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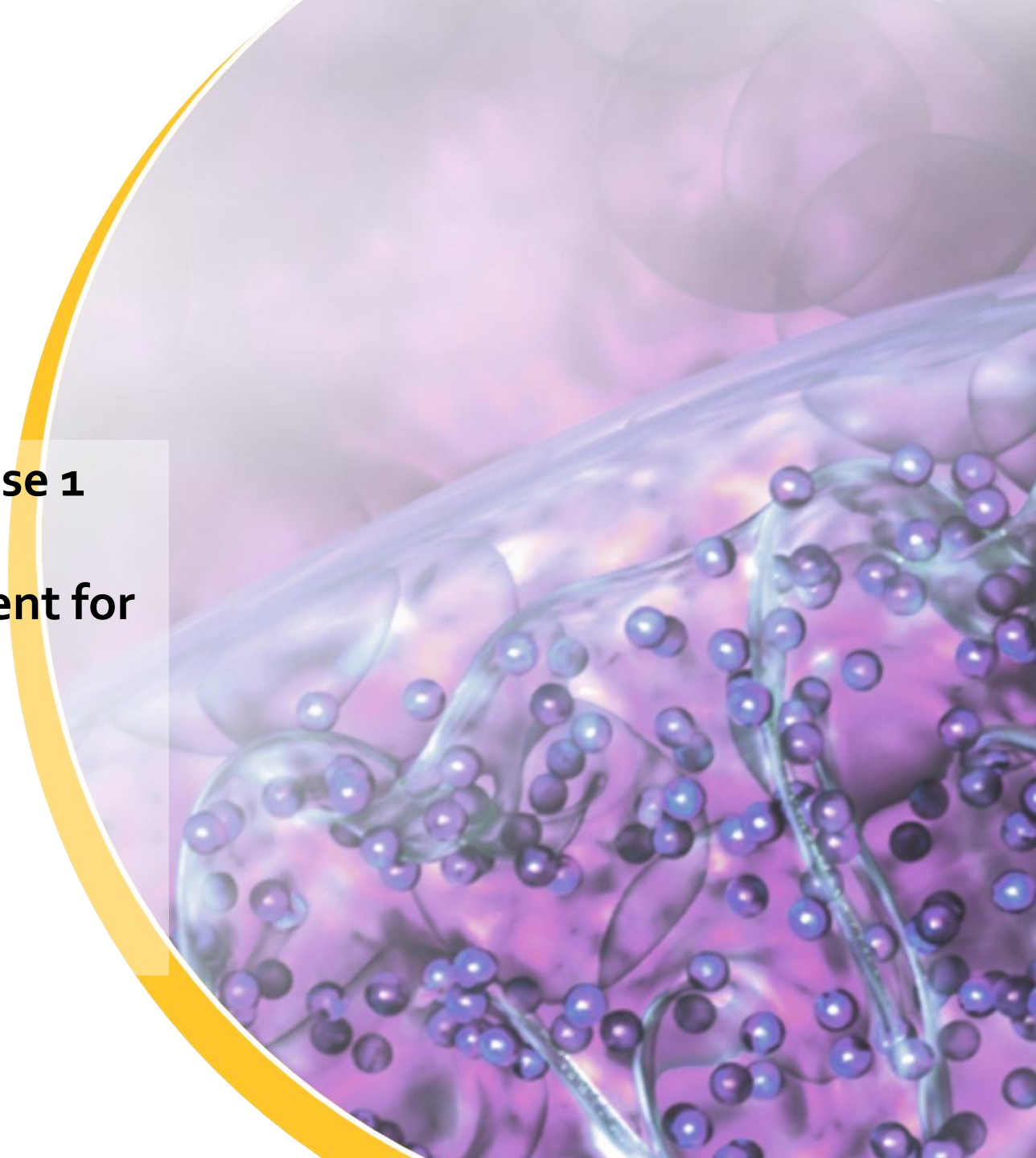
Bridging Preclinical Efficacy with Phase 1 Target Engagement of MF-300, an Investigational First-in-Class Oral Agent for Sarcopenia

ICFSR 2026 – Washington, D.C.

Micah Webster, PhD
Senior Director, Translational Science



Disclaimers

- Micah Webster, PhD, is currently employed by Epirium Bio.
- MF-300 is an investigational product candidate being evaluated for safety in healthy volunteers. MF-300 has not been approved by any regulatory authority, and its safety and efficacy have not been established.

15-PGDH Inhibition - Unifying Biology Addressing Unmet Need in Aging & Inflammatory Disease

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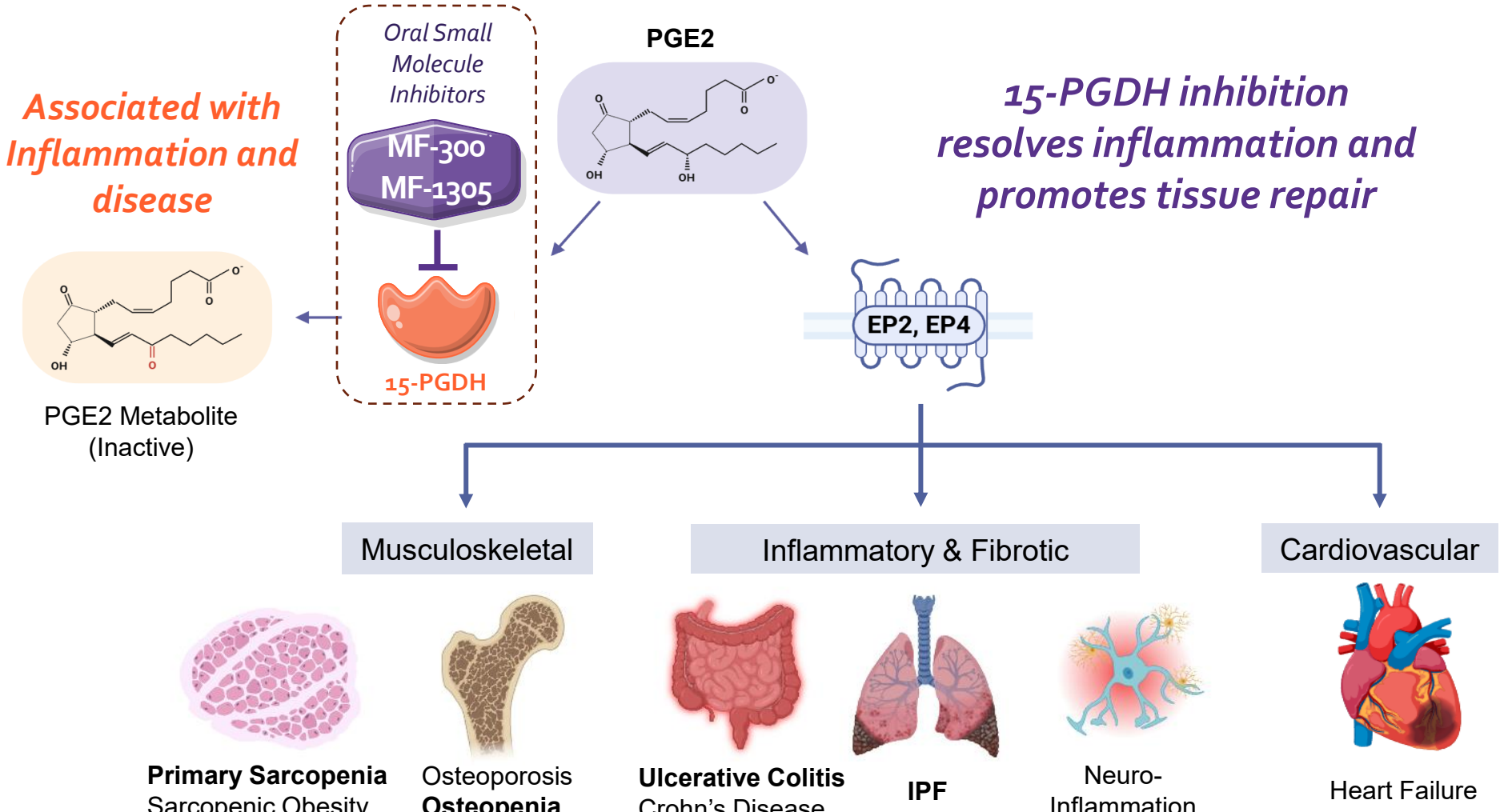
Inhibiting 15-PGDH to leverage PGE2 signaling for resolution of inflammation and tissue repair



