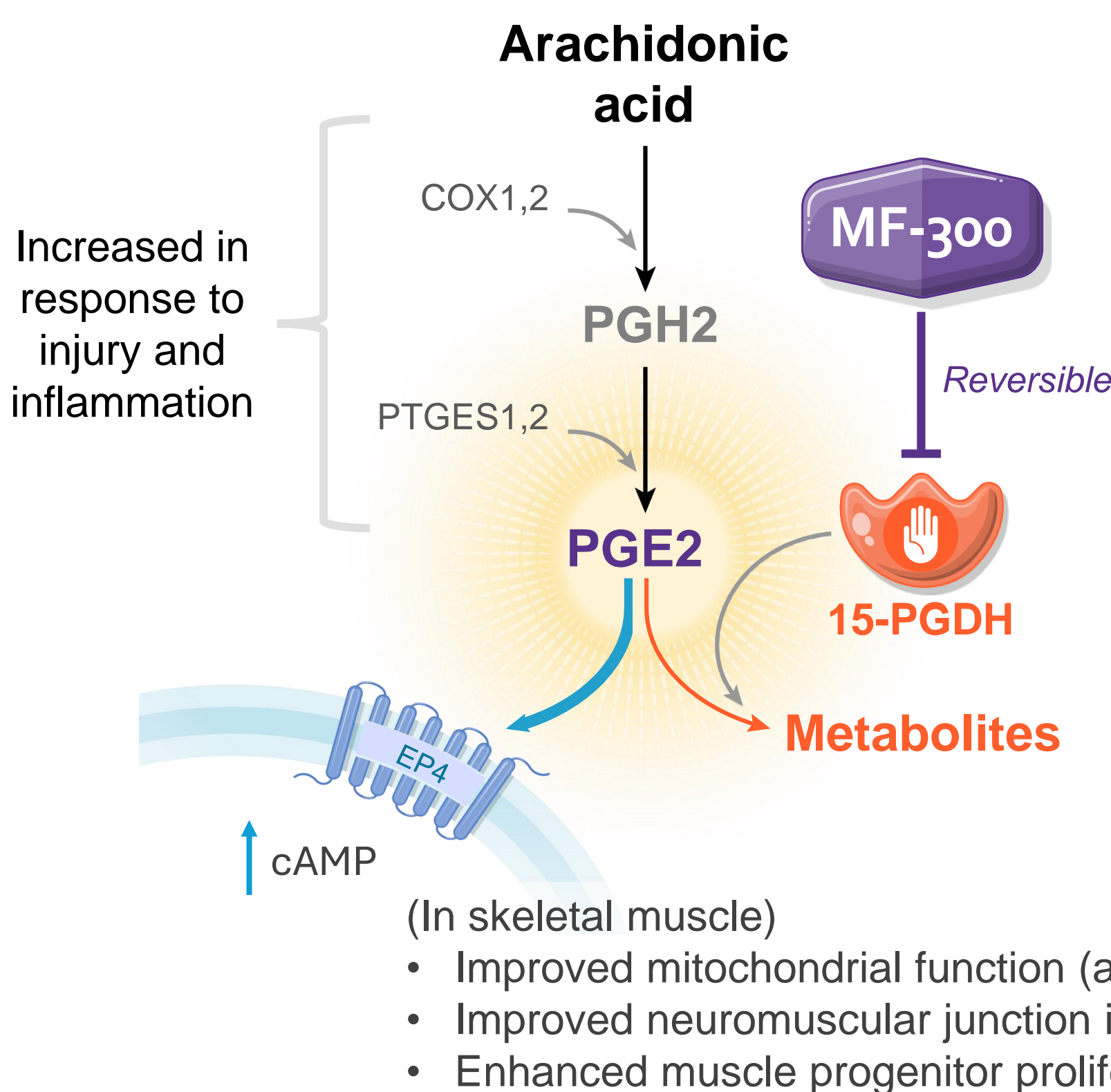


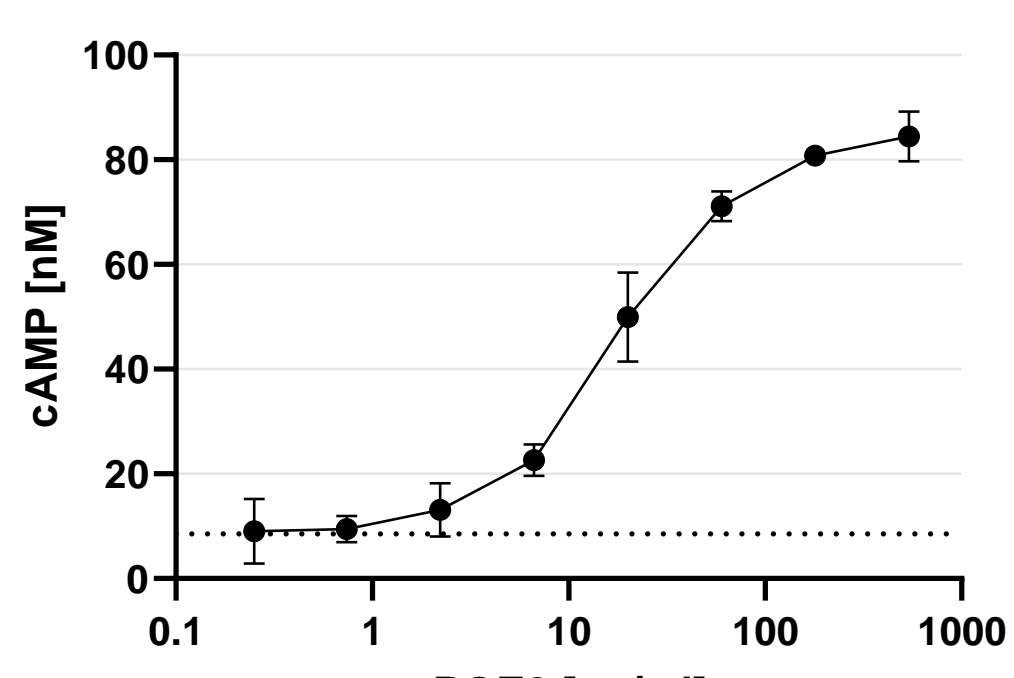
1. Introduction

- Progressive muscle denervation that occurs with aging contributes to sarcopenia.
- Slowing denervation or enhancing re-innervation may be strategies to mitigate progression of sarcopenia.
- In mice, inhibiting 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the enzyme that metabolizes prostaglandin E2 (PGE2), improves structure of the neuromuscular junction in aged muscle and accelerates recovery of muscle force following nerve injury.^{1,2}
