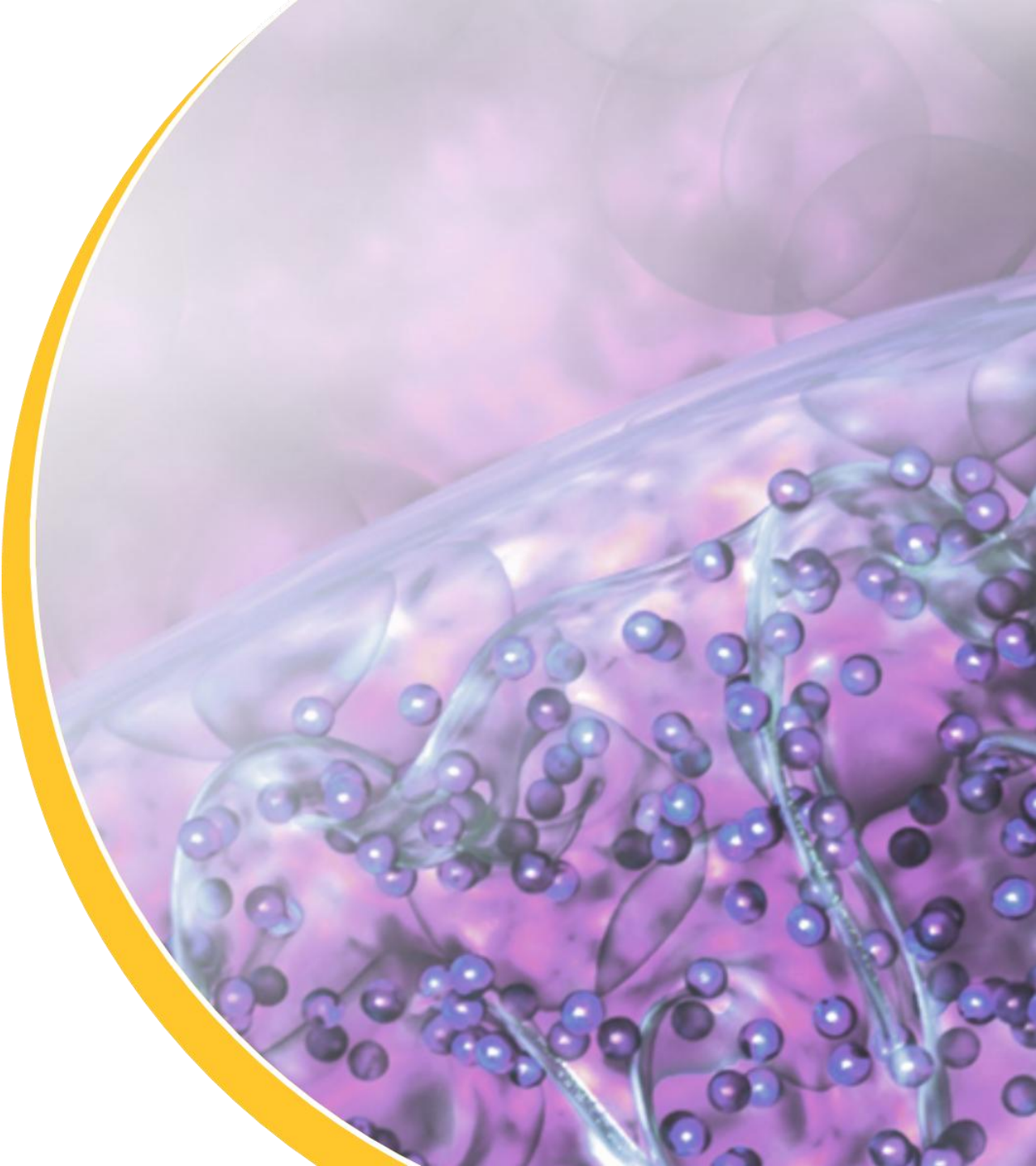




## **Oral 15-PGDH Inhibitor Platform:**

Leveraging PGE<sub>2</sub> Signaling to Treat Sarcopenia, Neuromuscular & Inflammatory Diseases (IBD):

- **MF-300 in Phase 2b Start-up for Sarcopenia**



# Experienced Team with a Demonstrated Track Record of Success



## Epirium Leadership Team



### Alex Casdin, CEO

30+ 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)



### Leigh MacConell, Ph.D. Chief Development Officer

25 years drug development, primarily in metabolic and liver disease

Led multiple drug approvals including first in class for T<sub>2</sub>DM (GLP-1) and primary biliary cholangitis (PBC)

Collaborated with FDA to define approval pathways for disease areas without regulatory precedence, including PBC & MASH



### Eric Miller, CFO

Head Finance, Synthorx (acquired by Sanofi) Corp. Controller & Head FP&A, Acadia Pharm.

Cadence Pharm. (acquired by Mallinckrodt)

## Consultant Advisors



### Daniel Cooper, M.D. Medical Lead

Over 20 years in drug development

Formerly VP Pharmacovigilance Orexigen, Affymax; Clinical and Safety Scientist roles at Roche, Johnson & Johnson

Multiple successful NDAs supporting pre- and post-marketing approvals



### 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

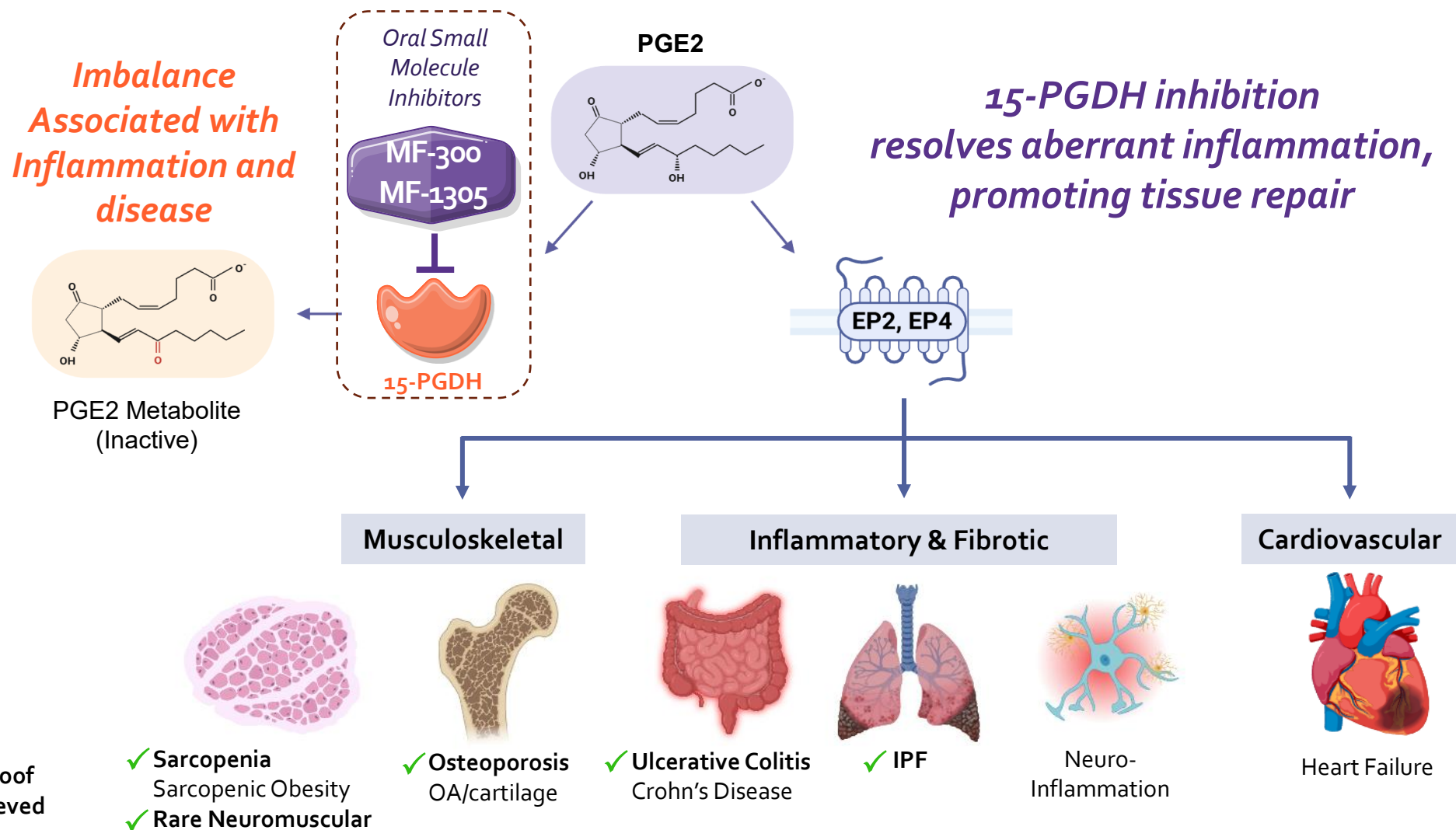


### Lois Lee, Pharm.D. Clinical Development

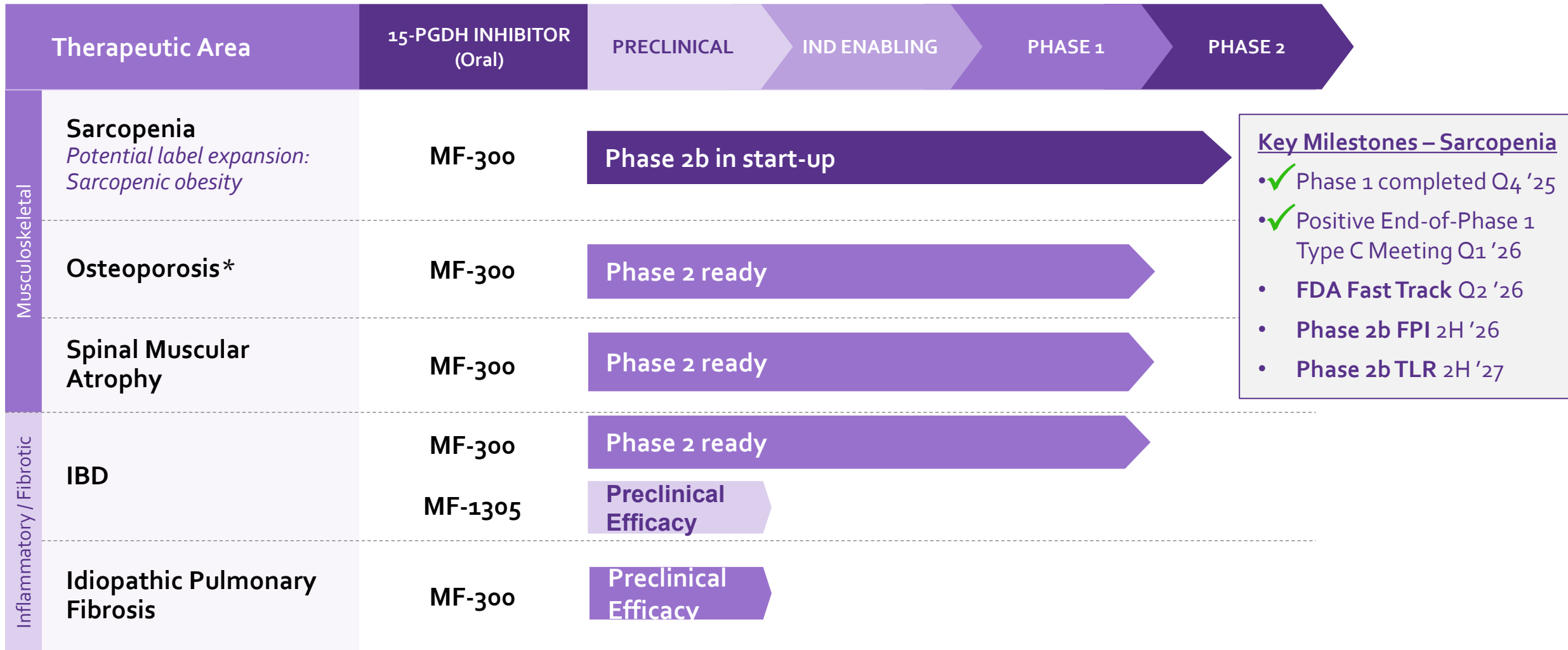
20+ years of industry experience leading early- and late-phase drug development across multiple TAs including liver, metabolic, and neurodegenerative diseases.

