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Tau Protein-Targeted Therapies in Alzheimer's Disease: Current State and Future Perspectives

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Abstract: Drugs available on the market for the treatment of Alzheimer's disease show only low symptomatic efficacy and phase 3 clinical trials against amyloid have been negative over the past 20 years. As dysfunctional tau protein is more closely correlated with dementia than amyloid, targeting tau protein may be more effective in improving cognitive function in cases of Alzheimer's disease. It should be emphasized that the development of tau protein therapy is in many ways more complicated than the development of anti-amyloid therapy. Several antibodies to the tau protein and two vaccines are currently undergoing clinical trials. Relatively speaking, tau protein therapy for Alzheimer's disease is still in its infancy. The purpose of this chapter is to draw the readers' attention to the various uncertainties and barriers to the success of tau protein therapy in treating Alzheimer's disease, and to show how future research and clinical trials can avoid previous limitations or mistakes.

Keywords: Alzheimer's disease; immunotherapy; neurofibrillary tangles; tau protein; vaccine for Alzheimer's disease

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INTRODUCTION

Alzheimer's disease is an age-related disorder characterized clinically by gradual memory loss and cognitive impairment. The disease affects more than 47 million people worldwide, and this number is expected to reach over 131 million by 2050. Alzheimer's disease is considered the most common cause of dementia (1, 2), covering about 60–80% of dementia cases worldwide (3). Available data indicate that the incidence of sporadic Alzheimer's disease is common and reaches 10–50% persons over the age of 65 (4). Factors that may be involved in the development of the disease include lifestyle habits such as diet, exercise, education, cognition and aging, immunosenescence, chronic infections and inflammation, latent infections, vascular factors, sleep problems and more (5–9). It has been suggested that intestinal microorganisms and ischemic episodes may also be involved in the development of this disease (10–13). Heritability of this form of dementia is high and estimated at 70–79% based on twin-studies. However, most evidence points to a heterogeneous etiology, with the disease resulting from a combination of many genetic, environmental, vascular and other currently unknown factors (5, 6, 10, 14–16). One particular genetic factor, the epsilon allele in the apolipoprotein E gene, has been identified as being associated with an increased risk of sporadic Alzheimer's disease, but a large percentage of the genetic risk remains unidentified. Alzheimer's disease is the leading cause of acquired disability in the world, affecting 1 in 2 in women and 1 in 3 in men (17). Alzheimer's disease is described as one of the unsolved problems of modern medicine (18), one which has a significant impact on the global economy, society and the families of the sick (19). In addition to significant personal costs, the total estimated worldwide financial burden due to dementia in 2010 was USD 604 billion (19). This is a serious public health problem that can grow to epidemic proportions over the next few decades if the disease cannot be prevented or slowed down (18).

Neuropathologically, Alzheimer's disease is characterized by the accumulation of amyloid in the form of plaques in the extracellular space and tau protein dysfunction in the form of neurofibrillary tangles present in the intracellular space, which are important in the final *post-mortem* diagnosis. The most neurotoxic forms of amyloid and tau protein are believed to be oligomeric forms that spread extracellularly as soluble oligomers through a prion-like mechanism (20, 21). The causes or mechanisms of amyloid plaques and neurofibrillary tangles formation are not yet well understood, but they are generally considered to be the result of a process of misfolding of proteins that leads to the development of pathological phenomena. Alzheimer's disease develops due to a combination of different neuropathological processes in the brain that cause massive neuronal death and loss of synapses. The resulting atrophy causes patients' brains to weigh about a third less than age-matched non-demented people (3). Today we know that the onset of Alzheimer's disease begins between 15 (in familial cases) and 20–30 years (in sporadic cases) before any clinical symptoms appear (2, 8, 22). By the time the clinical phenotype is recognized, significant neuronal and synaptic degeneration and massive neuroinflammatory changes have already occurred. Though the cause of Alzheimer's disease is not completely certain, it has been proven by

diagnostic methods based on the analysis of the patient's brain images that the accumulation of amyloid in the brain precedes the appearance of clinical symptoms and indicates a number of pathological factors that are ultimately not defined.

