ACE-2494, a Novel GDF Ligand Trap, Increases Muscle Mass upon Systemic Administration in Mice

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Introduction

- Myostatin (GDF8), a member of the BMP/TGF-β superfamily of growth factors is a known negative regulator of muscle mass.
- GDF8 binds to the activin receptor type III (ActRIIB) on the cell surface, leading to phosphorylation of SMAD 2/3 proteins and the activation of SMAD- responsive genes.
- Treatment of GDF8 deficient mice (Mstn−/−) with inhibitors of ActRIIB signaling promotes an additional increase in muscle mass, suggesting that other ligands signaling through the ActRIIB receptor also are negative regulators of muscle mass. Ligands such as GDF11 and activins have been implicated as additional negative regulators of muscle mass that signal through the activin receptor pathway.
- Trapping of multiple ligands capable of signaling through the ActRIIB receptor is an attractive strategy for the development of therapeutic agents that may benefit patients with muscle weakness.
- An experimental therapeutic agent, ACE-031, was designed using the ligand-binding portion of ActRIIB to bind and inhibit multiple ligands capable of signaling through the ActRIIB receptor complex. In preclinical experiments, and in human clinical trials, ACE-031 increased muscle mass, but clinical development was terminated as a consequence of side effects on the vasculature. The vascular effects of ACE-031 are now generally attributed to inhibition of BMP9, another ligand that binds to ActRIIB and primarily regulates vascular development and maintenance of the vascular system.

- ACE-2494 is a protein-based ligand trap engineered to bind myostatin and other ligands to achieve muscle effects similar to ACE-031 with minimal binding to BMP9.

ACE-2494 Ligand Selectivity

Fig 1. ACE-2494 maintains affinity for GDF8, GDF11 and Activins similarly to ActRIIB-Fc, but shows significantly reduced binding to BMP9.

Fig 2. ACE-2494 inhibits GDF8, GDF11, Activin A and Activin B signaling, while inhibition of BMP9 signaling is significantly reduced in a Reporter Gene Assay

Experimental details: The ability of ACE-2494 and ActRIIB-Fc to antagonize SMAD2/3 signaling induced by Activin A, B, GDF8 and GDF11 was tested in a reporter gene assay in A204 cells using the CAGA12-luciferase reporter gene. The ability of ACE-2494 to inhibit BMP9 signaling was measured in TB9G cells using a BWE-luciferase reporter construct.

ACE-2494 Increases Muscle Mass In Vivo

Fig 3. ACE-2494 has dose dependent increases in muscle mass comparable to an ActRIIB-Fc

Experiments details: 8 week old male C57BL/6 mice (n=9 per group) were treated with ACE-2494 (3 and 10 mg/kg), ActRIIB-Fc (10 mg/kg) or vehicle (PBS) twice per week by sc injection for 4 weeks. At the end of the treatment the gastrocnemius, rectus femoris and pectoralis muscles were isolated and weighed. Each muscle weight was normalized to the initial body weight of the animal. Values are expressed as mean % change from vehicle (Figure 3). All muscles were significantly different than the vehicle controls (p=0.01).

Fig 4. Muscle mass increases correlate to an increase in body mass

Conclusions

- ACE-2494 in a novel ligand trap that inhibits multiple negative regulators of muscle growth.
- Unlike soluble ActRIIB-Fc, ACE-2494 has reduced inhibition of BMP9 which has been implicated in regulation of vascular maturation.
- Systemic administration of ACE-2494 leads to a significant dose-dependent increase in muscle mass. Gastrocnemius, rectus femoris and pectoralis muscle weights were increased relative to the vehicle control in the 3 and 10 mg/kg dosing cohorts. These increases were comparable to the magnitude of muscle mass increase observed with soluble ActRIIB-Fc.
- These data suggest that ACE-2494 may be useful as an agent to treat muscle wasting.

Experimental details: SPR experiments were performed using a Biacore T100/7200 biosensor (Biacore/GE Healthcare) at 37°C. ACE-2494 and ActRIIB-Fc were captured on an anti-Fc IgG chip and ligands were injected over the captured test molecule. All experiments were performed in duplicate.