# Emerging role of immune therapy in treatment of neurodegenerative diseases

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**Abstract.** Neurodegenerative disorders, a category of illnesses that develop as neurons gradually become defective and eventually die, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Slowly progressing neurodegenerative disorders are accompanied by cognitive decline and functional impairment, significantly burdening individuals and society. At present, clinical treatment is still mainly symptomatic support. The incidence rate has been rising in recent years, and there is a trend toward younger age, which has a negative impact on people's physical health and quality of life. The worldwide burden will continue to increase as the population of the elderly grows, with latent impacts due to prolonged disease durations and changing environments. Unfortunately, such disorders are still untreated because of their complicated pathophysiology. The primary goals of current therapies are to reduce disease symptoms and halt disease progression. Pre-clinical studies for therapeutic methods for AD, PD, and HD have shown promise for AAV intraparenchymal injections and cerebrospinal fluid (CSF) delivery. While CRISPR/Cas9-mediated approaches have been employed to develop disease models, identify pathogenic genes, elucidate pathogenesis mechanisms, and as a potential therapeutic approach. This review not only systematically introduces the current situation and diffuse subsets of neurodegenerative diseases, but also discusses treatments for neurodegenerative diseases.

**Keywords:** neurodegenerative diseases, therapy, Alzheimer's disease, Parkinson's disease, Huntington's disease.

## 1. Introduction

Dementia is a generic term for a particular group of symptoms featuring amnesia, and progressive impairment of language and problem-solving ability, indicating pathological changes in the brain. Accompanying the acceleration of ageing, dementia with neurodegeneration has become an urgent social issue. In the world today, more than 55 million individuals are affected with dementia. Additionally, it is predicted that this figure will rise by 10 million per year, with more than 60% of the cases occurring in low- and middle-income nations [1]. Since dementia is the seventh leading reason of death worldwide, resulting in disability and institutionalization, the economic burden exceeds 1 trillion US dollars annually [2,3].

Accounting for a notional 60% to 80% of dementia occurrences, AD is the most prevailing disease with a syndrome of dementia worldwide [4]. β-amyloid, a protein that builds up outside neurons, and tau, a protein that builds up inside neurons, are the hallmarks of AD. Neuronal loss and damage to brain

tissue coexist with external senile plaques and intracellular neurofibrillary tangles. The symptoms of AD are aggravated progressively, resulting in severe disability and dependence. Therefore, the long duration from the onset of the disease to death causes significant burdens to society. In 2021, 271.6 billion dollars were provided to people who take care of dementia patients, approximately resembling the total revenue of Google in 2022 (279.8 billion U.S. dollars) [5]. The total lifetime expenditure of caring for a patient was $ 364,641 (in 2022 dollars) [6,7].

PD, which affects more than 6 million people globally, is the second most prevalent neurodegenerative illness. This number has doubled over the past 25 years due to the growing number of older people, longer disease duration, and environmental changes [8, 9]. The symptoms of PD include movement disorder and non-motor symptoms, resulting in gradual loss of cognitive ability and mobility. The motor syndromes of PD include symptoms such as slow movement, tremors while at rest, stiffness in muscles, and changes in posture and walking. The progression of motor disability results in postural instability, gait difficulties, dysphagia, and dysarthria. Parkinson's disease can cause various non-motor symptoms such as impaired sense of smell, cognitive decline, psychiatric issues, sleep disturbances, problems with the autonomic system, pain, and fatigue [10].

## 2. Therapy

### 2.1. Current therapeutic approaches to treat ND

Currently, there is no panacea for NDs. Therapies aim to control the progression of the disease rather than cure it thoroughly. Management of neurodegenerative disorders is specific to different conditions, as the treatment usually involves a combination of medication and psychotherapy, depending on individual symptoms. The drugs typically cover neurotransmitter regulators, monoclonal antibodies targeted aggregated proteins, and medicines that alleviate dementia and psychosis-related symptoms (Table 1).

**Table 1.** The drugs typically used to treat neurodegenerative diseases.

| Disease | Type of Medication Category | Mechanism | Medicine |
|---|---|---|---|
| Alzheimer's disease | Amyloid-targeted antibody | Target and eliminate amyloid-beta plaques. | Aducanumab |
| | Cholinesterase inhibitors | Avoid the reduction of acetylcholin. | Donepezil, rivastigmine, galantamine |
| | Glutamate regulators | To increase the signal-to-noise ratio of glutamatergic transmission, inhibit the NMDA receptor. | Memantine |
| Parkinson's disease | Precursor of dopamine | Restore depleted dopamine levels. | Levodopa |
| | Decarboxylase inhibitors | Prevent the breakdown of levodopa in the peripheral system. | Carbidopa |
| | Dopamine agonist | Create effects similar to dopamine. | Apomorphine hydrochloride, pergolide, pramipexole dihydrochloride, ropinirole hydrochloride, rotigotine |
| Huntington's disease | Vesicular amine transporter 2 inhibitor | Reduce the levels of dopamine | Xenazine, Austedo |

