# Treatment strategies behind Alzheimer's disease: amyloid-beta and tau as novel drug targets

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**Abstract:** Alzheimer's Disease (AD) is a neurodegenerative disease with complex pathogenesis. Clinically, it is the leading cause of dementia, leading to cognition and memory decline, behavioural changes, and loss of daily functions. Currently, two biological hallmarks have been identified: extracellular deposits of amyloid-beta (Aβ) and intracellular tau-containing neurofibrillary tangles (NFT). Before the approval of aducanumab, all four treatments available targeted the clinical dementia stage, which only brings modest reliefs from symptoms without slowing down the progression of the disease. Since the establishment of the amyloid cascade hypothesis over 30 years ago, Aβ remains the promising target for a potential cure of AD. Numerous Aβ-directed monoclonal antibodies were designed, however, none have shown statistically significant efficacy in a dosage-dependent manner with minimal side effects. Although the approval of aducanumab provided novel treatment to the AD community, inconsistency in result analysis gained significant doubts on its validity, among other issues. With such unsuccessful clinical trial results targeting Aβ, anti-tau therapeutics become the center of treatment development. Multiple mechanisms of action, including GSK-3β and tau aggression inhibitors, microtubule stabilizers, and immunotherapies, have been considered. However, this remains a novel and under-researched field. Only one tau aggression inhibitor has reached phase 3 clinical trials, while four monoclonal antibodies and a vaccine in phase 2 studies. This review aims to briefly explain Aβ and tau as biomarkers of AD and targets of AD treatment development; and to summarise current treatment development up to date with future directions.

## 1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease with complex pathophysiology comprising many intertwined sub-pathologies [1]. Clinically, it is characterized by cognitive impairment, loss of memory and daily functional abilities, as well as behavioral changes. It is the most common cause of dementia and the leading cause of death in the United States, with an estimated 50 million worldwide prevalence. This number is expected to surpass 150 million by 2050 [2]. However, after more than 100 years of effortful research and investment, AD remains fatal, with no cure and little effective treatment up to date. Previously approved treatment for AD (donepezil, galantamine, rivastigmine and memantine) are labelled for the clinical dementia stage and brings only modest and temporary relief from the symptoms. However, it cannot stop or slow down the progression of the disease. Moreover, AD usually starts up to 20 years before early symptoms of dementia reveal themselves, resulting in a common late diagnosis, causing this not well-understood disease to be even more challenging to tackle [3]. Therefore, studies to lead towards a better understanding of the pathogenesis of AD for the future discovery of potential targets for the development of novel therapeutics has been a priority for decades.

Based on current understanding, AD is characterized by two neuropathological hallmarks: extracellular deposition of amyloid-beta (Aβ) plaques and intracellular tau-containing neurofibrillary tangles (NFT). This review aims to summarise the development of understanding AD, with a special focus on the development of treatments up to date. Aβ would be firstly introduced with an overview

of its formation process and biological functions involved in the progression of AD, followed by the explanation of the amyloid cascade hypothesis. Then several amyloid-directed monoclonal antibodies developed would be reviewed by examining its current stage and data in clinical trials with future directions in discovering the cure of AD provided. Secondly, the other hallmark of AD, intracellular NFT containing tau and its association with Aβ, would be introduced, with examples of novel treatment development with different targets and mechanisms.

## 2. Amyloid-beta (Aβ)

### 2.1 Overview of Aβ

Aβ is a heterogeneous mixture that encompasses a small group of peptides ranging from 37-43 amino acids in length and was first reported in patients with Down Syndrome in 1984 [3, 4]. As shown in Figure 1, it is produced through a much larger precursor molecule called amyloid precursor protein (APP) via the proteolytic process. APP is a single transmembrane glycoprotein widely produced by brain neurons, as well as vascular, blood cells and platelets, and plays a significant role in various neuronal processes, including development, signaling, and aspects of homeostasis. Once the APP spans the cell membrane, the process of two subsequent proteolytic cleavages starts. Firstly, β-secretase (β-APP-cleaving enzyme-1 (BACE1)) at the ectodomain would cleave the APP, releasing the soluble APP beta (sAPPβ) into the extracellular space. It is then followed by the cleavage of the remaining membrane-bound portion at intra-membranous sites by γ-secretase, which consists of Presenilin 1 or 2, Nicastrin (NCT), PEN2 and APH-1. Once this action has succeeded, soluble Aβ monomers are formed and released into the extracellular space like sAPPβ, while the remaining part, known as APP intracellular domain (AICD), stays intracellularly [3, 5].

