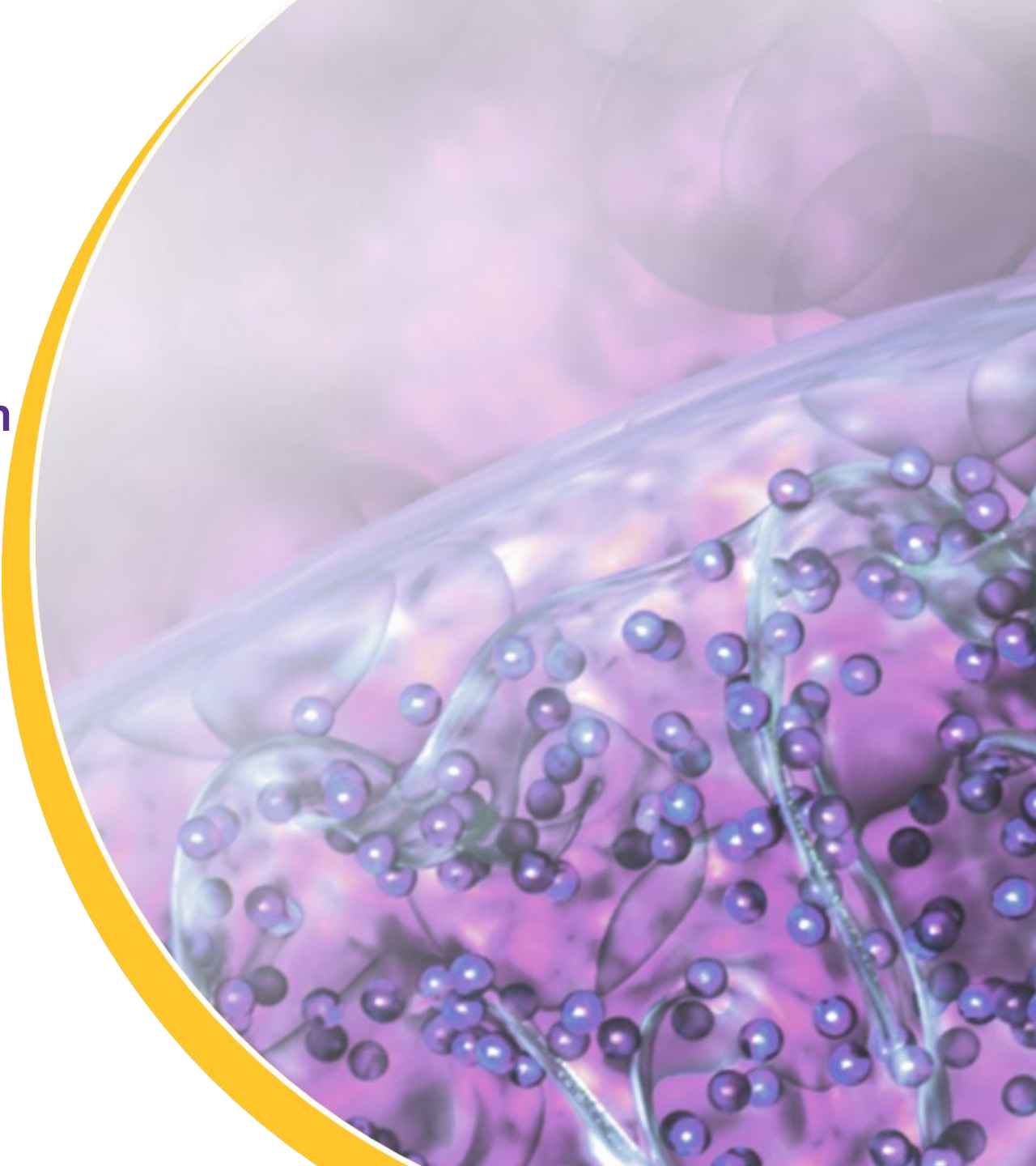




## Novel Platform: Pipeline in a Mechanism Oral Treatments for Neuromuscular Diseases

- Lead Program: MF-300, a “First-in-Class” Oral Therapy for Sarcopenia: Age-Induced 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 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



### Bruce Fahr, Director, Med Chem

Ph.D. Synthetic Organic Chemistry, UCLA

Medicinal Chemistry leader 4 companies

Coinventor Rezatapopt (in registrational clinical trial for cancer)

## 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

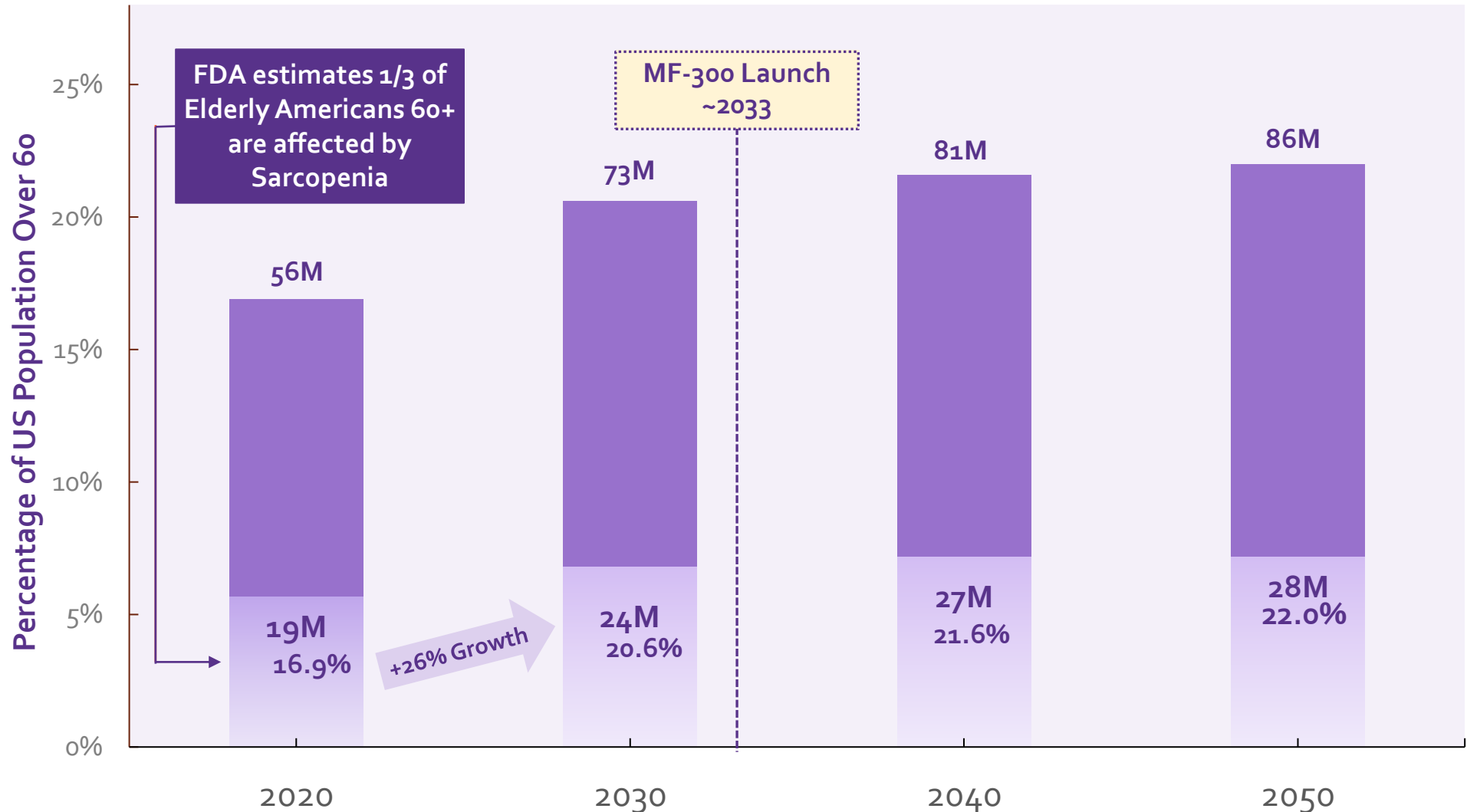
# Large and Growing Unmet Medical Need No FDA Approved Therapy

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:

