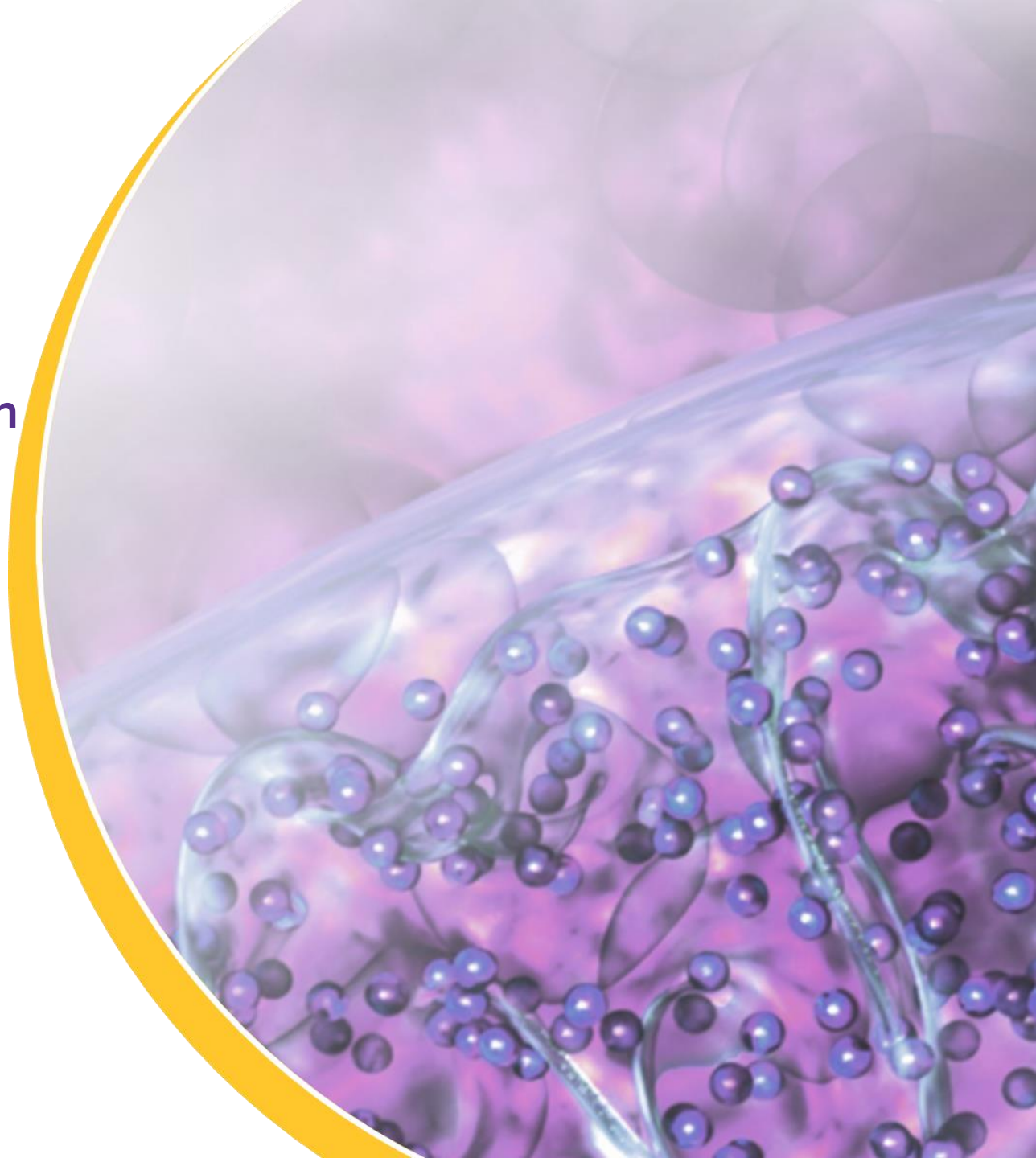
Epirium Bio

Novel Platform: Pipeline in a Mechanism Oral Treatments for Neuromuscular Diseases

- Lead Program: MF-300, a "First-in-Class" Oral Therapy for Sarcopenia: Age-Related Muscle Weakness
- Additional Rare Disease Opportunities:
  - Neuromuscular: Spinal Muscular Atrophy (SMA)
  - Fibrotic: Idiopathic Pulmonary Fibrosis (IPF)



Experienced Team with a Demonstrated Track Record of Success

Epirium Bio

Epirium Leadership Team

Alex Casdin, CEO

25+ year track record success in biotech & healthcare:

Port. Mgr: Pequot Capital; CEO & PM: Cooper Hil Partners, Reneo Capital

VP Finance, Amylin; CFO, Sophiris

Investor, Board Member & Audit Chair – Ignyta (acq. Roche), Erasca;

Board: Dusa (acq. Sun Pharma) , 454 Life Sciences (acq. Roche)

Eric Miller, CFO

Synthorx (acq. Sanofi)

Acadia Pharm -Commercial Stage

Cadence Pharm. (acq. by Mallinckrodt)

Micah Webster, Sr. Director, TS

Ph.D. Cellular and Molecular Biology, JHU

Scholar Rock, Associate Director, Translational Science

Discovery programs & Biomarker Strategy for apitegromab

Key Consultant Advisors

Leigh MacConnell, Ph.D. Clinical Development

25 years drug development, primarily in metabolic and liver disease

Led multiple drug approvals including first in class for T2DM (GLP-1) and Primary Biliary cholangitis (FXR agonist)

Successfully worked with FDA to define drug approval pathways for disease areas without prior regulatory precedence including NASH

Elaine Chiquette, Pharm.D. Scientific Affairs

C-Suite executive with 20+ years experience in pharma, biotech, and medical device

Led regulatory approvals for NDA, BLA, PMA across USA, EU and China

Formerly served as CSO and head of regulatory & medical affairs at Gelesis

Roger Fielding, Ph.D. Professor of Medicine

Researcher studying the underlying mechanisms contributing to the age-associated decline in skeletal muscle mass

Published over 200 per-reviewed papers and 8,000 citations

Conducted numerous studies examining the roll of skeletal muscle power on physical performance in older adults

Large and Growing Unmet Medical Need
No FDA Approved Therapy

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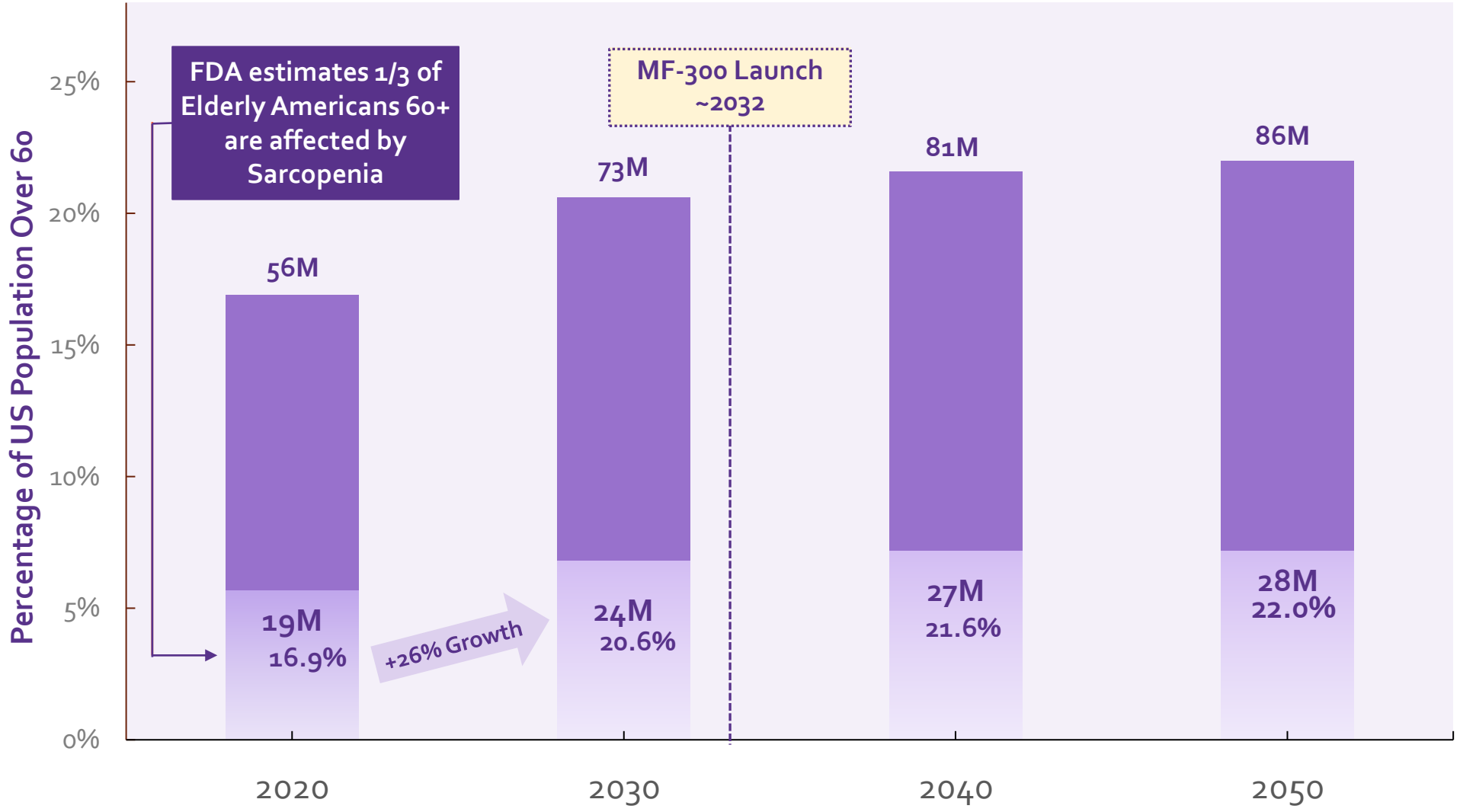
Current U.S. Healthcare Sarcopenia Spending Estimated >$40 Billion Annually