Extensive experience in collaborating with FDA and EMA on indications lacking regulatory precedent including MASH, MASH cirrhosis, and Alexander disease

Inhibiting 15-PGDH to leverage the potential of prostaglandin E2 (PGE<sub>2</sub>) to promote tissue function



# Epirium 15-PGDH Inhibitor Platform: "Pipeline in Mechanism"



\*Human proof of concept (bone biomarkers & bone mineral density) to be generated in Sarcopenia Phase 2b study

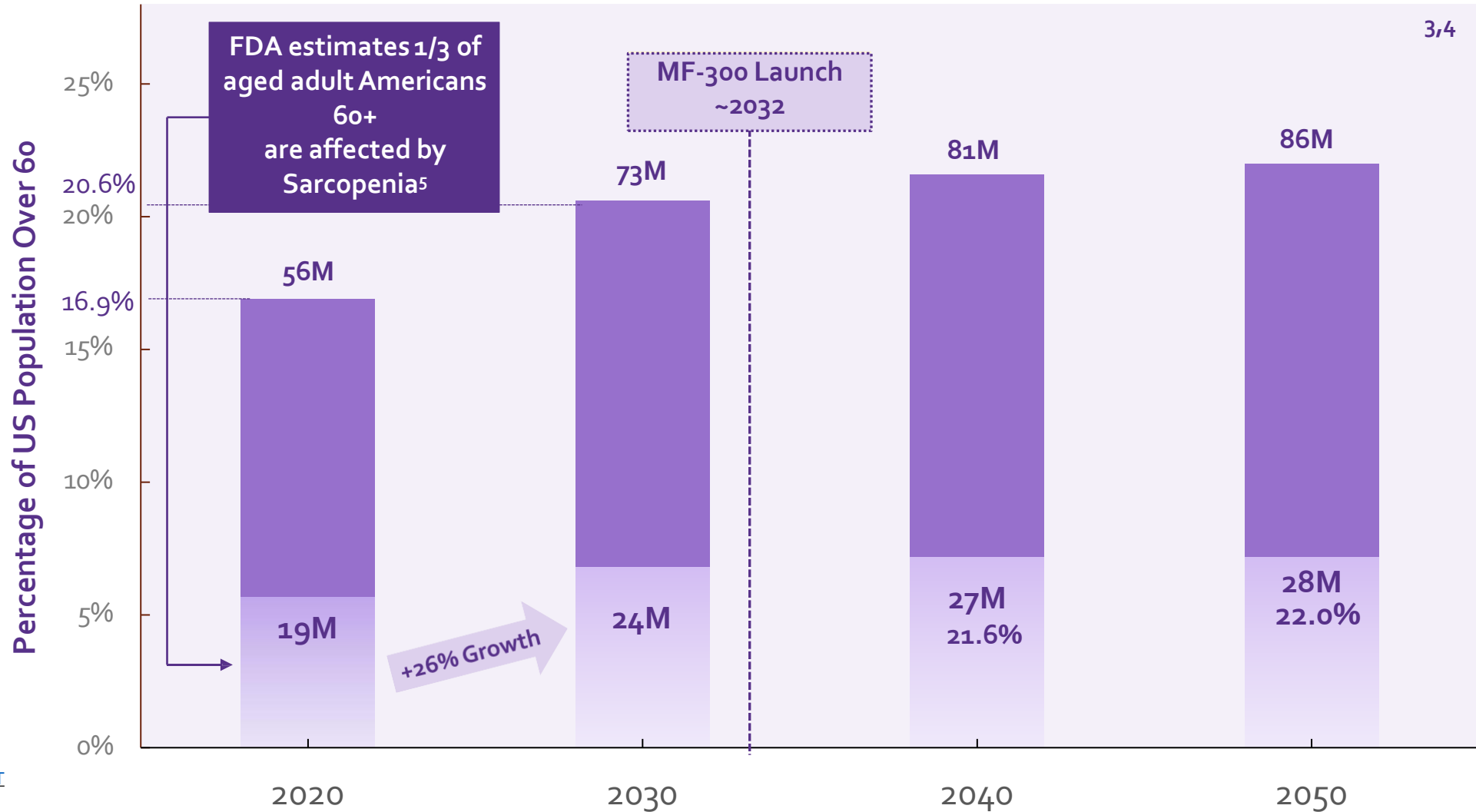
# Sarcopenia: Large and Growing Unmet Medical Need w/ No FDA Approved Therapy

Current U.S. Healthcare Sarcopenia Spending Estimated >\$40 Billion Annually<sup>1</sup>

**Dependence**  
Increased risk losing independence

**Falls**  
Increased Morbidity & Mortality<sup>2</sup>

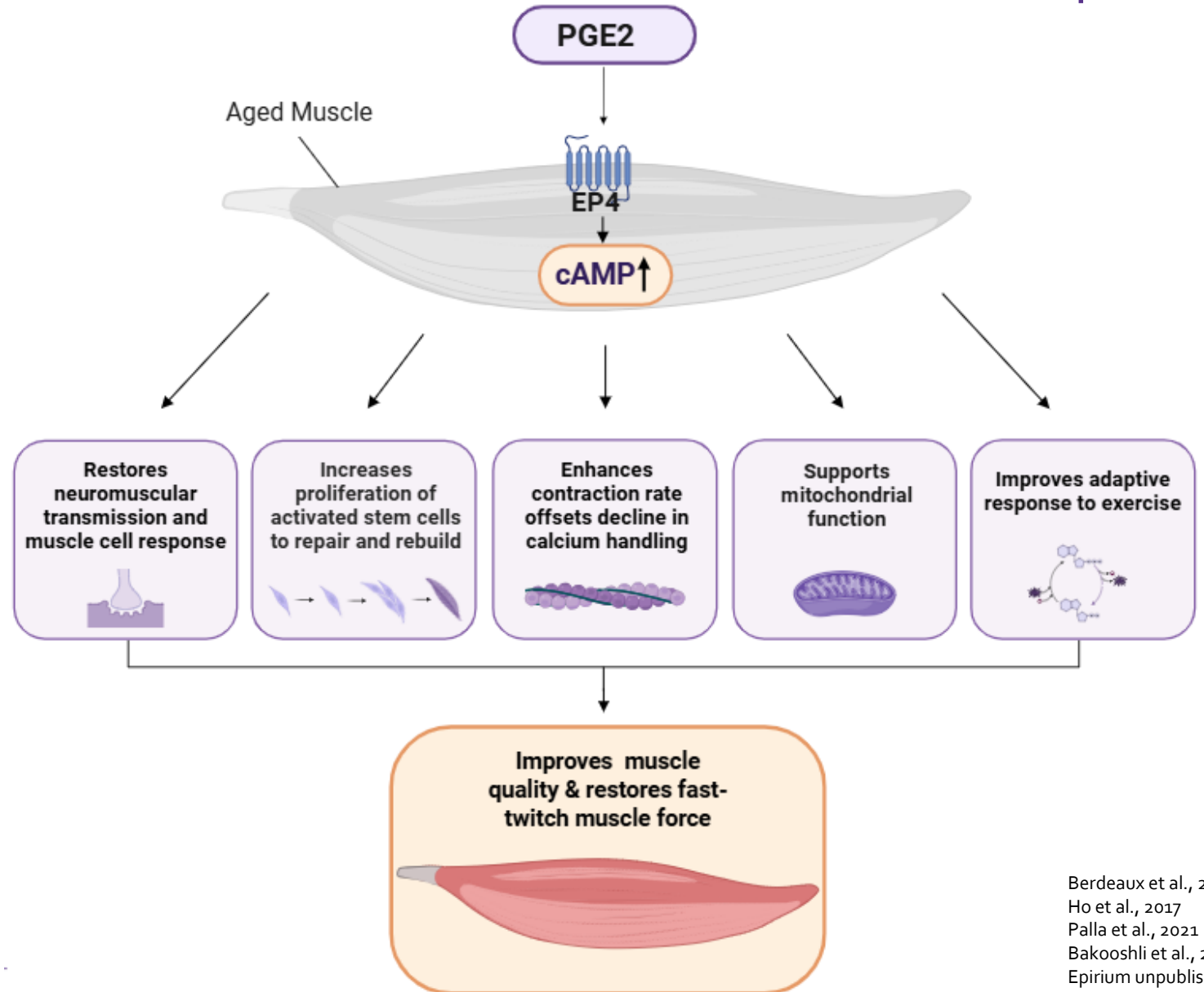
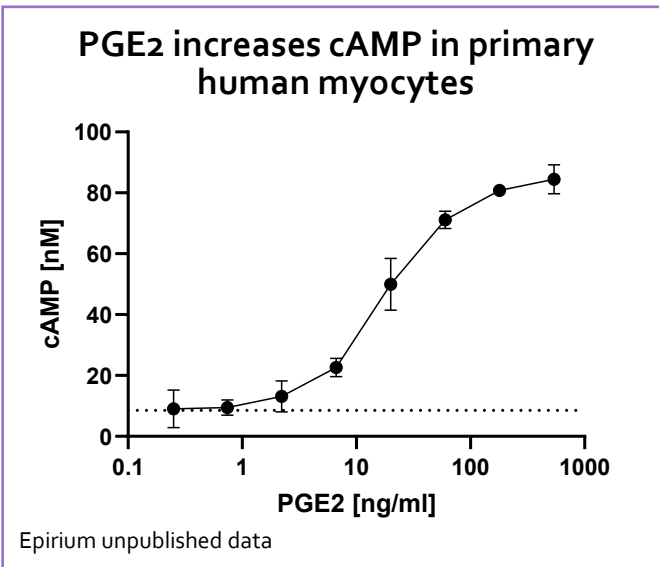
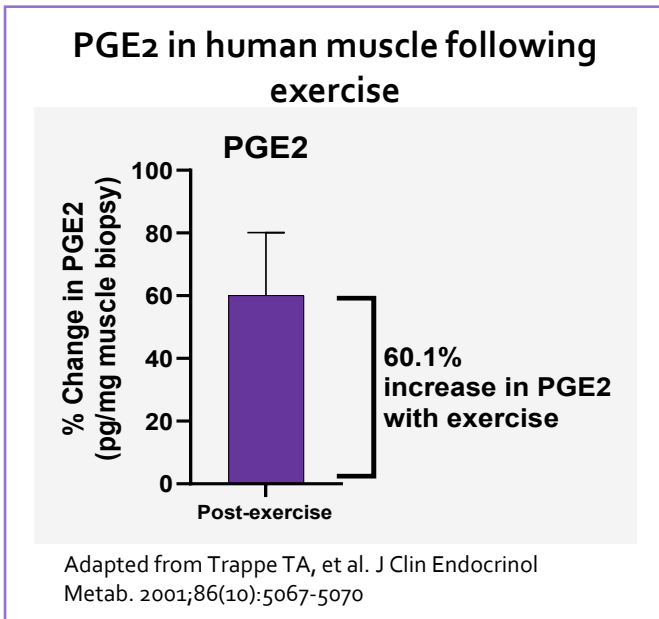
**Mortality**  
Increased risk of death<sup>2</sup>



U.S. Population est. 331M

1. Goates S, et al. J Frailty Aging. 2019.
2. [www.agingresearch.org](http://www.agingresearch.org). Sarcopenia Facts and Figures
3. Burns ER, J Safety Res. 2016.
4. Papadopoulou SK. Nutrients. 2020.
5. <https://www.fda.gov/files/about%20of%20fda/published/T%20he-Voice-of-the-Patient--Sarcopenia.pdf>

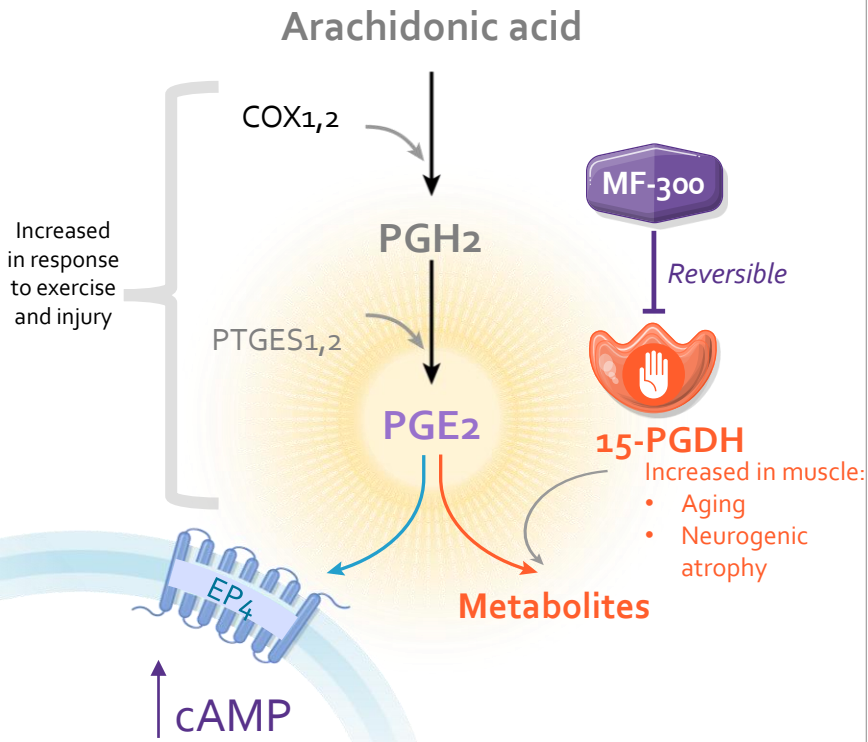
# PGE2-EP4 Signaling Elevates cAMP to Promote Muscle Function



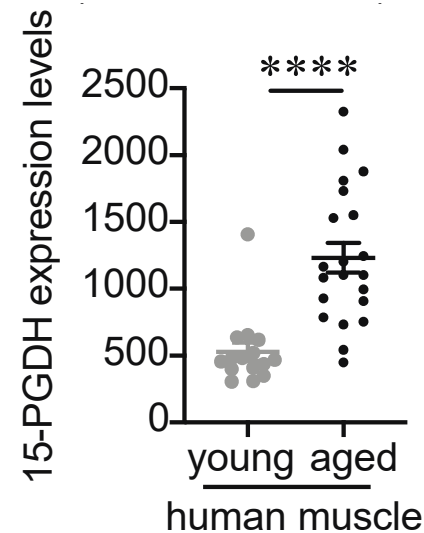
Berdeaux et al., 2012  
 Ho et al., 2017  
 Palla et al., 2021  
 Bakooshli et al., 2023  
 Epirium unpublished data

# 15-PGDH, an Enzyme that Degrades PGE<sub>2</sub>, is Upregulated in Aged Muscle

**15-Hydroxyprostaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE<sub>2</sub>**

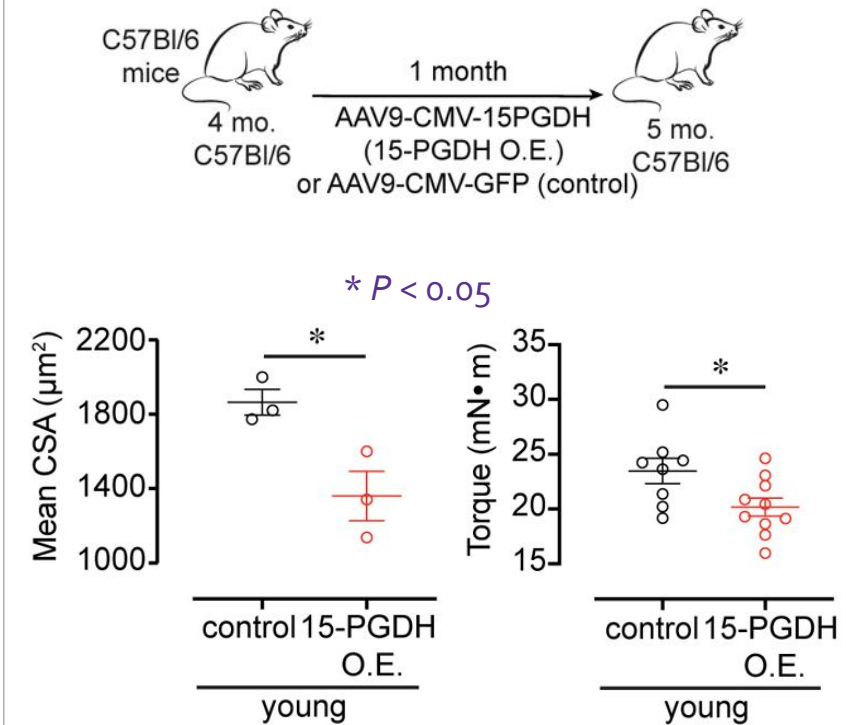


**15-PGDH expression Elevated in aged human muscle<sup>1</sup>**



- Vastus lateralis (microarray)
- Younger, N=15 (25±3 y.o.)
- Older, N=21 (78±6 y.o.)
- \*\*\*\* P < 0.0001

