

# The efficiency, safety, and clinical potential of semorinemab in the treatment of Alzheimer's disease

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**Abstract.** Alzheimer's disease (AD) has become a global high-impact disease. Research from the last century to the present day has not revealed the underlying pathological mechanisms of its development. The most authoritative hypotheses about the cause of AD have been proposed in relation to tau and A $\beta$  proteins. Drugs used in clinical practice today for the treatment of AD provide only relative symptomatic relief. Using tau P301L mutant mice, it was demonstrated that in AD brain structures, tau proteins form tangles that produce toxins that affect normal neuronal function. These experiments confirm the link and interaction between A $\beta$  and tau proteins, highlighting the importance and potential of interventions targeting the aggregation of both proteins in the development of new therapeutic strategies for AD. The aim of this paper is to study a human monoclonal antibody for semorinemab, using tau P301L-Tg mice and Crab monkeys as experimental models, and to investigate the therapeutic effect of semorinemab on AD in the early stages is more significant results, and has a high safety and stability. However, semorinemab did not show significant therapeutic results in mid-stage AD clinical trials. Phase II studies of semorinemab in AD are ongoing.

**Keywords:** Alzheimer's disease; Tau proteins; Tau P301L mutant mice; IgG4 monoclonal antibody; Semorinemab.

## 1. Introduction

Alzheimer's disease (AD) is the progressive neurodegenerative disease. AD is characterized by the brain changing of some protein precipitates, and brain cells die over time, typically beginning with the loss part of memory, and executive function decline, ultimately leading to a loss of independent daily living capabilities. In advanced stages of AD, severe loss of brain function can result in dehydration, starvation, and infection. These problems can result in death. Surveys indicate that about 1% of people at the age of 60 have AD, and this proportion increases to about 30% by the age of 85. By 2050, this figure is expected to rise to about 13.2 million [1]. Official death certificates from 2019 indicate that AD was cause of death for 121,499 individuals, formally ranking is as the sixth leading cause of death in the United States.

In the field of medicine, dementia syndromes are generally recognized as complex diseases caused by multiple factors. In AD, the most common form of dementia, the exact etiology and pathogenesis remain incompletely understood compared to diseases such as cancer or AIDS, although researchers have proposed a variety of overlapping pathological mechanisms, such as amyloid deposition, tau protein abnormalities, neuroinflammation and oxidative stress. This incomplete understanding of etiology and pathogenesis, in turn, has led to challenges in the development of pharmacological treatments for AD and other forms of dementia, which, to date, remain an unresolved clinical challenge. So far, only five drugs have been approved for the treatment of AD, involving only two classes of drugs, cholinesterase inhibitors and memantine. Three cholinesterase inhibitors have been approved for the treatment of mild to moderate AD. Another treatment option for moderate to severe AD is memantine. Meanwhile, antipsychotics and antidepressants are used for behavioral symptoms of the disease [2]. The function of these drugs is to control symptoms, not to alter the course of the disease. In addition, during the last decade, there are relatively few clinical trials for AD, and the failure rate of these trials is 99.6% [2].

With the increasing incidence of AD and the severe limits of existing pharmacological therapies in slowing disease development and lowering clinical symptoms, there is a pressing need to

investigate and develop innovative therapeutic options. Current therapy techniques are symptom-focused and lack effective therapies for the disease's underlying pathological underpinnings. The purpose of this paper is to provide an overview of the most recent scientific advances in AD research as well as an in-depth analysis of the development of innovative pharmacological models, emphasizing the importance of developing targeted and effective novel pharmacological therapeutic regimens in the face of this increasingly pressing global public health challenge.

## 2. Early intervention and targeted therapies

Although AD has become a global dementia disease. To this day, the exact cause of AD remains undiscovered. According to the current research, several overlapping principles have been suggested to explain the causes of AD. The more prominent species hypotheses are Amyloid cascade hypothesis, Tau hypothesis, cholinergic hypothesis, and excitotoxicity [2]. All these hypotheses are focused on lesions of the nerves inside the brain. For the patients, parts of the brain and internal nerves are damaged. This leads to a decrease in the reactivity of the neurotransmitters responsible for transmitting information between cells, resulting in symptoms such as loss of memory, slowness of movement and inattention. Typically, AD causes the development of Beta-amyloid deposit, neuritic (senile) plaques, and neurofibrillary tangles inside the brain, along with elevated levels of tau in the brain. These abnormal proteins may cause other proteins to misfold as well, leading to the development of the disease [3].

