (2024) The effects of nitric oxide in Alzheimer's disease. Med Gas Res 14:186-191.
Weekman EM, Sudduth TL, Caverly CN, Kopper TJ, Phillips OW, Powell DK, Wilcock DM (2016) Reduced efficacy of anti-Aβ immunotherapy in a mouse model of amyloid deposition and vascular cognitive impairment comorbidity. J Neurosci 36:9896-9907.
West T, Hu Y, Verghese PB, Bateman RJ, Braunstein JB, Fogelman I, Budur K, Florian H, Mendonca N, Holtzman DM (2017) Preclinical and clinical development of ABBV-8E12, a humanized anti-tau antibody, for treatment of Alzheimer's disease and other tauopathies. J Prev Alzheimers Dis 4:236-241.
Wiessner C, Wiederhold KH, Tissot AC, Frey P, Danner S, Jacobson LH, Jennings GT, Lüönd R, Ortmann R, Reichwald J, Zurini M, Mir A, Bachmann MF, Staufenbiel M (2011) The second-generation active Aβ immunotherapy CAD106 reduces amyloid accumulation in APP transgenic mice while minimizing potential side effects. J Neurosci 31:9323-9331.
Willbold D, Strodel B, Schröder GF, Hoyer W, Heise H (2021) Amyloid-type protein aggregation and prion-like properties of amyloids. Chem Rev 121:8285-8307.
Willis BA, Lo AC, Dage JL, Shcherbinin S, Chinchen L, Andersen SW, LaBell ES, Perahia DGS, Hauck PM, Lowe SL (2023) Safety, tolerability, and pharmacokinetics of zagotenemab in participants with symptomatic Alzheimer's disease: a phase I clinical trial. J Alzheimers Dis Rep 7:1015-1024.
Winblad B, Andreasen N, Minthon L, Floesser A, Imbert G, Dumortier T, Maguire RP, Blennow K, Lundmark J, Staufenbiel M, Orgogozo JM, Graf A (2012) Safety, tolerability, and antibody response of active Aβ immunotherapy with CAD106 in patients with Alzheimer's disease: Randomised, double-blind, placebo-controlled, first-in-human study. Lancet Neurol 11:597-604.
Wisniewski T, Goñi F (2014) Immunotherapy for Alzheimer's disease. Biochem Pharmacol 88:499-507.
Wisniewski T, Goñi F (2015) Immunotherapeutic approaches for Alzheimer's disease. Neuron 85:1162-1176.
Wojtunik-Kulesza K, Rudkowska M, Orzeł-Sajdłowska A (2023) Aducanumab-hope or disappointment for Alzheimer's disease. Int J Mol Sci 24:4367.
Yang T, Dang Y, Ostaszewski B, Mengel D, Steffen V, Rabe C, Bittner T, Walsh DM, Selkoe DJ (2019) Target engagement in an alzheimer trial: Crenezumab lowers amyloid β oligomers in cerebrospinal fluid. Ann Neurol 86:215-224.
Yang X, Zhangyi Z, Yu A, Zhou Q, Xia A, Qiu J, Cai M, Chu X, Li L, Feng Z, Luo Z, Sun G, Zhang J, Geng M, Chen S, Xie Z (2024) 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:e14847.
Ye J, Wan H, Chen S, Liu GP (2024) Targeting tau in Alzheimer's disease: from mechanisms to clinical therapy. Neural Regen Res 19:1489-1498.
Yu HJ, Dickson SP, Wang PN, Chiu MJ, Huang CC, Chang CC, Liu H, Hendrix SB, Dodart JC, Verma A, Wang CY, Cummings J (2023) 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 94:104665.
Yu YJ, Watts RJ (2013) Developing therapeutic antibodies for neurodegenerative disease. Neurotherapeutics 10:459-472.
Zhang H, Wei W, Zhao M, Ma L, Jiang X, Pei H, Cao Y, Li H (2021) Interaction between Aβ and tau in the pathogenesis of Alzheimer's disease. Int J Biol Sci 17:2181-2192.
Zhao J, Liu X, Xia W, Zhang Y, Wang C (2020) Targeting amyloidogenic processing of APP in Alzheimer's disease. Front Mol Neurosci 13:137.

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靶向β-淀粉样蛋白和 Tau 蛋白病的阿尔茨海默病免疫治疗研究进展
文章特色分析

一、文章重要性

1. 聚焦阿尔茨海默病核心病理机制

文章系统综述了 AD 两大核心病理蛋白——Aβ 和 Tau 的免疫治疗进展，涵盖了从基础研究到临床转化的全过程，具有明确的临床与科研指导价值。

2. 回应未满足的临床需求

AD 目前缺乏有效治愈手段，传统药物仅能缓解症状。本文重点介绍了近年来获批或进入临床试验的免疫疗法（如 lecanemab、donanemab、aducanumab），为临床治疗提供了新方向。

3. 推动早期干预理念

文章强调在 AD 早期甚至无症状阶段进行免疫干预的重要性，推动 AD 治疗策略从“对症”向“对因”转变，具有重要的公共卫生意义。

二、文章创新性特色

1. 全面梳理 Aβ 与 Tau 免疫治疗进展

不仅涵盖已获批的抗体药物（如 aducanumab、lecanemab），还系统总结了多种处于临床试验阶段的主动与被动免疫策略，包括疫苗和单克隆抗体。

2. 强调联合治疗与多靶点策略

文章提出 Aβ 与 Tau 病理之间存在协同作用，联合靶向两者可能比单一靶点更有效，为未来 AD 治疗提供了新思路。

3. 深入分析免疫治疗的挑战与对策

如血脑屏障穿透性、抗体特异性、免疫相关不良反应（如 ARIA）等，并探讨了纳米技术、鼻内给药、电穿孔等新型递送系统的潜力。

4. 提出“早期诊断+早期干预”新模式

结合生物标志物（如 PET、脑脊液检测）和认知量表，推动 AD 防治关口前移，具有前瞻性。

三、对学科的启示

1. 免疫治疗成为 AD 研究的新支柱

文章系统展示了免疫疗法在 AD 治疗中的潜力，标志着神经退行性疾病治疗范式的转变——从神经递质调节到免疫调节。

2. 推动精准医疗与个体化治疗

通过分析不同抗体对不同病理蛋白形式的特异性，提示未来需根据患者病理亚型、APOE 基因型等选择个体化治疗方案。

3. 促进多学科交叉融合

文中涉及免疫学、神经科学、生物工程、药物递送等多个领域，鼓励跨学科合作以突破治疗瓶颈。

4. 为其他神经退行性疾病提供借鉴

如帕金森病、额颞叶痴呆等同样存在蛋白异常聚集的疾病，可借鉴 AD 免疫治疗的策略与经验。

总结

该文是一篇系统、前沿且具有临床指导意义的综述，不仅总结了当前 Aβ 和 Tau 免疫治疗的最新进展，还深入剖析了其机制、挑战与未来方向。其创新性在于整合多靶点治疗策略、强调早期干预、并提出新型递送技术与联合疗法，对推动 AD 乃至整个神经退行性疾病领域的研究与治疗具有重要启示作用。