The hallmarks and existing therapies of Parkinson's Disease

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Abstract. Parkinson's disease is the world's second most popular neurodegenerative disease. Aggregation of alpha-synuclein is agreed to be the significant hallmark of it. Three hallmarks: alpha-synuclein aggregation, autophagy dysregulation, and mitochondrial dysfunction have interconnected relationships as they are within mutual restraints. Gene mutations such as PINK1 and PARK6 could lead to dysfunction of lysosome and proteasome, which promote the cell death of mitochondria and aggregated alpha-synuclein. Alpha-synuclein fibrils at the same time could attack autophagic substrate and trigger neuron cell death, and they end up secreting dopaminergic pigment cells and end with motor symptoms of Parkinson's disease. Existed therapies such as the medicine levodopa and vaccination of antibodies provided possible pathways to cure this disease. We focused on antibodies BIIB054, ABBV-0805, and PRX002 to discuss their clinical data and their effectiveness and safety. In this review, a comparison between passive immunization and other treatments is also made to show a comprehensive perspective on current therapies to provide researchers with pathways to develop other therapies.

Keywords: Parkinson's disease, Alpha-synuclein, Passive immunization.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease affecting the second largest number of people after Alzheimer's disease (AD) [1]. The prevalence of PD has shown rapid growth over the past 25 years as from 1990 to 2015 there is an increase of over 118% of individuals having PD. Overall, the risk and incidence of PD are directly proportional to age, meanwhile aging population is a global issue, and it triggers the rise of individuals having PD. By the year 2040, number of people affected by PD will reach over 12 million with conservative prediction [2, 3]. Environmental factors could also increase the risk of getting PD. One of the main factors is by-products of industrialization, including pesticides, solvents, and heavy metals. For example, paraquat and trichloroethylene, two of the toxic substances that could result in the dysfunction of mitochondria, are all in high usage, which increases the risk rate of getting PD [4].

Symptoms of PD can be split into two aspects: non-motor symptoms (NMS) and motor symptoms (MS). MS usually presents as a motor syndrome, which can greatly affect daily living, and is the main sign to diagnosis PD. NMS is also associated with PD as MS is the representative of the loss of dopamine as the secreting of dopaminergic (DA) pigmented cells in the compacta region of substania nigra while NMS is related to neurodegeneration on other structures. Some NMS appear before patients experience significant MS, therefore NMS work as useful evidence of the early phase of PD. Classical MS includes bradykinesia, which means slowness of movement as lack of dopamine makes the signal from the brain to muscle slow, reducing arm swing and facial expression, shorter footsteps, also leads to leaning forward. It could appear as freezing of gait at the late phase of PD, rigidity as movement is achieved by a group of muscles: one being excited as the other relax, but PD patient might appear with activating both muscles, leading to stiffness. Tremor is most widely known as over 70% of patients experience it. It is usually prominent at distal parts of the body (limbs, lip, jaws) in a frequency between 4-6Hz. NMS includes Neuropsychiatric features (>40%), for example, depression and anxiety led by pressure given by movement disorder in public, hyposmia (>70%), a sleep disorder caused by unpleasant dreams, difficulty sleeping, and drowsiness, pain by muscle rigid or loose and dementia (~30%)[1, 4].

The pathological hallmark used to diagnose PD is Lewy body dementia, which is composed of the aggregation of these 140 amino-acid alphas-synuclein (aSyn) proteins. Misfold of this protein leads

to other dysfunctions of cells which build up other hallmarks of PD, including dysfunction of mitochondria, neuroinflammation, and oxidate stress [4]. Existing therapeutic strategies treating PD could be divided into three types. The first is dopamine-related, as oral-based pharmacotherapy levodopa and deep brain stimulation (DBS) targets motor symptoms only, second type of drug controls other neurotransmitters to reduce symptoms, for example, anticholinergic agents that regulate tremor and rigid. The last type is therapies such as vaccination that control non-motor symptoms [5].

Levodopa is an important drug to improve the effects of PD as it can pass through one of the main obstacles of drugs targeting central nerves: Blood Brain Barrier (BBB) and directly control one of the symptoms of PD and it manually increases the level of dopamine, therefore, reduce MS, however, it is still not a cure of PD, same condition as anticholinergics [5]. Drugs that researchers wanted to develop are those that can intervene and limit the development of PD, or even prevent it, which need adaptive immune systems to be involved. Anti-aSyn immunotherapy shows a good result in effectiveness in animal models and clinical trials, which provided a pathway and inspiration for researchers to further develop vaccination targeting PD.

