Scientists Think Alpha-synuclein is the Most Promising Target for Parkinson’s Treatment

Today’s available Parkinson’s disease (PD) treatments mask symptoms, for a limited time, while damage to the brain – the cause of the symptoms – continues to progress. Since The Michael J. Fox Foundation (MJFF) opened its doors in 2000, one of our top priorities has been the development of a treatment that can go beyond one that treats the daily symptoms of PD. For patients and families, it’s the single most urgent need, or simply, “a cure.” But to our Foundation, our foremost goal.

That is why the Foundation has invested millions of donor-raised capital in the most promising target for a Parkinson’s therapy that could slow, stop or even reverse the progression of the disease, something no current treatment can do: the protein Alpha-synuclein. The hallmark pathology of Parkinson’s disease (PD) — shared by nearly everyone with the disease — is aggregation of this protein into clumps called Lewy bodies. Researchers hypothesize Lewy bodies are toxic to brain cells, causing cell degeneration/death that leads to the progression of symptoms. Therefore, theoretically, preventing or degrading Lewy bodies could slow, stop or prevent Parkinson’s disease.

Since nearly all people with PD have Lewy bodies, a therapy targeting alpha-synuclein will likely help the greater PD population.

And as other related brain diseases — Lewy body dementia and multiple system atrophy — also show alpha-synuclein pathology, this line of therapeutics may have even more widespread application.

Momentum is building and we have seen more early-stage alpha-synuclein studies move into later-stage studies and testing in Parkinson’s patients. We are optimistic about the progress but sober about the work that remains. Our Foundation regularly adapts our ongoing strategy to balance continued support for promising individual alpha-synuclein therapies (more shots on goal!) while also addressing the well-articulated field-wide challenges around alpha-synuclein measurement. These combined efforts hold the potential to dramatically accelerate the evaluation of any alpha-synuclein-targeted treatment.
Nine Alpha-synuclein Treatments (and Counting!) are Testing in Parkinson’s Patients

While the protein alpha-synuclein was discovered by researchers in 1997, it took 15 years for the first alpha-synuclein-based treatment to reach the earliest stages of human testing. The initiation of the first study in 2012 was made possible from $1.5 million in funding from MJFF to Austrian biotech AFFiRiS to study a vaccine of synthetic alpha-synuclein to elicit an antibody response (like how the flu vaccine works) in people living with mild PD. A few months after the announcement of MJFF’s investment, two venture capital firms signed on to provide an additional $30 million in follow-on funding to further develop the vaccine, as well as others targeting PD and Alzheimer’s disease. Long-term data from the series of vaccinations and “boost” vaccines given over a total of four years showed the therapy was safe and tolerable and showed an immune response. Today, AFFiRiS is currently planning a Phase II trial.

Fast forward to the last few years, and the pipeline is bursting with opportunity for this promising target. Today, an additional eight alpha-synuclein-targeted treatments are in testing with Parkinson’s patients (for safety and efficacy) and several additional therapeutic programs knocking on the door to human trials. Three new programs have advanced to human trials in the past year alone while existing projects are launching new studies. Four of these MJFF-funded projects are led by pharmaceutical companies Neuropore/UCB, Alterity Therapeutics (formerly known as Prana Biotechnology), Proclara (formerly known as Neurophage), and AFFiRiS and have been joined by clinical programs funded by AbbVie, AstraZeneca/Takeda, Biogen, Lundbeck and Prothena/Roche.

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<th>Sponsor</th>
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There is a lot of progress for people living with Parkinson’s to be optimistic about. The unprecedented number of treatments and new mix of ideas that are being tested in Parkinson’s patients are drawing attention and investment from more industry partners and pharmaceuticals.

The following is an update on each alpha-synuclein treatment in testing:

**Preventing Toxic Protein Clumps:** In 2015, Neuropore Inc. conducted a single dose Phase Ia study testing its NPT200-11 compound, which binds to a specific region of alpha-synuclein and blocks its accumulation into toxic clumps in healthy human control volunteers. The compound was well-tolerated, and this study had no safety issues. Belgian-based pharma company UCB has taken over leadership of the project and just announced a multicenter Phase Ib study to look for safety and tolerability in people with Parkinson’s.

