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Therapeutic Applications of Antibodies - Antibodies in Non-Infectious Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease (HD) or amyotrophic lateral sclerosis (ALS) are all characterized histologically by the presence of deposits of misfolded proteins, tau and amyloid- β , α -synuclein, huntingtin or superoxide dismutase respectively. Currently these illnesses do not have any disease modifying treatment options. A novel therapeutic strategy that is being pursued is immunomodulation, which is using the body's immune system to target the self proteins that are deposited. Most of these promising approaches are still in preclinical development whilst some have progressed to Phase III clinical trials. As new insights are gained, it is hoped that these immunotherapies will be effective tools at slowing the progression of these debilitating diseases.

Keywords

Antibody; Alzheimer's disease; amyloid β ; amyotrophic lateral sclerosis; Huntington's disease; huntingtin; immunotherapy; neurodegeneration; Parkinson's disease; superoxide dismutase; α -synuclein; tau; protein misfolding; vaccination

Introduction

In 1796, the English physician Edward Jenner, was amongst the first to test out the principle of immunisation or vaccination. Jenner showed that by infecting a young boy with cowpox and then exposing him to smallpox, the young boy did not develop the disease and had gained immunity to smallpox. The work pioneered by Louis Pasteur a century later, wherein a weakened form of anthrax or rabies virus was developed and used to gain immunity, showed that the notion of vaccination could be successfully applied to prevent severe illnesses. Thus it could be readily argued that vaccination has probably made the greatest contribution to safeguarding human health.

The idea that immunotherapy could be used to treat neurodegenerative diseases is a relatively new one. Why would you use a vaccine to treat a non-infectious disease? And it had always been assumed that the presence of the Blood Brain Barrier (BBB) made the

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central nervous system/brain an immunoprivileged site and therefore not amenable to antibody treatment. However, after decades of attempts, researchers have now begun to make some headway in the fight against cancer, and even some neurological disorders (reviewed in [1-2]).

The focus of this review will be to provide an overview of the current literature with regards to the therapeutic application of antibodies in non-infectious neurodegenerative diseases. Specifically, we will examine the use of vaccination therapy in the common neurodegenerative disorders, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS).

Alzheimer's disease

AD is a progressive and devastating neurodegenerative disease. Currently it is the sixth leading cause of all deaths in the US. Over 5 million Americans are thought to have AD and by 2050 the estimated prevalence is 11 to 16 million people. The cost to society has been estimated at almost \$150 billion annually [3]. The pathological hallmarks of AD are the presence of extracellular amyloid plaques composed of amyloid beta ($A\beta$), and intracellular neurofibrillary tangles made up of the hyperphosphorylated cytoskeletal protein tau. Along with the presence of these two pathologies AD is characterised by extensive loss of neurons/synapses in temporal and cortical regions. Currently, there is no viable treatment for the prevention or cure of AD. Pharmacotherapy for patients is limited to drugs that modify acetylcholine neurotransmitter levels - acetylcholinesterase inhibitors or, to decrease N-methyl-D-aspartate (NMDA) receptor activity with an NMDA receptor antagonist, and are of variable clinical benefit but more importantly do not treat the underlying causes of the disease, and thereby do not slow its progression. More recently, new therapeutic approaches targeting $A\beta$ have been discovered and developed with the hope of modifying the natural course of the disease. Several active and passive immunotherapy approaches are under investigation in clinical trials with the aim of accelerating $A\beta$ clearance from the brain of AD patients. The most advanced of these immunological approaches is bapineuzumab, composed of a humanized anti- $A\beta$ monoclonal antibody, that is being tested in a Phase III trial [4].

Active immunisation

Studies in transgenic mice showed that immunization with aggregated $A\beta$ 1-42 was able to reduce $A\beta$ levels and associated pathology [5]. A follow up study showed that passive immunisation with anti $A\beta$ antibodies was also able to clear plaque accumulation [6]. Based on the stunning results shown by these vaccination studies, a Phase I clinical study in mild to moderate AD patients, using full length human $A\beta$ 1-42 (AN1792, Elan/Wyeth) in QS-21 adjuvant was initiated. A positive antibody response was reported in over half of the study participants [7]. The subsequent Phase IIa study had to be halted because 6% of the patients developed meningoencephalitis [8-9].

