

## Targeted Therapies for Alzheimer's Disease: An Overview

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**Keywords:** Alzheimers' disease, Targeted, Therapies, Review.

**Abstract:** Dementia is the most common onset of Alzheimer's disease (AD). The main neuropathological characteristics of AD are extracellular amyloid plaques and intracellular accumulation of hyperphosphorylated Tau protein. Because of the complexity of the pathogenesis, the most treatment options are not effective at present. Conventional treatment strategies, acetylcholinesterase inhibitors and N-methyl-d-aspartate receptor antagonists, are only able to alleviate the symptoms of AD. The research on AD therapy has had limited success. Consequently, targeted therapy will become potential ways to treat Alzheimer's disease in the future. This paper makes a brief review on this aspect.

### Introduction

Dementia is the most common onset of AD. The main neuropathological characteristics of AD are extracellular amyloid plaques and intracellular accumulation of hyperphosphorylated Tau protein. Aging is a key risk factor for AD. Nowadays, there is no ideal strategy for the treatment of the AD, the current treatment is limited to relieve symptoms.

### The Present Status of Treatment of Alzheimer's Disease

Some progress has been made about the treatment of AD in recent years, but it is a pity that there is no good effect on the clinical treatment of AD. Such as, acetylcholinesterase inhibitors and N-methyl-d-aspartate receptor antagonists, are only able to alleviate the symptoms. Although numerous biotech drugs have been developed from studies of the molecular pathogenesis of AD, few can be used in clinical treatment[1]. In addition, conventional treatment strategies, such as acetylcholinesterase inhibitor drugs, often fail due to their poor solubility, lower bioavailability, and ineffective ability to cross the blood-brain barrier (BBB)[2]. The brain is separated from the rest of the body by formidable barriers that hinder delivery of therapeutic agents to central nervous system (CNS). In the human brain there are approximately 100 billion capillaries that have a net surface area of nearly 20 square meters. Despite its enormous surface area, the BBB lacks intercellular cleft and fenestrae and significantly restricts the entry of solutes to the brain from the periphery[3].

### Targeted the Rapy-A New Therapeutic Modality for AD

Targeted therapy is a new type of treatment strategy, which has a high degree of selectivity. It can not only improve the treatment efficiency, but also reduce side effects. Targeted therapy for AD, which will become a potential way in the future. Among of these ways, liposomes and nanoparticles can penetrate the lipid membrane, which has the characteristics of cell compatibility. Practice has proved that Liposome

and nanoparticles can be used as the carrier of drug delivery. We can take advantage of the specific properties of liposomes and nanoparticles to inject the specific parts of the drug into the specific site of the degradation of amyloid plaques and terminate the purpose of nerve fibers. As for immune therapy, we will review immuno-therapeutic approaches have been used to target both the A $\beta$  and phosphorylated tau. This new antibody can promote pathological protein degradation, improve the cognitive status of the patients and to avoid adverse reactions, which is considered to be a promising therapeutic strategy. In addition, for the gene therapy of AD, its application is aims to over expres of beta degradation enzymes. With the development of the research on the mechanism of gene expression regulation, gene therapy will become an important new method for AD.

### **Liposomes in the Treatment of Alzheimer's Disease**

Based on the specific properties of liposomes, it can play a role that wrapped drugs are used to target the specific parts of the brain to achieve the purpose of treatment of AD . This will be a potential way to treat Alzheimer's in the future. The first one, the H102 peptide-loaded liposomes prepared for nasal administration could effectively deliver H102 into the brain. H102 nasal formulations showed little toxicity on the nasal mucosa. After intracerebro-ventricular injection, it could improve the spatial memory impairment of A $\beta$  precursor protein (APP) transgenic mice and reduce the quantity of senile plaques and the level of APP and A $\beta$ , as well as enhance the activity of choline acetyltransferase (ChAT) and decrease the activity of acetylcholinesterase (AChE). This indicates that H102 maybe a promising drug for AD treatment[4]. The second one, a result shows that bi-functionalized mApoE-PA-LIP significantly destabilize preformed A $\beta$ 42 aggregates, mApoE-PA-LIP did not affect the cell viability, BBB monolayer integrity, NO production and did not induce ER stress. residues on A $\beta$  aggregates. So, the study suggest that mApoE-PA-LIP have the capability to affect A $\beta$  aggregation/disaggregation paradigm and to cross the BBB [5].

