Inhibition of myostatin activation by SRK-015 promotes muscle strength in a multiple mouse models of SMA

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Abstract

Pharmacological inhibition of myostatin is a promising therapy for many muscle diseases. Multiple anti-myostatin therapies are currently in the clinic, many of which also inhibit related family members, such as GDF11 and Activin A. This lack of selectivity has the potential to result in unwanted side effects, some of which may be particularly important to avoid in pediatric populations.

Myostatin is expressed as an inactive proprotein and undergoes two cleavage steps to release and activate the mature growth factor. While the mature form of myostatin is highly homologous to other TGFβ family members, most notably GDF11, their pro-domains are very divergent. We therefore targeted the pro-domain of myostatin to generate highly specific antibodies that prevent release from the pro-domain. One such antibody, SRK-015, inhibits the second cleavage step, preventing activation of mature myostatin.

We have confirmed that SRK-015 specifically binds pro- and latent myostatin and does not recognize mature myostatin or any forms of GDF11 or Activin A. We have also shown that SRK-015 increases muscle mass and force in healthy mice and prevents muscle loss in a dexamethasone-induced model of atrophy.

Here we demonstrate that the parental clone of SRK-015, SRK-015P, improves muscle function in multiple models of SMA. We first assessed the ability of SRK-015 to increase muscle function in two variants of the Δ7 model. The first variant aimed to approximate type II SMA. Δ7mice were administered a subtherapeutic dose of the SMN splice modulator SMN-C1 from birth until day 24, after which the dose was increased to high, therapeutic dose, and SRK-015 treatment initiated. The second variant aimed to model type III/IV SMA: Δ7 mice were administered muSRK-015P into clinical trials for SMA in patients being treated with SMN- elevating therapies and as a monotherapy for selected groups of patients.

Myostatin specificity is difficult to achieve

TRADITIONAL APPROACHES

Most mature myostatin inhibitors also inhibit mature GDF11 (and in many cases other growth factors as well)

SCHOLAR ROCK APPROACH: INHIBIT MYOSTATIN PROFORMS

- GDF11 (or other pro and mature family members)
- ProGDF11
- ProMyostatin
- Selectivity is achieved by designing antibodies to only interact with the prodomain of myostatin

Benefits of Scholar Rock Approach

- Identifies myostatin specific antibodies
- Selectivity achieved by designing antibodies to only interact with the prodomain of myostatin

C57Bl/6 mice (9 weeks old) were treated for 4 weeks with muSRK-015P (the parental clone of SRK-015) on a mouse IgG1 framework. (A) Gastrocnemius weight. (B) In vivo plantarflexor functional performance normalized to limb length. (C) EDL weight. (D) In vitro EDL performance normalized to EDL length. N=9 (EDL muSRK-015P) or N=10 all other groups. Data are mean ± s.e.m. and were analyzed by two way ANOVA. * Main effect P<0.003 (Plantarflexor) or P<0.0003 (EDL).}

Summary

• SRK-015 is a specific inhibitor of myostatin activation. The lack of binding to related family members may reduce the potential for unwanted side effects that may occur with less specific inhibitors.
• Inhibition of myostatin activation is an effective way to increase muscle mass and strength in multiple pre-clinical models, including mouse models of SMA with varying degrees of severity.
• Preparations are underway to move SRK-015 into clinical trials for SMA patients being treated with SMN- elevating therapies and as a monotherapy for selected groups of patients.