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**[2,4]
  - Existing muscle is weaker, contracts slower
  - Disproportionate loss of fast twitch muscle force
  - Progressive denervation of muscle
  - Reduced regenerative potential of muscle stem cells

"Maintaining or gaining muscle mass does not prevent aging-associated declines in muscle strength"[5]

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

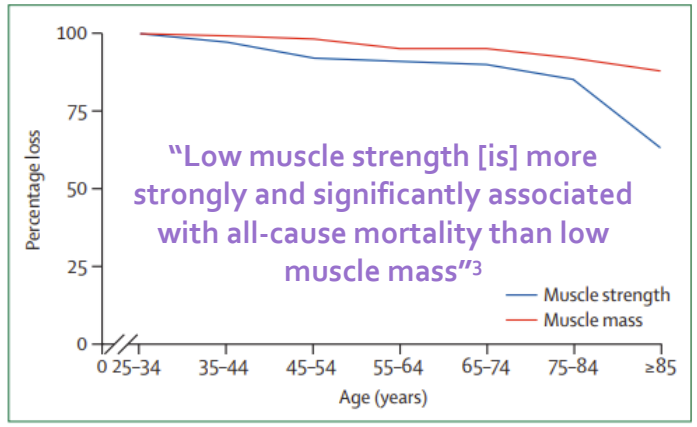
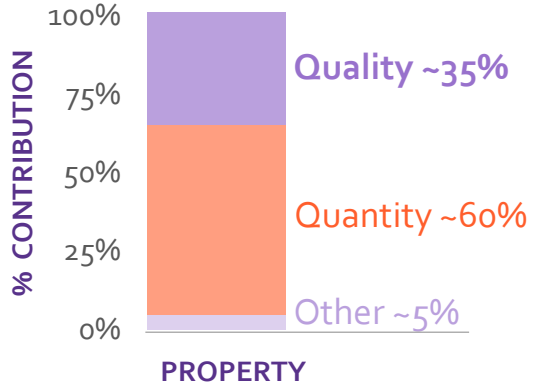


Figure 1: Percentage loss of muscle mass and muscle strength with age in men

Reduction in Muscle Quality Contributes Significantly to Loss in Muscle Force[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] Mohien et al., *eLife*, 2019
[5] Goodpaster et al., *J Gerontology*, 2006

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

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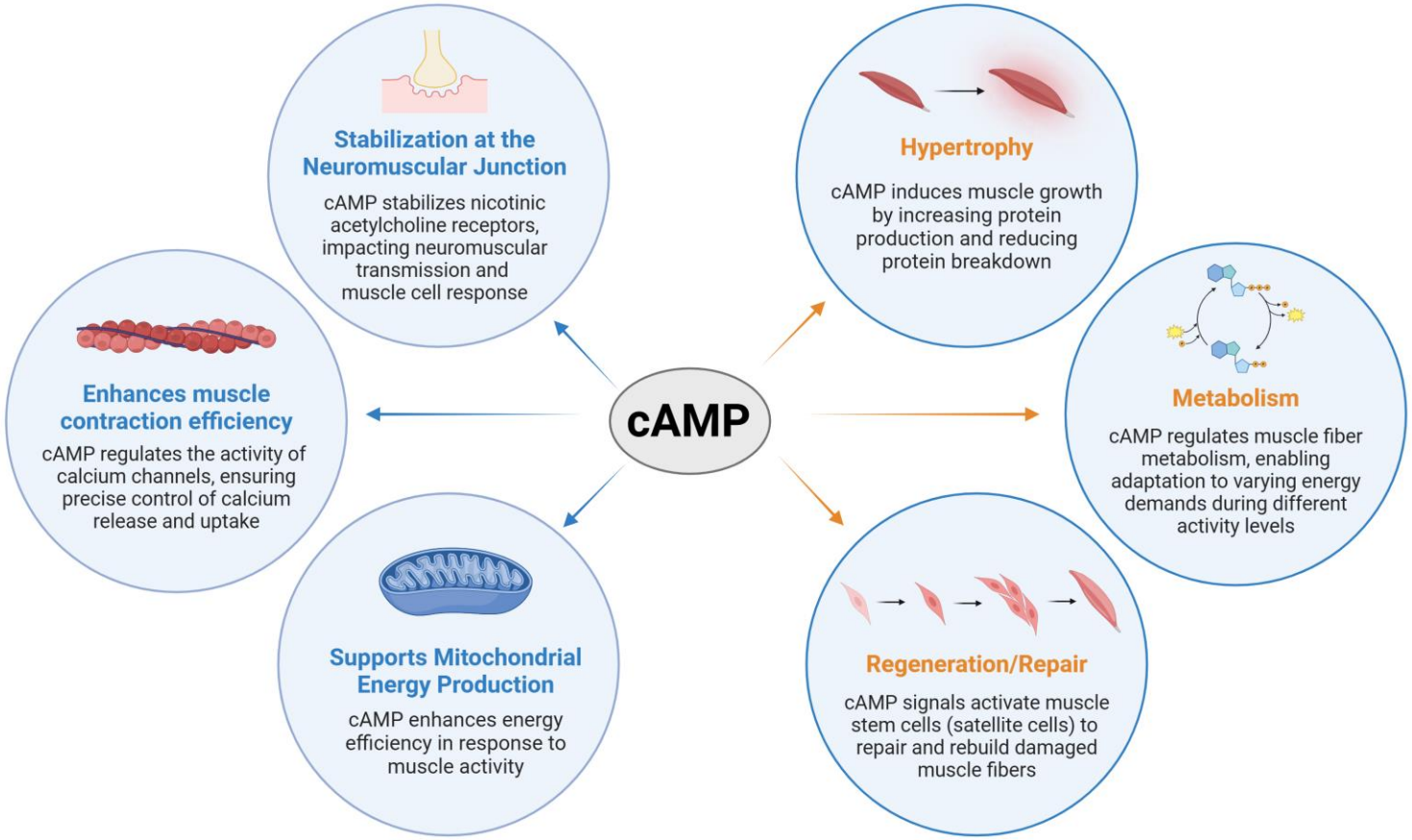
Increasing cAMP to Improve Muscle Quality

- **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**[2]
- **Increasing cAMP in muscle improves function** in preclinical studies[2]

Multiple Beneficial Effects of cAMP on Muscle Function[1]



[1] Berdeaux et al., *Am J Phys Endo Met*, 2012
[2] Marco-Bonilla et al., *Int J Mol Sci*, 2023

