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Targeting alpha-synuclein via the immune system in Parkinson's disease: Current vaccine therapies

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is defined pathologically by the abnormal accumulation of the presynaptic protein alpha-synuclein (aSyn) in the form of Lewy bodies and Lewy neurites and loss of midbrain dopaminergic neurons in the substantia nigra pars compacta. Because of aSyn's involvement in both sporadic and familial forms of PD, it has become a key target for the development of novel therapeutics. Aberrant aSyn is associated with multiple mechanisms of neuronal dysfunction and degeneration including inflammation, impaired mitochondrial function, altered protein degradation systems, and oxidative stress. Inflammation, in particular, has emerged as a potential significant contributor early in the disease making it an attractive target for disease modification and neuroprotection. Thus, immunotherapies targeting aSyn are currently being investigated in pre-clinical and clinical trials. The focus of this review is to highlight the role of aSyn in neuroinflammation and discuss the current status of aSyn-directed immunotherapies in pre-clinical and clinical trials for PD.

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Keywords

Parkinson's disease; Alpha-synuclein; Immunotherapy; Clinical trial; Synucleinopathy

1. Introduction

Parkinson's disease (PD) cases are projected to increase to over a million people in the United States by 2030 (Marras et al., 2018). At the time of diagnosis patients typically display a combination of motor symptoms including bradykinesia, resting tremor, rigidity, and postural instability. There are also a host of non-motor symptoms associated with PD that include gastrointestinal and autonomic dysfunction, cognitive impairments, and neuropsychiatric dysfunction. The pathological hallmarks of PD are the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SN) and the development

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Declaration of competing interest

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of proteinaceous inclusions in Lewy bodies and Lewy neurites in the brain and periphery. While PD was first described in 1817 by James Parkinson, it was not until the late 1990s that alpha-synuclein (aSyn) was first linked to the disease (Polymeropoulos et al., 1997; Spillantinin et al., 1997; Krüger et al., 1998). Since then, studies on aSyn and its role in PD have permeated the field and aSyn is now a key target for therapeutic development.

Alpha-synuclein is a 140 amino acid presynaptic protein involved in plasticity, vesicular handling, and neurotransmitter release (Cabin et al., 2002; Vargas et al., 2014; Yavich et al., 2004). The protein is divided into three distinct regions that include a N-terminal lipid binding region, a central non-amyloid-β component, and an acidic C-terminal region (Ahn et al., 2006; Sode et al., 2007; Rodriguez et al., 2015). In its soluble form, aSyn is primarily monomeric and unfolded. When pathological, aSyn misfolds into oligomeric and fibrillar structures along with post-translational modifications that include phosphorylation at Ser129 (Conway et al., 2001; Fujiwara et al., 2002). In the earliest familial forms of PD, missense mutations in the SNCA gene that encodes for aSyn were identified with one family having the amino acid substitution alanine-to-threonine at codon 53 and another with an alanine-to-proline substitution at codon 30 (Krüger et al., 1998; Polymeropoulos et al., 1997). At that same time, it was also shown that aSyn was a major component of Lewy bodies, implicating it in both familial and sporadic forms of PD (Spillantini et al., 1997). Now, a direct role for aSyn in PD pathophysiology is supported by multiple studies showing mutations, multiplications, and polymorphisms in the aSyn gene in sporadic and familial PD (Polymeropoulos et al., 1997; Spillanitini et al., 1997; Krüger et al., 1998; Singleton et al., 2003; Chartier-Harlin et al., 2004; Pankratz et al., 2009; Simon-Sanchez et al., 2009).