- Severe loss of muscle strength and mass with aging
- Strength declines faster than muscle mass<sup>1</sup> due to Diminished muscle quality<sup>2,4</sup>
  - 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”<sup>5</sup>**

<sup>1</sup> Cruz-Jentoft and Sayer, *Lancet*, 2019

<sup>2</sup> Jubrias and Conley, *Fun. Neurobio. of Aging*, 2001

<sup>3</sup> Li et al., *Med Sci Sports & Exercise*, 2017

<sup>4</sup> Mohien et al., *eLife*, 2019

<sup>5</sup> Goodpaster et al., *J Gerontology*, 2006

## Strength decline outpaces reductions in muscle mass with aging<sup>1</sup>

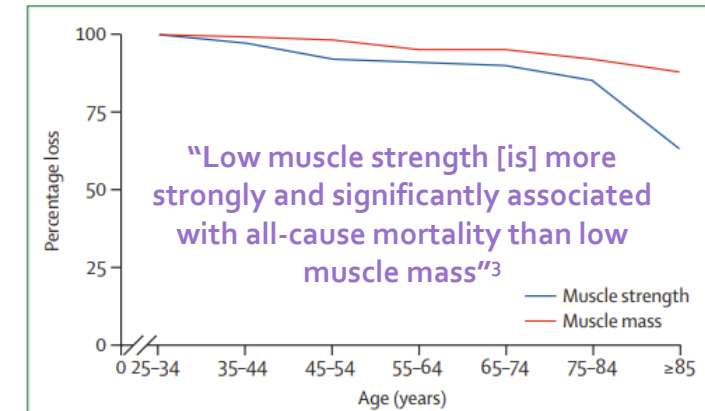
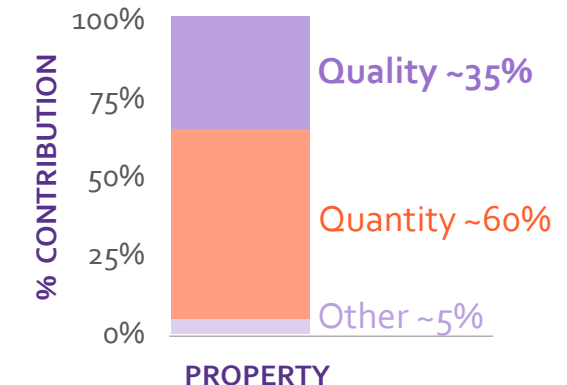


Figure 1: Percentage loss of muscle mass and muscle strength with age in men

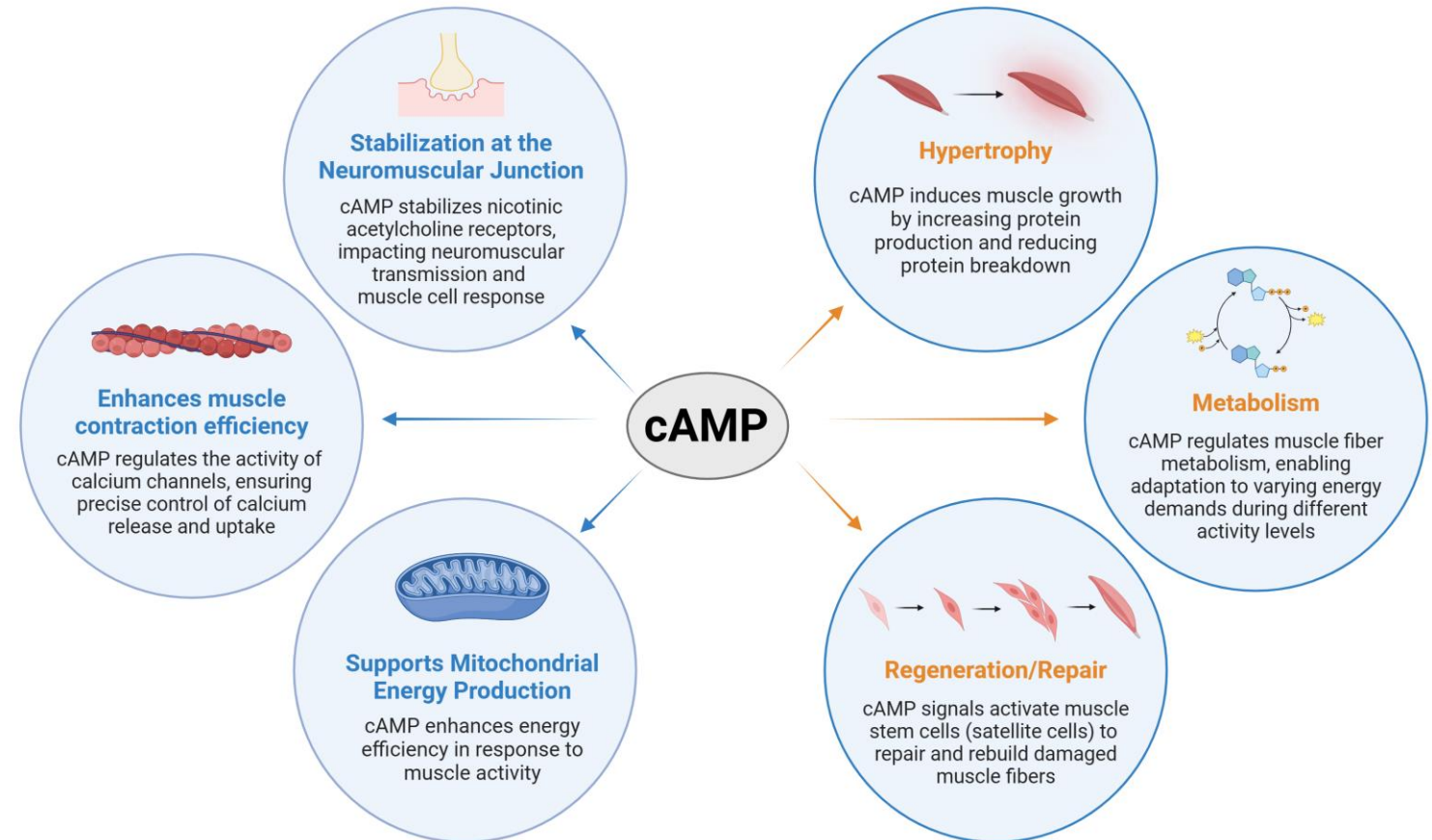
## Reduction in Muscle Quality Contributes Significantly to Loss in Muscle Force<sup>2</sup>



## 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<sup>2</sup>**
- **Increasing cAMP in muscle improves function in preclinical studies<sup>2</sup>**