Alteryx Therapeutics (formerly Prana Biotechnology) just released interim results from its Phase I study of its small-molecule drug, PBT434. In single- and multiple-dose cohorts, data shows that PBT434 is well tolerated and crosses the blood-brain barrier. The company also reported that tested doses achieve concentrations in the brain that exceed those associated with efficacy in disease models. The study is expected to complete mid-2019.

Boston-based Proclara Corporation (formerly known as Neurophage) is developing a fusion protein drug candidate, NPT088, which can bind to proteins including beta-amyloid, tau and alpha-synuclein. This compound binds in a conformation-specific manner and reduces aggregation. MJFF previously funded Proclara to show whether NPT088 would be efficacious in a PD-specific alpha-synuclein model. After completing a single-dose safety and tolerability study in control volunteers, Proclara is conducting a Phase I trial in Alzheimer’s disease due to the availability of a beta-amyloid imaging agent. If they can show target engagement, they will test NPT088 in Parkinson’s patients, as well. Results are expected later this year.

**Introducing Antibodies against Alpha-Synuclein:** Pharma giants AstraZeneca and Takeda have teamed up to jointly develop and commercialize MEDI1341, an alpha-synuclein antibody. Results are expected in late 2019.

Pharmaceutical firm Biogen also is testing an anti-alpha-synuclein antibody. After demonstrating positive results in a trial that studied a similar therapy in Alzheimer’s patients, Biogen researchers successfully completed studies testing the BIIB-054 alpha-synuclein antibody in control participants and Parkinson’s patients. Biogen is using data from MJFF’s Parkinson’s Progression Markers Initiative for determining exclusion and inclusion criteria and endpoints for its ongoing Phase II trial. Recruitment has closed, and results are expected in 2022.

San Francisco-based pharmaceutical company Prothena is introducing an anti-alpha-synuclein antibody directly into humans, in an alternative immunotherapy approach. Prothena presented clinical results from a Phase I study in people with Parkinson’s disease, which showed the drug (previously PRX002 now RO7046015) was safe and well-tolerated and reduced serum levels of alpha-synuclein. Partnering with Roche, Prothena is conducting a Phase II trial, and results are expected next year.
More recently entering clinical trials, **Lundbeck** and **AbbVie** also are testing alpha-synuclein-targeting antibodies in Phase I studies. AbbVie has partnered with BioArctic on its project.

The alpha-synuclein drug development pipeline, however, does not stop with these projects. A handful of other programs are “knocking on the door” and could begin clinical testing within the next year, and additional projects contribute to a rich alpha-synuclein portfolio in pre-clinical stages.

Given the heightened interest by large pharmaceutical companies, it is an opportune time to aggressively deploy increased resources in service of continued progress. Toward that goal, The Michael J. Fox Foundation for Parkinson’s Research (MJFF) is also **supporting several novel approaches such as cutting-edge gene therapy and advanced compounds targeting genetic messengers.** *(SEE APPENDIX A).*

**Where Do We Go from Here: Addressing Field-wide Challenges and Finding Solutions to Speed Progress**

The robust alpha-synuclein therapeutic pipeline is a cause for optimism. However, proving an alpha-synuclein-targeted treatment removes alpha-synuclein aggregates and has clinical efficacy remains a significant field-wide challenge.

In fact, for potential drug makers in late-stage alpha-synuclein programs, perhaps the biggest challenge is this lack of ability to directly monitor alpha-synuclein aggregates in people living with Parkinson’s, whether through the brain, biofluids or peripheral tissues. This information is critical to determining whether an alpha-synuclein treatment is having the desired biological effect (decreasing aggregates), selecting proper doses of therapies, choosing trial participants most likely to benefit from a certain drug, and giving confidence to pharmaceutical industry funders who will need to shoulder the costs of large-scale Phase III trials.

A breakthrough that enhances our ability to measure any of these domains can help, and we may benefit from more than one read-out. As industry and private investment has moved into supporting the alpha-synuclein therapeutic pipeline, philanthropic support and MJFF focus plays an even more important role in the area of these needed alpha-synuclein measurements.