The main focus of therapeutic approaches for managing AD is to target different pathways of disease progression in order to alleviate symptoms. The main focus of therapeutic approaches for managing AD is targeting different pathways of disease progression to alleviate symptoms. In June 2021, the US FDA approved Aducanumab, making it the first disease-modifying drug to receive approval [11]. It is an IgG1 monoclonal antibody administrated by intravenous injection, specifically binding to and clearing the extracellular Aβ plaques. While clinical data suggests that aducanumab can reduce the load of Aβ plaques, there is no evidence to support the idea that it can improve cognitive ability in patients. Cholinesterase inhibitors are another category of drugs for AD, as they limit acetylcholine degradation, an associated factor for the loss of cholinergic neurons [12]. Currently, the main cholinesterase inhibitors used clinically are donepezil, rivastigmine, and galantamine. Cholinesterase inhibitors are labeled as symptomatic treatment and cannot effectively cross the blood-brain barrier at significant doses, although they may improve patients' cognitive ability to some extent. Cholinesterase inhibitors are labeled as symptomatic treatment and cannot effectively cross the blood-brain barrier at significant doses, although they may somewhat improve patients' cognitive levels [13]. Glutamates confer neuronal damage by excessively activating postsynaptic neurons such as NMDA receptors. Therefore, the uncompetitive NMDA receptor antagonist memantine was created to prevent patients from overactivation NMDA receptors and the side effect caused by complete inhibition of NMDA receptors [14]. However, it merely alleviates symptoms instead of addressing AD pathology.

At present, treatments for PD focus on addressing motor and non-motor symptoms individually to provide relief for patients. One of the primary ways is using levodopa and carbidopa together to restore lowered dopamine levels in the substantia nigra region of the brain. Dopaminergic agonists are also available since they can produce effects equal to dopamine. The next group of medications that can be used to stop the oxidative deamination of dopamine and stop dopamine depletion are monoamine oxidase inhibitors [15]. Besides, rivastigmine, donepezil, galantamine, clozapine, quetiapine, pimavanserin, and melatonin are used to address dementia, psychosis, and sleep-related symptoms [16].

The licensed medications for the symptomatic management of Huntington's disease target abnormalities of voluntary and involuntary movement as well as symptoms associated with psychiatry. The first medication for chorea, the primary motor sign of HD, to receive FDA approval was tetrabenazine (Xenazine). It primarily acts as a reversible inhibitor of vesicular amine transporter 2, which reduces the amounts of dopamine and other monoamine transmitters produced by the presynaptic terminal in the central nervous system [17]. Austedo, the improved version of Xenezine, is also approved and has better physicochemical properties. Antidepressants and neuroleptics are also currently being utilised to treat the psychological symptoms that HD patients suffer on a worldwide scale. The psychological symptoms that persons with HD experience are currently being treated with a variety of neuroleptics and antidepressants worldwide [18].

The blood-brain barrier, which prevents the administration of adequate dosages, is the key obstacle to overcome. Drug molecules have limited access from the blood to the brain since the diffusion and transport of small molecules and proteins are impeded by different cells. Drug carriers must be capable of crossing the BBB by a paracellular or transcellular pathway. As a result, physical parameters such as size, molecular weight, surface activity, lipid solubility, and charge are essential. Numerous clinical studies focus on this conundrum, yet there is still a long way to go.

### 2.2. AAV

Symptoms of some subsets of NDDs have a genetic component, which leads to pathogenesis by affecting the physiological function of cellular processes. Neuromuscular disorders (NMDs) that are observed in the late stages of PD, for example, are featured by progressive muscle weakness and have a genetic predisposition. Hence genetic therapeutics are appealing for treating these groups of diseases.

Since the gene carried by these vectors does not integrate into the patient's genome, adeno-associated viral vectors (AAV) are excellent choices for the viral delivery of therapeutic genes. The Parvoviridae family of viruses includes AAV, which can naturally exist in host cells in a latent condition. A 4.7 kb single-stranded (ss) genome is present in its non-enveloped icosahedral capsid. To create a replication-

defective vector with the necessary safety feature, open reading frames (ORFs) are cut out of the viral genome [19].

AAV has been employed in numerous human trials over the years to gauge the positive clinical profile of this gene therapy platform. For instance, multiple pre-clinical trials for lysosomal storage diseases (LSDs), AD, PD, and HD have shown promise for AAV intraparenchymal injections and cerebrospinal fluid (CSF) administration. AAV intraparenchymal injection was tested in the first phase I/II trial for Canavan disease, a paediatric neurodegenerative disability caused by a mutant gene that codes for aspartoacylase (ASPA). The outcomes demonstrated the viability and safety of administering AAV through numerous vector delivery sites [20]. The function of basal forebrain cholinergic neurons, which degenerate rapidly in AD, is promoted by nerve growth factor (NGF). It has showed promise to offer neuroprotection in preclinical studies using monkey models [21]. Ten patients who received rAAV2-NGF gene transfer in the basal forebrain region were given NGF as part of a phase-I clinical trial [22]. Axonal sprouting in the direction of the NGF source and cholinergic neuronal hypertrophy was observed in the patient's brains as trophic responses to NGF. Additionally, two patients' cellular signalling was discovered to be activated, which led to an increase in cerebral glucose uptake and a reduction in the overall pace of cognitive decline. Additionally, hemiparkinsonian monkeys with AVV-induced overexpression of aromatic l-amino acid decarboxylase (AADC), which accounts for converting l-dopa to dopamine and is reduced in PD patients, exhibited a 50% improvement in l-dopa responsiveness [23].

