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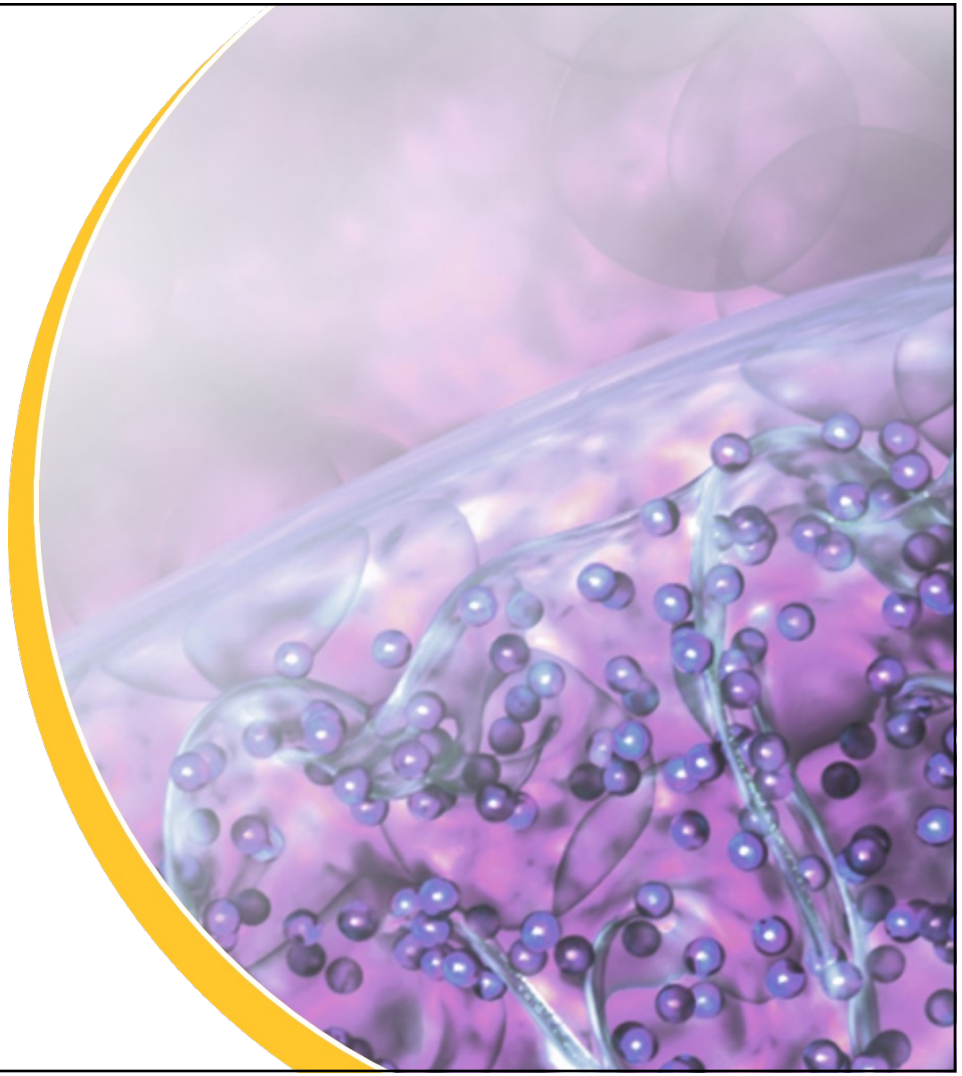
Novel Platform: Oral Treatments for Neuromuscular Diseases:

- Lead Program: MF-300 a "First-in-Class" Oral Therapy for Sarcopenia
- Additional Opportunities in Rare Neuromuscular (SMA) & Fibrotic (IPF) Disease



MF-300: "First-in-Class" Treatment for Sarcopenia:

