MF-300 (15-PGDH Enzyme Inhibitor) Reverses Age-Related Muscle Weakness in Mice by Restoring Muscle Quality

Micah Webster, PhD[1], Jennifer Martin, BSc[2], Bruce T. Fahr, PhD[1], Ramzi J. Khairallah, PhD[2]

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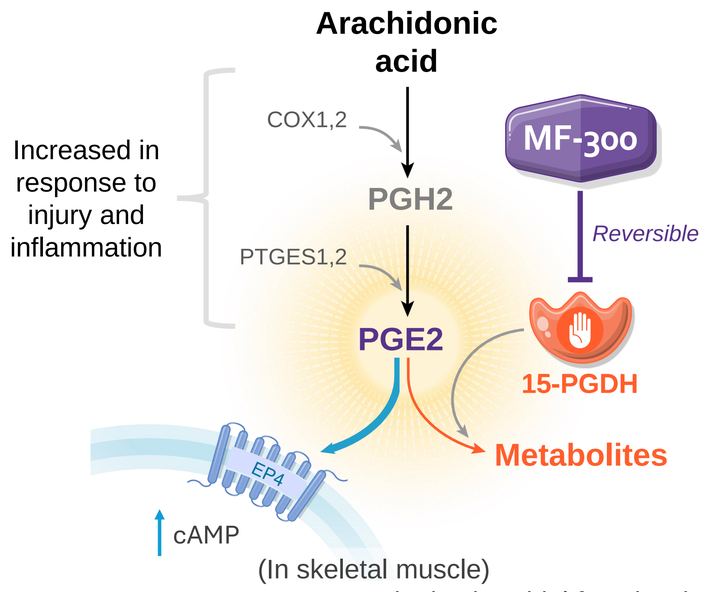
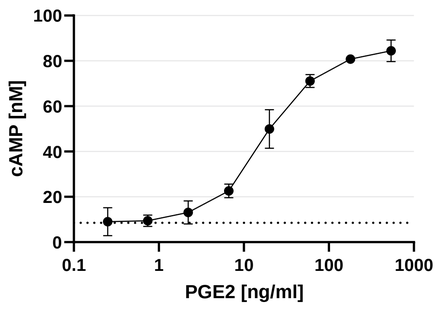
1. Introduction

- Sarcopenia, age-induced muscle weakness, is caused by reduced muscle quality & muscle quantity and disproportionally affects fast-twitch muscle.
- Muscle force and contraction rate are reduced in sarcopenia.
- Improving quality of fast-twitch muscle in aging is a strategy to enhance strength and slow progression of sarcopenia.
- Prostaglandin E2 (PGE2), via EP4 signaling, induces cAMP activity in muscle and improves muscle function in aged mice[1,2].
- MF-300, an oral inhibitor of the enzyme that metabolizes PGE2, 15-hydroxyprostaglandin dehydrogenase (15-PGDH), increases levels of PGE2 in muscle and improves muscle quality and force in aged mice. 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



(In skeletal muscle)

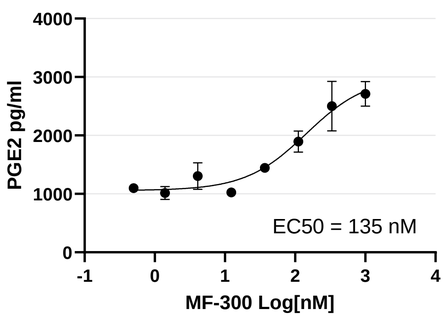
- Improved mitochondrial function (aging)[1]
- Improved neuromuscular junction integrity (aging, nerve injury)[2]
- Enhanced muscle progenitor proliferation (muscle repair)[3]

MF-300 reduces 15-PGDH activity

Biochemical assay

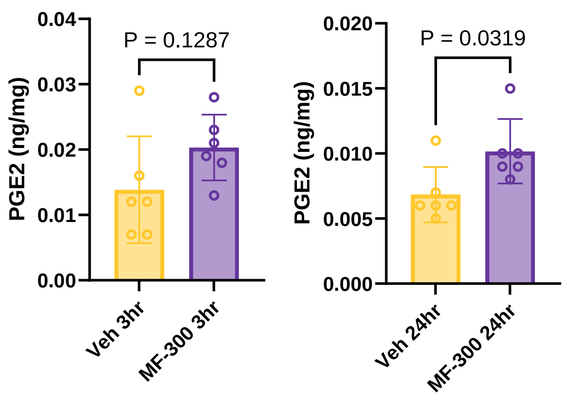
Species	15-PGDH % Identity to Human	MF-300 IC_{50} (nM)
Human	100%	0.84
Dog	94%	1.5
Mouse	89%	1.0
Rat	88%	4.0