Although AAV is a possible method for gene therapy for neurodegenerative diseases, there are still a number of challenges: (1) high doses of the vector are needed; (2) intravenous injection exposes the vector to anti-AAV antibodies in people exposed to AAV previously; (3) increased danger of hepatotoxicity; (4) additional safety risks [19]. As a result, improved versions of AAV capsids that have better CNS targeting efficiency are required, which would improve the efficacy of treating NDDs.

### 2.3. CRISPR/Cas9

CRISPR/Cas9-mediated gene editing is another possible therapy for neurodegenerative diseases. An essential component of the microbial adaptive immune system, CRISPR detects external nucleic acid sequences and destroys them via Cas9. Small noncoding RNAs (nucleic), which are translated from CRISPR loci, are used to identify foreign nucleic acids and direct Cas9 cleavage. The CRISPR system has been used in a number of industries since 2010, including medicine, agronomy, and animal breeding.

The issue that the earlier mice models typically do not develop frank neurodegeneration has been resolved by the application of CRISPR/Cas9 technology in the creation of AD, PD, and HD models that demonstrate better disease phenotypes [24]. Additionally, CRISPR/Cas9-mediated gene editing is a potential therapy technique and aids in the screening of pathogenic genes and the elucidation of pathogenesis mechanisms. For instance, in Tg2576 mice, CRISPR/Cas9-mediated deletion of the APP mutant gene reduces AD-like disease [25]. Another intriguing therapeutic strategy based on CRISPR/Cas9 is the use of guide RNA to direct Cas9, which transports transcriptional activators or inhibitors that may raise or decrease the expression of a given gene to the target location [26]. Several examples of CRISPR/Cas9 in neurodegenerative disorders are shown in Table 2.

**Table 2.** Examples of CRISPR/Cas9 in three diffuse neurodegenerative disorders.

| Pathology | Target | Model | Result |
|---|---|---|---|
| AD | APPswe nutation | Tg2576 mice | decreased pathogenic Aβ |
| | Mapt gene | C57Bl/6J mice | young mice with reduced susceptibility to excitotoxic seizures also showed normal memory formation |
| | PLCG2 gene variant | C57BL/6J mice | the microglial functions in Plcγ2-P522R KI mice have been improved |
| PD | DNAJC6 mutations | human embryonic stem cells | loss of DNAJC6 function causes autophagy defects |
| | VPS35 | mouse | pathogenicity is likely to be conferred by the Vps35D620N KI allele through a partially dysfunctional mechanism |
| | PINK1 and DJ-1 gene (knock out) | adult male rhesus monkeys | classic PD symptoms |
| HD | HTT gene | mouse | alleviated motor deficits in HD140Q knock in mice |

The possibility of CRISPR/Cas9-mediated treatment in AD patients has been demonstrated by research utilising the mouse model. In vitro and in vivo, CRISPR/Cas9 can specifically disrupt the APPSW allele, lowering pathogenic A and reducing the symptoms of AD syndrome [25]. The susceptibility to excitotoxic seizures was significantly reduced in tau knock-out mice, while the memory formations among young mice were rehabilitated [27]. A polyglutamine repetition in the Huntingtin gene (HTT) causes HD, a form of neurodegenerative disorder. CRISPR/Cas9-mediated inactivation can successfully minimise early neuropathology and limit endogenous mHTT production in the striatum of HD140Q-knockin mice. Besides, CRISPR/Cas9 can generate disease models and validate genes related to neurodegenerative diseases. Vps35, DNAJC6, PINK1, and DJ-1 were proved to be relevant to PD by this approach [28-30]. Notably, the combination of AAV and CRISPR/Cas9 seems promising, as a few studies used AAV to deliver the CRISPR/Cas9 system to edit target genes directly.

However, CRISPR/Cas9-mediated gene editing also confronts challenges. The implementation of this approach may be hampered by the potential for off-target cleavages by Cas9 and result in serious problems. Additionally, as a therapeutic approach, gene editing is limited to familial neurodegenerative disease cases and may be invalid in sporadic cases.

## 3. Conclusion

Overall, patients, their families, and society as a whole have been heavily burdened by neurodegenerative illnesses like AD, PD, and HD. Current therapies mostly concentrate on halting the disease's course and easing symptoms rather than fully treating it. Although newly developed therapeutic approaches such as CRISPR/Cas9 and AAV-mediated therapies are prospective, a few challenges need reasonable and accessible solutions.

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