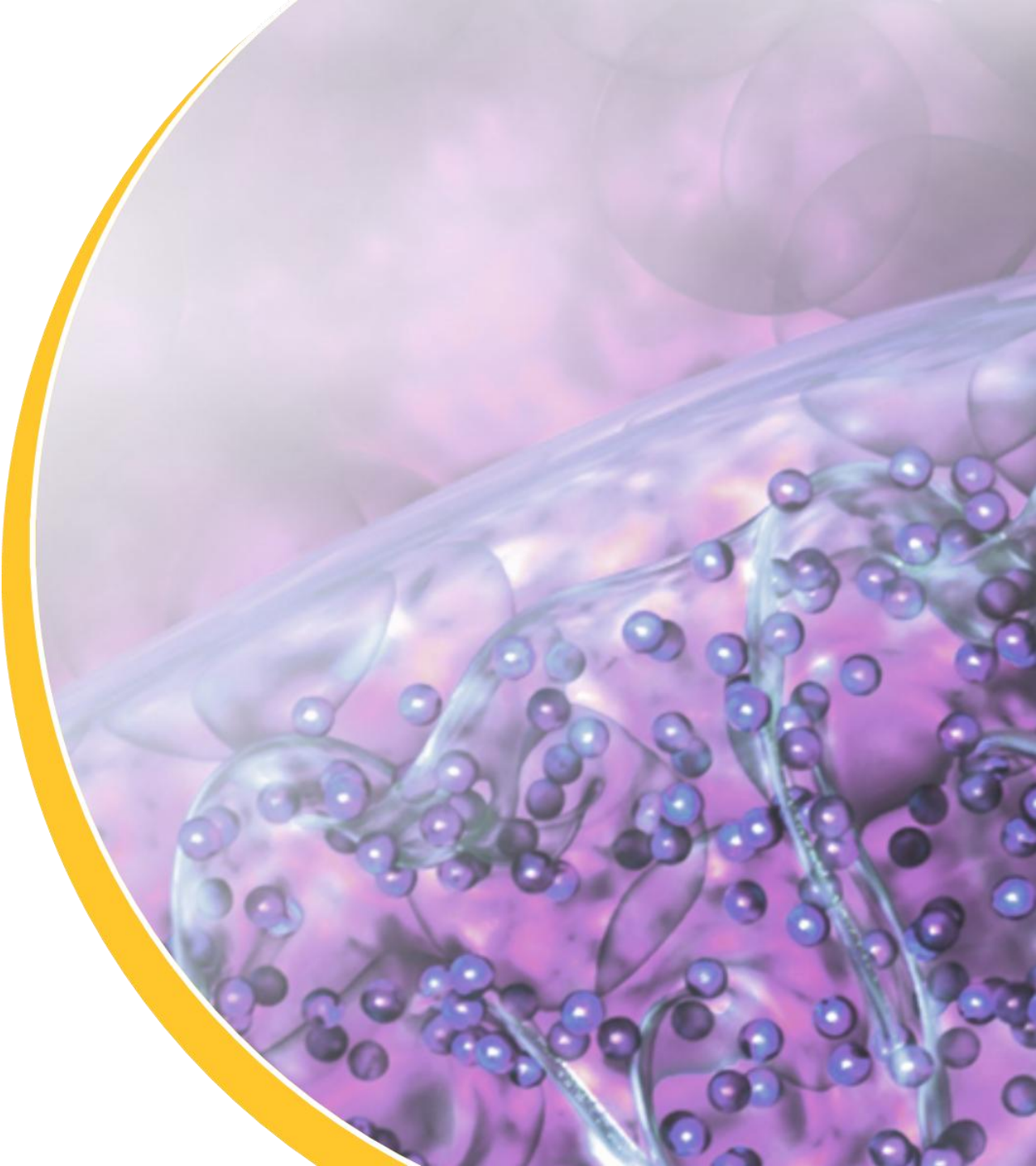




Oral 15-PGDH Inhibitor Platform:

Leveraging PGE₂ 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 T₂DM (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