Currently, AD is treated with drugs such as cholinesterase inhibitors and memantine, which only work in remission, but the current drugs are usefulness to slow the progression of the disease. Therefore, it is necessary to develop targeted and effective drugs. Based on previous studies, the current direction of research is to develop drugs that inhibit the growth of abnormal proteins in the brain caused by AD. In clinical trials, both amyloid- $\beta$  ( $A\beta$ ) peptides and tau proteins are seen as primary targets for the treatment of AD [4]. According to research, the main feature of AD is the co-existence of two abnormal structures in the brain, extracellular amyloid plaques and intra-neuronal transplacental fibrillary tangles. Notably, both structural proteins are composed of highly insoluble and closely packed filaments. And AD manifestations such as memory and cognitive decline may be linked to the accumulation of these plaques and tangles. At the same time, it can also lead to synaptic damage, which can cause neuronal death. And clinical trials have confirmed that the soluble forms of  $A\beta$  and tau proteins can interact with each other even if they do not form such accumulations of material as plaques and tangles. This phenomenon leads to neuronal toxicity and death [5]. This finding has important implications for understanding the pathogenesis of neurodegenerative diseases such as AD. Soluble toxic aggregates of  $A\beta$  and tau proteins can replicate and spread on their own in the brain in a prion-like manner. For therapeutic interventions in AD, it would be extremely beneficial to detect these toxic aggregates and intervene in the destructive biochemical processes they initiate, before the development of plaques, tangles, and cognitive deficits. This implies that early actions could effectively halt the progression of the disease. In short, early detection and interruption of the process of formation and spread of these toxic aggregates may be the key to successful treatment of AD [5].

## 3. Pioneering Strategies in AD by targeting Amyloid- $\beta$ and Tau protein interactions

Jada Lewis and her team revealed for the first time a functional link between  $A\beta$  and tau proteins through an innovative experimental design. The study was carried out in two main experimental phases, both using transgenic mouse models. First, the researchers selected mice carrying the tau P301L mutation, which is associated with non-Alzheimer-type frontotemporal dementia. These mice naturally accumulate fibre tangles associated with the disease [5].

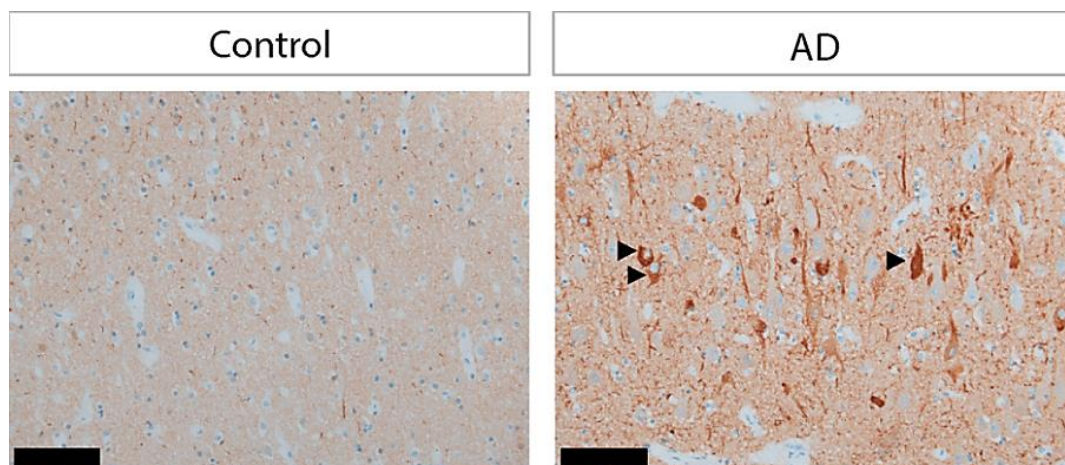
In one experiment, by injecting synthetic A $\beta$  into the brains of these mice, a significant five-fold increase in the number of fibrous tangles was observed near the region of injection. This result strongly demonstrates the role of A $\beta$  in promoting abnormal tau protein aggregation.