This review aims to have an introduction on the connection between the hallmarks of PD and analyze three existing monoclonal antibodies targeting aSyn. It causes adaptive immune response and the active body itself to react to misfold aSyn therefore resulting in curing and preventing PD. Their animal test and clinical trials, effectiveness, and safety of these strategies will be compared and discussed in this paper.

2. Hallmarks of PD

Even though PD has been discovered and recorded examples in human history for hundreds of years, diagnosing PD at the clinical stage still has to improve its accuracy as it is synucleinopathy, while other neurodegeneration diseases are all under this category such as AD and dementia with Lewy body, meaning their hallmarks might overlap [1]. There are no effective biological markers that could help us 100% confirm the appearance of PD, however, imagining techniques such as the study of the brain, and PET help characterize PD at the clinical stage with an accuracy of 95% [5]. However, there are still hallmarks/biological symptoms of PD that are common among all PD patients, which are aSyn aggregation, dysfunction of mitochondria, dysfunction of lysosomal and protease, and neuroinflammation. The relation of the first three hallmarks is complicated. Different factors might trigger any of them, for example, genetic mutation and environmental factors, but any of them that occur will cause the appearance other two as well. For example, aggregation of aSyn could cause dysfunction in both lysosome and mitochondria, The same situation to lysosome as it will cause damage in mitochondria and end with a loss of dopamine, directly causing symptoms of PD, but dysfunction of mitochondria might lead only to environmental factors and patient with purely mitochondria issue will not appear with aggregated aSyn or LB.

2.1. Alpha-synuclein aggregation

aSyn is a 14kDA, 140 amino-acid long intraneuronal protein, present as “natively unfolded” since there is no certain three-dimensional structure of it in aqueous solution. The primary structure of this protein could be divided into three domains: N-terminal domain (NT), NAC domain in the middle, and C-terminal domain (CT). NT is responsible for binding with the membrane, it’s also where most of the mutations that cause PD are found. NAC domain can form amyloid fibrils, which build the main structure in aggregated aSyn. CT is where most posttranslational modification (PTM) takes place, whereas it changes its interaction between ions such as Ca2+ [6]. Therefore, targeting NT of fibril could effectively reduce cytotoxicity as no binding with membrane means no dysfunction of cells and also limited the spread of aggregated aSyn [7].

Under normal conditions, aSyn appears as soluble [6]. When abnormal aggregation occurs, it first folds into oligomers, known as “on-pathway” species. These are also soluble. And finally, folds into

fibrils in a beta-sheet structure [7]. Both oligomers and fibrils are cytotoxic, and when they are endocytosed by other neuron cells, it will lead to neurodegeneration and inflammation. Studies show oligomers have better cytotoxicity rather than fibrils as the amphipathic NT region in alpha-helices helps it to bind cell membrane, and its core has a beta-sheet structure as well that ruins membrane integrity which again increases its cytotoxicity [7]. Cell culture experiments also proved fibril has lower cytotoxicity [6]. There are many causes of the aggregate of aSyn, such as gene mutation of SNCA, which is the gene in the human body that codes for aSyn. Mutation of this gene will directly cause misfolding aSyn and oligomers built by this will also destroy cell-to-cell contact as well as malfunctions of organelles. This is an autosomal dominant mutation that could be inherited [8]. Mutations at the cellular level might also trigger aggregation, such as the phosphorylation of aSyn. Multiple studies have agreed phosphorylation at Ser129 is the most common site found in PD patients [6, 9].

2.2. Mitochondrial dysfunction, reactive oxygen species (ROS), and Ca2+

The reason mitochondrial dysfunction is important to PD is because mitochondria work as an energy supply for cells. Lack of functioning mitochondria will result in a reduction of DA cells, which triggers the symptoms of PD. Keeping a balanced environment in the brain area is important to cells as any changes could have huge effects [4].