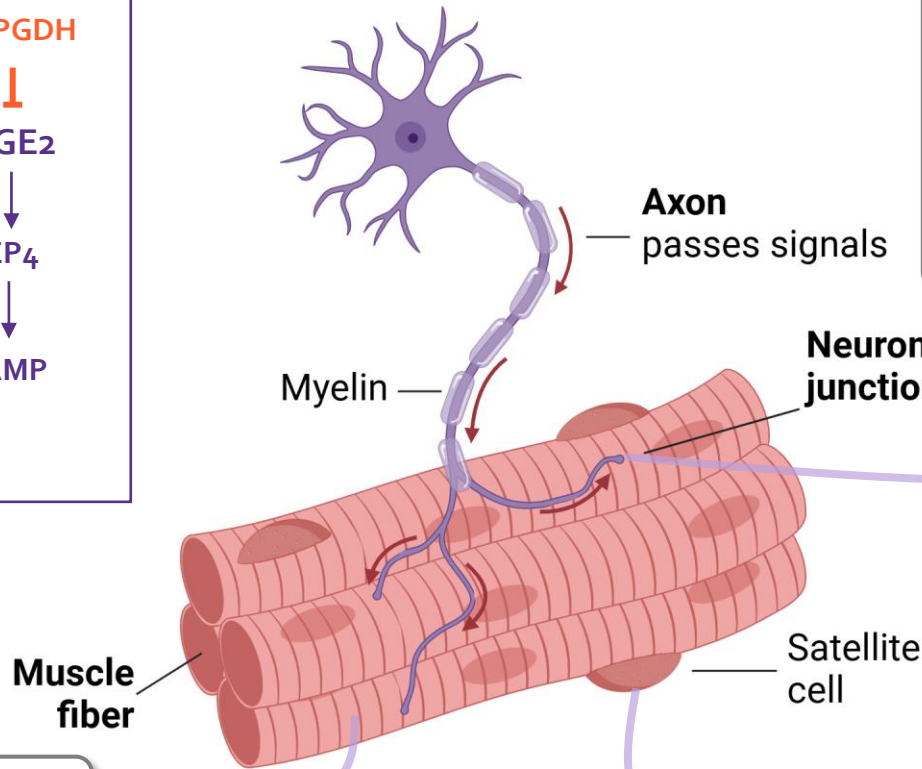
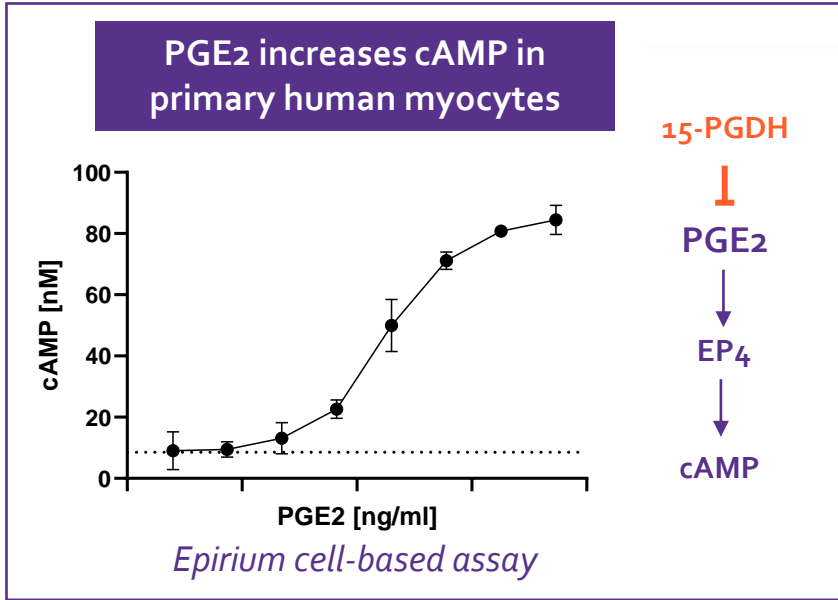
## Multiple Beneficial Effects of cAMP on Muscle Function<sup>1</sup>



<sup>1</sup>Berdeaux et al., *Am J Phys Endo Met*, 2012

<sup>2</sup>Marco-Bonilla et al., *Int J Mol Sci*, 2023

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



## 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<sup>1†</sup>, Yu Xin Wang<sup>1,2+\*</sup>, Elena Monti<sup>1</sup>, Shiqi Su<sup>1</sup>, Peggy Kraft<sup>1</sup>, Minas Nalbandian<sup>1</sup>, Ludmila Alexandrova<sup>3</sup>, Joshua R. Wheeler<sup>4,5</sup>, Hannes Vogel<sup>4,5</sup>, Helen M. Blau<sup>1\*</sup>

## Muscle Intrinsic Effects

RESEARCH ARTICLE



AGING

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

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

## Stem-Cell Proliferation

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

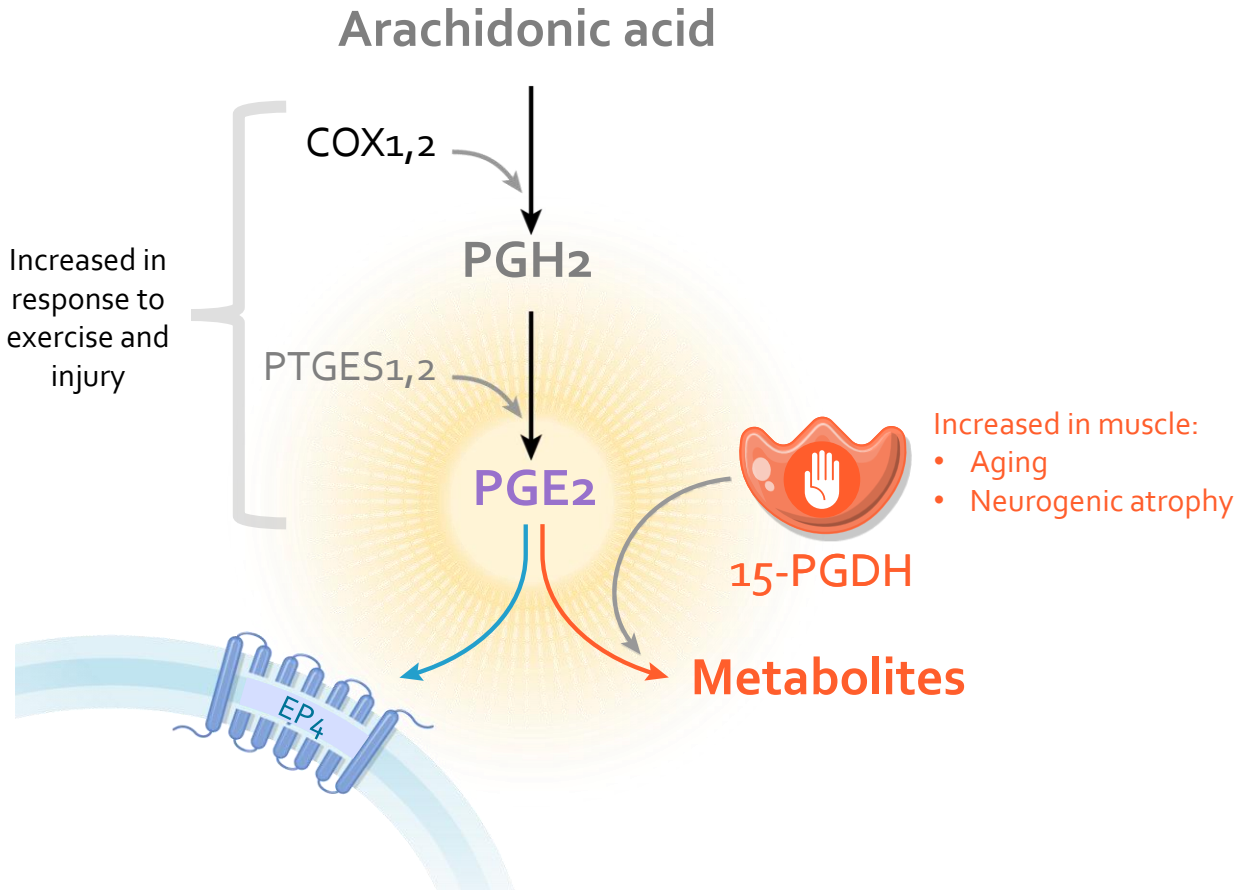
Andrew T. V. Ho<sup>a,1</sup>, Adelaida R. Palla<sup>a,1</sup>, Matthew R. Blake<sup>a</sup>, Nora D. Yucel<sup>a</sup>, Yu Xin Wang<sup>a</sup>, Klas E. G. Magnusson<sup>a,b</sup>, Colin A. Holbrook<sup>a</sup>, Peggy E. Kraft<sup>a</sup>, Scott L. Delp<sup>c</sup>, and Helen M. Blau<sup>a,2</sup>

<sup>a</sup>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; <sup>b</sup>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 <sup>c</sup>Department of Bioengineering, Stanford University School of Medicine, Stanford, CA 94305

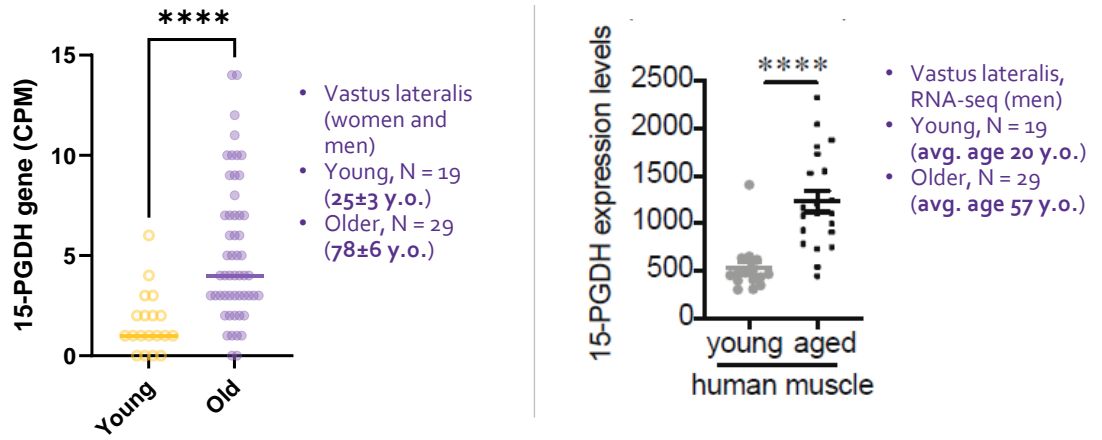
# 15-PGDH, a Gerotherapeutic Target that Reduces PGE2 Levels, is Upregulated in Aged Muscle