Large Unmet Medical Need with No FDA Approved Therapy

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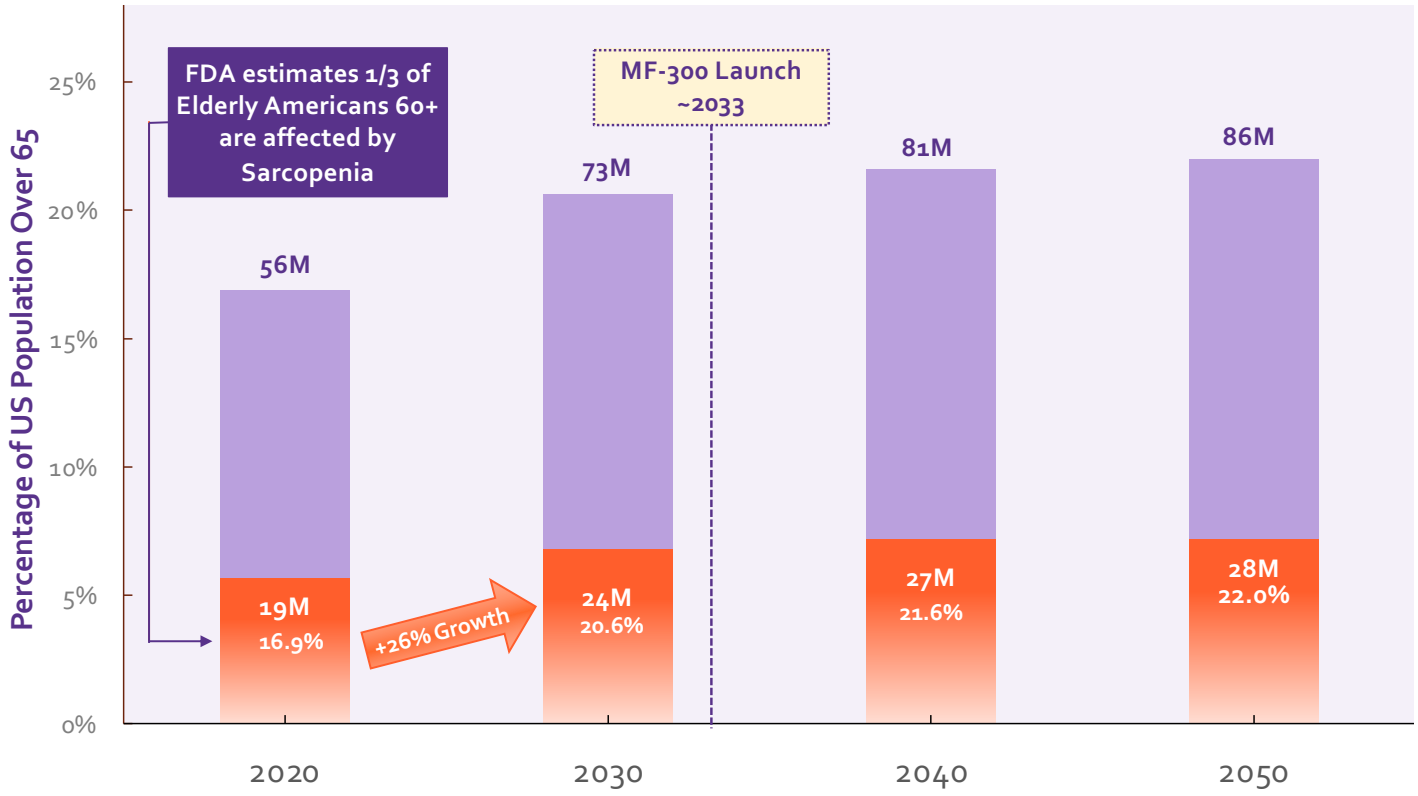
Current U.S. Healthcare Sarcopenia Spending Estimated >$40 Billion Annually

Dependence
"At-risk" of losing independence

Falls
Increased Morbidity & Mortality

Mortality
Increased risk of death



Source: Burns ER, J. Safety Res. 2016, U.S. Population est. 331M

Sarcopenia Root Cause: Diminished Muscle Quality

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Sarcopenia:

- **Severe loss of muscle strength** and mass with aging
- **Strength declines faster than muscle mass**[1] due to **Diminished muscle quality**[5]
  - Existing muscle is weaker, contracts slower
  - Disproportionate loss of fast twitch muscle force
  - Progressive denervation of muscle
  - Reduced regenerative potential of muscle stem cells

Strength decline outpaces reductions in muscle mass with aging[1]

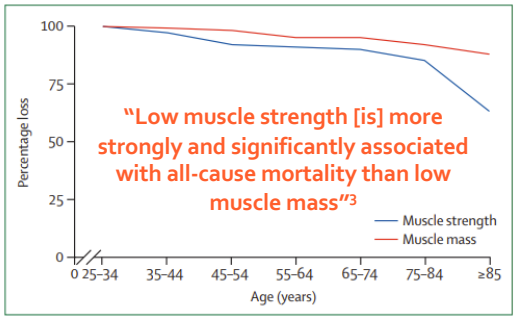
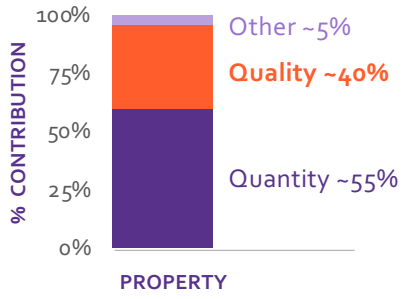


Figure 1: Percentage loss of muscle mass and muscle strength with age in men

Reduction in Muscle Quality Contributes >30% to Loss in Muscle Force in Elderly[2]