The amyloid hypothesis of Alzheimer's disease suggests that increased amyloid aggregation causes Alzheimer's disease by triggering toxic events leading to progressive neurodegeneration. However, no drug candidate targeting amyloid has yet led to effective treatment (3, 23). It is currently speculated that treatment requires early targeting of amyloid when the changes remain reversible, and clinical trials should focus on assessing amyloid compounds in pro-dromal Alzheimer's disease. There is no prophylactic or causal therapy for the disease, and the lack of knowledge about etiology and when or why the disease really begins, significantly complicates the work of physicians (24). Currently available treatments for Alzheimer's disease are only aimed at mitigating clinical symptoms and delaying cognitive decline. The development of a therapy for Alzheimer's disease has resulted in only a few approved drugs that provide temporary symptomatic relief in some patients. None of these clinically used drugs stop or slow the progression of the disease. Currently, the only drugs that have an impact, albeit modest and transient, on the main symptoms in patients with mild to moderate dementia of Alzheimer's disease are acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. For therapeutic measures to have a significant effect on the delay or actual prevention of Alzheimer's disease, it is likely that patients will need to be diagnosed at the stage of preclinical Alzheimer's disease (i.e., presence of Alzheimer's disease neuropathology, but without clear clinical symptoms) or during early signs of Alzheimer's disease that could be treated with disease modifying agents. Treatments that target the etiological mechanisms of Alzheimer's disease are urgently needed.

That treatments targeting amyloid plaques have proven ineffective draws attention towards another pathologic hallmark of Alzheimer's disease, neurofibrillary tangles arising from hyperphosphorylation of the tau protein. Experimental evidence indicates that the symptoms of Alzheimer's disease appear in the presence of both accumulating amyloid and dysfunctional tau protein (3), and research has shown a strong correlation between the accumulation of neurofibrillary tangles and the deterioration of cognitive functions (3, 25, 26). Thus, it is believed that tau protein dysfunction cannot be ignored as an etiological factor of Alzheimer's disease. Compounds that prevent tau protein hyperphosphorylation may therefore affect disease progression; however, the failure of previous trials to treat tauopathy in progressive supranuclear palsy (26) gives a strong warning of a possible failure. Nonetheless, the importance of tau protein as a potential independent cause of Alzheimer's disease, and therefore a potential target for treatment, serves as the basis for ongoing clinical trials against the protein. Despite the lack of an in-depth understanding of the role of tau protein in the pathology of Alzheimer's disease, efforts are underway to develop new therapies targeting tau protein in Alzheimer's disease. This chapter presents some of the proposed therapeutic compounds in preclinical and clinical studies that may affect the development of the next generation of anti-Alzheimer's disease drugs.

SUBSTANCES PREVENTING TAU PROTEIN POST-TRANSLATIONAL CHANGES

The strong correlation between tau protein phosphorylation and its influence on the development of pathological processes gave rise to the search for tau protein kinases inhibitors as potentially effective therapeutic agents in Alzheimer's disease. The most advanced strategy for inhibiting protein kinase in the clinic is currently directed at glycogen synthase kinase-3 (GSK-3) (27). To this end, pilot studies were performed to determine the clinical effects of lithium in patients with Alzheimer's disease; however, the results of this study were inconsistent, perhaps due to the small number of patients, low susceptibility and narrow therapeutic range of lithium (28).

Tideglusib (NP031112, NP-12) is a GSK-3 inhibitor that, in preclinical studies, reduced neuronal loss, gliosis and tau protein phosphorylation, and improved spatial memory deficit in transgenic mice (29). Further investigation with human trials included a pilot study conducted on 30 patients affected with Alzheimer's disease who were treated for 5 months with Tideglusib in a placebo-controlled phase IIa increasing dose clinical trial (NCT00948259). The results showed overall positive, but not significant, trends in their cognitive health, though the study affirmed the safety of the drug (30). Another 6-month phase IIb study on 308 patients affected with Alzheimer's disease was conducted at 55 centers in Europe (NCT01350362). Tideglusib proved to be safe in the study, but those treated with the drug did not show significant clinical benefit (31).

