Review

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Monoclonal antibody therapy for Alzheimer's disease focusing on intracerebral targets

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SUMMARY Alzheimer's disease (AD) is one of the most common neurodegenerative diseases. Due to the complexity of the disorder and the presence of the blood-brain barrier (BBB), its drug discovery and development are facing enormous challenges, especially after several failures of monoclonal antibody (mAb) trials. Nevertheless, the Food and Drug Administration's approval of the mAb aducanumab has ushered in a new day. As we better understand the disease's pathogenesis and identify novel intracerebral therapeutic targets, antibody-based therapies have advanced over the past few years. The mAb drugs targeting β-amyloid or hyperphosphorylated tau protein are the focus of the current research. Massive neuronal loss and glial cell-mediated inflammation are also the vital pathological hallmarks of AD, signaling a new direction for research on mAb drugs. We have elucidated the mechanisms by which AD-specific mAbs cross the BBB to bind to targets. In order to investigate therapeutic approaches to treat AD, this review focuses on the promising mAbs targeting intracerebral dysfunction and related strategies to cross the BBB.

Keywords Alzheimer's disease, blood-brain barrier, pathological mechanism, monoclonal antibodies, target

1. Introduction

Alzheimer's disease (AD), as the leading neurodegenerative disease, is a major cause of dementia that occurs in the middle-aged and elderly population (*1*). As aging of the population intensifies, the disease's incidence increases yearly, seriously affecting the life quality of patients and their families (*2*). The pathogenesis of AD is complex and has yet to be fully elucidated. Hyperphosphorylated tau, β-amyloid (Aβ) plaques, and neuroinflammation are considered core pathological factors (*3,4*).

Over the past few years, research has focused on early detection, diagnosis, and treatment of AD (*5*). Immune therapy, and especially disease-modifying therapy, has played an essential role in disease prevention and treatment due to its unique target specificity. Along with the discovery of the intracerebral targets and biomarkers of AD, antibody-based drugs have shed new light on AD, and this is especially true since the approval of the monoclonal antibody (mAB) aducanumab for AD. As a highly homogeneous antibody produced from a single B cell clone, mAbs work at a specific epitope (*6*), which means they have a high level of target specificity. However, the blood-brain barrier (BBB), a highly selective membrane barrier that prevents 98% of small-molecule drugs and almost 100% of large-molecule drugs from crossing (*7*), poses a considerable challenge to drug development.

Several reviews have discussed advances in research on mAbs against Aβ (*8-11*). However, new etiologic and pathological factors have been uncovered based on the Aβ hypothesis over the last two decades. At the same time, new strategies have emerged to bypass the BBB for better efficacy. Based on the pathogenesis and targets of AD, this review has summarized the intracerebral dysfunction of the disease, outlined the use of AD-specific mAbs, and discussed the strategies by which antibody drugs cross the BBB to treat AD.

2. Pathogenesis of AD

Although the pathogenesis of AD remains unclear, intracerebral senile plaques, neurofibrillary tangles (NFTs), and concomitant neuroinflammation are believed

to play significant roles (*12,13*). Later, morphological changes happen, including atrophied brain tissue, reduced weight, and even numerous neuronal losses in the brain (*14*). Although the factors and mechanisms that cause these changes remain unclear, age is undoubtedly the most important one. Several factors, including sex, genetic mutations, and lifestyle habits, affect neuronal regeneration through changes in hormone levels, systemic validation, and so on, contributing to the formation of senile plaques and NFS and activation of neuroinflammation in the brain (*15-17*).

2.1. Aβ hypothesis

Evidence has indicated that Aβ peptide plays a vital role in the pathogenesis of AD, so Aβ is often used as a neuropathological diagnostic criterion for AD (*18,19*). Physiologically, Aβ is widely present in the body and brain and is involved in neuronal growth, regulation of synaptic function, protection against oxidative stress, and even the innate immune system (*20,21*). Aβ production and elimination are altered with aging, leading to downstream activation. A study has indicated that Aβ promotes astrocyte senescence *via* NLRP3 pathway activation (*22*). Moreover, Aβ1-42 oligomers induce secretion of senescence factors such as p16 and SA-β-gal in adult mouse hippocampal neural stem cells (*23*). Presenilin (PSEN) 1 and PSEN2, two presenilin genes, can affect amyloid precursor protein (APP) cleavage by influencing the expression of β-secretase and γ-secretase. In AD encephalopathy, APP is successively cleaved by β-secretase and γ-secretase to produce neurotoxic monomer Aβ (*24*). These products from anomalous enzyme shearing lead to monomeric Aβ misfolding, and the consequent oligomers further fold into protofibrils and fibrils, eventually forming amyloid plaques to induce a cytotoxic effect (Figure 1).

Aβ accumulation is associated with AD processes, both in familial and sporadic AD (*25-27*). The gene mutations, such as PSEN 1, PSEN2, and APP, are also associated with Aβ aggregation in familial AD, causing cognitive impairment in patients with AD carrying these mutations (*28*). Based on the amyloid hypothesis, excessive Aβ plaque deposition in the brain can induce a series of downstream pathological changes, such as tau-associated network disruption, chronic inflammation, failure of metabolic activity, abnormal microglial activation, oxidative stress, cholesterol-associated neuronal distress, and autophagy deficit (*8,29,30*). Additional studies have indicated that the