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

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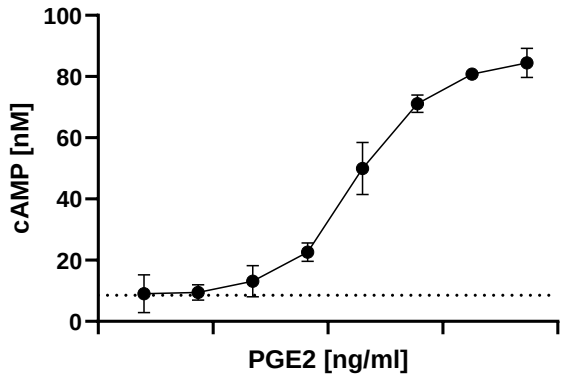
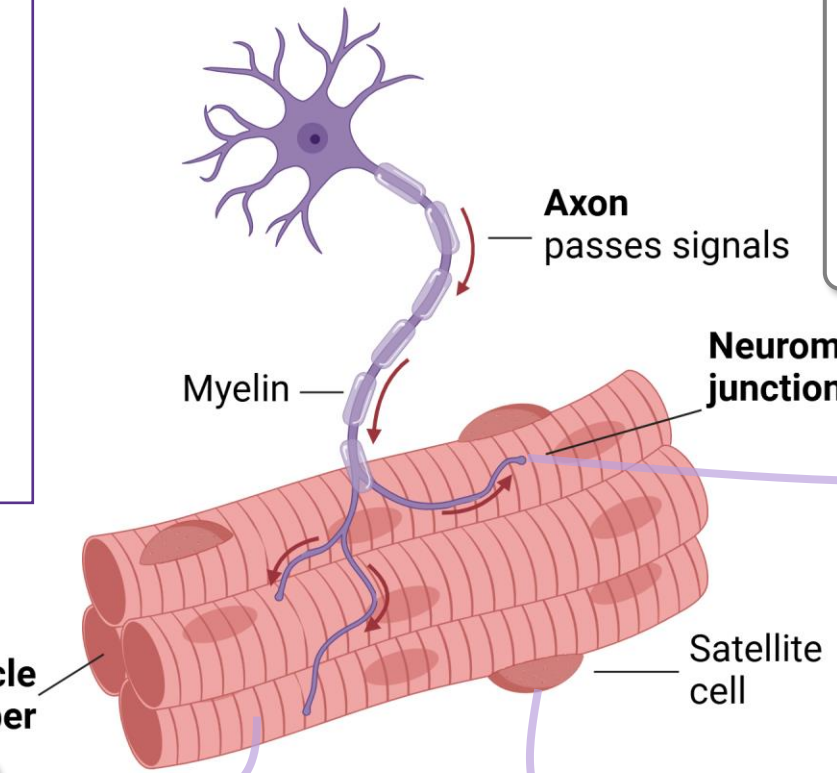
PGE2 increases cAMP in primary human myocytes



Epirium cell-based assay

15-PGDH ⊣ PGE2 → EP4 → cAMP



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*]

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]†

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

15-PGDH, a Gerotherapeutic Target that Reduces PGE2 Levels, is Upregulated in Aged Muscle

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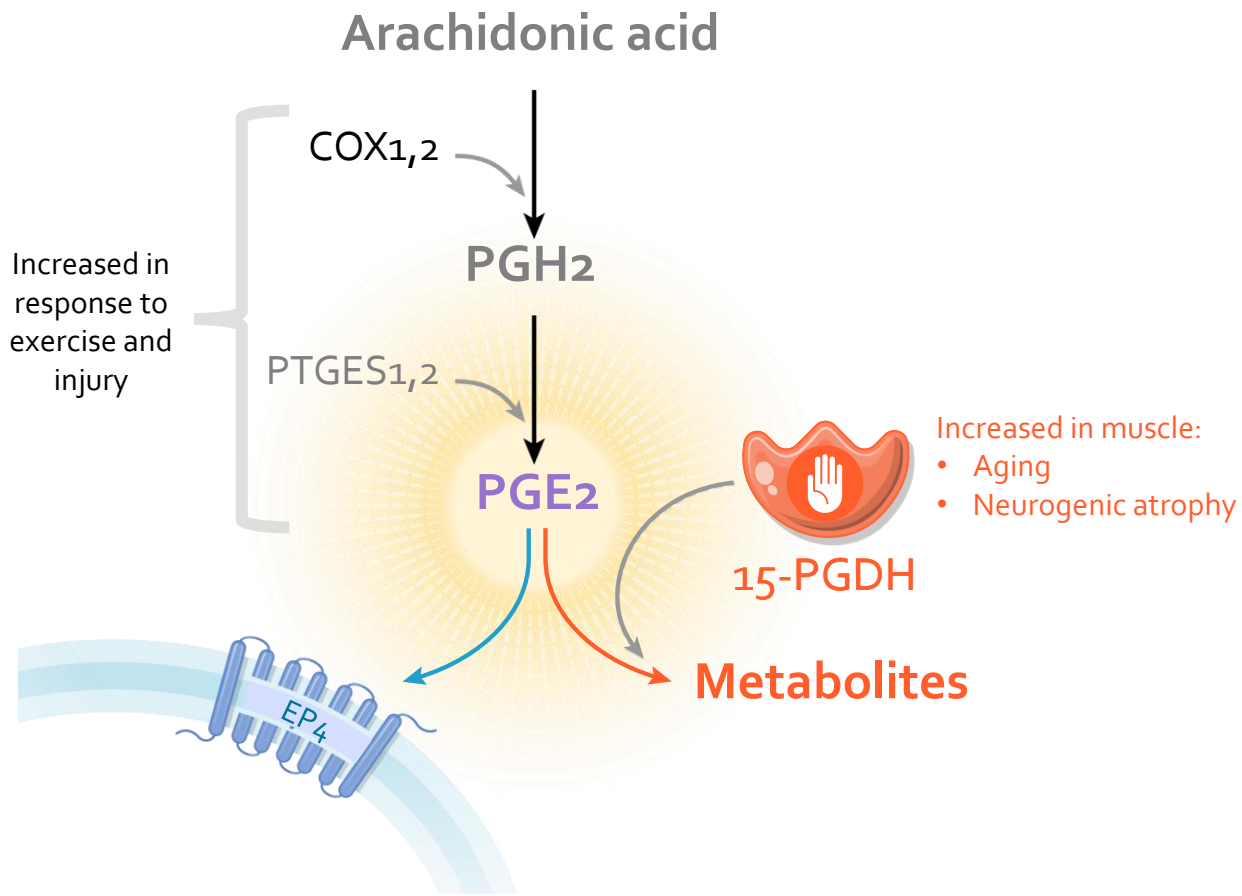
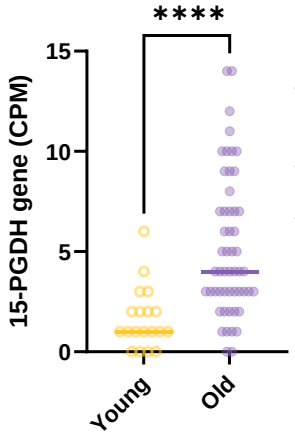
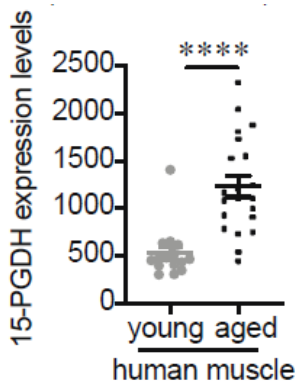
15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2



15-PGDH gene expression Elevated in aged human muscle[3,4]

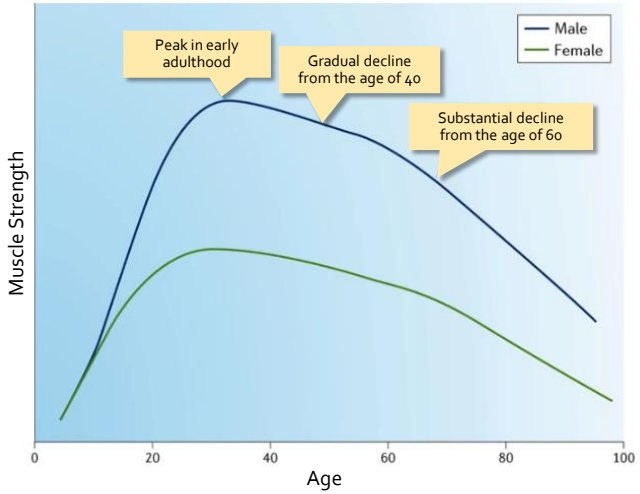


- Vastus lateralis (women and men)
- Young, N = 19 (**25±3 y.o.**)
- Older, N = 29 (**78±6 y.o.**)



- 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]

