Scholar Rock's Novel Approach to Improving Muscle Function in SMA Patients

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Myostatin is a protein that prevents muscle growth

Mutations that prevent myostatin from functioning result in larger muscles in multiple species, including humans.

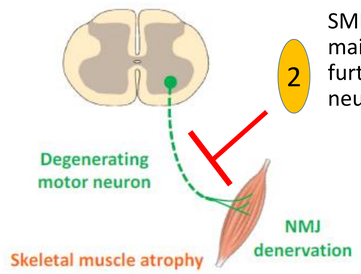
Animals that lack myostatin appear healthy; there have been no observed pathologies of other organ systems in the absence of myostatin.

This suggests that using a drug to prevent myostatin from functioning could be an effective way to increase muscle growth and strength in patients with SMA.

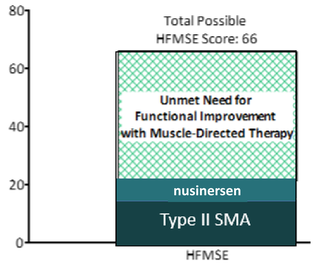
There is an unmet medical need for a muscle therapy in SMA

SMN2 gene — Splice modulators
SMN1 gene — Gene therapy

1 SMN upregulators are having important impacts on neuromuscular function in SMA patients.



2 SMN upregulators work mainly by preventing further loss of motor neurons.



3 But SMN upregulators have less effect on muscle atrophy that is already present in patients.

Myostatin inhibition has the potential to improve muscle function in SMA

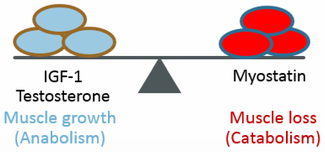
- Myostatin inhibition preferentially affects Type II (fast twitch) muscle fibers. Fast twitch muscle is critical for short duration, power driven movements, such as rising to a standing position and lifting objects from the floor.
- In SMA, fast-twitch muscle is often atrophied.
- Myostatin inhibition alone (e.g. in ambulatory type III patients) or in combination with any SMN splice modulator (e.g. in type II and non-ambulatory type III patients) may provide benefits to SMA patients.

Acknowledgements

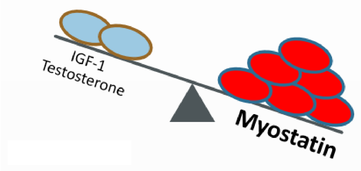
Scholar Rock would like to acknowledge the SMA Foundation for their support and guidance in conducting preclinical SMA studies.

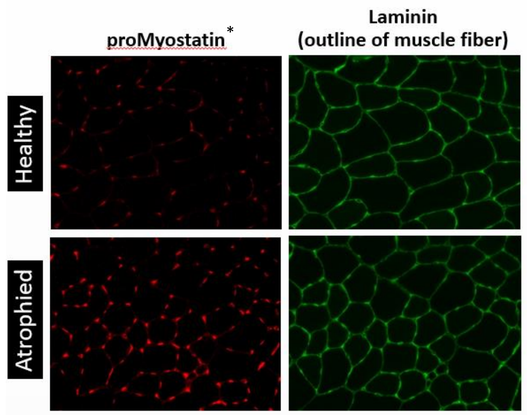
Myostatin promotes muscle protein breakdown

Muscle size is a balance between protein synthesis and protein breakdown



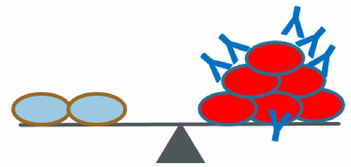
In disease, protein breakdown exceeds protein synthesis, leading to atrophy and weakness





* The myostatin precursor

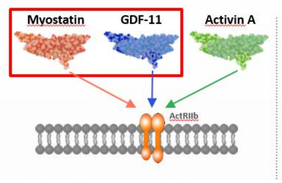
Blocking myostatin prevents protein breakdown and allows muscle to grow



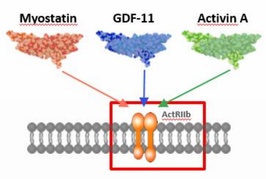
Most myostatin inhibitors also target related proteins

Specificity for myostatin is difficult to achieve.