The cause of the meningoencephalitis observed between the Phase I and Phase IIa trials has been investigated and reported to be due to the addition of polysorbate 80 in the formulation used throughout the Phase IIa trials and which had only been included in the final stages of the Phase I study [7; 10]. In fact, the report of the phase I AN1792 trial which was only published after the suspension of the Phase IIa trial, did indicate that one patient from the immunised group had developed meningoencephalitis that was diagnosed after death and 219 days after discontinuing from the study, and reported as being not directly related to study treatment [7]. However the autopsy report of this patient indicated that T-lymphocyte meningoencephalitis was present and that it was likely to be a side effect of AN1792 vaccination [11]. The Phase I study elicited mainly a IL-2 positive and INF- γ -negative

immune response which would indicate a class II CD4⁺ Th2-type response in the immunised patients, whereas in the Phase IIa study most responders had both IL-2 and INF- γ -positive, CD4⁺ Th1-type response [10]. To overcome the proinflammatory problems associated with the modified peptide formulation, Wyeth/Elan have initiated new active immunisation trials in AD patients using a novel peptide-carrier protein conjugate [10].

Despite the suspension of the clinical trial, there were several positive outcomes. Neuropathological examination of three cases stunningly showed that all major A β containing species had been removed and there was a resolution of tau containing dystrophic neurites [12]. In a more recent study, phospho-tau AT8 immunostaining in the brains of 10 AD patients who were actively immunised with AN1792 was compared with 28 unimmunised AD cases. The AT8 load was significantly lower in the immunised AD group than the control AD group in several brain regions including the cerebral cortex, hippocampus, subiculum and entorhinal cortex. Interestingly, the decrease in AT8 immunostaining was found to be confined to neuronal processes, i.e. neuropil threads and dystrophic neurites, although the AT8 staining in the neuronal cell bodies, contributing to neurofibrillary tangles, appeared not to be affected [13]. A similar finding was found when PHF-1 immunostaining was examined, but there was no change in Alz50 or thioflavin-S staining levels [14]. Also, cognitive testing of the Zurich cohort indicated that of the patients who were immunized and generated antibodies to A β , there was a significantly slower rate of decline of cognitive functions and activities of daily living [15]. But this promising finding was not detected in the overall analysis of all the study sites, although a trend for cognitive stabilization was observed [9]. And disappointingly, more recent autopsy data from a few subjects from the trials indicates that complete clearance of A β plaques does not appear to halt the progression of AD dementia [16].

On the whole the data accumulated so far from the active immunisation trials of AN1792 have proven to be challenging to interpret. There has been tremendous heterogeneity in terms of immune response, biochemical changes in A β peptides measured, differences in brain volume analysis by MRI, clearance of plaques and assessment of cognitive performance, to draw any definitive conclusions as to the overall efficacy and safety of this treatment strategy. For example, data assessing cerebral volume changes in patients immunized with AN1792 who were antibody responders showed a greater brain volume decrease and greater ventricular enlargement, but no worsening of cognitive performance compared with placebo treated patients [17].

A recent study by Maarouf et al., examined the biochemical changes in post mortem brain tissue of nine patients who had been immunised with AN1792. They highlight the variability in response with immunotherapy and conclude analogous to Holmes et al. [16] that although in some cases plaques are totally eliminated there is no apparent clinical benefit and so the A β deposits alone are not the underlying cause of dementia [18]. It is conceivable that immunotherapy targeting different A β species, the oligomers rather than aggregated plaques, maybe more beneficial. This is because it has been suggested that soluble A β oligomers are more cytotoxic and affect neuronal activities such as long term potentiation (LTP), as well as correlating better with the extent of synaptic loss and cognitive impairment (reviewed in [19]). Thus active or passive immunisation targeting various A β oligomers may prove to be more beneficial in terms of preventing cognitive decline in AD patients. However, such conformational antibodies may recognise natural endogenous β -sheet structures [20], that could result in adverse reactions.