BOLD = Efficacy in Disease Model with 15-PGDH Inhibitor

PGE2–EP4 Signaling Elevates cAMP to Promote Muscle Function

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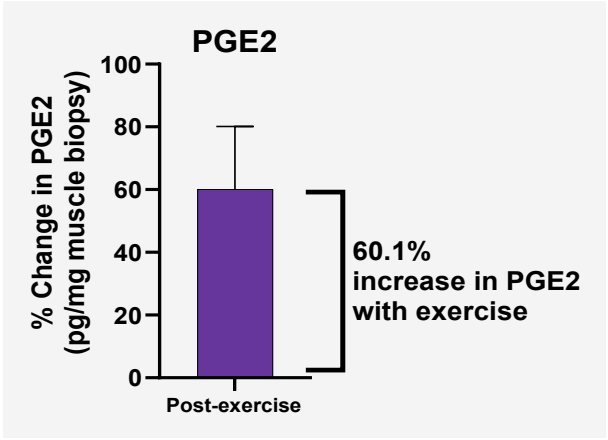
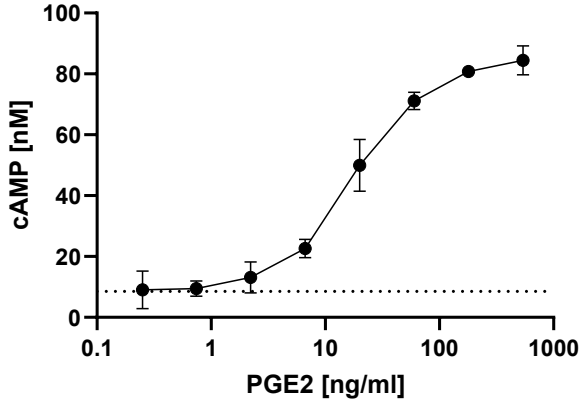
PGE2 in human muscle following exercise

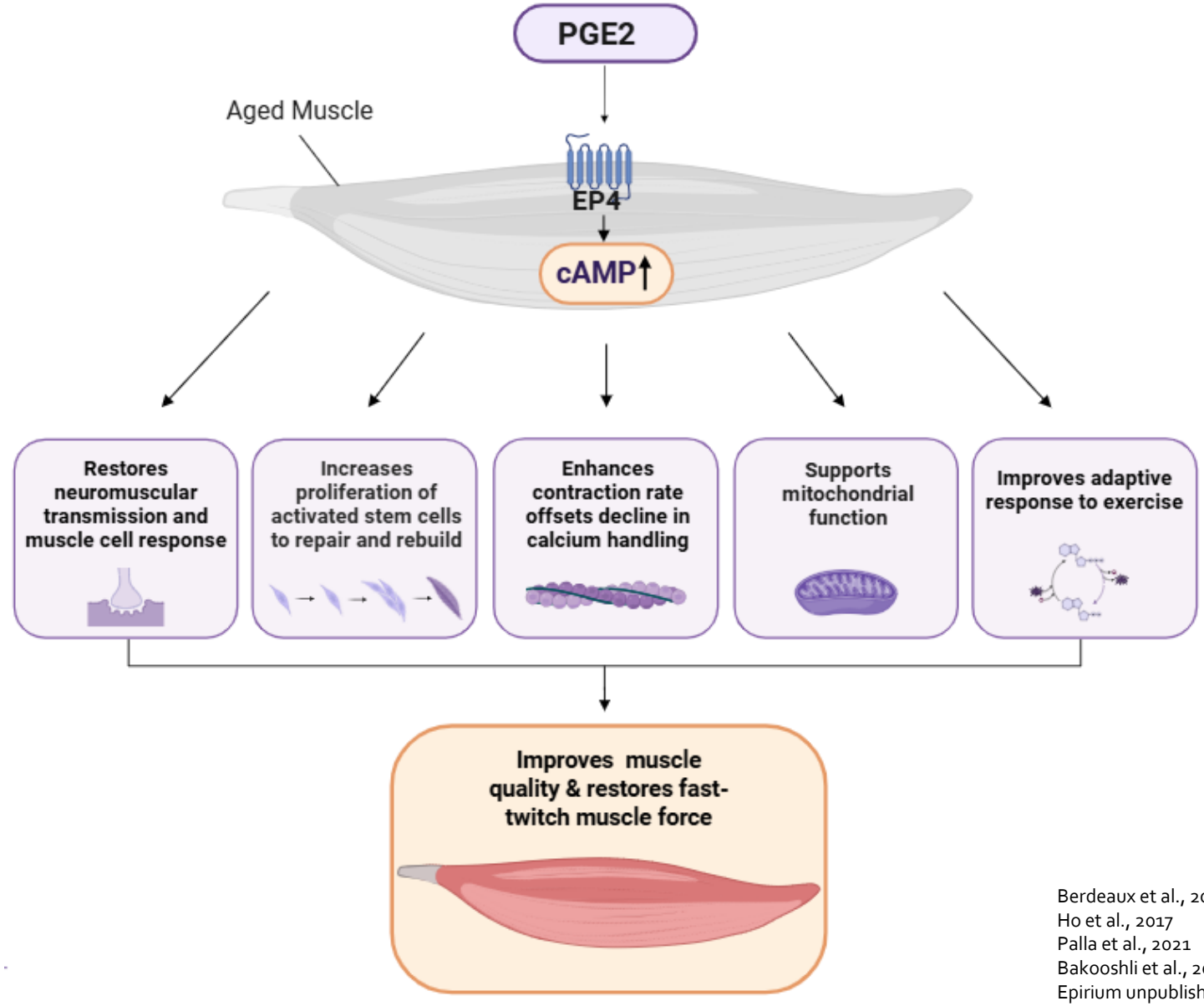


Adapted from Trappe TA, et al. J Clin Endocrinol Metab. 2001;86(10):5067-5070

PGE2 increases cAMP in primary human myocytes



Epirium unpublished data



Berdeaux et al., 2012
Ho et al., 2017
Palla et al., 2021
Bakooshli et al., 2023
Epirium unpublished data

15-PGDH, an Enzyme that Degrades PGE2, is Upregulated in Aged Muscle

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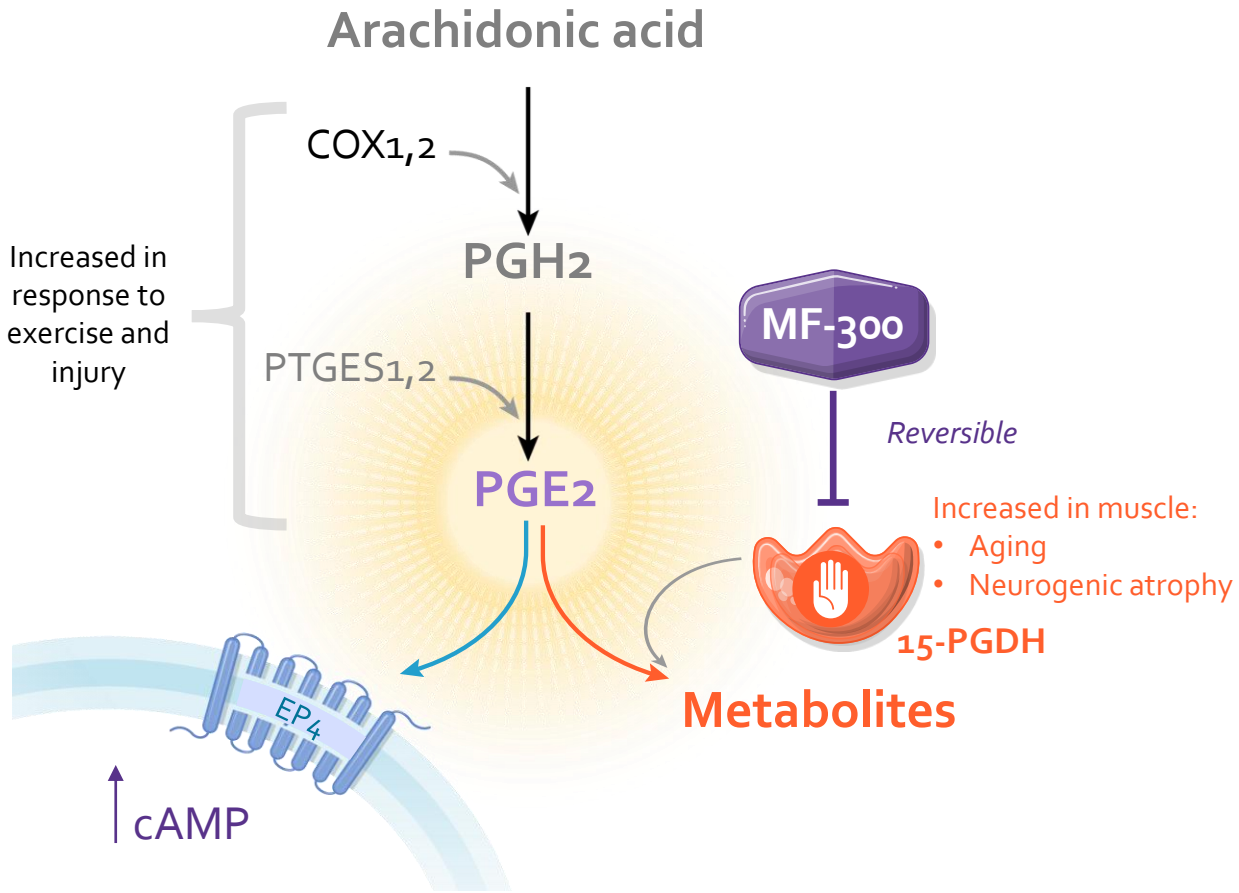
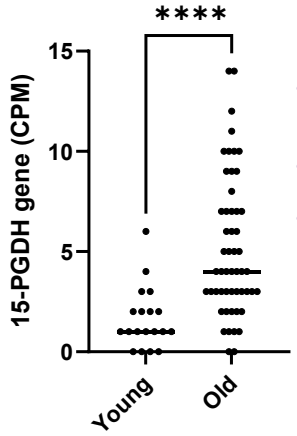
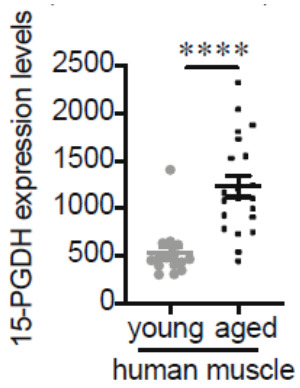
15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2



