ACE-083, a ligand trap for members of the TGFβ superfamily, increases muscle mass locally in a mouse model of Duchenne muscular dystrophy

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Background

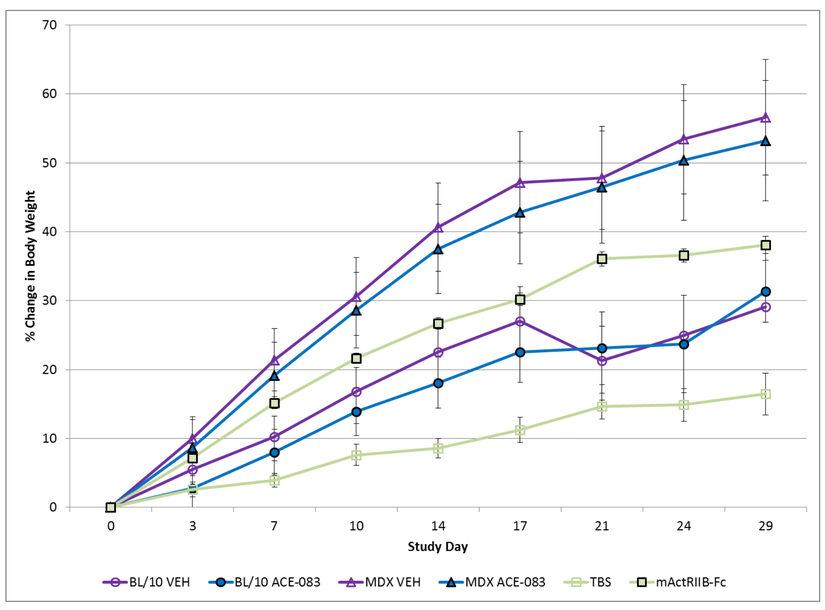
- To investigate a new therapeutic strategy for asymmetrical myopathies, we generated a modified cysteine-knot ligand trap, ACE-083, which acts locally to increase muscle mass.
- ACE-083 binds to activins and myostatin, among other ligands in the TGFβ superfamily, and inhibits their signaling.
- Previous studies determined that ACE-083 increased muscle mass in the injected muscle, with no systemic effects on other, more distant, muscles.
- In the current study we investigated the ability of ACE-083 to increase muscle mass locally using a mouse model of Duchenne muscular dystrophy.
- ACE-083 was administered by direct injection into the gastrocnemius muscle twice per week for four weeks.

Methods

- Four week old male C57BL/10ScSn-*Dmd*^{mdx}/J (*Mdx*) or Wildtype C57BL/10SnJ (BL/10) mice were used in this study (N=10/treatment group).
- All animals received an equivalent injection volume of 50 µL of either ACE-083 or Vehicle (VEH) control
- ACE-083 was administered as an IM injection of 100 µg twice weekly into the left gastrocnemius muscle for a total of four weeks.
- Body weight and overall animal health were assessed during the dosing period.
- At the conclusion of the study a terminal serum sample was collected and muscle weights were determined in each study group.