Passive immunisation

As mentioned above, an alternative method of immunisation that is also being pursued is passive immunisation. Monoclonal A β antibodies targeting various epitopes – N-terminus

(A β ₁₋₅), central domain (A β ₁₃₋₂₈) and the C-terminus (A β ₃₃₋₄₀), and others, are in various stages of clinical trials [21]. Three recent reviews have thoroughly covered the status of passive immunotherapy in the AD field and readers are encouraged to refer to them [22-23; 21]. Whilst both active and passive immunotherapeutic strategies have been shown to reduce amyloid plaque burden in various mouse models of AD and in the AN1792 trial, passive immunisation has the advantage of being generally a safer treatment option as it is less likely to induce an adverse immune response, but it has the disadvantage of being inconvenient as it requires monthly infusions and expensive due to the costs involved in manufacturing large quantities of antibodies. The ideal option would be a cheap, safe and efficacious active vaccine.

Intravenous immunoglobulin

Another quite novel immunological approach aimed at tackling AD pathology is to use intravenous immunoglobulin (IVIG). The group of Richard Dodel and colleagues has been at the forefront in the development of IVIG as a possible treatment for AD (reviewed in [24]). They discovered that naturally occurring antibodies against A β exist and can be found in healthy individuals but were reduced in AD patients, suggesting supplementation could be therapeutic [25-27]. An initial pilot study with five AD patients receiving IVIG infusions monthly for six months was carried out. The findings showed a decrease in the concentration of A β ₁₋₄₀ in the CSF and an increase in serum. A β ₁₋₄₂ levels were unchanged as were assessments of cognitive function [28]. Two further studies were carried out by Relkin et al. with eight and 24 AD patients respectively and improvements on MMSE and ADAS-cog were reported [29]. Based on these encouraging findings, a large Phase III clinical trial is now underway and data should be available in 2011 [24].

The clearest conclusion that may be drawn at this point from the A β immunisation trials is that therapy should be started presymptomatically for the greatest likelihood of clinical benefits. The most appropriate candidates would be individuals with familial forms of AD and subsequently those with the apoE4 isoform. With continued advances in identifying biomarkers for AD, others could then be enrolled if considered at risk for developing AD.

Tau immunotherapy

The other pathological hallmark of AD that is often overlooked is the intracellular neurofibrillary tangle (NFT). In the early sixties, ultrastructural analysis by electron microscopy showed that NFT's were composed of paired helical filaments (PHF) [30]. Thereafter, in 1985 it was discovered that tau, a heat stable microtubule associated protein, was a major component and antigenic determinant of PHF [31]. It was also shown that PHF's from AD brain were composed of tau in an abnormally phosphorylated state [32-33]. This was of significance as it had been shown that tau's ability to bind and stabilise microtubules is inversely related to its phosphorylation state [34-35].

The discovery that mutations in the tau gene alone could result in diseases collectively termed tauopathies [36-37] has reinvigorated efforts on the development of treatment strategies aimed at rectifying tau dysfunction. Tau mutations fall under two categories, 1) those that affect the alternative splicing of Exon 10, thereby affecting the ratio of 3 repeat versus 4 repeat tau isoforms, and 2) those that affect tau microtubule interactions. Thus, it has been proposed that in the tauopathies there is a loss of tau function i.e. microtubule binding ability, followed by a gain of toxic effect – the enhanced ability to form tau aggregates. Since tau hyperphosphorylation is thought to precede its cleavage, misfolding and aggregation [38-39], the most favoured treatment strategy aimed at preventing tau pathogenicity has been to target the putative tau kinases and phosphatases which may be involved in causing abnormal tau phosphorylation (for a recent review on tau treatment

options for neurodegenerative diseases see [40]). Our lab has developed tau immunotherapy as another potential therapeutic strategy. Tau immunotherapy had not been pursued previously since it was assumed that targeting an intracellular protein such as tau or phosphorylated tau species, would not be accessible to antibodies. The rationale for and putative mechanisms involved in antibody mediated removal of tau aggregates has been reviewed in detail, see [41-42].