2. Inflammation in Parkinson's disease

2.1. Clinical evidence

There is considerable support for a key role of the immune system in neurodegeneration in patients with synucleinopathies that include PD, multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). Early evidence of neuroinflammation in PD showed increased human leukocyte antigen DR expression in the SN indicative of activated microglia, the resident immune cells of the brain, in postmortem brains (McGreer et al., 1988). When activated, microglia alter their morphology, become phagocytic, express increased levels of major histocompatibility complex (MHC) antigens, and release both proinflammatory and anti-inflammatory cytokines. Indeed, increased cytokine expression has also been found in PD including tumor necrosis factor-α (TNFα) in SN, striatum, and cerebral spinal fluid (CSF), interleukin (IL)-1β, and IL-6 in striatum and transforming growth factor (TGF)-β1 in striatum and ventricular CSF. (Boka et al., 1994; ; Mogi et al., 1994a,b, 1995). Later studies highlight activated microglia, increased MHC class II cells that correlate with aSyn deposition in the SN in PD, altered CD3, CD4, CD8 T cells, increases in the leukocyte marker CD45, and altered cytokine profiles in PD, MSA, and DLB (Imamura et al., 2003; Croisier et al., 2005; Rydbirk et al., 2017; Surendranathan et al., 2018; Williams et al., 2020). Positron emission tomography studies using the radiotracer [^{11}C]*(R)*-PK11195 for activated microglia corroborate postmortem analyses and show increased microglial activity that correlates with dopamine transporter binding and motor severity in PD (Ouchi

et al., 2005; Gerhard et al., 2006). The imaging work also indicates microglial activation can be an early pathological event in PD. While debatable, some epidemiological studies suggest the use of nonsteroidal anti-inflammation drugs (NSAIDs) may reduce the risk of developing PD (Chen et al., 2003a, b; Gagne and Power, 2010; Gao et al., 2011). Taken together, the postmortem, imaging, and epidemiological work make a compelling case for inflammation as an important mechanism of pathology in PD. How to target the inflammatory response therapeutically in PD is now an urgent area of study in the field with several current potential immunotherapies for PD specifically targeting aSyn in clinical trials.

2.2. Inflammation and aSyn animal models

Both innate and adaptive immune systems have been implicated in PD. The innate immune system is immediate and reacts rapidly to invading pathogens. It is antigen-independent and the pathogenic patterns it can recognize are limited. In contrast, the adaptive immune system is antigen specific and dependent which results in a slower response or activation time but has the capacity for memory to recognize pathogens it was previously exposed to. Both systems work together with the innate system tuning and influencing the adaptive immune response, and collectively they protect the body from harmful pathogens. As microglia are the resident innate immune cells in the brain, it is not surprising they play a key role in the immune response in PD (Allen Reish and Standaert, 2015). Microglia respond to injury to limit damage but have the potential to be both beneficial and detrimental to neurons. Reactive microglia and astrocytes are the most common inflammatory processes measured and reported in the brain in animal models of PD. Indeed, work in animal models of synucleinopathy has been essential in facilitating our understanding of the time course and series of immune-related events that can occur in PD (Table 1). They have also been instrumental in testing potential aSyn-directed immunotherapies that are now in clinical trials.

The Thy1-aSyn (line 61) mouse line overexpressed human wildtype aSyn under the Thy1 promotor (Rockenstein et al., 2002). This model has been extensively studied and develops multiple pathologies and behavioral deficits reminiscent of what is found in PD (Chesselet et al., 2012). Thy1-aSyn mice also develop a robust inflammation phenotype throughout aging making it a useful model for studying potential immunotherapeuties (Watson et al., 2012). As early as one month of age, Thy1-aSyn mice show increased microglial activation and increased TNF-α mRNA and protein in the striatum. At 5–6 months, TNF-α remains upregulated in the striatum but was also found to be increased in the SN and serum. Further, toll-like receptors (TLRs) 1, 4, and 8 were increased in the SN. By 14 months of age, TLR 2 was increased in the SN, and MHCII was increased in the striatum. By 22 months of age, peripheral CD4 and CD8 positive T cells were increased in blood. Collectively, these changes occur in the presence of aSyn overexpression but without frank neurodegeneration (Watson et al., 2012). Transgenic mice expressing mutated forms of aSyn report activated microglia and astrocytes in the brain but in general their immune response has been less characterized compared to the Thy1-aSyn mouse line (Giasson et al., 2002; Gomez-Isla et al., 2003). There is one reported transgenic rat line, the bacterial artificial chromosome (BAC) human aSyn rat, that develops a significant immune phenotype (Krashia et al., 2019;

Nuber et al., 2013). These rats develop increased CSF interferon gamma (IFN-γ) at 2 months of age and increased microglial density and activation in the SN and striatum at 4 months of age. They also show increased MHCII and CD68 positive monocytes in the periphery (Krashia et al., 2019). The transgenic aSyn models have been important in the identification and validation of different inflammation-related mechanisms in PD.

