ACE-083, a Locally-Acting GDF/Activin Ligand Trap, Augments Dorsiflexor Muscle Function in a Murine Model of Charcot-Marie-Tooth (CMT) Disease

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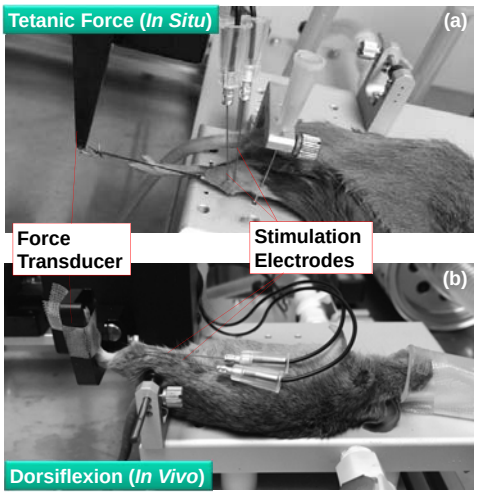
Background and Aims

- Charcot-Marie-Tooth (CMT) is the most common hereditary peripheral neuropathy and is characterized by demyelination and/or axonal damage of peripheral nerves and muscle weakness. Foot drop, steppage gait, and foot deformities are typically seen in CMT patients. Consequently, falls are commonly reported in these patients.
- Improvement of dorsiflexor muscle function to prevent falls may improve quality of life and activities of daily living in patients with CMT.
- ACE-083, a locally-acting ligand trap that binds growth and differentiation factors (GDFs) and activins, has previously been shown to increase muscle mass and force in both Duchene muscle dystrophy (DMD) and amyotrophic lateral sclerosis (ALS) mouse models.
- In the current study, we evaluated the therapeutic effects of ACE-083 to improve muscle strength in the trembler (Tr-J) mouse model of CMT1A. These mice harbor a mutation in the peripheral myelin protein 22 (PMP22) known to cause CMT1A.

Methods

- Seven-month old (B6.D2-*Pmp22*$^{Tr-J}$/J) mice (n = 22) were administered either vehicle or ACE-083 (100µg, twice weekly) intramuscularly to the unilaterally tibialis anterior (TA) muscle for 4 weeks.
- The contractility of the TA muscle was evaluated during isometric contraction. It was performed both *in situ* and *in vivo*. Figure 1a demonstrated how tetanic force was measured from the isolated TA muscle (*in situ*). To assess alterations of ankle dorsiflexion strength over disease course, dorsiflexor muscle force was measured in live animal (*in vivo*) (Figure 1b).
- Pathological and biochemical assessments were examined to evaluate the morphology of muscle fiber and the degree of muscle atrophy.
- All data were compared to the uninjected contralateral control hind-limb.

Figure 1. Isometric Contraction



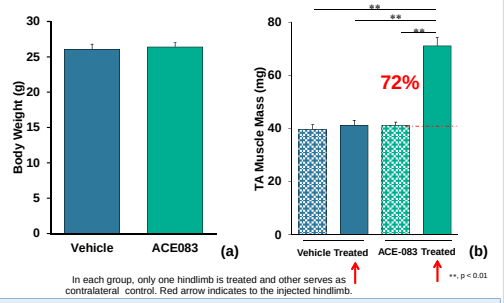
Results

I. ACE-083 Increased TA Muscle Mass

- There was no body weight difference between vehicle control and ACE-083 treated mice (Figure 2a).
- However, the TA muscle mass was increased by 72% (p<0.01) in ACE-083 treatment, comparing to its contralateral control hind-limb (Figure 2b).

- ACE-083 treatment selectively increased muscle mass.

Figure 2. Selective Effects on TA Muscle Mass

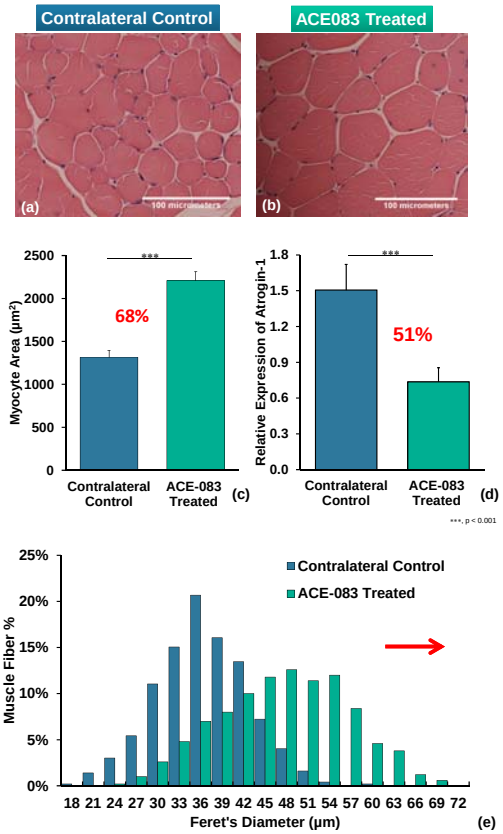


In each group, only one hindlimb is treated and other serves as contralateral control. Red arrow indicates to the injected hindlimb.