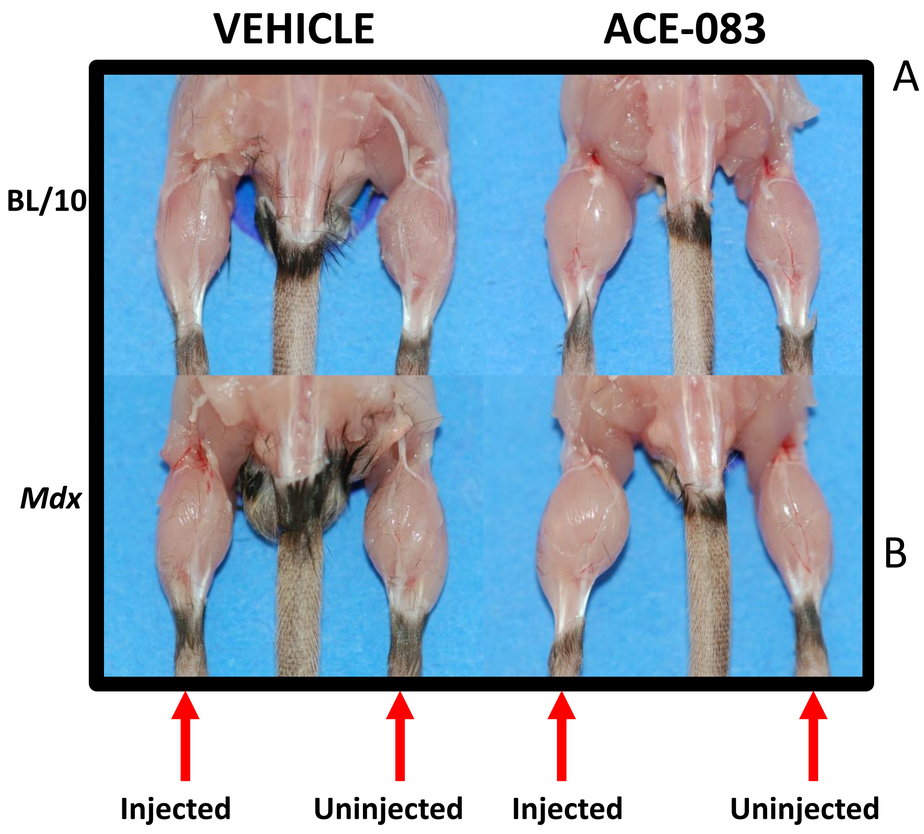
Results

Fig.1 ACE-083 Does not Alter Body Weight



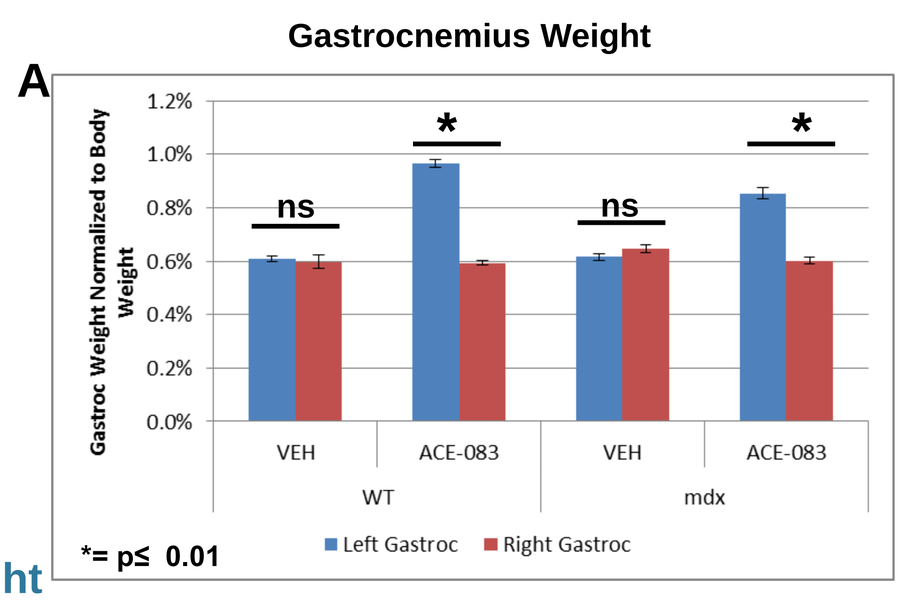
Body weights in all of the groups increased steadily over the course of the four week treatment period, and did not show any significant differences among the groups. There were no cases of body weight loss due to any acute toxicity of the drug treatment. Previously we have determined that in wild type C57BL/6 mice, IM injection of a murine ActRIIB-Fc protein increased overall body weight and was shown to increase muscle mass systemically relative to a TBS control (Green Squares in graph). In this study ACE-083 treated mice did not demonstrate an increase in body weight compared to VEH treated controls suggestive of there being no systemic drug effects on muscle mass.