[1] Cruz-Jentoft and Sayer, *Lancet*, 2019
[2] Jubrias and Conley, *Fun. Neurobio. of Aging*, 2001
[3] Li et al., *Med Sci Sports & Exercise*, 2017
[4] Heinze-Milne et al., *Mech Aging Dev*, 2022
[5] Mohien et al., *eLife*, 2019

Cyclic AMP (cAMP) is Critical for Muscle Function and is Reduced in Aged Muscle

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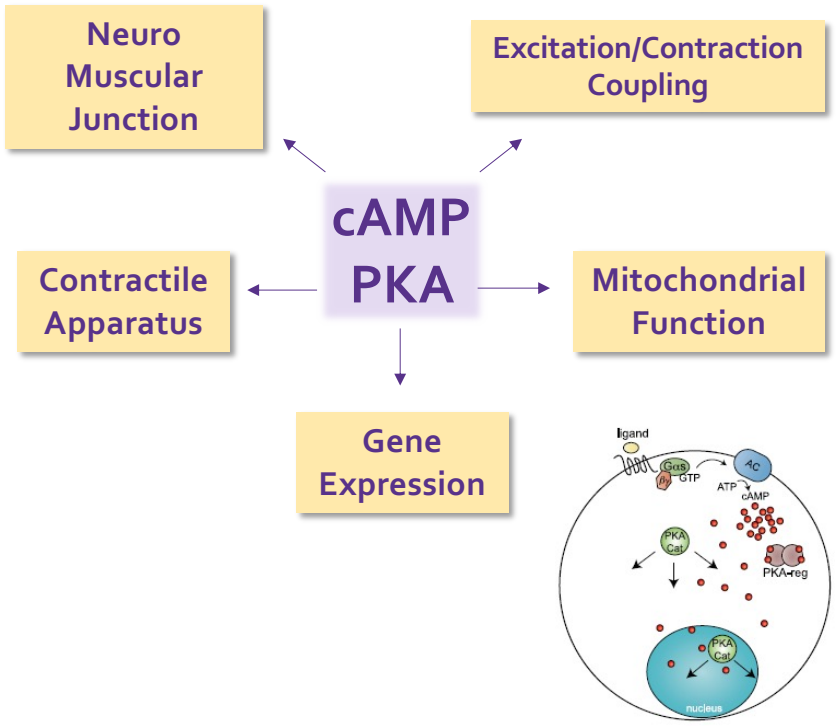
MF-300: First-in-Class Oral Therapy Increasing cAMP to Improve Muscle Quality

- **cAMP signaling - Multiple beneficial effects on muscle**:
  - **Acute – increased contraction rate & muscle force**
  - **Chronic – exercise related adaptation**
- Levels of **cAMP in muscle reduced with aging**
- **Increasing cAMP in muscle improves function** in preclinical studies

Multiple Effects of cAMP Signaling on Muscle Function[1]



[1] Berdeaux et al., *Am J Phys Endo Met*, 2012

PGE2: Increases cAMP in Human Muscle Cells & Improves Muscle Function in Aged Mice

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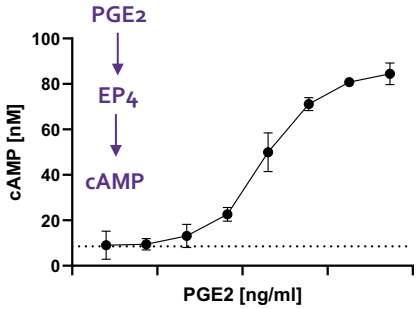
PGE2 increases cAMP in primary human myocytes



Epirium cell-based assay

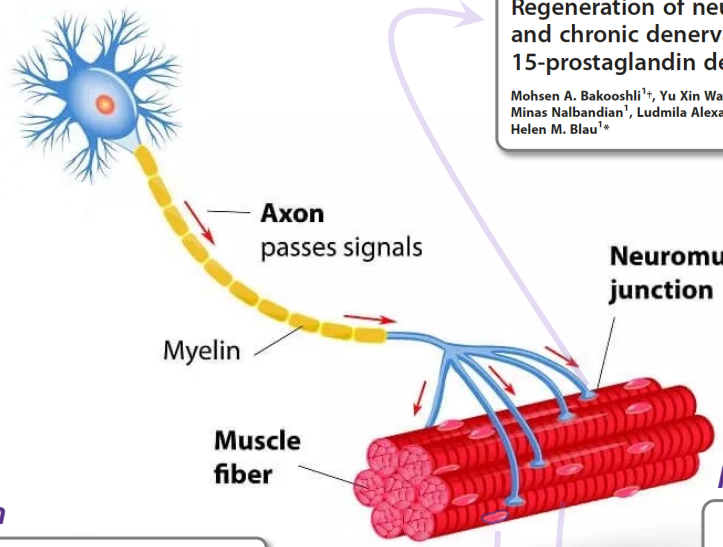
NMJ Integrity

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

MUSCLE PHYSIOLOGY

Regeneration of neuromuscular synapses after acute and chronic denervation by inhibiting the gerozyme 15-prostaglandin dehydrogenase