Recent studies from our group have demonstrated that active immunization with peptides containing pathologically hyperphosphorylated tau epitopes resulted in a decrease in levels of aggregated tau which importantly included the prevention of cognitive impairments and reduction in other functional impairments in two tauopathy mouse models [43-44]. Hence, clearance of NFTs or their precursors could reduce the amount of synaptic and neuronal loss associated with AD. Of significance, the functional outcome correlated well with the reduction of tau aggregates [43-44]. Studies from related fields have helped to add credence to our tau immunotherapy approach as a viable treatment strategy. While our studies were underway, vaccination with recombinant α -synuclein was shown to lead to clearance of intraneuronal aggregates of the same sequence in transgenic Parkinson's disease model mice [45], and subsequently anti-A β antibodies were shown to be taken up into neurons in culture and promote the clearance of intracellular A β aggregates via the endosomal-lysosomal pathway [46]. Following our initial publication [43] there have been a few reports by other groups at various meetings supporting the feasibility of tau immunotherapy, one of which was recently published [47].

The idea that an immunological approach could be used to target an intracellular protein has met with a fair deal of skepticism. However, we have showed that following intracarotid injections of FITC-labeled anti-tau antibodies in tangle model mice, these antibodies are detected within brain neurons bound to tau aggregates [43]. Furthermore, clearance of extracellular tau may also be beneficial, as it may be toxic and/or have a role in the spread of tau pathology throughout the brain [48; 42]. The addition of various recombinant tau constructs to the culture media of SH-SY5Y has been shown to increase cell death [49]. More recently it was reported that extracellular tau aggregates, but not monomer, can be taken up by cultured cells and displace tubulin, co-localize with dextran, a marker of fluid-phase endocytosis, and induce fibrillization of intracellular full-length tau [50]. This interesting finding was extended by an in vivo study that indicated that extracellular tau mediates the spread of tau pathology through anatomically connected regions [51]. These findings clearly enhance the value of an immunotherapeutic approach targeting tau as these antibodies should have better access to the extracellular pool of tau compared to its intracellular one.

Using the 3XTg mouse model, immunotherapy targeting A β cleared early tau pathology but hyperphosphorylated or aggregated tau was not affected as in the human studies [52]. A β clearance in the AN1792 trial did not appear to affect tangle pathology [12], but two recent papers did report a significant decrease in AT8 and PHF1 density in immunised AD patients compared to non-immunised AD patients [13-14]. These findings indicate that anti-A β immunisation can clear both plaque and also some tau pathology. On the whole it would appear that the optimal immunotherapeutic strategy for AD would be one that targets both A β and NFT sequelae.

Parkinson's disease

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disease which manifests clinically in the loss of motor function. Patients present with the classical symptoms of tremor, rigidity, bradykinesia and postural instability (reviewed in [53]). A

diagnosis of PD can only be confirmed following post-mortem examination of brain tissue. Histological analysis shows the loss of dopaminergic neurons in the pars compacta of the substantia nigra and the presence of Lewy bodies (LB). LB's form in the substantia nigra, but also elsewhere in the brain. They are intracellular inclusions composed principally of α -synuclein [54]. The etiology of sporadic PD is unknown, but mutations in several genes have been discovered including SNCA (encoding the α -synuclein protein), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or dardarin), PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2 (reviewed in [55-56]. Other risk factors such as environmental toxins e.g. pesticides, mitochondrial impairments and oxidative stress, amongst others have also been proposed as being causative of sporadic PD [57-59].

As with AD there are no preventative or curative treatments for PD, but options such as medications and surgery can be used to provide relief from the symptoms. The most widely used treatment regimen is pharmacological to enhance levels of dopamine by 1) taking the dopamine precursor levodopa (L-dopa), 2) taking drugs that directly stimulate dopamine receptors bypassing the presynaptic dopamine neurons and 3) taking drugs that block the metabolism of dopamine [60-61]. Surgical interventions for PD had included transplant of foetal dopaminergic neurons into the striatum, but the initial promising outcomes proved to be short lived and resulted in debilitating dyskinesias [62]. Also it has been recently reported that in two subjects that received fetal mesencephalic dopaminergic grafts, the grafts had survived 11 to 16 years but had also developed α -synuclein positive Lewy bodies. The authors propose that the α -synuclein aggregation and deposition observed in the transplanted dopaminergic neurons was triggered by misfolded α -synuclein in the host, which was transmitted into grafted cells [63]. Further evidence for the transmissibility of α -synuclein was also shown in primary neuronal cultures and in two different neuronal cell lines [64]. This finding in clinically affected PD patients is akin to the report of the spreading of tau pathology in mice [51], and similar to the transmission of prionoses. More recent surgical options include deep brain stimulation (DBS), in which subthalamic nuclei receive high frequency stimulation from an implanted electrode(s). This procedure can help to reduce motor symptoms and improve quality of life (see [65] for a detailed review).

