Advancing muscle repair for disorders

Specialised muscle cells possess the ability to divide in a way that promotes muscle repair and regeneration. Discovering key regulatory elements of this process and molecules to enhance it has been the core work of Satellos, a company pioneering novel small-molecule medicines for Duchenne muscle dystrophy and other muscle disorders. In this exclusive interview, Frank Gleeson Cofounder, CEO and Board Member, Satellos Therapeutics explores further.

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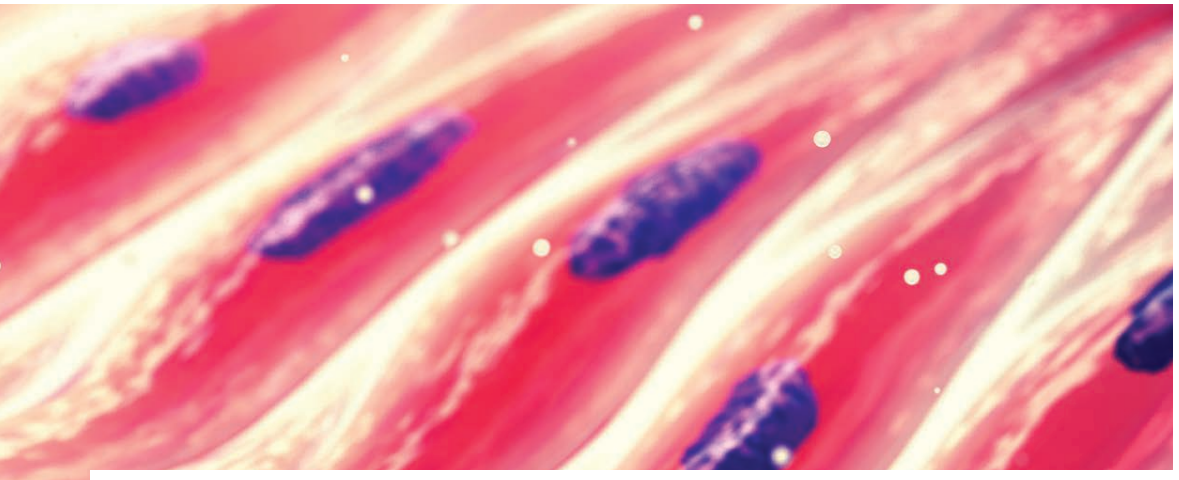
Can you explain in more detail how muscle stem cells utilise 'stem cell polarity' to regulate muscle repair and regeneration throughout life, as discovered by Dr Michael Rudnicki, and its significance in Duchenne muscular dystrophy (DMD)?

Muscle stem cells use 'polarity' to undergo a special type of cell division, known as 'asymmetry'. Polarity refers to the geospatial orientation of the mitotic spindle during stem cell mitosis. During asymmetrical division, two types of stem cells are created: an identical copy of the stem cell and a new type of cell, known as a muscle progenitor cell. Muscle progenitor cells are responsible for all muscle repair and regeneration that occurs throughout life. In DMD, this polarisation process is impaired, and thus the generation of progenitor cells declines. The inability to repair and regenerate prevents muscles from maintaining muscle fibre repair in the absence of dystrophin.

Could you elaborate on the specific regulatory defects in stem cell polarity that lead to the failure of muscle repair and regeneration in DMD, and how this discovery represents a previously unrecognised root cause of the disease?

We discovered that the dystrophin protein is expressed in muscle stem cells. Dystrophin plays



a signalling role in directing muscle stem cells to establish polarity and produce progenitor cells. In DMD, the gene that codes for the dystrophin protein is mutated, so the dystrophin protein is either not made or is severely impaired. Because of this, stem cells do not polarise efficiently and thus, are not effective at producing adequate numbers of progenitor cells needed to continuously repair and regenerate muscle tissue.

What sets Satellos' small molecule approach apart from other potential therapies for DMD? How does this novel therapeutic aim to address the defect in stem cell polarity and provide a disease-modifying treatment for DMD and other muscular dystrophies?

Satellos' small-molecule drug candidate is designed to replace the signalling function of the dystrophin protein and restore progenitor production and muscle regeneration. This small molecule does this by interacting with an alternative signalling pathway that's independent of dystrophin. Satellos has discovered this alternative signalling pathway is capable of re-establishing stem cell polarity, allowing muscles to effectively repair the damage occurring at the muscle fibre level.

What preclinical evidence or research has been conducted to support the development of the small-molecule therapeutic for DMD? Are there any promising findings or insights that have been observed in animal models or *in vitro* studies?

Our preclinical data, conducted in the most widely used animal model for DMD research – the mdx mouse – clearly show that restoring stem cell polarity with our small-molecule drug candidate leads to an increased number of progenitor cells. This increase translates to muscle repair and ultimately restoration of muscle strength and function. Importantly, this all occurs without the need to replace dystrophin in the stem cells. Our data suggest that correcting muscle stem cell polarity in the absence of dystrophin has the potential to enable the muscle of people living with DMD to (1) repair accumulating muscle fibre damage and (2) improve muscle function.

Considering the complex nature of DMD and the challenges in developing effective treatments, what are the key milestones or next steps in the development of Satellos' small-molecule therapeutic, and what are the company's expectations for its potential impact on patients with DMD?

Our next major milestone is submission of an IND filing to the FDA and commencing clinical studies. If our preclinical results translate in the clinic, we expect to not only slow the progression of this disease, but to potentially rebuild muscle that was previously lost.

Beyond DMD, are there other muscular dystrophies or related conditions that Satellos' small molecule approach could potentially target? Could you discuss any future plans or research initiatives to explore the broader applicability of this therapeutic for other muscle-related disorders?

Our MyoReGenX platform could potentially generate small-molecule drug candidates for any indication where muscle tissue has been lost or where enhanced muscle tissue repair is required. This could include additional genetic muscular dystrophies as well as indications such as sarcopenia (age-related muscle loss), cachexia associated with cancer or other disease conditions, or muscle loss due to surgery or unforeseen trauma (eg, combat, accidents, injuries).

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Frank Gleeson, MBA

Co-founder, CEO and Board Member, Satellos Therapeutics

During his career, Frank Gleeson has been a key party to building more than 20 biomedical companies from breakthrough research and technologies, including as Co-founder and CEO of Verio Therapeutics which was acquired by Fate Therapeutics. Prior to co-founding Satellos in 2018, he was Chief Commercial Operations at Centre for Probe Development and Commercialization, where he played a principal role in building a global radiopharmaceutical manufacturing business and supporting the creation of two spin-out companies.