Starting as monomers, Aβ can be found in various types of intermediate aggregation states, including oligomers, protofibrils and fibrils, which plaques accumulate from, known as one of the most well-researched biological hallmarks of AD. This aggregation process is also known as the Aβ cycle, in which all species mentioned above exist in a steady state and can convert from one form to another bidirectionally. Just as monomers, oligomers are also soluble, which allows their rapid spread throughout the brain. However, this results in high neurotoxicity and specific immune responses, leading to a chain of inflammation reaction distinguishable from other forms of Aβ, such as monomers and fibrils. Moreover, oligomers vary in size, ranging from low-molecular-weight ones including dimers, trimers, tetramers, and pentamers, to higher molecular weight ones such as dodecamers. High-molecular-weight species are favourable during the accumulation process, resulting in a heterogeneous size distribution in general. Large soluble protofibril is another intermediate species formed during the Aβ cycle well studied in rat models. Aβ protofibrils are particularly harmful due to their negative impact on neurons, hippocampus, and glial cells, resulting in neurotoxicity, pivotal cognitive and behavioral function impairments, and inflammatory responses, respectively. Aβ protofibrils could become an important therapeutic target for AD treatment due to such broad and negative impact on the brain. In contrast to the species mentioned above, fibrils and plaques are insoluble and larger in size. High free energy barriers prevent these more stable formats of Aβ aggregate in a concentration-dependent manner, which is typical for proteins in normal circumstances. However, this process is accelerated by the unique environmental condition seen in AD patients, including various proteins with poor solubility and a vulnerable protein homeostasis system. Once the formation of Aβ fibrils has succeeded, they would further deposit into plaques, which is known as the defining molecule of this biological hallmark [3, 5].