15-PGDH gene expression Elevated in aged human muscle[1,2]

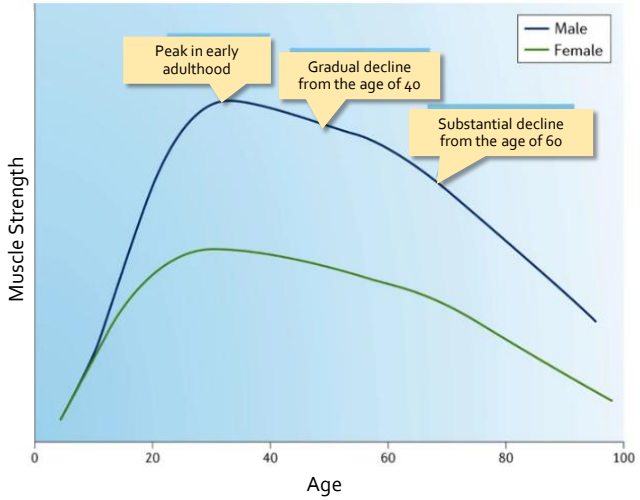


- Vastus lateralis (women and men)
- Young, N = 19 (**25±3 y.o.**)
- Older, N = 29 (**78±6 y.o.**)



- Vastus lateralis, RNA-seq (men)
- Young, N = 19 (**avg. age 20 y.o.**)
- Older, N = 29 (**avg. age 57 y.o.**)

Grip strength, a predictor of sarcopenia risk, declines with age[3]



[1] GEO167186, [2] Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), [3] Dennison et al., *Nat Rev Rheum* 2017

MF-300, an Oral 15-PGDH Inhibitor for Restoring PGE2 Signaling in Aged Muscle

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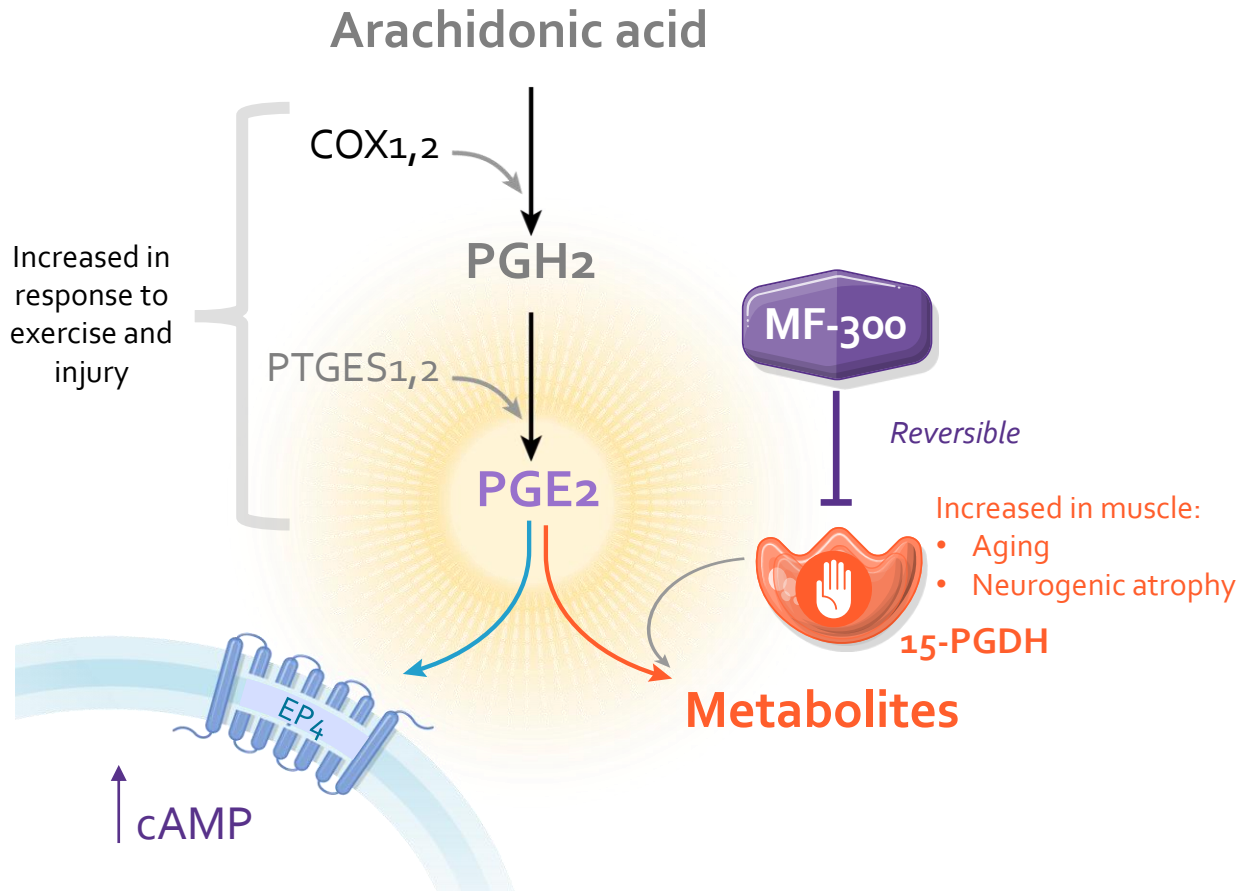
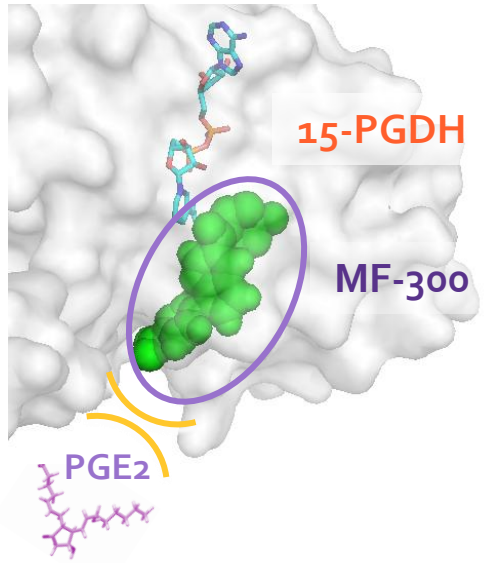
15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2