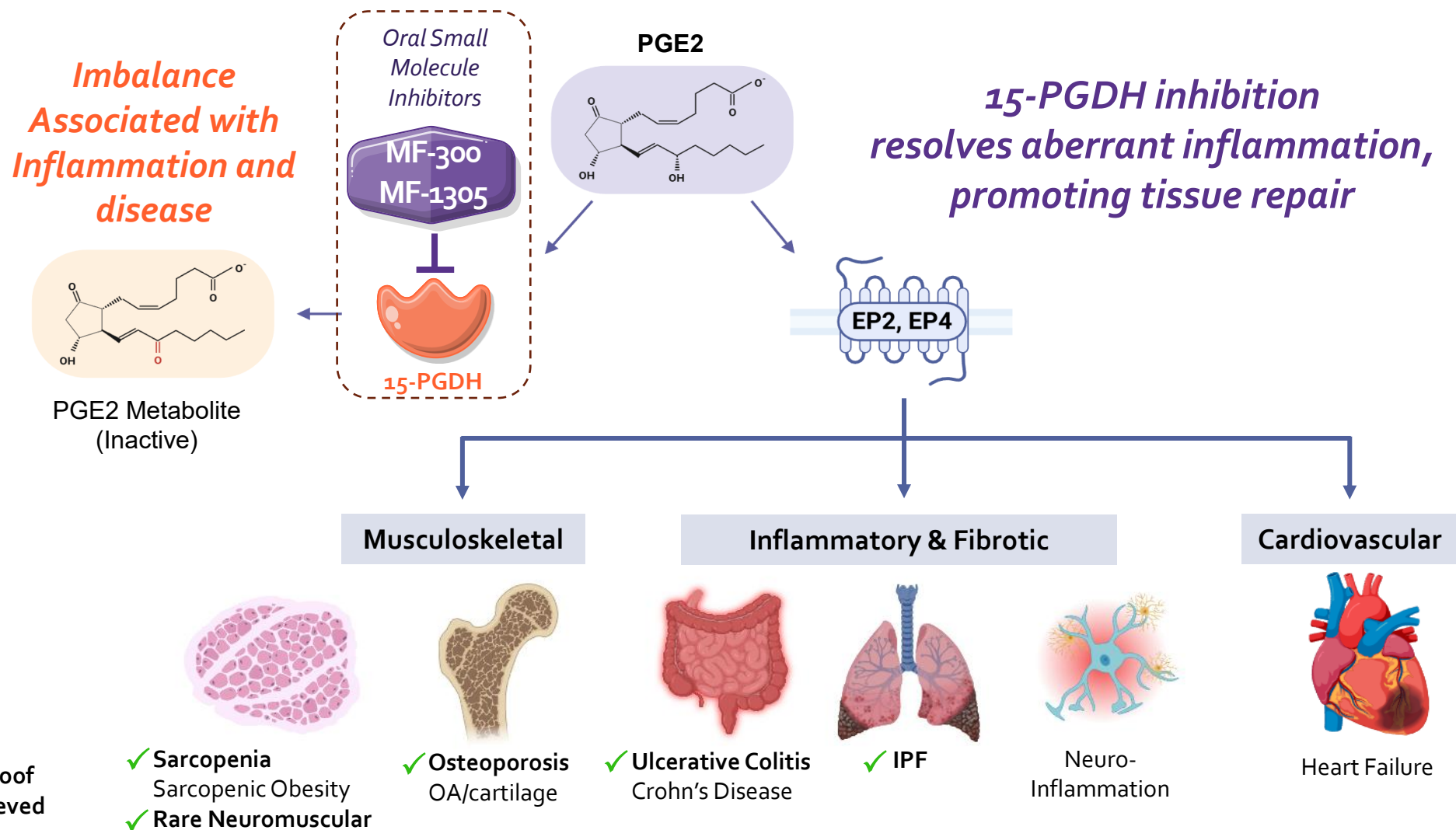


Lois Lee, Pharm.D. Clinical Development

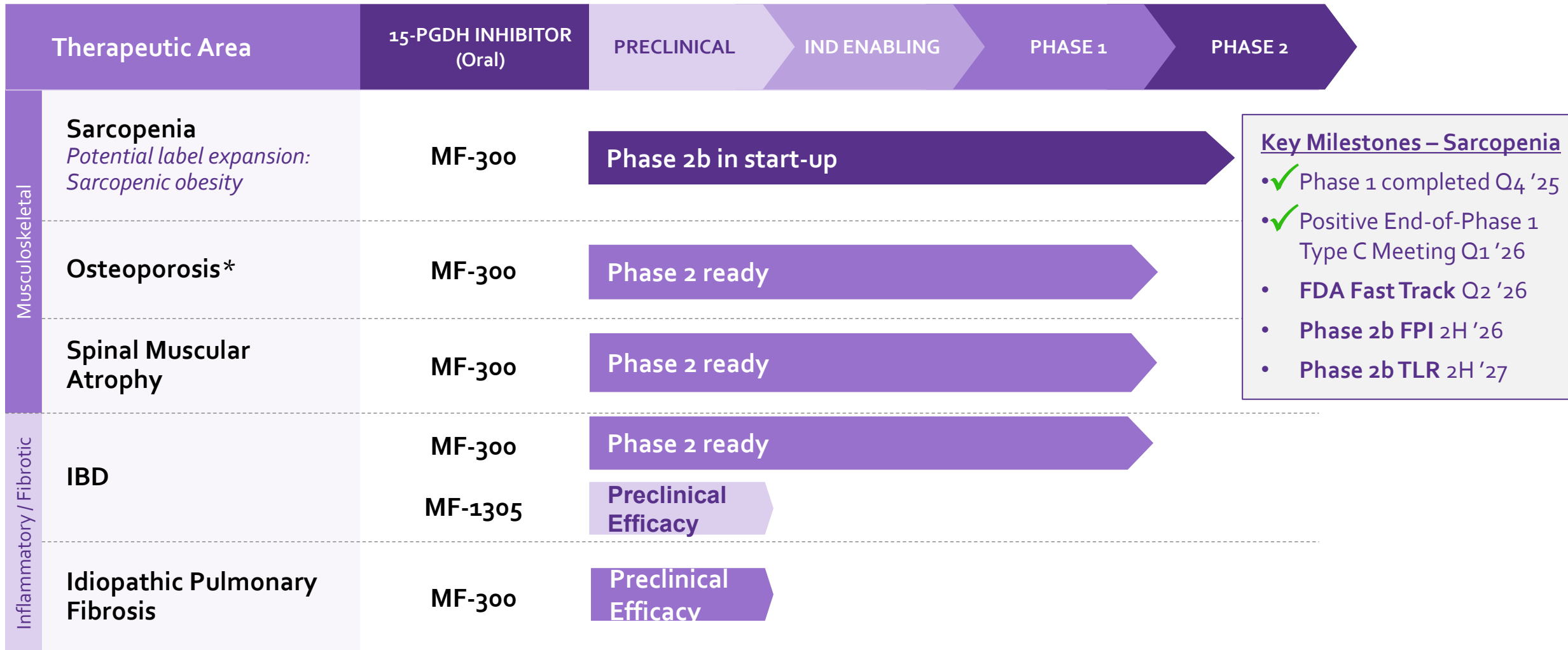
20+ years of industry experience leading early- and late-phase drug development across multiple TAs including liver, metabolic, and neurodegenerative diseases.

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 (PGE₂) 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