- MF-300 is an orally administered inhibitor of 15-PGDH that increases PGE2 in muscle. MF-300 is being studied in a Phase 1 clinical trial in healthy human volunteers for safety, pharmacokinetics, and pharmacodynamic target engagement.

2. Therapeutic strategy: Inhibit 15-PGDH with MF-300 to increase PGE2/EP4 signaling and cAMP activity in muscle



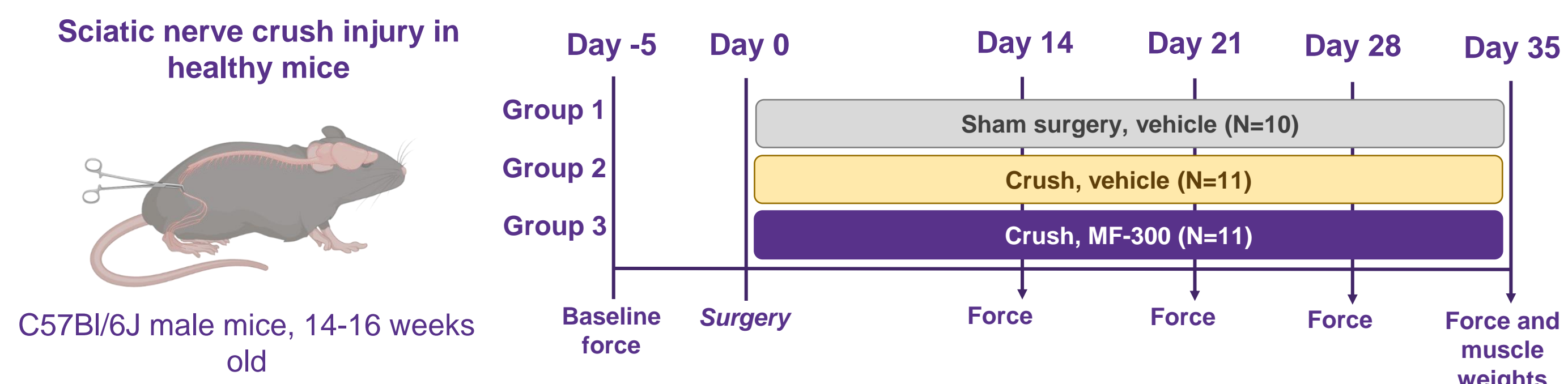
PGE2 increases cAMP in primary human myocytes