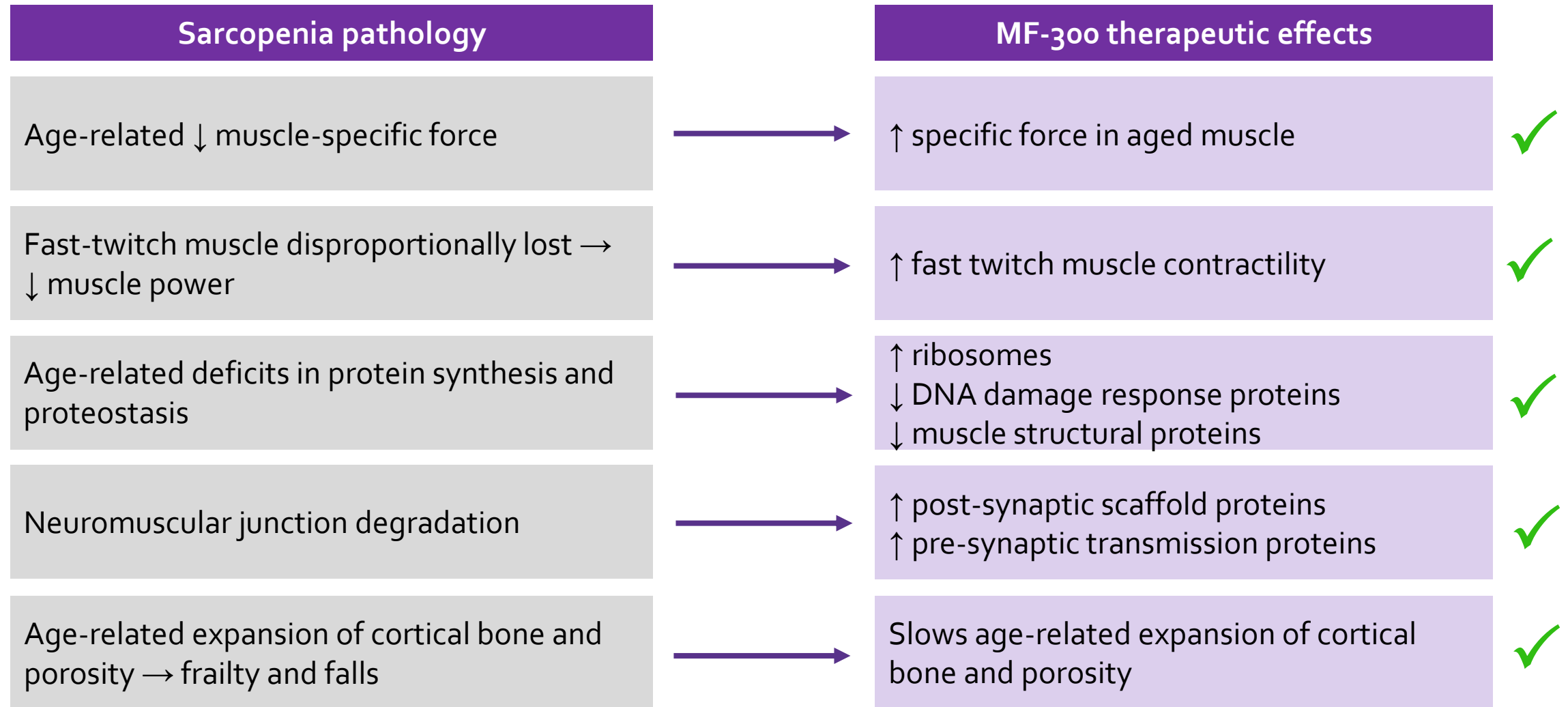
**15-PGDH overexpression (O.E.) Reduces myofiber cross-sectional area (CSA) and muscle force<sup>2</sup>**



cAMP, cyclic adenosine monophosphate; COX<sub>1,2</sub>, cyclooxygenase enzymes 1 and 2; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; PGH<sub>2</sub>, prostaglandin H<sub>2</sub>; PTGES<sub>1, 2</sub>, prostaglandin E synthase 1,2; y.o., years old

<sup>1</sup> Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), <sup>2</sup> Palla et al., *Science* 2021

# Improving Muscle Quality (Intrinsic Strength) Addresses High Unmet Need in Sarcopenia



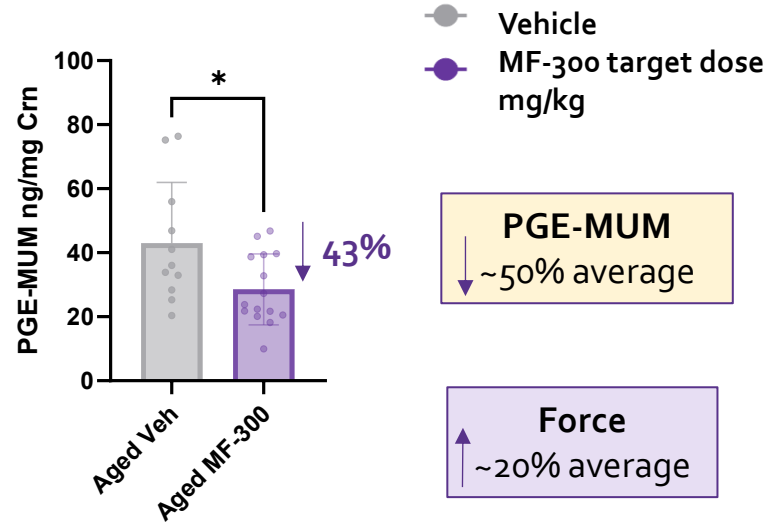
↑ urinary PGE2 levels and ↓ PGE-MUM demonstrates target engagement and use as translational biomarkers

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

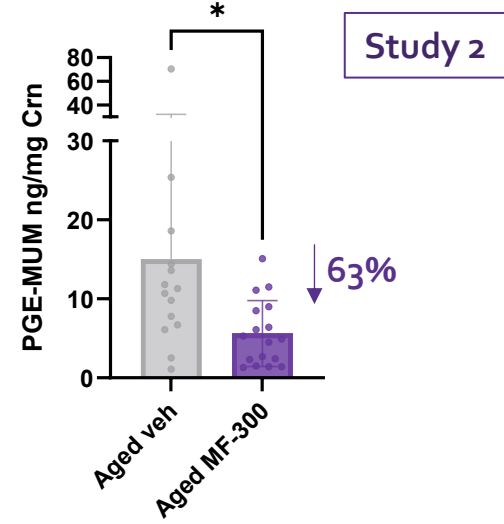
## Preclinical Sarcopenia Studies

**MF-300 target dose**  
Increased muscle force and reduced PGE<sub>2</sub> Metabolite in aged mice

Study 1

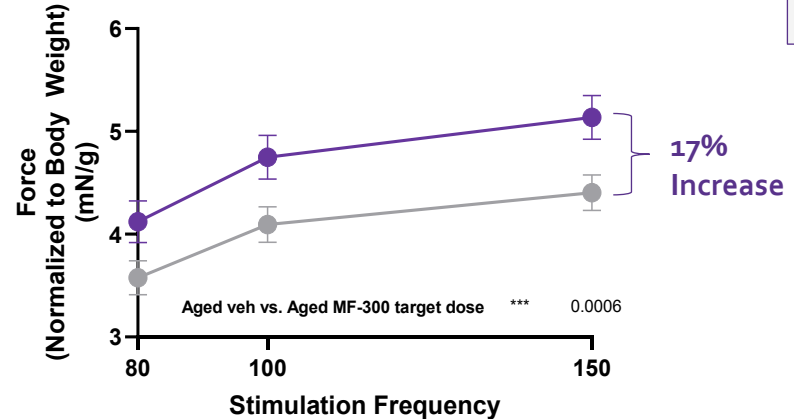
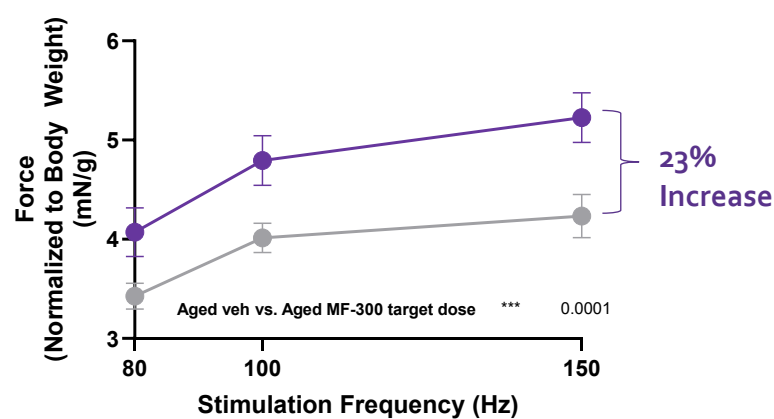


Study 2



**Target Engagement Biomarker**

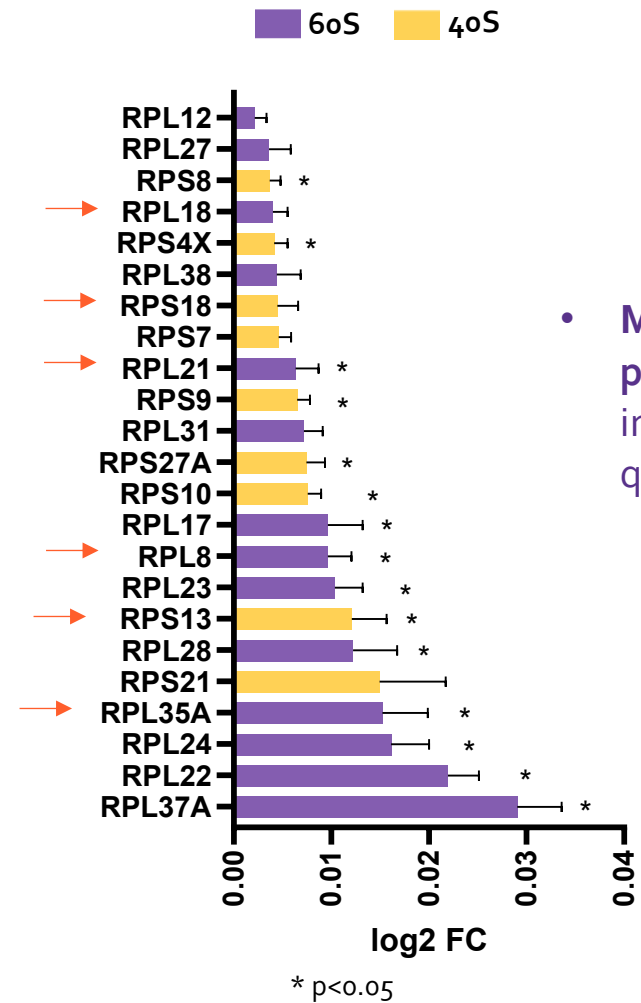
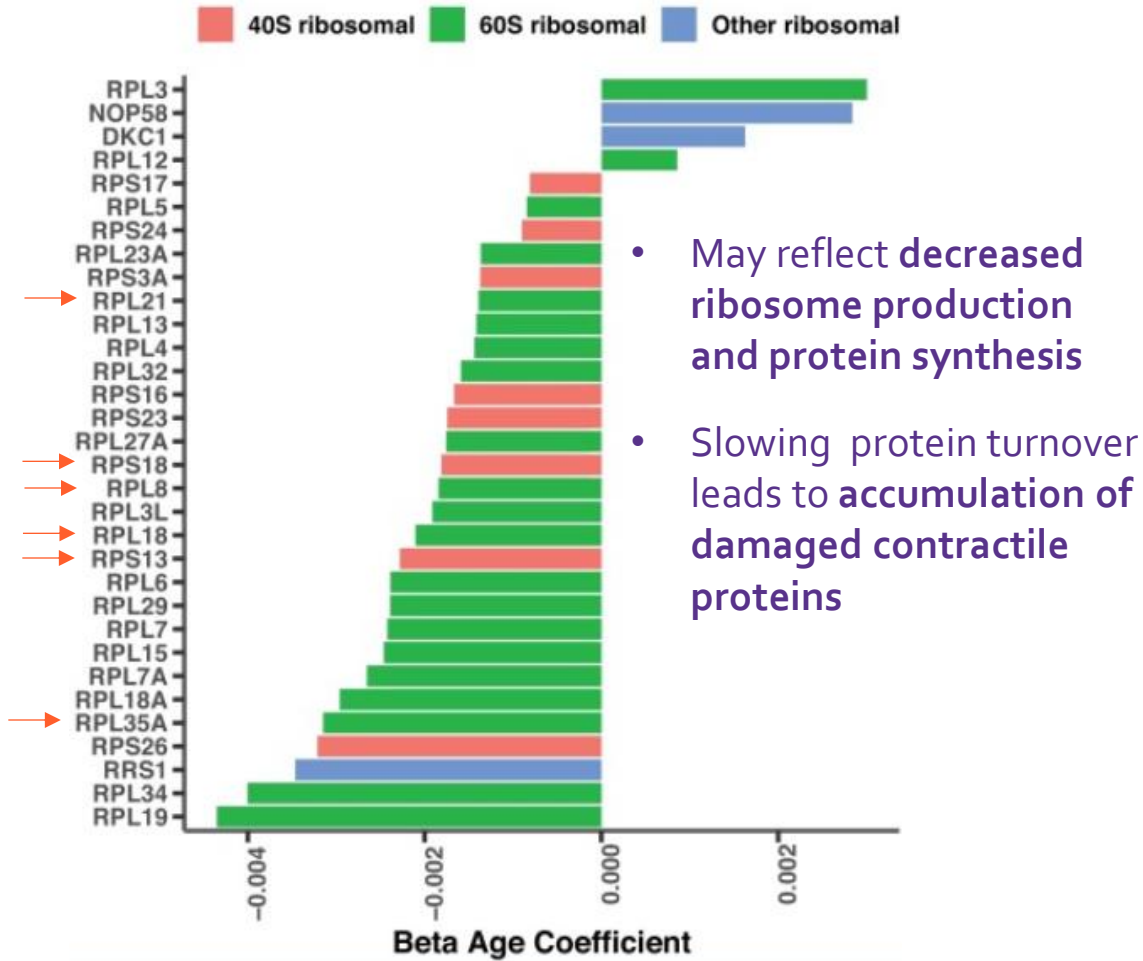
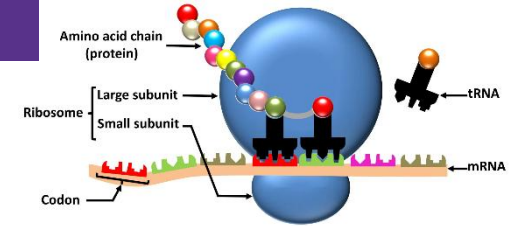
- ~50% reduction in PGE-MUM is correlated with
- ~20% improvement in muscle force