Fig.2 ACE-083 Increases Muscle Size Locally in both Wildtype and *Mdx* Mice

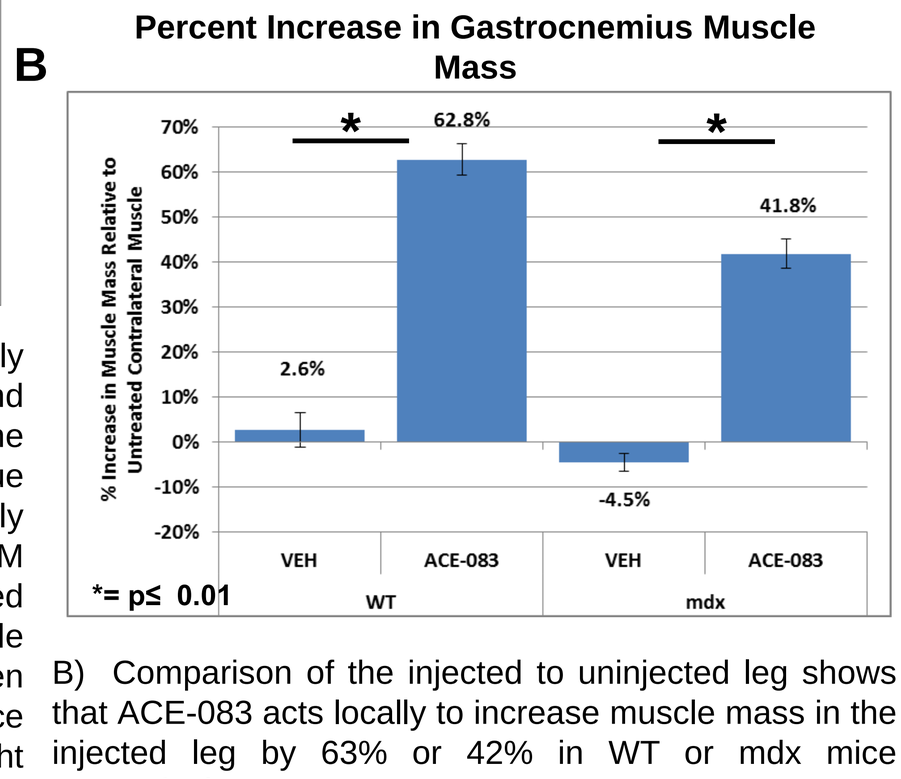


Representative images of animals from each treatment group demonstrating that ACE-083 showed a noticeable increase in the size of the injected (left gastrocnemius) muscle with no increase in uninjected muscles (right gastrocnemius) .

Fig.3 ACE-083 Increases Muscle Mass in the Injected, but not in the Uninjected Leg

