Excessive muscle growth of myostatin deficient mice is accompanied by a fibre type conversion towards fast glycolytic fibres. In the present study, we determined the energetic and functional consequences of such altered muscle phenotype. Mitochondrial respiration rates, measured on skinned fibres from mstn−/− mice, showed a 40% decrease in complexes II and IV activities compared to controls, whereas the activity of complex I remained unchanged. Non-invasive muscle energetic measurements (31P MR spectroscopy), using a rest-electrical stimulation-recovery protocol, revealed a larger energy consumption per specific workload in mstn−/− animals, whereas the initial rates of [PCr] consumption and [PCr] resynthesis were normal. In addition, the end-of-stimulation intracellular pH was more acidic in mstn−/− animals, whereas the initial rates of [PCr] consumption and [PCr] resynthesis were normal. Moreover, mstn−/− muscle fatigue much faster than WT muscle and force subsided to WT levels compared to wildtype (WT) muscle. However, mstn−/− muscle showed a 40% decrease in complexes II and IV activities compared to controls, whereas the activity of complex I remained unchanged. Non-invasive muscle energetic measurements (31P MR spectroscopy), using a rest-electrical stimulation-recovery protocol, revealed a larger energy consumption per specific workload in mstn−/− animals, whereas the initial rates of [PCr] consumption and [PCr] resynthesis were normal. In addition, the end-of-stimulation intracellular pH was more acidic in mstn−/− animals, whereas the initial rates of [PCr] consumption and [PCr] resynthesis were normal. Moreover, mstn−/− muscle fatigue much faster than WT muscle and force subsided to WT levels following 3 min of repetitive tetanic stimulations. This increased muscle fatigability was further confirmed by a 25% shorter run-to-exhaustion time following treadmill exercise, and this earlier exhaustion was associated with a pronounced lactic acidosis. Interestingly, the maximal rate of oxygen consumption (VO2max) was increased by 15% in mstn−/− mice but this increase was disproportionately low considering the more than twofold greater muscle mass. Moreover, both groups reached VO2max at similar running velocities indicating that the corresponding energetic cost of running was larger in mstn−/− animals. Mstn−/− mice displayed also a strongly reduced spontaneous motor activity in addition to the exercise induced fatigability.

In conclusion, lack of myostatin compromises mitochondrial activity on one side and increases total energy cost on the other side which renders hypertrophied mstn−/− muscle more fatigable as well as energetically less efficient.

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P3.18
A Phase 1 multiple ascending dose study to assess the pharmacodynamic effects of ACE-031, an inhibitor of negative muscle regulators, in healthy volunteers
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Objectives: To evaluate the safety, tolerability and pharmacodynamic (PD) activity of ACE-031 following multiple escalating SC doses in healthy volunteers. Background: ACE-031 is a fully human fusion protein consisting of a form of the extracellular domain of the activin receptor type IIB (ActRIIB) linked to the IgG1 Fc domain. ACE-031 binds with high affinity to myostatin and other negative regulators of muscle growth and blocks their signaling through ActRIIB. In animal models of neuromuscular disease, including DMD and ALS, ACE-031 increased muscle mass and strength. In a Phase 1 single ascending dose study in healthy volunteers, ACE-031 increased lean mass and muscle volume. Design/methods: Sixty healthy postmenopausal women were randomized in 6 cohorts of 10 subjects each to receive ACE-031 or placebo (8:2) at dose levels ranging from 0.1 to 3 mg/kg given every 2 or 4 weeks for 4 weeks (2 or 3 doses). Safety was reviewed for each cohort prior to dose escalation. Subjects were followed for 12 weeks following last dose. Lean mass (DXA) and muscle volume (thigh MRI) were obtained at baseline and weeks 5, 8, and 16. Other pharmacodynamic endpoints included grip strength, 6 minute walk test, stair climb test, and biomarkers of bone formation, bone resorption and fat metabolism. Results: Enrollment of the 6 cohorts is complete and the follow-up phase is ongoing. Initial findings indicate that multiple doses of ACE-031 up to 3 mg/kg are well tolerated. Safety and pharmacodynamic results will be presented at the meeting. Conclusions: Preliminary data from this multiple-dose study affirm findings from the single-dose study that ACE-031 is well tolerated and has the potential to promote lean mass and muscle volume. These results support the advancement of ACE-031 to explore its therapeutic benefits to increase muscle size, strength and function in neuromuscular diseases such as DMD and ALS.


P3.19
Decrease of sarcolemmal nNOS as a molecular marker of muscle atrophy in inherited and acquired forms of myopathy
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Muscle atrophy is a widespread clinical finding common to many congenital and acquired conditions. Maintaining mobility and muscle integrity is crucial for the management and quality of life of these patients. Previous research indicated that neuronal nitric oxide synthase (nNOS) contributes to preservation of muscle mass and blood flow. In healthy muscle, nNOS is associated with the dystrophin–glycoprotein complex (DGC) at the sarcolemma via interactions with alpha-syntrophin. Loss of sarcolemmal nNOS is associated with atrophy in hindlimb suspension mouse models and exercise-induced decrease in muscle blood flow and fatigue in dystrophin-deficient muscular dystrophies, such as Duchenne muscular dystrophy. To assess the expression pattern of nNOS in a variety of myopathic conditions we analyzed patient muscle biopsies. We find that patients presenting with congenital hypotonia, including structural myopathies, mitochondrial disorders, and metabolic myopathies, or uncharacterized hypotonia syndromes exhibit loss or decrease of sarcolemmal nNOS. Moreover patients with acquired forms of myopathy such as immobilization atrophy, denervation, and steroid-induced myopathy show decreased or loss of nNOS expression from the sarcolemma. Interestingly, all of these patients share significant muscle fatigue associated with varying degrees of disuse. Similarly, in mouse models for muscle atrophy such as steroid-induced myopathy and fasting atrophy, we find a decrease in sarcolemmal nNOS accompanied by well-characterized indicators of muscle atrophy.