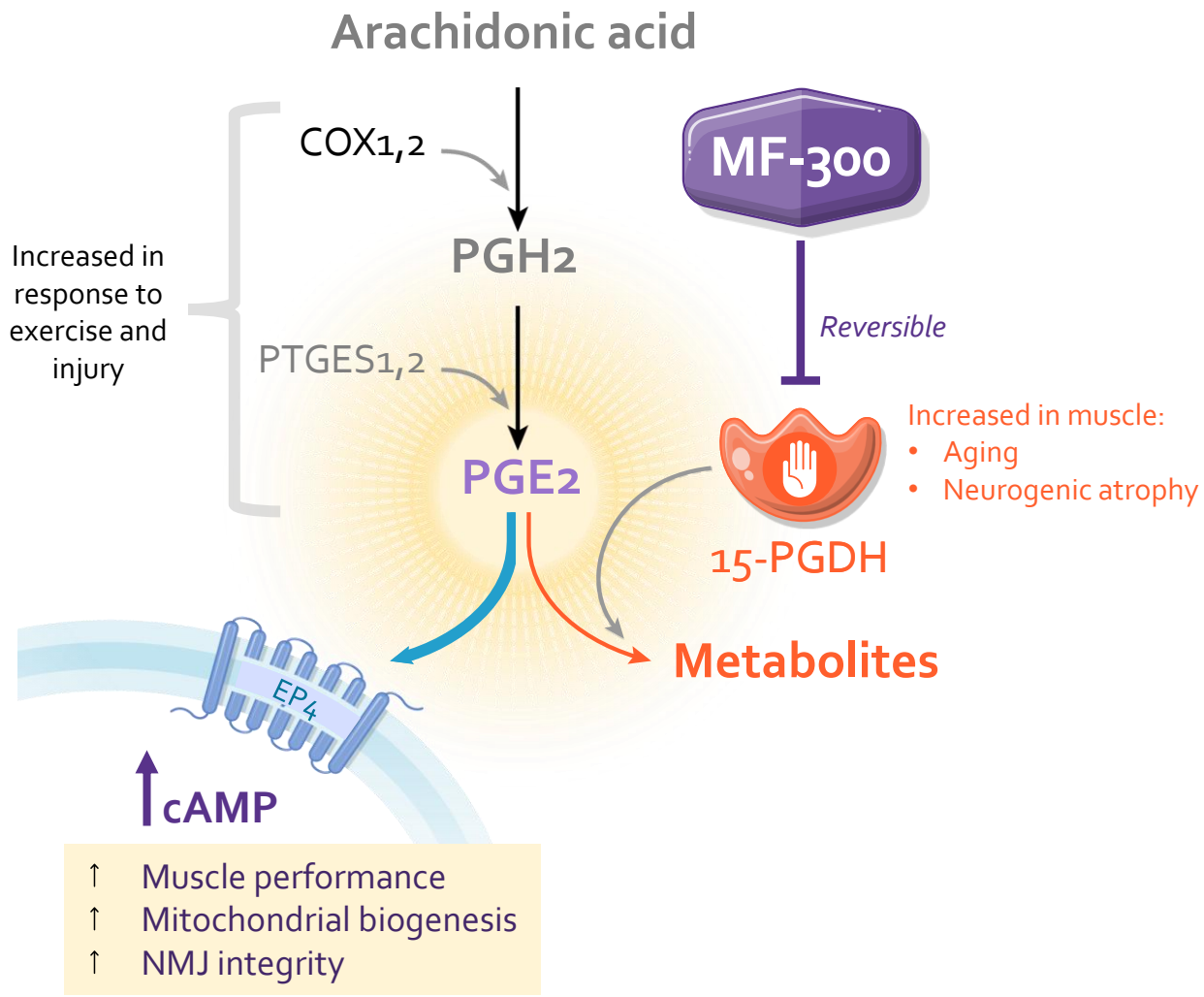


[3] GEO167186, [4] Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), [5] Dennison et al., *Nat Rev Rheum* 2017

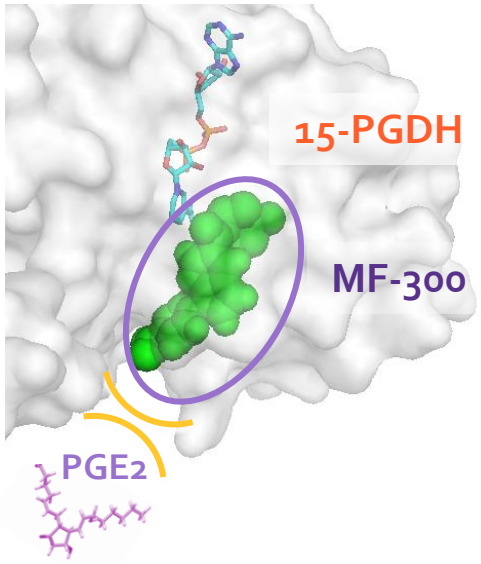
MF-300: Epirium's Therapeutic Strategy to Increase PGE2 Levels in Aged Muscle

Epirium Bio

MF-300
Inhibits 15-PGDH to increase levels of PGE2



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



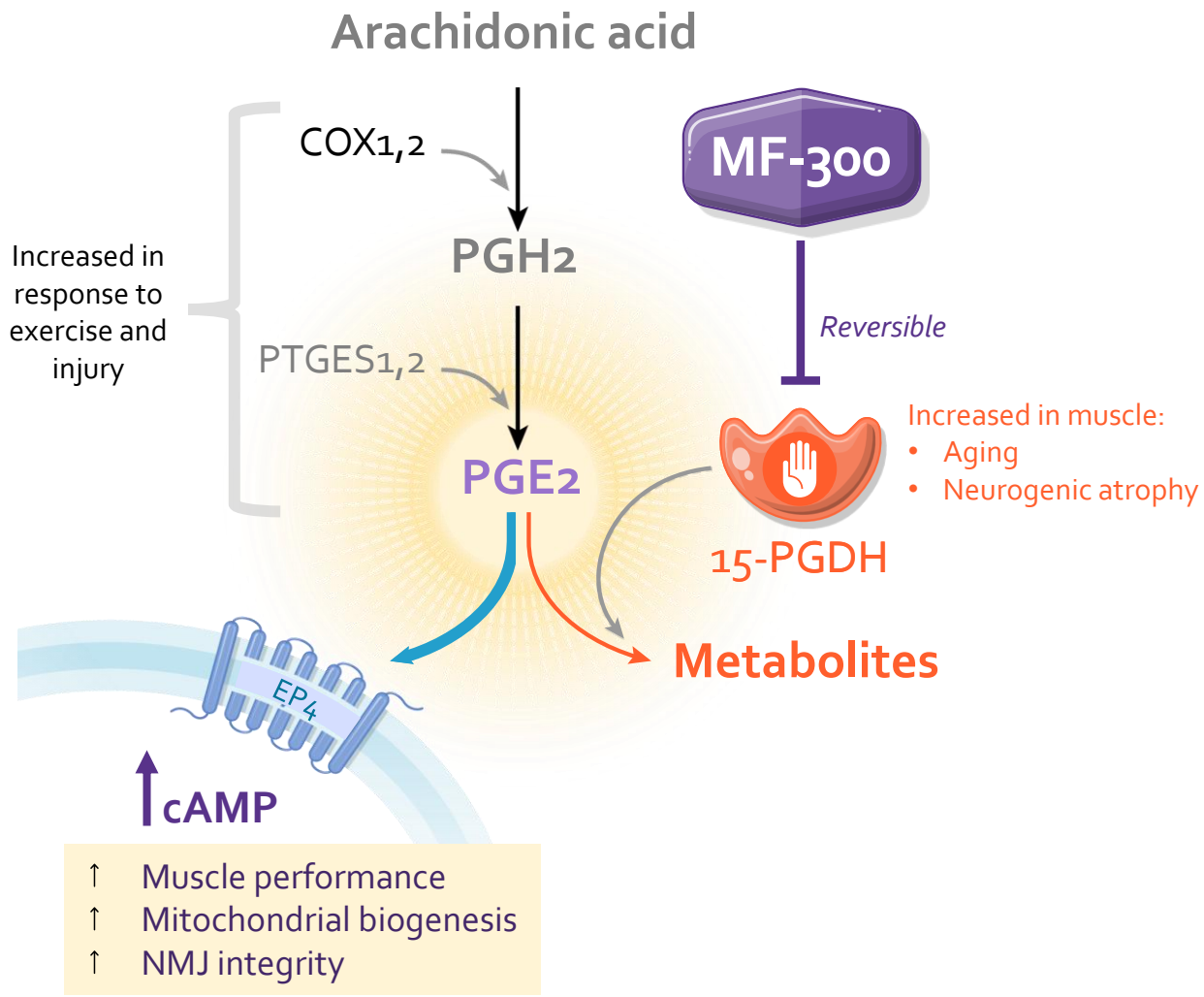
MF-300 potent inhibition of 15-PGDH across species

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

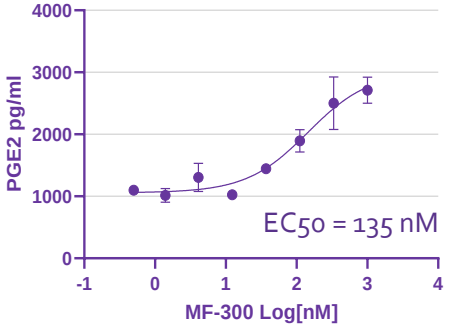
MF-300: Epirium's Therapeutic Strategy to Increase PGE2 Levels in Aged Muscle

Epirium Bio

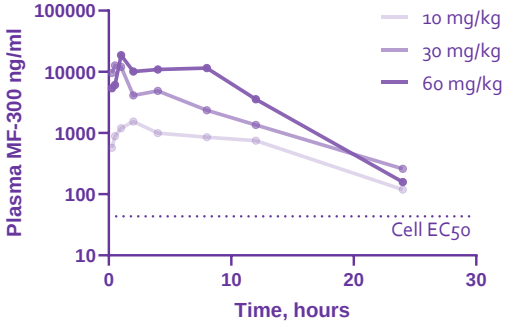
MF-300
Inhibits 15-PGDH to increase levels of PGE2