MF-300 increases PGE2 in cell-based assay



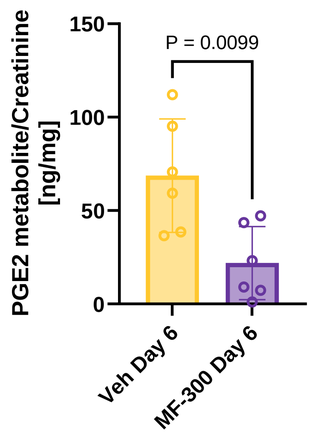
MF-300 increases PGE2 in healthy rat gastrocnemius muscle

Single dose, PO



MF-300 reduces PGE2 metabolite in healthy rat urine

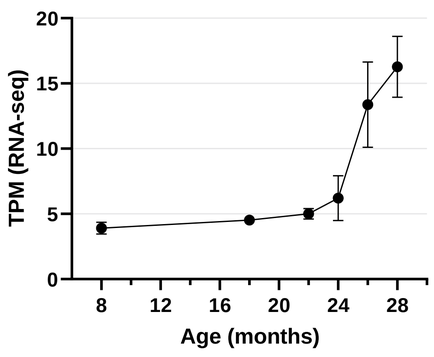
Steady state, PO



3. 15-PGDH gene expression is elevated in aging muscle in mouse and human

15-PGDH gene expression elevated in aged mice

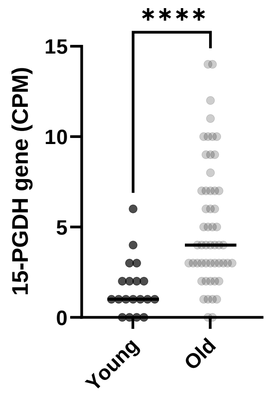
- Male mice (C57BL/6JRj)
- Gastrocnemius muscle



Graph generated from publicly available data[4]

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.)

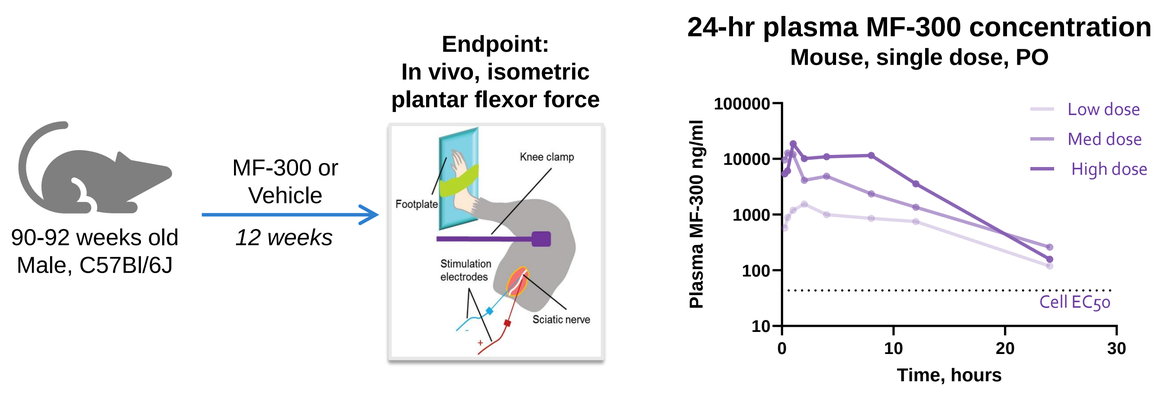


Graph generated from publicly available data[5]

4. Methods & Study Design

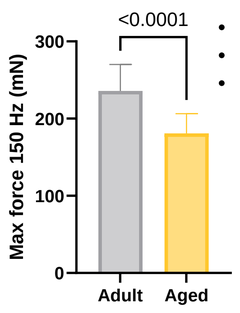
- Male mice, C57Bl/6J, 90-92 weeks old (aged) or 39-54 weeks old (adult)
- N = 18 / grp aged, N = 15 / grp adult
- MF-300 or vehicle was administered orally for 12 weeks
- Muscle force was measured in vivo (isometric plantar flexion) or ex vivo (isometric force of the extensor digitorum longus (EDL) muscle) with a 305C muscle lever system (Aurora Scientific Inc., Aurora, CAN)
- Statistical analyses: One-Way ANOVA with a Holm-Šídák post-hoc or a Two-Way Repeated Measures ANOVA with a Holm-Šídák post-hoc, or Students t-Test for pairwise comparisons

Efficacy study to test effect of MF-300 on muscle force in aged mice



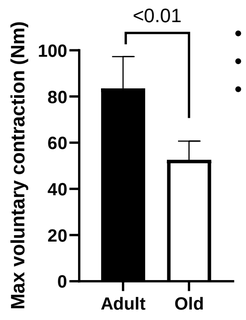
Modeling age-induced muscle weakness with isometric plantar flexion in mouse

23% reduced isometric plantar flexor force in aged mice



- Male mice (C57Bl/6J)
- Adult (N=15): 12 m.o.
- Aged (N=18): 23 m.o.