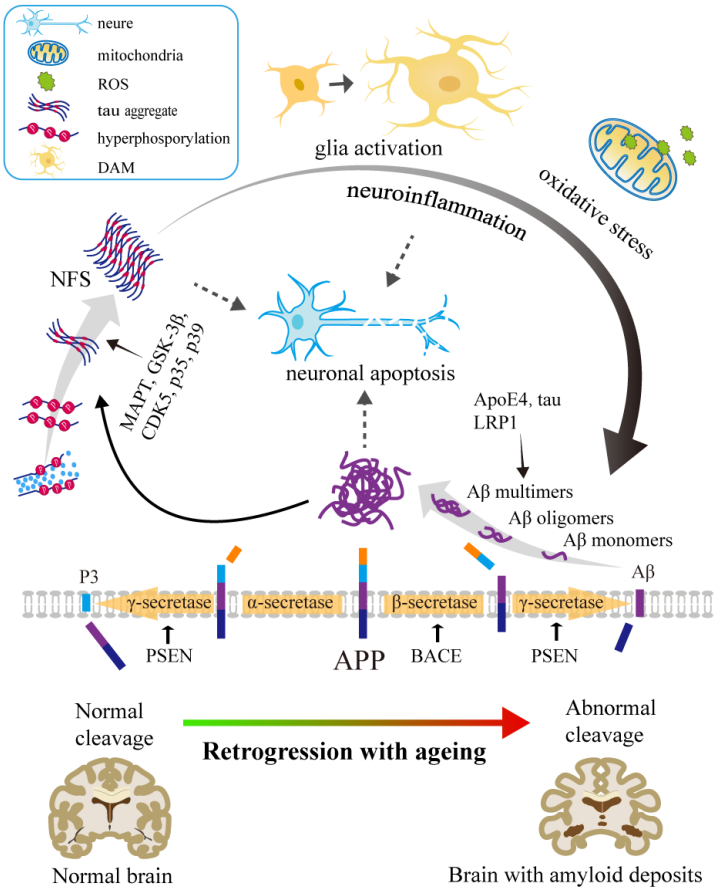

Figure 1. AD pathological processes. Accompanying aging, abnormal APP clearance contributes to Aβ accumulation, which induces AD pathological processes such as tau accumulation, abnormal glial activation, release of inflammatory factors, and neuronal damage. PSEN and BACE genes affect the formation of Aβ monomers by regulating γ-secretase and β-secretase, while ApoE, tau, and neuroinflammation promote the accumulation of Aβ. P3, a non-amyloidogenic peptide, is a cleavage product of APP and lacks pathological effects due to its solubility.

damage is caused by soluble Aβ, including oligomers consisting of a small number of Aβ peptides, rather than an accumulation of aggregated Aβ (*31,32*), and especially in early neuronal toxicity (*33*). Injecting soluble Aβ42 oligomers isolated from the brains of patients with AD into healthy rats impairs memory, reduces the number of synapses, and enhances long-term synaptic inhibition in the rodent hippocampus (*34*). This may be because Aβ localization induces mitochondrial dysfunction by impeding the electron transport chain of the mitochondrial membrane and by increasing reactive oxygen species (ROS) production, finally leading to neuronal death (*35,36*).

Large-scale genome-wide studies have identified sporadic AD as the most commonly occurring type of dementia worldwide and a multifactorial disease caused by diverse genetic factors (*37,38*). ApoE, a lipid and cholesterol carrier that responds to transporting nutrients from astrocytes to neurons *via* transmembrane transport and regulating neurons in the central nervous system, is highly expressed by glial cells around Aβ plaque (*39*). *In vitro* and *in vivo* studies have indicated that ApoE isoform, especially ApoE4, promotes the progression of Aβ peptides to Aβ oligomers, protofibrils, and fibrils and inhibits the clearance and enzymatic degradation of intracerebral Aβ (*40,41*). Neurons carrying ApoE4 grow at a lower rate and density than those carrying ApoE3, making individuals with the ApoE4 more vulnerable to attacks of AD (*42*). Moreover, neprilysin and insulin-degrading enzymes are required for Aβ clearance, and the expression of ApoE4 appears to decrease the activity of both enzymes, unlike in cadavers carrying the non-ApoE gene (*43,44*).

In summary, Aβ has a wide range of pathologic roles in AD progression. Although the exact mechanism remains unclear, clinical trial results have indicated that reducing either soluble Aβ, or amyloid plaques, or both, in the brain to non-pathological levels — that is, below the level that provokes tau pathology spread — may be of therapeutic benefit to patients with AD (*45*).

2.2. Tau protein-related mechanisms

Tau protein, enriched in axons, regulates intraneuronal transport, microtubule dynamics, and synaptic transmission. However, pathological tau protein is the basis of intracellular NFTs, which are another contributor to AD pathogenesis. Tau protein has a microtubule-binding domain expressed by a continuous sequence of repetitive conserved sequences at the carboxyl terminus (*46,47*). These conserved sequences, as the sites for microtubule binding, constitute the structure of mature and stable microtubules (*48*). Tau protein usually occurs as monomers, small oligomers, and pairs of helical and straight filaments. They tend to dissociate from microtubules and tangle in the neuro when their excessive or abnormal phosphorylation forms pathological structures (*49,50*). Once the tau protein loses its ability to bind to microtubules, the neural cell architecture is destroyed, leading to disruption of signal processing and transport of the substance between neuronal synapses, eventually inducing neuronal apoptosis (*51*). Therefore, hyperphosphorylated pathological tau protein can degenerate neurons due to its cytotoxicity and disturbance of microtubules (*52*). Hyperphosphorylated tau proteins are also thought to spread because they are taken up by surrounding normal neurons *via* synaptic transmission, exosomal release, or direct extracellular secretion, leading to abnormal aggregation of tau proteins in healthy neurons and the continuous production of pathological tau (*46*). Thus, hyperphosphorylated tau protein has become a biomarker for disease diagnosis (*53*). Although the exact mechanisms of tau hyperphosphorylation are still unclear, Aβ appears to be involved, according to the amyloid hypothesis during cascade (*54*).

However, a differing view is that tau pathology may be a prerequisite for causing Aβ in AD. Autopsies have revealed that tau pathology appears to precede Aβ accumulation and that it is closely related to the patient's cognitive impairment. The reason why is related to the regulation of kinases and genetic variation (*55*). Several kinases are involved in accomplishing the phosphorylation of tau protein. Glycogen synthase kinase-3β (GSK-3β) and cyclin dependent kinase 5 (CDK5) are two of the most critical kinases. GSK-3β regulates tau phosphorylation mainly *via* PI3K/AKT/GSK-3β pathway, while CDK5 is regulated by p35 and p39. Once overactivated, the kinases promote tau hyperphosphorylation and cause neuronal injury, Aβ aggregation, inflammation, and mitochondrial dysfunction (*56*). MAPT, another gene associated with tau pathology, prompts tau expression as 3R (exon ten exclusion) or 4R (exon ten inclusion), two isoforms associated with tau aggregation (*57*). The pathologic changes of AD contain approximately equal amounts of 3R-tau and 4R-tau, which are thought to play an important role in AD pathology (*58*). Misrepresentation and mistranslation of MAPT lead to 3R and 4R expression (*59*). Moreover, ApoE4 promotes tau-induced neurodegeneration and atrophy in that ApoE affects the ability of tau to bind to LRP1, accelerating tau diffusion (*60,61*). In addition, inflammation is a factor that promotes tau hyperphosphorylation (*62*). Tau protein aggregation is associated with cellular senescence in the brain. Aging-associated secretory phenotypes and NF-κB activation upregulate tau by impairing mitochondrial function (*63*). In addition, upregulation of the Cdkn2a gene is related to NFT formation (*63*).