MF-300 increases PGE2 in cell-based assay



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



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

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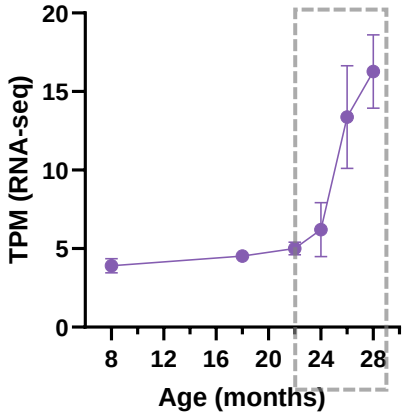
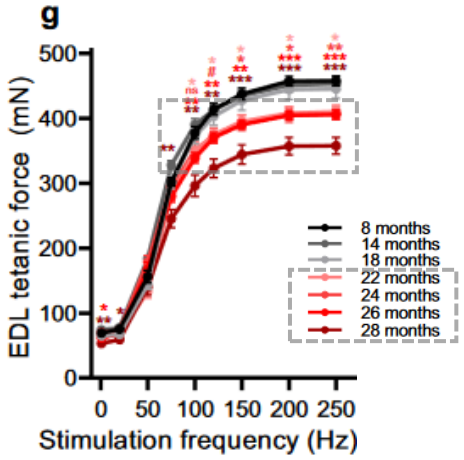
15-PGDH gene expression Elevated in aged mouse muscle

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



- C57BL/6JRj, male
- Gastrocnemius

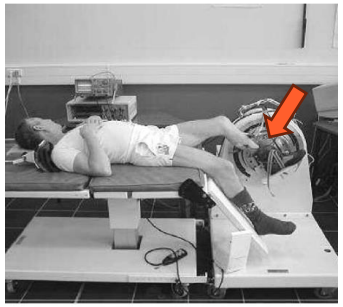
Muscle strength declines during window of elevated *Hpgd*[2]

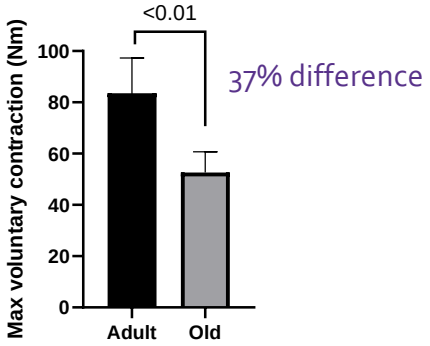


[1] https://sarcoatlas.scicore.unibas.ch/ GSE145480 , [2] Borsch et al., *Com Bio* 2021

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

Maximal voluntary contraction



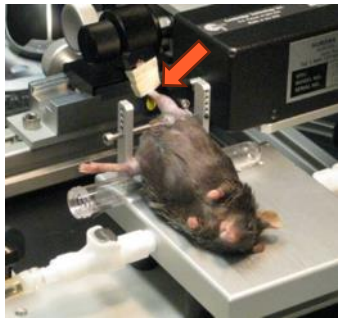


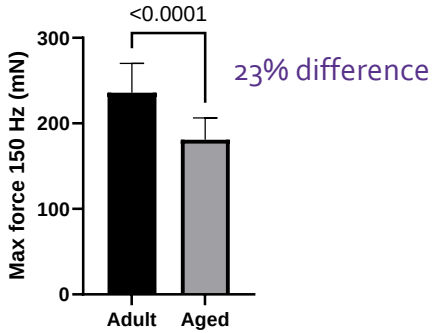
37% difference

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

Graph data and image:
Ochala et al., *Exp Ger*, 2004

Electrical nerve-evoked contraction





23% difference

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

Mouse image:
https://aurorascientific.com/

MF-300 Increases Muscle Force with Correlated Reduction in PD Biomarker

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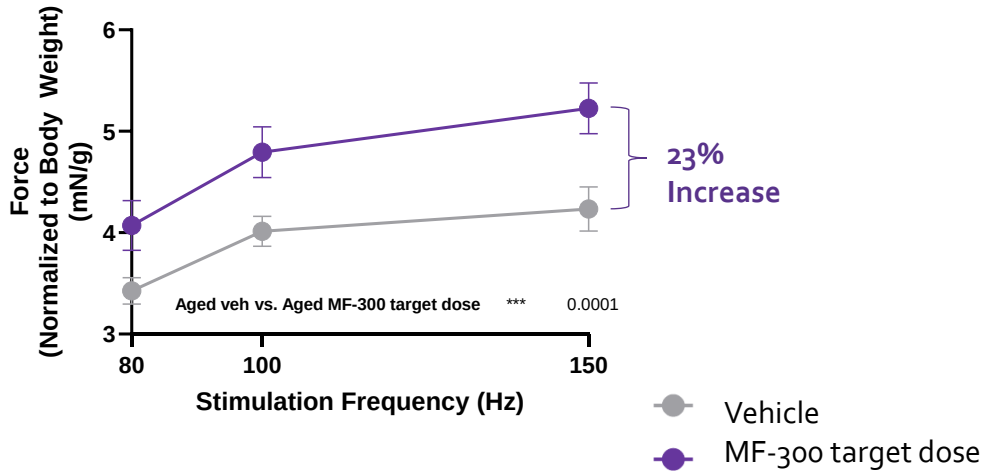
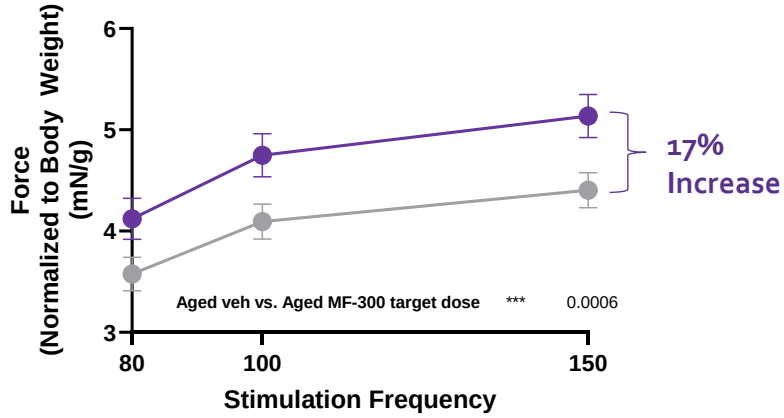
MF-300
Increased muscle force in aged mice

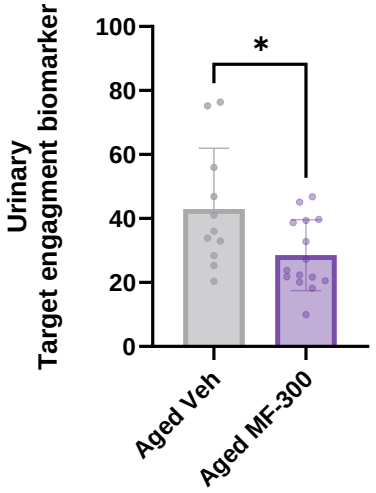
Study 1

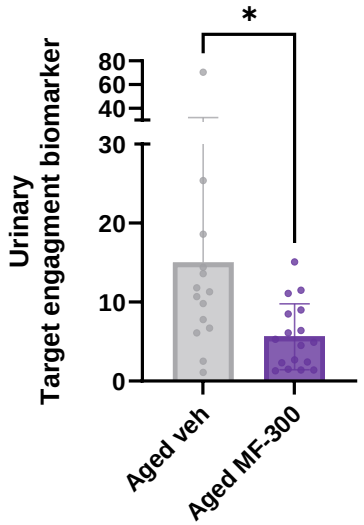


Study 2



MF-300
Reduced urinary metabolite of PGE2





More Force = More Power

MF-300's 17-23% Force Improvement Potential to be Clinically Meaningful

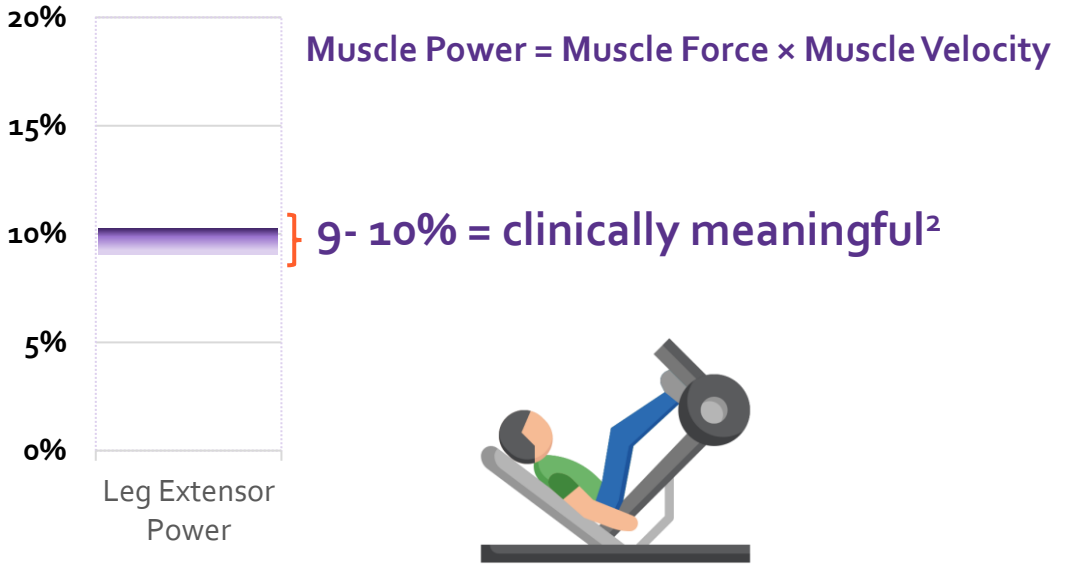
"Many older people **highly value their independence with the desire outweighing other needs.** Individuals go to great lengths to achieve independence…."