# MF-300 Increased Many of the Ribosomal Proteins Reduced in Aging Skeletal Muscle

Reduced ribosomal protein abundance in muscle correlates with aging in human

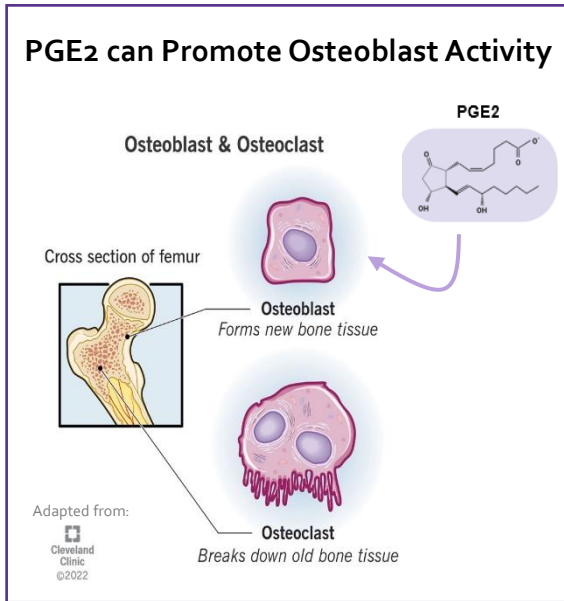
MF-300 increased abundance of large and small ribosomal proteins



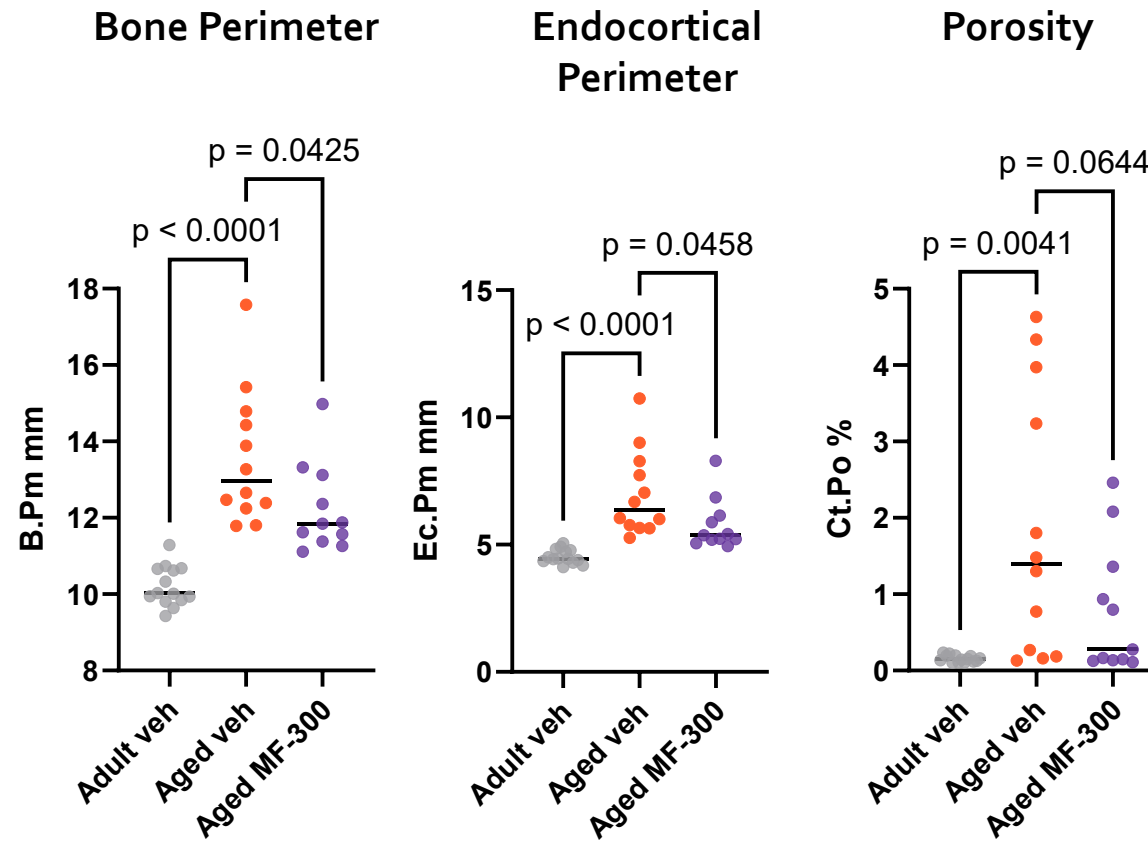
- MF-300 may increase protein turnover rate, improving muscle quality

# MF-300 Delays Age-Related Alterations in Bone Micro-Architecture

- Cortical bone increases in perimeter and develops pores with aging in rodents and humans
- More porous cortical bone is strongly linked to hip and wrist fractures, vertebral fragility
- PGE<sub>2</sub> supports bone remodeling by balancing bone formation and resorption

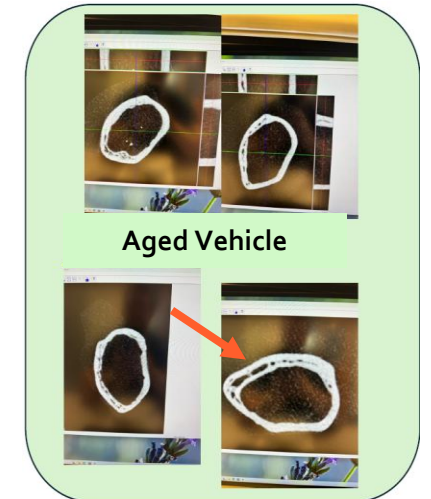
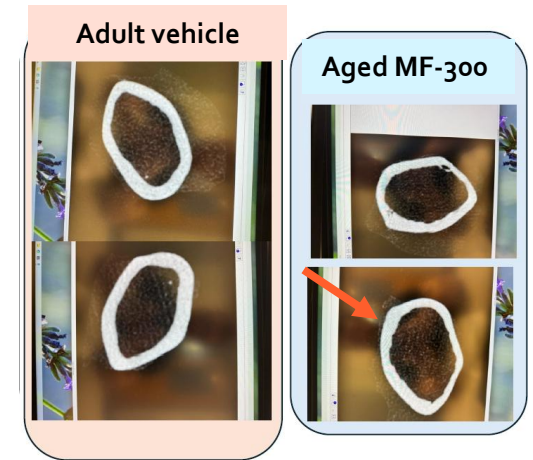


**Mouse cortical bone**  
Micro-Computed Tomography (μCT)



12 weeks MF-300 oral administration

## Cortical porosity by μCT



Data generated by: Myologica

# Phase 1 Clinical Study: Evaluating the Safety, Pharmacokinetics and Pharmacodynamics of MF-300 in Younger and Older Adults

**Design:** Double-blind, randomized, placebo-controlled

**Objectives:**

- Assess safety and tolerability of MF-300
- Characterize MF-300 pharmacokinetics and pharmacodynamics (PGE<sub>2</sub>, PGE-MUM)

**Populations:**

- Younger adults  $\geq 18 - \leq 65$  years; Healthy volunteers
- Older adults  $>65 - \leq 75$  years; Controlled chronic conditions and stable concomitant medications permitted

**Single Ascending and Multiple Ascending Dose Cohorts:**

- Single Ascending Dose (SAD): 5 dose levels (75–800 mg), older adults received 125 mg
- Multiple Ascending Dose (MAD): 3 dose levels (75, 125, 200 mg) administered once daily (QD) for 5 days, older adults received 200 mg

## Part 1a SAD

- 5 younger adult cohorts, 1 older adult cohort\*
- N=8 per cohort (2 pbo, 6 MF-300)
- Single dose
- Doses: 75, 125, 250, 500, & 800mg



## Part 2 MAD

- 3 younger adult cohorts, 1 older adult cohort\*
- N=10 per cohort (2 pbo, 8 MF-300)
- QD dosing for 5 days
- Doses: 75mg, 125mg, 200mg

\*Older adults received MF-300 125mg in the SAD phase and MF-300 200mg in the MAD phase.

- All predefined Phase 1 success criteria across Safety, PK, and PD were achieved
- Comparable clinical profile between younger and older adults
- Study results enable advancement into Phase 2b

### Safety

- ✓ Safe and well-tolerated
- ✓ No unexpected or dose-limiting findings
- ✓ Majority of adverse events mild and self-limiting
- ✓ No discontinuations due to adverse events

### PK

- ✓ Exposure increases predictably with dose
- ✓ Half-life supports once daily dosing
- ✓ Human PK exposures aligned with preclinical efficacy targets

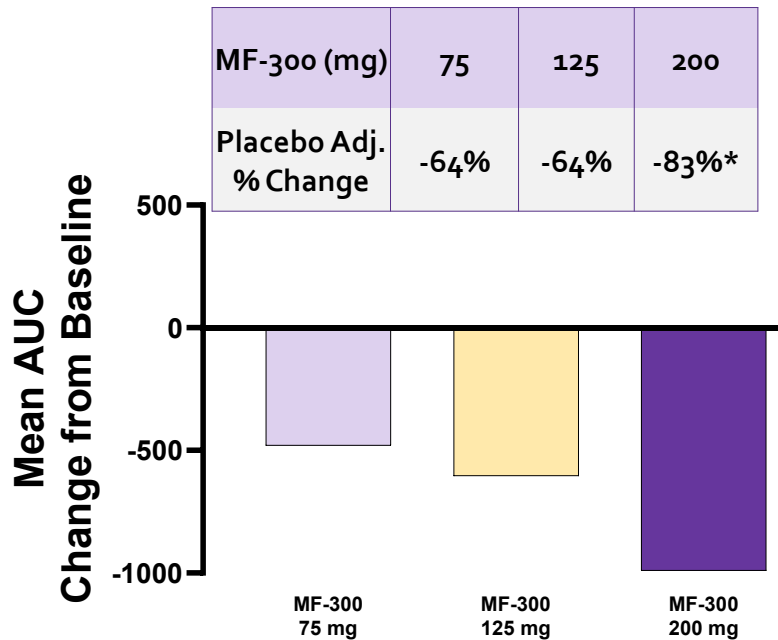
### PD

- ✓ Evidence of target engagement (15-PGDH) w/ substantial reductions in PGE<sub>2</sub> metabolites
- ✓ Proof of mechanism: Clear evidence of mechanism with dose-related increases in PGE<sub>2</sub> levels
- ✓ Clear dose-response relationship defining therapeutic range, supportive of Phase 2b dose selection

# Biomarker Data Provides Proof of Mechanism for MF-300 in Younger Adults

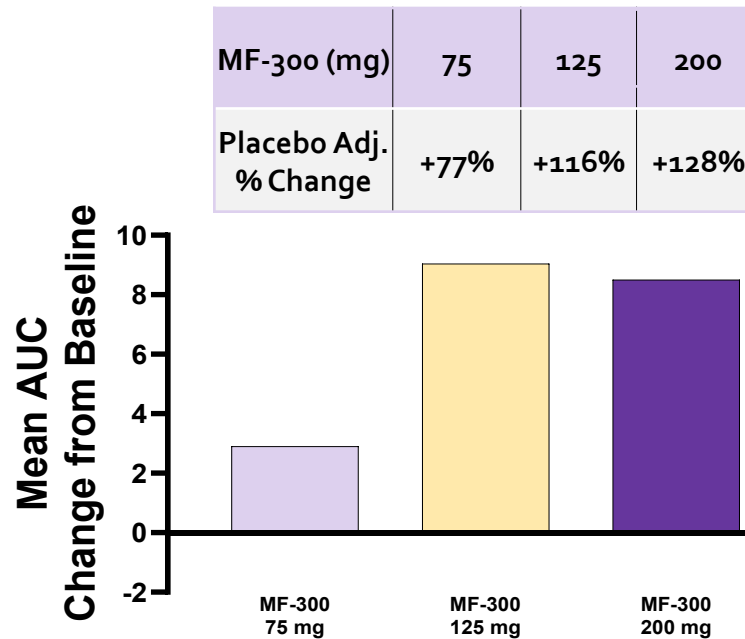
- PGE-MUM Reductions Consistent with ~20% improvement in muscle force in sarcopenia mouse model
- PGE2 Increases consistent with that following eccentric exercise in humans (~60%)

## Placebo-adjusted PGE-MUM Change from Baseline



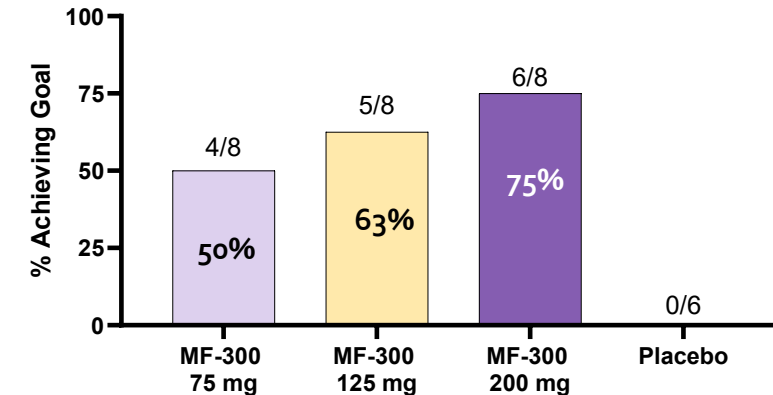
\*p<0.05 versus placebo (95% CI does not include 0)

## Placebo-adjusted PGE2 Change from Baseline

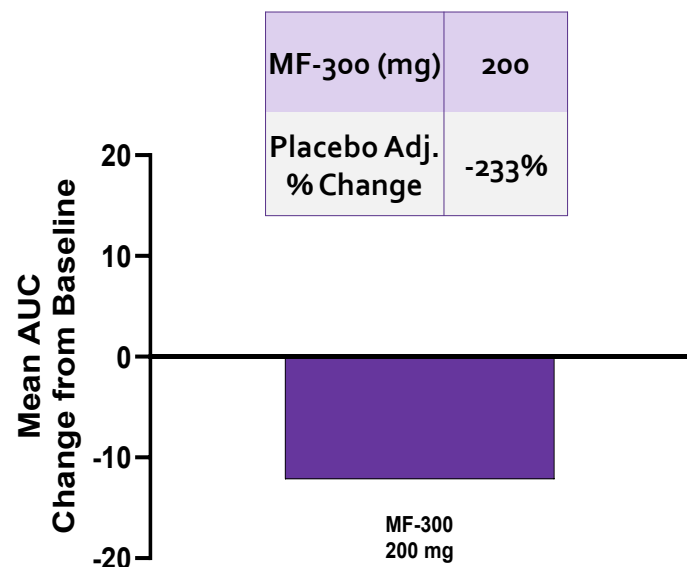


Note: Two outlier subjects in the 75 mg group, with markedly greater PGE2 responses due to low baseline values, were excluded from analysis, including the two subjects = 614% increase in MF-300 75 mg dose group.