II. ACE-083 Increased Muscle Fiber Area

- As the representative H&E pictures show below (Figure 3a and 3b), much larger muscle fiber size was found in ACE-083 treated muscle comparing to its contralateral control muscle.
- Quantitative results demonstrated 68% ($p < 0.001$) increase in myocyte area with ACE-083 treatment comparing to the contralateral control muscle (Figure 3c). In addition, mRNA expression of muscle atrophy biomarker, atrogin-1, was reduced 50% ($p < 0.001$) by ACE-083 treatment (Figure 3d).
- Figure 3e presents the distribution of muscle fiber, it shows a shift towards right, indicating increased number of larger muscle fibers in ACE-083 treated muscle than contralateral control muscle.

Figure 3. Improvement in Myocyte Morphology

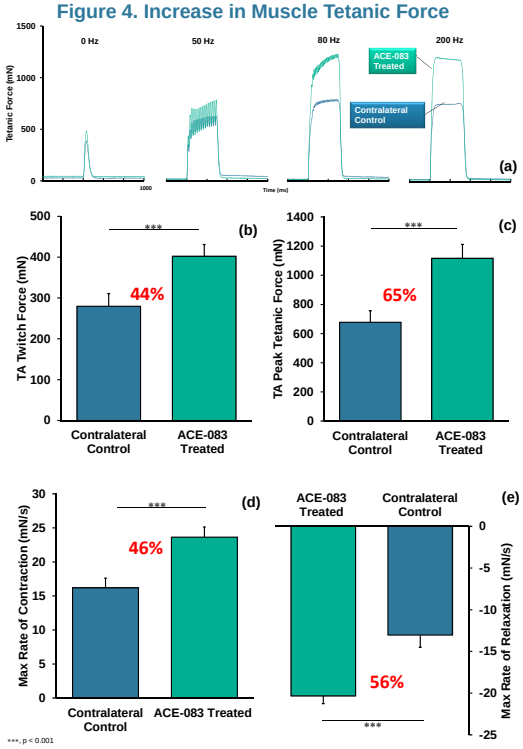


III. ACE-083 Improved TA Muscle Strength

- *In situ* study showed that TA muscle force was improved by ACE-083 treatment. The representative force responses at various frequencies are illustrated in Figure 4a. As presented, TA muscle with ACE-083 treatment generated larger tetanic force than contralateral control at all frequencies.

- ACE-083 treatment improved both twitch force (Figure 4b) and peak tetanic force (Figure 4c) by 65% ($p<0.001$) and 44% ($p<0.001$) respectively.
- In addition, temporal properties during isometric contraction, such as maximum rate of contraction (Figure 4d) and relaxation (Figure 4e), were accelerated by 46% and 56% respectively ($p<0.001$) in the ACE-083-treated TA muscle compared to its contralateral hind-limb.

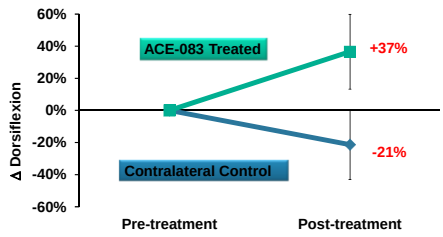
Figure 4. Increase in Muscle Tetanic Force



IV. ACE-083 Improved Ankle Dorsiflexion

- *In vivo* study demonstrated that ACE-083 treatment was able to attenuate ankle dorsiflexion weakness. As shown in Figure 5, over 4 weeks treatment, ankle dorsiflexion of ACE-083 treated hind-limb was improved by 37% from its baseline level; while ankle dorsiflexion of contralateral control hind-limb was dropped by 21% from its baseline.

Figure 5. Alterations of Ankle Dorsiflexion



Longitudinal study: pre-treatment (7 months old) to post-treatment (8 months old)

Conclusions

- ACE-083 (i) increases muscle mass and contractile properties; (ii) increases muscle fiber size; and (iii) reduces atrogin-1 expression and muscle atrophy in the mouse model of CMT1A.
- The current study provides proof of concept for the use of ACE-083 as a potential therapy for CMT to improve dorsiflexor muscle function and alleviate foot drop.
- ACE-083 is currently in phase 2 clinical trial to evaluate ankle dorsiflexion weakness in CMT patients.