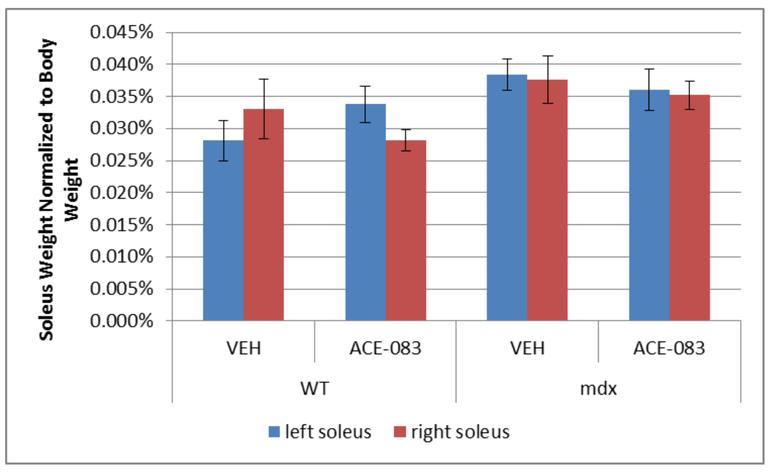


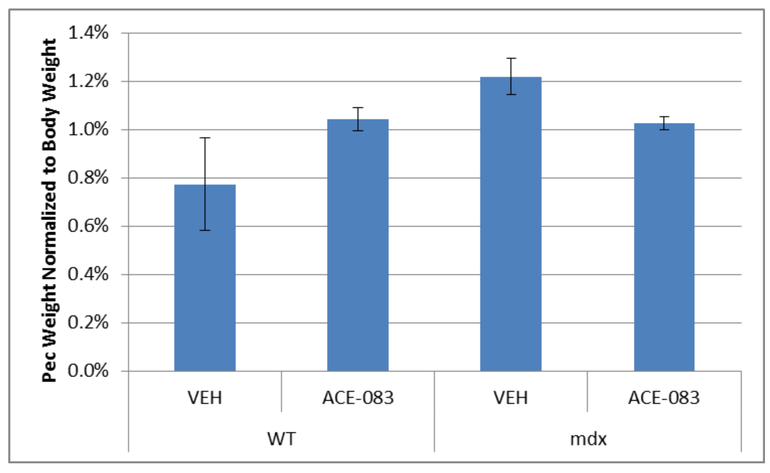
A) At necropsy the left (injected) and right (uninjected) gastrocnemius muscle was dissected and weighed. When normalized to overall body weight both wildtype and mdx mice treated with ACE-083 had significant increases in the injected, but not the uninjected, muscle compared to VEH treated mice.



B) Comparison of the injected to uninjected leg shows that ACE-083 acts locally to increase muscle mass in the injected leg by 63% or 42% in WT or mdx mice respectively.

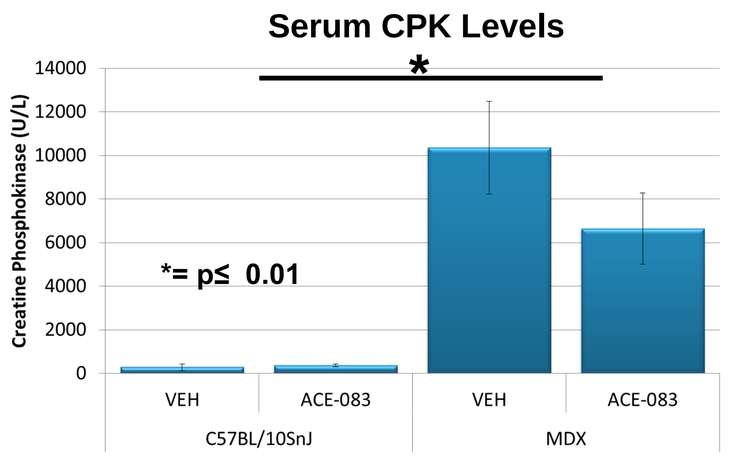
Fig.4 ACE-083 Has no Effect on Uninjected Muscles





Additional muscles were collected to determine if ACE-083 entered circulation and had a biological effect on adjacent or distal muscle groups. Neither the soleus (A) or pectoralis (B) muscles displayed a significant increase in muscle size in any of the treatment groups.

Fig.5 ACE-083 May Improve Muscle Integrity in Mdx mice



To determine if ACE-083 improved muscle integrity in mdx mice, serum was analyzed for creatine phosphokinase, a biomarker of muscle damage. All mdx mice had significantly higher CPK levels compared to WT controls (p≤0.01). The ACE-083 treated mice had a trend towards lower CPK levels, but did not reach significance (p=0.182). This may be due to improvement in only the injected muscle group, and not having effects systemically.

Conclusions

- These data demonstrate that local ACE-083 administration in muscle increases muscle mass in the injected muscle and does not affect uninjected muscles.
- ACE-083 elicits demonstrable effects in both WT and in a mouse model of Duchenne muscular dystrophy.
- Local administration of ACE-083 may be useful in the treatment of diseases affecting a select set of muscles such as inclusion body myositis or facioscapulohumeral muscular dystrophy.

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