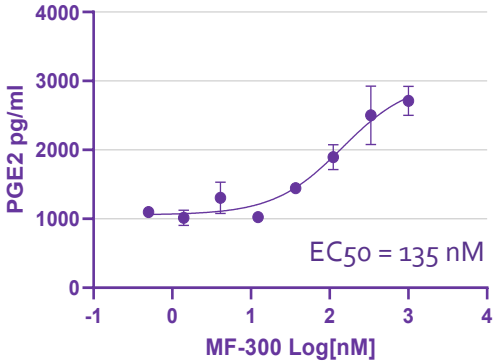


MF-300 reversibly occupies the PGE2 binding site of 15-PGDH

Based on crystallography



MF-300 increases PGE2 in a cell-based assay



MF-300, an Oral 15-PGDH Inhibitor for Restoring PGE2 Signaling in Aged Muscle

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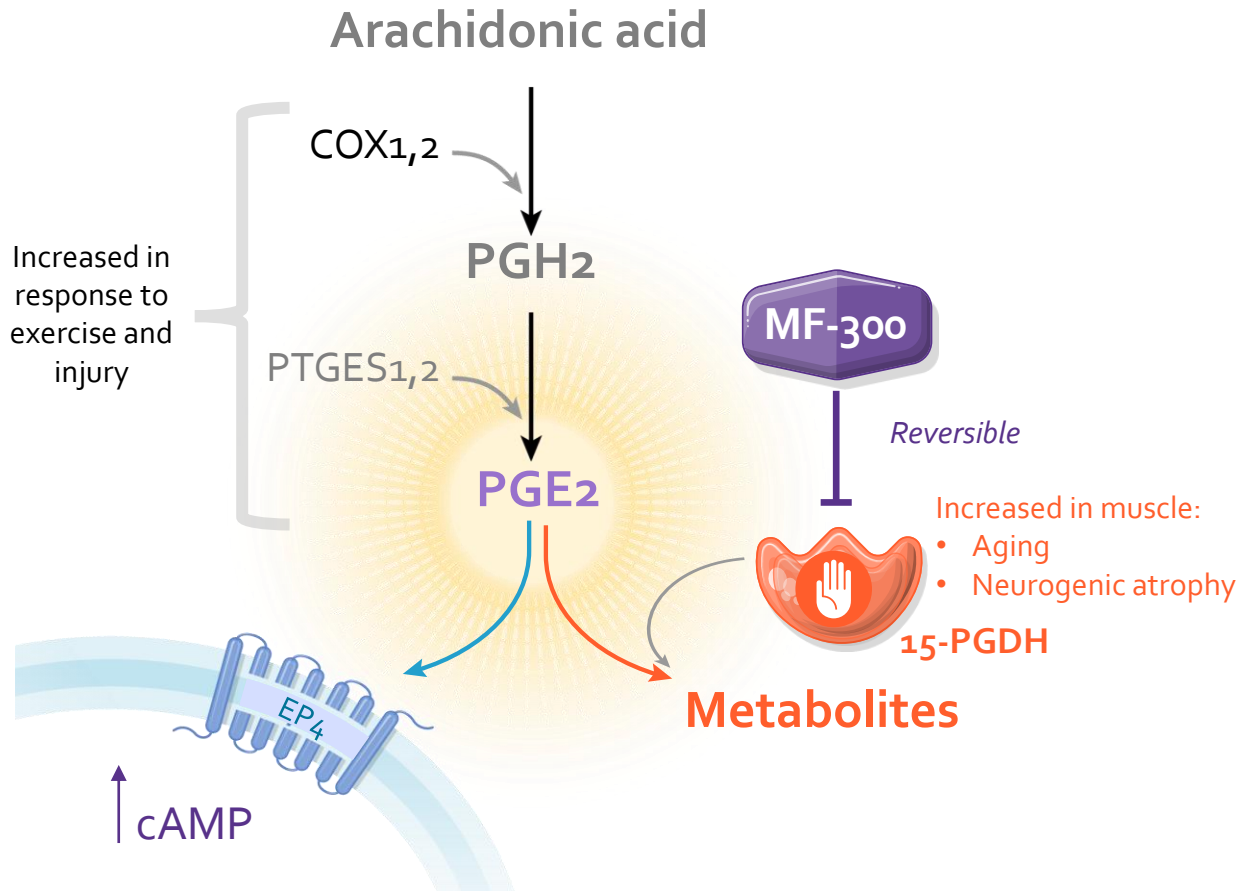
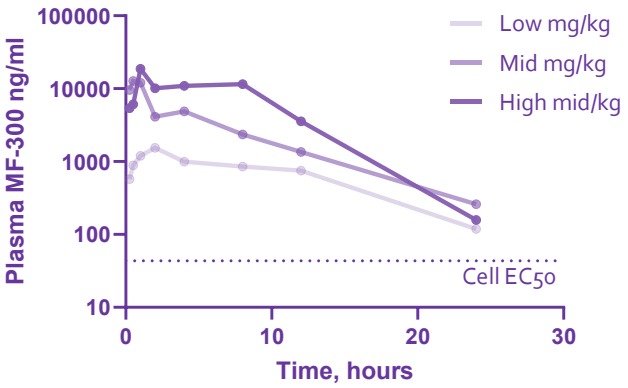
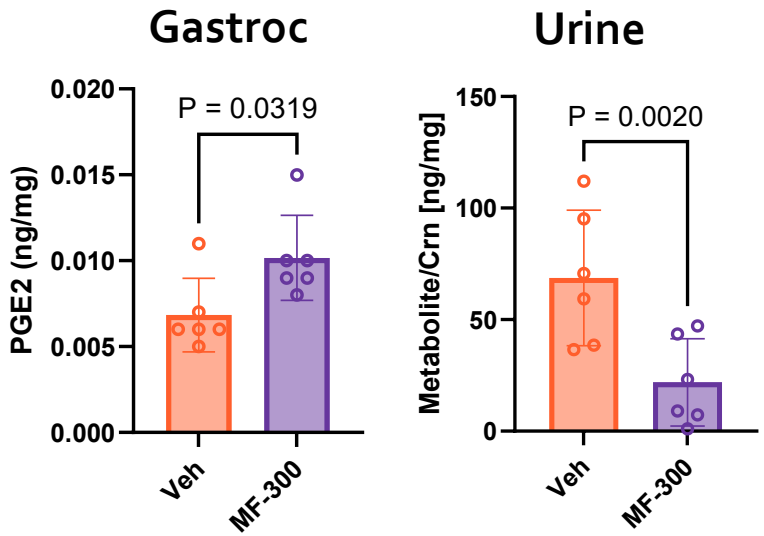
15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2



MF-300 is bioavailable and stable in vivo (oral administration)



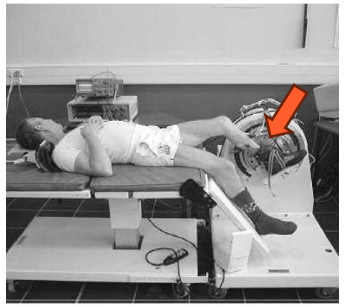
Demonstration of MF-300 target engagement in healthy rat

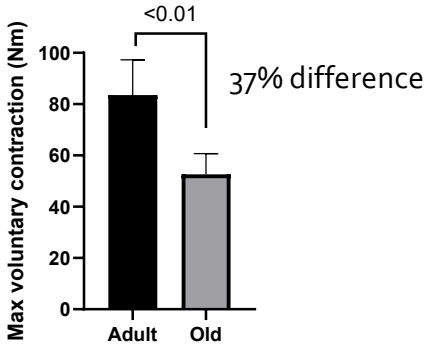


The Aged Mouse as a Model to Study MF-300's Effect on Muscle Quality

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

Maximal voluntary contraction

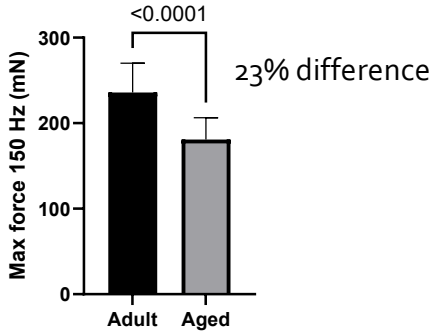




Male
Adult (N=12): 19-24 y.o.
Old (N=11): 61-74 y.o.

Data and image:
Adapted from Ochala et al., *Exp Ger*, 2004

Electrical nerve-evoked contraction

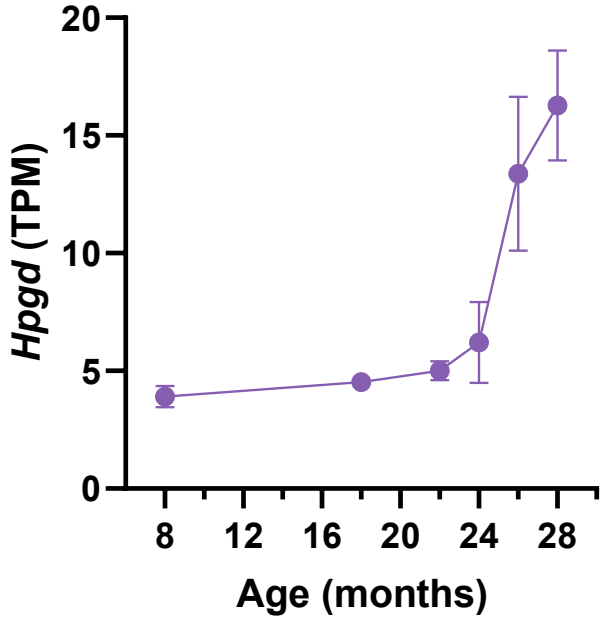


Male (C57Bl/6J)
Adult (N=15): 12 m.o.
Aged (N=18): 23 m.o.