Targeted overexpression of human wildtype or mutated aSyn using recombinant adeno-associated viral (AAV) or lentiviral vectors in animals has proven to be a good model for studying the aSyn-related immune response. In this model, aSyn is typically overexpressed in the SN resulting in a protracted loss of nigrostriatal dopamine neurons (Kirik et al., 2002, 2003; Lo Bianco et al., 2002; Eslamboli et al., 2007; St. Martin et al., 2007; Theodore et al., 2008; Subbarayan et al., 2020). Targeted aSyn overexpression in mouse and rat models show increased CD68 positive microglia, increased MHCII expression, infiltration of B and T lymphocytes, increased proinflammatory cytokines, and increased immunoglobulin. Similarly, targeted overexpression of aSyn using AAV in non-human primates also resulted in upregulated microglial activation with increased MHCII expression in SN one year after injection.

In the newer aSyn preformed fibril (PFF) model of PD, synthetic aSyn fibrils are injected into the striatum or SN where they are taken up by neurons and act as seeds to induce endogenous aSyn to aggregate into pathological phosphorylated aSyn inclusions and ultimately leads to cell death (Luk et al., 2012). In these models, increased activated microglia, increased MHCII expression, infiltration of B and T cells, and activation of the microglial NLR family pyrin domain containing 3 (NLRP3) inflammasome have been reported (Harms et al., 2017; Duffy et al., 2018; Gordon et al., 2018; Earls et al., 2019). When AAV-aSyn and PFFs are combined in the rat similar increases in activated microglia and infiltration of CD4 and CD8 positive T cells have been shown. Taken together, the available aSyn animal models of PD display a robust inflammatory response and have been important in contributing to understanding the role of inflammation in PD and for the development of novel aSyn-targeted immunotherapies.

While vaccination approaches for treating PD have been investigated and refined over the last 15 years, the aSyn animal models have been instrumental in the identification of novel inflammation-related targets. For example, specific inhibitors targeting the NLRP3 inflammasome include Baicalein, flufenamic and mefenamic acids, and Hypoestoxide (HE) which all show anti-inflammatory effects in PD models (Rui et al., 2020; Daniels et al., 2016; Valera et al., 2015). Additionally, drugs including lenalidomide and AZD1480 regulate pro-inflammatory cytokines such as T cells have been shown to inflammation pathology in aSyn PD models (Valera et al., 2015; Qin et al., 2016).

3. aSyn-directed immunotherapies: preclinical studies

Immunotherapies can be classified as either passive or active immunization. Active immunizations are classic vaccination strategies that activate a prolonged humoral response through the administration of antigens to trigger the generation of specific antibodies (Baxter, 2007). Whereas passive immunization refers to the direct administration

of laboratory engineered antibodies. This type of immunization does not generate a humoral response and these antibodies can be humanized to prevent unwanted reactions. Additionally, this type of immunization can be closely monitored and even ceased if adverse side effects develop. Passive immunization, however, can require repeated administration of antibodies potentially long-term (Marcotte et al., 2015; Shahaduzzaman et al., 2015).

Multiple vaccination strategies have been tested in aSyn models of PD (Table 2). In one of the first approaches, Masliah et al. (2005) used active vaccination and immunized transgenic aSyn mice (Line D) for 8 months with recombinant human aSyn in *E. coli* from sequence verified human aSyn cDNA. Immunization in aSyn mice produced high affinity antibodies to aSyn and was associated with decreased accumulation of aSyn in neurons and reduced neurodegeneration. In A30P transgenic mutant mice the antibody mAb_{47} that is selective for aSyn protofibrils was tested in older (14 months) symptomatic mice. Administration of this antibody resulted in lower levels of soluble and membrane-associated aSyn protofibrils within the spinal cord and reduced motor symptoms (Lindström et al., 2014). A dendritic cell based vaccination approach in A53T transgenic mice was also shown to generate specific anti-aSyn antibodies and reduced IL-1α and improved motor function (Ugen et al., 2015). Similarly, the human-derived antibody BIIB054, which is highly selective for aggregated aSyn and has an 800-fold higher affinity for fibrillar aSyn over monomeric aSyn, was studied in multiple transgenic aSyn mouse lines (Weihofen et al., 2019). In this study wildtype, transgenic A53T mice under the prion promoter, and BAC A53T mice were injected with aSyn PFFs targeting the striatum. Treatment with BIIB054 was administered prior to and following PFF injections, resulting in reduced spreading of aSyn pathology, reduced loss of dopamine transporter in striatum, and improved motor function (Weihofen et al., 2019).