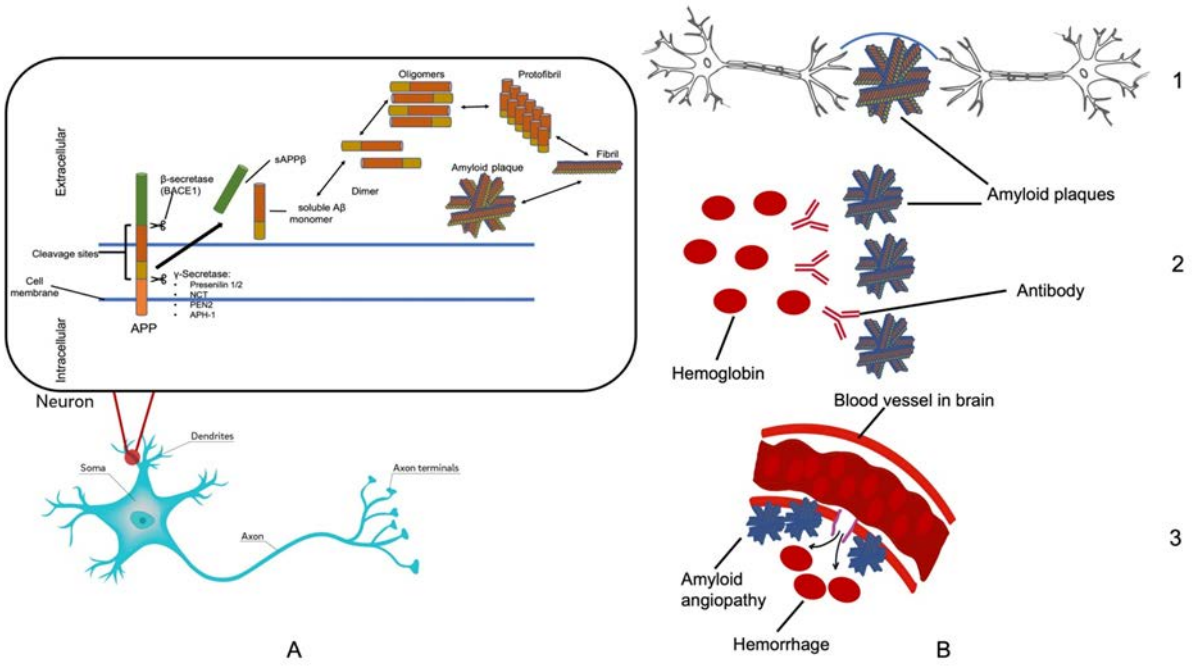


Figure 1. A) Overview of the amyloidogenic pathway and the Aβ cycle in degenerated neurons of patients with AD B) Three major consequences of Aβ plaque aggregation; 1: Disruption of the signaling process between two healthy neurons; 2: Initiation of an immune response, which results in inflammation and damage of surrounding neurons; 3: Deposition on the outer side of the blood vessel, also known as angiopathy, which causes hemorrhage or vessel rupture [3, 6, 7].

### 2.2 The amyloid cascade hypothesis

Although never universally accepted, the amyloid cascade hypothesis has been at the center of AD research for over 30 years. It proposes that deposits of extracellular Aβ peptides formed by the Aβ cycle are the primary cause of AD, leading to clinical manifestations including neurotoxicity, neurodegeneration, and dementia. Due to the inconsistent and unconvincing clinical trial results of several Aβ-directed monoclonal antibodies, a reasonable amount of doubt has arisen on the scientific accuracy of this hypothesis. However, Aβ aggression is still highly likely to have a strong connection with AD development, which has been proven in several aspects with an enormous amount of biomarker data gathered by independent laboratories and clinics worldwide [5, 8].

On a genetic level, it has been suggested that mutations in the human APP, PSEN1 and PSEN2 genes are the most relevant to AD progression. In early-onset familial AD, mutations of the APP gene, which encodes the amyloid precursor protein, leads to Aβ aggression into plaques and other brain pathologies. These Alzheimer's-like brain pathologies caused by mutations of the APP gene have also been observed and proven in other diseases such as Down Syndrome.

The gene dosage of APP is increased by the trisomy of chromosome 21 in patients with Down Syndrome, resulting in compromised cognitive functions and intellectual difficulty very early onset. These Aβ-related symptoms are usually indistinguishable from AD, which further supports the association between the development of AD symptoms and Aβ deposits [5, 8]. Moreover, mutations in the human APP gene are close to the γ-secretase site, making it more vulnerable to mutations itself as well. Thus, it is not surprising that mutations also occur in the genes PSEN1 and PSEN2, which significantly affects the physiological activities of γ-secretase [5]. These mutations cause the earliest and most aggressive forms of familial AD [8]. Additionally, due to the complexity of AD, genetics is not the only factor attributing to the progression of symptoms. Mutations in APP, PSEN1 or PSEN2 are not always detected in early-onset families. Rather, cleaving processes of γ-and β-secretase are also affected by additional proteins, which have also been suggested to involve in the hyperphosphorylation of tau and the development of neurofibrillary tangles. This also supports the hypothesis that Aβ is connected to tau and the development of NFT profoundly. Misfolding of the

extracellular Aβ could induce the misfolding of the intracellular deposition of tau in NFT, which causes memory loss and confusion, resulting in personality and cognitive decline over time [5].

Similar to early-onset AD, late-onset AD is also contributed by both genetic and non-genetic factors. Clinical manifestations of neurodegeneration of AD are caused by several common Aβ-related pathogeneses, including production, aggregation, clearance and degradation, which are impacted by risk-factor genes [5]. Among all risk genes identified so far, APOE is the one that has been studied the most extensively. Alleles occurring at the APOE loci ε2, ε3 and ε4 have all been proved to increase the risk of AD, while APOE4 protein has been shown to significantly decrease the efficiency of Aβ clearance in the brain in both human and mouse models [8].