Mouse image:
https://aurorascientific.com/
Data:
Epirium unpublished

Muscle 15-PGDH gene expression (*Hpgd*) increases during age-related muscle weakness in mice[1,2]

- C57BL/6JRj, male
- Gastrocnemius



[1] https://sarcoatlas.scicore.unibas.ch/ GSE145480 , [2] Borsch et al., *Com Bio* 2021

MF-300 Increases Muscle Force in Aged Mice

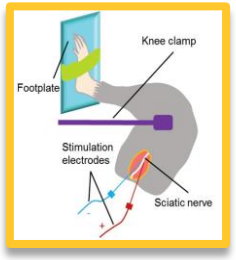
MF-300 increased maximal force of isometric plantar flexion in aged mice

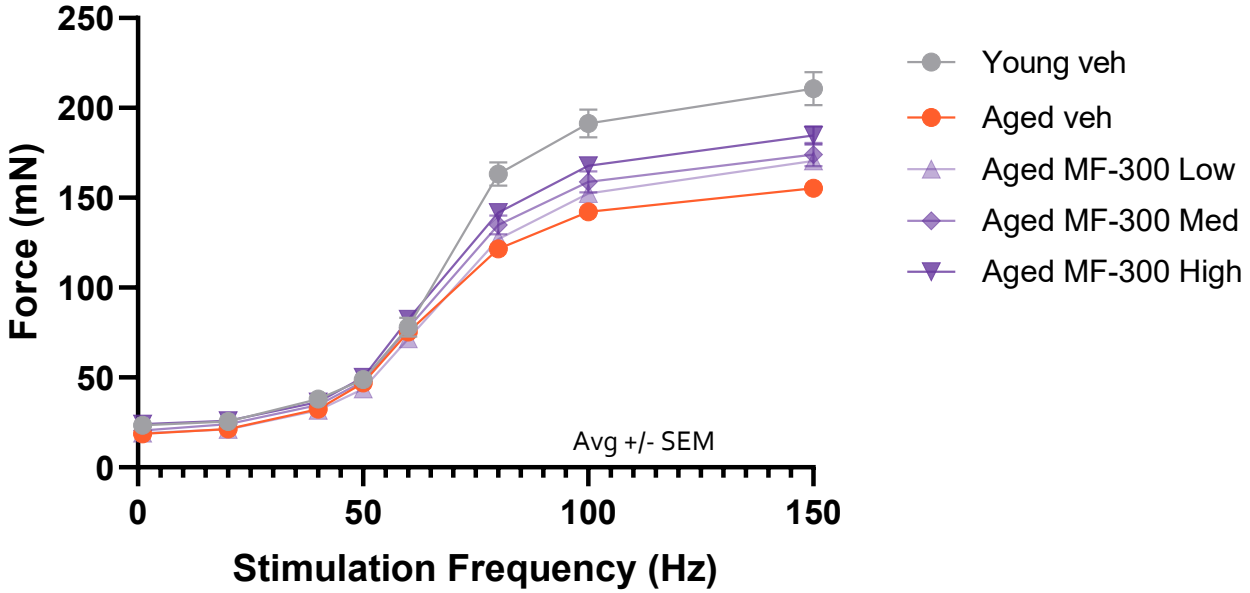
Aged: 90-92 weeks old
Adult: 45 weeks old
Young: 16 weeks old
Male, C57Bl/6J

MF-300 or Vehicle, PO Q2D

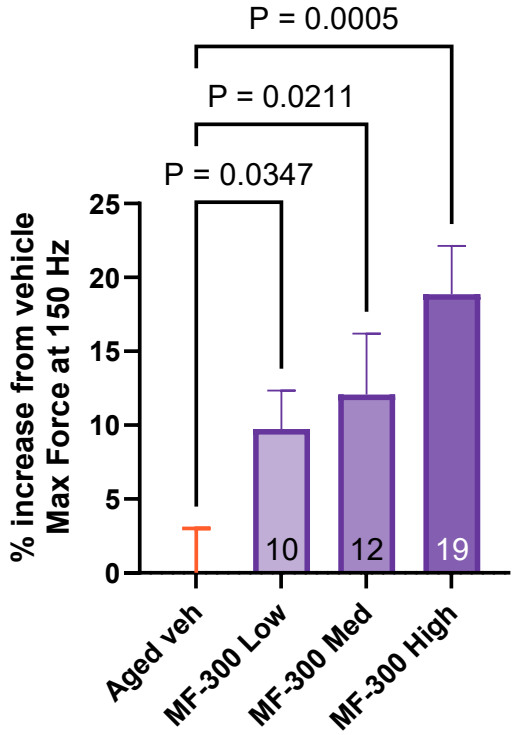
12 weeks

Endpoint: In vivo, isometric plantar flexor force





Aged veh vs:	2way ANOVA w/ Holm-Šídák's multiple comparisons test
MF-300 Low	ns
MF-300 Med	p < .0001
MF-300 High	p < .0001

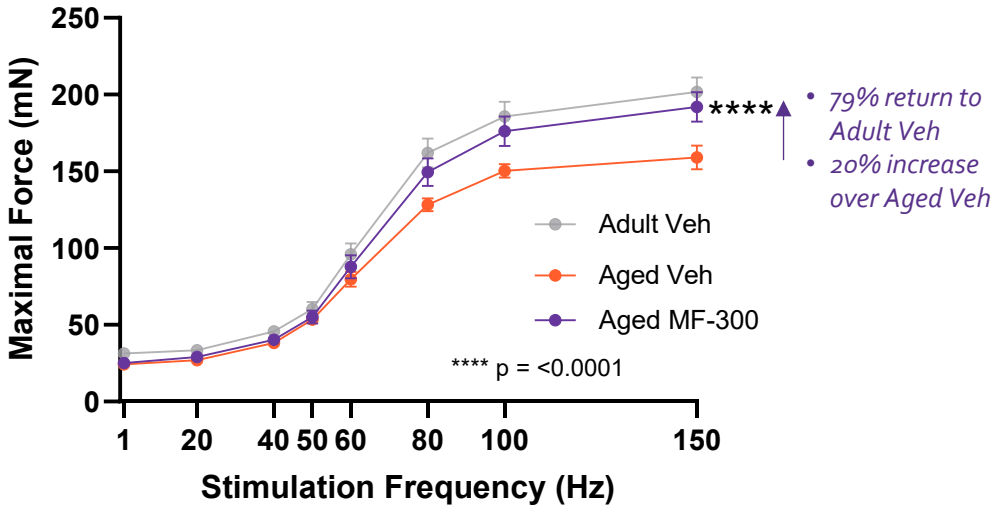


Avg +/- SEM; 1way ANOVA

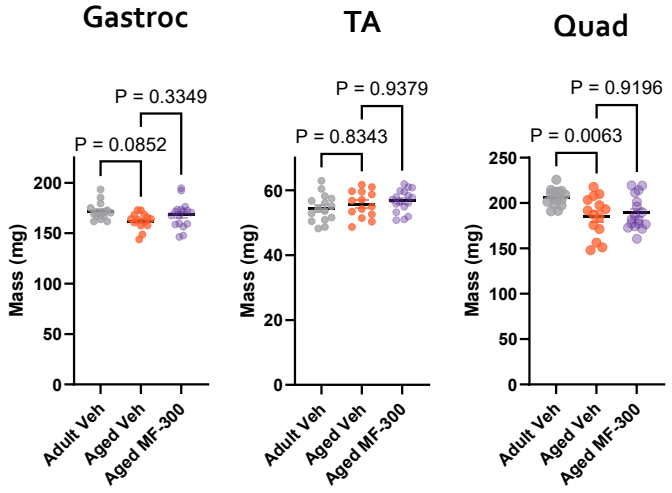
Data generated by: Myologica

MF-300 Improves Muscle Quality in Aged Mice

MF-300 increases force without changes to muscle mass

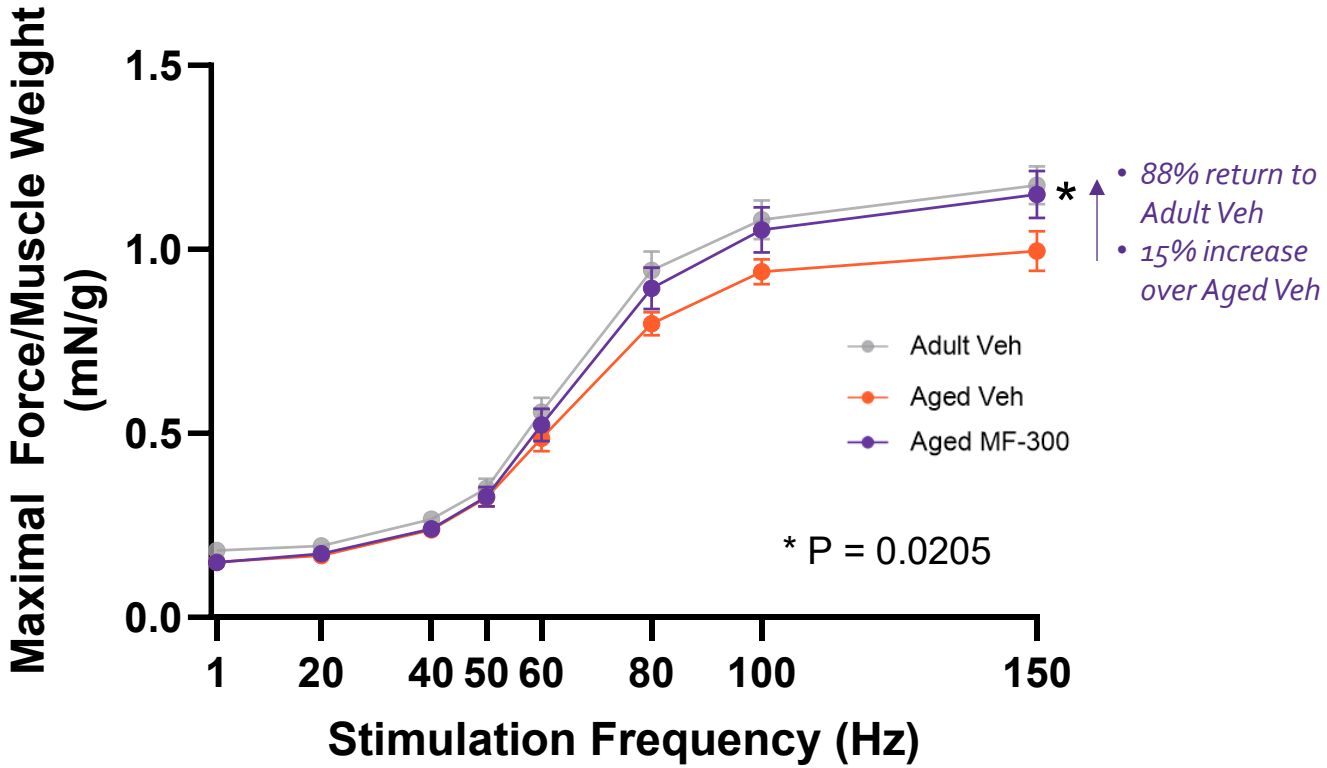


Mean ±SEM; Two-Way Repeated Measures ANOVA with a Holm-Šídák post-hoc



MF-300 increases Specific Force (i.e., Quality)