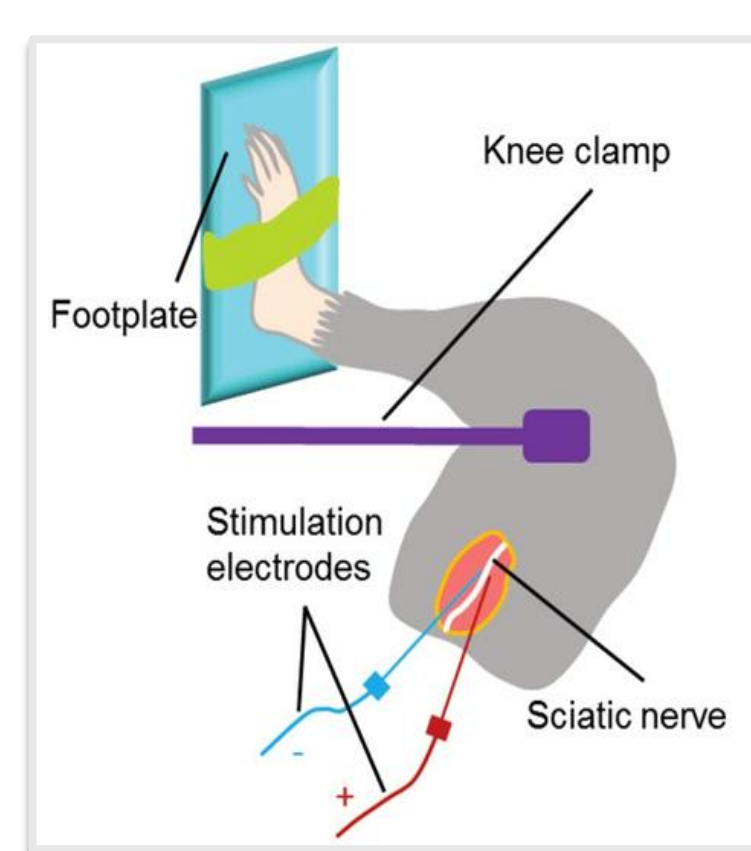
4. Methods & Study Design

- C57Bl/6J male mice, 14-16 weeks old
- Nerve crush N=11, sham control N=10
- MF-300 or vehicle administered PO
- Muscle force was measured in vivo (isometric plantar flexion) with a 305C muscle lever system (Aurora Scientific Inc., Aurora, CAN)
- Statistical analyses: One-Way ANOVA with a Holm-Šidák post-hoc or a Two-Way Repeated Measures ANOVA with a Holm-Šidák post-hoc

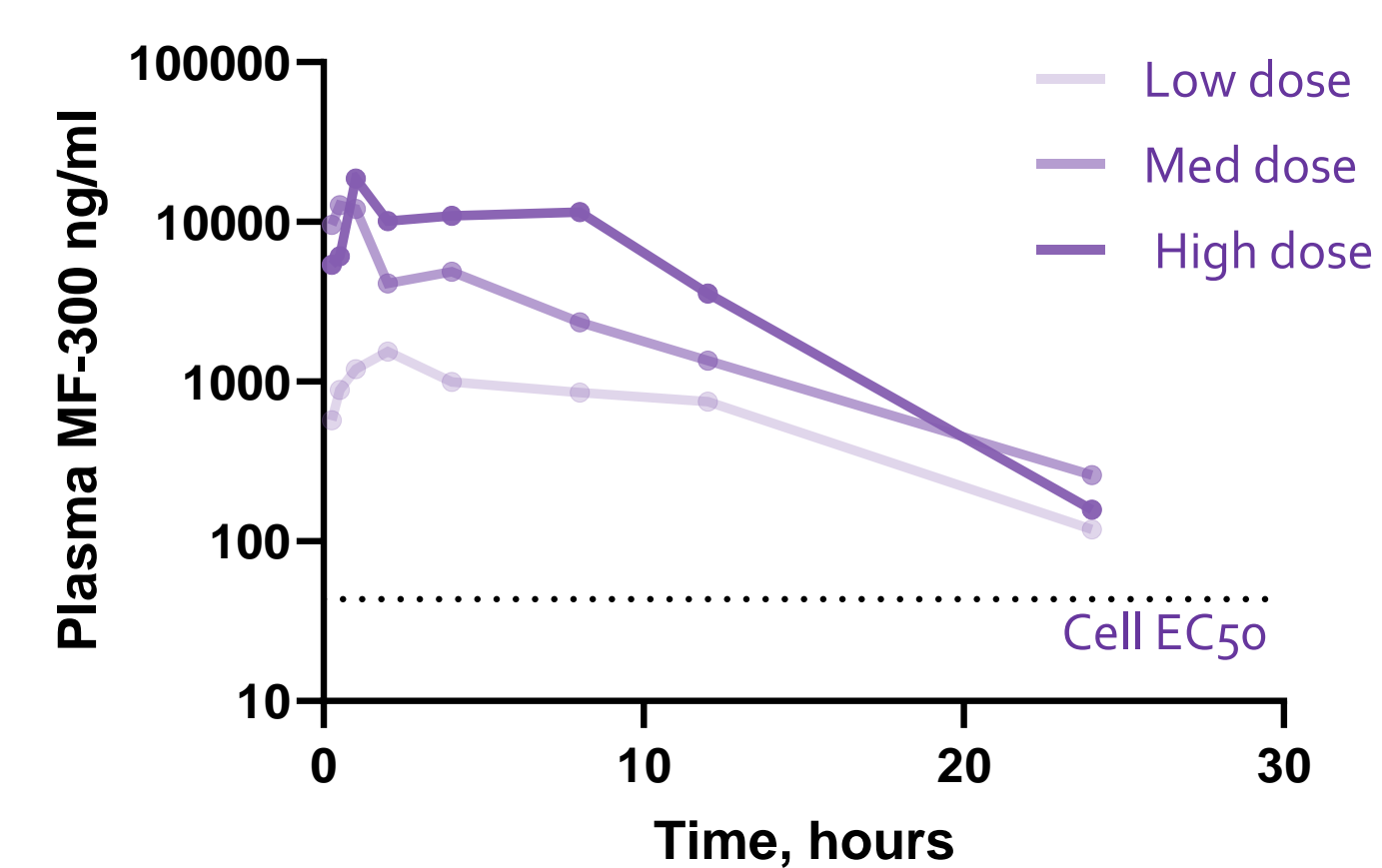
Efficacy study to test effect of MF-300 on muscle force following nerve injury