The first immunotherapeutic approach to PD treatment was carried out in a mouse model of Lewy body disease (LBD). Masliah and colleagues used recombinant human α -synuclein (α -syn) to immunise α -syn transgenic mice. Mice that developed a strong immune reaction were found to have reduced accumulation of α -synuclein aggregates in the cell bodies and synapses and reduced neurodegeneration, giving encouragement to the potential use of vaccination against α -synuclein in treating LBD including PD [45]. The authors also investigated a potential mechanism for the antibody mediated clearance of intracellular α -syn, they detected that α -syn-immunoreactive structures co-localised with the lysosomal marker cathepsin D. Thus indicating that lysosomal pathways could be activated by the internalised α -syn antibodies and facilitating the degradation of α -syn aggregates [45]. This study is also of significance since it showed that immunotherapy against α -synuclein, an intracellular protein, could be effective and providing support to the proof of principle for the tau immunotherapy studies undertaken by our group. It remains to be determined if this approach results in functional improvements. This would be of interest clinically since it would be necessary to show that immunotherapy for PD patients results in improvements in Parkinsonism symptoms. Also, in a more recent study, Benner et al., offer a note of caution. In their study, mice were immunised with a modified nitrated α -synuclein and this led to a break in immune tolerance and activated the adaptive immune system. Vaccination led to increased neuroinflammation and unfortunately also accelerated dopaminergic cell loss - analogous to the meningoencephalitis seen in the AN1792 trial [66]. This same group has now shown that using vasoactive intestinal peptide (VIP) as an adjuvant, they could promote

a regulatory T cell response in VIP injected mice. Splenocytes and regulatory T cells were then isolated from VIP treated or nitrated α -synuclein immunised mice, and transferred separately or together to mice treated with MPTP (a mouse model of PD). As previously reported, MPTP treated mice receiving splenocytes from only nitrated α -synuclein immunised mice had an elevated inflammatory response and increased neuronal death. But in MPTP treated mice that received pooled VIP and nitrated α -synuclein splenocytes, there was an attenuation of the inflammatory response that amazingly led to robust nigrostriatal protection [67]. Obviously as with the AD immunotherapy findings further studies are required examining the full range of immune response elicited by vaccinating with self or modified self epitopes.

Huntington's disease

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder that usually presents in adulthood with characteristic motor and cognitive features and with variable and diverse psychiatric disturbances [68]. HD is caused by an unstable CAG (coding for glutamine) repeat expansion in the huntingtin gene which encodes the huntingtin protein. The normal huntingtin gene has fewer than 36 CAG repeats, above 36 CAG repeats the gene is considered to have an expanded polyglutamine tract and beyond 40 repeats always results in HD [69]. The number of CAG repeats is clinically important since there is an inverse correlation between repeat length and age of disease onset [70-71]. As with AD and PD, HD also has a defined pattern of neuronal loss. Neuropathological examination shows atrophy in the striatum, including the caudate and putamen, and extending to other cortical regions as the disease progresses [72]. Additionally, microscopic aggregates of misfolded huntingtin protein is also present similar to the intracellular deposits of AD and PD. The discovery of the CAG expansion in the huntingtin gene allowed researchers to create transgenic mouse models of HD so that the pathobiology of the disease process could be studied. Data from these early mice models suggested that intranuclear accumulation of mutant huntingtin and the formation of neuropil aggregates precede neurological symptoms and neurodegeneration. Intranuclear huntingtin may affect nuclear function and the expression of genes important for neuronal function, whereas neuropil aggregates may interfere with neuritic transport and function. These early pathological events, which occur in the absence of neurodegeneration, may contribute to the neurological symptoms of HD and ultimately lead to neuronal cell death [73]. However, data from cellular models has indicated that intranuclear inclusions may reflect a cellular mechanism to protect against huntingtin-induced cell death [74]. Thus although new insights have been gained into the mechanisms of the disease process, again as with AD and PD, no effective disease-modifying therapy has been identified.