Specific force = force/mass



Mean ±SEM; Two-Way Repeated Measures ANOVA with a Holm-Šídák post-hoc

Data generated by: Myologica

MF-300 Improves Muscle Quality in Clinically Relevant Fast-Twitch Muscle

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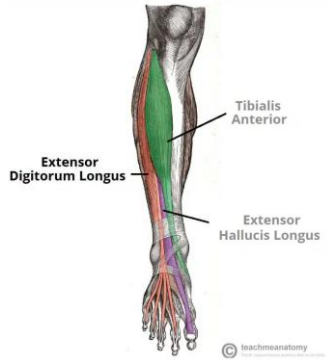
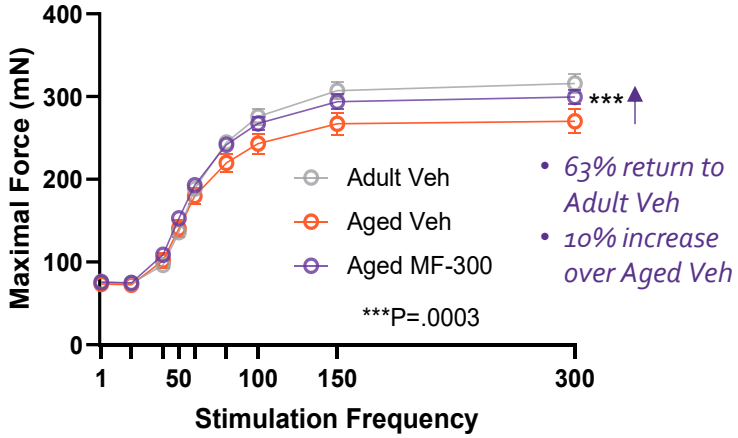
Mouse EDL is predominantly fast twitch



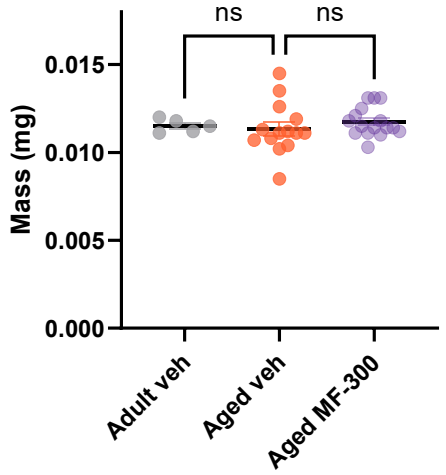
Ex vivo isometric force measurement

Image courtesy of Myologica

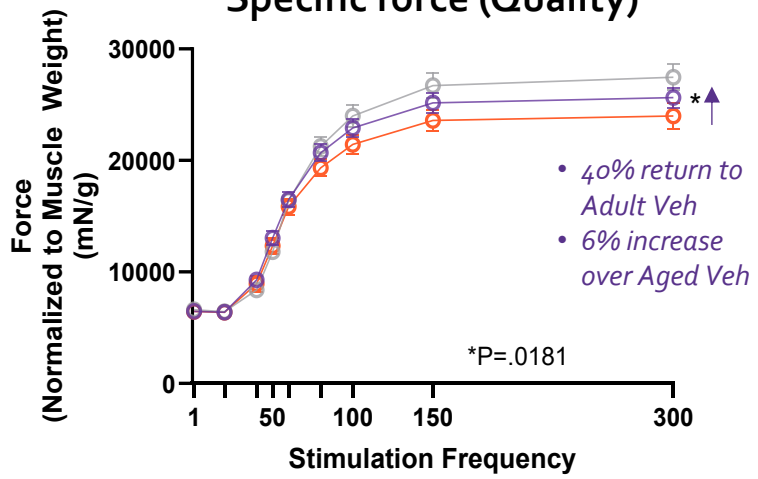
Absolute force



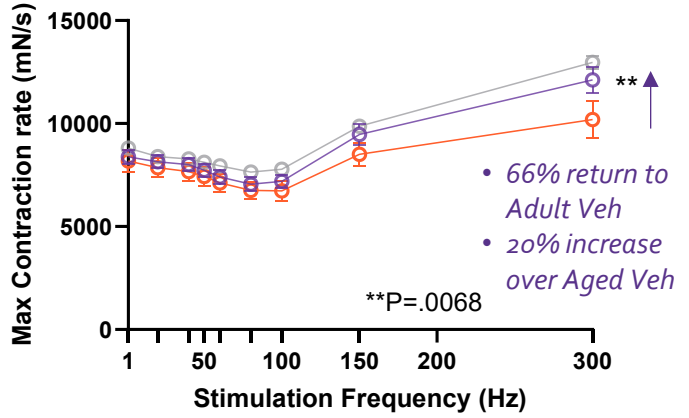
EDL Muscle Mass



Specific force (Quality)



Contraction Rate (Quality)



Data generated by: Myologica

Discovery Proteomics Identifies Molecular Effects of MF-300 on Muscle Quality

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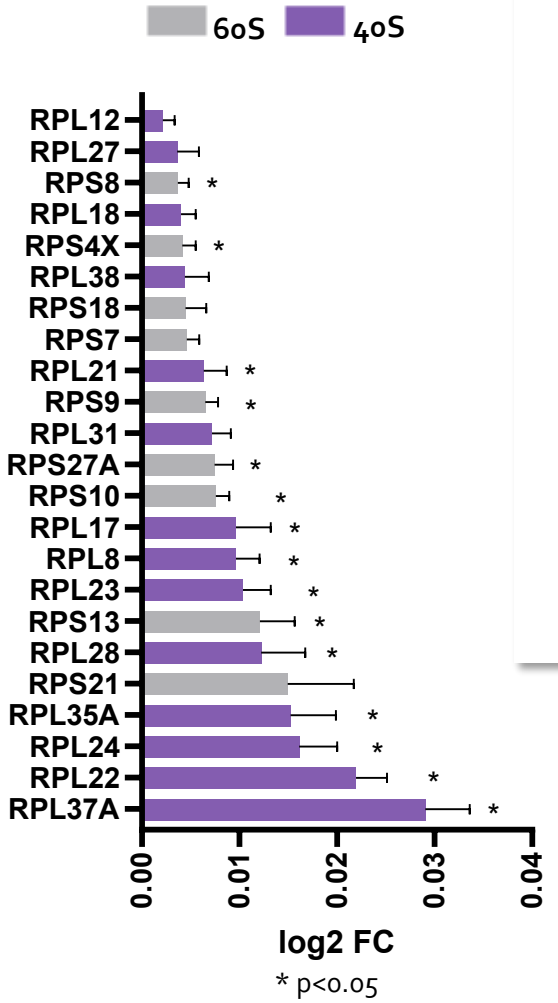
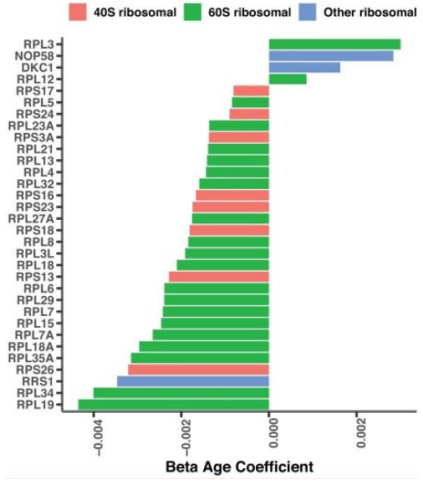
MF-300 increased abundance of ribosomal proteins