-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

Functionally Relevant Increases in Muscle Power



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*

**Short Physical Performance Battery*

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

Phase 1 Overview:

Objectives: Assess the safety and tolerability of MF-300 following single ascending doses (SAD) and multiple ascending doses (MAD) along with:

- MF-300 Pharmacokinetics (PK) & Pharmacodynamics (PD), including target engagement (TE) biomarkers
- Potential for food effect on the PK of MF-300 following a single oral dose
- Characterize the PK/PD, PK/safety relationships, allowing for Ph2 dose selection

Population: Adult healthy volunteers ≥ 18 - < 65 years of age & Healthy Elderly Cohort ~65-75 years of age

Part 1a SAD

- N=8 per cohort (2 pbo, 6 MF-300)
- Broad range of doses
- Large safety margin
- Allows for flexible dosing (including de-escalation)
- Elderly cohort dose selected

Single Ascending Dose
5 dose adult cohorts, 1 elderly cohort
MF-300 125 mg – 1150 mg

Part 1b Food Effect

- N=12 (all MF-300)
- MF-300 administered in the fed or fasted state

Food Effect
2 sequence 2 period cross-over

Part 2 MAD

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

Multiple Ascending Dose
3 dose adult cohorts & 1 Elderly cohort

Phase 1 Expected Results: Conclusions & Phase 2 Dose Selection

Safety and Tolerability

- Single and multiple doses of MF-300 are well-tolerated at the tested doses with a maximum tolerated dose determined or a safe dose range determined
  - AEs, Physical exams, Vitals, ECGs, & Labs

Pharmacokinetics

- MF-300 exhibits linear or non-linear PK over the dose range tested
- Food intake did or did not affect MF-300 absorption and bioavailability
- PK profile and key PK parameters were well-characterized
  - Cmax, Tmax, AUC, T ½

Pharmacodynamics

- Proof of concept: Initial biomarker responses suggest target engagement at certain doses
- Dose response, exposure-response (E-R) relationships characterized to allow Ph2 dose selection
- Micah will review Ph 1 proof concept target engagement biomarkers
  - Urine: PGE-MUM, PGA-M, Bicyclo-PGE2
  - Plasma: PGE2, 15-Keto-PGE2, Bicyclo-PGE2

Implications for Phase 2

Data Supporting Phase 2 Dose Selection:

- Identified therapeutic window informing Phase 2 dose selection based on safety and PK findings, supplemented by Efficacy - Response (E–R) relationships:
  - Strong E–R relationship is observed, positioned to determine optimal dose / exposure target for Phase 2 dose selection
  - Should resulting E–R be unclear, a broader dose range may be tested in Phase 2

Current Phase 2 Design: 24-week Duration w/ 12-week Interim Analysis

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Overview

- 24 week randomized, double-blind, placebo-controlled, adaptive design
- Part 1: 3 arm, dose-finding (60/arm)
- Part 2: 2 arm with optimized dose

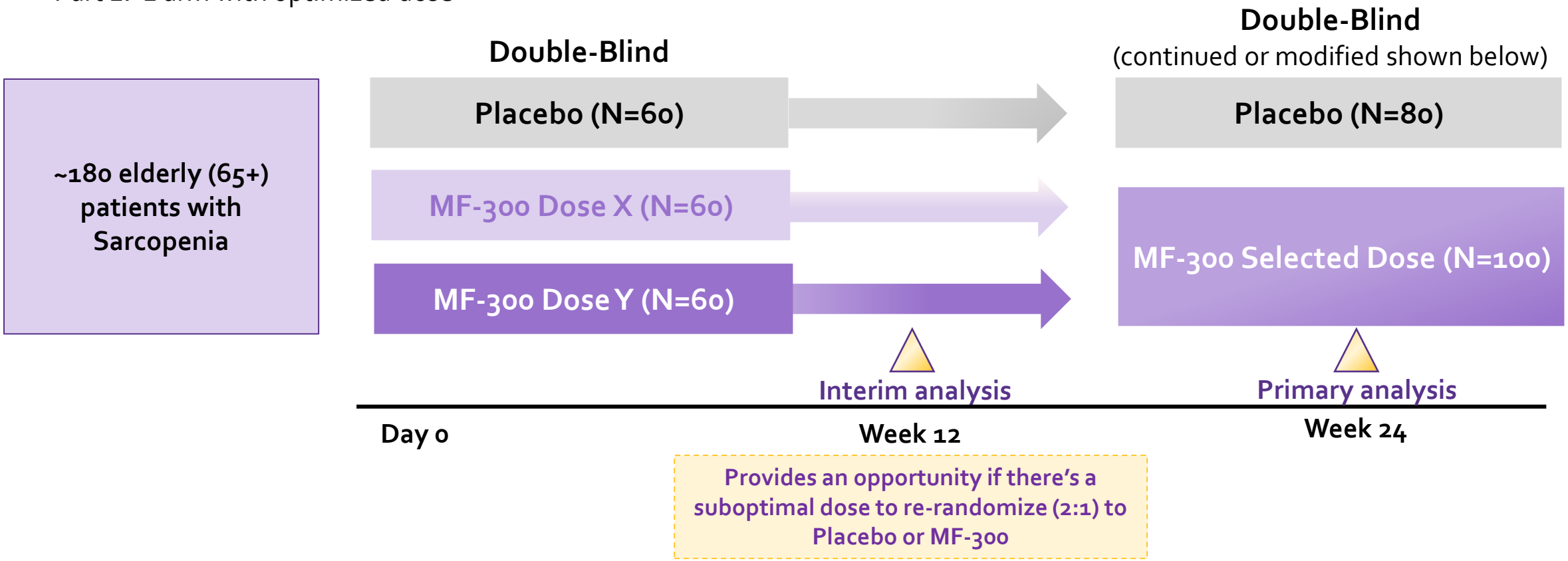
Interim Analysis

Analysis 20/arm at Week-12

- SPPB, "Timed Up and Go," grip strength, biomarkers, safety

Primary Analysis

Potential Endpoint: Change from baseline in SPPB at Week 24



Phase 2 Planning, Assumptions & Endpoint Diligence during '25

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Potential Endpoints and Powering Assumptions

- **Performance Measures:**
  - SPPB, Sit Stand test, Stair Climb test, Grip Strength
  - Leg Strength (double leg strength, double leg power)
  - Isometric Plantar Flexion, Walk Test(s)
  - *Potential wearable & remote monitoring technology (e.g., SV95c, iphone video monitoring)*
- **Patient Reported Outcomes**
- **Muscle Quality:** MRI (e.g., muscle degeneration)
- **PD & Disease Response Biomarker:** *(dependent on upcoming preclinical results)*
  - PGE2 & Metabolites & Circulatory Biomarkers: (e.g., DLGAP1, Agrin fragment)
- **180 patients provides 80% power assuming 15% effect size for change in SPPB at week 24**

Q1 2025	Q2 2025	Q3 2025	Q4 2025
KOL discussions and introductions • Int'l Conference of Frailty and Sarcopenia Research (ICFSR) ○ Clinical Endpoints workshop with KOLs	**Engaging w/ KOLs on Ph 2 Endpoints & Trial Design** • Roger Fielding • Luigi Ferrucci • Beth Barton • David Cella (PRO) • Zan Flemming	**End of Phase 1 Briefing book submitted** • Gerontological Society of America (GSA) Research Meeting • Sarcopenia PRO Study (FDA Sponsored) w/ performance outcomes (e.g., SPPB)	**Type D meeting FDA** • Sarcopenia, Cachexia & Wasting Disorders (SCWD) Meeting • FDA feedback on PRO study