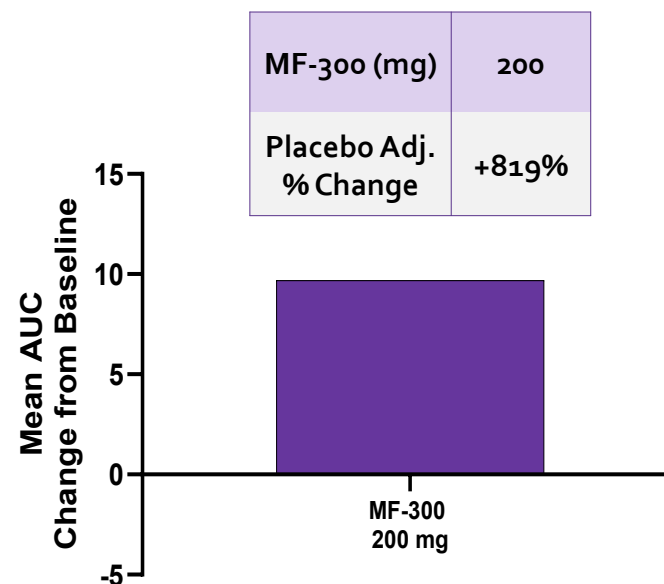
## % Subjects with ≥50% decrease in PGE-MUM & ≥60% Increase in PGE2



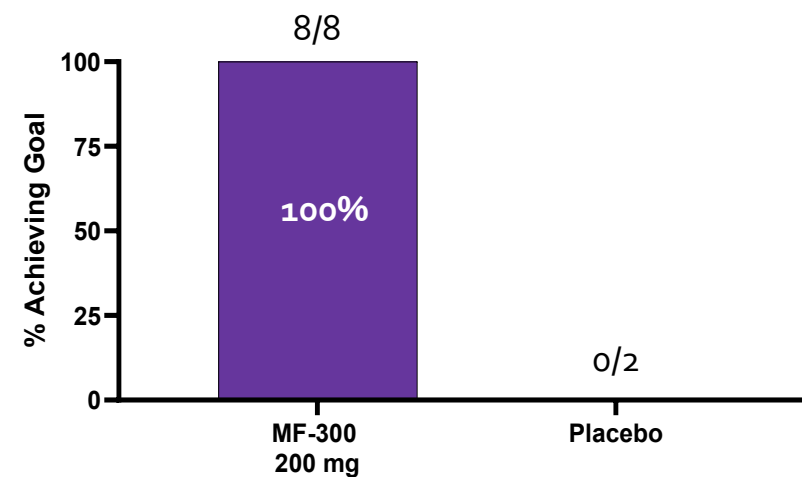
## Placebo-adjusted PGE-MUM Change from Baseline



## Placebo-adjusted PGE<sub>2</sub> Change from Baseline

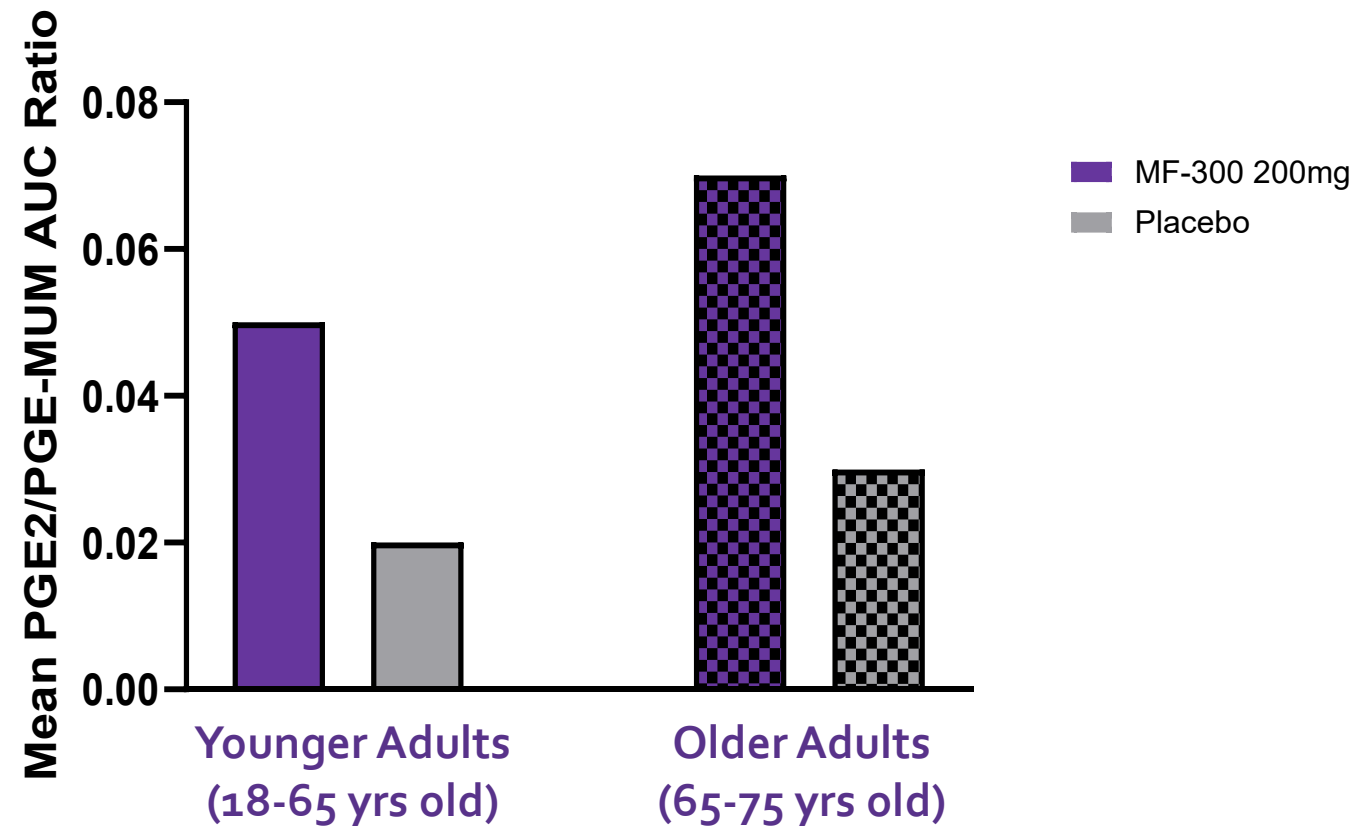


## % Subjects with $\geq 50\%$ decrease in PGE-MUM & $\geq 60\%$ Increase in PGE<sub>2</sub>

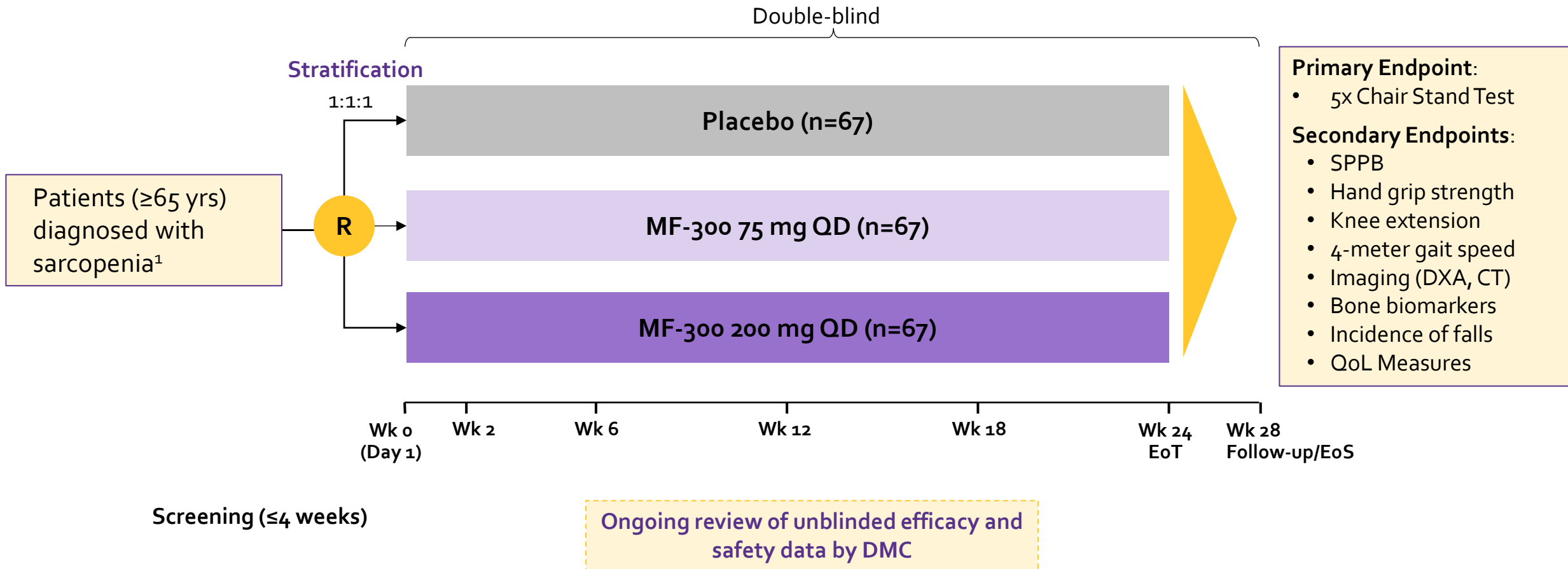


# MF-300 Increases the Ratio of PGE<sub>2</sub>/PGE-MUM Consistent with Reduced PGE<sub>2</sub> Catabolism in Both Age Groups

2-fold increase in PGE<sub>2</sub>/PGE-MUM Ratio in both Age Groups— Consistent Functional Inhibition



# Phase 2b 24-week Randomized, Double-blind, Placebo-controlled Study (N≈200)



DMC=Data Monitoring Committee; EoT=end of treatment; EoS=end of study; R=randomization; SDOC=Sarcopenia Definitions and Outcomes Consortium; SPPB=Short Physical Performance Battery; Wk=week; yo=years old

1. Bhasin S, et al. J Gerontol A Biol Sci Med Sci. 2023;78:S86–S93.

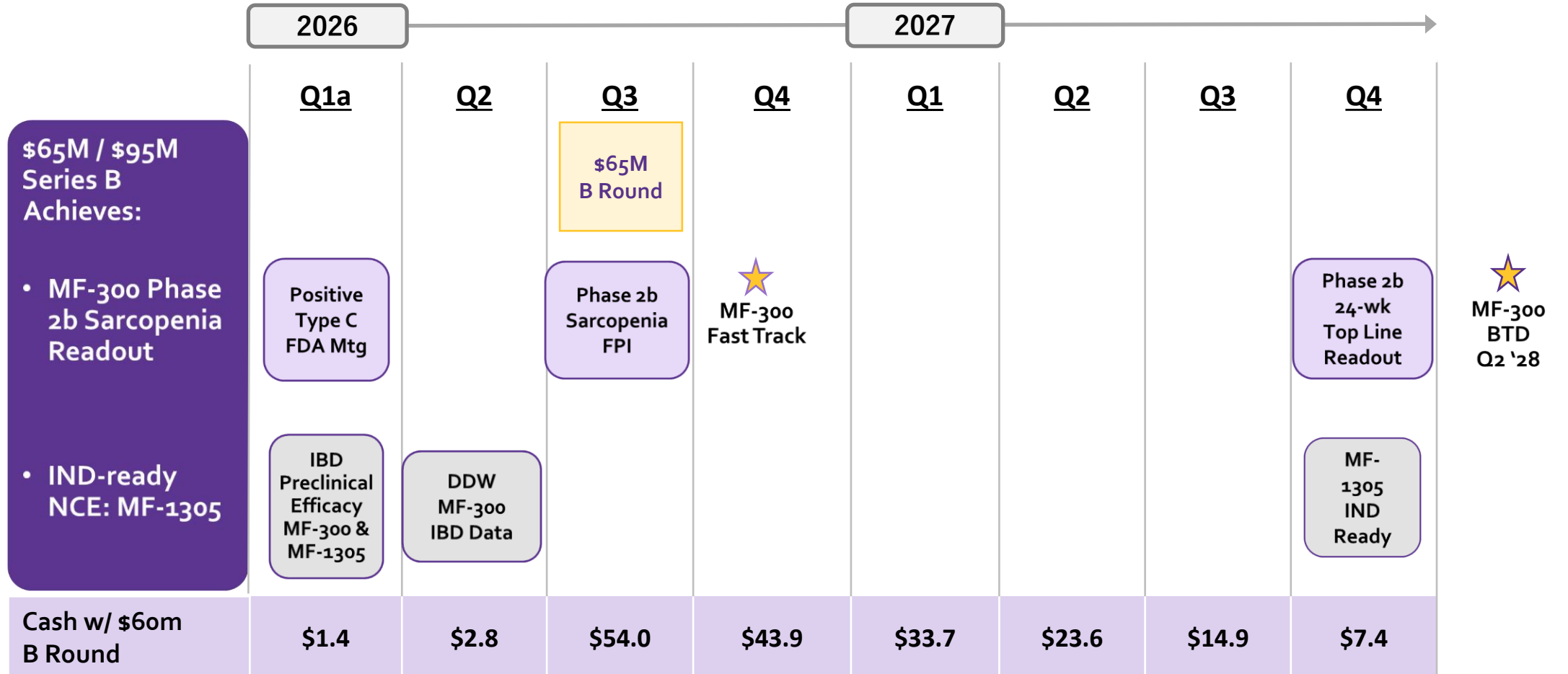
## Key Outcomes

- The **FDA's written feedback was overall positive and constructive**
- **The Phase 2b study design was endorsed**, including FDA agreement to the patient population, primary and secondary efficacy endpoints, treatment duration and dosing regimen of MF-300
- **FDA agreed that the efficacy endpoints evaluated in the Phase 2b study will inform Phase 3 endpoint selection**
- **FDA supports pursuing Fast Track Designation**, signaling that they consider Sarcopenia a serious condition and that MF-300 has the potential to address an unmet need