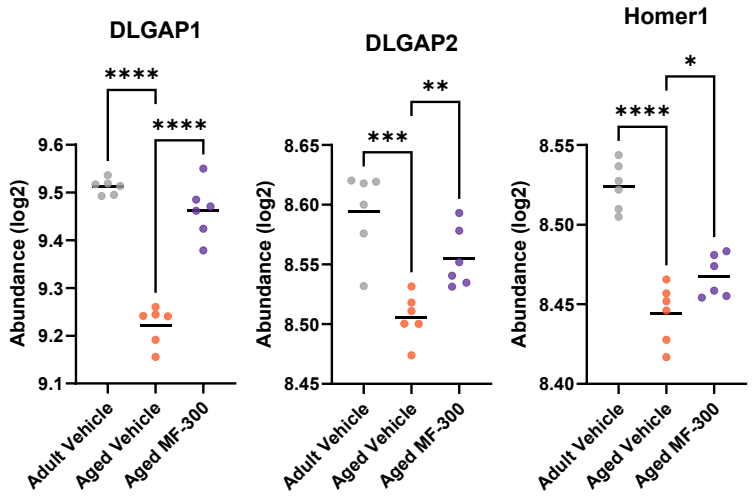
* p<0.05

Human aging is associated with reduction in muscle ribosome abundance



Ubaida-Mohien et al., *eLife*, 2019

MF-300 increased abundance of post-synaptic scaffold proteins



Whole Genome Linkage and Association Analyses Identify DLG Associated Protein-1 as a Novel Positional and Biological Candidate Gene for Muscle Strength: The Long Life Family Study

Adam J. Santanasto, PhD, MPH,[1] Sandeep Acharya, BS,[2,3] Mary K. Wojczynski, PhD,[4] Ryan K. Cvejkus, MS,[1] Shiow Lin, MS,[4] Michael R. Brent, PhD,[2,3] Jason A. Anema, PhD,[4] Lihua Wang, PhD,[4] Bharat Thyagarajan, MD, PhD,[5] Kaare Christensen, MD, PhD,[6] E. Warwick Daw, PhD,[4] and Joseph M. Zmuda, PhD[1,*]; on behalf of the Long Life Family Study

[1]Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[2]Division of Computational and Data Sciences, Center for Genome Sciences and Systems Biology, Washington University in St. Louis, St. Louis, Missouri, USA.
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[4]Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA.
[5]Department of Laboratory Medicine and Pathology, School of Medicine, University of Minnesota, Minneapolis, Minnesota, USA.
[6]Epidemiology Unit, Institute of Public Health, The Danish Aging Research Center, University of Southern Denmark, Odense, Denmark.
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Decision Editor: Lewis A. Lipsitz, MD, FGSA (Medical Sciences Section)

Data generated by: Spectrus

Positive Effect on Aged Bone Micro-Architecture, Consistent with PGE2 Biology

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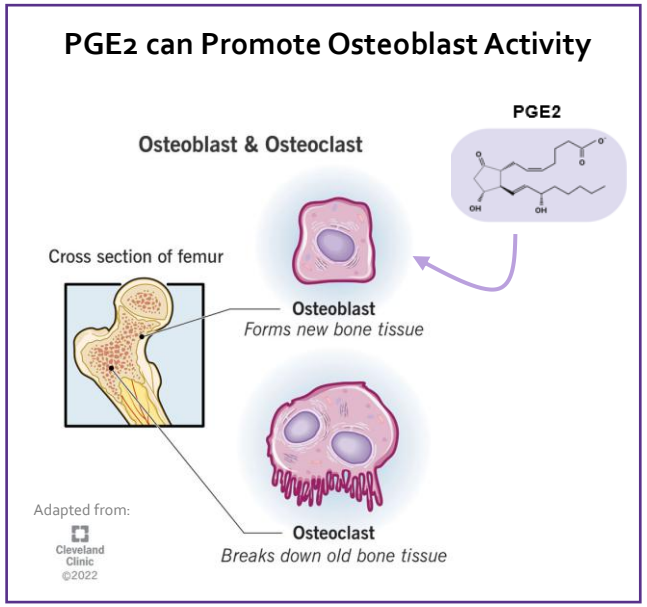
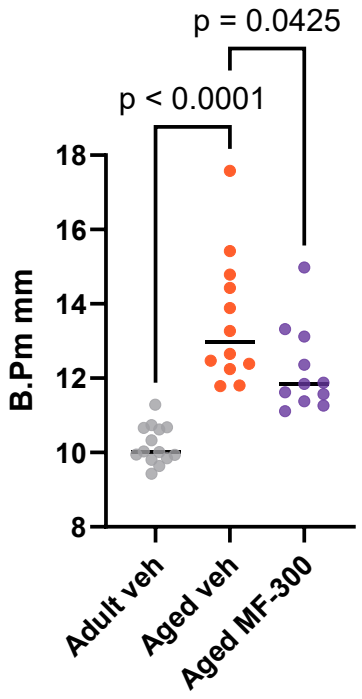


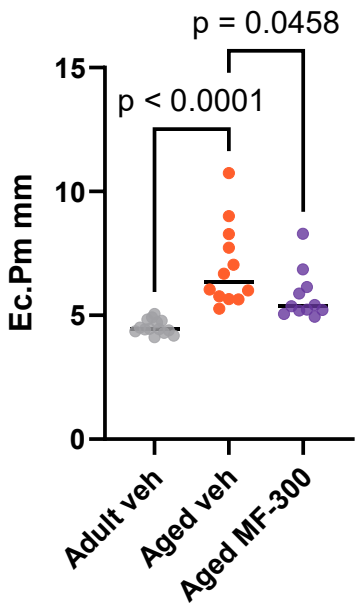
Mouse cortical bone

Micro-Computed Tomography (µCT)

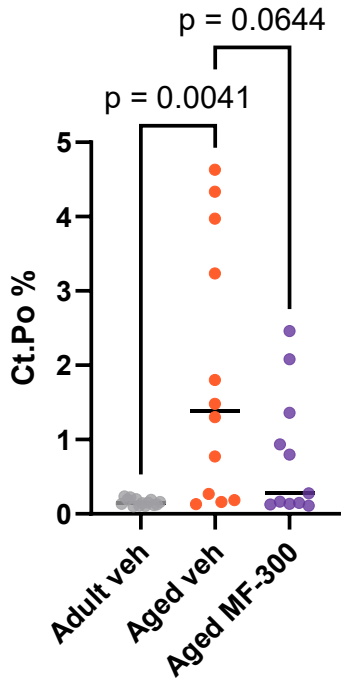
Bone Perimeter



Endocortical Perimeter

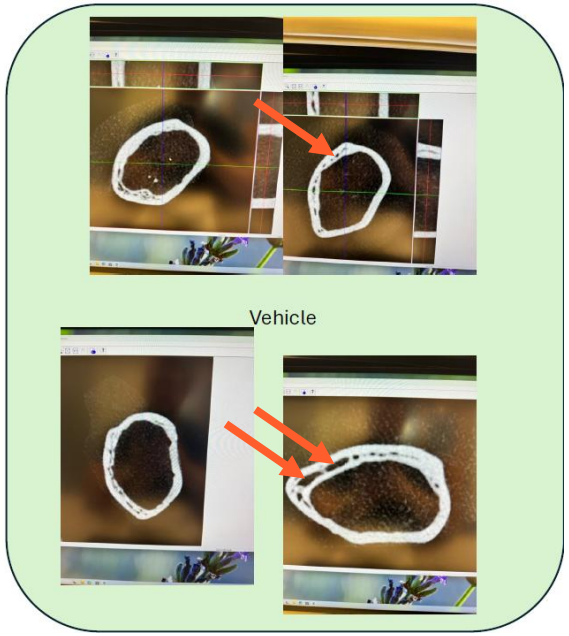


Porosity



Illustrative µCT data

Cortical porosity (arrows)