Mitochondrial dysfunction could be caused by genetic mutation. PARK genes are mutations in genes that are heritable and associated with PD. [10] PINK1 protein mutation is an autosomal recessive gene mutation on PARK6 loci, responsible for coding PTEN-induced kinase, causing mitochondrial dysfunction and mitochondrial calcium mishandling [8]. As well as Parkin, an E3 ubiquitin ligase protein, participates in the mitochondrial autophagic (as known as mitophagy) pathway. Both proteins have been found at endoplasmic reticulum (ER) and are responsible for regulating contact with mitochondria. Destroying this pathway could lead to misfunctioned Ca2+ homeostasis, mitochondrial metabolism, and apoptosis [10].

Autophagy is a gene-modifying process as it removes dysfunctional cellular components, such as wrong-worked mitochondria and misfolded protein, to prohibit the accumulation of and provide a healthy environment for neurons. This is selective autophagy and it needs receptors to recognize and target damaged cells. PINK1 targets mitochondria through translocase of the outer membrane (TOM) localized on the outer mitochondrial membrane (OMM). Accumulated PINK1 on TOM could activate Parkin, a marking protein that works as a sign for proteasome and leads to the degradation of damaged components. The relationship between PINK1 and Parkin is a positive feedback loop as the accumulation of PINK1 on OMM and phosphorylation of it actives Parkin, and as a ligase protein ubiquitin protein is attracted, providing more substance for PINK1 to phosphorylate [11]. Therefore lacking or overexpressed of both proteins could lead to aggregation of damaged components or over-cleaning of healthy cells, causing brain diseases.

The question of how Ca2+ homeostasis could be affected by gene mutation has not been agreed, but it is being affected. First is the finding that PINK1-led function loss of mitochondria could be redeemed by medicine specific to Ca2+ absorption of mitochondria, this stated these are related. The findings from Ghandi et al. and Heeman et al. supported two opposite opinions on PINK1 lead dysfunction causes mitochondrial Ca2+ overload or lack of it, respectively. Recent studies also found that PINK1 phosphorylates a certain mitochondrial inner membrane protein (LETM1), which mediates Ca2+ exchange, which leads to a high possibility for neuron cell death which reduces dopamine levels since DA cells have high sensation on increased Ca2+ level [4, 10].

Mitochondrial dysfunction could also be caused by a direct attack by aSyn oligomer. Reaches have revealed that aSyn oligomers can damage mitochondrial complex I, which is the first enzyme in the respiration chain. Damaging this meanwhile, damages all respiration of mitochondria depends on complex I, therefore impacting the normal function of mitochondria and ending with a burst of the cell due to an over-opened osmotic transition pore. Limited mitochondria function could destroy calcium homeostasis as well. Studies also found that aSyn oligomers have a high affinity toward

TOM20 peptide, one of the receptors on mitochondria, and interrupt its binding with TOM22, increasing ROS. Mitochondria can also be affected in several ways led by oligomers such as organelle fragmentation and blocking its transport [7]. ROS level could be measured and work as a marker of mitochondrial dysfunction, so it's a hallmark of PD.

Mitochondrial dysfunction could be caused by environmental factors. Such as a side product of a narcotic drug called MPTP, which is an inhibitor of complex I, results in the dysfunction of mitochondria. Insecticides might also affect mitochondria and patients could experience similar symptoms as PD patients [4]. However, gene-lead mitochondria dysfunction is more likely to have hallmarks of aggregated aSyn as well, but environment-triggered PD patients might not have LB or aggregated protein. This is the reason to increase accuracy in diagnosis, multiple hallmarks should all be tested.

2.3. Dysfunction of lysosomal and proteasomal dysfunction

Unlike the relation between aggregation of aSyn and other hallmarks of PD, which is led by it, dysfunction of lysosomal and proteasomal are more a parallel cause or factor of PD as they are the checks and balance system of aSyn aggregation. There are mainly two pathways for attacking misfolded proteins, which are the ubiquitin-proteasome system (UPS) and the autophagy-lysosomal pathway (ALP). Dysfunction mitochondria are cleaned by ALP mainly, but UPS is more used in aggregated proteins such as aSyn [7].

Attacked by oligomer could also end with dysfunction of the proteasome. Studies have shown soluble oligomers can inactivate the 20S and 26S proteasome by prohibiting other proteasome substrates from entering it, which will trigger aggregation of aSyn and lead to neurodegeneration. Another way is to affect the primer of proteasome which is ubiquitin. The same ligase as mentioned in the dysfunction of mitochondria, parkin could also be mediated by oligomer and cause oxidation/nitrification of it and decrease its level. This will result in increased aggregated damaged protein and neuron cell death. Genetic mutation of GCase enzyme could lead to dysfunction of the lysosome [11]. In summary, any of the two degradation pathways is mistaken and could all raise the risk of one's getting PD. Being aware of this hallmark could help us prevent and diagnose PD in an earlier stage.