Force endpoint In vivo, isometric plantar flexor force



24-hr plasma MF-300 concentration Mouse, single dose, PO

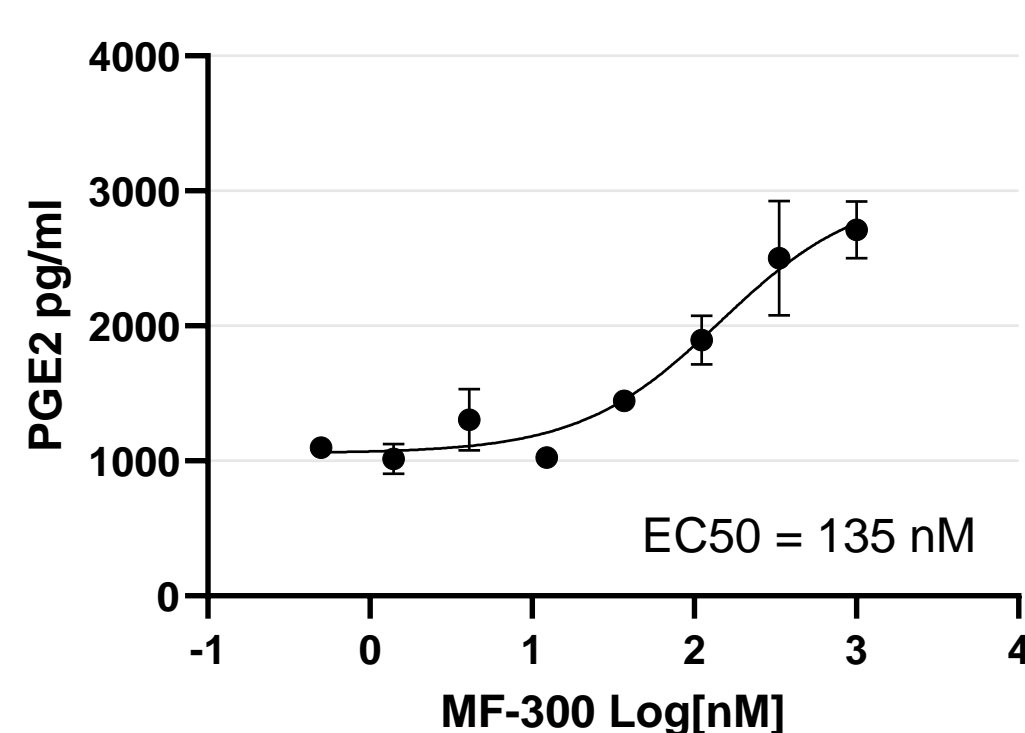


5. Results: MF-300 accelerated recovery of muscle force

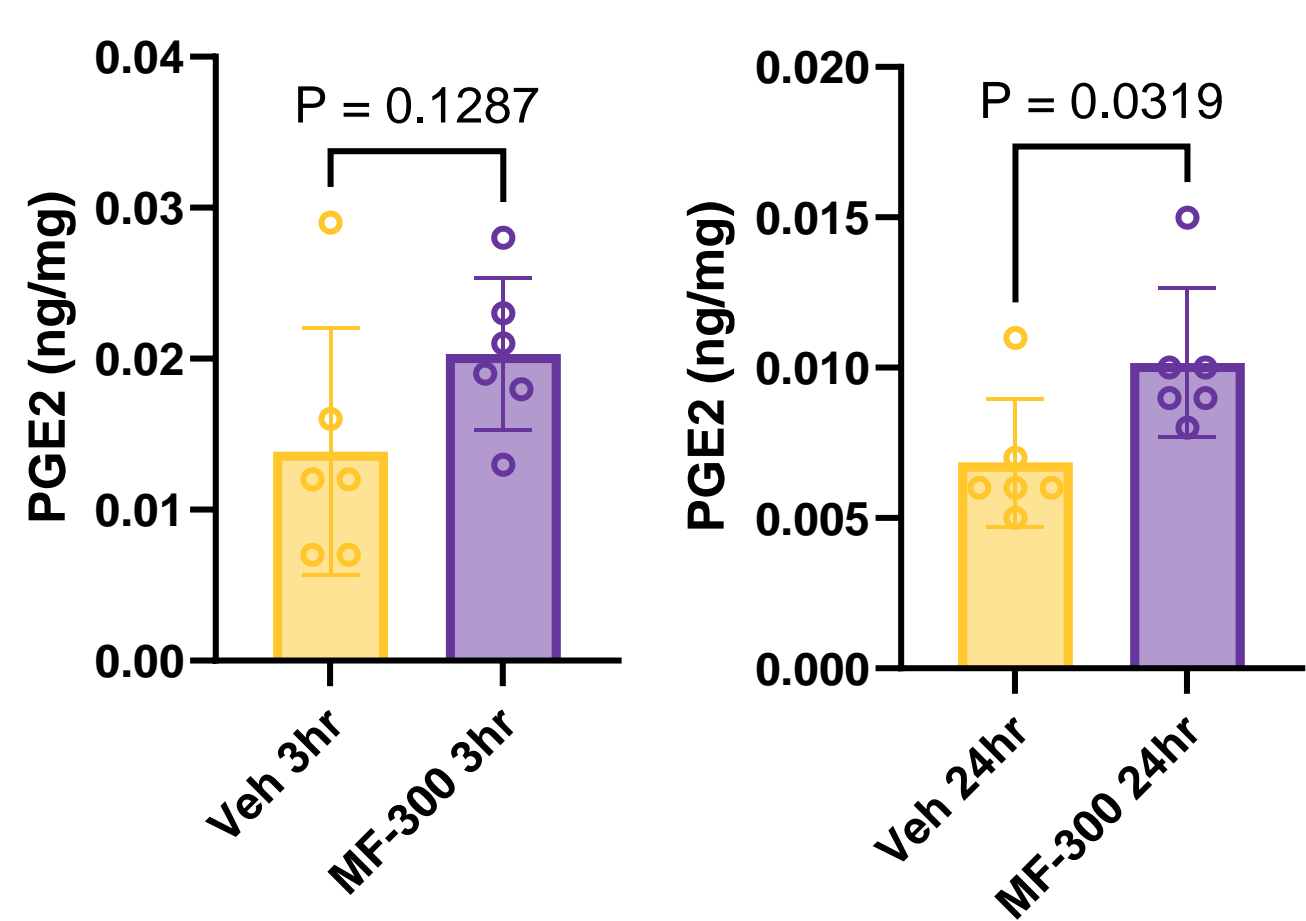
MF-300 reduces 15-PGDH activity Biochemical assay