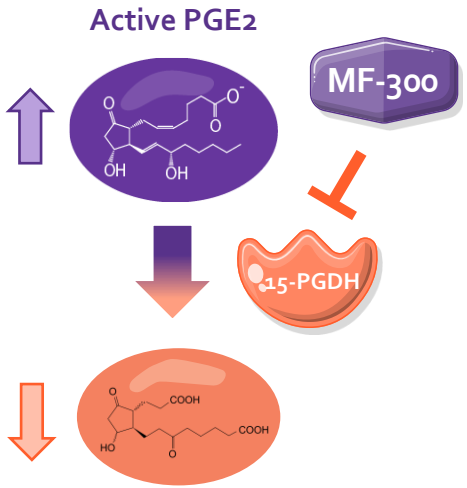


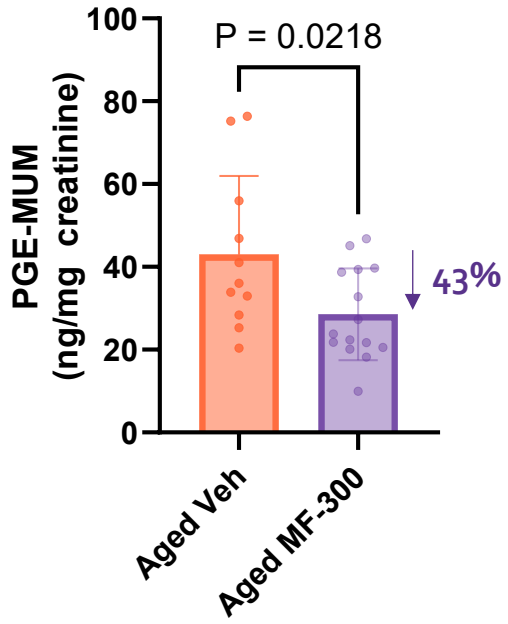
12 weeks MF-300 oral administration

Data generated by: Myologica

Urinary PGE2 Metabolite Biomarker Correlates with Efficacy

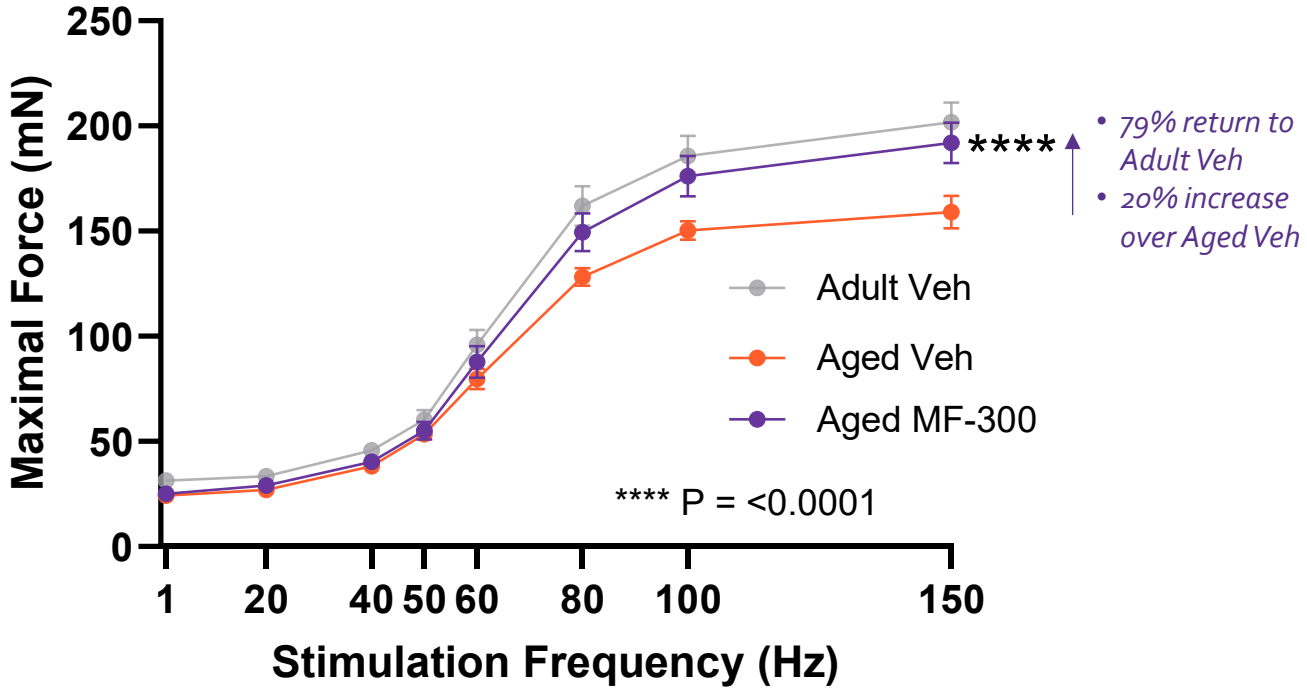
Reduced PGE2 metabolite is evidence of in vivo target engagement correlated with efficacy





Unpaired t test

MF-300 increased isometric force in aged animals



Mean ±SEM; Two-Way Repeated Measures ANOVA with a Holm-Šídák post-hoc

Data generated by: Nextcea & Myologica

Biomarker Data Support Translation of MF-300 Efficacious Exposure in Humans

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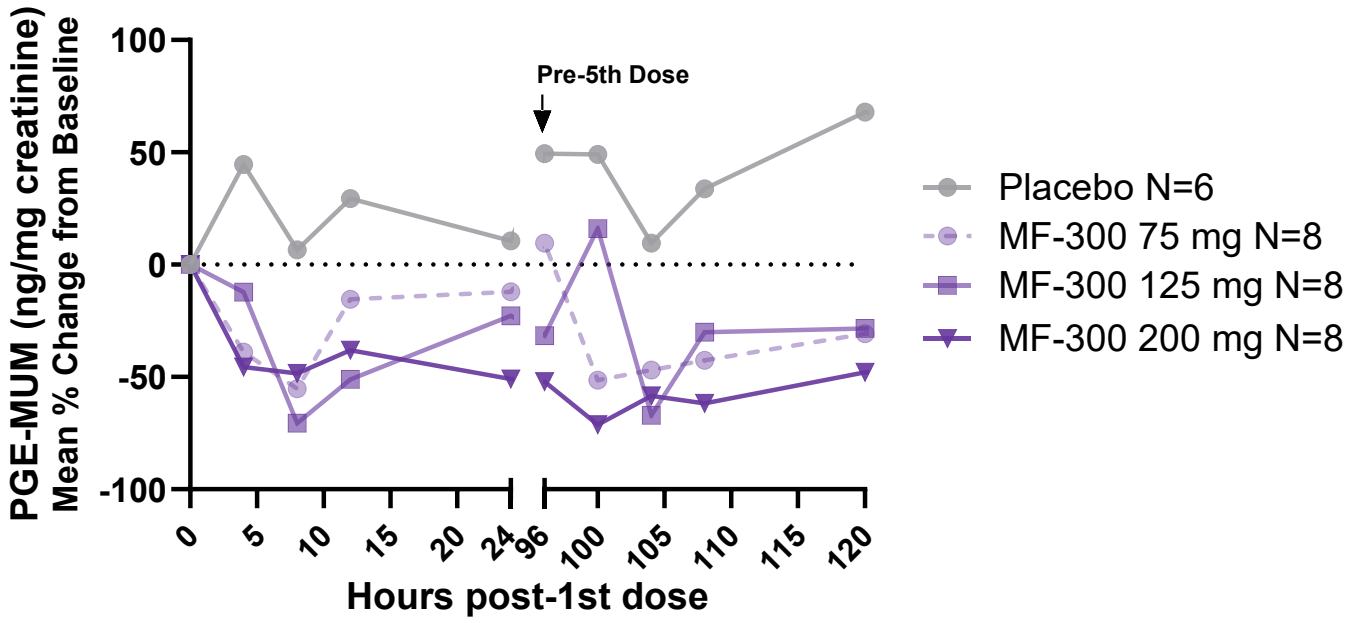
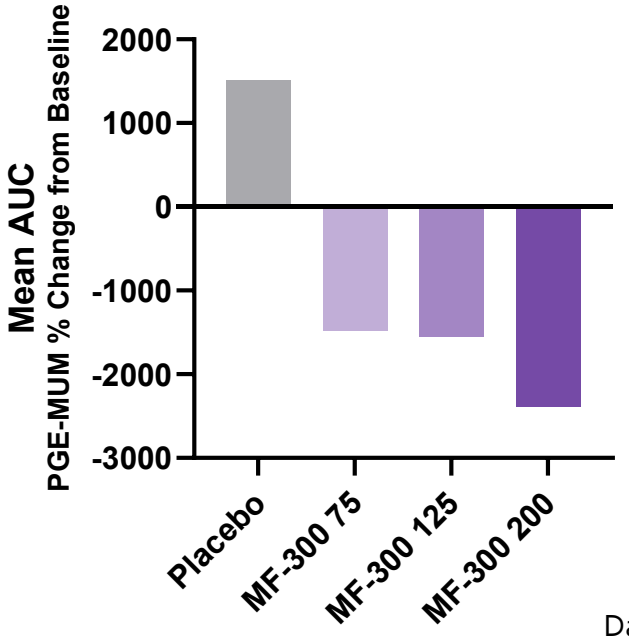
Phase 1 Study Evaluating the Safety, Pharmacokinetics and Pharmacodynamics of MF-300

Multiple Ascending Dose (≥ 18 - ≤ 65 years)

- N=10 per cohort (2 pbo, 8 MF-300)
- Daily dosing for 5 days to achieve steady state PK
- Doses: 75mg, 125mg, 200mg

Magnitude of PGE-MUM reduction in human is comparable to reduction coincident with efficacy in aged mice





Data generated by: Nextcea

Summary

- MF-300 is an orally bioavailable small molecule inhibitor of 15-PGDH enzyme activity that restores physiological levels of PGE2 in muscle tissue (preclinical).
- Oral administration of MF-300 improves muscle quality in aged mice.
  - Increased force and contraction rate of fast-twitch muscle.
  - Increased abundance of ribosome subunit proteins as well as scaffold proteins linked to improved muscle function in human aging.
- Reduction of the target engagement biomarker, PGE-MUM, correlates with efficacy in aged mice. A similar magnitude of reduction in PGE-MUM in healthy volunteers administered MF-300 supports translation of efficacious exposure to the clinic.

Acknowledgements

Epirium Bio
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Leslie Stringer
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Leigh MacConell, PhD
Amrik Shah, PhD
Diane Mould, PhD
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Bruce Fahr, PhD
Virginia Grant, PhD

Myologica (Muscle/Bone CRO)
Ramzi Khairallah, PhD
Jennifer Martin
Joseph Stains, PhD

Nextcea (LC-MS/MS CRO)
Frank Hsieh, PhD
Lily Li, PhD

Spectrus (Proteomics CRO)
Enrique Arevalo, PhD