## Strategic Implications

- Supports advancement of MF-300 to a Phase 2b study
- Phase 3 endpoint strategy is conditionally endorsed – regulatory risk around endpoints is reduced
- Fast Track, if accepted, will allow greater access to FDA during development and enable priority review, potentially accelerating development timelines

# Series B Funded Milestones: MF-300 Phase 2b Data Readout & IND Ready NCE



- 5xs Chair Stand
- MF-300 force improvement comparison to m-apitegromab in Translational Delta7 SMA Mouse Model
- Epirium's Sarcopenia Development Council
- IBD UC Endpoints and Supportive Data

- **Accepted proxy measure of lower limb power and strength**

- Endorsed by World Health Organization (WHO) ICOPE<sup>1</sup> & EWGSOP<sup>2</sup>

- **Strong predictor of clinical outcomes**

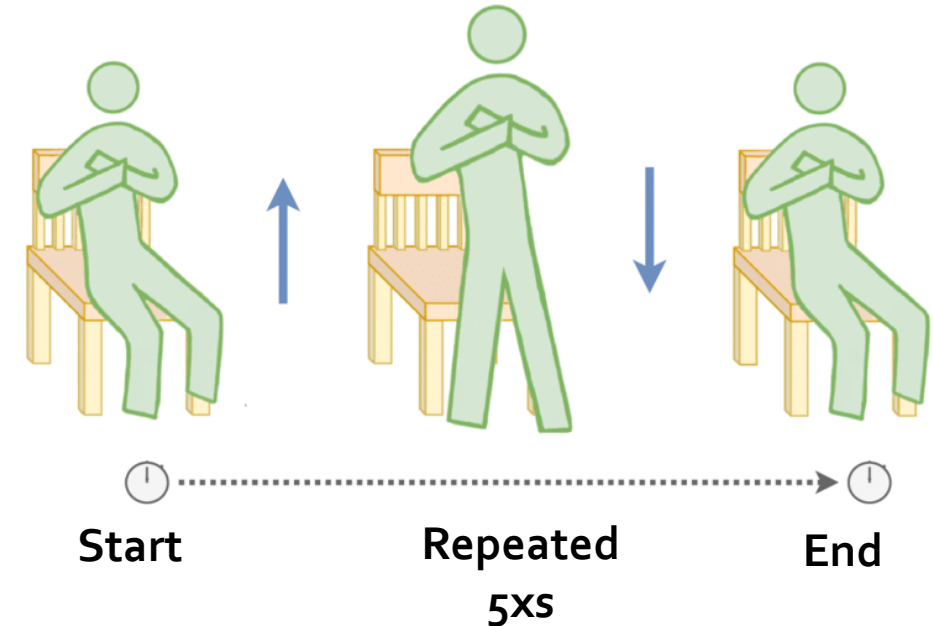
- Activities of daily living
- Fall Risk
- All-Cause Mortality

- **Loss of 1 second (~10%) per year is accepted as clinically meaningful**

- **Aligns directly with MF-300's mechanism of action**, which targets fast-twitch muscle and primarily lower limb strength

- Limited variability and modifiable within 6 months

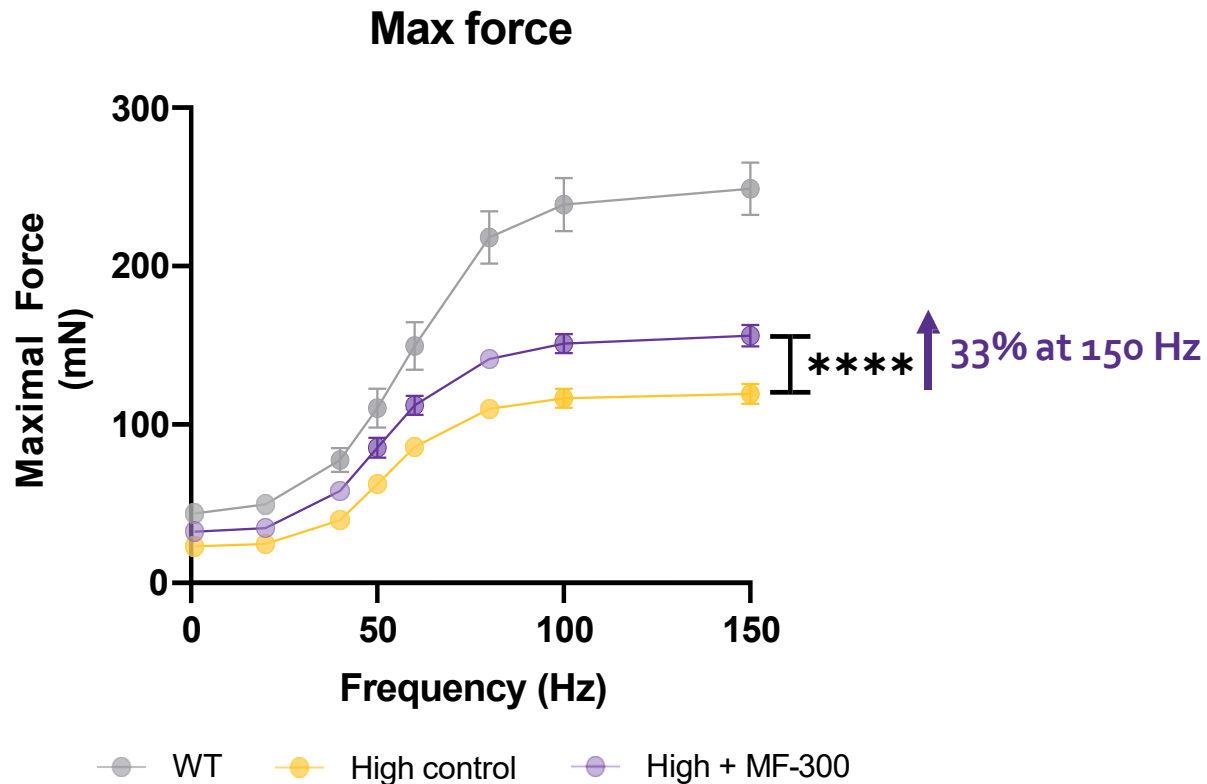
## 5xs Chair Stand Test



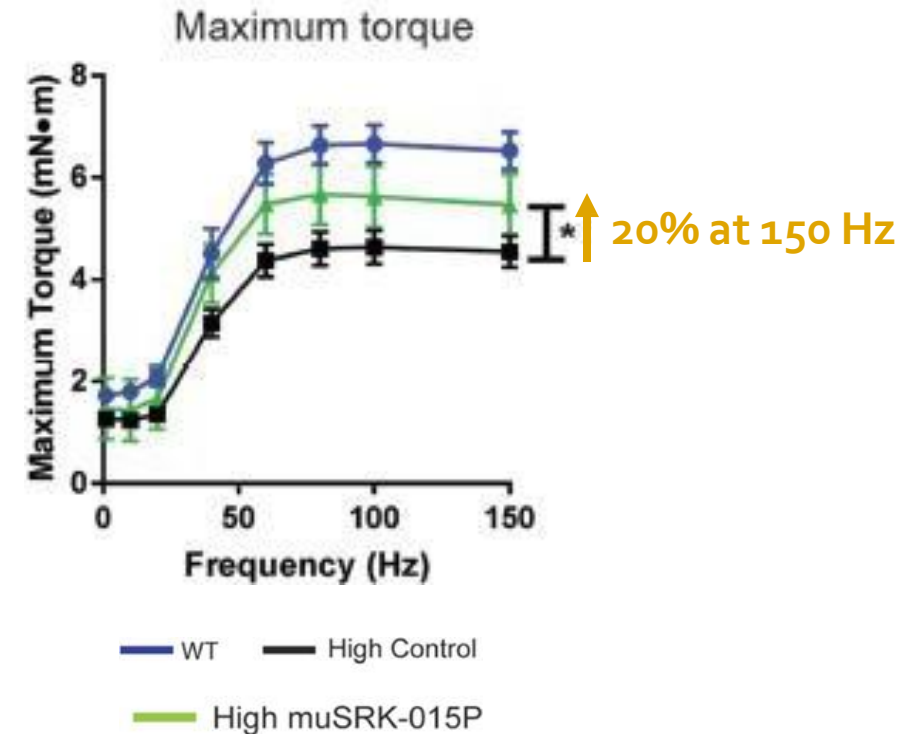
1. ICOPE=Integrated Care for Older People ([9789240103726-eng.pdf](https://www.who.int/publications/i/item/9789240103726-eng))

2. EWGSOP2=European Working Group on Sarcopenia in Older People 2 (CRUZ-JENTOFT AJ, et al. Age and Aging. 2019;48:16-31).

## MF-300 in SMN $\Delta$ 7 High/High Male mice



## mSRK-015P in mouse $\Delta$ 7 High/High Male and female mice

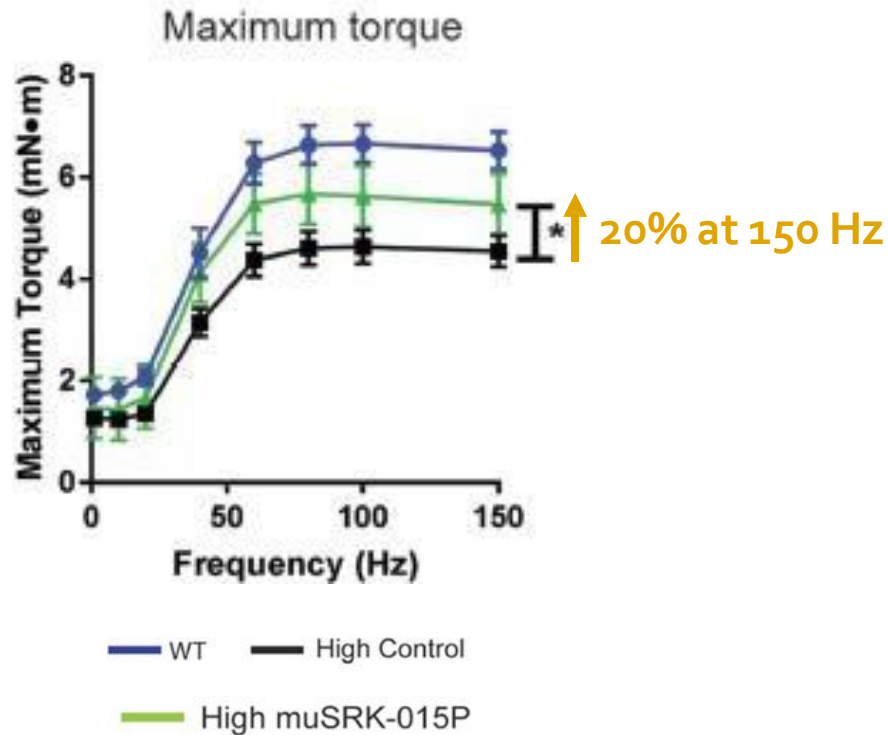


Force = Torque

# MYOLOGICA

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

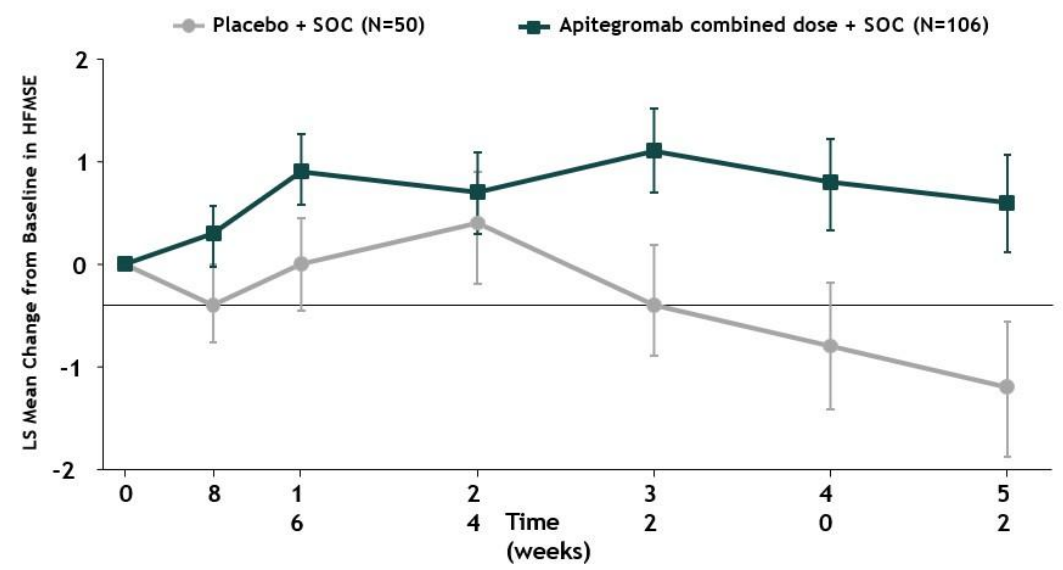
mSRK-015P in mouse  $\Delta 7$  High/High



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

Apitegromab in SMA + SOC (Ph 3 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
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

# Epirium Sarcopenia Clinical Development Advisors



**David Cella, PhD**

Director, Institute for Public Health and Medicine (IPHAM)

*Northwestern University*  
International leader in PRO;

Key leader in the development of PROMIS® ;

FDA advisor on Care Outcome Set.