All the above-mentioned experimental data have suggested a profound connection between the development of AD symptoms with the aggression and production of extracellular Aβ. Although the amyloid cascade hypothesis has not fully comprehended the complexity of AD yet, especially its association and mechanism with tau and the formation of NFT, the hypothesis itself is still supported by an abundant amount of reliable scientific results.

### 2.3 The wave of Aβ-directed monoclonal antibodies

Since the amyloid cascade hypothesis has been proposed for more than 30 years and is one of the most well researched and accepted hypotheses for AD pathogeneses, Aβ has become an obvious and promising novel target for AD treatments. Among all formats of therapeutics, passive immunotherapy has been the most investigated in late-stage clinical trials up to date. Passive immunotherapy refers to the approach of an injection of Aβ-directed monoclonal antibodies [2]. As it could be seen in table 1, 6 Aβ-directed monoclonal antibodies have reached phase 3 clinical trial, along with a combinational approach of two anti-amyloid compounds in clinical trials. Although some levels of Aβ plaque reduction have been seen in some of the drugs, the clinical trial results have been inconsistent, while all compounds lack effectiveness in general. Moreover, amyloid-related imaging abnormalities (ARIA) has been observed in all therapeutics tested in clinical trials as one of the most common side effects.

Aducanumab, marketed as Aduhelm, developed by Biogen Inc. and Eisai Co., Ltd, is arguably the most promising drug among all monoclonal antibodies. It is the first novel therapy approved for AD since 2003 and is currently the only treatment option available to slow down the progression of AD instead of symptomatic treatment in patients with mild cognitive impairment and dementia. The PRIME study, a double-blind, placebo-controlled phase 1b randomized trial (ClinicalTrials.gov Identifier NCT01677572), has been reported with successful results. In this one-year study with patients suffering from prodromal or mild AD, clearance of Aβ plaques have been measured by amyloid PET imaging in the aducanumab group that received monthly intravenous infusions and shown in a time- and dosage-dependent manner. Moreover, a reduction in cognitive decline has also been observed. However, side effects of ARIA-E in a dose-dependent and APOEe4-related manner have been observed in 22% of aducanumab-treated subjects [2, 9, 23]. The two identical phase 3 clinical trials, namely EMERGE and ENGAGE, which were initiated in 2015, have failed to show clinical results during the initial data analysis and has then been terminated for futility in March 2019. However, in October 2019, Biogen announced its reanalysis of results of ENGAGE with significant cognitive improvement in patients treated with high doses of aducanumab, which eventually led to its accelerated approval by the FDA in June 2021. Despite its official FDA approval and successful marketing, the inconsistency in clinical trial results has led to numerous controversies, including FDA's potential personal involvement in the approval process [2, 23]. Since the extensive debates surrounding aducanumab, it has been argued that the lack of consistent clinical results should be analyzed critically and carefully. One of the hypotheses is that the patients included in the clinical trials are suffering from formats of AD that are too advanced, symptomatic, and aggressive to have positive results demonstrated. Another hypothesis suggested that aducanumab lacks selectivity of specific forms of Aβ and the ability to consistently penetrate the blood-brain-barrier, which results in the deficiency in neurotoxicity reduction and drug absorption, respectively [8, 24]. To further study and evaluate the long-term safety and tolerability of aducanumab, another clinical trial has recruited patients who have participated in previous trials, and it is expected to complete in 2023 [2].

One of the first Aβ-directed monoclonal antibodies tested in phase 3 clinical trials is solanezumab, developed by Eli Lilly & Co. Both phase 3 double-blind, randomized controlled trials, namely EXPEDITION and EXPEDITION2, had more than 1000 patients with mild to moderate AD randomly assigned to either receive placebo or solanezumab every four weeks for 18 months. The primary outcomes were not reached for both trials and failed to deliver promising cognitive and functional ability improvements [20, 21]. However, solanezumab is relatively safer despite its deficiency, with less frequent ARIA reported. This might be due to its selectivity and specific binding towards soluble Aβ monomers instead of insoluble fibrils [2]. A later phase 3 clinical trial involving more than 2000 patients with mild dementia due to AD has also failed to improve cognitive decline significantly [19]. Moreover, solanezumab is currently being tested in 'The A4 study', a phase 3 clinical trial targeting preclinical AD patients without cognitive impairments but is Aβ-positive in PET imaging. This study is expected to be finished in 2023 [23].

Gantenerumab is the first fully humanized monoclonal antibody targeting Aβ. A randomized, double-blind, placebo-controlled phase 3 study called SCarlet RoAD was terminated early for futility. However, dose-dependent effects were observed during exploratory analyses on selected clinical and biomarker endpoints, which suggested the need for further investigations on potential clinical effects with higher dosage. Additionally, high percentages of ARIA have been reported in a dose-dependent frequency, especially in APOE ε4 carriers, with ARIA-E occurring in up to 15% of patients and ARIA-H in 32% [14, 23]. These side effects have been further studied in the other phase 3 clinical trial, Marguerite RoAD, but the frequency of such abnormalities was still significantly higher in the treatment group than the placebo group despite a gradual dosage increase. It was also concluded that high dosage has significantly reduced PET amyloid levels and Aβ plaque removal after two years of therapy. Indications of potential clinical efficacy seen in high dosage resulted in another two phase 3 clinical trials conducted in patients with prodromal to mild AD, which are both expected to be finished by May 2023 [2, 15, 23]. In addition, gantenerumab is tested in combination with solanezumab in the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU). This study has a special focus on healthy individuals at risk of developing sporadic AD or with a type of early-onset AD caused by a genetic mutation. This prevention-focused study is currently recruiting and is expected to be finished by July 2022 [22].

Two clinical trials have been conducted on donanemab, during which promising results, i.e., reduction of Aβ plaques, have been observed through Florbetapir F18 Imaging. However, a large percentage of patients developed treatment-emergent antidrug antibodies, lowering the efficacy of the drug. Moreover, ARIA was the most common side effect similar to several other anti-amyloid agents [12]. During the phase 2 study named TRAILBLAZER-ALZ, clinical benefits such as cognition enhancement and better ability to perform daily living activities were highlighted initially. However, later analysis revealed that the second endpoint was not met with mixed outcomes. Therefore, there was no substantial difference between the placebo and the donanemab group. Moreover, brain swelling, also known as cerebral edema or ARIA-E, were seen with patients on high dosages, mixed with both symptomatic and asymptomatic, but mostly asymptomatic. It is also worth noticing that the adverse event of antidrug antibodies discovered during phase 1 studies was still detected, with approximately 90% of the participants treated with donanemab during the intervention period [13].

Lecanemab is the most recent monoclonal antibody to enter phase 3 clinical trials. Despite enormous effort, it failed to reach the 12-month primary endpoint. However, later analysis has shown some promising results, including consistent reduction of amyloid in the brain accompanied with clinical decline across several clinical and biomarker endpoints [16]. These findings have led to the application of a marketing license directly via the accelerated pathway to the FDA in September. Moreover, the phase 3 clinical trial named AHEAD 3-45 are recruiting 1400 participants and plan to complete the study at the end of 2027 [17]. While the other one, named Clarity AD, is already underway with more than 1700 participants, and it is estimated to complete primarily by 2022 and study by 2024 [18].

Due to the lack of consistent and promising results of Aβ-directed monoclonal antibodies, several different targets involved in the formation of Aβ plaque deposits have also been targeted for novel

therapy design. This includes inhibitors of BACE-1 (β-Secretase), γ-secretase, and Aβ aggregation; as well as γ-secretase modulators. However, among all published results, no current drugs in late-stage clinical trials have demonstrated clinical efficacy by reducing cognitive and functional dysfunctions, sometimes even worsened. Additionally, the majority of these therapeutics have been reported with several adverse effects, including hepatotoxicity, skin cancer, infections, and deaths. On the other hand, active immunotherapy, i.e., anti-Aβ vaccines, appeared as a more promising therapy format with a number of ongoing and recruiting clinical trials [2].