2.3. The roles of inflammatory factors

Complex and prolonged neuroinflammation also contributes to AD pathogenesis. Neuroinflammation

in the early development of AD clears neurotoxins such as Aβ and tau by phagocytosis; in the later stages, however, persistent neuroinflammation is a facilitator of neurological damage (*64*). As the resident immune cells, microglia and astrocytes are housekeeping phagocytes, playing a crucial role in neuroinflammation. Typically, microglia can remove diseased neurons by phagocytosis and endocytosis (*65*). Astrocytes play an important role in the maintenance of cellular metabolism homeostasis, providing energy substrates and nutrition to neurons. In addition, astrocytes, as the composition of the BBB, are involved in regulating the pH level, energy balance, neurotransmitter removal, and metal ion balance of the brain (*66*). Microglia and astrocytes can respond accordingly to poisons such as Aβ or tau. They release pro-inflammatory factors to accelerate the metabolism of these toxins, thereby maintaining homeostasis in the brain (*13*). Moreover, microglia secrete glial-derived and brain-derived neurotrophic factors to repair neurons (*67*). Once neuroprotective feedback is disrupted, however, microglia and astrocytes are overactivated in response to oligomer Aβ and tau, leading to chronic neuroinflammation that can damage neurons and induce synaptic death and nerve cell senescence (*68,69*). The complement system and multiple gene mutations are also involved (*4*). Furthermore, lifestyle habits and diseases may be other promoters (*70*).

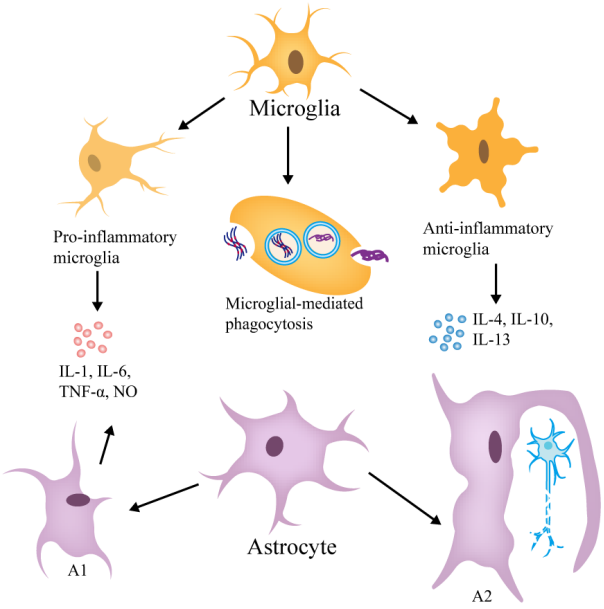

Figure 2. The roles of microglia and astrocytes in different phenotypes after activation. Pro-inflammatory microglia and A1 astrocytes secrete pro-inflammatory factors such as IL-1, IL-6, TNF-α, and NO. Correspondingly, anti-inflammatory microglia release IL-4, IL-10, and IL-13 to counteract inflammation. Astrocyte cells are activated in the A2 phenotype and then grow to form a physical barrier around the lesion, blocking the propagation of pathologic products.

2.3.1. Abnormal activation of glial cells

As the resident immune cells, microglia and astrocytes are housekeeping phagocytes, playing a crucial role in neuroinflammation (Figure 2). Disease-associated microglia (DAM) are aberrantly activated and associated with neuroinflammation and Aβ aggregates (*71*). They interact with Aβ to release pro-inflammatory factors, including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and reactive nitrogen oxides, mediating neuroinflammation and interfering with synaptic sprouting and axonal growth (*72*). Moreover, abnormal microglia activation may be associated with tau hyperphosphorylation (*73*), which may be related to the fact that microglia trigger the NLRP3 pathway during Aβ clearance (*74*). Astrocytes play an equally important role in AD pathology and chronic inflammation. Similar to microglia, astrocytes have different phenotypes after pathological stimulation in AD. The A1 astrocyte phenotype is dominated by NF-κB pathway-mediated inflammation, and the A2 astrocyte is dominated by gliosis dependent on the signal transducer and activator of transcription 3 pathway (*69*). Typically, A1 astrocytes are associated with neurological injury, while A2 is associated with neuroprotection in AD. A1 astrocytes induce neuronal death by releasing inflammatory factors and activating the complement system (*75*). Stimulated by IL-1α and TNFα released by microglia, A1 astrocytes are activated, which further induces neuronal death and phagocytosis (*75*). In addition, they activates the complement system and induce long-term neuroinflammation (*75*). A2 astrocytes enlarge upon activation and exhibit overexpression of glial fibrillary acidic protein. These proteins form a physical barrier around the lesion, blocking the spread of pathologic products (*76*). In turn, neuroinflammation exacerbates the accumulation of Aβ and tau. Inflammatory factors such as IL-1β, lipopolysaccharide, and prostaglandin E2 reduce the oligomeric Aβ and tau uptake by microglia, promoting the accumulation of pathological products (*76,77*).

2.3.2. Involvement of the complement system

The complement system plays a regulatory role in glial cell-mediated neuroinflammation. Aβ and tau can activate the complement system. When Aβ activates the NF-κB pathway, A1 astrocytes release C3, which can aggravate tau accumulation and microglia activation (*78,79*). In contrast, complement C3aR inactivation on the surface of microglia and astrocytes attenuates tau pathology and reverses dysregulated immune networks in a model of tau disease (*80*). DAM in turn mediate neuronal clearance by astrocytes through the release of C1q (*69,81*). Inhibition of C1q, C3, or the microglia complement receptor CR3 reduces the number of phagocytic microglia (*82*). C5a induces a chronic inflammatory state in microglia by binding to the receptor C5aR1, which causes cell lysis by forming the membrane attack complex MAC. Inhibition

of the C5a cascade response blocks neuronal damage by the complement system (*83*). Therefore, the complement system may be a potential therapeutic target for AD.