### **Nanoparticles in the Treatment of Alzheimer's Disease**

Nanoparticles have a further advantage over other different administration methods. Firstly, nanoparticles has high drug loading. Secondly, as a new targeting drug delivery system, drug-loaded nano-particles system has great potential , which can improve the curative effect, but also can reduce the side effects of drugs. The possibility of delivering a drug into the brain using polymeric nanoparticles may open a new perspective for the treatment of AD. Pulmonary administration is non-invasive delivery route for nanoparticles to cross the BBB and reach the brain parenchyma. The identification of a therapeutically relevant concentration has been clearly demonstrated by the reduction of  $\beta$ -amyloid in AD animal models[6]. Compared with intraperitoneal administration, Pulmonary administration is non-invasive. It is deserved further research and utilization.

Secondly, Apolipoprotein E3-reconstituted high density lipoprotein (ApoE3-rHDL), which presents high binding affinity to A $\beta$ , might serve as a novel nanomedicine for disease modification in AD by accelerating A $\beta$  clearance. Surface plasmon resonance, transmission electron microscopy, and co-immunoprecipitation analysis showed that ApoE3-rHDL demonstrated high binding affinity to both A $\beta$  monomer and oligomer. It also accelerated the microglial, astroglial, and liver cell degradation of A $\beta$  by facilitating the lysosomal transport. The findings here provided the direct evidence of a biomimetic nanostructure crossing the blood-brain barrier, capturing A $\beta$  and facilitating its degradation by glial cells, indicating that

ApoE3-rHDL might serve as a novel nanomedicine for disease modification in AD by accelerating A $\beta$  clearance, which also justified the concept that nanostructures with A $\beta$ -binding affinity might provide a novel nanoplatform for AD therapy[7]. Some researchers made an attempt to target the anti-Alzheimer's drug rivastigmine in the brain by using poly (n-butylcyanoacrylate) nanoparticles. The drug was administered as a free drug, bound to nanoparticles and also bound to nanoparticles coated with polysorbate 80. In the brain a significant increase in rivastigmine uptake was observed in the case of poly(n-butylcyanoacrylate) nanoparticles coated with 1% polysorbate 80 compared to the free drug. The results show that polysorbate 80 coated poly(n-butylcyanoacrylate) nanoparticles significantly transported the drug rivastigmine in comparison with the free drug to the brain. The high concentrations of rivastigmine achieved in the brain may be a significant improvement for treating Alzheimer's disease[8].

Besides, evidence is increasingly showing that epigallocatechin-3-gallate (EGCG) can partly protect cells from A $\beta$ -mediated neurotoxicity by inhibiting A $\beta$  aggregation. Given the low delivery efficiency of EGCG@Se to the targeted cells and the involvement of selenoprotein in antioxidation and neuroprotection, which are the key factors for preventing the onset and progression of AD, we synthesized EGCG-stabilized selenium nanoparticles coated with Tet-1 peptide (Tet-1-EGCG@Se, a synthetic selenoprotein analogue), considering the affinity of Tet-1 peptide to neurons. We revealed that Tet-1-EGCG@Se can effectively inhibit A $\beta$  fibrillation and disaggregate preformed A $\beta$  fibrils into nontoxic aggregates. In addition, we found that both EGCG@Se and vv Tet-1-EGCG@Se can label A $\beta$  fibrils with a high affinity[9]. Another study suggests that Se nanoparticles coated with B6 peptide (B6-SA-SeNPs) are a promising candidate drug for treating AD. They not only effectively inhibited Ab aggregation and disaggregated Ab fibrils, but were capable of protecting PC12 cells against Ab-induced toxicity. More importantly, B6-SA-SeNP successfully passed the BBB, and accumulated within PC12 cells. Further experiments in vitro and in vivo are required to validate these findings, thereby better demonstrate the potential of B6-SA-SeNPs as a therapeutic nanovehicle to treat AD[10].