Another protein kinase that is increasingly being considered as a potential therapeutic target is Fyn tyrosine kinase, which phosphorylates tau protein at the N-terminal domain, and also plays a role in the amyloid signaling pathway (32). Saracatinib (AZD0530) is a Fyn inhibitor that improves memory deficiencies in transgenic mice and is considered safe and well tolerated based on a phase I clinical trial (NCT01864655) (33). A multicenter phase IIa study in 159 Alzheimer's disease patients treated with Saracatinib is still ongoing (NCT02167256).

The tau protein is also modified post-translation by lysine acetylation, which leads to impaired protein activity and triggers pathological aggregation. This suggests that acetyltransferase inhibitors may be a potential therapeutic strategy for Alzheimer's disease (34). A phase 1 clinical trial of salsalate has recently started to assess its safety and tolerability in patients with Alzheimer's disease (NCT03277573). Patients will be randomly assigned to receive salsalate or placebo twice a day for 1 year. At present, the results of this study have not been published.

Phase I studies on substance AZP2006 are coming to an end for Alzheimer's disease cases in France, but no detailed results are available as yet. The oral substance has been proposed to block phosphorylation of the tau protein thereby preventing the tau protein from folding incorrectly. In addition, it appears to stimulate macrophages, inducing the removal and elimination of an incorrectly folded tau protein.

Nilotinib is a c-Abl tyrosine kinase inhibitor, and the rationale for the use of nilotinib in cases of Alzheimer's disease is based on the clearance of tau protein and amyloid accumulated in the brain in neurodegenerative processes. Although the exact molecular mechanism is uncertain, nilotinib appears to cross the

blood–brain barrier and trigger autophagy in neurons to remove both tau protein and amyloid. The properties of nilotinib mentioned formed the basis of a randomized, double-blind, placebo-controlled, phase II trial to assess the effect of nilotinib on safety and clinical outcomes in patients diagnosed with Alzheimer's disease (NCT02947893).

SUBSTANCES THAT PREVENT MICROTUBULE DESTABILIZATION BY AMYLOID

The observation that amyloid oligomers destabilize microtubules and interfere with rapid axonal transport by activating calcineurin in tau protein-deficient mice has led to the conclusion that microtubule destabilization may be a key process during neurodegeneration (35). Epothilone D (BMS-241027), a small molecule stabilizer of microtubules that can pass through the blood–brain barrier, was able to increase the density of microtubules in axons, and improved cognitive function in a mouse transgenic tauopathy model; only insignificant changes in tau protein pathology were noted in the study (36). The substance was also tested in a double-blind, randomized, placebo-controlled, multicenter phase I clinical trial (NCT01492374) intended to assess its safety and tolerability in patients with Alzheimer's disease, but no results have been published and use of the drug in Alzheimer's disease has been suspended.

Recently, a small molecule called abeotaxane (TPI-287) was tested in a phase I study to assess safety and tolerability in patients with Alzheimer's disease (NCT02133846). Abeotaxane was administered intravenously for 9 weeks once per 3 weeks, with the option of extending the open label to 3 months. Ultimately, treatment was not well tolerated by people with Alzheimer's disease, and exploratory cognitive endpoints showed no significant improvement.