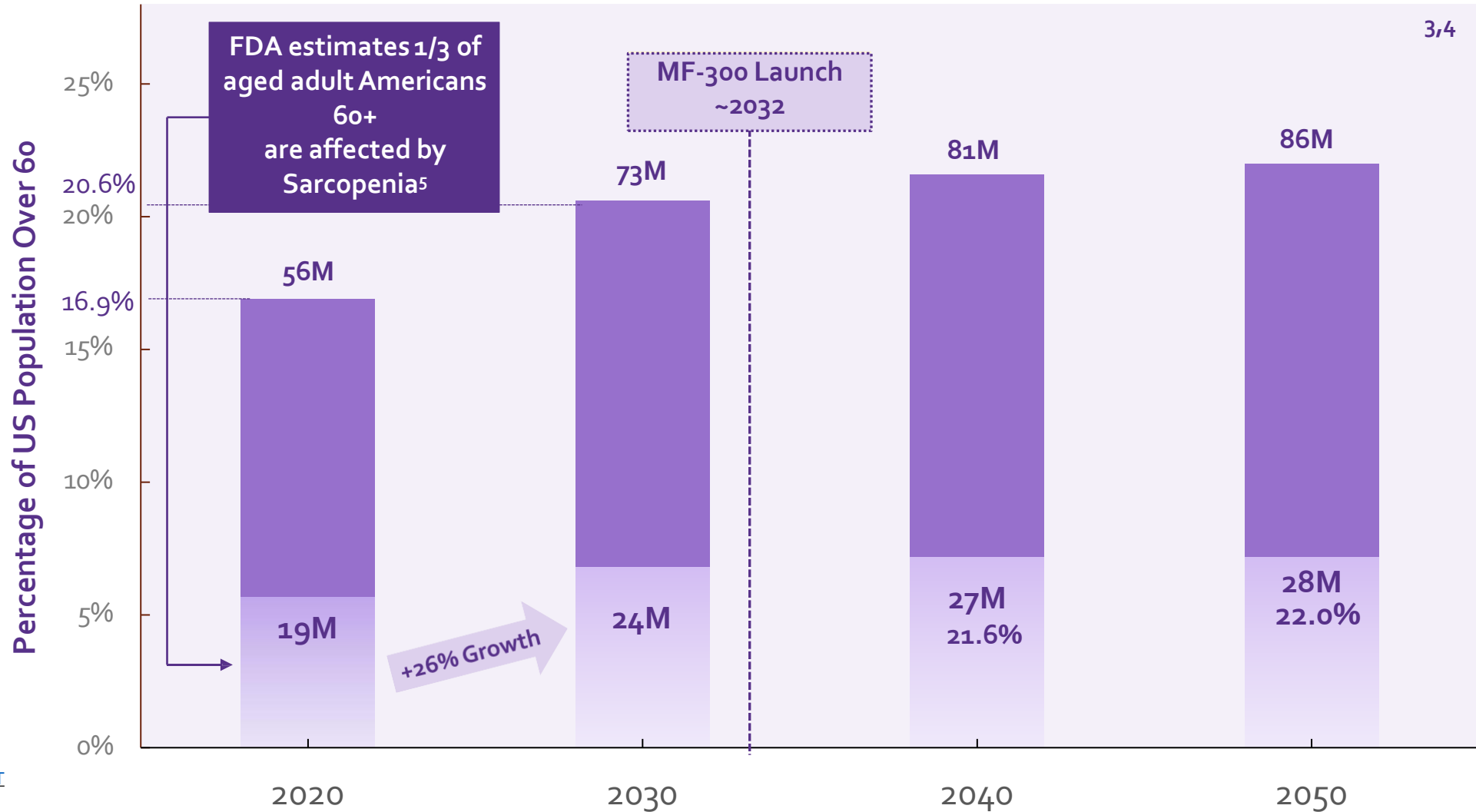
Sarcopenia: Large and Growing Unmet Medical Need w/ No FDA Approved Therapy

Current U.S. Healthcare Sarcopenia Spending Estimated >\$40 Billion Annually¹

Dependence
Increased risk losing independence

Falls
Increased Morbidity & Mortality²

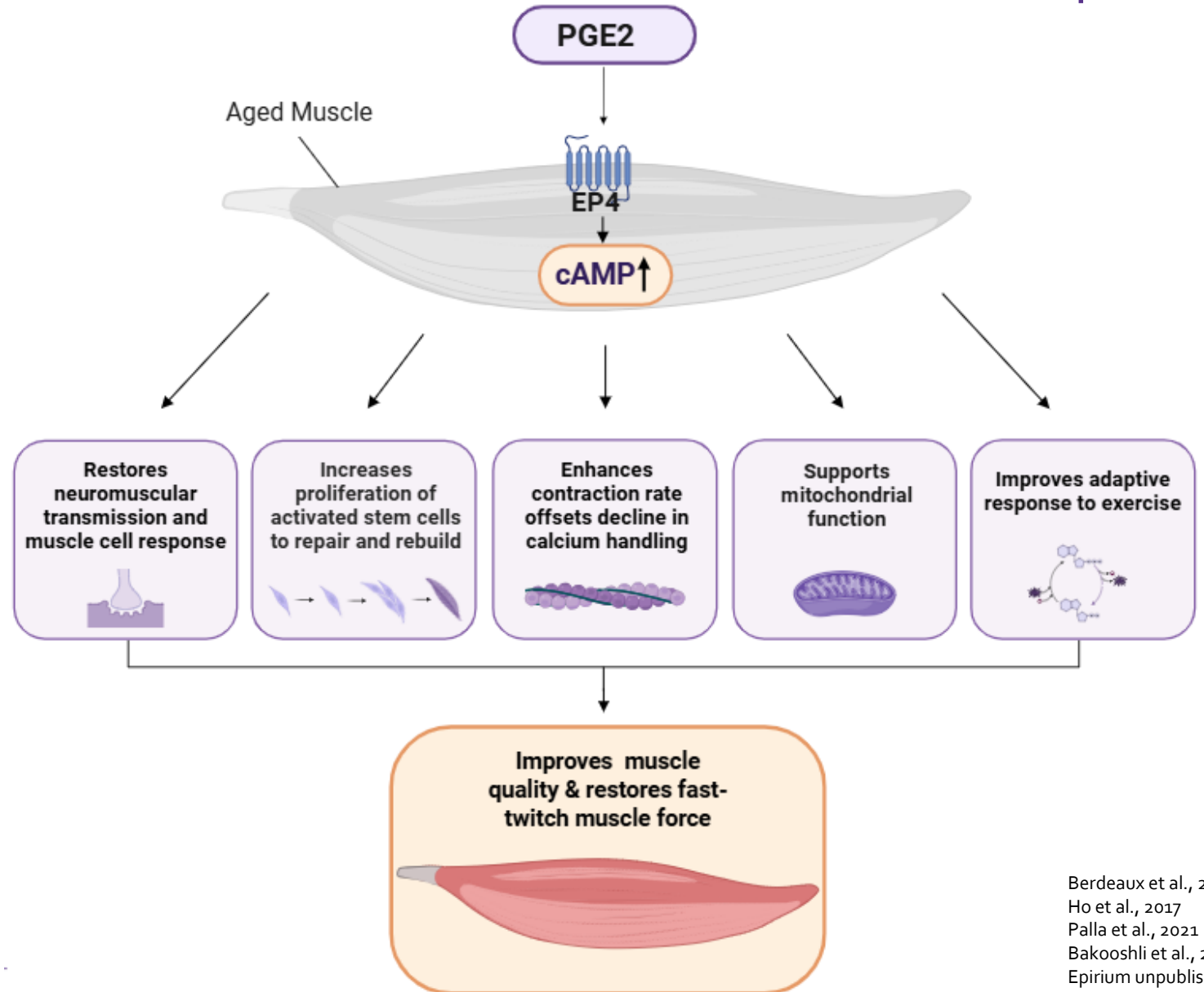
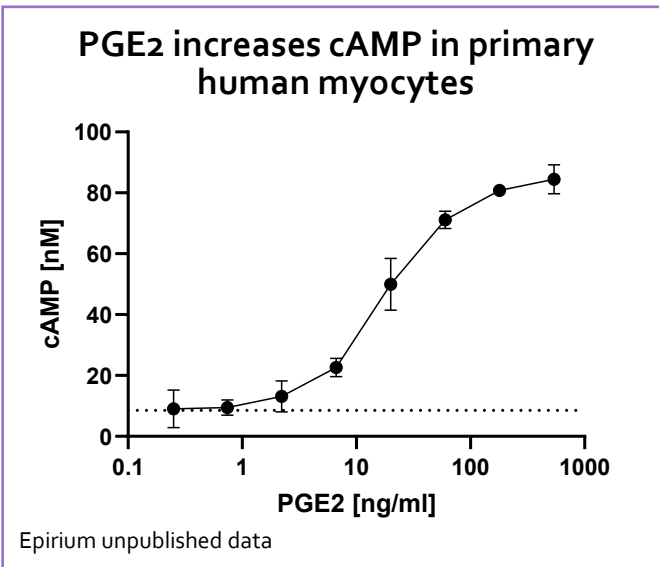
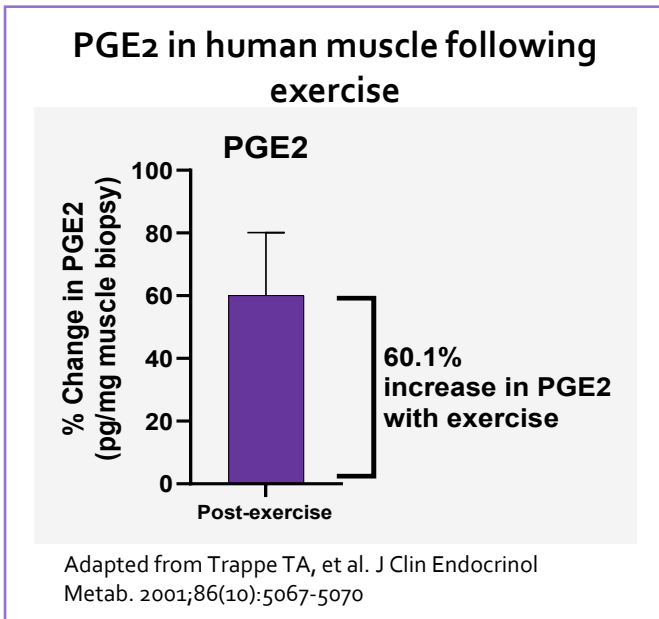
Mortality
Increased risk of death²