Mohsen A. Bakooshli[1†], Yu Xin Wang[1,2†*], Elena Monti[1], Shiqi Su[1], Peggy Kraft[1], Minas Nalbandian[1], Ludmila Alexandrova[3], Joshua R. Wheeler[4,5], Hannes Vogel[4,5], Helen M. Blau[1*]



Stem-Cell Proliferation

PNAS

Prostaglandin E2 is essential for efficacious skeletal muscle stem-cell function, augmenting regeneration and strength

Andrew T. V. Ho[a,1], Adelaida R. Palla[a,1], Matthew R. Blake[a], Nora D. Yucel[a], Yu Xin Wang[a], Klas E. G. Magnusson[a,b], Colin A. Holbrook[a], Peggy E. Kraft[a], Scott L. Delp[c], and Helen M. Blau[a,2]

[a]Baxter Laboratory for Stem Cell Biology, Department of Microbiology and Immunology, Institute for Stem Cell Biology and Regenerative Medicine, Stanford School of Medicine, Stanford, CA 94305-5175; [b]Department of Signal Processing, Autonomic Complex Communication Networks, Signals and Systems Linnaeus Centre, Kungliga Tekniska Högskolan Royal Institute of Technology, 100 44 Stockholm, Sweden; and [c]Department of Bioengineering, Stanford University School of Medicine, Stanford, CA 94305

Muscle Intrinsic Effects

RESEARCH ARTICLE

Science

AGING

Inhibition of prostaglandin-degrading enzyme 15-PGDH rejuvenates aged muscle mass and strength

A. R. Palla[1,2], M. Ravichandran[1,2], Y. X. Wang[1,2], L. Alexandrova[4], A. V. Yang[1,2], P. Kraft[1,2], C. A. Holbrook[1,2], C. M. Schürch[2,3], A. T. V. Ho[1,2]*, H. M. Blau[1,2]†

MF-300's Novel Therapeutic Strategy: Inhibiting PGE2 Degrading Enzyme (15-PGDH)

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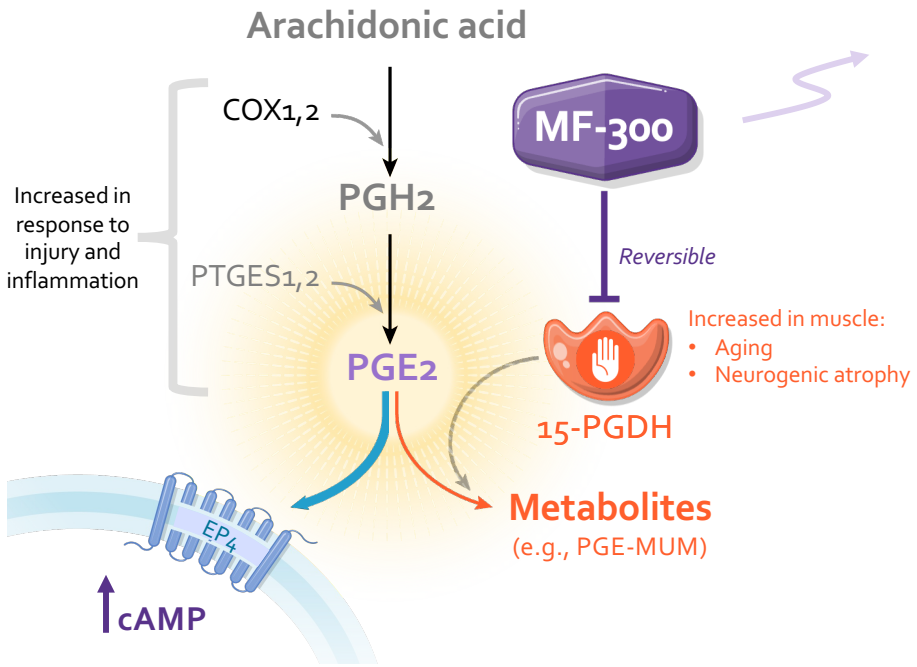
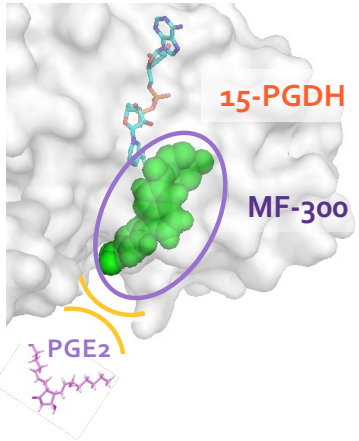
Inhibiting 15-PGDH to increase PGE2 mediated cAMP signaling