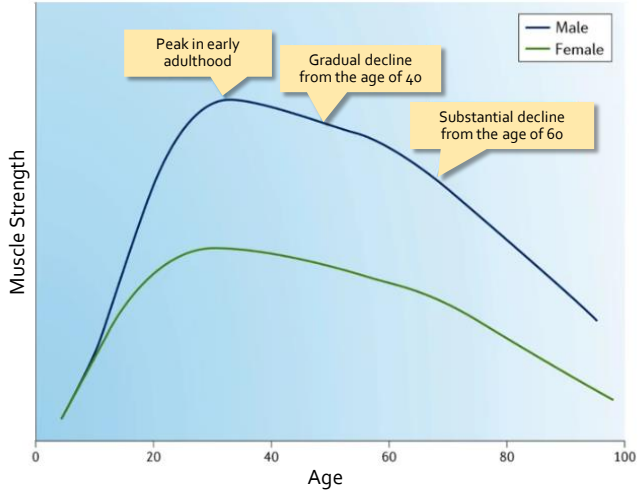
## 15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2



## 15-PGDH gene expression Elevated in aged human muscle<sup>3,4</sup>



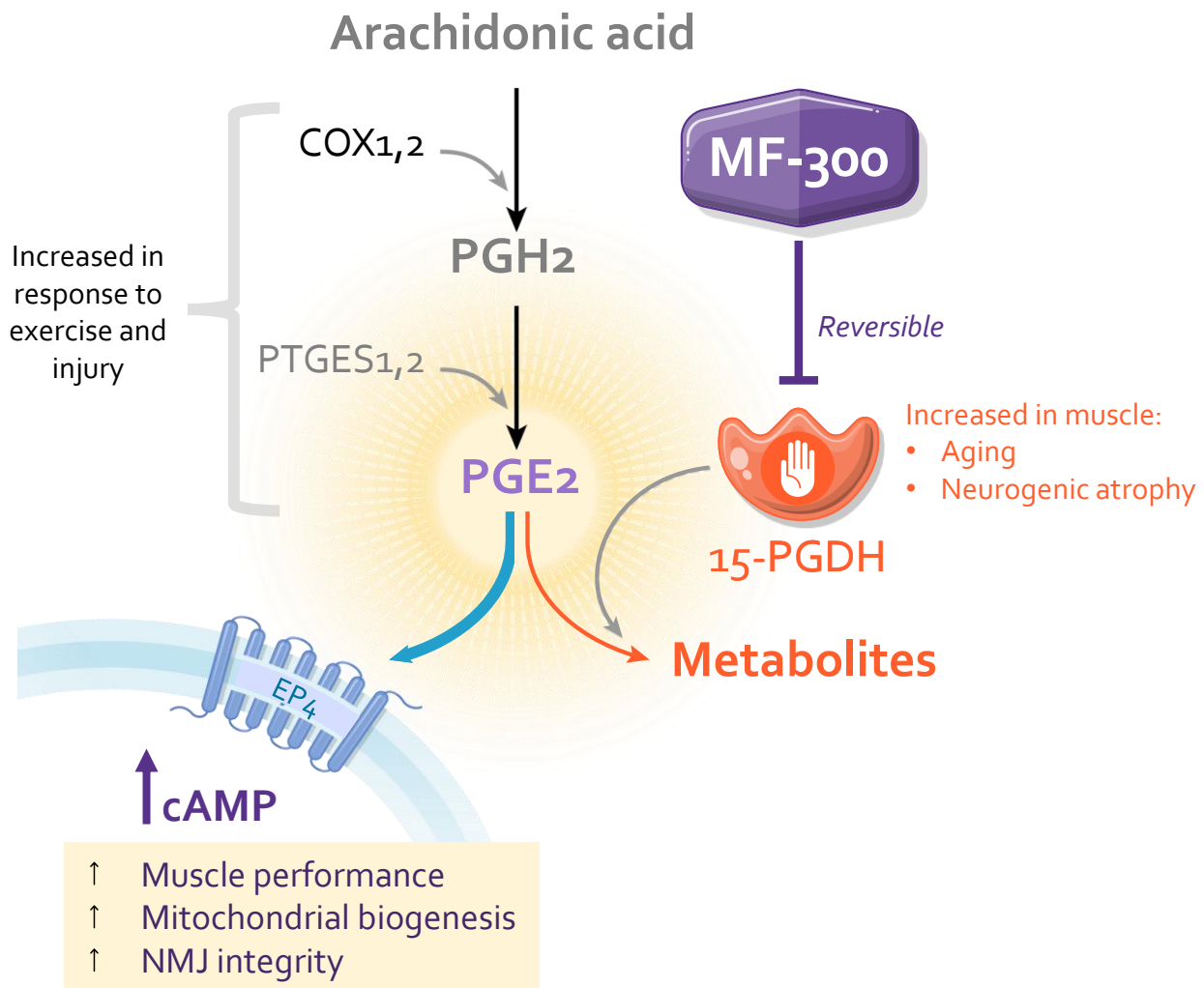
### Grip strength, a predictor of sarcopenia risk, declines with age<sup>5</sup>



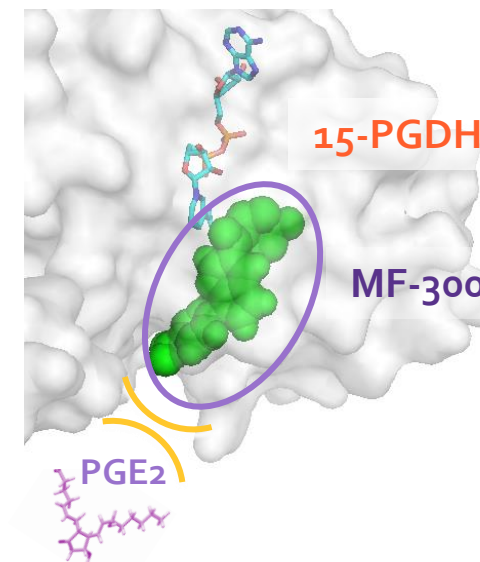
<sup>3</sup> GEO167186, <sup>4</sup> Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), <sup>5</sup> Dennison et al., *Nat Rev Rheum* 2017