In 2003 Miller et al., reported the first study examining the use of a DNA vaccine against mutant huntingtin in a HD mouse model. Plasmid immunisation was favoured over peptide immunisation as poly-Q-containing proteins are not readily soluble, and they suggest the antigen is kept in a more physiological context [75]. The incidence of diabetes in HD patients is increased and since the particular transgenic mouse model used in their study develops a diabetic phenotype, Miller and colleagues sought to examine if vaccination could ameliorate the diabetic phenotype. The results showed that DNA vaccination with a plasmid encoding a fusion protein of the first 17 $\alpha\alpha$ of huntingtin plus 103 CAG repeats plus green fluorescent protein was able to improve glucose tolerance and insulin deficiency in immunoresponsive mice [75]. Unfortunately, this trial did not examine the effects of vaccination on the more relevant HD behavioural or pathological phenotypes, and thus far no human trials have been conducted.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease in the USA, is the most common adult motor neuron disease - affecting both upper and lower motor neurons. The disease's primary hallmark is the selective dysfunction and death of the neurons in the motor pathways. This leads to spasticity, hyperreflexia (upper motor neurons), generalized weakness, muscle atrophy, and paralysis (lower motor neurons) [76]. Most individuals with ALS die from respiratory failure, usually within three to five years from the onset of symptoms [77]. As with the other major neurodegenerative diseases, most cases of ALS are sporadic, but about 10% of patients have an inherited familial form of the disease with a clear family history [78]. In 1993 Rosen and colleagues reported the discovery of mutations in the gene encoding copper/zinc superoxide dismutase 1 (SOD1) in 13 familial ALS pedigrees [79]. SOD1 mutations account for 20% of familial ALS cases and approximately 2 to 5% of sporadic cases. No consensus has yet emerged as to how SOD1 mutations lead to selective premature death of motor neurons, except that damage within motor neurons expressing mutant SOD1 drives disease onset, whereas damage within their glial cell neighbours expressing mutant SOD1 accelerates disease progression, see [80] for a recent review. Potential mechanisms include the ability of misfolded mutant SOD1 to trigger aberrant mitochondrial function, endoplasmic reticulum stress pathways, axonal transport defects, or excessive production of extracellular superoxide radicals [80]. Recently, mutations in a pair of DNA/RNA-binding proteins called TDP-43 and FUS/TLS have also been reported as causes of familial and sporadic forms of ALS [81-85]. Treatment options for ALS are limited and are aimed at alleviating symptoms of the disease rather than trying to cure it. Based on the experimental vaccination treatments for AD with A β Jean-Pierre Julien's group have carried out studies using active and passive immunization protocols with recombinant anti human SOD1 and antibodies against misfolded forms of SOD1 in transgenic mice models of ALS. They report that in the G37R SOD1 transgenic mouse model with late onset of disease, active immunisation with G93A SOD1 and adjuvant was able to delay the onset of disease, extend life span and attenuated neuronal loss in the spinal cord of the immunised mice. Interestingly, they also showed that a passive immunotherapeutic approach was effective at alleviating symptoms and delaying disease onset in a transgenic mouse model expressing high levels of mutant SOD1 protein [86]. Julien's group have extended these studies recently by testing passive immunisation with monoclonal antibodies that are specific to misfolded forms of SOD1. One of their candidate antibodies was able to decrease levels of misfolded SOD1 protein in the spinal cord and prolong the lifespan of treated transgenic mice [87].

The authors suggest that the data from their in vivo studies offer encouragement that antibody based treatments can be viable for the treatment of ALS patients with familial forms of ALS with SOD1 mutations [87].

Conclusion

The use of immunomodulation to treat neurodegenerative diseases has undergone rapid development in the past decade. The positive outcomes reported in animal models of diseases such as AD have not always been replicated precisely in clinical trials but so far only A β targeting immunotherapies have been assessed in humans. Since this class of debilitating disorders has few disease modifying treatment options, further studies on the use of an immunotherapeutic approach are clearly warranted, and hopefully additional targets besides A β will be assessed in the clinic in the near future

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