2.3.3. Receptors and genes regulate neuroinflammation

Specific receptor expression and genetic variants are associated with aberrantly activated glial cells. Toll-like receptor (TLR) 4 on the surface of microglia is recognized by Aβ, which can prolong microglia activation, increase phagocytosis and cytokine production, and stimulate Aβ accumulation (*76,84*). Inflammasomes are involved in initiating and maintaining the innate immune response and activating IL-1β and IL-18 (*85*). The NLRP3 inflammasome consists of a sensor (NLRP3), an adaptor (apoptosis-associated speck-like protein (ASC) or PYARD), and an effector (caspase 1) (*86*). Aβ binds to ASC to form the ACS-Aβ complex and activates NF-κB (*87*), which promotes NLRP3 activation and the release of inflammatory mediators such as IL-1β and IL-18 from microglia to induce apoptosis (*88*). Studies have indicated that ACS inhibition can mitigate Aβ aggregation (*89,90*). Crosstalk among TLR4, the NLRP3 inflammasome, and complements promotes neuroinflammation in AD. In addition, aggregated Aβ phagocytosed by microglia damages lysosomes and leaks into the cytoplasm, also contributing to inflammasome activation. Inflammasome-induced cellular pyroptosis leads to the secretion of IL-1β and ASC speckles, which bind to Aβ, leading to further Aβ aggregation. This vicious cycle exacerbates the pathology of Aβ (*87*).

Triggering receptor expressed on myeloid cells 2 (TREM2) may be an AD protective receptor because of its anti-inflammatory functions. TREM2 interacts with the junction proteins DAP12 and DAP10 to affect tyrosine phosphorylation and promote microglial chemotaxis and phagocytosis of toxicants and damaged synapses (*91*). TREM2-associated pathway activation modulates microglia phagocytosis, accelerates Aβ plaque clearance, and ameliorates AD pathology (*92-94*). In addition, TREM2 inhibits tau protein phosphorylation by inhibiting GSK-3β, a tau phosphorylation-related kinase (*95*). In contrast, reduced expression or mutation of TREM2 is associated with high levels of pro-inflammatory mediators such as TNF-α, IL-6, and IL-1 (*96*). Mutations and polymorphisms of the TREM2 gene have been associated with a significantly increased risk of AD; among the various variants, the R47H variant is associated with decreased Aβ, tau clearance, and severe neuroinflammation (*97*). Thus, activation of TREM2 may be a potential therapeutic target of AD (*98*).

ApoE also plays a crucial role in neuroinflammation. Microglia and astrocytes encoded with the ApoE4 variant display an immunomodulatory effect, actively participating in neuroinflammation. Transcriptomics studies have suggested that gene expression of ApoE is altered during DAM activation (*99,100*). In addition, ApoE4 mediates higher levels of inflammatory factors (TNF-α, IL-6, and IL-1β) than other phenotypes (*101*). In addition, microglia expressing ApoE4 but not ApoE3 inhibit CNS-associated macrophages from responding to pathological changes in AD (*102*). Animal models have indicated that mice expressing ApoE4 exhibit increased lipid droplet formation and synaptic dysfunction in the brain, while mice expressing ApoE3 have improved memory and synaptic plasticity (*102,103*). ApoE4 is also associated with astrocytes with a lower autophagic flux, reducing the clearance of neurotoxic substances such as Aβ (*104*). In addition, the interplay between ApoE4 and Aβ oligomers may result in synaptic loss. When ApoE expression is eliminated in astrocytes during the phase of Aβ accumulation, the burden of Aβ plaques can be reduced (*105*), indicating its vital role in inflammatory response (*106*). This may explain the poor efficacy and high rate of edema as a complication of existing monotherapy antibody drugs for patients with the ApoE4 mutation (*107,108*). In conclusion, ApoE is an essential modulator in the AD process and is mainly considered to be a risk factor, while ApoE2 has more protective properties.

2.3.4. Impact of lifestyle and diseases

Neuroinflammation in AD is also associated with other factors such as aging, alcoholism, and chronic life stress. Animal experiments have indicated that sustained proliferation of DAMs increases βgal activity, a senescence-associated transcriptional signature, and telomere shortening, leading to cellular senescence (*109*). Kanchan discovered dark microglia, a new phenotype predominantly associated with pathological states, that are expressed primarily in chronic stress, aging, and AD (*110*). In addition, alcohol abuse affects microglia-mediated neuroinflammation, leading to synapse elimination and exacerbating cognitive impairment (*111*). Chronic life stress induces stressful heterogeneity in astrocytes, leading to the pyrolytic death of astrocytes, which may be related to stress-induced changes in glucocorticoids that affect astrocyte cell-associated targets (*112*). Interestingly, aside from brain inflammation, systemic inflammation affects AD as well. Gut flora interact with AD *via* multiple pathways. Alterations in gut flora activate pro-inflammatory cytokines, alter the systemic inflammatory milieu, and trigger systemic inflammation-derived pro-inflammatory factors that enhance neuroinflammation (*113,114*). Intestinal permeability is also increased when gut flora are altered, resulting in the transfer of Aβ oligomers from the gut to the brain (*115*). In addition, AD may be complicated by obesity and type 2 diabetes. Those conditions cause aberrant activation of the NLRP3 signaling pathway, which contributes to the activation of the inflammatory vesicle complex and the release of IL-1β and IL-18; NLRP3 pathway activation may be key

to the link between AD and obesity and type 2 diabetes (*116*). In short, inflammation is part of AD development that cannot be ignored.

3. Use of mAbs in AD

A breakthrough in immunology was the hybridoma technology developed by Milstein and Kohler in 1975, allowing the production of unlimited quantities of mAbs (*117*). Due to their target specificity, mAbs have become powerful tools in biochemistry, molecular biology, and medicine today, and especially for preventing and treating AD. Passive immunization (antibodies) and active immunization (vaccines) are currently used clinically to inhibit or clear Aβ accumulation and hyperphosphorylated tau protein. In addition, antioxidants or anti-free radical drugs are also considered potential drugs for the induction of oxidative damage in current targeted therapy (*118*) (Table 1).

3.1. mAbs against the Aβ proteins

3.1.1. mAbs reduce Aβ aggregation

Therapies targeting Aβ have been the focus of AD treatment for the past 30 years, along with passive immunization using exogenous mAbs (*119*). Over the past few years, Aβ immunotherapy has mainly included γ-synthase inhibitors, γ-secretase and β-secretase inhibitors, and Aβ aggregation inhibitors. These inhibitors are designed to reduce Aβ formation and promote Aβ degradation in the brain, that is, to regulate the cell signaling mechanism, promote the α-secretase pathway, and inhibit the β-secretase pathway. mAb drugs targeting Aβ proteins have been extensively developed and have undergone human trials over the past 15 years.

