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, 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 mutation in Parkinson’s patients with a mutation in the GCase gene before running a much larger trial in idiopathic Parkinson’s.

At least one other company is developing small molecules targeting GCase for 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.

Krainc 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 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 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.

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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