Table.1. Overview of clinical trials of passive immunotherapies (anti-amyloid antibodies)

| Drug | Company | Study population | Phase | Results/Status | Clinical Trial Identifier | Reference |
|---|---|---|---|---|---|---|
| Aducanumab | Biogen Inc. Eisai Co., Ltd | Early AD | III | Terminated | NCT02477800 ENGAGE NCT02484547 EMERGE | [9] |
| Crenezumab | AC Immune Genentech Inc. | Prodromal to Mild AD | II & III | Terminated | NCT02670083 CREAD NCT03114657 CREAD 2 NCT03491150 CREAD OLE | [10, 11] |
| Donanemab | Eli Lilly & Co | Early AD | III | Recruiting (Study should be completed by 2023;2027) | NCT04437511 TRAILBLAZER-ALZ 2 NCT05026866 TRAILBLAZER-ALZ 3 NCT05108922 TRAILBLAZER-ALZ 4 | [12, 13] |
| Gantenerumab | F. Hoffmann-La Roche AG | Early AD; Prodromal to Mild AD | III | Active, not recruiting; Recruiting (Study should be completed by 2023); Completed | NCT03444870 GRADUATE1 NCT03443973 GRADUATE 2 NCT02051608 Marguerite RoAD NCT01224106 SCarlet RoAD | [14, 15] |
| Lecanemab | Biogen Inc. | Early AD; Preclinical AD & Early preclinical AD | III | Active, not recruiting; Recruiting (Study should be completed by 2024;2027) | NCT03887455 Clarity AD NCT04468659 AHEAD 3-45 Study | [16-18] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Solanezumab | Eli Lilly & Co | Prodromal to Mild AD; Older Individuals Who May be at Risk for Memory Loss | III | Completed; Terminated; Active, not recruiting (Study should be completed by 2023) | NCT00905372 EXPEDITION 1 NCT009046832 EXPEDITION 2 NCT01900665 EXPEDITION 3 NCT02008357 A4 | [19-21] |
| Solanezumab and Gantenerumab | Eli Lilly & Co F. Hoffmann-La Roche AG | Individuals with an AD-causing mutation | II / III | Recruiting | NCT01760005 DIAN-TU | [22] |

## 3. Tau

### 3.1 Overview of tau

Tau is a protein encoded by the MAPT gene located on chromosome 17. It was first discovered in 1975 and is mainly found in the neurons in the central nervous system and, to a lesser extent, in glial cells. Belonging to the microtubule-associated protein (MAP) family, it plays a significant role in microtubule regulation, including microtubule polarisation, stabilisation, and assembly, which all contributes to the proper organization and trafficking of the cytoskeleton [25, 26]. It has also been argued that it is one of the most abundant MAP proteins required for neural growth [7]. Among many biological processes tau undergoes, such as proteolytic cleavage, glycosylation, and acetylation, phosphorylation has been argued to be the most associated with the neuropathological hallmark of AD [26].

Phosphorylation and dephosphorylation of tau constantly occur for the regulation of physiological functions. However, when this homeostasis is interrupted, tau would shift more toward phosphorylation, resulting in hyperphosphorylation, decreasing microtubule affinity. This dysregulation of the tau-microtubule complex would further lead to the instability and detachment of tau, resulting in the disassemble of the microtubule, interrupting microtubule-dependent transportation, leaving cellular polarity and viability severely impaired. Moreover, hyperphosphorylation of tau causes an increase in its cytosolic form, which is more vulnerable to aggregation. It has also been shown in vitro that these abnormally phosphorylated tau secrete more efficiently than non-phosphorylated ones, which negatively impact neighboring tau partners with abnormally altered physiological properties. Although the complete phosphorylation process has not been completely identified and understood, it has been well established that abnormal phosphorylation is strongly connected to the self-aggregation of tau, which eventually accumulates into NFT. Deposits of NFT containing hyperphosphorylated and insoluble tau is not only found in patients with AD but also observed in several other tauopathies such as frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and Pick's disease (PiD). Since synaptic loss is one of the neurodegeneration-associated consequences of tau hyperphosphorylation, it has been suggested that phosphorylation is also associated with the spreading of the disease.

