NeuroPhage Pharmaceuticals is a late-stage preclinical company, founded in 2007, with a novel technology that simultaneously targets multiple misfolded proteins implicated in neurodegenerative diseases including α-synuclein, amyloid-β (Aβ), tau, and prion. NeuroPhage is headquartered in Cambridge, MA. The Company has raised $35M to date with investors including Shire LLC and Mérieux Développement. NeuroPhage has also received two awards from The Michael J. Fox Foundation for Parkinson’s Research.

The Company has 18 employees led by an experienced senior management team. Richard Fisher, PhD (formerly of Biogen & UCB), is the Chief Scientific Officer and Kimberley S. Gannon, PhD (formerly of Eli Lilly and Company), is Senior Vice President of Preclinical Research and Development. Drs. Fisher and Gannon have extensive experience in drug development. Jonathan Solomon, MBA, and Hampus Hillerstron, MBA, serve as CEO and CFO, respectively. NeuroPhage is supported by a strong Board of Directors and guided by a Scientific Advisory Board of key opinion leaders in the field of neurodegenerative disease including Paul Aisen MD, Andres Lozano MD, Brad Hyman MD, Franz Hefti PhD, Greg Petsko PhD, and David Hafler MD.

Opportunity Overview

NeuroPhage Pharmaceuticals is developing a first-in-class, broad-acting and disease-modifying therapeutic platform for the treatment of neurodegenerative diseases, including Parkinson’s disease (PD). The Company’s technology is unique in that it targets multiple misfolded proteins such as α-synuclein, amyloid-β (Aβ), tau, and prion protein (PrP). The recently elucidated mechanism of action represents a highly novel approach for reducing levels of pathologic misfolded proteins. NeuroPhage’s leading drug candidate, NPT002, is highly purified and formulated native filamentous bacteriophage M13. Mechanism of action studies of bacteriophage M13 mutants led to the identification of a 25 KDa structural motif that mediates NPT002’s unique amyloid-targeted activity. The isolated General Amyloid Interaction Motif (or “GAIM”) targets oligomers and amyloid fibers of misfolded proteins and prevents their self-assembly. This discovery allows for the potential development of antibody-like IgG-GAIM fusion compounds that are currently being tested following systemic administration in preclinical models.

- **GAIM** represents a novel approach based on a coat protein of bacteriophage M13 that binds, disaggregates and prevents the formation of multiple amyloid structures implicated in neurodegenerative disease.
- **GAIM** selectively targets a broad spectrum of misfolded proteins by recognizing a common amyloid conformation, the product of misfolded protein aggregation in diseases such as PD and Alzheimer’s disease (AD).
- NeuroPhage’s technology addresses known interactions between different classes of misfolded proteins that have been shown to exacerbate disease progression and severity.
- **GAIM** recognizes all stages of amyloid assembly (i.e., oligomers to fibrils) and effectively mediates the clearance of pre-existing amyloid aggregates in animal models of disease.
- Increased therapeutic potential compared to current therapeutic modalities by targeting early amyloid assemblies as well as pre-existing aggregates.
- Significant development potential in additional diseases characterized by misfolded proteins, such as orphan indications (Huntington’s, ALS, CJD, systemic amyloidosis).

A highly compelling and comprehensive preclinical data package demonstrates biochemical, *in vitro* and *in vivo* activity against α-synuclein, Aβ, tau, and prion protein (PrP). In addition to targeting pre-existing plaque, GAIM technology targets oligomers and prevents fibril formation. *In vivo* studies show dramatic and long lasting effects on plaque reduction after a single treatment. Pilot toxicology studies in nonhuman primate (NHP) have produced no test article related adverse events. NonGLP NHP pharmacokinetic and biodistribution PET studies have been completed.