Given the enormous resources required to fund each individual therapeutic effort, it is difficult for industry to lead the equally challenging crusade to measurement. Without a coordinated, all-holds-barred campaign around measurement, there is a risk the search for a breakthrough will remain under-resourced. Lack of measurements increases trial costs and slow trial times — two disincentives we endeavor to overcome.
While undeniably important, development of tools to measure alpha-synuclein is not guaranteed. MJFF has, for several years now, stepped in to lead scientists and chemists from PD and beyond to find and validate the key measures needed to take alpha-synuclein programs into Phase III trials.

We have experienced a series of fits and starts, but progress is mounting and MJFF’s expert staff remains well-suited to harness worldwide intellect and drive multiple efforts to deliver the breakthrough needed. The Foundation is funding a multi-pronged effort actively managing consortia and independent labs across various approaches concurrently.

**Imaging Alpha-synuclein in Living Parkinson’s Brain Would Revolutionize Drug Development**

Ideally, we would be able to capture objective information about alpha-synuclein aggregates where we know they are forming — in the living human brain. The Michael J. Fox Foundation continues to support several efforts to develop an alpha-synuclein tracer that would feature a radioactive tag, bind to alpha-synuclein in the brain and be read by a positron emission tomography (PET) scan.

Last year saw the **first clinical trial of a selective PET tracer for alpha-synuclein in an MJFF-funded study**. This tracer would allow us to visualize alpha-synuclein aggregates in the brain and thereby diagnose PD earlier, track pathology over time, and evaluate the efficacy of therapeutics aimed at reducing alpha-synuclein aggregates. Validated biomarkers would not only advance existing programs but may attract new drug developers to Parkinson’s research with opportunity for smaller, faster and less expensive studies. Results from the tracer trials are expected later this year.

Thanks to funding from MJFF each of the efforts outlined below continues to gather momentum as they work to develop an alpha-synuclein imaging agent.
**PET Tracers for Synucleinopathies**

With funding from MJFF, Swiss biopharmaceutical company **AC Immune** is testing a selective alpha-synuclein PET tracer in humans. With the help of an earlier grant from MJFF, the group was able to accelerate its timeline and test its compound sooner than expected. Results are expected later this year. MJFF also is funding independent studies at the University of Tübingen in Germany and the University of Pennsylvania to screen for tracer compounds that selectively bind to alpha-synuclein. In addition, our Foundation recently launched a **$10 million funding program** (partially funded by a $7.5 million gift from a single donor) to encourage more experts to enter this field and drive progress. Funding multiple studies increases the likelihood of successful development of this tool and multiple versions. Different tracers may have advantages in testing different types or stages of disease.

**Alpha-synuclein and Tau Imaging Project**

In partnership with the Rainwater Charitable Foundation, The Michael J. Fox Foundation is funding a project to concurrently identify and test potential tracers for alpha-synuclein and the protein tau. Tau aggregates are associated with neurological diseases such as progressive supranuclear palsy and Alzheimer’s disease, but are also seen in some people with later-stage Parkinson’s. As tracer candidates must be screened against assays of both proteins (among others), pursuit of these tools together, rather than in parallel, is more efficient. This project is led by the University of Pittsburgh and MedChem Imaging LLC.

**Alpha-synuclein Imaging Prize**

To attract research teams to this priority area and accelerate momentum to speed the development of this tool, **the Foundation is sponsoring a $2 million prize** to the first team to develop a viable selective alpha-synuclein PET tracer and agree to make that tracer available broadly. Academic and industry researchers, MJFF funded or not, are eligible, and there is no deadline for submission. The prize will go to the first team that shows compelling evidence.
Developing Measures of Protein Species in Biofluid Is Highly Valued

While MJFF works to develop an imaging tracer, which would allow direct visualization of pathological alpha-synuclein in the brain, it is imperative to advance additional measurement tools. We have already led significant collaborative efforts to find surrogate ways to measure total alpha-synuclein in cerebrospinal fluid (CSF) and whole blood. Consensus on the best tools can be applied across clinical trials for reliability of results and comparison across studies. The team is conducting round-robin assessment of tools in the same samples at different laboratories. In parallel, the MJFF-sponsored Systemic Synuclein Sampling Study (S4) is looking for which biofluid or tissues are best for reliable, consistent results in measuring alpha-synuclein. These biomarker efforts — imaging the brain and using the best tests in the best samples — lay a foundation for quickly assessing current therapies and fertilizing a robust pipeline.