Species	15-PGDH % Identity to Human	MF-300 IC ₅₀ (nM)
Human	100%	0.84
Dog	94%	1.5
Mouse	89%	1.0
Rat	88%	4.0

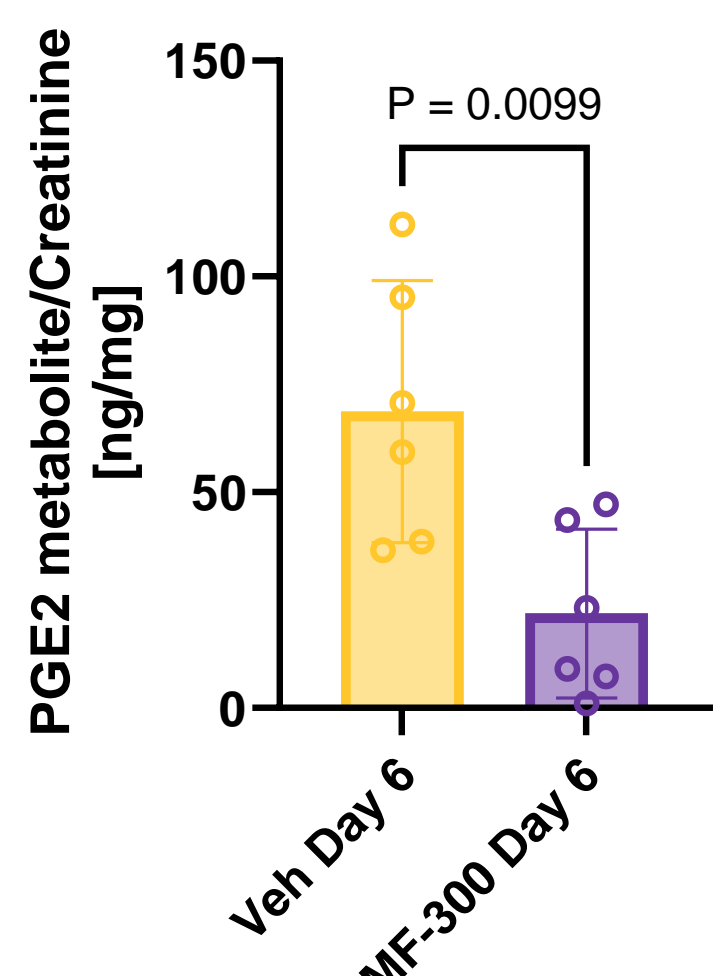
MF-300 increases PGE2 in cell-based assay



