Emerging Company Profile

Lysosomal: Activating GCase

By Jennifer Rhodes
Staff Writer

Lysosomal Therapeutics Inc. is developing brain-penetrant small molecules for a genetically validated Parkinson's target that it believes will be disease-modifying for idiopathic PD and potentially other synucleinopathies.

The biotech has a license from **NIH** to allosteric modulators that increase glucocerebrosidase (GBA; GCase) activity in the lysosome. Lysosomal expects its recent $4.8 million seed round will provide the runway to generate lead-stage compounds in the next 12-18 months.

GCase is best known for its role in Gaucher's disease — a genetic lysosomal storage disorder in which the enzyme is deficient or defective.

In 2011, co-founder Dimitri Krainc published work in *Cell* showing the functional loss of GCase impairs lysosomal protein degradation and can lead to the accumulation of alpha-synuclein (SNCA), a protein linked to Parkinson's.

The exact link between Gaucher's and Parkinson's is not well understood, but as lysosomal GCase activity goes down in Gaucher's patients, SNCA levels go up.

Krainc is a professor at **Northwestern University Feinberg School of Medicine** and director of the school's Center for Rare Neurological Diseases.

About 20% of Type I Gaucher's patients are ultimately diagnosed with PD, and "if you take a biopsy of a Gaucher's brain, it looks like the brain of a Parkinson's patient," said Kees Been, president and CEO of Lysosomal.

Parkinson's patients also have levels of GCase activity that are below normal. According to Been, the greatest risk factor for Parkinson's is a single-allele mutation in the GBA1 gene.

An early NIH compound increased lysosomal GCase activity compared with a control in midbrain neurons from Parkinson's and Gaucher's patients ($p<0.05$ for both). In neurons, the compound increased GCase activity in lysosomes and selectively reduced SNCA levels.

Been said the company's ultimate goal is to develop a treatment for idiopathic Parkinson's, noting that GCase activity is compromised even in PD patients without a mutation in the GCase gene. He thinks the compounds could potentially be used to prevent the onset or progression of PD in patients with a GCase mutation.

"Interfering early in the disease by enhancing GCase activity would suggest that you lower the risk of Parkinson's and delay the onset of the disease," he said.

Lysosomal has not yet determined a clinical development pathway but said it could start by establishing proof of concept that the compounds increase GCase activity in the lysosome and decrease SNCA in a Phase IIa trial in about 20-25 Gaucher's patients.

The company could then evaluate a compound in Parkinson's patients with a mutation in the GCase gene before running a much larger trial in idiopathic Parkinson's.

Been said Lysosomal may also develop a separate compound for Gaucher's disease patients, but said it is too early to know exactly how a compound could be used in the Gaucher's disease treatment paradigm.

At least one other company is developing small molecules targeting GCase for Gaucher's and Parkinson's. **Amicus Therapeutics Inc.**'s AT3375, a next-generation GCase chaperone, is in preclinical development. Amicus said AT3375 crosses the BBB.

Last year, Amicus partnered with **Biogen Idec Inc.** to discover, develop and commercialize small molecules targeting GCase for PD. The program is in discovery.

Been said Lysosomal is focused on increasing GCase activity in the lysosome, while he said Amicus is focused on stabilizing GCase and moving the enzyme to the lysosome.

Lysosomal CSO Peter Lansbury said other programs that directly target SNCA target the extracellular transmission of SNCA and may be complementary to Lysosomal's, which is targeting intracellular SNCA.

At least five other companies are directly targeting SNCA for Parkinson's. Two programs, one from **Prothena Corp. plc** and partner **Roche** and one from **Affiris AG**, are in Phase I testing.

Several companies are also developing potentially disease-modifying PD therapies against a variety of other targets. But Lansbury said he is not aware of another target for PD that has been genetically validated for the disease where a mutant phenotype also has been generalized to the larger PD population.

He also noted, "It is unlikely that a single target will be important in all (or even most) cases of PD."

Been said Lysosomal plans to start a second program for another to-be-determined lysosomal storage disease that is genetically linked to a neurodegenerative disease.

The company has two pending patents covering composition of matter and method of use for allosteric modulators targeting GCase.

Lysosomal Therapeutics Inc.

Cambridge, Mass.
Technology: Small molecule allosteric modulators of glucocerebrosidase (GBA; GCase)
Disease focus: Neurology
Clinical status: Discovery
Founded: 2011 by Henri Termeer, Bob Carpenter, Peter Wirth and Dimitri Krainc
University collaborators: Northwestern University
Corporate partners: None
Number of employees: 7
Funds raised: $4.8 million
Investors: Atlas Venture; Hatteras Venture Fund; Lilly Ventures; Roche Venture Fund; Sanofi-Genzyme BioVentures; Partners Innovation Fund; angel investors
CEO: Kees Been
Patents: None issued

COMPANIES AND INSTITUTIONS MENTIONED

Affiris AG, Vienna, Austria
Amicus Therapeutics Inc. (NASDAQ: FOLD), Cranbury, N.J.
Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Lysosomal Therapeutics Inc., Cambridge, Mass.
National Institutes of Health (NIH), Bethesda, Md.
Northwestern University Feinberg School of Medicine, Chicago, Ill.
Prothena Corp. plc (NASDAQ:PRTA), Dublin, Ireland
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland