NIH and DoD-backed Ridgeline targets muscle decline

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Biotech start-up readies for clinical trials of an oral drug that rejuvenates aged muscle

stem cells – increasing muscle repair, strength and function.

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University of Texas spinout Ridgeline Therapeutics is on a mission to reverse a host of chronic global health problems, including age-related muscle degeneration (sarcopenia), obesity, and muscular dystrophies. The biotech start-up is focused in part on developing small molecule inhibitors of nicotinamide N-methyltransferase (NNMT), an enzyme highly expressed in select tissues, where it plays a critical role in regulating energy metabolism and epigenetic pathways.

Longevity.Technology: An effective treatment that prevents and even reverses the loss of muscle strength that occurs during aging would help people stay active, healthy and independent longer, and be hugely beneficial to our aging society. Ridgeline's technology has already caught the eye of some influential organisations. The company is backed by more than $10 million in grant funding from the US Department of Defense and National Institutes of Health. It is now raising an initial $8 million in equity funding for clinical trials of its lead compound, targeting sarcopenia. To learn more, we caught up with the company's founder and CEO, Dr Stan Watowich.

Watowich is a professor of biochemistry and molecular biology at the University of Texas. About five years ago, his lab conducted some "ground-breaking research" that showed potential in the obesity and metabolic space and appeared to have applications in the muscle aging space.

"We were able to develop some novel small molecule inhibitors in our lab, and get provisional patents around them," says Watowich. "We realised that the fastest way to move our discoveries into the hands of patients was through a biotech company, and so we launched Ridgeline Therapeutics. The company is doing focused translational studies to advance our small molecules into clinical trials. These studies are balanced with the synergistic research that continues in the academic lab.

"We've been moving rapidly, expanding into different clinical indications. We now have different molecules that target several different diseases. But, as we have limited resources, we strategically picked muscle regeneration in the elderly as the first medical indication for clinical trials."

Dr Stan Watowich, co-founder and CEO – Ridgeline Therapeutics

Key enzyme hits multiple pathways

The key behind the formation of Ridgeline involved “connecting the dots” around research on the NNMT enzyme.

“The cool thing about NNMT is that it exists at the intersection of at least two major biochemical pathways in the cell,” says Watowich. “One is the NAD+ salvage cycle pathway, which controls energy within your cells, feeding the mitochondria and regulating how you process glucose and fat in the cells. When NNMT is upregulated, it essentially shuts down that pathway by syphoning off the metabolites going into it.”

The other critical pathway affected by NNMT is the methionine cycle.
"This regulates another major series of biochemical reactions in the cell that process and cycle methionine," says Watowich. "The methionine pathway helps regulate the epigenetics of the cell, and we have some interesting data showing that, as NNMT is upregulated or downregulated, it changes the epigenetics inside the cell quite dramatically."

A path to muscle rejuvenation

Watowich says Ridgeline's data indicates that, as NNMT is inhibited, not only is muscle function improved, but the epigenetic profile appears to be shifting to a younger profile.

"No, we're not making you younger – let me repeat, we're not making you younger!" says Watowich. "But what we are looking to do is prevent muscle degeneration and decline.

We're going to enable your muscles to better regenerate as you age, so you're much stronger when you're older.

"Our goal is to target how muscles rebuild and how energy moves through muscle cells, thus allowing your muscles to perform as they did when you were young. So, yes, we improve the muscle but, by modulating these pathways, we also reactivate the stem cells that control your muscle growth and repair."

The muscle rejuvenation aspect of Ridgeline's technology is what drove the interest and funding from the US NIH.

Translating preclinical results to humans

Ridgeline aims to publish new papers on its more recent work, but some of its initial progress is documented in this 2019 paper in *Biochemical Pharmacology*, which showed that inhibiting NNMT improved the regenerative capacity of skeletal muscle in older mice.

"We could see the muscle repair happening very quickly," says Watowich. "When we treated old animals, within one week, we were already doubling the strength and doubling the size of the muscle. In three weeks, we're almost back to the normal size muscle. We both improved the rate of the treatment and enabled full recovery – and we doubled the number of stem cells that help rebuild this muscle."

The next step for Ridgeline is to see if this work translates into humans, and the company is now raising $8 million to conduct a Phase 1 safety trial scheduled for late 2022.

"The trial will take six months and another six months to analyse the data," says Watowich. "So, it'll be another year before we begin the Phase 2 sarcopenia trials.

"We've had more than $10 million in funding from the DoD and NIH, but this is our first round of non-dilutive funding. We're looking for investors who have deep enough pockets to fund a subsequent $25 million round to support our Phase 2 trial."

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