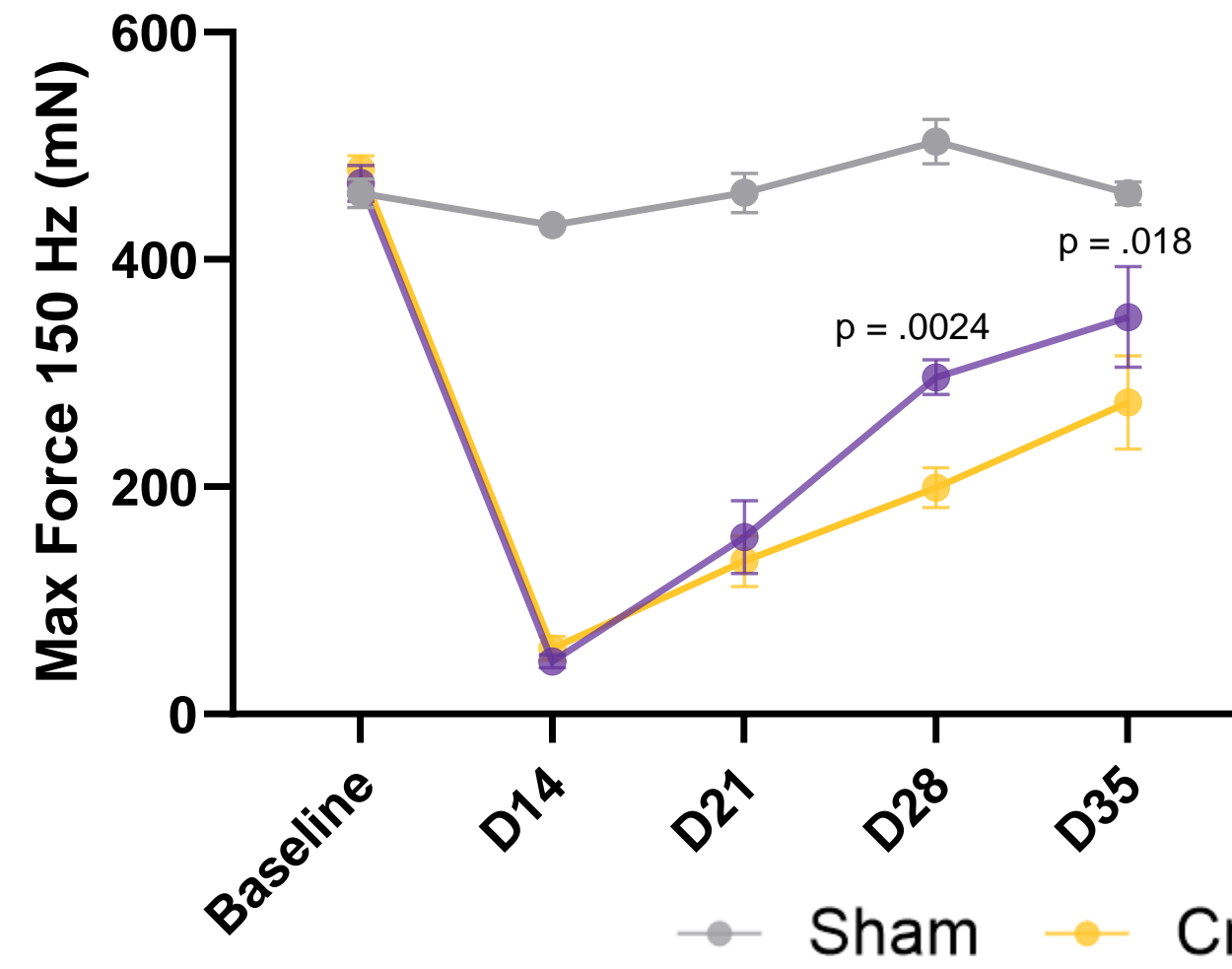
MF-300 increases PGE2 in healthy rat gastrocnemius muscle Single dose, PO



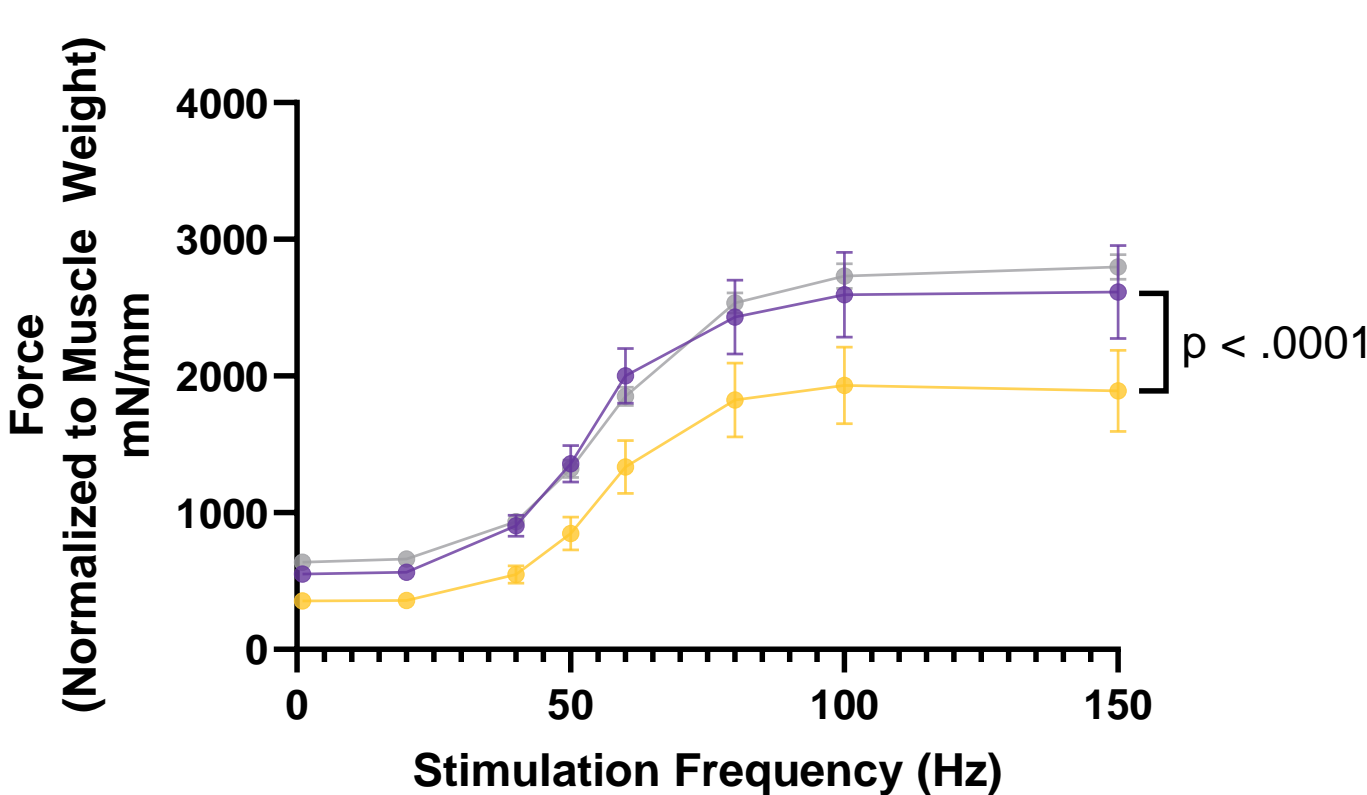
MF-300 reduces PGE2 metabolite in healthy rat urine Steady state, PO