Drugs for Aβ clearance include aducanumab, lecanemab, donanemab, crenezumab, solanezumab, gantenerumab, bapineuzumab, and GSK933776. Their targets are different stages of Aβ formation: monomers, oligomers, and plaques. Due to differences in targeted epitopes, drugs have differing ability to bind to and clear different forms of Aβ (*3*). Aβ is highly heterogeneous. Broadly speaking, the N-terminus of Aβ is exposed during aggregation and folding, while the C-terminus is hidden inside (*120*). Therefore, most of the drugs target epitopes at the N-terminus of Aβ, *e.g.*, aducanumab (3-7), lecanemab (1-16), and donanemab (p3-7). Aducanumab and lecanemab can bind equally to monomers, oligomers, and plaques of Aβ, while donanemab is designed to target pyroglutamate-modification of Aβ(AβN3pE) found almost exclusively in Aβ plaque. Thus, donanemab targets existing amyloid plaques. In addition, gantenerumab can bind two discontinuous regions of Aβ located at the N- and C-termini, respectively.

The strategy for selecting the N-terminal as an epitope was found to be feasible in advanced clinical trials. In two large randomized double-blind controlled phase 3 trials with more than 3,200 patients with early AD, results indicated a significant dose- and time-dependent reduction in pathophysiological markers but a low clinical response rate after aducanumab treatment (*121*). In contrast, lecanemab is designed to respond to the E22G (APP E693G) mutation, a pathogenic missense mutation that affects the twenty-second amino acid of Aβ peptides. Patients carrying the E22G mutation have a high level of Aβ protofibrils and lecanemab has a higher selectivity for it. An 18-month multicenter double-blind phase 3 trial including 1,795 subjects with early AD found that intravenous lecanemab every two weeks (10 mg/kg) significantly reduced the brain amyloid burden and score on the 14-item cognitive subscale of the AD Assessment Scale (ADAS-cog14). However, the sum of boxes on the Clinical Dementia Rating (CDR-SB) scale, which was the primary outcome, did not change markedly (*122*). A study reported infusion-related reactions in 26.4% of subjects and amyloid-related imaging abnormalities (ARIA) with edema in 12.6% (*122*). In an open-label trial, disease progression in patients with early AD can be mitigated by lecanemab over 24 months after the drug was discontinued (*123*). The study also suggested that lecanemab is better at maximum plaque removal, regardless of the ApoE4 status (*123*). Even APOEε4 carriers might respond better to lecanemab (*120*). In addition, TRAILBLAZER-ALZ2, a recent 76-week phase 3 randomized double-blind parallel multicenter placebo-controlled trial, suggested that donanemab significantly slowed AD progression in both low/medium tau and high tau populations (*124*). In the low/medium tau patients in particular, the clinical outcome was achieved in 52% of subjects based on amyloid clearance criteria; what is exciting is that a pronounced improvement in cognition was observed (*124*). This may be related to the high selectivity of donanemab for plaque.

Unlike the three aforementioned drugs that target the N-terminus, solanezumab and crenezumab target mid-sequence epitopes of amyloid fibrils. Solanezumab (LY2062430), which has a Fab fragment that can specifically bind to amino acid residues 16-26 of the Aβ protein, recognizes monomeric Aβ. It is supposed to capture and eliminate peripheral and central Aβ proteins, leading to the degradation of Aβ protein plaques (*125*). A phase 2 trial suggested that solanezumab seemed to shift Aβ equilibria to mobilize Aβ(1-42) from amyloid plaques, accompanied by increased unbound Aβ(1-42) in cerebrospinal fluid (CSF) in a dose-dependent manner (*126*). However, the cognitive scores of the trial's subjects did not change significantly, which was consistent with the results of a phase 1 trial (*127*). However, several subsequent phase 3 clinical trials were terminated after failing to demonstrate clinical efficacy (*128-130*). Crenezumab has a high affinity for higher molecular weight species such as fibrils, plaques, and oligomers but

Table 1. Monoclonal antibodies against Aβ and tau proteins in clinical trials (current as of February 2, 2024)

Drugs	Category	Major targets	Study phases	Subjects	Effectiveness	Main adverse events	*Ref.*
Aducanumab	Removes Aβ	Aβ multimers	3	Early AD	Slowing cognitive decline; improved markers of amyloid	ARIA	Budd *et al*., 2022
Lecanemab	Removes Aβ	Aβ oligomers	3	Early AD	Improved markers of amyloid	ARIA	van Dyck *et al*., 2023
Gantenerumab	Removes Aβ	Aβ multimers or monomers	3	Early AD	Reduced Aβ plaque	ARIA	Bateman *et al*., 2023
Crenezumab	Removes Aβ	Aβ multimers or monomers	3	Early AD	Neither cognitive decline nor markers of amyloid	Rare, mild ARIA	Ostrowitzki *et al*., 2022
Solanezumab	Removes Aβ	Aβ monomers	3	Preclinical AD	Neither cognitive decline nor markers of amyloid	ARIA with microhemorrhage or hemosiderosis	Sperling *et al*., 2023
Bapineuzumab	Removes Aβ	soluble Aβ; Aβ protein	3	Mild-to-moderate AD	Neither cognitive decline	Rare ARIA; falls, agitation, and urinary tract infections	Salloway *et al*., 2018
GSK933776	Removes Aβ	soluble Aβ	1	Mild AD	Improved markers of amyloid	Increased levels of blood creatine phosphokinase	Andreasen *et al*., 2015
Donanemab	Removes Aβ	Aβ plaque	3	Early AD	Slowing cognitive decline; Reduced Aβ plaque	ARIA with microhemorrhages and hemosiderin	Sims *et al*., 2023
Semagacestat	Reduces Aβ production	γ-secretase	3	Mild-to-moderate AD	Exacerbated cognitive impairment	Skin cancer and infections	Doody *et al*., 2013
Verubecestat	Reduces Aβ production	BACE1	3	Mild-to-moderate AD	Improved markers of amyloid	Rashes and hair color changes	Egan *et al*., 2018
Atabecestat	Reduces Aβ production	BACE1/2	2b/3	Preclinical AD	Exacerbated cognitive impairment	Liver toxicity	Sperling *et al*., 2021
Lanabecestat	Reduces Aβ production	BACE1/2	3	Early or mild AD	Improved markers of amyloid	Psychiatric adverse events, weight loss, and hair color changes	Wessels *et al*., 2020
JNJ-63733657	Inhibits aggregation	Thr217	2	Early AD	Not yet determined	Not yet determined	Janssen Research & Development, LLC, 2020
Zagotenemab	Inhibits aggregation	aggregated misfolded tau	2	Early AD	Not yet determined	Sinus bradycardia, headaches, falls, and bronchitis	Willis *et al*., 2023
E2814	Inhibits aggregation	microtubule-binding domain	2	Early AD	Not yet determined	Not yet determined	Eisai Inc., 2021
Gosuranemab	Eliminates tau aggregates	tau monomers and fibrils	2	Early AD	Improved markers of amyloid	Falls, nasopharyngitis, arthralgia, headaches, diarrhea, and constipation	Shulman *et al*., 2023
Semorinemab	Eliminates tau aggregates	full-length tau	2	Mild-to-moderate AD	Neither cognitive decline nor markers of amyloid	Falls, nasopharyngitis, and injection-related reactions	Teng *et al*., 2022