U.S. Population est. 331M

1. Goates S, et al. J Frailty Aging. 2019.
2. 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>

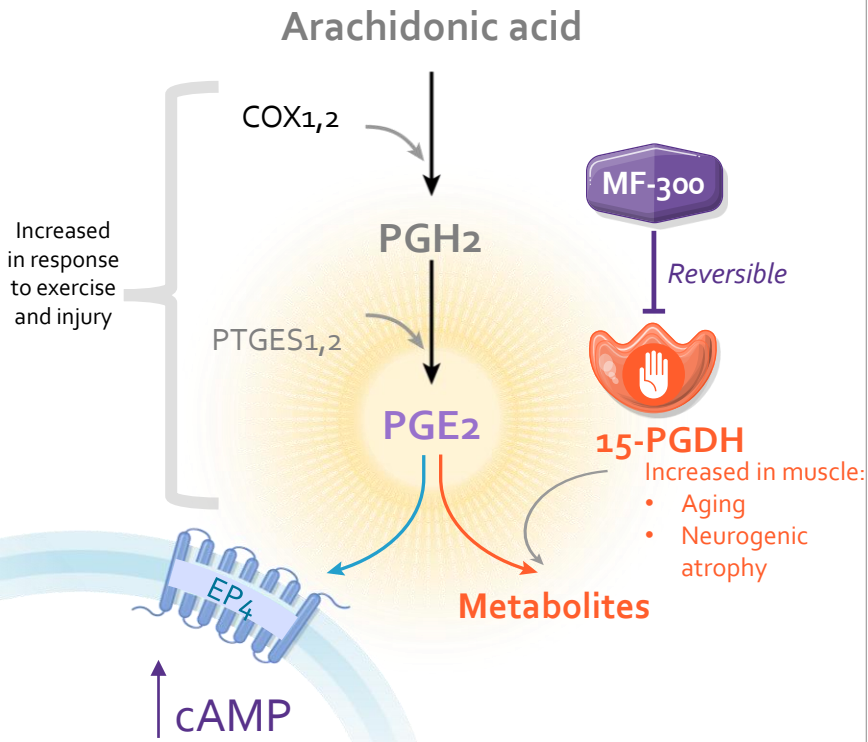
PGE₂–EP₄ Signaling Elevates cAMP to Promote Muscle Function



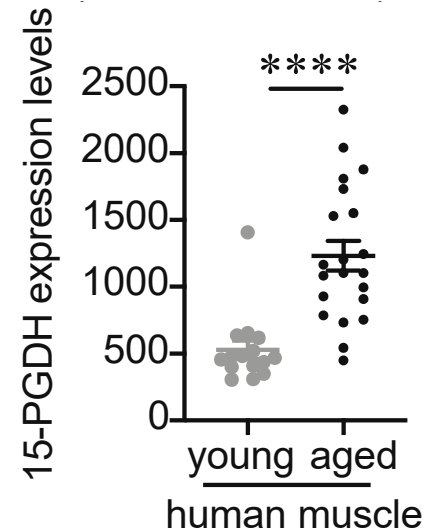
Berdeaux et al., 2012
 Ho et al., 2017
 Palla et al., 2021
 Bakooshi et al., 2023
 Epirium unpublished data