CMC process development is nearing completion. NeuroPhage had a preIND meeting with FDA in August 2012 and has received clear support for the development plan through Phase 1.
Details of MJFF Grant

NeuroPhage's first MJFF-awarded grant (2011) supported a study of NPT002 in an α-synuclein overexpressing mouse model. Previously, NPT002 had been shown to disrupt and clear a variety of amyloid aggregates in the brain. In addition to reducing Aβ and tau aggregates (hallmarks of Alzheimer’s disease) in mice, preliminary studies indicated that NPT002 also disrupted α-synuclein fibrils which are thought to play a role in PD. The MJFF-funded project investigated the effects of multiple dose levels of NPT002 on neuropathology and motor performance in aged transgenic mice expressing human α-synuclein. The study produced positive results which are summarized below.

NeuroPhage’s second, recently awarded MJFF grant will support a NHP toxicology study to demonstrate safety and evaluate brain distribution of repeated administration of NPT002, a potential therapeutic for PD that targets α-synuclein deposits in the brain. The GLP toxicology study will involve four months of repeated monthly dosing to assess safety and tolerability. Secondary endpoints will include pharmacokinetics and qPCR evaluation of drug levels in various brain areas relevant to PD.

Results and Potential Next Steps

The results of a study funded by NeuroPhage’s first MJFF award showed that NPT002 reduced α-synuclein deposits, increased tyrosine hydroxylase and improved motor performance in a PD mouse model after a single treatment. Six-month-old female mThy-1-hα-synuclein transgenic mice and age-matched non-transgenic control mice were treated with one of three dose levels of NPT002 or PBS. Animals were tested for motor performance on a beam walking test with subsequent immunohistochemical and biochemical analyses of brain tissue. NPT002 significantly (p<0.0001) and dose-dependently reduced levels of proteinase K resistant α-synuclein in the basal ganglia of transgenic mice. NPT002 significantly (p<0.0001) and dose-dependently increased levels of tyrosine hydroxylase immunostaining in the basal ganglia. Western blot analysis of tissue homogenates prepared from basal ganglia revealed significant (p < 0.001) decreases in levels of α-synuclein protein in the soluble fraction at all doses of NPT002 administered. NPT002 at the highest dose significantly (p<0.05) reduced the number of errors or slips that transgenic α-synuclein mice made walking on a small-diameter test beam. These exciting results indicated that a single NPT002 treatment could reverse the neuropathology and motor coordination impairments exhibited by α-synuclein overexpressing mice, a recognized preclinical model of PD.

A next step in the development of the lead candidate, NPT002, for PD is to determine the safety, pharmacokinetics and brain distribution of repeated monthly dosing in NHP to support repeated clinical administration. To this end, NeuroPhage’s second MJFF award will fund a four-month repeated dose study of NPT002 in NHP with primary endpoints being safety and brain distribution in PD relevant areas.

NeuroPhage is poised to launch IND-enabling single dose toxicology to support first-in-human Phase 1 studies with the lead candidate. In addition, second generation GAIM-based candidates have been developed that allow systemic administration, and preclinical efficacy in transgenic mouse models is comparable to that found with NPT002 treatment. De-immunization of the lead second-generation candidate is ongoing. NeuroPhage is planning a Phase I clinical program that will evaluate safety and tolerability of the GAIM technology (e.g., NPT002 and/or second generation molecules) in PD and AD patients. The use of imaging biomarkers will be incorporated in the early studies to demonstrate target engagement. Currently, a validated imaging agent is available for Aβ, with α-synuclein imaging agents in development. NeuroPhage is seeking a partner to provide funding for clinical trials in neurodegenerative disease and subsequent commercialization of the technology.

Intellectual Property Status

NeuroPhage technology is protected by a strong worldwide IP portfolio consisting of licensed patents and patent applications for compositions and methods for diagnosis, prevention and treatment by reducing plaque in neurological diseases, such as PD and AD. Additional NeuroPhage patent filings extend pharmaceutical composition, mechanism and manufacturing coverage potentially out to 2032.