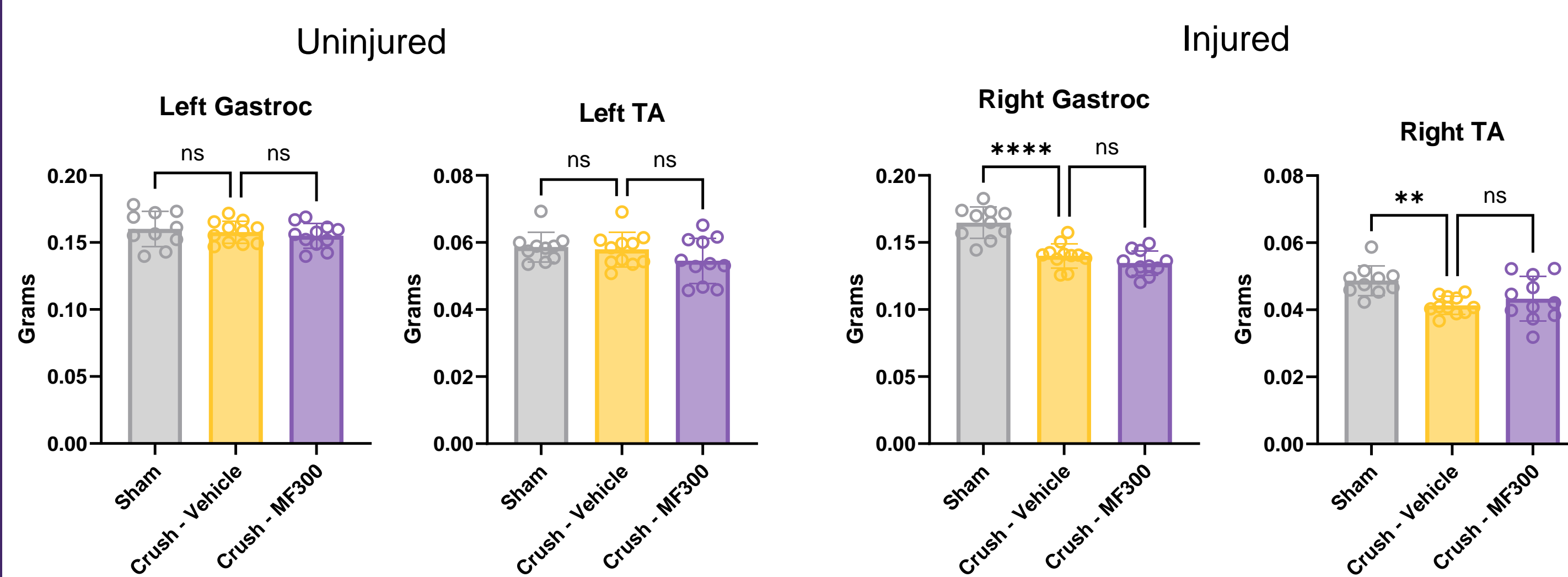
Accelerated recovery of absolute force



Recovery of muscle specific force at D35 (force per muscle mass)



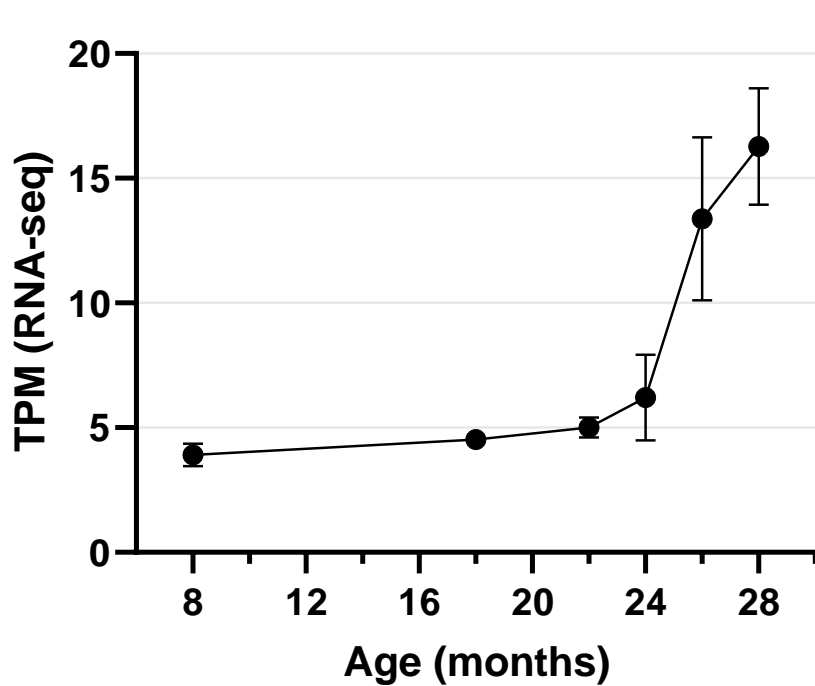
MF-300 did not increase muscle mass (D35)