**Short Physical Performance Battery*

Phase 2 Study Key Milestones: Interim data Q4 '26 & Topline Readout Q2 '27

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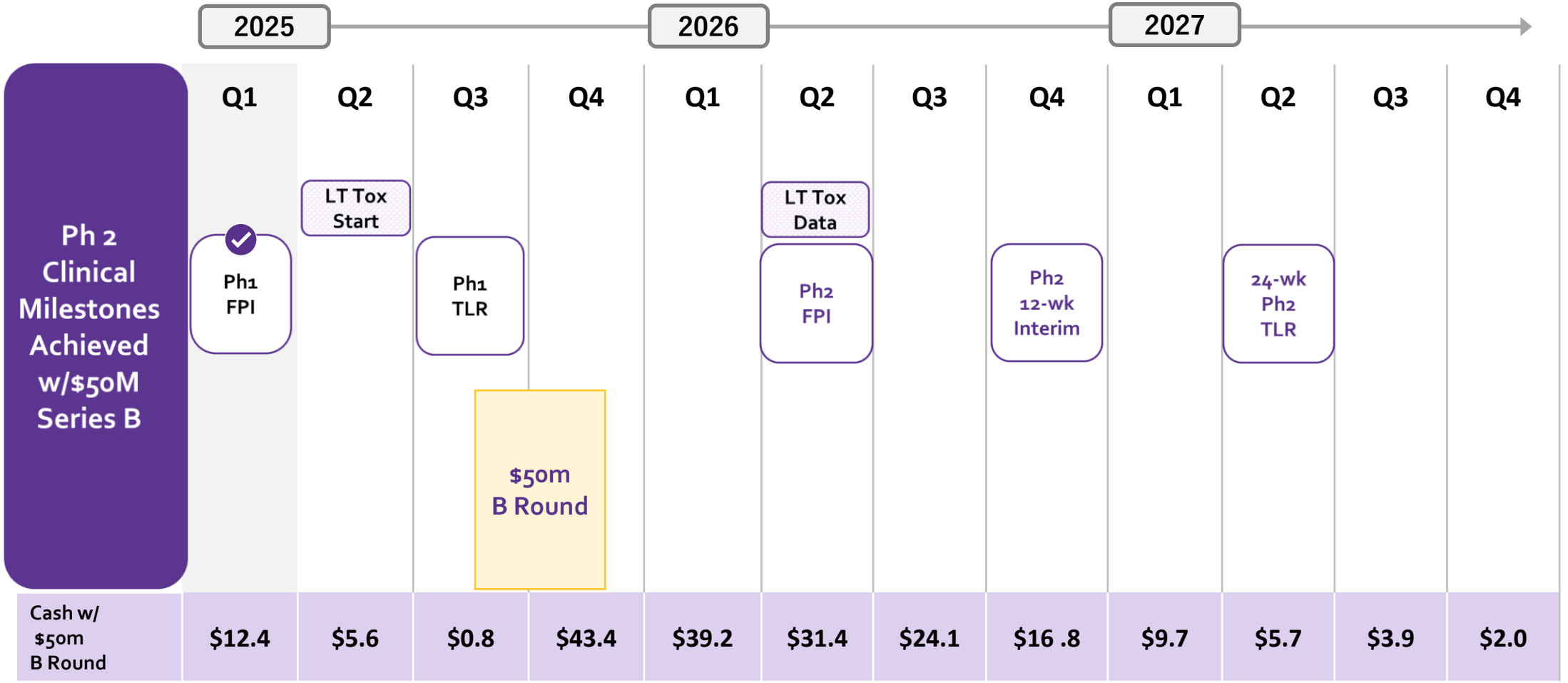
Current cash-on-hand achieves Phase 1 data



MF-300 Value Creating Milestones and Activities in 2025

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Phase 1 Topline Results Readout (TRL) Ontrack for Q3 '25

- Inclusion of healthy Elderly Cohort (~65-75 yrs old)
- Ontrack for PK/PD, Target Engagement (TE) Biomarker Data

Phase 1 Target Engagement Biomarkers

- Measuring in Urine & Plasma

24-week Phase 2 FDA guidance Q4 '25

- Targeting Type D FDA Meeting, Supported by KOL input
- Disease Response Pharmacodynamic Biomarkers Validation Ongoing

Increasing MF-300's Efficacy Profile with Sarcopenia KOLs

- ICFSR Two Poster Presentations Planned, Clinical Endpoints Meeting Mar. '25
- Invited Speaker at Boston National Institute of Aging Pepper Center Mar '25

Opportunistic SMA Study in Delta7 mice Data Q2 '26

- Efficacy of MF-300 & SRK's Apitegromab vs Apitegromab alone
- Success significantly broadens aperture re: additional indications

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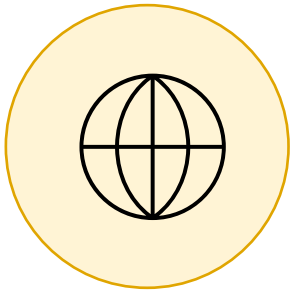
Thank you!



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Supplemental Information:

- Phase 1 Overview
- MF-300 & Apitegromab in SMA Delta 7 Mice, Apitegromab Phase 3 Results
- MF-300 Nerve Injury Data

MF-300 Phase 1 Ongoing & Ontrack Top Line Expected Readout Q3 '25

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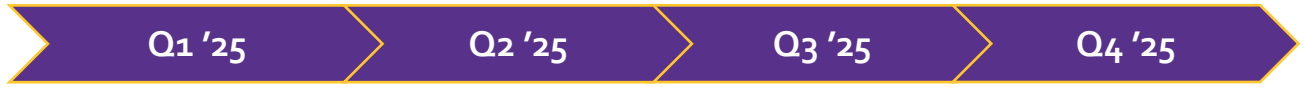
Phase 1 SAD/MAD Timeline



Phase 1
First Patients Dosed

Phase 1 SAD/MAD
Top Line Data

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 Profile, w/ Target Engagement Biomarkers
  - Assess exposure-response and exposure-safety relationships to identify target dose range for Ph 2a in Sarcopenia

MF-300 Attractive Profile in Translational SMA Model

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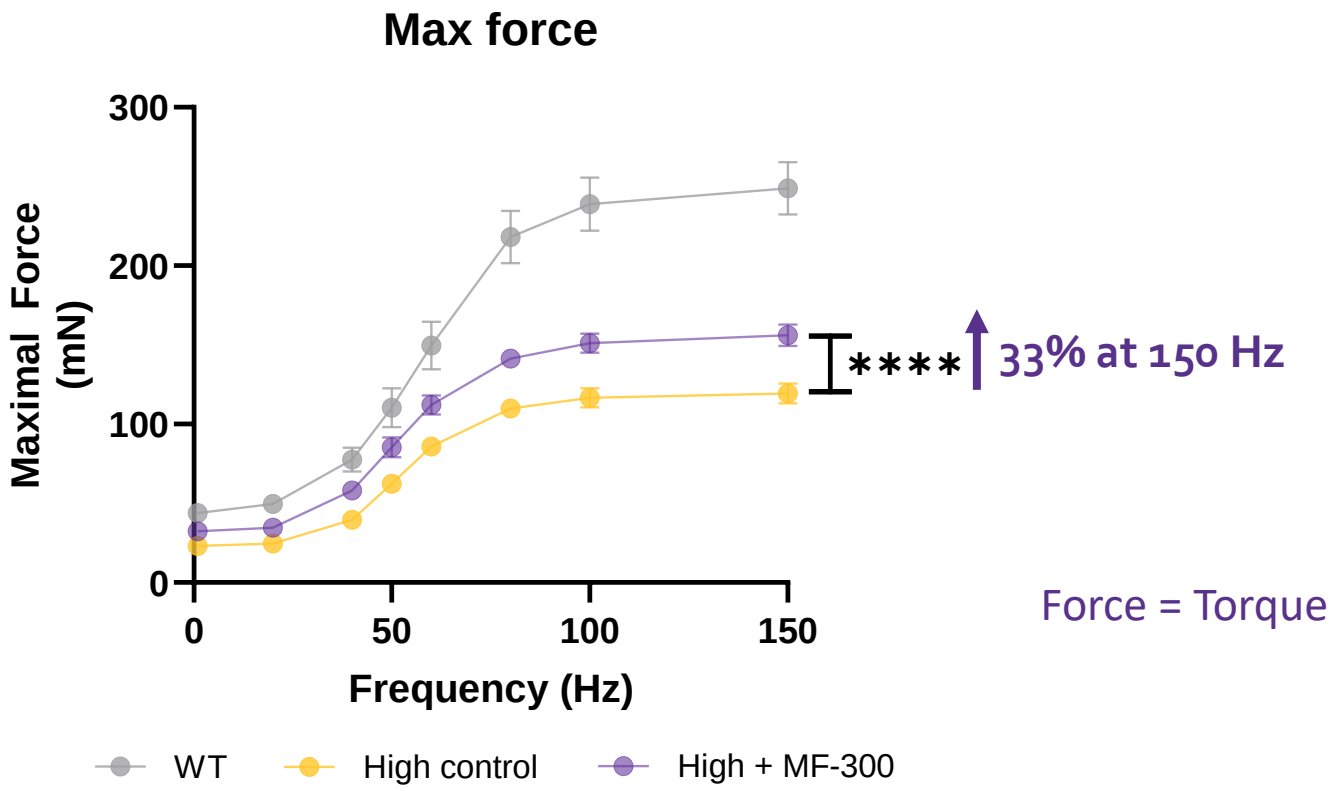
MF-300 in mouse Δ7 High/High