TRADITIONAL APPROACHES



Most mature myostatin inhibitors can also inhibit other proteins



Antibodies to the receptor inhibit signaling of multiple proteins

Safety concerns raised by lack of myostatin selectivity

Myostatin is part of a large family of 33 related proteins which have a wide range of biological functions.

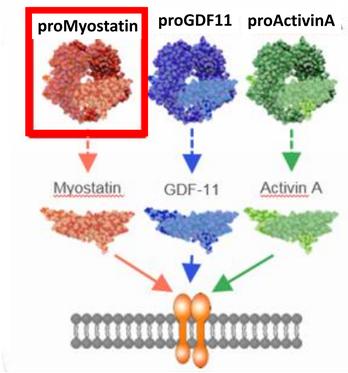
Some of these proteins are very similar to myostatin, so not all myostatin inhibitors can distinguish between myostatin and related proteins.

If a drug blocks multiple family members, there may be unwanted side effects.

Drugs that inhibit only myostatin, and not similar proteins, have the potential to limit possible safety concerns due to "off target" effects.

SRK-015 specifically inhibits myostatin activation

Selective targeting of proMyostatin, the myostatin precursor

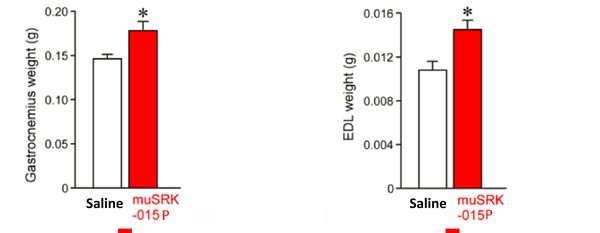


SRK-015 binding to myostatin and related proteins

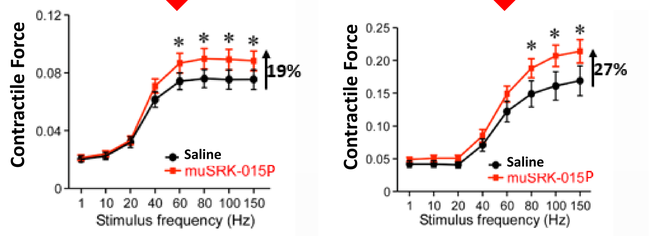
	SRK-015 binding
ProMyostatin	++
Latent Myostatin	++
Myostatin	-
ProGDF11	-
GDF11	-
ProActivin A	-
Activin A	-
BMP9	-
BMP10	-
TGFβ1	-

Inhibition of Myostatin improves muscle mass and strength in healthy mice

Muscle weight



Muscle strength



Muscle function in a mouse model of SMA is improved upon inhibition of Myostatin activation

Overview of mouse model of SMA

SMA mice are engineered with the same genetic make-up as human SMA Type I/II patients

*Small molecule corrector SMN-C1

Normal Low-high Low-high + muSRK-015P

SRK-015 Offers Therapeutic Potential for SMA

SRK-015 is a specific inhibitor of Myostatin activation.

The specificity of SRK-015 for myostatin makes it particularly suited to investigation in pediatric indications.
The lack of binding to related family members may reduce the potential for unwanted side effects that may occur with less specific drugs.

Scholar Rock has demonstrated that inhibition of myostatin activation is effective at increasing muscle mass and strength in multiple pre-clinical models, including a mouse model of SMA.

We anticipate SRK-015 to enter clinical trials ~mid-2018 in:
Type II and non-ambulatory Type III in combination with an SMN splice modulator.

Ambulatory Type III as a monotherapy.