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

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



MF-300 reversibly occupies the PGE<sub>2</sub> binding site of 15-PGDH



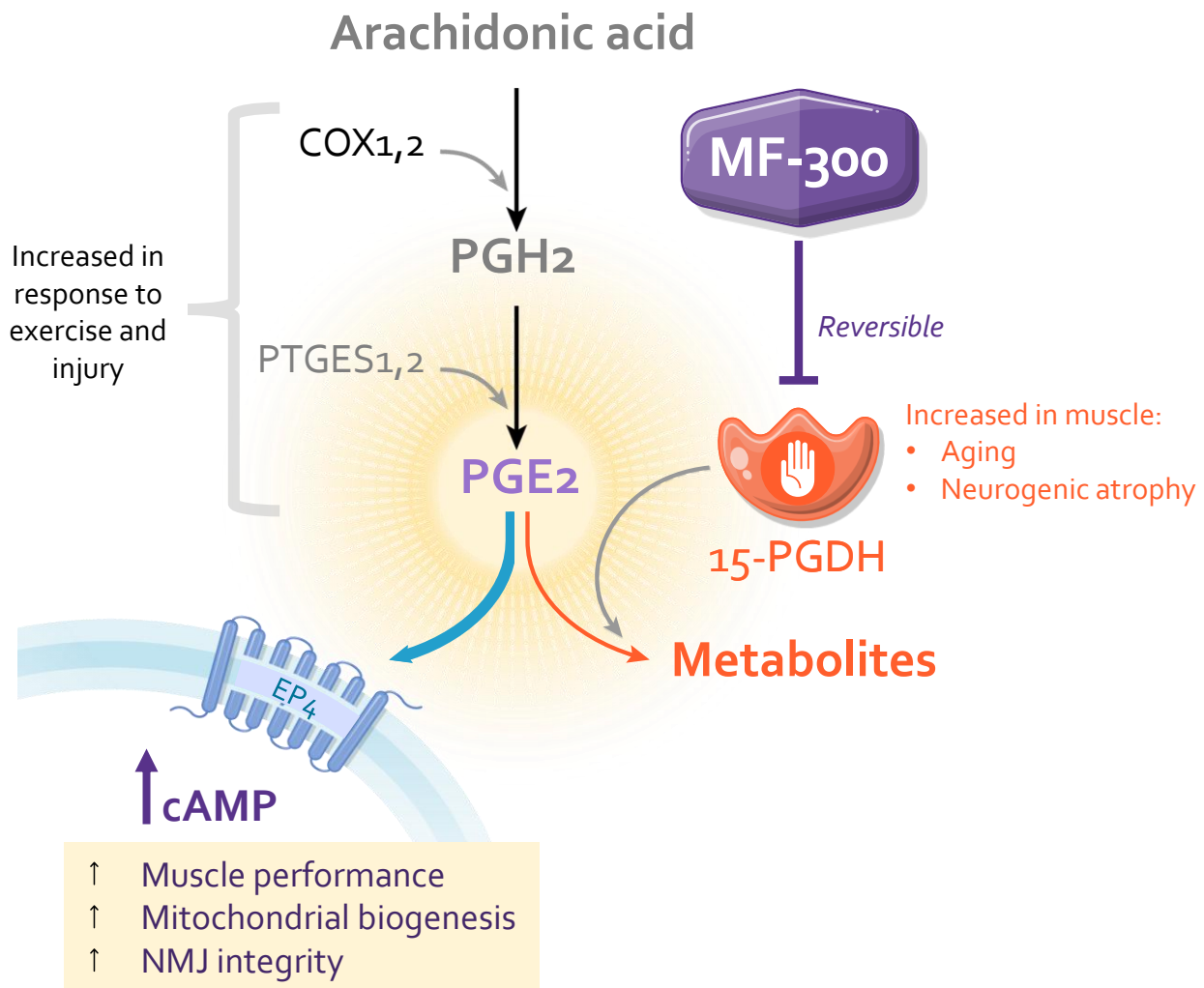
MF-300 potent inhibition of 15-PGDH across species

Species	15-PGDH % Identity to Human	MF-300 IC <sub>50</sub> (nM) (Biochemical assay)
Human	100%	0.8
Dog	94%	1.5
Mouse	89%	1.0
Rat	88%	4.0

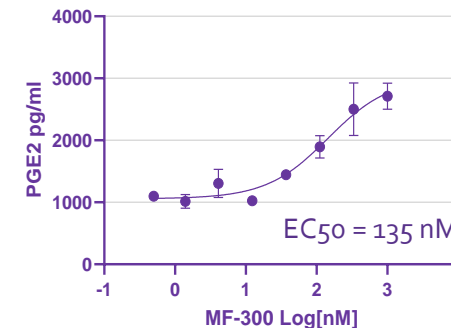


# MF-300: Epirium's Therapeutic Strategy to Increase PGE2 Levels in Aged Muscle

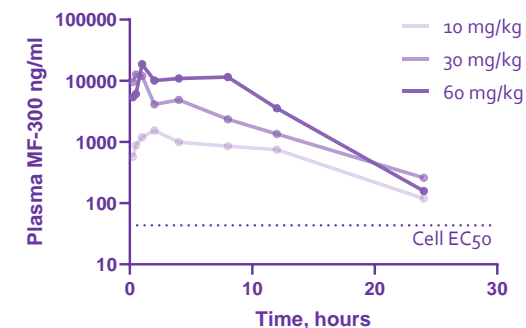
**MF-300**  
Inhibits 15-PGDH to increase levels of PGE2



MF-300 increases PGE2 in cell-based assay

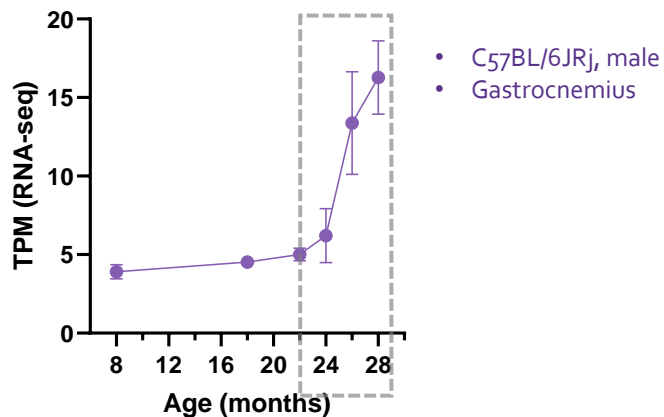


MF-300 is bioavailable and stable in vivo (oral administration)

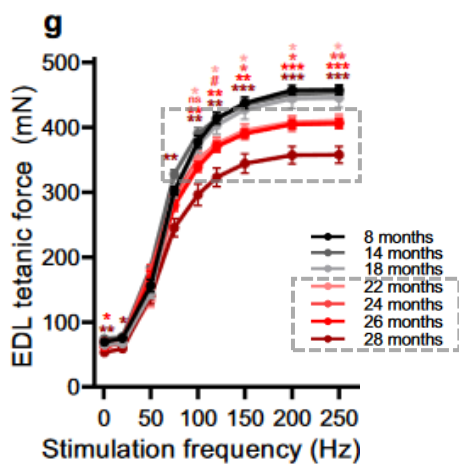


## 15-PGDH gene expression Elevated in aged mouse muscle

Muscle 15-PGDH gene expression (*Hpgd*) increases during aging<sup>1</sup>

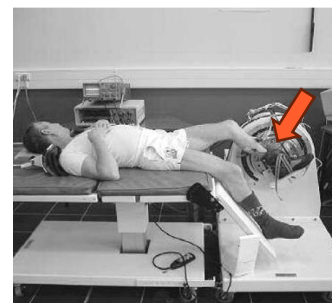


Muscle strength declines during window of elevated *Hpgd*<sup>2</sup>

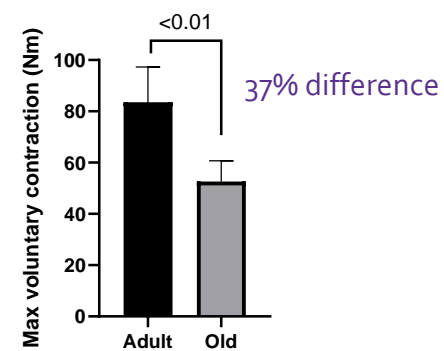
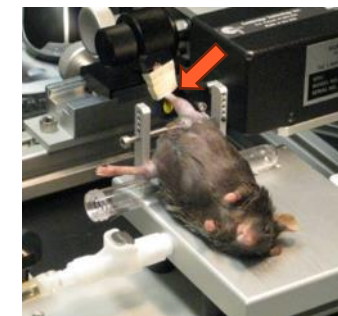