Force = Torque

MYOLOGICA

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

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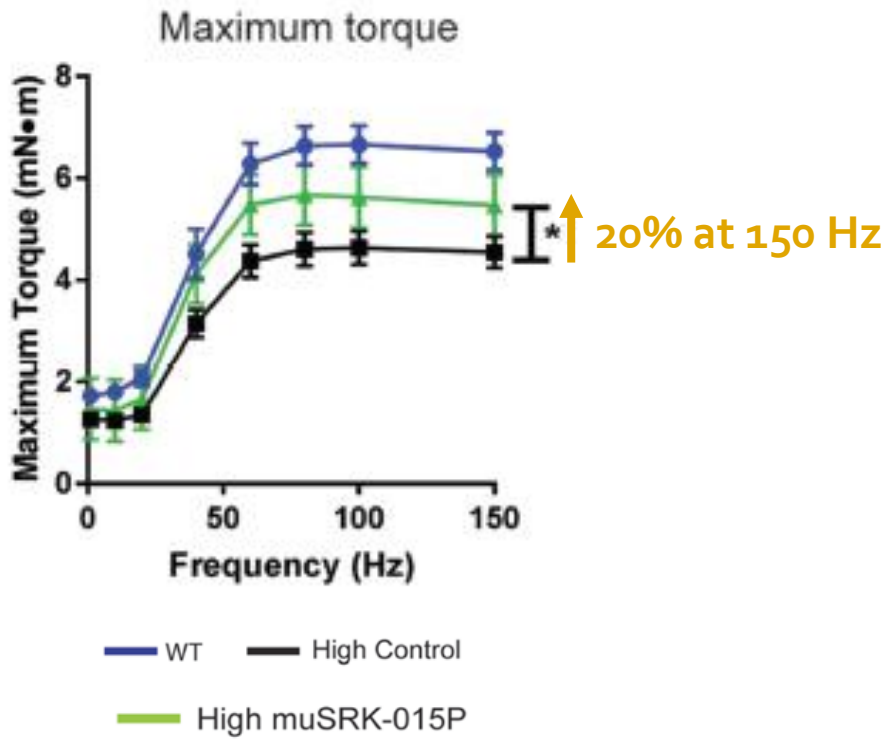
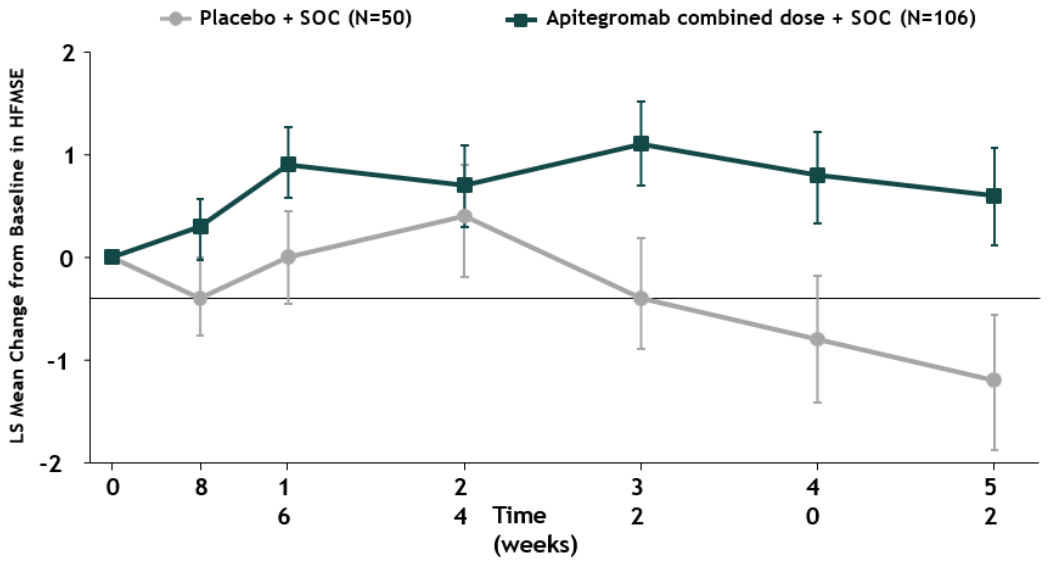
Demonstrates that a 20% increase in isometric plantar flexor force in mice translates to clinical benefit

mSRK-015P in mouse Δ7 High/High



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

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

MF-300 Accelerated Recovery of Muscle Force Following Sciatic Nerve Injury

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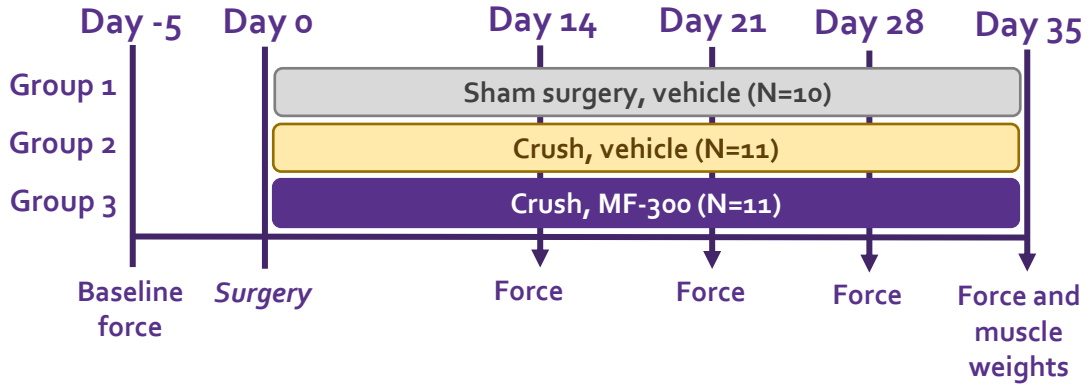
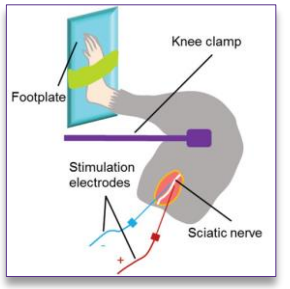
Sciatic nerve crush injury in healthy mice

C57Bl/6J male mice, 14-16 weeks old

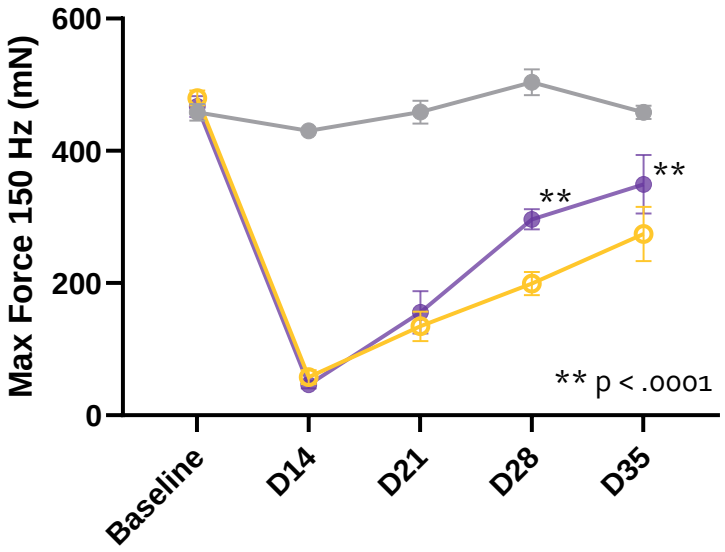


Plantar Flexor Force Measured

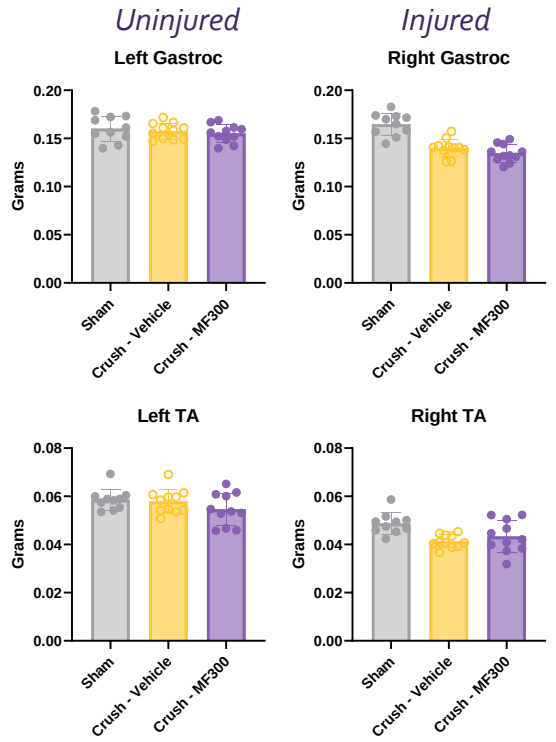


- Sciatic nerve stimulation
- Muscle torque = force x moment arm
- Plantar flexor muscle group (GA/Sol)

Accelerated recovery of force



MF-300 did not increase muscle mass



CRO: Myologica