MF-300, an orally bioavailable small molecule inhibitor of 15-PGDH, improves muscle force in preclinical models of neuromuscular dysfunction and disease

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Introduction
- Prostaglandin E2 (PGE2) is a lipid signaling molecule critical for muscle regeneration and function.
- Therapeutic inhibition of the PGE2-degrading enzyme, 15-Prostaglandin Dehydrogenase (15-PGDH), improved muscle strength in aged mice.
- MF-300 is an orally bioavailable small molecule inhibitor of 15-PGDH.
- Administration of MF-300 in mice increased strength in two models of Spinal Muscular Atrophy (SMA) as well as an inducible model of muscle atrophy (sciatic nerve crush).

Figure 1) PGE2 Pathway
- MF-300 blocks binding of PGE2 to 15-PGDH
- Increased stem cell proliferation (1)
- Increased muscle force (1, 2)
- Improved mitochondrial function (2)
- MF-300 inhibits 15-PGDH in vitro

Figure 2) MF-300 MoA and PK
- 15-PGDH Inhibition (Biochemical Assay)
- MF-300 inhibits 15-PGDH in cell-based assay
- PGE2 Stability (Cell-based Assay)
- MF-300 inhibits 15-PGDH in cell-based assay

Figure 3) MF-300 administration (IP) in SMN Δ7 mice
- MF-300 significantly increased force in Δ7 (high/high) mice
- SMN Δ7 Mouse Model – Severe phenotype mediated by therapeutics administration of the SMN splice enhancer, SMN-C3 (5).
- High/High = moderate phenotype (SMN-C3) mice
- Endpoint - isometric plantar flexor force.
- Conclusion - MF-300 increased force at all dose levels.

Figure 4) MF-300 administration (PO) in SMNΔC mice
- MF-300 dose responsive increase in force in SMNΔC mice
- SMNΔC is a genetic mouse model for mild phenotypic SMA.
- Endpoint - isometric plantar flexor force.
- Conclusions:
  - MF-300 increased force in a dose responsive manner
  - Increased force was independent of any effect on muscle mass.

Figure 5) MF-300 administration (PO) in a sciatic nerve crush model
- MF-300 accelerated rate of force recovery following nerve crush injury
- Healthy animals - surgery to expose the sciatic nerve
- Nerve crush for 30 sec (sham + no crush injury).
- In vivo muscle force (isometric plantar flexor) - baseline and then once weekly starting at 14 days post injury.
- MF-300 accelerated force recovery at 18- and 35-days post injury.
- Conclusions:
  - Therapeutic administration of MF-300 increased muscle force and function in mouse models of SMA. Preliminary RNA-seq analysis suggests that MF-300 corrected dysregulated expression of multiple genes in Δ7 muscle.
  - Increased muscle force was independent of changes in muscle mass. Comparing nerve- to muscle-stimulated contraction suggests that MF-300 has a muscle intrinsic effect on force after 1 week of treatment. An effect on NMJ is also possible, given these data.
  - MF-300 accelerated force recovery following sciatic nerve injury in healthy mice. Timing of effect on force recovery suggests improved regeneration of functional neuromuscular junctions (2) and/or enhanced sensitivity of the muscle to contractile stimuli.

References
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