3. 15-PGDH gene expression is elevated in muscle during aging and following nerve injury

15-PGDH gene expression elevated in aged mice

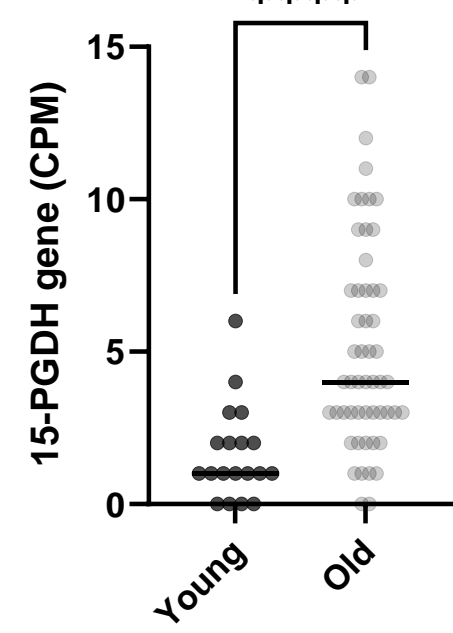
- Male mice (C57Bl/6JRj)
- Gastrocnemius



Graph generated from publicly available data⁴

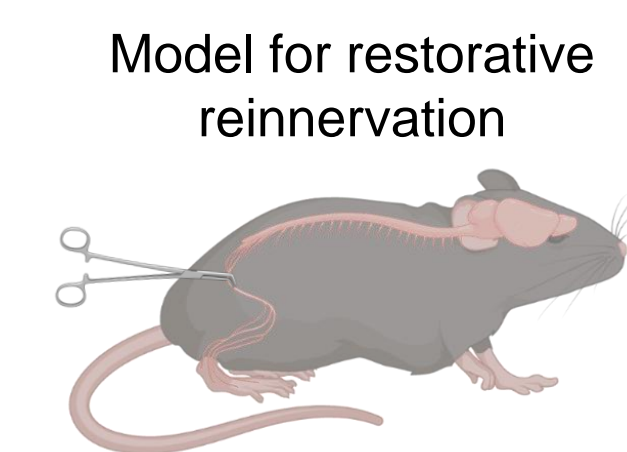
15-PGDH gene expression elevated in aged humans

- Vastus lateralis (women and men)
- Young, N = 19 (25±3 y.o.)
- Old, N = 29 (78±6 y.o.)

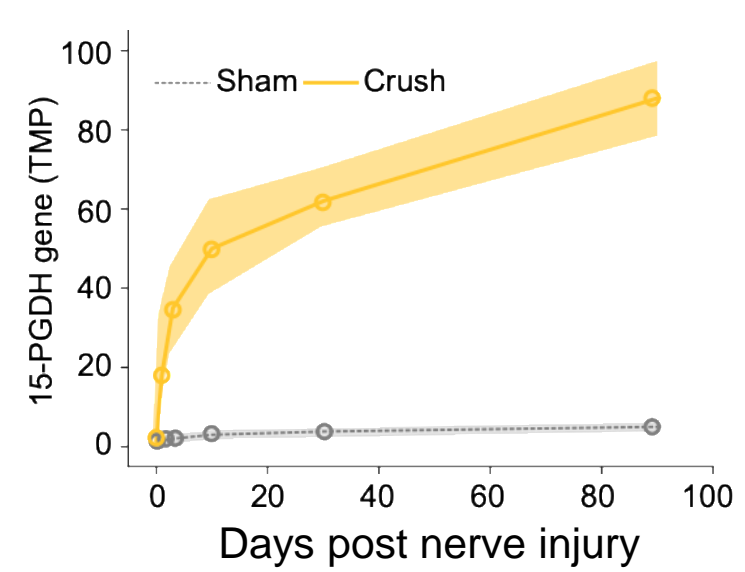


Graph generated from publicly available data⁵

Sciatic nerve injury in healthy mice Model for restorative reinnervation



15-PGDH gene expression elevated following nerve injury



Graph generated from publicly available data⁶

6. Discussion

- Sciatic nerve crush caused substantial atrophy and loss of isometric plantar flexor force.
- In Veh and MF-300 groups, recovery of muscle force started at Day 21 post injury and continued to end of study Day 35.
- Oral administration of MF-300, which increases PGE2 levels in gastrocnemius muscle, accelerated recovery of muscle force compared to Veh.
- MF-300 improved specific muscle force (i.e., increased absolute force without changing muscle mass) at Day 35 post injury.
- These data suggest that MF-300 accelerated nerve reinnervation following crush injury.

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Acknowledgements:

We thank Andrew Ho, PhD, for contributions to data analysis and thought partnership, Elaine Chiquette, PharmD, for literature research and contributions to Epirium's communication efforts, Siva Lavu, PhD, for supporting bioanalytical activities. We thank the talented CRO's and vendors who contributed to study operations and sample analysis including HD Bio (Sand Diego, CA), Nextcea (Woburn, MA), ZenBio (Durham, NC), and Unitides (Madison, WI).