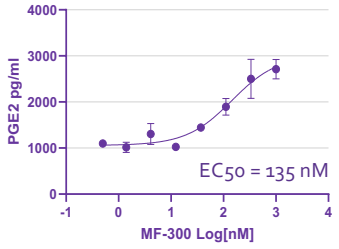




Species	15-PGDH % Identity to Human	MF-300 IC_{50} (nM) (Biochemical assay)
Human	100%	0.8
Dog	94%	1.5
Mouse	89%	1.0
Rat	88%	4.0

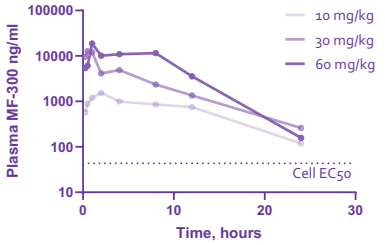
PGE2 increased by MF-300

A549 cells treated with IL-1β



Stable in vivo exposure

24-hr Plasma PK, Healthy Mouse
Oral admin



MF-300 Target: 15-PGDH Upregulated in Aging Muscle, Correlated w/ Strength Loss

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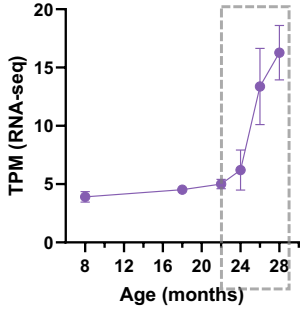
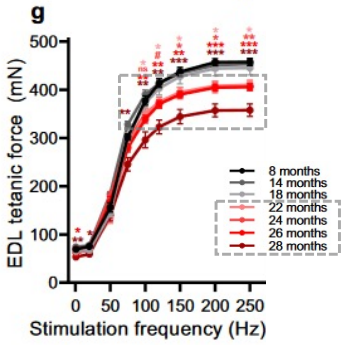
Aged Mice: 15-PGDH elevated

Muscle 15-PGDH gene expression (*Hpgd*) increases during aging[1]



- C57BL/6JRj, male
- Gastrocnemius

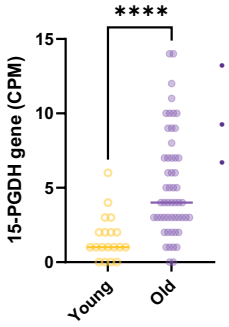
Muscle strength declines during window of elevated *Hpgd*[2]



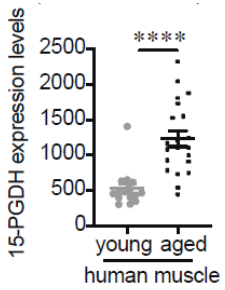
[1] https://sarcoatlas.scicore.unibas.ch/ GSE145480 , [2] Borsch et al., *Com Bio* 2021

Elderly Humans: 15-PGDH elevated

15-PGDH gene expression is elevated with aging in human muscle[3,4]

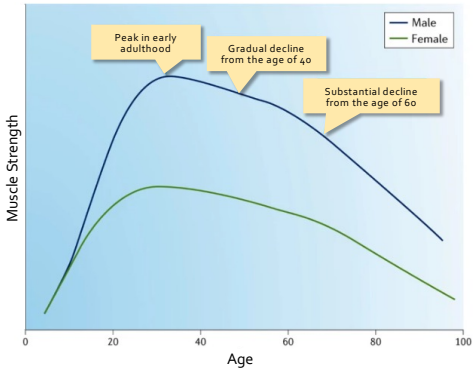


- Vastus lateralis (women and men)
- Young, N = 19 (**25±3 y.o.**)
- Older, N = 29 (**78±6 y.o.**)



- 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[5]



[3] GEO167186, [4] Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), [5] Dennison et al., *Nat Rev Rheum* 2017

MF-300 Increases Muscle Force in Aged Mice & Efficacy Correlated with TE Biomarker

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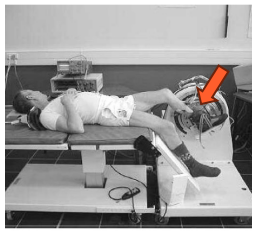
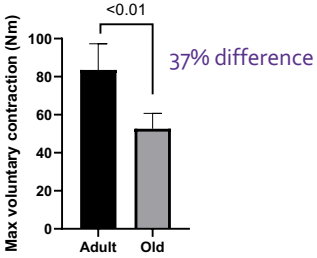
Modeling age-induced muscle weakness with isometric plantar flexion in mice