2.4. Microglial Activation in PD – neuroinflammation

Neurodegeneration might be caused by inflammatory responses led by microglial, which has been proven fibril aSyn can activate microglia in substantia nigra [6]. Microglial are macrophage cells that exist in the Central Nerve System (CNS), which will be activated to M1 proinflammatory phenotype by misfolded and aggregated protein such as aSyn and controlling Blood-blood-brain barrier's (BBB) permeability, thus strengthening the local immune response. Activating microglial will lead to the releasement of high-level proinflammatory substances, which will get positive feedback to activate more microglial and meanwhile damage neuron cells and cause neurodegeneration [12]. In conclusion, this cycle will increase the symptoms of PD.

3. Immunotherapy for PD: Monoclonal Antibody

3.1. How can antibodies affect PD

As introduced, aSyn is the most significant hallmark as well as a causing factor of other hallmarks such as mitochondrial, and proteasome dysfunction and such. Therefore antibodies targeting aSyn should be the most effective and direct pathway to control the progress of disease. Meanwhile, this misfolded and aggregated protein is a strong substrate for antibody-based therapy since it could have high specificity due to special target sites for degradation. Understanding how aSyn spreads around the body is also important to know to create more effective vaccinations. aSyn shows a prion-like way to spread around the body, meaning it follows seed effect or permissive templating ---- one existing misfolded protein triggers other normal proteins to fold at the same time, attracting them to

aggregate and resulting in spreading around all areas quickly. A spread observed from the human brainstem to the neocortex proved the assumption of cell-to-cell transport of aSyn [9]. Even though the final fibril of aSyn is insoluble, oligomers, the middle substance could form into a soluble type that could enter the cell membrane and increase cytosolic aggregation of aSyn[7]. The transportation between cells of oligomer provides a good target since its aggregated aSyn widely exists in PD patients' bodies [9]. There are three options for controlling the symptoms of the existence of aSyn, which are damaging formed fibril/oligomer, entering cells and targeting in-cell aSyn, and limiting the cell-to-cell spread of aSyn. Immunization towards aSyn could be built in two ways: active immunization and passive immunization, caused by antibodies created by the body itself and antibodies directly vaccinated inside the body, respectively. After entering BBB, for outside cell aSyn, it could be cleared by the immune cell in the brain area, e.g. microglia, and for inside cell aSyn, it could trigger lysosomal degradation [13]. In the following text, there will be a summary and analysis of three existing monoclonal antibody-based therapies BIIB054, PRX002, and ABBV-0805, targeting fibril aSyn, in cell aSyn, and oligomer-specific antibodies, respectively [6, 7].

3.2. Existed monoclonal antibody (mAb): Cinpanemab (BIIB054), ABBV-0805, and Prasinezumab (PRX002)

BIIB054 is a human-derived monoclonal antibody, targeting site is the end of N termination (4-10) on aggregated aSyn [6]. This antibody was selected from healthy elderly's memory B-cells with no signs of neurodegenerative diseases. It has 800 times higher affinity and specificity on folded protein compared to single aSyn. Specificity towards aSyn, not beta or gamma, and also the specificity of BIIB054 to aggregate aSyn compared to other antibodies that prefer to bind with monomers to the same preference, as well as showing preferences towards aggregated aSyn compared to normal protein. At the same time delaying the development of the disease [14]. In the demonized phase 1 clinical trial of BIIB054, human tolerance was tested to reach around 90mg/kg, and adverse events (AE) (extreme side effects) were recorded at around 135mg/kg. however, the study also showed the possibility that antibodies that existed in the human body could bind with BIIB054 to make it dysfunctional [15]. In the double-blind phase 2 trial, participants extended from 48 to 357, this trial ended with unpleasant results as the control group and the treated group had no significant differences, including after a long-term treatment (52-72 weeks) there were no improvement in the aspect of symptoms such as sleeping condition and balance. The common AE of this antibody among participants were headache, falling, back pain, arthralgia, and nasopharyngitis. Due to poor results, this antibody was announced to be out of development after 72 weeks of phase 2 trial [16].