Immunotherapy targeting the C-terminal region of aSyn has also been shown to be effective in transgenic aSyn mice (Games et al., 2014). C-terminus truncation of aSyn is associated with increased aSyn oligomerization, propagation, and toxicity (Li et al., 2005; Michell et al., 2007). Using the Thy1-aSyn (line 61) model, mice were immunized with antibodies directed against the C-terminus of aSyn. Antibodies 1H7 and 5C1 were most effective at decreasing higher molecular weight aggregates, decreasing C-terminus aSyn levels and improving DA pathology and behavior (Games et al., 2014).

Using the AAV aSyn rat model, Sanchez-Guajardo et al. (2013) vaccinated rats using human recombinant aSyn prior to injection of AAV-aSyn into the SN. They showed aSyn vaccination decreased aSyn accumulation in striatum and this correlated with microglial activation, MHCII expression, and CD4 positive T cell infiltration. Importantly, this study also showed early and persistent recruitment of Foxp3 positive cells in the SN which suggests the induction of the Treg system that prevents detrimental autoimmunity and promotes tolerance (Schwab et al., 2020; Tan et al., 2020). However, PD is not the only synucleinopathy model used for developing and testing aSyn-directed immunotherapies. Using an active immunization approach, the AFFITOPE® vaccine AFF 1 was administered in a transgenic mouse model of MSA (Mandler et al., 2015). This vaccine induced aSyn specific antibodies in myelin basic protein (MBP) aSyn transgenic mice (Mandler et al., 2015). Immunization with AFF 1 decreased the accumulation of aSyn aggregates within

oligodendrocytes, reduced activated microglia, and slowed the spread of aSyn indicating encouraging translational potential to the clinical population (Mandler et al., 2015).

4. aSyn-directed immunotherapies: clinical trials

Immunotherapy trials for synucleinopathies are currently underway, with several completing phase 1 clinical trials that test for safety and tolerability (Table 3). The vaccines PD01A and PD03A developed by AFFiRiS were designed to target the C-terminal region of aSyn. The phase 1 randomized trial for PD01A and PD03A was conducted in patients with MSA (Meissner et al., 2020). Both treatments triggered an antibody response with PD01A resulting in an increased response compared to PD03A. These vaccinations show some promise in immunotherapy treatment for MSA, although they warrant further investigation. The safety and tolerability of PD01A and PD03A were also evaluated in PD. In a randomized, single-blinded phase 1 trial, PD01A was administered to PD patients and was deemed safe and well tolerated with no serious adverse events reported. This active immunization resulted in a substantial immune response against the aSyn epitope. (Volc et al., 2020). PD03A immunotherapy was also assessed in a randomized, placebo-controlled, phase 1 clinical trial in PD patients (Poewe et al., 2021). This trial evaluated immunological activity following immunization as a secondary objective. Immunization resulted in a sustained IgG antibody response against the peptide PD03 and was determined to have a good safety and tolerability profile in PD (Poewe et al., 2021). Another active immunotherapy, UB-312, targeting aSyn oligomers is currently ongoing in a phase 1 clinical trial (Table 3) (Nimmo et al., 2020). This study will determine the safety, tolerability, and immunogenicity of UB-31 in healthy participants and PD patients.

Passive immunization approaches targeting amyloid-β in Alzheimer' s disease have been used previously and demonstrate the ability of the immunotherapy LY3002813 (Donanemab) to reduce amyloid plaque deposition (Lowe et al., 2021). A recent study on a phase 2 clinical trial testing Donanemab in early symptomatic Alzheimer's disease replicated the reduction in amyloid plaques seen in phase 1 studies. However, Donanemab showed only a modest effect on cognitive decline, no effect on tau load, and one in four participants developed amyloid-related imaging abnormalities with edema or effusions (Mintun et al., 2021). These results from immunotherapy studies in Alzheimer's suggest the mere reduction in amyloid burden is likely insufficient to alter the course of the disease. Clinical trials of immunotherapies in synucleinopathies are currently not as advanced as those in Alzheimer's but it will be important to learn from those studies and proceed cautiously in future trials.