Maximal voluntary contraction

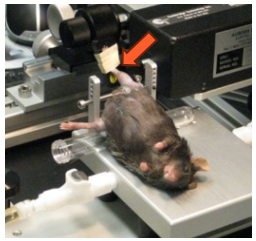


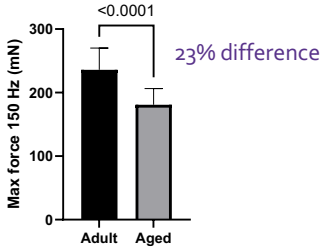


37% difference

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

Electrical nerve-evoked contraction

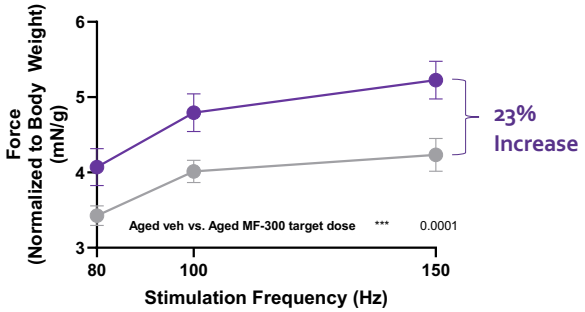




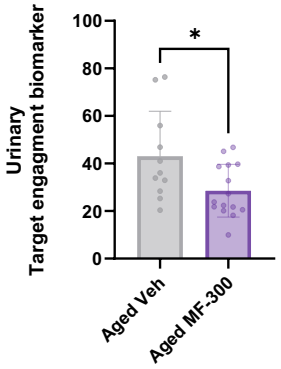
23% difference

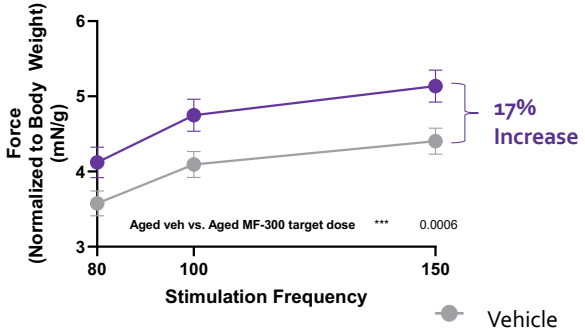
Male (C57Bl/6J)
Adult (N=15): 12 m.o.
Aged (N=18): 23 m.o.

MF-300: increased muscle force correlated with reduced urinary PD biomarker in aged mice

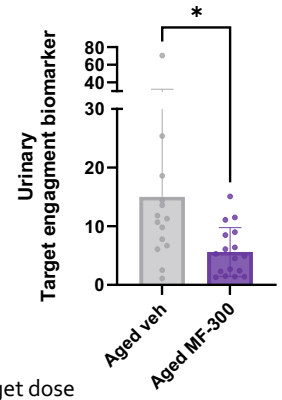


23% Increase





17% Increase



Vehicle
MF-300 target dose

MF-300 Potential to Provide Clinically Meaningful Improvement in Sarcopenia

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"Many older people **highly value their independence with the desire outweighing other needs.** Individuals go to great lengths to achieve independence…."

-Older Adults' Perspective of Independence Through Time: Results of a Longitudinal Interview Study[1]

"A significant number of sarcopenia patients are on the cusp of losing their independence**. If MF-300's preclinical efficacy results are replicated in the clinic, MF-300 should provide a clinically meaningful benefit**, allowing sarcopenia patients to remain independent."

***-**Prof. Roger A. Fielding, Ph.D, Senior Scientist & Team Lead, Human Nutrition Research Center on Aging, Tufts University*

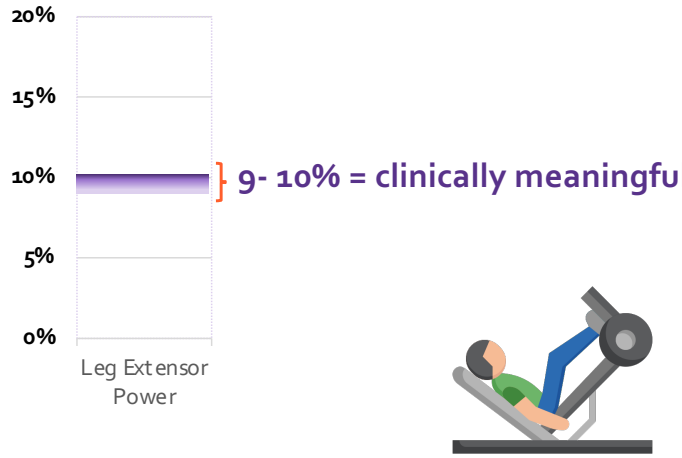
Leg Power Dependent Key Functional ADLs:

- Climbing stairs, Getting out of a chair, Bathing

Reflective Efficacy Endpoints (Leg Power):