ABBV-0805 is the humanized product of antibody mAb47 from the mouse, an IgG4 monoclonal antibody. After humanization, ABBV-0805 shows a higher affinity towards aggregated aSyn and has high specificity to both oligomer and aSyn fibril. It also prevents the aggregation of aSyn and reduces cell death. Unfortunately, only animal tests have been done but no clinical date of this antibody yet, therefore evaluation of AE is not applicable [17].

PRX002 is a human-derived monoclonal antibody targeting the CT of aSyn. In the phase 1 trial, the safe dose is around 0.3-30mg/kg, narrower than BIIB054 (1-135mg/kg). And has an average terminal half-life of around 18.2 days while BIIB054 has 28-35 days [15]. This trial shows a significant decrease in free aSyn in serum but doesn't have cerebrospinal fluid collection (CSF)to prove the effectiveness of passing through BBB. AEs have also appeared in PRX002 but at a lower rate (<5%), including headaches, salivary hypersecretion, nausea, fatigue, and body pain are the mains and no anti-PRX002 antibody is recorded [18]. A trial in 2018 tested CSF and proved that PRX002 antibodies can pass through BBB. Phase 2 trial of this antibody was also double-blind and placebo-controlled for 52 + 52 weeks. The dose was tested from 1500mg to 4500mg. The result of this trial was presented by multiple scales evaluations of emotions, daily life commands, movements, and complications. In conclusion, patients with treatment show a decrease in number and have a better life quality [19].

A common issue that appeared in these antibodies, is that by only vaccination, it will be hard to say the process of PD is fully controlled or limited. It seems like multiple treatments targeting different hallmarks will have a more effective change of the disease. Meanwhile, a definite diagnosis of PD could only be done post-life, therefore there are also limitations on how to track the development of protein inside the brain with better scanning [15, 19]. To effectively treat and cure PD, there is still a long way to go.

4. Comparison of mAb and traditional treatments

Oral-based medicine and building immune system response are two main therapies nowadays. However, medicines such as levodopa only control motor symptoms, but the immune response from our body is the pathway that has the potential to affect and limit the development of PD [6]. Discovering and testing different antibodies that target different hallmarks of PD has been a popular topic nowadays.

4.1. Advantages of mAb

Immunoregulatory therapies by vaccination could be split into two ways: passive immunization, meaning inserting antibodies into the body, and active immunization, meaning inserting antigens into the body, has little differences in terms of effectiveness and other factors. mAbs belongs to passive immunization, which needs to have multiple and long-term treatment, but it generally has great results in affinity, and regulating and has the least activation on T cell response. Compared to active immunization, it works better on people with weak immune responses, such as the elderly, who are yet susceptible individuals of PD [6]. At the same time, active immunization, meaning targeting proteins existing inside the human body also has a high risk of triggering neuroinflammation, which could aggravate PD symptoms [9]. This proved the advantage of mAb.

4.2. Limitations of mAb

There are also a few limitations of mAb. First of all, mAb usually uses outer cell aSyn as substrate, meaning it cannot directly cure cells that engulfed misfolded aSyn, which the process of cell burst and cell death cannot be prevented, it can only prohibit the spread of aSyn among cells. Second is the effectiveness of the vaccinated object passing through the BBB, as it blocks out hormones and antibodies, passing rate of antibodies from the peripheral is only around 0.1%. The third limitation is the half-life is mAb is only 2-5 weeks, meaning patients must take frequent vaccinations, which leads to a high cost of therapy. Nanobodies seem to be the solution to all three limitations, as first, they show better results in passing BBB as it's much smaller than mAb, could be expressed as an antibody that could exist inside the cell, able to deal with inner cell aSyn, and reduce cell death, and also have longer half-life. But it also has a higher risk of immune inflammation than mAb [9].

5. Conclusion

In conclusion, Parkinson's disease being one of the unsolved problems in the world, does have complex relationships between the main hallmarks and has multiple concerns for researchers to design effective antibodies as the disease takes place in the brain. But recently there are more and more therapies launched and shown several great results in the clinical stage. Continue with this speed, a future with safe and effective treatment for Parkinson's disease will not be far.

References

[1] Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. The Lancet Neurology, 2021, 20(5):385–97.