Our urgent effort now will focus on measuring oligomeric and phosphorylated alpha-synuclein. These forms have been shown to be important intermediate species between native monomeric and pathological aggregated Lewy bodies, and researchers have already developed early-stage tests (called assays) to measure these species.

In order to coordinate efforts to meet this goal, MJFF has formulated and organized the Investigating Synuclein Consortium, a collection of biomarker experts from industry, contract research labs and academia for development, cross-validation and replication of various alpha-synuclein assays. As part of this consortium, two all-star teams researching pathological alpha-synuclein are sharing data and reagents in real time to facilitate collaboration and speed progress, with the goal of nominating the best assay to measure pathological alpha-synuclein species in CSF and blood.

This project is being conducted in two phases. The first concluded protein standard characterization and demonstration of assay selectivity and inter/intra assay reliability. The ongoing phase two is a round-robin study with samples from a combined 50 Parkinson’s volunteers and control participants. Results from this initiative will be applied to the design of alpha-synuclein therapeutic trials, underscoring the urgency of this program.

Validating Alpha-synuclein Biomarker Could Allow for Early Disease Detection

Validation of a peripheral alpha-synuclein biomarker that could be measured in a fluid or tissue sample would provide a valuable tool for confirming the diagnosis of PD and a potential means of monitoring efficacy of potential therapeutic agents. As the current literature suggests alpha-synuclein pathology may begin in peripheral tissues in the pre-motor stage of disease and then move centrally to involve the central nervous system (CNS), such a tool could also allow for better identification of the disease in its
earliest stages. Understanding the peripheral alpha-synuclein burden may ultimately be key to the development of treatments to prevent progression of the disease into the CNS.

With this goal in mind, MJFF’s Systemic Synuclein Sampling Study (S4) provides the opportunity to evaluate alpha-synuclein species in multiple tissues and biofluids within the same subject and has employed standardized collection, processing and analysis methodology across sites. Understanding the alpha-synuclein burden along the spectrum of disease severity (early untreated to advanced disease) will inform the next steps for utilizing these markers in the drug development process.
APPENDIX A

Support for Novel Projects Assures Treatment Pipeline Remains Robust

Despite our enthusiasm for the current state of the alpha-synuclein therapeutic portfolio, given the high failure rate of such programs, we believe it is strategic to continue to promote new entrants (particularly novel ones) into the field to avoid putting all our eggs in too few baskets.

Quickly advancing these novel projects through pre-clinical stages is critical to diversify the portfolio around our most promising target for a treatment that will slow or stop progression. Two such projects, among others, have begun pre-clinical stage testing:

*Novel Intracellular Alpha-synuclein-lowering Strategies based on CRISPR Interference Technology*

Deniz Kirik, MD, PhD; Lund University, Sweden & Birgitt Schuele, PhD; Stanford University, California

These two teams are using cutting-edge gene-therapy technology to test their hypotheses that reducing the production of alpha-synuclein in diseased brain cells will help improve their survival and function. Researchers are testing multiple components of the CRISPRi technology to reduce alpha-synuclein levels to an optimal level. As native, non-pathological alpha-synuclein is a normal functional protein, inhibition must not be too low as to cause deleterious effects. Additionally, these teams are testing multiple administration routes to determine the best delivery system for penetration and distribution across the brain.

*Antisense Oligonucleotides as Drug Candidates for Alpha-synuclein-linked Diseases*

Epaminondas Doxakis, PhD, MBA; Biomedical Research Foundation, Academy of Athens, Greece

These researchers will design and test antisense oligonucleotides (ASOs), man-made molecules that destroy messenger RNA, the template from which a protein is built. Treatment with ASO molecules is expected to decrease the production of alpha-synuclein and prevent its abnormal buildup and spreading in PD. Dr. Doxakis’ team will first test the validity and functionality of their designed ASOs in human cells that produce alpha-synuclein. The most efficient ASOs will then be tested in disease models to assess the reduction of alpha-synuclein levels.