Another experiment was performed by crossing mice carrying the tau P301L mutation with another transgenic mouse that naturally accumulates plaques by overexpressing human amyloid precursor protein (APP) with a Swedish double mutation (K670N/M671L). The inbred mice demonstrated similar plaque formation as the parental APPSwe mice, but with significantly faster fibrous tangle formation. These experiments not only further confirm the interaction between A $\beta$  and tau proteins, but also highlight the potential value of targeting the aggregation of these two proteins for intervention in the development of new AD treatments. To investigate the interaction between tau proteins and A $\beta$  amyloid and its role in the pathogenesis of AD, innovative gene crossover experiments have been applied to develop drug models. Genetically modified mouse models were used to gain insight into the interaction between tau protein and A $\beta$  (beta-amyloid) and its impact on AD development. This approach involved crossing two specific transgenic mice: a PS19 mouse expressing the human tauP301S mutant protein associated with frontotemporal lobe dementia, and a PDAPP mouse expressing the human APP V717F mutant protein, which causes familial early-onset AD [5]. With this cross, the researchers were able to observe an accelerated rate of change in tau protein pathology, while at the same time, A $\beta$  plaque formation was not significantly affected. This finding implies that A $\beta$  may play a role in the pathological process of AD by acting prior to tau protein pathology, playing some sort of triggering or catalytic role. On the other hand, by crossing mice with the tau gene removed with mice carrying the APP mutation, the researchers found that the degree of plaque accumulation was like that of normal APP transgenic mice containing both tau genes, even in the complete absence of tau protein. This result suggests that A $\beta$ -induced pathological changes are not entirely dependent on the presence of tau protein. More strikingly, instead of exacerbating the pathological features of the disease, reducing the number of tau genes was able to protect the mice to some extent from typical symptoms of AD such as learning memory deficits and excitotoxicity. This suggests that reducing tau protein levels in the brain may have potential therapeutic value in preventing or delaying the development of AD. Whereas tau is a microscopic protein, the main component of NFT is the binding of hyperphosphorylated tau protein. In clinical studies, tau protein is a better target. These studies provide new insights into the complex pathological mechanisms of AD and emphasize the need to consider dual targets against both A $\beta$  and tau proteins when developing therapeutic strategies against AD [5, 6].

Based on the former experimental model, it can be hypothesized that A $\beta$  develops upstream of tau protein, and therefore a therapeutic concept can be proposed: i.e., removing A $\beta$ , which is responsible for the progression of AD, and preventing the slowing down of its deposition with tau protein and its accumulation inside the neurofibrillary tangles, and at the same time reducing tau protein in the brain by drugs, thus preventing synaptic damage of neurons in the brain, and further slowing down the decline of cognitive ability.

In patients with AD, pathological changes in tau protein spread along neuronal network pathways, suggesting that the mechanism of propagation involves trans-synaptic processes. Immunotherapy tau proteins in the extracellular space of the brain as a means of slowing down the aberrant aggregation and propagation of tau proteins between cells. Semorinemab, crafted as a human sourced IgG4 monoclonal antibody for AD therapy, zeros in on the tau protein. Research focused on semorinemab and its mouse analogs explored how they engage with tau protein variants across various species, spanning diverse phosphorylation and aggregation phases, including their capacity to latch onto the pathological proteins found in the brains of AD suffers. It has been demonstrated that mice carrying semorinemab, in a 2N4R-Tg mouse model of human tau expressing the carried P301L mutation (TauP301L-Tg), have a relatively reduced concentration of tau protein and attenuate the disease. Meanwhile, experiments on neuron-microglial co-culture *in vitro* confirmed the neuroprotective effect of semorinemab, which can provide a certain degree of prevention of AD, as well as early therapeutic intervention in the early stage of AD, thus forming an effective humanized IgG4

monoclonal antibody in the brain [6]. In the observation of experimental phenomena, muMTAU binds to the major human tau isoforms in lysates from normal brains and brain samples from brains with AD. As shown in Fig. 1 [6], it can be clearly seen that muMTAU undergoes a binding reaction with neurofibrillary tangles (nft) in AD brain slices. This demonstrates that muMTAU has some ability to specifically bind to tau protein aggregates in the AD brain, and semorinemab exhibits similar binding and selectivity to muMTAU, suggesting that semorinemab can also possess the same specific recognition and bind to tau protein aggregates. Using epitope localisation, semorinemab was found to bind to the N-terminus of tau proteins in AD brain section samples, with the most significant binding to tau protein fragments containing amino acids 6 to 23 [6].