Passive immunization approaches in PD include the randomized phase 1 clinical trial of the anti-aSyn monoclonal antibody PRX002/RG7935 (PRX002) in patients and showed antibody binding in peripheral aSyn, increased PRX002 in CSF, and demonstrated good safety and tolerability (Jankovic et al., 2018). These findings supported a phase 2 study (PASADENA) of Prasinezumab (RO7046015/PRX002) in patients with early PD (Jankovic et al., 2018; Pagano et al., 2021). The primary conclusion of this study was that the PASADENA study population proved suitable to investigate the potential of Prasinezumab to slow PD progression (Pagano et al., 2021). The secondary endpoints, including a

reduction in the Part 3 (motor) MDS-UPDRS in the active arm, encouraged a phase 2b study (PADOVA) which is actively recruiting. Also in PD, the randomized phase 1 clinical trial of the monoclonal anti-aSyn antibody, BIIB054 (Cinpanemab), was conducted to evaluate this antibody's safety, tolerability, and pharmacokinetic action in patients with PD (Brys et al., 2019). Although this treatment appeared to be safe and tolerable, phase 2 recruitment of BIIB054 was terminated due to not adequately meeting the primary or secondary outcome measures resulting in the development of BIIB054 to be discontinued and the study to be closed. This negative outcome compared to the more promising Prasinezumab could be due to the different binding sites of aSyn as Cinpanemab binds to the amino-terminus of aSyn, while Prasinezumab binds to aSyn's C-terminus. Currently, another passive immunotherapy is ongoing in a phase 1 clinical trial investigating multiple ascending doses of MEDI1341 (Astra Zeneca) in PD patients. This study is estimated to be complete by May 2022. Previously, a single ascending does study of MEDI1341 in healthy volunteers was recently completed in March 2021 (Schofield et al., 2019). Results from these studies will ascertain the safety and tolerability of single ascending doses in healthy volunteers as well as multiple ascending doses in patients with PD.

5. Conclusions and future directions

Targeting the immune response in PD and related synucleinopathies is an active and growing area of research. Our knowledge of how the immune system reacts and behaves in these diseases has increased dramatically over the last decade. Active and passive vaccination approaches are currently in clinical trials and new links between peripheral and central immune responses and aSyn support the development of novel aSyn-directed immunotherapies and immune-related biomarkers for PD. Studies showing an association between monocytic changes in blood and PD are certainly compelling (Nissen et al., 2019). Recent work also suggests the monocyte-specific biomarker soluble CD163 in CSF may be a useful biomarker for PD as it inversely correlates with cognitive scores (Nissen et al., 2021). Interestingly, peripheral monocyte markers also correlate with immune and dopamine changes in the brain in REM behavior sleep disorder which is a common autonomic symptom in PD and a risk factor for synucleinopathies. Other well established non-motor symptoms in PD such as gastrointestinal dysfunction also implicate the peripheral immune system in PD and are actively being examined to determine novel therapeutic strategies for disease modification (Aho et al., 2021). These recent findings support an already strong rationale for targeting the immune system to help identify biomarkers of disease progression and disease-modifying therapies for PD.

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Abbreviation

AAV	adeno-associated viral vector
aSyn	alpha-synuclein

CSF	cerebrospinal fluid
DA	dopaminergic
DLB	dementia with Lewy bodies
IFN-γ	interferon gamma
IL	interleukin
MHC	major histocompatibility complex
MSA	multiple systems atrophy
NLRP3	NLR family pyrin domain containing 3
PD	Parkinson's disease
PFF	preformed fibril
SN	substantia nigra pars compacta
TGF	transforming growth factor
TLR	toll-like receptor
TNF-α	tumor necrosis factor alpha

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Table 1

Inflammation Profiles in aSyn Models.