### **Immunotherapy in the Treatment of Alzheimer's Disease**

Immunotherapy is a new modifying therapy for AD, whose main goal is to reduce the production of A $\beta$  peptides and/or increase the clearance of A $\beta$  peptides. Passive immunization in AD mouse models have shown satisfactory results, and more research is needed in clinical applications. For example, the performance of anti-A $\beta$  antibodies in transgenic mice models of AD showed they are delivered to the central nervous system (CNS), preventing and/or dissolving A $\beta$ . Moreover, these antibodies protected the mice from learning and age-related memory deficits. Development of such antibodies via passive immunization against A $\beta$  peptide fragments has been proposed for AD immunotherapeutic strategies. In spite of the fact that it will take considerable effort to establish a suitable immunization procedure, these results clearly strengthen the hypothesis that A $\beta$  plays a central role in AD, stimulating a new area for development of Alzheimer's immunotherapeutics[11].

The abnormal hyperphosphorylation and intraneuronal aggregation of this protein are early events in the evolution of the AD. Accordingly, immunotherapeutic targeting of the tau aggregation pathology during the very early pre-tangle phase is currently considered to represent an effective and promising therapeutic approach for AD [12]. Anti-tau oligomer antibodies which block tau aggregation have been shown to be

effective in P301S Tg mice; however, this study used cranial intra-ventricular injections, limiting its clinical translatability [13]. Recent studies have demonstrated that anti-tau antibodies can cross the BBB, be taken up by neurons via low-affinity Fc receptors and bind to pathological tau within the endosomal/lysosomal system [14].

### **Gene Therapy in the Treatment of Alzheimer's Disease**

The majority of clinical trials in AD have targeted amyloid pathology, and the results have been largely disappointing. For that reason, the concept of gene therapy is proposed. Gene therapy can directly introduce DNA or RNA into target cells through vector mediated gene transfer technology, which can realize that the expression of protective or therapeutic proteins and the silence of some pathogenic genes.

For example, nerve growth factor (NGF) could provide an alternative or complementary strategy to slow down neuronal atrophy in AD. The findings suggest that genetic delivery of NGF might help prevent or reduce loss of cholinergic neurons in AD. Degeneration of cholinergic neurons is an early and prominent contributor to cell loss and cognitive decline in AD [15]. NGF specifically prevents the death and stimulates the function of basal forebrain cholinergic neurons that undergo early and prominent degeneration in AD [16]. Likewise, siRNA therapy is a new molecular approach in the search for efficient AD therapy based on the principle of RNA interference. Some studies using RNA interference (RNAi) technology have examined the ability of siRNA to silence BACE. It is reported that BACE1 siRNA specifically influences the  $\beta$ -cleavage of APP and may be a potential therapeutic approach for treating AD. Suppression of BACE1 expression by siRNA was not found to change the subcellular distribution of APP and Presenilin 1, indicating that loss of BACE1 elicits no profound cellular defects. This finding confirms that BACE 1 is a potential therapeutic target for the treatment of AD [17].

Neprilysin (NEP) is a zinc metallopeptidase that efficiently degrades the amyloid  $\beta$  ( $A\beta$ ) peptides believed to be involved in the etiology of Alzheimer disease (AD). NEP is an attractive enzyme to use because it efficiently lowers brain  $A\beta$ , yet did not affect the levels of other peptides. The studies suggest that the use of muscle expressed Neprilysin (NEP) via adeno-associated virus (AAV) gene transfer may be an effective way to lower brain  $A\beta$  levels in AD patients. Through further study, NEP gene therapy could be an effective treatment for AD [18].

### **Conclusions and Perspectives**

As the ageing of the population becomes more and more serious, increasing prevalence of Alzheimer's disease, serious harm to the elderly people's health and quality of life. It is a key issue in the field of neurology to find effective treatment, prevent disease progression, and clarify the pathogenesis of Alzheimer's disease. Although various targeted therapies have their own advantages and disadvantages, we believe, with the development of science and technology, there will be a variety of safe and effective targeted therapies for AD.