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

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

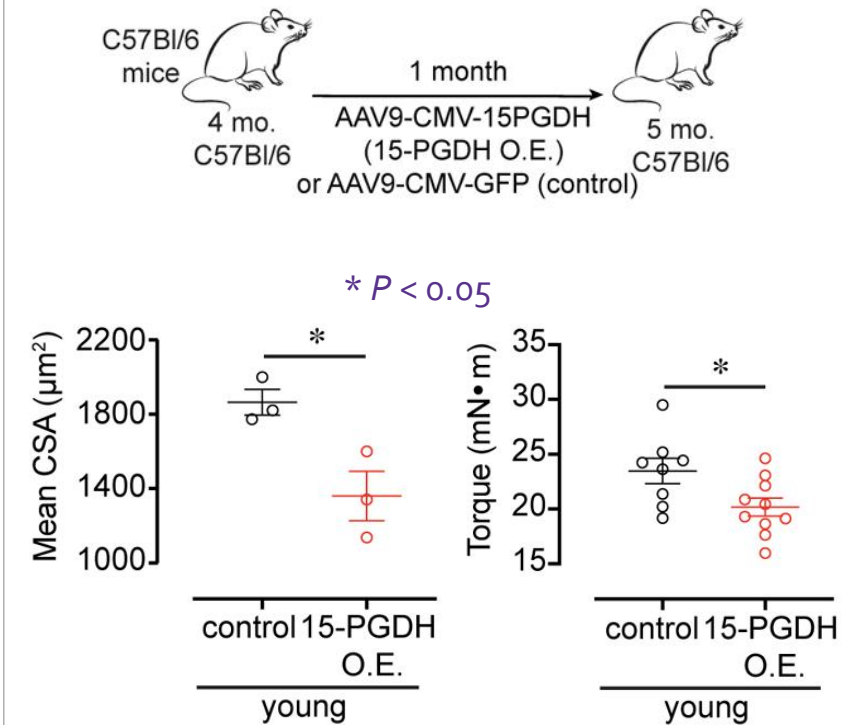


15-PGDH expression Elevated in aged human muscle¹



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

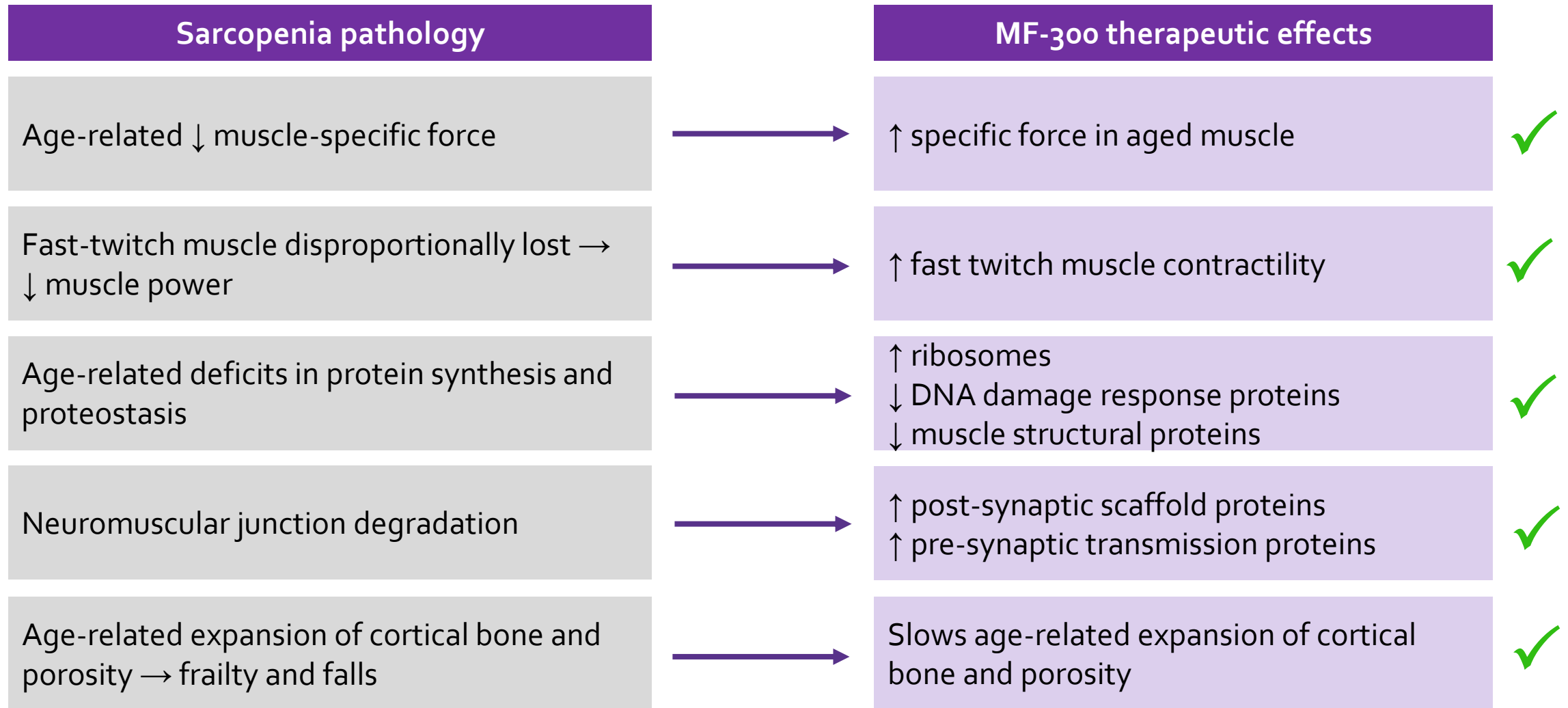
15-PGDH overexpression (O.E.) Reduces myofiber cross-sectional area (CSA) and muscle force²



cAMP, cyclic adenosine monophosphate; COX_{1,2}, cyclooxygenase enzymes 1 and 2; PGE₂, prostaglandin E₂; PGH₂, prostaglandin H₂; PTGES_{1, 2}, prostaglandin E synthase 1,2; y.o., years old

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

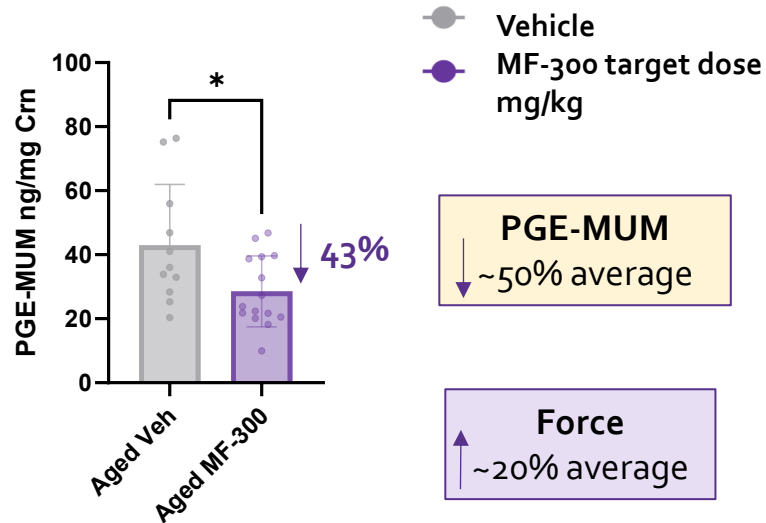
PGE2, prostaglandin E2; PGE-MUM, prostaglandin E major urinary metabolite