### 3.2 Treatment development targeting tau

Since phosphatases and kinases play an essential role in abnormal tau hyperphosphorylation, which leads to the formation of NFT, it has become a critical aspect for novel therapy development. Among those, glycogen synthase kinase 3-beta (GSK-3β), whose deregulation has been strongly associated with the neurodegeneration of AD, has been one of the most important targets for therapeutic

approaches. As shown in Table 2, the ARGO study was a phase II, double-blind, placebo-controlled trial of a GSK-3β inhibitor named tideglusib. During this short-term study that lasted for 26 weeks, no clinical benefits were observed, which led to the termination of further investigations in this drug. Although tideglusib has been well-tolerated and presented a relatively safe profile [2, 27]. Another potential inhibitor of GSK-3β is lithium, which has long been used to treat bipolar disorder. Although in 2 earlier studies conducted in 2008 and 2009 respectively did not support this hypothesis and neither reported clinical benefits, a more recent phase 2 study has delivered promising results with the reduction in biomarkers including phosphorylated tau in cerebrospinal fluid (CSF) concentrations, along with clinical improvements in cognition and daily performance [2, 28].

Tau aggression inhibitors have also shown some promising results during clinical trials. Methylthioninium chloride, also commonly known as methylene blue, has long been shown to reduce tau aggression in vitro [2]. In an exploratory, dose-finding phase 2 study, significant treatment benefits were reported at 24 weeks, with continued clinical benefits observed on both mild and moderate subjects at 50 weeks. However, the highest dose was impaired due to dose-dependent dissolution and absorption issues, especially seen in the absence of food [29]. Based on these findings, a reduced derivative of methylene blue, Leuco-methylthioninium bis (hydromethanesulfonate; LMTM), has been developed as a more stable form of selective inhibitor targeting tau aggression. Although the initial analysis revealed some negative results of LMTM as an add-on treatment for patients with mild to moderate AD, later reanalysis suggested that monotherapy with LMTM could have potential benefits, which is currently being tested in another phase 3 clinical trial to be completed in December 2022 [2, 30].

Microtubule dysregulation has been strongly associated with tau hyperphosphorylation and aggression, resulting in the loss of cellular function of microtubules, especially transportation, which plays a significant role in the neurodegeneration of AD. Davunetide (AL-108) is a microtubule stabiliser, which presented itself as safe and well-tolerated during preclinical and clinical studies. However, there has not been statistically significant cognitive or memory differences between treatment or placebo groups [31]. Although the complete mechanism to stabilise microtubules remains unclear, it has also been studied to potentially treat other diseases, including predicted tauopathies, progressive supranuclear palsy and schizophrenia.

Immunotherapies selectively targeting pathological forms of tau have gained extensive attention, especially after numerous unsuccessful results of such approach targeting Aβ. Active immunotherapies are usually in the format of vaccination that aims to induce the immune system to develop antibodies from aggregated forms of tau. AADvac1 became the first-in-human anti-tau vaccine tested in 2013 to be used in patients with mild to moderate AD. During the first two phase 1 trials, it presented itself with a favorable safety profile with excellent immunogenicity. MRI evaluation has also shown slower atrophy with a reduction in cognition decline [32, 33]. In the 2-year phase 2 study started in March 2016, AADvac1 has also been proven safe and very well-tolerated. 98.2% of patients reported positive immunogenicity, while more than 80% developed high-affinity tau antibodies. Moreover, positive changes in blood and CSF biomarkers have also been reported, suggesting the efficacy of AADvac1 in tau aggression and cortical atrophy decline [2, 37].