Model	Age	Inflammatory Profile	References
Transgenic			
Thy1-aSyn (line 61)	1, 5–6, 14, 22 months	↑Activated Microglia (Str, SN), ↑TNF-α (Str, SN, serum), ↑TLRs 1,2,4,8, ↑MHCII (Str), ↑$CD4^+$, $CD8^+$ T cells (blood)	Watson et al. (2012)
A53T and A30P mice		↑Astrogliosis and microgliosis (ctx, hpc, spinal cord)	Giasson et al. (2002); Gomez-Isla et al. (2003)
BAC aSyn Rat	2, 4 months of age	↑Activated microglia (SN, Str), ↑IFN-γ (CSF), ↑ Monocytes (periphery), ↑MHCII (periphery), ↑CD68 (periphery)	Krashia et al. (2019); Nuber et al. (2013)
AAV-aSyn			
Mouse	4, 12 weeks p.i.	↑CD68+ Microglia, infiltration of B and T lymphocytes, ↑proinflammatory cytokine markers (TNF, ICAM-1, IL-6, IL-1α), ↑immunoglobulin	Theodore et al. (2008); Harms et al. (2013)
Rat	4, 8, 15 weeks p.i.	↑MHCII and $CD68^+$ microglia, ↑CD4 and $CD8^+$ T cells; ↑proinflammatory cytokine markers (TNF-α, IL-1β, IFN-γ)	Chung et al. (2009); Sanchez-Guajardo et al. (2010)
Non-human Primate	12 months p.i.	↑Activated microglia, ↑MHCII, B cell infiltration	Barkholt et al. (2012)
PFF aSyn			
Mouse	5 months	↑NLRP3 inflammasome, ↑Activated Microglia and Astrocytes, Infiltration of B and CD4 and $CD8^+$ T cells	Gordon et al. (2018); Earls et al. (2019)
Rat	2 month p.i.	↑Activated Microglia, ↑MHCII	Harms et al. (2017); Duffy et al. (2018)
AAV + PFF			
Rat	10 days p.i.	↑Activated Microglia, Infiltration of CD4 and $CD8^+$ T cells	Thakur et al. (2017)

Table 2

Pre-clinical immunotherapy studies.

Model	Compound	Route of Administration	Mechanism	Effect on aSyn	Effect on Inflammation	Effect on Behavior	References
MBP- aSyn transgenic mice	AFFITOPE® (AFF 1)	SC	Targets C-terminus of aSyn	Reduced aSyn aggregates	AFF1 activated microglia; ↑ anti-inflammatory IL-1Ra, IL-3, and IFNγ	Motor improvements: ↓ errors on round beam test	Mandler et al. (2015)
Transgenic mice mThy1- aSyn, line 61	PRX002	IP	Targets C-terminus of aSyn	Reduced intracellular aSyn	↓ astroglia and microglia; preserved TH in striatum	Motor, learning, and memory improvements: ↓ errors on round beam; ↓ path and latency to platform in water maze	Games et al. (2014)
Transgenic aSyn A53T (M83) mice & Transgenic BAC aSyn A53T	BIIB045	IP	Targets N-terminus on aSyn aggregates	Reduced aSyn pathology	Not measured	Motor improvements: ↑ latency in time to fall in wire hang test	Weihofen et al. (2019)

Table 3

aSyn-directed Immunotherapy Clinical Trials.

Active/Passive Immunotherapy	Compound	Route of Administration	Mechanism	Findings	Effect on α-syn	References
Active	PD01A/AFFiRiS	Subcutaneous injection	Mimics α-syn C-terminal; acts as B cell epitope	Completed; safe and tolerable	↓ CSF α -syn oligomers; IgG antibody response to α-syn epitope	Volc et al. (2020)
Active	PD03A/AFFiRiS	Subcutaneous injection	Mimics α-syn C-terminal; acts as B cell epitope	Completed; safe and tolerable	Sustained IgG antibody response to α-syn epitope	Poewe et al. (2021)
Passive	PRX002/RG7935 (Prasinezumab)/ Prothena Biosciences Limited	Intravenous infusion	Targets α-syn C-terminal to halt α-syn neuronal transmission	Completed; safe and well tolerated; Phase II is ongoing	Reduced free serum α-syn	Jankovic et al. (2018)
Passive	BIIB054 (Cinpanemab)/ Biogen	Intravenous infusion	Targets aggregated α-syn	Completed; did not meet primary or secondary outcomes; Phase II terminated	BIIB054/α-syn complex formation	Brys et al. (2019)
Passive	MEDI1341/Astra Zeneca	Intravenous infusion	Targets monomeric and aggregated aSyn	Phase I is ongoing	Currently unavailable	Schofield et al. (2019)
Active	UB-312	Intramuscular injection	Targets aggregated aSyn	Phase I is ongoing	Currently unavailable	Nimmo et al. (2020)