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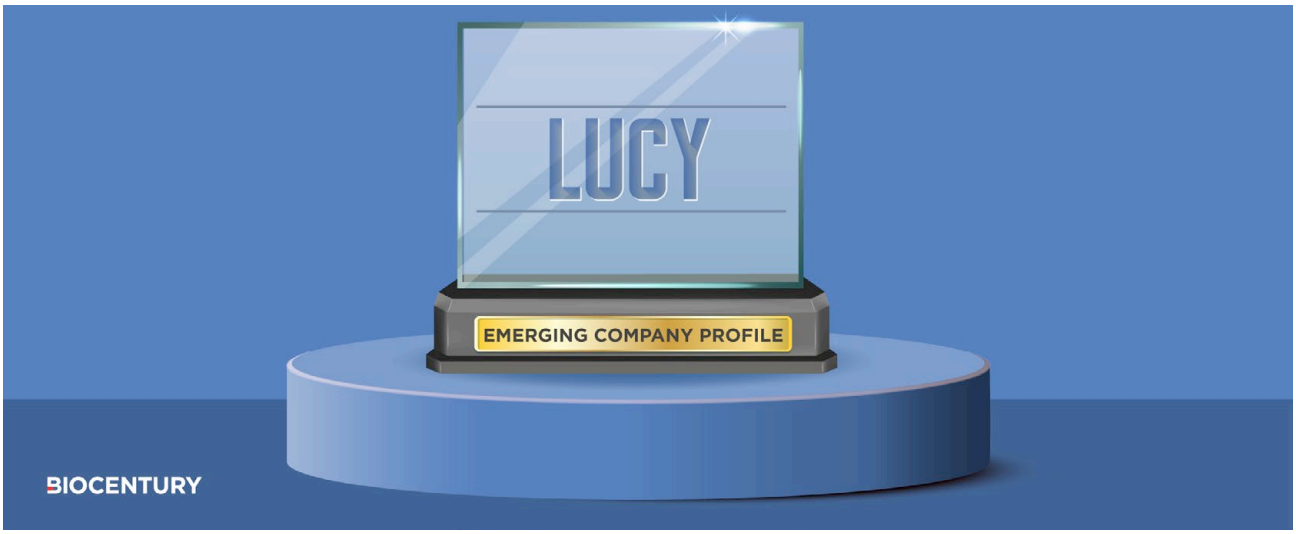
Lucy: mitochondrial solutions to CNS diseases

BY RICHARD GUY, BIOPHARMA ANALYST



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Lucy Therapeutics views mitochondrial dysfunction as a common and core driver of many CNS diseases, and aims to build a pipeline of programs against "rate-limiting" targets that gate the progression of that dysfunction. First up is a program targeting F-ATPase to treat Parkinson's disease and a second against an undisclosed GPCR for Rett syndrome.

Cambridge, Mass.-based Lucy Therapeutics Inc. has raised about $24 million across a $4 million seed round, a $15 million series A financing in December 2021, and a grant of $4.9 million from The Michael J. Fox Foundation. The company's investors include Pivotal bioVenture Partners, Safar Partners, The Engine and the Massachusetts Life Science Center.

First-time CEO Amy Ripka told BioCentury that when she was working at CNS company EnVivo Pharmaceuticals Inc. she realized "everybody was on the hunt for new targets, but coalescing around the same markers. That was the impetus for me to say, 'Is this the only way to approach this problem?'"

Ripka's idea was to identify targets based on their involvement in disease "bottlenecks" — processes that may not necessarily represent the initial insult or disease trigger, but are key to progression. That led her to mitochondria.

"The genesis of Lucy was the idea that to find targets that matter, you have to find the bottlenecks of the disease," she said. Much of the neurology field is focused on genetic drivers of disease, but patients often develop sporadic cases of unknown origin. Mitochondrial function, by contrast, is seen in many patients across many CNS diseases and could be fundamental to progression, she said. "You have mitochondria in every cell — why are we not looking at them?"

Ripka believes mitochondrial dysfunction is not only a unifying feature of many CNS diseases, but a mechanism that can often explain non-neural features of the diseases — in particular heart and muscle dysfunction.

"The motor symptoms associated with Parkinson's are brain-related, but other symptoms of the disease such as incontinence and autonomic cardiac dysfunction start decades earlier. Many complex CNS diseases have a similar pattern," she said.

Parkinson's disease has long been linked to mitochondria dysfunction. In the 1980s, a contaminant in a synthetic form of morphine, MPTP, caused rapid-onset Parkinson's in users via disruption of complex 1 of the mitochondrial electron transport chain. Moreover, the field has identified several rare mutations and risk alleles that are linked to mitochondrial function, including PARK2, PINK1, LRRK2 and CHCHD2.

Lucy is not targeting any of those genetic risk factors and has instead opted for a mitochondrial target it thinks will be relevant regardless of disease etiology. The target, F-ATPase, is a protein complex in the mitochondrial electron transport chain that, under normal conditions, synthesizes ATP by pumping protons from the inter-mitochondrial space into the matrix. However, the ATPase can also operate in reverse, hydrolyzing ATP to restore falling membrane potential, which can in turn result in hyperpolarization of the membrane, generation of reactive oxygen species, and lack of correct PARK2 recruitment. Lucy hypothesizes that this reversal is a common feature of Parkinson's and core to its progression.

Lucy's small molecules selectively inhibit ATP hydrolysis by F-ATPase, sparing normal ATP production. The company has preclinical evidence suggesting compounds also reduce levels of α-synuclein, a major constituent of Lewy bodies, pathological hallmarks of Parkinson's.

In Rett syndrome, Lucy is targeting an undisclosed GPCR not previously associated with a CNS disease.

"We've shown that drugging this target can reverse many of the symptoms of Rett," said Ripka. "There's an animal model that mimics a type of seizure that girl Rett patients have, and our compounds can reverse those seizures."

Ripka said that Lucy hopes to raise a series B round to fund clinical work, but has not finalized a timeline. The company intends to have development candidates ready in 2023, and it is open to either partnering out products or advancing them on its own.

COMPANY PROFILE
LUCY THERAPEUTICS INC.
Cambridge, Mass.

Technology: Small molecules targeting mitochondria dysfunction in CNS diseases

Origin of technology: In-house

Disease focus: Neurology

Clinical status: Preclinical

Founded: 2017 by Amy Ripka

Academic collaborators: None

Corporate partners: None

Number of employees: 14

Funds raised: $24 million

Investors: Pivotal bioVenture Partners, Safar Partners, The Engine and the Massachusetts Life Science Center

CEO: Amy Ripka

Patents: None issued

Other companies targeting mitochondrial mechanisms to treat Parkinson's include NRG Therapeutics Ltd., which is developing mPTP inhibitors, and Mitochon Pharmaceuticals Inc., which is developing small molecules that reduce free radicals and improve how mitochondria handle calcium. Pretzel Therapeutics Inc., which counts neurology among its interests but has not yet disclosed a lead indication, is developing a mitochondrial quality control platform to eliminate dysfunctional mitochondria. Caraway Therapeutics Inc. aims to remove dysfunctional mitochondria by a different mechanism, targeting the lysosomal potassium channel TMEM175, in which loss-of-function mutations increase risk for Parkinson's. All four companies are preclinical.

Ripka said she was not aware of another company targeting the F-ATPase to treat Parkinson's.

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