## Modeling age-induced muscle weakness with isometric plantar flexion in mice

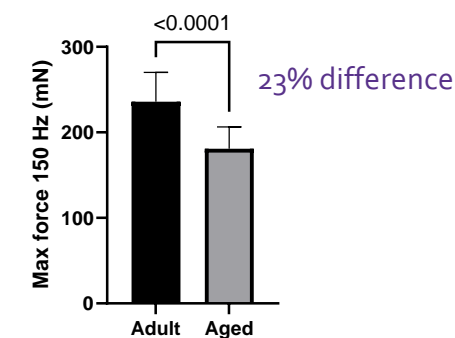
Maximal voluntary contraction



Electrical nerve-evoked contraction



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



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

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

Mouse image:  
<https://aurorascientific.com/>

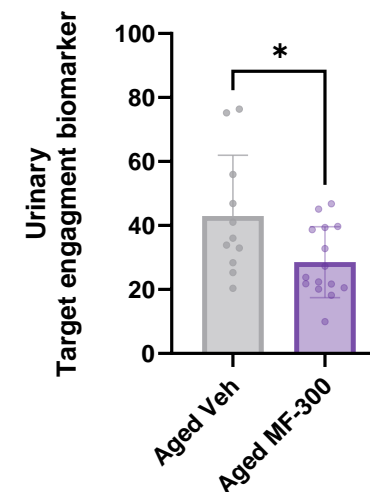
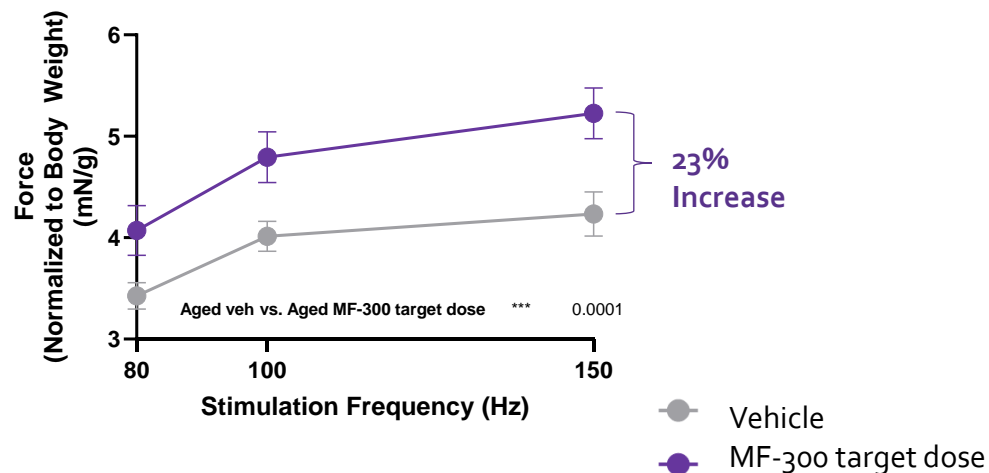
<sup>1</sup> <https://sarcoatlas.scicore.unibas.ch/> GSE145480, <sup>2</sup> Borsch et al., *Com Bio* 2021

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

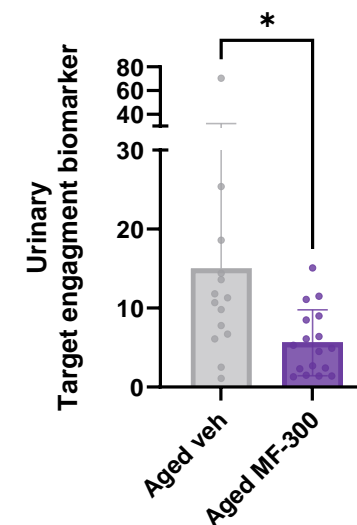
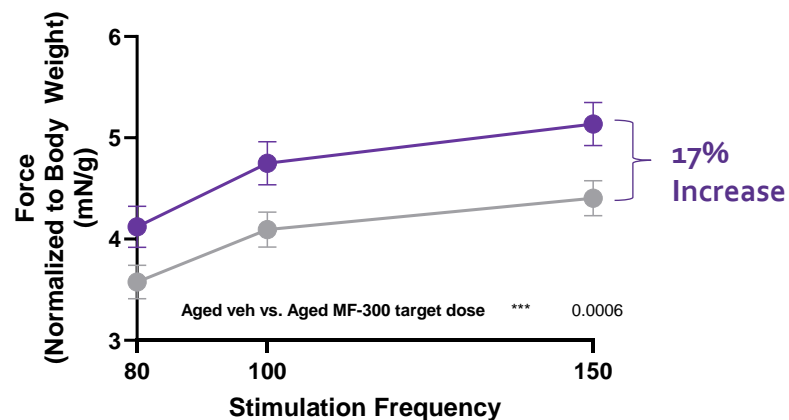
## MF-300 Increased muscle force in aged mice

## MF-300 Reduced urinary metabolite of PGE<sub>2</sub>

### Study 1



### Study 2



# 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....”

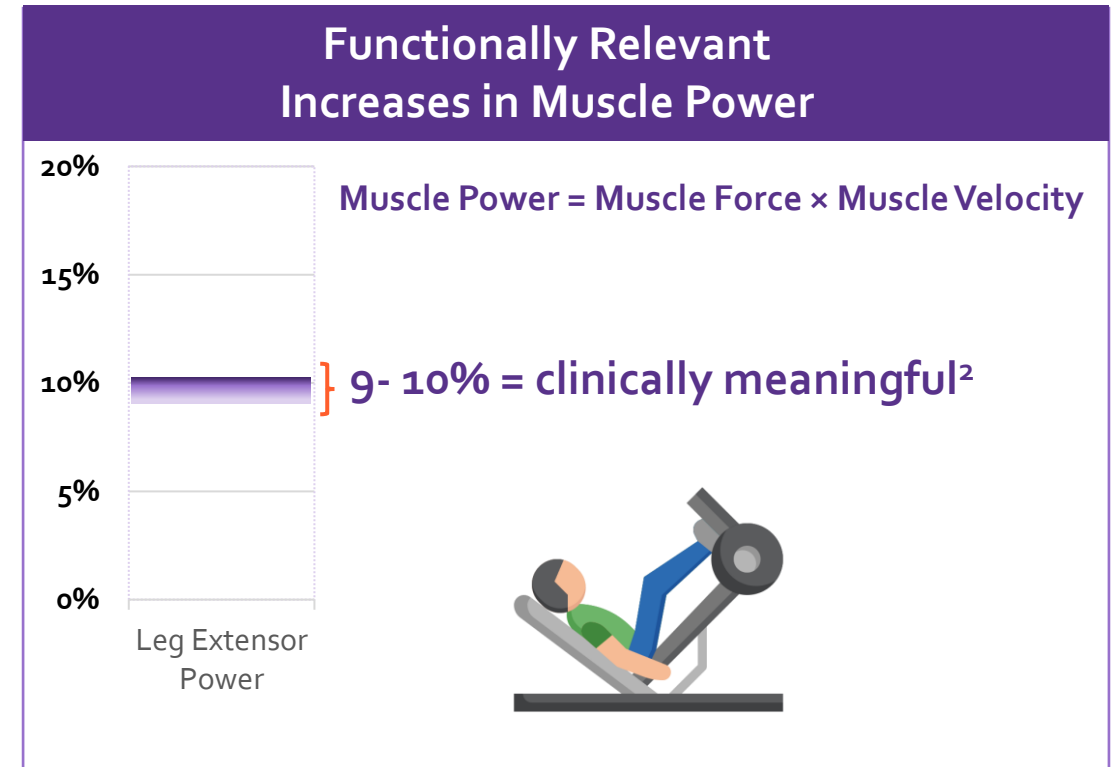
*-Older Adults' Perspective of Independence Through Time: Results of a Longitudinal Interview Study<sup>1</sup>*

“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*

<sup>1</sup>Taylor et al, *The Gerontologist*, 2023

<sup>2</sup>Kirn et al., 2016



### 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

## 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

\*Short Physical Performance Battery

## Ph 1 SAD/MAD Study Ongoing & On Track for Topline Results Q3 '25

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

## Ph 1 Target Engagement Biomarkers

- Urine: PGE-MUM, PGA-M, Bicyclo-PGE<sub>2</sub>;
  - Plasma: PGE<sub>2</sub>, 15-Keto-PGE<sub>2</sub>, Bicyclo-PGE<sub>2</sub>
- 

## Finalization of 24-week Phase 2 Efficacy Endpoints & Design

- Disease Response Pharmacodynamic Biomarkers validation ongoing
  - Type D meeting with FDA Endpoints Response & Guidance on Endpoints post Ph 1
- 