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

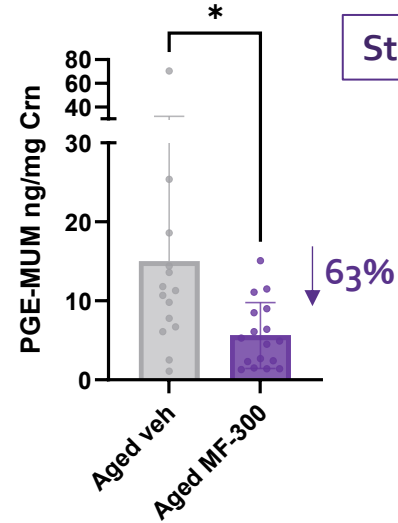
Preclinical Sarcopenia Studies

MF-300 target dose
Increased muscle force and reduced PGE₂ Metabolite in aged mice

Study 1

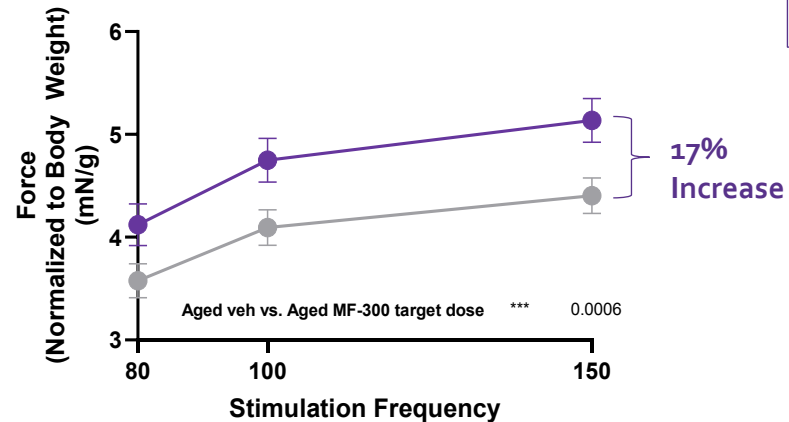
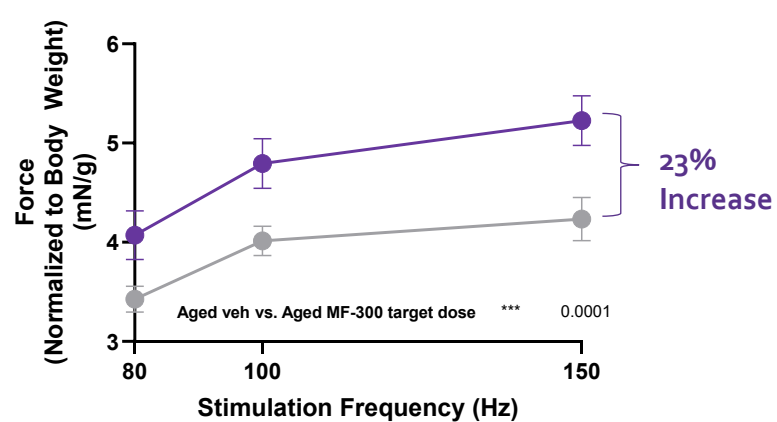


Study 2



Target Engagement Biomarker

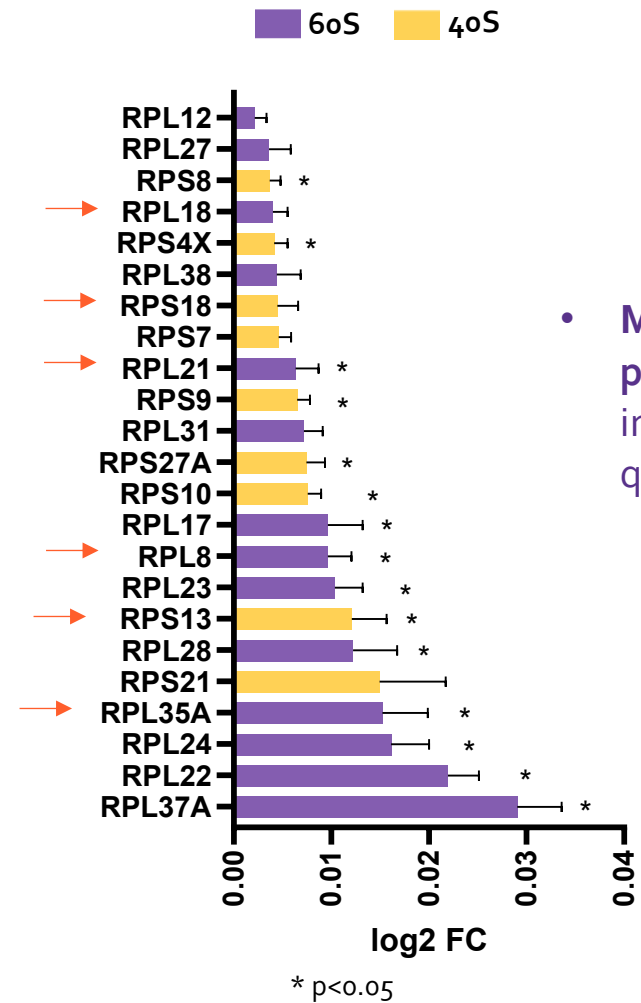
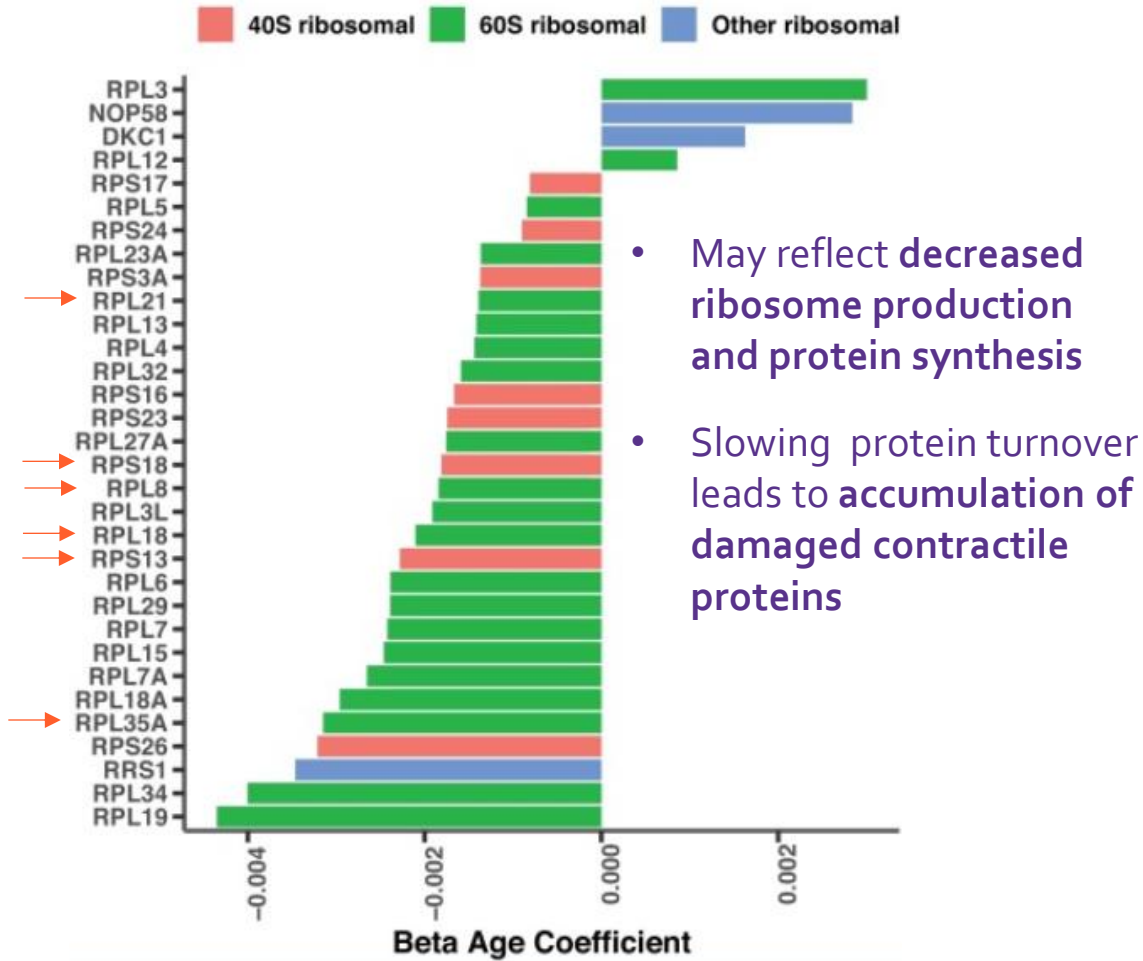
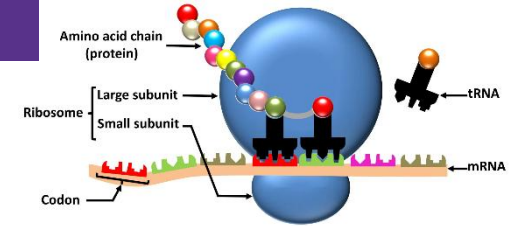
- ~50% reduction in PGE-MUM is correlated with
- ~20% improvement in muscle force