**Fig 1.** The interaction between muMTAU and neurofibrillary tangles (NFTs) in human AD brain sections was confirmed through the application of immunohistochemical techniques [6].

#### 4. Discussion

In previous studies and reports, it has been confirmed that in the nervous system, the propagation of tau proteins from one neuron to another occur mainly through their extracellular release, and in particular this process occurs particularly frequently in the synaptic gap. The toxic substances released by these tau proteins can be effectively blocked as well as removed by monoclonal antibodies. Although there is currently little understanding of the pathological mechanism of tau protein formation and release toxicity, it is proposed that semorinemab can be utilized to bind to extracellular tau proteins based on the properties of semorinemab, as well as its substitutes, for binding in vitro. This approach is used to thereby mitigate the rate of propagation of toxins produced by pathological tau between neurons. In clinical trials, no adverse reactions and other safety concerns related to muMATU were observed by injecting a dose of 300mg/kg of the drug into TauP301L-Tg model mice and cynomolgus monkeys. And testing of AD volunteer participants revealed that the final situation remained largely consistent with the clinical results [6, 7]. This confirms the safety of semorinemab. This series of clinical trials has confirmed that semorinemab has a relatively significant outcome in the early stages of AD and is now moving into mid stage AD studies.

The P301L-Tg mouse model was used as a clinical trial model. Although useful experimental data can be derived using mice, there may be other characteristics that may have some error and impact with human clinical trial results. Moreover, no clinically significant therapeutic effect was found in semprinemab treatment of patients at a dose of 8100 mg over a period of approximately 73 weeks. Although seprinemab and improvement in ADAS-Cog11 testing, this phenomenon did not have a greater positive therapeutic impact on functional performance or overall therapeutic outcomes for AD.

## 5. Conclusion

The results of the study show that semorinemab, a humanized IgG4 monoclonal antibody against AD, illustrated significant potential in targeting tau proteins. By binding to mutant forms of tau proteins from multiple species, particularly in the phosphorylated and aggregated states, semorinemab and the mouse analogue were able to efficiently link to pathological proteins found in the brains of AD patients. Experimental data support that semorinemab demonstrates potential for preventive and early therapeutic interventions in AD by reducing tau protein concentrations and attenuating disease manifestations in the 2N4R-Tg mouse model.

In addition, the binding of muMTAU to the major tau isoforms in normal human brain samples and AD brain samples, as well as the specific binding of semorinemab to the N-terminal end of tau proteins in AD brain slices, particularly the significant binding to tau fragments containing amino acids 6 to 23, provide further evidence for the mechanism of action of semorinemab. These findings highlight the potential utility of semorinemab in inhibiting the spread of pathological tau proteins between neurons. Nonetheless, clinical trial results suggest that semorinemab shows some potential in the early AD stage, but its efficacy in mid-stage AD studies needs to be further evaluated. In addition, while no adverse reactions or safety concerns associated with muMATU were observed in the TauP301L-Tg mouse model, the results of these preclinical models may differ from the results of human clinical trials. Although the safety of semorinemab has been confirmed at an early stage, its long-term safety and efficacy need to be validated through more extensive clinical trials.

AD remains a worldwide disease and conquering it will not be easy. Current research is more limited to alleviating existing symptoms, while the true pathological mechanisms underlying the development of AD remain an unsolved mystery. In the future, multinational studies and clinical trials can be added to the clinical research and treatment to explore the effect of the combined application of the treatment of AD. Increase deeper research on the effects of tau and A $\beta$  proteins on the brain nerves and explore the pathways by which they disseminate toxins. The development of more effective Alzheimer's treatments would have far-reaching humanitarian and global health implications. It also advances a deeper understanding of the mechanisms of neurodegenerative diseases and opens new avenues for future medical research and treatment strategies, with the goal of improving the health of all humans.

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