**Scott Delp, PhD**

Founding Chairman of the Department of Bioengineering at Stanford

*Stanford, Wu Tsai Center Biomedical Engineering*

Stanford engineer pioneering biomechanics, muscle performance, and wearable monitoring technologies.



**Jerome Feige, PhD**

Adult Health Science Lead & Senior Expert in Musculoskeletal Health

Led drug discovery for muscle diseases at Novartis, contributing to development of new therapies.

Built muscle biology and translational programs leading to commercialization of several products and start-ups.



**Roger Fielding, PhD**

Co-Director, Boston NIA Center

*Tufts University*

Researcher studying the underlying mechanisms contributing to the age-associated decline in skeletal muscle mass. Published landmark studies in sarcopenia, frailty and muscle function. Conducted numerous studies examining the roll of skeletal muscle power on physical performance in older adults.



**Jose M. Garcia, MD, PhD**

Physician-Scientist at the Puget Sound VA Health Care System

*University of Washington, Seattle*

Directing the Clinical Research Unit and the GRECC. Expert in wasting disorders, leading basic and clinical research on ghrelin, androgens, and other anabolic pathways.



**Jack Guralnik, MD, PhD**

Professor, Epidemiology & Public Health

*U of Maryland, Medical School*

Developed the SPPB, a gold-standard functional outcome; expert in disability and mobility trials.



**George Kuchel, MD**

Professor of Medicine, Travelers Chair in Geriatrics and Gerontology, and Director of the UConn Center on Aging and Pepper Center

*University of Connecticut*

Researcher studying functional decline, mobility, and cognition, in older adults, with a mission of precision gerontology to tailor interventions to individual variability.



**Nathan K. LeBrasseur, PhD**

Director, Robert & Arlene Kogod Center on Aging

*Mayo Clinic*

Noaber Foundation Professor of Aging Research

Department of Physical Medicine & Rehabilitation

Department of Physiology & Biomedical Engineering



**Se-Jin Lee, MD, PhD**

Presidential Distinguished Professor

*University of Connecticut School of Medicine*

Professor, The Jackson Laboratory.

Studying the mechanism of action of myostatin and how its activity is regulated.



**Naomi Lowy, MD**

Principal Drug Regulatory Expert

*Hyman Phelps*

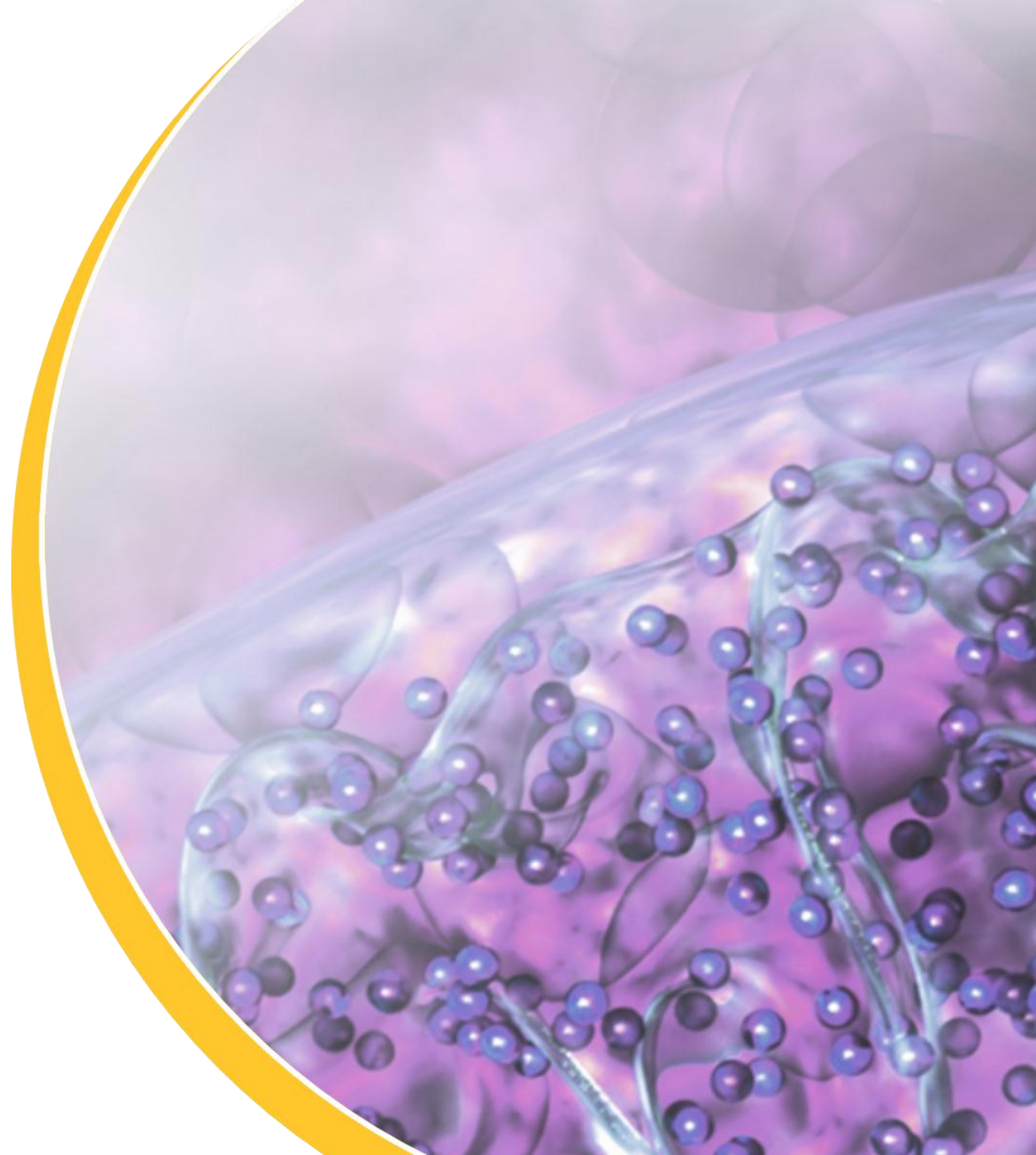
Fmr. FDA, Deputy Dir. Endocrinology Division

At FDA, provided leadership in drug policy and drug development in sarcopenia.



Epirium's 15-PGDH inhibitor platform:  
Rationale for 15-PGDH inhibition in  
IBD

- Mucosal Healing in DSS Colitis with MF-300



# Proven Mechanistic Rationale for the Treatment of IBD: Inhibiting 15-PGDH to Increase Physiological PGE<sub>2</sub>

The PGE<sub>2</sub>/EP<sub>4</sub> axis  
improves outcomes in DSS  
colitis models

15-PGDH



PGE<sub>2</sub>



EP<sub>4</sub>



↓ Inflammation

↑ Mucosal protection/healing

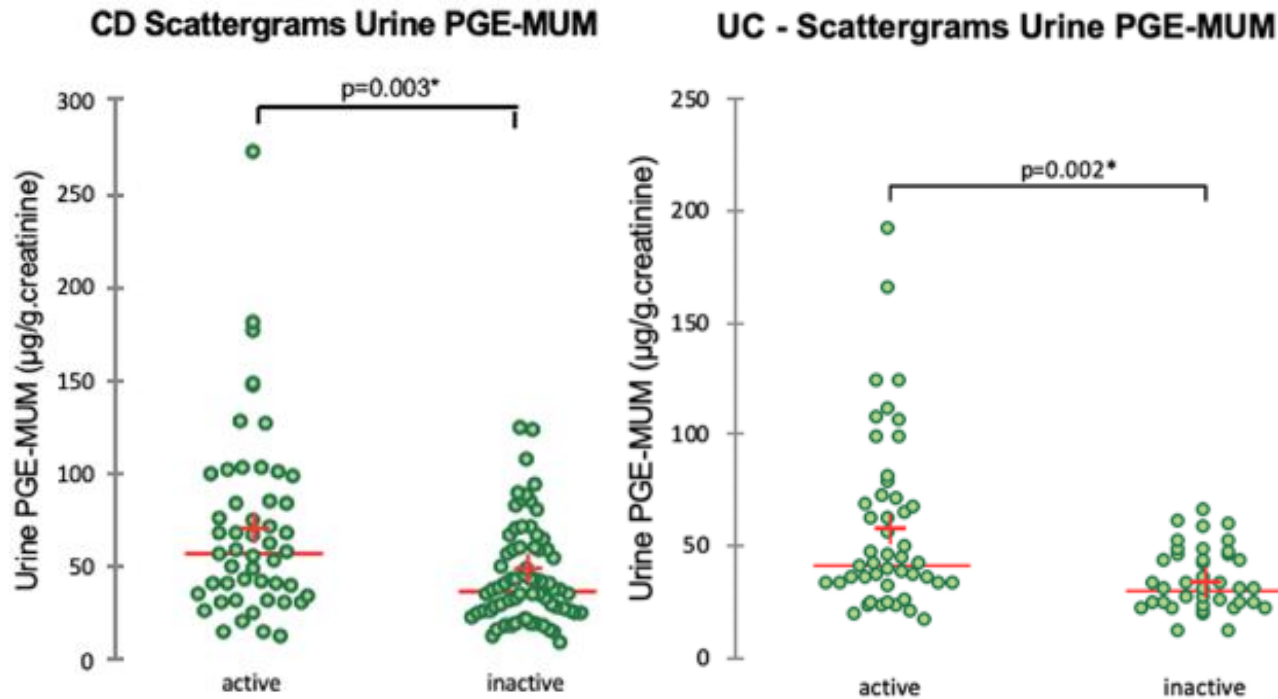
\*Potential for combining with therapeutics targeting  
suppression of inflammation (i.e., TL1A & TNF)

Intervention / genetic model	Species & colitis model	Key outcomes	Reference
SW033291 (15-PGDH inhibitor, IP)	Mouse, DSS colitis	<ul style="list-style-type: none"> <li>Reduced % ulcerated colon area</li> <li>Improved disease activity</li> <li>Reduced pro-inflammatory cytokines</li> <li>Increased crypt cell proliferation</li> </ul>	Zhang et al., 2015
HW201877 (15-PGDH inhibitor, PO)	Mouse, DSS colitis	<ul style="list-style-type: none"> <li>Improved DAI</li> <li>Improved colon length</li> <li>Improved histological measures</li> </ul>	Li et al., 2025
<i>Hpgd</i> knockout (15-PGDH gene)	Mouse, DSS colitis including older mice	<ul style="list-style-type: none"> <li>Minimize weight loss</li> <li>Improved colon length &amp; histology scores</li> </ul>	Zhang et al., 2015; Ho et al., 2022
AGN205203 (EP <sub>4</sub> agonist)	Mouse, DSS (and DSS+indomethacin) colitis	<ul style="list-style-type: none"> <li>Improved DAI</li> <li>Improved histology: preserved epithelium, reduced epithelial apoptosis, preserved goblet cells, enhanced epithelial regeneration</li> </ul>	Jiang et al., 2007
ONO-AE1-329 (EP <sub>4</sub> agonist)	Rat & Mouse DSS colitis	<ul style="list-style-type: none"> <li>Reduced erosion/ulceration</li> <li>Suppressed mucosal damage and inflammation</li> <li><i>EP<sub>4</sub> KO &amp; EP<sub>4</sub> antagonist worsened colitis</i></li> </ul>	Kabashima et al. (JCI) 2002; Nitta et al. 2002
KAG-308 (EP <sub>4</sub> agonist)	Mouse, DSS colitis	<ul style="list-style-type: none"> <li>Suppressed DSS colitis onset</li> <li>Promoted histological mucosal healing</li> <li>Reduced TNF<math>\alpha</math> production</li> <li><i>EP<sub>4</sub> antagonist increased mortality</i></li> </ul>	Watanabe et al., 2015
PGE <sub>2</sub> (Exogenous)	Mouse, DSS colitis	<ul style="list-style-type: none"> <li>Alleviated mucosal injury</li> <li>Promoted epithelial protection/healing</li> </ul>	Peng et al. 2017

# PGE2 Metabolite (PGE-MUM) Levels 30-60% Higher in Human Patients with Active vs Inactive IBD

PGE-MUM levels were 60.3% higher in active vs inactive CD, and 30.4% higher in active vs inactive UC