In contrast to active immunotherapies, passive immunotherapies function in the format of monoclonal antibodies directed against aggregated forms of tau by injection. Among the four antibodies that have reached phase 2 clinical trials, Semorinemab (RO7105705), developed by Genentech/AC Immune, and Zagotenemab (LY3303560), developed by Eli Lilly, has no formally published results up to date. Two phase 1 clinical trials have assessed Gosuranemab (BIIB092) as a treatment for prodromal to mild AD and progressive supranuclear palsy, respectively, which both have reported safe and well-tolerated profiles [34, 35]. However, the two phase 2 trials named PASSPORT and TANGO were terminated due to the lack of efficacy with unmet primary endpoints. Tilavonemab (ABBV-8E12) is another tau-directed monoclonal antibody. During the phase 1 study, the single dose of tilavonemab was studied in patients with prodromal to mild AD. After being reported to be safe and well-tolerated, it has moved onto a phase 2 trial to evaluate the safety and tolerability of multiple doses

of tilavonemab [36]. Although this study was completed in July 2021, no results have been formally published.

Table.2. Overview of clinical trials of antitau therapeutics

| Company | Target/Mechanism | Drug | Study population | Phase | Results/Status | Clinical Trial Identifier | Reference |
|---|---|---|---|---|---|---|---|
| Noscira | GSK-3β inhibitor | Tideglusib | Mild to moderate AD | II | Completed | NCT01350362 | [27] |
| University of São Paulo | Tau aggregation inhibitor | Lithium Carbonate | Prodromal AD | II | Completed | NCT01055392 | [28] |
| TauRx Therapeutics | | Methylene Blue | Mild to moderate AD | II | Completed | NCT00515333 | [29] |
| | | LMTM | Mild to moderate AD | III | Completed | NCT01689246 | [30] |
| Allon Therapeutics | Microtubule Stabilizer | Davunetide | Prodromal AD | II | Completed | NCT00422981 | [31] |
| Axon Neuroscience | Active Immunotherapy (Anti-tau vaccine) | AADvac1 | Mild AD | II | Completed | NCT02579252 | [32, 33] |
| Biogen | Passive Immunotherapy (Anti-Tau antibody) | Gosuranemab | Prodromal to Mild AD | II | Terminated | NCT03352557 | [34, 35] |
| AbbVie | | Tilavonemab | Prodromal to Mild AD | II | Completed | NCT02880956 | [36] |
| Genentech/ AC Immune | | Semorinemab | Prodromal to Mild AD; Moderate AD | II | Completed; Active, not recruiting (Study should be completed by June 2023) | NCT03289143 NCT03828747 | No formally published results |

## 4. Conclusions

Alzheimer's disease is a neurodegenerative disease with little effective treatment up to date. Although extracellular Aβ plaques and intracellular tau-containing NFT have been successfully identified as the two critical biological hallmarks of AD responsible for neurodegeneration, cognitive decline, and memory loss, some questions remain unanswered or not fully understood. For example, molecular mechanisms behind the transcription from aggregated forms of Aβ and tau into clinical

symptoms remain a critical topic. In order to answer such questions and lead to the better design and development of disease-modifying treatments, consistent and dedicated research and studies are essential. Genome- database-wide searches could be potentially beneficial to identify more genes and proteins associated with the pathogenesis of AD. Current clinical trial results targeting Aβ and tau have been disappointing. A majority of the therapeutics in various forms failed to show sufficient safety and tolerability or dosage-dependent efficacy by reaching primary endpoints during clinical trials. In addition to the unsuccessful results of Aβ-directed monoclonal antibodies, therapeutics targeting tau remains a relatively under-researched field, with most of the clinical trials still in early stages and results not published or analyzed comprehensively. However, it is crucial to analyze and interpret the current wave of unsuccessful results meticulously and objectively. Both abnormalities of Aβ and tau lead to aggression in various forms. Therefore, lacking selectivity towards more toxic forms could be a potential explanation for the lack of efficacy. Additionally, penetration through the blood-brain barrier remains unsolved, resulting in a potential lack of dosage and absorption in critical areas of neurons and the brain. Because the interaction between Aβ and tau is still not fully understood, abnormalities in one could induce the other, which suggests multi-target therapies in favour of monotherapy. In conclusion, it is important to investigate further the pathogenesis of AD based on current hypotheses, including the amyloid cascade hypothesis and the more recently established tau hypothesis. Meanwhile, it is also crucial to identify novel targets and design treatment with different mechanisms of action, such as immunotherapies and enzyme inhibitors.

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