Not yet determined: Clinical results are not yet determined because the trial has not concluded.

a low affinity for monomers (*120*). Notably, crenezumab causes a small incidence of ARIA, which may be related to its selection of the IgG4 backbone isotype. In a multicenter, double-blind 1b study, most adverse events were mild or moderate, and ARIA with edema was not reported, indicating that it is well-tolerated and safe (*131*). The same result was observed in two phase 3 multicenter randomized double-blind placebo-controlled parallel-group trials, which found that ARIA with edema is rare, mild, and transient (*132*). Unfortunately, however, there were no significant changes in clinical outcomes or biomarkers (*132*). However, a phase 2 trial of high-dose crenezumab in patients with mild AD yielded better results (*133*).

Gantenerumab mainly targets Aβ plaques and removes them *via* Fcγ receptor-mediated microglial phagocytosis (*134,135*). It causes little significant discomfort when injected and appears to help with the clinical progression of a high-dose and low-frequency strategy (*136,137*). A monthly high subcutaneous dose of 1,200 mg gantenerumab demonstrated acceptable long-term safety and robust plaque clearance in patients with prodromal to moderate AD; after two years of treatment, 51% of patients had sparse-to-no neuritic Aβ plaques with clinical decline trending in the same direction, suggesting its potential clinical benefit (*138*). However, a study with a large sample is necessary for validation.

ARIA is the most common adverse reaction to Aβ-clearing antibodies, which may be related to the stress-induced immune clearance of antibodies. Insoluble Aβ is present in the brains of both healthy older adults and patients with AD. mAbs also recognize it in addition to the toxic soluble Aβ and activate monocyte and lymphocyte recruitment and clearance (*139*). In this process, the antibody conjugate stimulates the expression of macrophage proteases through the Fc receptor, which degrades the extracellular matrix, disrupting the BBB and entry of tissue fluid into the brain. Ultimately, it manifests as ARIA with edema or hemorrhage (*140*). Bapineuzumab (AAB-001), a long-acting antibody administered in 13-week cycles, can clear Aβ by binding to 5 N-terminal residues of the Aβ protein (*141*). Still, it has an unsatisfactory incidence of AIRA and associated symptoms such as headaches (*142*). AAB-003, a derivative of bapineuzumab, has three amino acid residues in the lower hinge region of bapineuzumab to reduce inflammatory activation and cellular damage by the Fc-receptor, reducing the risk of ARIA and increasing the safe dosage. A first-in-human study of AAB-003 evaluated its safety, tolerability, and pharmacokinetic data at five dose levels (0.5, 1, 2, 4, and 8 mg/kg) (*142*). Results indicated that AAB-003 was safe and well-tolerated in patients with mild to moderate AD at up to 8 mg/kg for up to 91 weeks (*143*), with similar adverse events to bapineuzumab after the first or second injection. GSK933776, another drug that targets the N-terminus of the Aβ protein (amino acid disabled sequences 1-5) and that provides passive immunity, is thought to reduce the incidence of ARIA since it contains a variant amino acid sequence that substantially reduces the antibody's effect on the Fc region. In a two-part placebo-controlled first-in-human study in patients with mild AD, total plasma Aβ levels increased after single-dose and repeated-dose intravenous administration decreased free Aβ levels in a dose-dependent manner (*144*). No subjects in any of the dose groups had drug-related ARIA with edema or hemorrhage (*144*). Further studies are needed to prove the safety and clinical efficacy of GSK933776 in patients with AD. Put simply, reducing ARIA during antibody treatment by inhibiting the Fc receptor seems desirable.

3.1.2. mAbs reduce Aβ production

In addition to removing Aβ, counteracting amyloid deposition also reduces its production. As mentioned earlier, Aβ production requires the involvement of γ-secretase and β-secretase. Therefore, mAbs have been designed against γ-secretase inhibitors, like semagacestat, and β-secretase inhibitors, like verubecestat, atabecestat, and lanabecestat. Semagacestat reduces Aβ40 and Aβ42 production and secretion from its substrate APP, which seems to get to the root of the problem. Unfortunately, a phase 3 trial found that semagacestat led to a worse outcome and was associated with more adverse events, including skin cancer and infections, leading to the termination of the drug's development (*145*). Semagacestat may not be an γ-secretase inhibitor because it does not inhibit intracellular levels of γ-byproducts (product peptides of γ-secretase) (*146*). Subsequent validation found that semagacestat inhibited the transport of γ-byproducts and Aβ to the extracellular compartment, leading to intracellular accumulation and cytotoxicity (*146*). Given its high toxicity and low efficacy, clinical studies of semagacestat have been discontinued.

Another target for Aβ production is the beta-site amyloid precursor protein cleaving enzyme (BACE), also known as β-secretase. Verubecestat is an inhibitor of the β-secretase enzyme, which cleaves APP proteins into various Aβ peptides. As an oral medication, it is envisioned as long-term maintenance therapy to limit Aβ production (*147*). A preliminary clinical trial demonstrated its safety - adverse reactions were primarily rashes and hair color changes rather than ARIA (*148*). Similarly, no adverse effects, such as neurodegeneration or altered glucose homeostasis, were observed in an animal study (*147*). A randomized placebo-controlled phase 3 study conducted at 238 centers in 21 countries and involving 1,958 patients with mild-to-moderate AD indicated that verubecestat reduced biomarkers (Aβ:40: 71.1-80.6%, Aβ:42: 62.7-76.4%, sAPPβ: 76.6-86.1%); however, it did not alleviate cognitive decline in patients (*148*). Lanabecestat is another orally administered mAb that targets both BACE1 and BACE2. Biomarker data indicated that lanabecestat reduced blood Aβ40 and Aβ42

levels by 70 to 80% in both trials. Aβ levels measured in CSF dropped by 50 and 73% at the low and high doses, respectively (*149*). In addition, lanabecestat reduced brain amyloid on PET imaging in a dose-dependent manner (*149*). However, there was no significant alleviation of clinical symptoms. The high dose caused more dropouts because of psychiatric adverse reactions, weight loss, and hair discoloration (*149*). In addition, atabecestat, another β-secretase inhibitor that has similar pharmacologic effects to verubecestat, has worse efficacy and causes more serious adverse events (*150,151*). The drug induces liver toxicity. In one subject who discontinued treatment because of elevated liver enzymes, a liver biopsy revealed inflammation, infiltration of immune T and B cells, and hepatocyte death (*152*). Subsequently, drug-responsive T cells were detected in the subject with liver injury; these cells were generated by binding to atabecestat or its metabolites to antigen-presenting cells (*153*). Eventually, the development of the drug was terminated. In conclusion, γ-secretase and β-secretase inhibitors are promising as oral antibodies for ultra-early therapeutic use in AD. However, efficacy and dose-dependent adverse events need to be urgently addressed.