PGE-MUM levels were ~40% higher in patients with UC at relapse vs remission



Figures from d'Inca et al. *Scientific Reports*. 2025;15

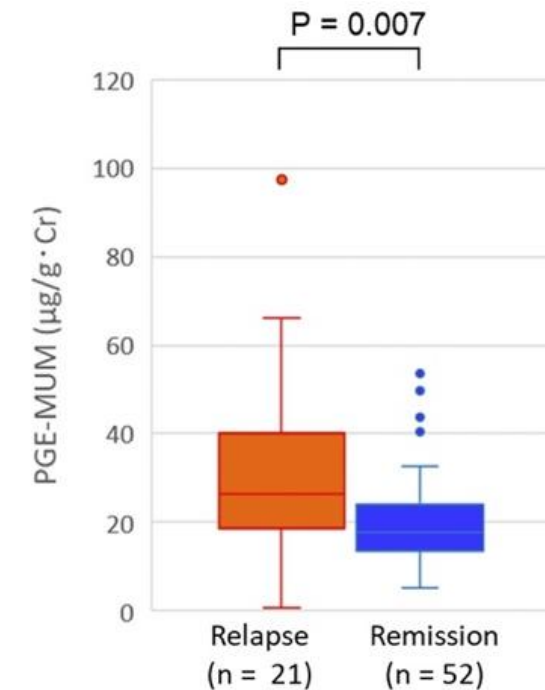


Figure from Ishida et al. *Clin Transl Gastroenterol*. 2022;13;7

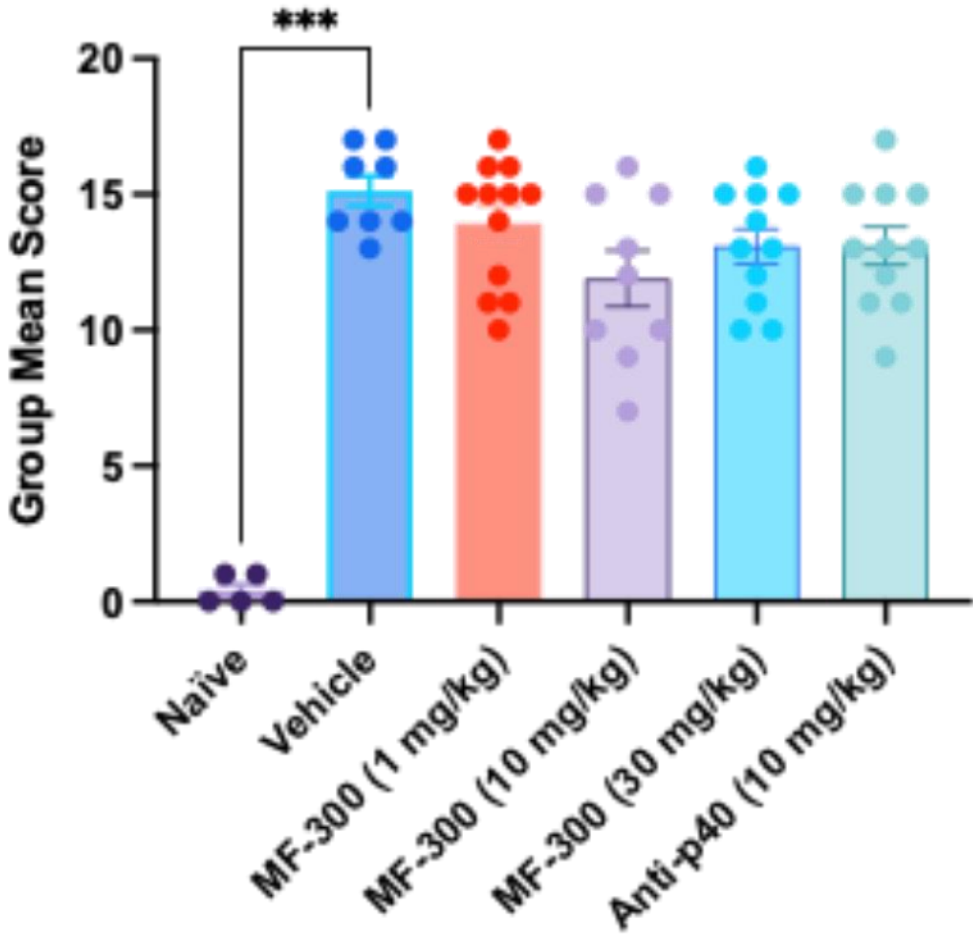
MF-300 reduced levels of PGE-MUM by 64-83% relative to placebo in healthy adults a Phase 1 clinical study (slide #19)



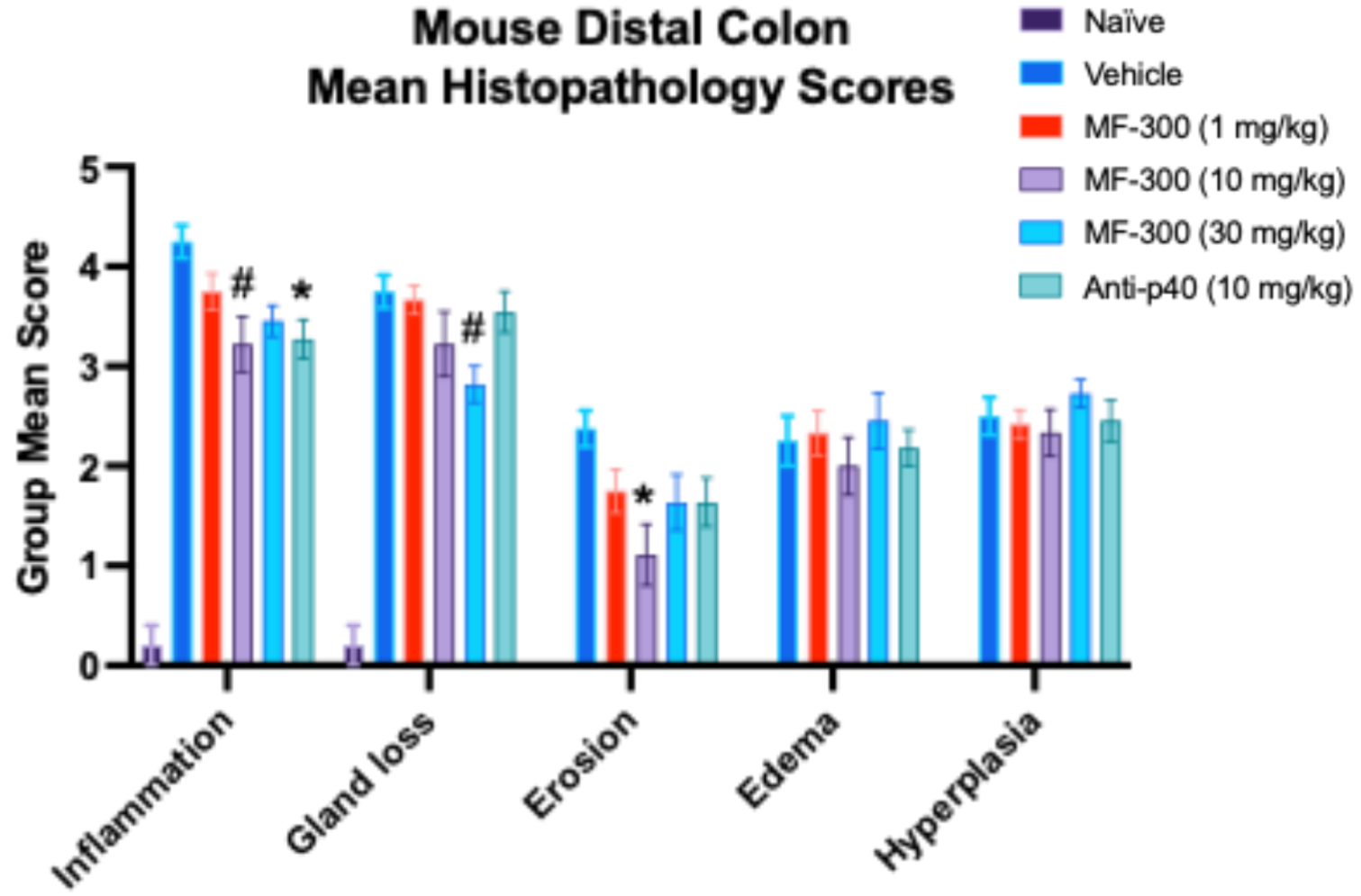
# Study #3: MF-300 Drives Broad Histological Improvement Across Multiple Disease Markers in DSS Colitis Equivalent or Better Than Anti-P40



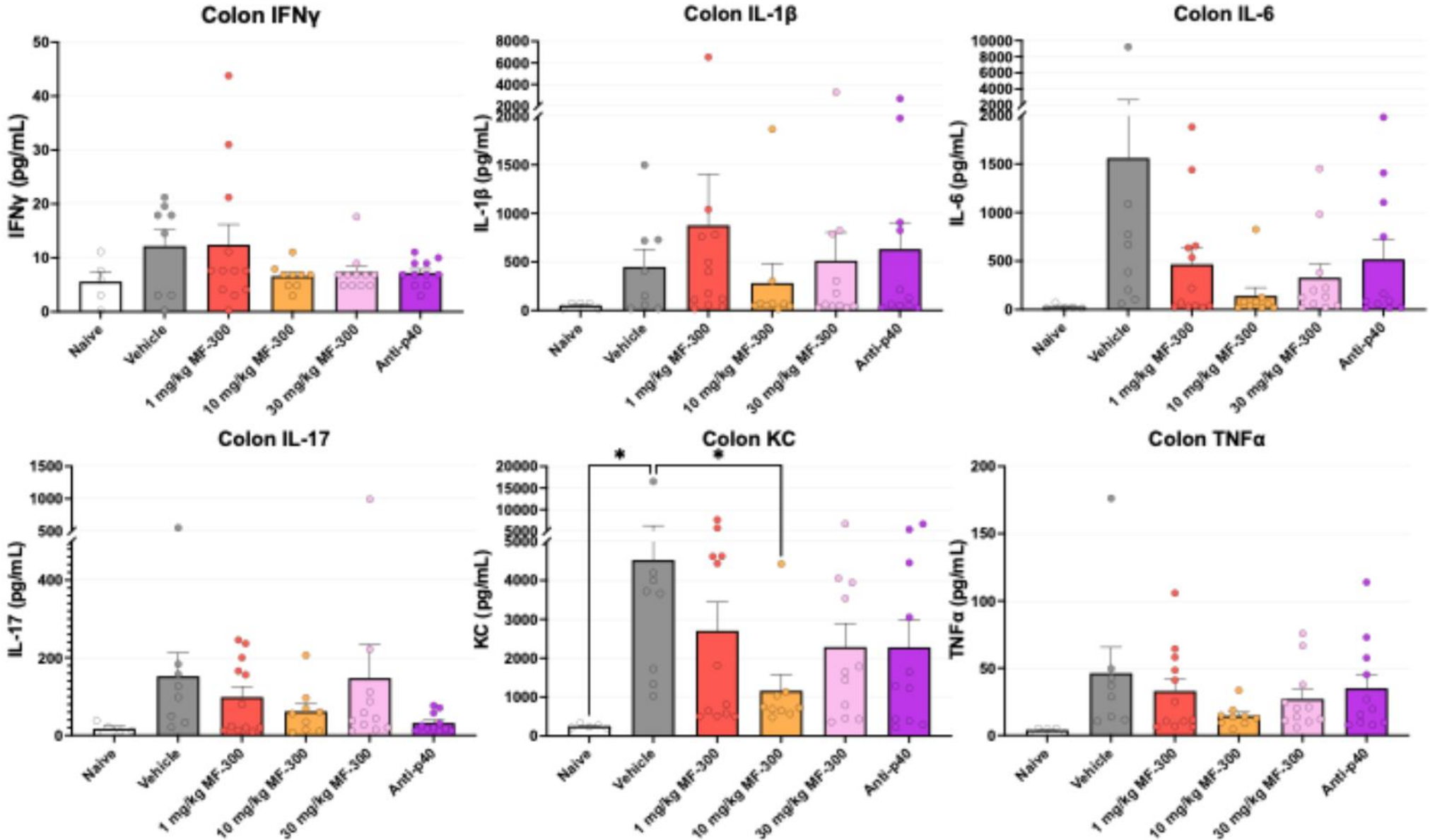
### Mouse Distal Colon Mean Sum Scores



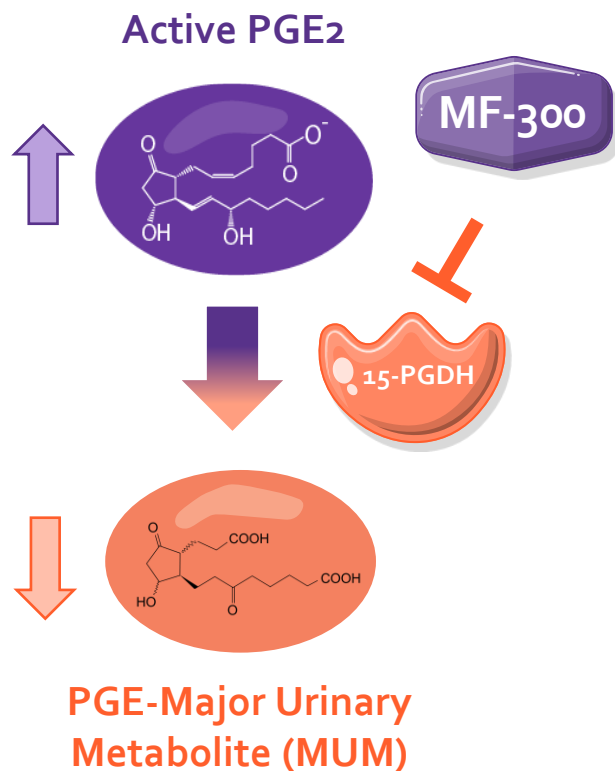
### Mouse Distal Colon Mean Histopathology Scores



# Study #3: MF-300 Reduced Cytokines Equivalent or Better Than Anti-P40



Elevated PGE-MUM correlates with active UC & CD in humans



## PGE-MUM is a disease response biomarker in IBD

- ✓ Stable PGE<sub>2</sub> metabolite<sup>1,2</sup>
- ✓ Elevated in active UC & CD; tracks to disease activity<sup>3,4,5</sup>
- ✓ Detects mucosal healing during clinical remission<sup>6</sup>
- ✓ Reflects CD endoscopic activity<sup>7</sup>
- ✓ Predicts relapse in long duration UC<sup>8</sup>
- ✓ Combination with fecal calprotectin may improve inflammation profiling in UC and CD<sup>9</sup>

<sup>1</sup> Miyamoto et al., 2024

<sup>2</sup> Gross et al., 2005

<sup>3</sup> Arai et al., 2014

<sup>4</sup> Arai et al., 2016

<sup>5</sup> Fujiwara et al., 2000

<sup>6</sup> Sakurai et al., 2022

<sup>7</sup> Ishida et al., 2025

<sup>8</sup> Ishida et al., 2022

<sup>9</sup> D'Inca et al., 2025

- **PGE-MUM** is a stable downstream metabolite of PGE<sub>2</sub>
- **Target engagement & disease biomarker hypothesis for IBD:** Reduced PGE-MUM will demonstrate inhibition of 15-PGDH and stabilization of therapeutic PGE<sub>2</sub> levels in the diseased intestine