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

Reduced ribosomal protein abundance in muscle correlates with aging in human

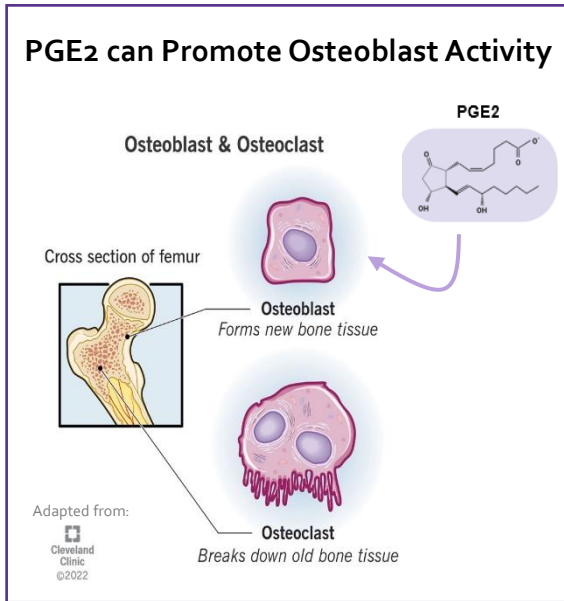
MF-300 increased abundance of large and small ribosomal proteins



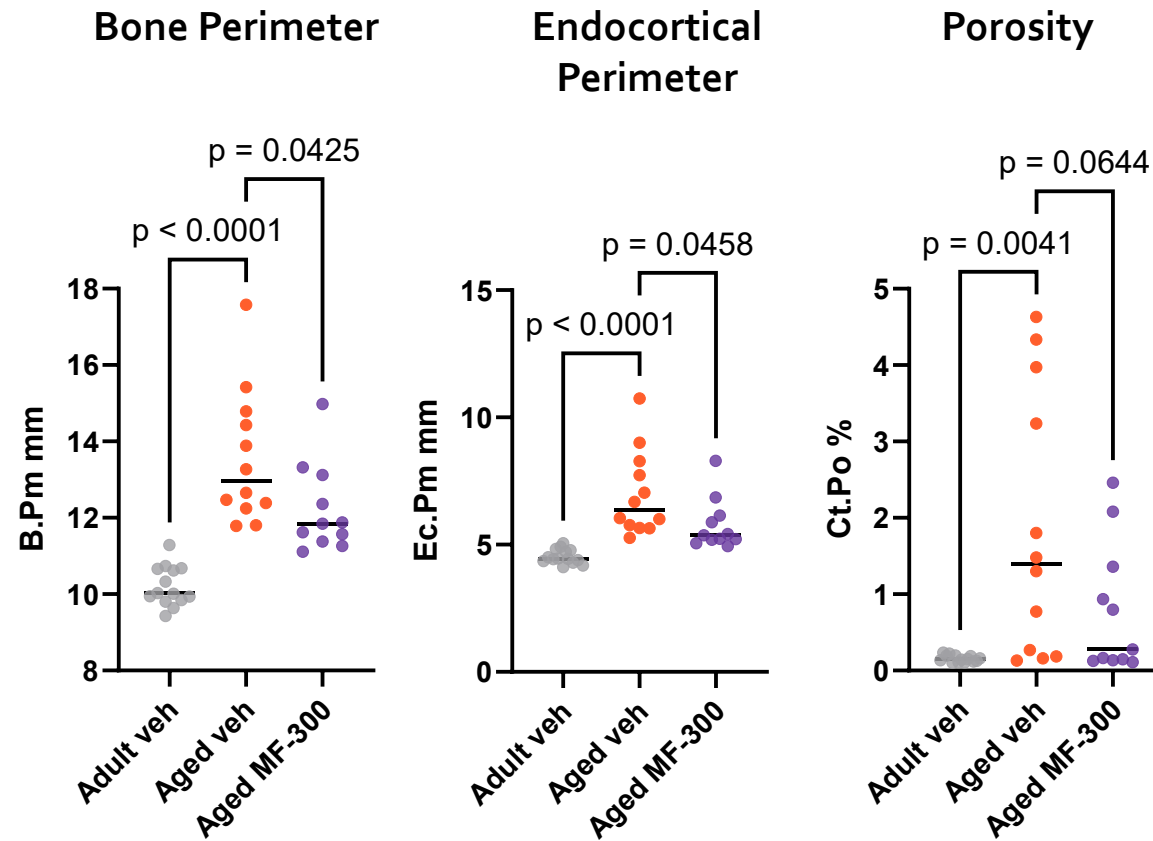
- MF-300 may increase protein turnover rate, improving muscle quality

