ACE-083, a Locally-Acting TGF-β Superfamily Ligand Trap, Increases Muscle Mass and Strength in a Mouse Model of ALS


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**Background**

- Myostatin (GDF8) is a member of the TGF-β superfamily and is a known negative regulator of muscle growth.
- GDF8 signals through the activin receptor type IIb (ActRIIib) to induce SMAD 2/3 phosphorylation and translocation to the nucleus to regulate gene transcription.
- ACE-083 is a locally-acting investigational protein therapeutic that functions as a trap for GDF8 and other negative regulators of muscle mass.
- We have previously demonstrated that ACE-083 induces muscle hypertrophy and strength locally in a dose-dependent fashion when injected into target muscles in wild type and mdx mice.
- Additionally, the hypertrophy translates into a functional benefit in terms of muscle strength.
- This study was conducted to determine the therapeutic effects of ACE-083 in the SOD1-G93A mouse model of amyotrophic lateral sclerosis (ALS).

**Methods**

- Twelve-week old B6.Cg-Tg(SOD1-G93A)1Gur/J mice (SOD1) or wild type C57BL/6J (B6) mice were used on study (N=10/group).
- Mice received either a vehicle control (VEH) or ACE-083 at 100 μg per dose.
- ACE-083 was administered by direct injection into the right tibialis anterior (TA) muscle twice per week for 4 weeks.
- The physiologic properties of the TA muscle from the right leg (treated side) was assessed according to Altamirano et al. Briefly, the patellar tendon was fastened to an immobile horizontal support and the distal tendon was attached to the lever arm of a calibrated dual mode muscle lever system. Platinum needle electrodes were inserted behind the knee for stimulation of the peroneal nerve via a bi- phasic muscle stimulator.
- After testing the muscles were dissected free and weighed.

**Results**

- Local administration of ACE-083 to the tibialis anterior muscle does not display any systemic effects of increased muscle mass since there was no effect on body weight.
- Mean body weights at the end of the study were 25.9 ± 0.4, 26.2 ± 0.6, 25.6 ± 0.4 and 25.2 ± 0.4 for the B6-VEH, B6-ACE-083, SOD1-VEH and SOD1-ACE-083 groups respectively.
- Administration of ACE-083 increased the TA muscle cross sectional area, indicative of muscle fiber hypertrophy in the injected muscle (Fig. 1).

**Summary**

- In normal B6 mice ACE-083 increased the TA muscle mass by 75% compared to the uninjected contralateral TA (Fig. 2A). The adjacent EDL was also increased by 118% compared to the uninjected leg (Fig. 2B).
- In untreated SOD1 mice, there was significant muscle atrophy of the TA muscle. ACE-083 treatment increased the TA muscle mass by 35% and the EDL by 32% compared to the uninjected contralateral leg.
- In B6 mice ACE-083 increased the absolute twitch force by 25% compared to vehicle treated TA muscle (Fig. 5).
- The absolute twitch force was significantly lower in the SOD1 vehicle treated mice; ACE-083 treatment of SOD1 mice showed a trend for increased twitch, but it was not significant.
- ACE-083 treatment increased the peak tetanic force of the TA muscle in B6 mice by 36% (Fig. 6).
- The absolute peak tetanic force was significantly reduced in SOD1 mice (18% of B6 mice); ACE-083 treatment increased the absolute tetanic force by 200 mN (72%) compared to the vehicle control.

**Table 1: ACE-083 Effect TA Muscle Force-Frequency Response**

<table>
<thead>
<tr>
<th>Group</th>
<th>P_max (mN)</th>
<th>P_max (mN)</th>
<th>K (Hz)</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6-V</td>
<td>377 ± 17</td>
<td>1528 ± 36</td>
<td>57 ± 2</td>
<td>4.56 ± 0.08</td>
</tr>
<tr>
<td>B6-A</td>
<td>479 ± 22*</td>
<td>2105 ± 60*</td>
<td>64 ± 2</td>
<td>4.98 ± 0.21</td>
</tr>
<tr>
<td>SOD1-V</td>
<td>88 ± 23*</td>
<td>274 ± 70*</td>
<td>43 ± 4</td>
<td>3.71 ± 0.33*</td>
</tr>
<tr>
<td>SOD1-A</td>
<td>140 ± 27*</td>
<td>469 ± 84*</td>
<td>43 ± 2</td>
<td>3.65 ± 0.14*</td>
</tr>
</tbody>
</table>

* Indicates a significant difference from vehicle-treated group of the same genotype.
• Indicates a significant difference in the mode of a cardiac treatment.

**Fig. 1** ACE-083 Has Localized Effect

**Fig. 2** ACE-083 Increases Muscle Mass In Injected Muscles

**Fig. 3** Frequency Response

**Fig. 4** Force-Frequency Responses

**Fig. 5** ACE-083 Increased Peak Twitch Force

**Fig. 6** ACE-083 Increased Peak Tetanic Force

ACE-083 induced significant hypertrophy of the injected muscle in both the B6 and SOD1 mice with no apparent effect on the contralateral muscle or on body mass consistent with a local effect on muscle hypertrophy.

SOD1 mice showed significant muscle atrophy in the TA muscle. The TA muscle of SOD1 mice was responsive to ACE-083 treatment, but was blunted compared to wildtype animals.

The atrophy of the TA muscle in SOD1 mice was manifest by greatly impaired function, with the TA only having 18% peak tetanic force of normal animals.

ACE-083 treatment showed a significant increase in absolute tetanic force compared to vehicle treated controls.

These findings indicate that localized administration of ACE-083 can improve muscle function in a neurogenic based muscle disease such as ALS.