SUBSTANCES THAT PREVENT TAU PROTEIN AGGREGATION

Methylthioninium chloride easily crosses the blood–brain barrier and prevents tau protein aggregation *in vitro*, as well as in cells and animals models (37). A double-blind clinical trial in which single-site, 6-month methylthioninium monotherapy was conducted on patients with Alzheimer's disease (NCT00515333) showed signs of benefit in moderate cases of the disease (38). Leuco-methylthioninium bis, a stable, reduced form of the methylthioninium moiety, acts as a selective inhibitor of tau protein aggregation both *in vitro* and in transgenic mouse models. The primary analysis using leuco-methylthioninium bis derivative of methylthioninium chloride in the treatment of Alzheimer's disease was negative and the results did not suggest therapeutic benefits for Alzheimer's disease (39). Recently, a second phase-III study in patients with Alzheimer's disease treated orally, twice daily, (NCT01689233) showed no effect on primary endpoints (40). The authors' explanations of the effectiveness after the secondary analysis of the post-hoc subgroup raised many doubts, mainly regarding the methodology used and the interpretation of the results. Although these studies

did not produce positive results, they are nevertheless an important step in the development of anti-tau protein drugs.

Since positron emission tomography (PET) tau protein imaging is currently used in conjunction with amyloid PET imaging in an increasing number of Alzheimer's disease clinical trials, our knowledge of the ideal stage of the disease for testing anti-amyloid, anti-tau protein or a combination of both will undoubtedly be improved. There is growing optimism that we have the right tools to evaluate compounds that can stop and even prevent Alzheimer's disease.

IMMUNOTHERAPY AGAINST TAU PROTEIN

The first mention of data on possible immunotherapy in Alzheimer's disease appeared during research into the possibility that human β-amyloid peptide 1–42 may be able to cross the blood–brain barrier (41, 42). Despite the disappointing data from several advanced clinical studies on anti-amyloid immunotherapy in the treatment of Alzheimer's disease (23), immunotherapy in neurodegenerative diseases is very actively sought as a promising approach for the removal of pathological proteins, particularly in Alzheimer's disease. Recently tested anti-tau protein immunotherapy strategies in animal models have shown that immunotherapy may be clinically viable to remove toxic protein species in tauopathies such as Alzheimer's disease (43). Anti-tau protein immunotherapy strategies involve the removal of pathological species of tau protein with antibodies, which may ultimately improve neuronal function (26, 43). Thus, choosing the right epitope is crucial for obtaining effective immunotherapy (26). Because hyperphosphorylation is thought to be the cause of tau protein aggregation and the development of neurofibrillary tangles, many phospho-epitopes have been tested in animal models with final positive effects (13, 26, 27, 29, 32, 33, 35–37, 44). It should be noted that the tau protein undergoes modifications other than phosphorylation during the transformation from soluble protein to insoluble aggregates and deposits (13, 27, 44). As mentioned above, the cascade of events leading to the development of neurofibrillary tangles may include post-translational modifications such as phosphorylation, glycosylation, truncation and ubiquitination (13, 27, 29, 34, 44). This gave rise to a series of active and passive immunotherapy programs in the treatment of patients associated with Alzheimer's disease (26). Some of the clinical studies of tau protein-targeted immunotherapy described below target different protein domains rather than specific phospho-epitopes (26).

At present, studies of anti-tau protein immunotherapies in clinical trials are in their early stages. AADvac-1 is an active immunotherapy (vaccine) based on a synthetic tau protein peptide containing residues 294–305 derived from a fragment of a misfolded tau protein. Phase I clinical trials of the therapy have been recently completed (NCT01850238). In this first-ever, randomized, double-blind, placebo-controlled study, 30 Alzheimer's disease patients aged 50–85 received subcutaneous injections of AADvac-1 for 3 months; generally mild, if any side effects were reported, and high tau protein titers indicated effective immunogenicity (45). The study was then extended to patients who completed the AADvac-1 phase 1 study to administer additional immunization doses that they received for the next 18 months (NCT02031198) (46). The recruitment of 185 Alzheimer's disease patients in a 24-month, randomized, placebo-controlled, double-blind, parallel

TABLE 1 Clinical trials of tau protein-targeted immunotherapies (21, 26, 45–55)

