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# Origami: Correcting or eliminating misfolded proteins

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As pharmas were exiting neuroscience in droves around 2015, Origami President and CEO Beth Hoffman decided to take the opposite tack: leveraging her background in neuroscience and protein folding correctors to bring a fresh MOA to the space.

Origami Therapeutics Inc. is gearing up to raise a seed round to fund the start-up, which is initially focusing on Huntington disease, said Hoffman, who was VP, discovery biology at Vertex Pharmaceuticals Inc. (NASDAQ:VRTX) in 2007-14. During that time, one of her scientists showed her data that a small molecule could turn a misfolded, non-functional protein into a properly folded, functional protein.

The small molecule was VX-809, now lumacaftor, the CFTR-targeting conformation corrector portion of cystic fibrosis drug Orkambi lumacaftor/ivacaftor. "It not only helps people get better, but over time the lungs can actually heal," Hoffman told BioCentury. "It's amazing what a small molecule can do to leverage a cell's own biology."

She said she could imagine a way to leverage the concept of conformation correctors to treat neurodegenerative diseases, as many are caused by protein misfolding.

Vyndamax tafamidis from Pfizer Inc. (NYSE:PFE) and Oxbryta voxelotor from Global Blood Therapeutics Inc. are marketed conformation correctors to treat transthyretin amyloid cardiomyopathy and sickle cell disease, respectively.

"I would say that the concept of a small molecule modulating protein folding has been demonstrated as a clearly viable approach," said Hoffman.

Origami's drug discovery platform, ORICISION, enables discovery of small molecule protein degraders and conformation correctors and then uses patient-derived disease models to match the best therapy type to treat each neurodegenerative disease.

The company chose Huntington disease as its first focus because the well understood disease biology and clinical development feasibility. "We know who to treat, roughly when to treat and what to measure," said Hoffman.

Huntington disease patients have an increased number of CAG repeats in their HTT gene, leading to a mutated protein (mHTT) that can misfold and form toxic aggregates, often

called inclusion bodies. A conformation corrector could stabilize mHTT in a wild-type-like conformation and prevent aggregation. The company is selecting brain penetrant molecules to treat all organs and cells in the body, most of which have demonstrated pathology in the indication.

Origami identifies conformation correctors using a combination of cell-based and biochemical assays, such as limited proteolysis. "If a protein unfolds, then it's more susceptible to being cleaved by proteases in the cell," said Hoffman. Cell fractionation and various imaging techniques can reveal if a protein is in the proper place in the cell.

And most important is to look for restoration of protein function. "In the case of a receptor, you might look for a second messenger. In the case of CFTR, we looked for a restoration of the flux of chloride ions," said Hoffman.

HTT is a scaffolding protein that doesn't have a simple functional readout like flux of an ion. Instead, the company screened for compounds that reduced aggregation. ORI-503 prevented the accumulation of mHTT aggregates without altering overall mHTT levels.

"Mutant huntingtin itself is functional, and so you don't want to get rid of all of it, you want to get rid of the misfolded portion," said Hoffman.

Origami's lead program, ORI-113, is an HTT degrader that selectively reduces mHTT protein, which in turn reduces aggregation. ORI-113 also restores more normal morphology of human neurons, as seen in a cell culture system of HD patient-derived neurons.

Proteins can be degraded by several cellular waste systems including the proteosome, autophagosome or lysosome. Hoffman said they don't know yet which cellular system is in play for HTT degradation by their molecules. "By structure, these don't look like they are binding to an E3 ligase like a molecular glue or PROTAC might be. Now, part of what we're doing is trying to understand the exact mechanism."

Hoffman, who has has self-funded the company so far, hopes to start a clinical trial in about three years, before which the company would seek series A funding.

The company is also interested in developing compounds for other neurodegenerative diseases with genetically identified targets that tend to misfold, such as APOE4 in Alzheimer's disease, SNCA in Parkinson's, various ataxins in spinocerebellar ataxias, and C9orf72 in amyotrophic lateral sclerosis and frontotemporal dementia.

Hoffman said Origami will stick to neurology indications, but the platform is applicable to any protein misfolding disease, and the company is open to partnerships.

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**COMPANY PROFILE**
**ORIGAMI THERAPEUTICS INC.**
San Diego, Calif.

**Technology:** Protein degrader and corrector platform
**Origin of technology:** In-house
**Disease focus:** Neurology
**Clinical status:** Preclinical
**Founded:** 2015 by Beth Hoffman
**Academic collaborators:** None
**Corporate partners:** N/A
**Number of employees:** 3
**Funds raised:** $2 million
**Investors:** Self-funded
**CEO:** Beth Hoffman
**Patents:** None

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