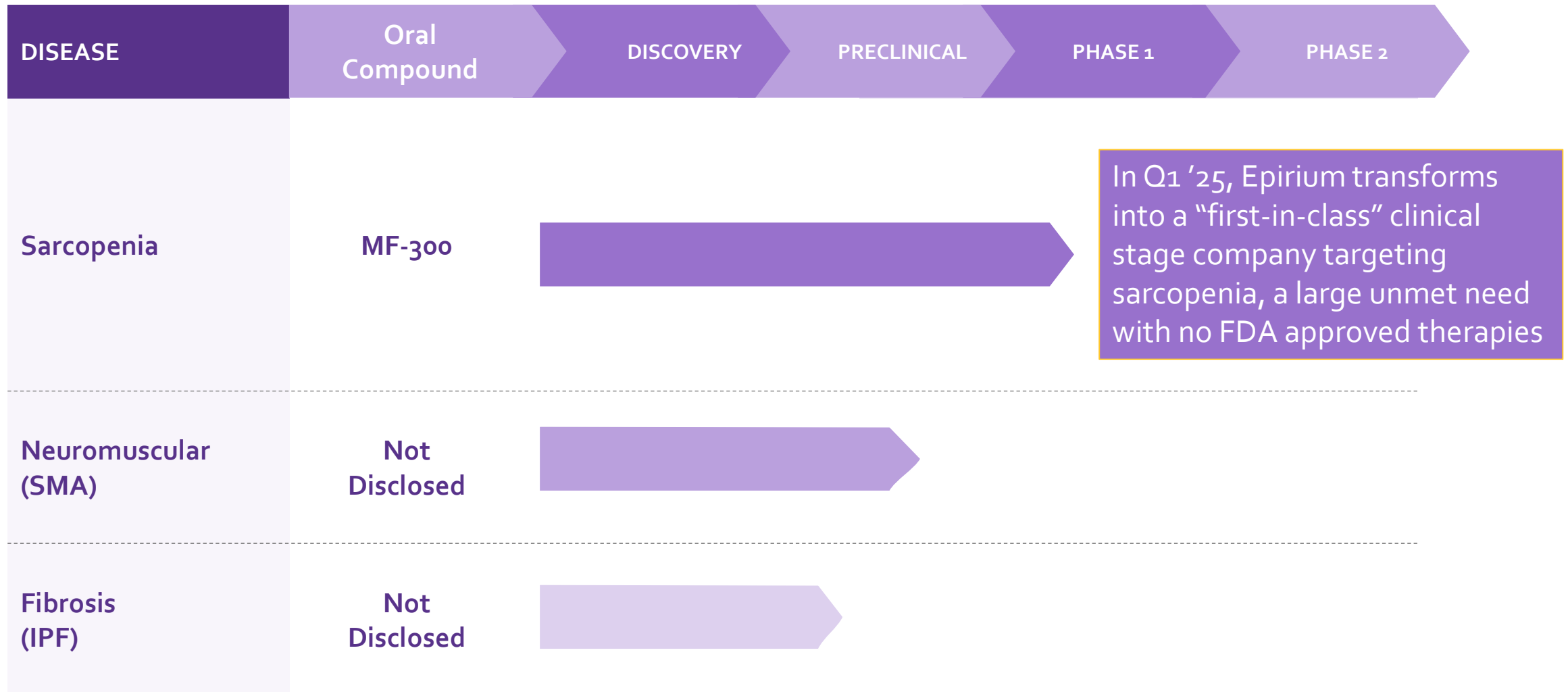
## Enhancing MF-300's Profile in Sarcopenia

- ICFSR Two Poster Presentations, Invitation-only Meeting on Clinical Endpoints Mar. '25
  - Speaker at Boston Pepper Lecture Series Mar '25
- 

## Opportunistic SMA Study in Delta7 mice Results end of Q2 '26:

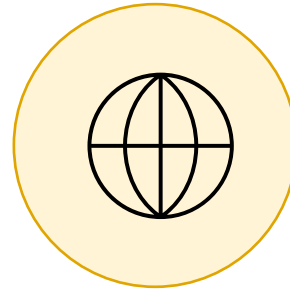
- MF-300 in combination with Scholar Rock's apitegromab
  - Success provides additional indications available to pursue
-

# Epirium Platform: Addressing High Value Indications with Unmet Medical Needs

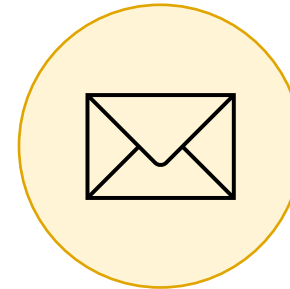




Thank you!



[www.epirium.com](http://www.epirium.com)



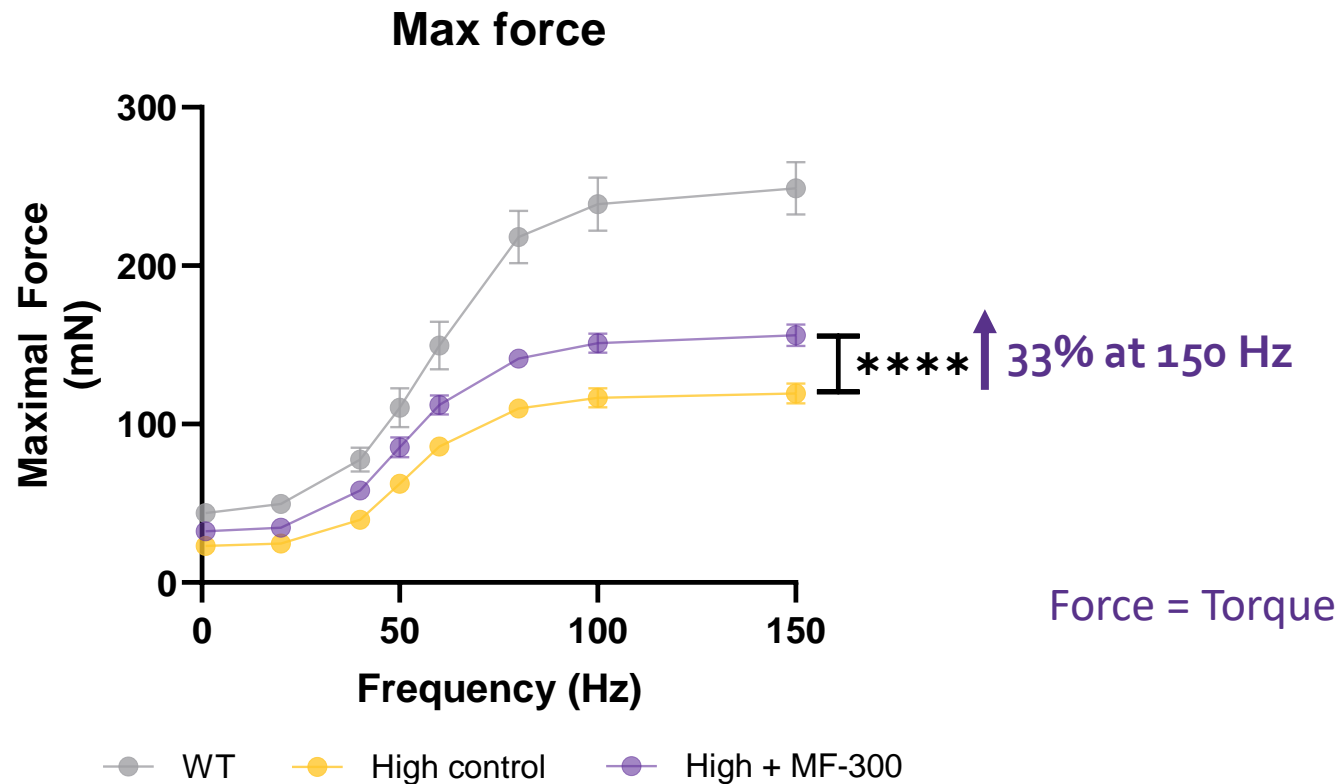
[info@epirium.com](mailto:info@epirium.com)