Compound	Isotype	Therapy type	Patients	Trial phase
AADvac1	IgG1	Active	Alzheimer's disease	1/2
ACI-35	n.a.	Active	Alzheimer's disease	1
BIB076	IgG1	Passive	Alzheimer's disease	1
BIB092	IgG4	Passive	Alzheimer's disease	2
LY3303560	n.a.	Passive	Alzheimer's disease	2
RO7105705	IgG4	Passive	Alzheimer's disease	2
JNJ-63733657	n.a.	Passive	Alzheimer's disease	2
LuAF87908	n.a.	Passive	Alzheimer's disease	1
ABBV-8E12	IgG4	Passive	Alzheimer's disease	2
UCB0107	IgG4	Passive	Alzheimer's disease	2
IVIg	pIgG	Passive	Alzheimer's disease	2/3

n.a, not available.

group study, multicenter clinical safety and phase II efficacy study for AADvac-1 began in 2016 with an option to end by 2019 (NCT02579252) (Table 1).

So far only limited data from clinical trials and only for the AADvac1 vaccine have been presented (45, 46). Administration of the AADvac1 vaccine induced an IgG response against tau protein in 29 of 30 patients and a response to the shortened form of tau protein (151-391/4R) was noted in 25 of 28 patients (45). Although the phase 1 trial was not designed as an efficacy study, inter-individual differences in AADvac1-induced antibody titers enabled an assessment of the relationship between antibody response potency and disease progression. Patients with higher antibody titers were characterized by slower cognitive performance and lower hippocampal atrophy (46). Adverse reactions were generally mild, with the most common being local injection-site reactions (45, 46).

ACI-35 (vaccine) is a synthetic peptide comprising the tau protein sequence of human protein 393–408, phosphorylated at S396 and S404. In animal models, its administration has been shown to reduce both the quantity of aggregates of phosphorylated tau protein and the total pathological protein, as well as improve some cognitive functions. The vaccine triggers a specific antibody against the tau protein and an immune response that is independent of T cells. There are ongoing multicenter, double-blind, randomized, placebo-controlled phase I studies to assess the safety, tolerability and immunogenicity of ACI-35 in patients with mild to moderate Alzheimer's disease (ISRCTN13033912) (Table 1).

Data for AADvac1 and the fact that no dangerous adverse effects were reported for ACI-35 indicate that active immunization may be a safe way to counteract tau protein pathology. The safety aspect will become more and more important as active tau protein-targeted immunotherapy switches from the treatment of neurodegeneration towards its prevention (46).

Intravenous immunoglobulin (IVIg) derived from human plasma, consisting of polyclonal serum IgG obtained from blood donors, is effective in anti-inflammatory and immunomodulating therapy in cases of neurological diseases (50).

A randomized, double-blind, placebo-controlled phase III study (NCT00818662) involving 390 patients with Alzheimer's disease found no improvement in cognitive ability and function after IVIg infusions every 2 weeks for 18 months (Table 1) (47). Two further trials, one phase II (NCT01300728) and one phase III (NCT01561053) for the treatment of Alzheimer's disease are underway. Interestingly, it was found that tau protein-specific antibodies are present in the IVIg Flebogamma® product that recognizes a recombinant tau protein fragment containing residues 155–421, as well as tau protein aggregates from the brains of Alzheimer's disease patients (51).

In addition to active immunotherapy, strategies for passive immunotherapy using various antibodies to the tau protein are also under investigation (Table 1). It has been shown that this approach can improve behavioral and cognitive impairment in mouse models (52). In the past few years, three passive immunotherapy programs based on tau protein antibodies have been opened in clinical trials, mainly for the treatment of Alzheimer's disease as outlined in Table 1. BIIB092 is a humanized IgG4 monoclonal antibody against the extracellular N-terminal of a tau protein isolated from pluripotent stem cells of a patient with familial Alzheimer's disease (Table 1) (53).