- Stair Climb, Double Leg Press, Knee Extension, SPPB*

Functionally Relevant Increases in Muscle Power



Muscle Power = Muscle Force × Muscle Velocity

*Short Physical Performance Battery

[1]Taylor et al, *The Genrontologist* , 2023 [2]Kirn et al., 2016; [3]Kirn et al., 2016

MF-300: On track to Deliver Significant Clinical Value in '25 & '26

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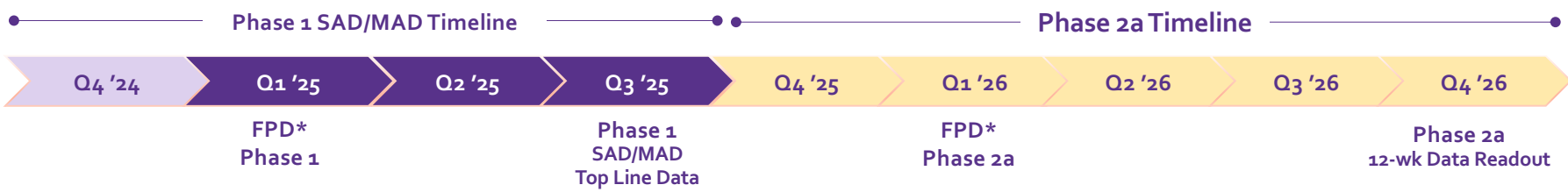
MF-300 "First-in-Class" Oral Sarcopenia Tx: Ph 1 w/ TE* biomarker Q3 '25, Ph 2a Efficacy Q4 '26



Ph 1 SAD/MAD Healthy Volunteer Endpoints:

- **Safety and tolerability**
- **MF-300 PK**
- **PD response**
  - PGE2 and target engagement biomarkers
- **Ph 1 Objectives:**
  - Demonstrate safety and tolerability of MF-300 across a range of doses
  - Characterize PK and PD (Target Engagement) profile
  - Assess exposure-response and exposure-safety relationships to identify target dose range for Ph 2a in Sarcopenia

Ph 2a : Study in Sarcopenic Elderly (65+):

- **Possible Entry Screening Criteria:**
  - SPPB*, Grip Strength, Lower Limb Function
- **Potential Efficacy Endpoints:**
  - Combination of performance measures of physical/muscle function coupled with QoL measures and disease response biomarkers; **SPPB* as primary endpoint**
- **Potential for Adaptive Design (12-week & 24-week read outs):**
  - Allowing for adjustments based on interim results, enhancing the study's responsiveness
  - Enabling informed adjustments to dose
  - Potential for an expansion cohort to further study response to optimized dose providing more robust data for decision-making

*TE= Target Engagement *FPD = First Patient Dosed *Short Physical Performance Battery

MF-300: Clinical Development Highlights

Epirium Bio

Ph 1 IND accepted - Enrollment Initiation Q4 '24

- Ph 1 data readout with Target Engagement (TE) Biomarker Q3 '25

Characterized MF-300's Potential Human Benefit

- Translation of MF-300 muscle benefit supported by Scholar Rock Ph 3 readout (SMA)
- Proteomic analysis identifies potentially relevant translational effects of MF-300
- Established PGE2-responsive human myocyte assay to test mechanistic hypotheses

Pharmacodynamic (PD) and Target Engagement Biomarkers Identified

- Correlated Biomarker to Target Dose (TD) Efficacy
- Potential for a circulatory biomarker tied to grip strength in aged population

Ph 2a Sarcopenia Study Plan: Transformational Value Creation Opportunity

- Efficacy study: SPPB*, QOL, Muscle Function & Disease Response Biomarker(s)
- First patient expected dosing Q1 '26, planned 12-week data readout Q4 '26
- Engaged with key stakeholders on FDA registrational primary endpoints (PE)

TD= Target Dose
SPPB = Short Physical Performance Battery
QOL= Quality of Life

Epirium Platform: Addressing High Value Indications with Unmet Medical Needs

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DISEASE	Oral Compound	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2
Sarcopenia	MF-300				
Fibrosis	NCE1				
Neuromuscular	NCE2				

In Q4 '24, Epirium transforms into a "first-in-class" clinical stage company targeting sarcopenia, a large unmet need with no FDA approved therapies

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Supportive Material Information:

- MF-300 Delta 7 Mouse Data
- Apitegromab in Delta 7 Mice & Phase 3 Results

MF-300 Attractive Profile in Translational SMA Model

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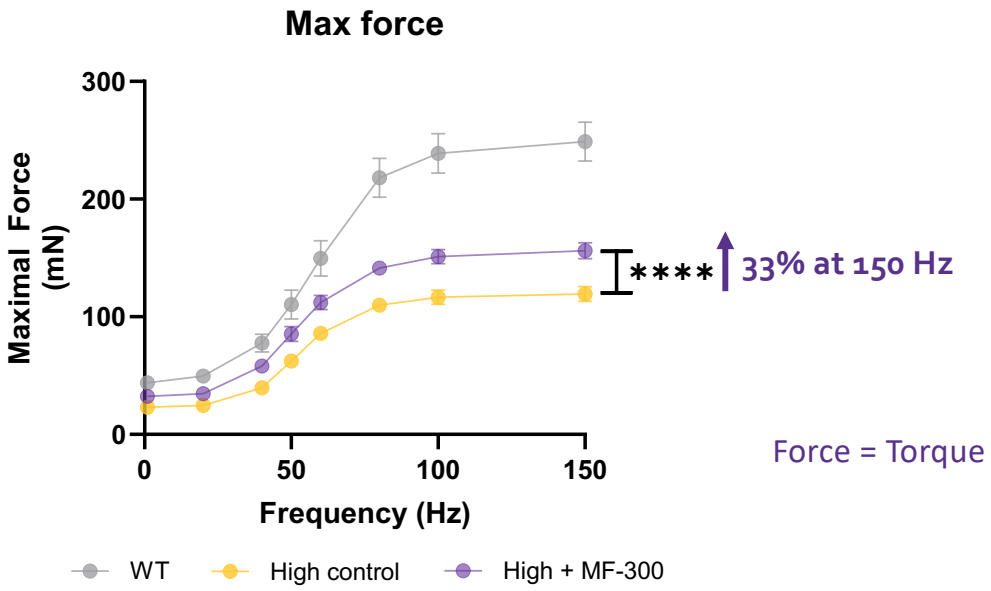
MF-300 in mouse Δ7 High/High



Force = Torque

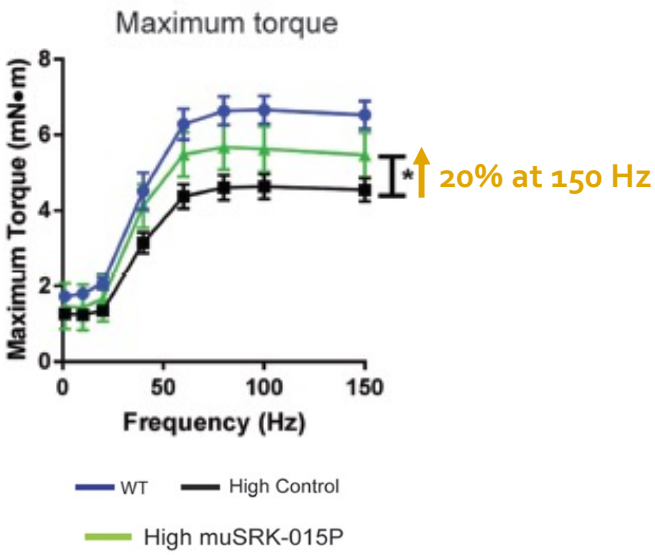
MYOLOGICA

Scholar Rock's Preclinical and Clinical Data Set Precedent for Translation of Efficacy

Epirium Bio

Demonstrates that a 20% increase in isometric plantar flexor force in mice translates to clinical benefit

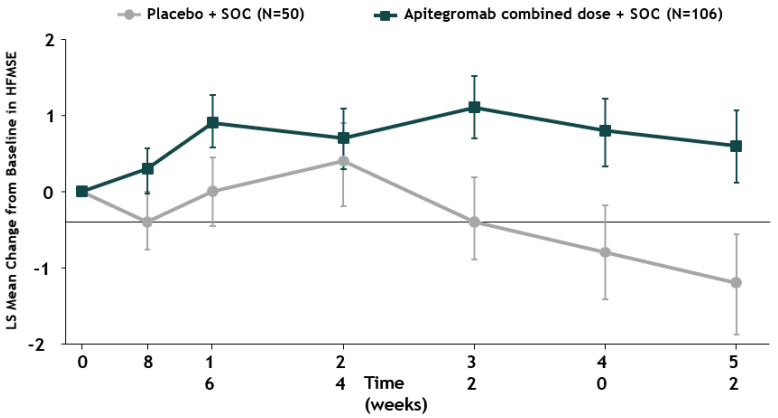
mSRK-015P in mouse Δ7 High/High



Long et al., *Hum Mol Gen*, 2016

Apitegromab in SMA + SOC (Ph 3 SAPPHIRE)

Least Squares Mean (+/- SE) Change from Baseline in HFMSE Total Score by Visit (MITT Set)



Change from Baseline in HFMSE Total Score

	Analysis	n	Results (vs Placebo, n=50)	Unadjusted *P*-value	
Primary Analysis	Apitegromab 10+20 mg/kg combined	106	1.8	0.0192*	Achieved Statistical Significance
	Apitegromab 20 mg/kg	53	1.4	0.1149*	
	Apitegromab 10 mg/kg	53	2.2	0.0121**	

ScholarRock