3.2. mAbs against the tau protein

Tau protein pathology has recently received more attention in AD treatment following the issues with Aβ immunotherapy (*154*). Tau pathology can be blocked in four ways: inhibition of phosphorylation/acetylation, inhibition of aggregation, elimination of tau aggregates, and promotion of microtubule stabilization (*120*). Development of mAbs focuses on inhibition of tau aggregation and removal of tau aggregates. The first study on passive immunization with tau used PHF1 antibodies against the pSer396/404 epitope in a mouse model of tauopathy (*155*). mAbs targeting tau may inhibit AD progression by retarding the accumulation of pathological tau. Table 1 summarizes the mAb drugs targeting tau protein in clinical trials over the past few years.

3.2.1. mAbs inhibit tau aggregation

Zagotenemab (LY3303560), derived from mouse mAb MCI-1, binds to and neutralizes soluble tau aggregates. MCI-1 is a conformationally selective anti-tau antibody that binds to an early pathological form of soluble tau conformation to avoid its accumulation (*156*). Thus, it might be useful for early prevention. A 16-week study evaluated the safety and tolerability of the doses of zagotenemab (70 mg or 210 mg, q4w with 49 weeks) in patients with AD and early cognitive impairment and healthy volunteers. Results revealed a dose-dependent increase in plasma tau concentration in the SUBJECTS study after zagotenemab was administered, but there was no significant alleviation of clinical manifestations. A phase 2 clinical study to evaluate its safety and efficacy in patients with early AD symptoms was completed in 2021 and yielded similar results (*157*).

JNJ-63733657 targets tau phosphorylated at Thr217, an epitope in the middle region of the tau protein. JNJ-63733657 recognizes the microtubule-binding region of tau and therefore interferes with the intercellular proliferation of pathogenic aggregated tau proteins more effectively than other antibodies. The latest phase 2 clinical trial to determine its safety and tolerability in patients with early AD is being conducted and is scheduled to conclude in 2035. The trial is divided into two parts: in the first part, healthy subjects received a single ascending dose of JN-63733657 or a placebo, and in the second part, patients with early AD received three doses of escalating intravenous injections for eight weeks (*158*). In addition, a study of JNJ-63733657 in healthy Chinese subjects and participants with early AD is currently underway (*159*).

E2814 targets a mid-range epitope in the microtubule-binding domain named HVPGG near the mid-structural domain of tau. This region is a major component of tau tangles and is involved in seeding and spreading pathogenic tau aggregates. E2814 is designed to bind extracellular tau, inhibit tau aggregation and seeding, prevent further accumulation of NFTs, and mediate microglia clearance (*58*). A phase 2 clinical trial, scheduled for 2024, is underway to evaluate the safety and tolerability of the drug administered intravenously to patients with dominant AD (*160*).

3.2.2. mAbs remove tau aggregates

Gosuranemab (BIIB092), a humanized IgG4 antibody that selectively binds to extracellular N-terminal tau fragments (residues 15-22), targets extracellular tau fragments, which may affect neurons and glial cells and seed neuropathology (*161,162*). A double-blind placebo-controlled parallel-group phase 2 trial involving subjects with mild cognitive impairment found it to be well-tolerated and safe overall; however, the trial was terminated based on a lack of effectiveness despite a significant reduction in the CSF levels of unbound N-terminal tau at 76 weeks (*163*). Just like gosuranemab targets the N-terminus of extracellular tau, semorinemab, a humanized IgG4 antibody, can bind to all forms of hyperphosphorylated and oligomeric tau with a high affinity and specificity (*164*). In preclinical studies, semorinemab reduced tau pathological changes in a transgenic mouse model. However, in a 73-week phase 2 randomized clinical trial, semorinemab did not prevent disease progression in patients with mild AD compared to a placebo. Nonetheless, it did have acceptable and well-tolerated safety (*164*). Data revealed the drug's favorable safety profile, and the most common adverse events included falls, nasopharyngitis, and injection-related reactions (*164,165*). Another phase 2 clinical trial

noted a 42.2% reduction in the rate of decline according to the 11-item Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog11) in the semorinemab treatment group compared to the placebo group.

4. Influence of the BBB

BBB, a highly selective semipermeable membrane structural and chemical barrier between the peripheral circulation and the central nervous system, mainly consists of capillary endothelial cells, pericytes, astrocytes, neurons, and tight junctions (*166,167*). The barrier prevents substances from reaching the brain and it stops specific macromolecules from entering the blood (*168*). Issues with AD treatment are the lack of effective therapeutic molecules as well as the difficulty of penetrating the BBB and reaching specific targets for disease treatment (*169*). More than 98% of small-molecule drugs and almost 100% of large-molecule medicines were precluded from reaching the brain during treatment (*170,171*). Conventional mAbs in particular cross less than 0.5% of the BBB (*69*).

Molecules are transported across the BBB in multiple ways. Some small hydrophilic and lipophilic molecules can enter the brain tissue by paracellular and extracellular diffusion (*172*). Other molecular substances that cannot diffuse through the cell membrane, such as glucose, amino acids, and nucleosides, can enter the brain *via* carrier-mediated transport systems, receptor-mediated endocytosis, and adsorption-mediated exocytosis (*173*). Like ordinary large-molecule substances, the passage of mAbs across the BBB is mainly accomplished by endogenous transport on endothelial cells, including adsorption-mediated cytosis, carrier-mediated cytosis (CMT), and receptor-mediated cytosis (RMT). Cytosis is a standard mode of drug uptake. Upon a receptor or carrier's recognition of a ligand signal, the cell membrane invaginates and encapsulates the drug and detaches from the plasma membrane to form a vesicle. Then, the drug is digested intracellularly by lysosomes and released into the brain; at the same time, the receptor and ligand can be transported back to the original plasma membrane by carrier vesicles for reuse (*174*). Several carrier proteins hold promise for research, including transferrin receptor (TfR), insulin receptor, and melanin transferrin. Trontinemab, a new drug for AD, consists of gantenerumab and a human TfR1-directed Brainshuttle™ module. *In vitro* experiments have indicated that it has a similar capacity to bind to Aβ fibers and plaques as gantenerumab. Animal experiments have indicated better brain and plasma pharmacokinetic parameters, approximately 4-18 times better than gantenerumab, according to nonlinear mixed-effects modeling with correction for tissue residual blood (*175*). In a 44-person study, trontinemab markedly cleared plaque in three-quarters of participants within six months with negligible to no AIRA (*176*). Pharmacokinetics indicated the concentration of mAbs in the brain is expected to be much lower than that in plasma because peripherally administered mAbs have difficulty crossing the BBB, leading to low safety and efficacy in AD treatment.