ABBV-8E12 is a humanized monoclonal antibody against tau protein for the treatment of Alzheimer's disease in clinical settings. Currently, recruitment for a phase II clinical trial is done to assess the effects of ABBV-8E12 in patients with Alzheimer's disease (NCT02880956) (Table 1). A multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ABBV-8E12 in 400 patients with Alzheimer's disease should be completed by 2020 (54). A final approach to passive immunotherapy in clinical trials is R07105705, an antibody against tau protein, whose features regarding its nature are very limited and its preclinical efficacy unknown (55). In 2016, patients with Alzheimer's disease were recruited for the first stage of the study (NCT02820896). Although no results have been published, recruitment was initiated at the end of 2017 to an 18-month, randomized, double-blind, placebo-controlled phase II study to evaluate the efficacy and safety of RO7105705 in 360 patients with Alzheimer's disease (NCT03289143) (Table 1). Patients who complete the double-blind therapy will be invited to an optional 24-month extension period.

In summary, many active and passive tau protein-targeted immunotherapies are already in the clinical trial stage for the treatment of Alzheimer's disease (Table 1). Due to the fact that new strategies for tau protein-directed immunotherapy are still being developed, a number of key questions need to be answered, in particular regarding the choice of the immunogen, the species of tau protein to be targeted, as well as mechanism of action and safety (56–58).

FUTURE PERSPECTIVES

Per the studies and data noted in this chapter, the status of tau protein targeting therapy in the treatment of Alzheimer's disease is unclear due to lack of evidence or mutually exclusive observations. The small number of studies, and variable non-uniform measures of results suggest the field to be in its infancy and limit the possibility of making generalized conclusions. Although Alzheimer's disease is a real challenge for the pharmaceutical industry, there has been no clear progress in

treatment options in the past few years. Current drugs on the market show only low effectiveness, and clinical studies from the last 20 years have ultimately proven to be negative in phase 3. This was perhaps due to the hegemony of the amyloid hypothesis and focus of therapeutic strategies on amyloid, while the focus on tau protein, the main component of neurofibrillary tangles which correlates better with the degree of dementia than amyloid (25) has only emerged in recent years. A limited number of studies provide evidence of low or very low quality. Some studies have shown side effects, although the study times were short and the long-term risk of side effects was not determined.

To date, several drug trials targeting the tau protein have failed in clinical trials. Although there are various causes for these failures, the following points can help improve the results of future attempts. Firstly, the tau protein should be ideally targeted intracellularly, since most pathologies of the tau protein affect neurons inside. Secondly, as previous anti-amyloid immunotherapy attempts have taught us, it is important to continue to develop second- and third-generation methods in the field of tau protein immunotherapy. Smaller antibodies that are fragments of whole antibodies should have better access to the inside of both the brain in general and the neurons themselves, while also enabling them to bind to different epitopes of the tau protein than whole antibodies, providing greater and more effective therapeutic benefits. Thus, due to their smaller size, they will also be better suited for gene therapy than whole antibodies. We will be looking forward to future preclinical studies examining antibody fragments as a novel therapeutic approach. Thirdly, in recent years, a major focus has been on the implementation of drug-screening models that have focused on preventing seeding or spreading aggregation. Much less attention has been paid to the identification of compounds that inhibit the neurotoxicity of these aggregates, which is not necessarily associated with their seeding or spreading tendency. Ideally, all these markers should be readings in a unified test or model. Fourthly, the variety of conformer or strain of aggregates complicates the development of drugs for small molecule aggregation inhibitors but will probably not pose a problem in antibody-based therapy. Fifthly, other more general goals related to neurodegeneration should still be pursued, but in many ways, they are more difficult to solve than the removal of amyloid and tau protein, which are the hallmarks of Alzheimer's disease. Sixthly, shifting the time of therapeutic intervention to the very early stages of Alzheimer's disease should be a feature of long-term clinical studies. Lastly, targeting the tau protein is likely to provide better therapeutic benefits at a later stage in the development of the disease because tau protein dysfunction is more closely correlated with performance on cognitive tests than amyloid (25). Based on the data discussed in this chapter regarding the presence and abundance of intra- and extracellular pools of tau protein and its epitopes, and the finding that antibodies can have disease-specific efficacy and separate efficacy against tau protein toxicity, are the right direction for future preclinical and clinical investigations.