[2] World Health Organisation. Parkinson disease, 2023.

[3] Dorsey ER, Sherer T, Okun MS, Bloem BR. The Emerging Evidence of the Parkinson's Pandemic. Brundin P, Langston JW, Bloem BR, editors. Journal of Parkinson's Disease, 2018, 8(s1):S3–8.

[4] Antony PMA, Diederich NJ, Krüger R, Balling R. The hallmarks of Parkinson's disease. FEBS Journal, 2013, 280(23):5981–93.

[5] Jagadeesan AJ, Murugesan R, Vimala Devi S, Meera M, Madhumala G, Vishwanathan Padmaja M, et al. Current trends in etiology, prognosis and therapeutic aspects of Parkinson's disease: a review. Acta Bio Medica: Atenei Parmensis, 2017, 88(3):249–62.

[6] Knecht L, Folke J, Dodel R, Ross JA, Albus A. Alpha-synuclein Immunization Strategies for Synucleinopathies in Clinical Studies: A Biological Perspective. Neurotherapeutics, 2022, 19(5):1489–502.

[7] Goedert M, Grazia Spillantini M, Serpell LC, Berriman J, Smith MJ, Jakes R, et al. From genetics to pathology: tau and a–synuclein assemblies in neurodegenerative diseases. Dobson CM, Ellis RJ, Fersht AR, editors. Philosophical Transactions of the Royal Society of London Series B: Biological Sciences, 2001, 356(1406):213–27.

[8] Pajares M, I. Rojo A, Manda G, Boscá L, Cuadrado A. Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. Cells, 2020, 9(7):1687.

[9] Castonguay AM, Gravel C, Lévesque M. Treating Parkinson's Disease with Antibodies: Previous Studies and Future Directions. Journal of Parkinson's Disease, 2021, 11(1):71–92.

[10] Sharma L, Lu J, Bai Y. Mitochondrial Respiratory Complex I: Structure, Function and Implication in Human Diseases. Current Medicinal Chemistry, 2009, 16(10):1266–77.

[11] Barazzuol L, Giamogante F, Brini M, Calì T. PINK1/Parkin Mediated Mitophagy, Ca2+ Signalling, and ER–Mitochondria Contacts in Parkinson's Disease. International Journal of Molecular Sciences, 2020, 21(5):1772.

[12] Kawahata I, Finkelstein DI, Fukunaga K. Pathogenic Impact of α-Synuclein Phosphorylation and Its Kinases in α-Synucleinopathies. International Journal of Molecular Sciences, 2022, 23(11):6216.

[13] Navarro-Romero A, Montpeyó M, Martinez-Vicente M. The Emerging Role of the Lysosome in Parkinson's Disease. Cells, 2020, 9(11):2399.

[14] Fleming SM, Davis A, Simons E. Targeting alpha-synuclein via the immune system in Parkinson's disease: Current vaccine therapies. Neuropharmacology, 2022, 202:108870.

[15] Weihofen A, Liu Y, Arndt JW, Huy C, Quan C, Smith BA, et al. Development of an aggregate-selective, human-derived α-synuclein antibody BIIB054 that ameliorates disease phenotypes in Parkinson's disease models. Neurobiology of Disease, 2019, 124:276–88.

[16] Brys M, Fanning L, Hung S, Ellenbogen A, Penner N, Yang M, et al. Randomized phase I clinical trial of anti–α-synuclein antibody BIIB054. Movement Disorders, 2019, 34(8):1154–63.

[17] Lang AE, Siderowf AD, Macklin EA, Poewe W, Brooks DJ, Fernandez HH, et al. Trial of Cinpanemab in Early Parkinson's Disease. New England Journal of Medicine, 2022, 387(5):408–20.

[18] Schenk DB, Koller M, Ness DK, Griffith SG, Grundman M, Zago W, et al. First-in-human assessment of PRX002, an anti-α-synuclein monoclonal antibody, in healthy volunteers. Movement Disorders, 2016, 32(2):211–8.

[19] Pagano G, Boess FG, Taylor KI, Ricci B, Mollenhauer B, Poewe W, et al. A Phase II Study to Evaluate the Safety and Efficacy of Prasinezumab in Early Parkinson's Disease (PASADENA): Rationale, Design, and Baseline Data. Frontiers in Neurology, 2021, 12:705407.