## Supplemental Information:

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

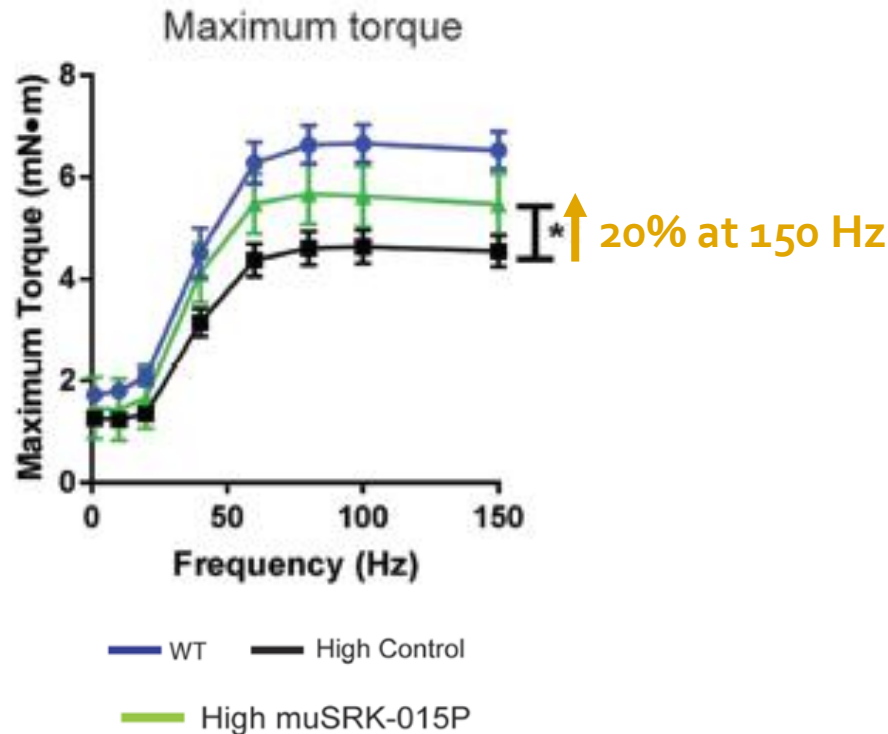
## MF-300 in mouse $\Delta 7$ High/High



# MYOLOGICA

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

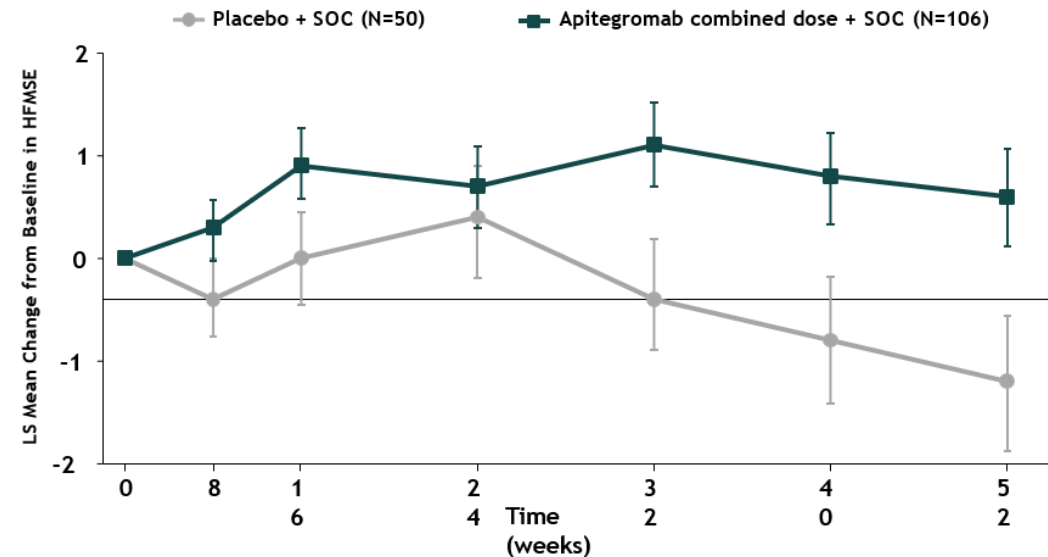
## mSRK-015P in mouse $\Delta 7$ High/High



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

## Apitegromab in SMA + SOC (Ph 3 SAPPHERE)

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



Change from Baseline in HFMS Total Score

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

Primary Analysis

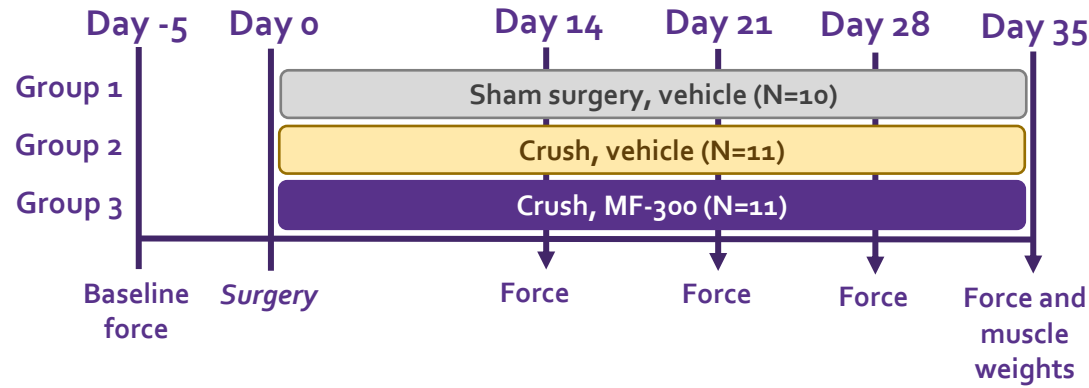
Achieved Statistical Significance

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

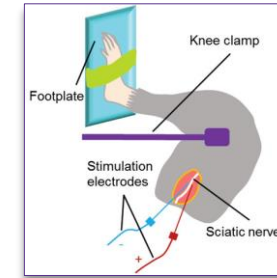
Sciatic nerve crush injury in healthy mice



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

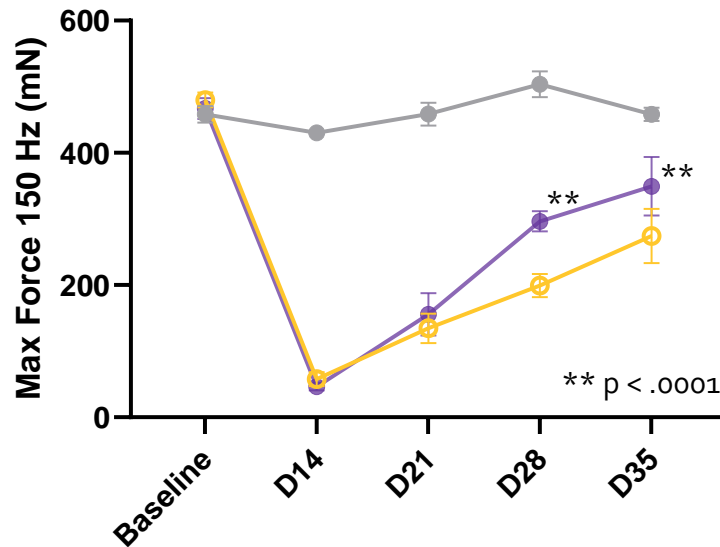


Plantar Flexor Force Measured

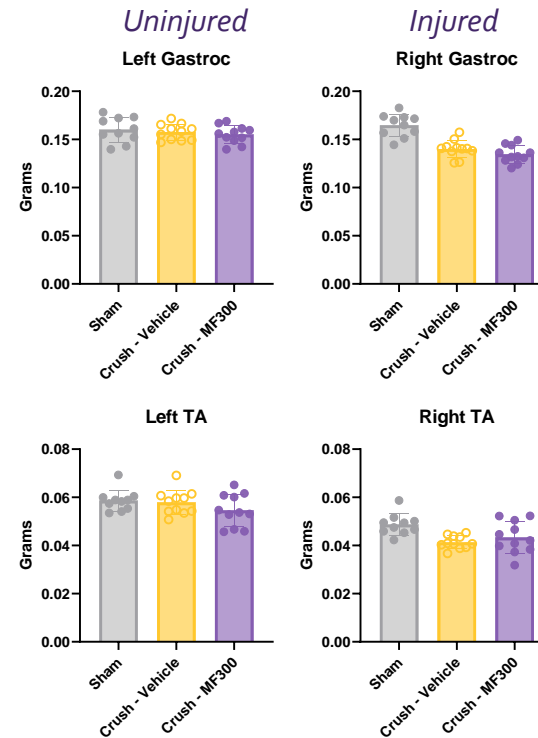


- Sciatic nerve stimulation
- Muscle torque = force x moment arm
- Plantar flexor muscle group (GA/Sol)

## Accelerated recovery of force



## MF-300 did not increase muscle mass



CRO: Myologica