37% reduced isometric plantar flexor force in aged human



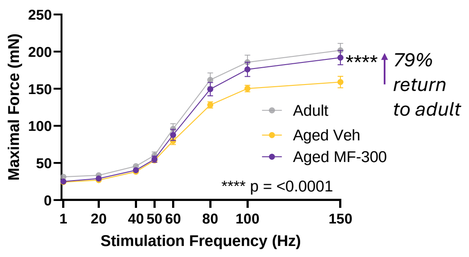
- Male human
- Adult (N=12): 19-24 y.o.
- Old (N=11): 61-74 y.o.

Graph generated from published data[6]

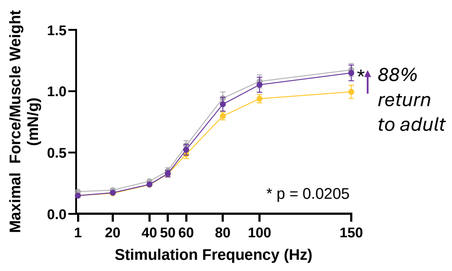
5. Results: MF-300 improved aged-muscle Quality

MF-300 increased absolute and specific force (i.e., Quality), in vivo

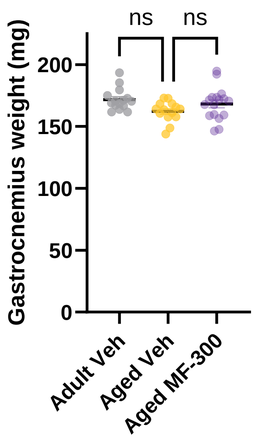
Increased absolute force



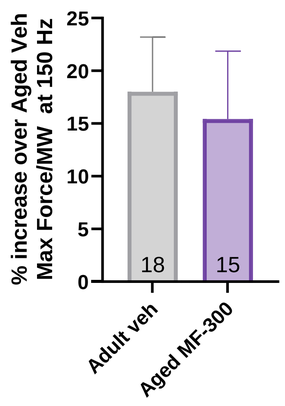
Increased specific force (Quality)



No effect on muscle mass

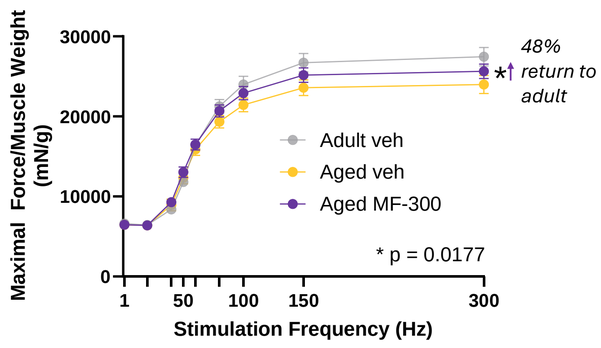


Specific force (Quality) substantially improved

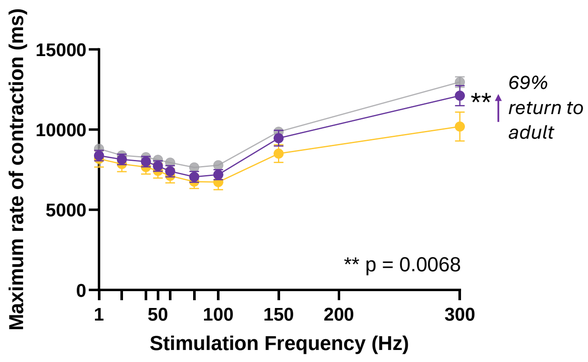


MF-300 increased specific force and contraction rate in clinically relevant fast-twitch muscle (i.e., EDL), ex vivo

Increased specific force (Quality)



Increased contraction rate



6. Discussion

- Oral administration of MF-300 reversed age-induced reduction of absolute and specific muscle force, as well as contraction rate, in clinically relevant fast-twitch muscle.
- MF-300 increased force without increasing muscle mass, suggesting that MF-300 improved the quality of aged muscle.
- Increased levels of PGE2 in gastrocnemius following MF-300 administration in rat support in vivo target engagement in skeletal muscle.
- Reduced levels of a PGE2 metabolite in urine of healthy rat favor utility of this metabolite as a pharmacodynamic biomarker in Phase 1 healthy volunteers.

References:

[1] Palla et al., *Science*, 2021
[2] Bakooshli et al., *Sci. Transl. Med.*, 2023
[3] Ho et al., PNSA, 2017
[4] https://sarcoatlas.scicore.unibas.ch/
[5] GEO167186 published in Perez et al., *Aging,* 2022
[6] Ochala et al., *Exp Gerantol*, 2004

Author affiliations:

1. Epirium Bio, 12670 High Bluff Drive, San Diego, CA 92130, c/o Latham & Watkins
2. Myologica, LLC., 6808 Woodridge Rd, New Market, MD 21774

For more information: Please contact Micah Webster, PhD (mwebster@epirium.com), visit Epirium.com, and follow on LinkedIn.

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