### **References**

- [1] Godfray, J. and P. Estibeiro, The potential of antisense as a CNS therapeutic, *Expert Opin Ther Targets*, 7(2003) 363-76
- [2] Fonseca-Santos, B.M.P. Gremiao, and M. Chorilli, Nanotechnology-based drug

delivery systems for the treatment of Alzheimer's disease, *Int J Nanomedicine*,10 (2015) 4981-5003

[3] Kabanov, A.V. and H.E. Gendelman, Nanomedicine in the diagnosis and therapy of neurodegenerative disorders, *Prog Polym Sci*, 32(2007)1054-1082

[4] Zheng, X.Y, et al, Intranasal H102 Peptide-Loaded Liposomes for Brain Delivery to Treat Alzheimer's Disease, *Pharmaceutical Research*, 32(2015)3837-3849

[5] Bana, L, et al, Liposomes bi-functionalized with phosphatidic acid and an ApoE-derived peptide affect Abeta aggregation features and cross the blood-brain-barrier: implications for therapy of Alzheimer disease, *Nanomedicine*,10(2014)1583-90

[6] Sancini, G, et al, Pulmonary administration of functionalized nanoparticles significantly reduces beta-amyloid in the brain of an Alzheimer's disease murine model, *Nano Research*, 9(2016)2190-2201

[7] Song, Q, et al, Lipoprotein-based nanoparticles rescue the memory loss of mice with Alzheimer's disease by accelerating the clearance of amyloid-beta, *ACS Nano*,8(2014)2345-59

[8] Wilson, B, et al, Poly(n-butylcyanoacrylate) nanoparticles coated with polysorbate 80 for the targeted delivery of rivastigmine into the brain to treat Alzheimer's disease, *Brain Res*, 1200 (2008) 159-68

[9] Zhang, J, et al, Epigallocatechin-3-gallate (EGCG)-stabilized selenium nanoparticles coated with Tet-1 peptide to reduce amyloid-beta aggregation and cytotoxicity, *ACS Appl Mater Interfaces*, 6(2014)8475-87

[10] Yin, T, et al, Sialic acid (SA)-modified selenium nanoparticles coated with a high blood-brain barrier permeability peptide-B6 peptide for potential use in Alzheimer's disease, *Acta Biomater*, 25 (2015) 172-83

[11] Solomon, B, Alzheimer's disease and immunotherapy, *Curr Alzheimer Res*, 1 (2004) 149-63

[12] Rub, U, et al, Alzheimer's Disease: Characterization of the Brain Sites of the Initial Tau Cytoskeletal Pathology Will Improve the Success of Novel Immunological Anti-Tau Treatment Approaches, *J Alzheimers Dis* (2017)

[13] Yanamandra, K, et al, Anti-tau antibodies that block tau aggregate seeding in vitro markedly decrease pathology and improve cognition in vivo, *Neuron*, 80(2013) 402-14

[14] Congdon, E.E, et al, Antibody uptake into neurons occurs primarily via clathrin-dependent Fcγ receptor endocytosis and is a prerequisite for acute tau protein clearance, *J Biol Chem*, 288(2013) 35452-65

[15] Malkki, H, Alzheimer disease, NGF gene therapy activates neurons in the AD patient brain, *Nat Rev Neurol*, 11(2015)548

[16] Tuszynski, M.H, et al, Nerve Growth Factor Gene Therapy, Activation of Neuronal Responses in Alzheimer Disease, *JAMA Neurol*,72(2015)1139-47

[17] Jablkowski, M, et al, New type of BACE1 siRNA delivery to cells, *Med Sci Monit*,20 (2014) 2598-606

[18]Liu, Y, et a, Expression of neprilysin in skeletal muscle reduces amyloid burden in a transgenic mouse model of Alzheimer disease, *Mol Ther*, 17(2009)1381-6