Future randomized clinical trials are needed to demonstrate the effectiveness of test substances and provide necessary data on several unresolved practical problems, that is, how and how long these substances can be administered to patients with Alzheimer's disease. What part of the tau protein is affected by immunotherapy and other test substances? How? What effect do treatment attempts have on the physiological and neuropathophysiological function of the tau protein? What human data was obtained to confirm this? These questions can

only be answered by undertaking large, multi-center clinical trials. At the moment, information on the use of anti-tau protein substances as drugs in the treatment of Alzheimer's disease seems interesting because of the possible effect on the accumulation of tau protein. The few clinical trials available to date have no genuine control and group randomization. Evidence has shown the causative factors and indicates the need for further research to show that anti-tau protein substances have a positive effect on patients with Alzheimer's disease. Though there is uncertainty regarding the potential of tau protein-targeting therapies in the treatment of Alzheimer's disease, and indeed the reasoning behind this skepticism is important to consider, it is still worthwhile to investigate. Though published studies on the subject are often flawed, and the findings should be taken with caution, the promising results should not be completely disregarded.

Another issue is the study design for substances directed against tau protein. Current ethical standards for clinical trials require that substances under investigation must be compared to the current treatment standard; this makes it difficult to conduct a true randomized, placebo-controlled study that is independent of potentially confounding treatments. This necessitates that the question of what standards of treatment serve as the best basis of comparison be answered prior to further study. Based on comprehensive pre-clinical results, as well as the initial clinical data, it is clear that the next step must be to test these substances in well-designed and controlled clinical trials. However, further double-blind studies are also needed to determine the efficacy of these substances in treatment. In conclusion, future clinical trials should focus on the proper selection of patients. Accurate and definitive explanation of the therapeutic properties of substances against tau protein can give hope for a long-lasting therapeutic effect. Based on the results of verified clinical trials, it may seem that the clinical effectiveness of substances that target tau protein is promisingly high, but this is not to be considered certain. We must be patient and wait at least a few years for thorough confirmation. No substances against the tau protein have been approved for use in the clinic. We hope that the evidence from ongoing clinical trials will help us better understand the therapeutic efficacy of substances against the tau protein and put them at the forefront of new therapies that patients and their doctors are eagerly awaiting. While some open questions and challenges remain, the data presented here encourages and demonstrates the potential of tau protein-based therapeutic strategies in the future treatment of Alzheimer's disease. The complexity of abnormal tau protein folding, aggregation and propagation of neuropathology, as well as the immune response during aging and neurodegeneration should be considered so that we can design and develop safe and effective treatment in a better way. Lessons must be learned from the disappointing experience accumulated over the past 20 years to develop disease-modifying therapies so that we can continue to progress, with caution, translating results from preclinical models into the development of drugs at the clinic. The growing interest in the tau protein will certainly lead to a deeper understanding of its function and will give new insight into the precise mechanisms and nature of tau protein species responsible for neuronal dysfunction and its causal role in the development of Alzheimer's disease. Hopefully, this will lead to an extension of the range of potentially useful therapeutic tools for treating such a devastating condition as Alzheimer's disease.

CONCLUSION

Although both amyloid and tau protein are very important, their relationship in causing Alzheimer's disease remains unknown. Treatment directed to amyloid and tau protein may be individually effective, but the convergent progression of amyloid and tau protein pathology suggests that combination therapy may eventually be required, especially in late stages when both are abundant. While ongoing works focused on single-goal therapies, the approach to double-targeting amyloid and tau protein is more likely to lead to a breakthrough (3). Referring to the above observations, it should be stated that Alzheimer's disease is an age-related neurodegenerative disease whose various neuropathological and therapeutic aspects are still being investigated and are not fully explained; pending success in the development of an effective treatment for Alzheimer's disease, it may be best to focus on preventive measures (59).

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