Nanoparticles have been widely used as auxiliary tools to treat neurological diseases because their physicochemical properties and multifunctionalities enable them to cross the BBB (*177*). They can work as a carrier to treat several contributors to AD, including tau pathology, Aβ accumulation, and AD-associated neuroinflammation (*178*). Several nanoparticles (solid lipid particles, dendrimers, nanofibers, nanotubes, PLA/PLGA NPs, *etc.*) are currently being developed for preclinical or biomedical use (*179*). Advantageously, nanoparticles are more likely to target specific tissues by covalently binding to various ligands (*180*); a liposome, a highly flexible and biocompatible drug delivery system, has the potential to carry biologically active molecules, effectively improving the bioavailability of drugs. A phase 1b randomized clinical trial indicated that liposome-based anti-amyloid ACI-24 has good safety and specific efficiency in treating Down syndrome. There was no ARIA with edema or cerebral microhemorrhage, and increases in anti-Aβ immunoglobulin G titers were observed in 4 of 12 participants (33.3%) receiving ACI-24 (*181*). Intranasal drug delivery has been developed and utilized since first-pass metabolism, systemic clearance, and enzymatic degradation of drugs are other essential factors affecting efficacy and safety. Intranasal administration brings the drug to the brain in two ways. One is absorption through the venous vessels of the nose into the cavernous sinus and subsequently directly into the brain's arteries. This approach, although inevitably passing through the BBB, avoids the first-pass metabolism and degradation (*182*). The other way is diffusion through the nervous system, including intracellular and extracellular pathways. The drug passes through the olfactory epithelium trigeminal nerve and olfactory nerve receptors to reach the nerve endings and enters the neurons by pinocytosis. It is encapsulated in vesicles as exosomes, translocated to axon terminals, and discharged into the postsynaptic cells of the olfactory bulb. There, the lipophilic molecules can exert their pharmacological action by reaching the lamina propria *via* transcellular transport. Transportation of the drug to the brain in this way takes about 24 hours, while other peptides and hydrophilic drugs can reach the central system *via* the extracellular pathway in less than 30 minutes (*183*). In this way, drugs diffuse through the perineural space between the olfactory neuron-ensheathing cells and the olfactory neural fibroblasts. This space continues from the olfactory epithelium to the olfactory bulb and, more importantly, connects to the subarachnoid space, meaning that the drug directly enters the CSF (*183*). Animal studies have indicated that nanoparticles for nasal administration require a lower dosage and have a higher bioavailability than those for

conventional oral administration, which means they are safer and more efficient (*184,185*). Regrettably, however, there appear to be no clinical trials on nanoparticle drugs yet.

5. Conclusions and prospects

Over the past few decades, our understanding of the pathogenesis, diagnosis, and treatment of AD and other related neurodegenerative diseases has improved significantly. Nowadays, the higher incidence of AD and its impact on patients and their families has undoubtedly attracted more attention from researchers. Brain targets and biomarkers have been gradually discovered, significantly promoting the diagnosis and treatment of AD. mAbs have emerged as a promising tool for precisely binding drugs to their targets, blocking or modulating their effects, reducing the intensity of the immune response, and potentially eliminating the pathological process of AD. However, clinical trial data suggests that while these therapies can reduce AD-related markers such as Aβ, they do not consistently produce satisfactory clinical outcomes. This may be linked to the complex and incompletely understood pathology of AD. Recently, the question has been raised as to whether the priority of the Aβ hypothesis in the progression of AD needs to be reconsidered (*45*).

Immunoprophylaxis is receiving more attention based on setbacks in immunotherapy. AD presents with intracerebral pathology, such as accumulation of Aβ, 20-30 years before the onset of cognitive impairment (*186,187*). Given the growing pathologic complexity of the disease, the clinical benefit that can be expected from Aβ-removing therapies alone is unclear at this point in time. Thus, targeting aberrant Aβ as immunoprevention is likely to be most successful when initiated during or prior to the stage characterized by the emergence and seeded propagation of aberrant Aβ and Aβ-associated pathologies (*3*). As anti-Aβ therapy, KHK6640, a novel anti-amyloid beta oligomer-specific antibody, tended to perform well in the treatment of patients included prodromal AD, with nonsignificant AIRA (*188*). In contrast, anti-tau mAbs have made better progress. A phase 1 study demonstrated that atabecestat reduces Aβ isoforms and precursor protein (sAPPβ) in the CSF of patients with preclinical AD by an average of 67% (*189*). Semorinemab is safe but not effective (*164*). In addition, several trials on antibodies for AD are currently in the first phase to demonstrate the effectiveness of immunoprophylaxis (*190,191*).

In addition, the existence of the BBB poses enormous challenges to AD treatment. Antibodies are highly attractive due to their target specificity, long serum half-life, precise mechanism of action, and limited target deficiencies, compared to small molecule drugs for treating neurological diseases. However, crossing the BBB and penetration efficiency is a major problem in developing monoclonal drugs for AD treatment. In addition, the efficiency of their penetration should not be overlooked. If the concentration of mAbs is too high in the periphery, this will cause adverse events such as AIRA. Therefore, in-depth pharmacokinetic studies are necessary. Researchers have proposed using bifunctional IgG fusion proteins, nanoparticles, and other methods to address these issues. Nasal administration has also been used to bypass hepatic first-pass metabolism and degradation by gastrointestinal enzymes. However, further clinical data on these approaches are needed. Although most therapeutic agents can prevent disease progression in preclinical studies, expected results were not yielded in clinical trials. Most drugs have only reached clinical phase 1 or 2 trials, and many of those that undergo phase 3 clinical trials are terminated due to poor efficacy. Although the FDA hastily approved aducanumab without conclusive clinical evidence, this may encourage patients with AD, indicating that drug development is advancing (*192*). However, we must remember that there may be a long way to go.

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