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
- PGE₂ supports bone remodeling by balancing bone formation and resorption

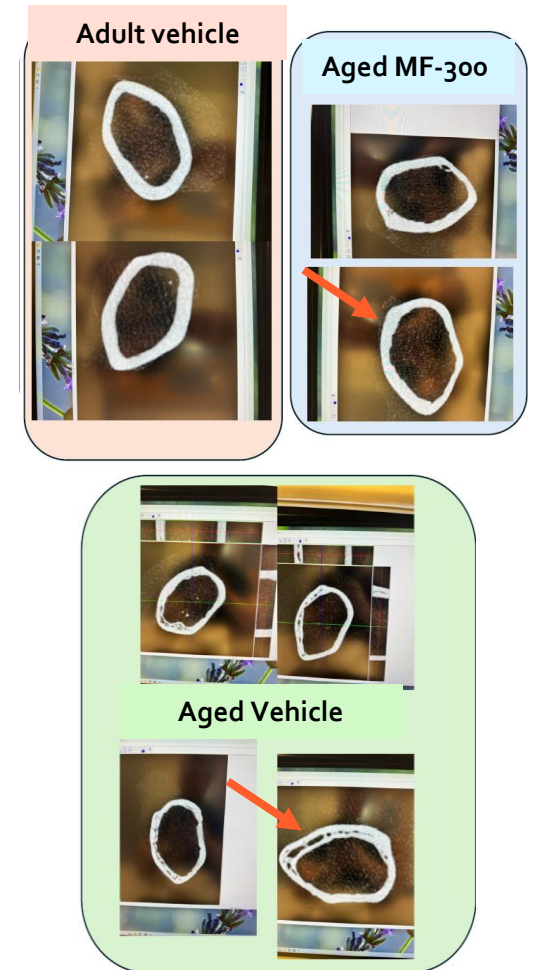


Mouse cortical bone
Micro-Computed Tomography (μCT)



12 weeks MF-300 oral administration

Cortical porosity by μCT



Data generated by: Myologica

Design: Double-blind, randomized, placebo-controlled

Objectives:

- Assess safety and tolerability of MF-300
- Characterize MF-300 pharmacokinetics and pharmacodynamics (PGE₂, PGE-MUM)

Populations:

- Younger adults ≥ 18 - ≤ 65 years; Healthy volunteers
- Older adults >65 - ≤ 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

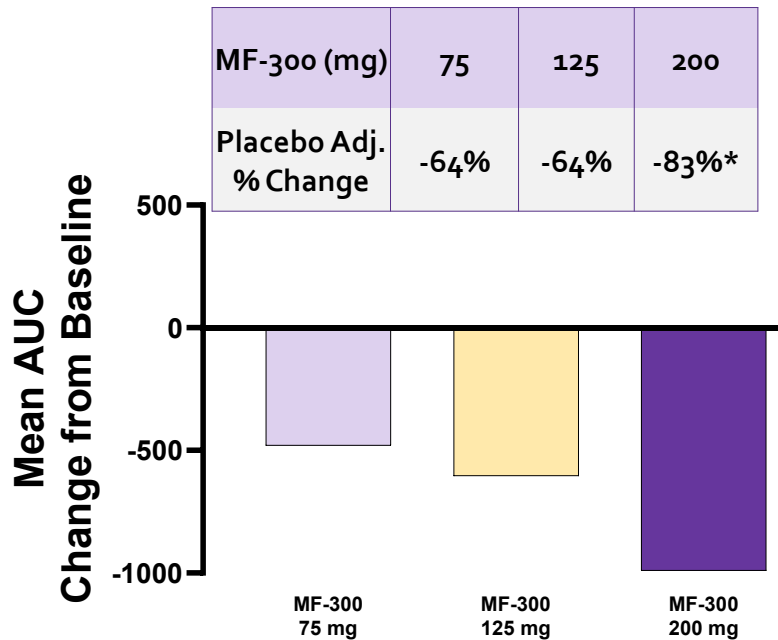
PD

- ✓ Evidence of target engagement (15-PGDH) w/ substantial reductions in PGE₂ metabolites
- ✓ Proof of mechanism: Clear evidence of mechanism with dose-related increases in PGE₂ 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

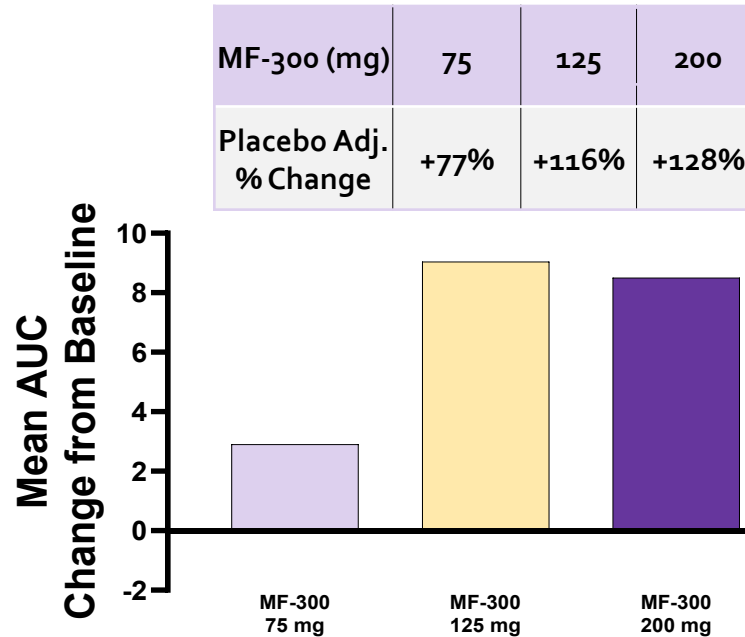
- PGE-MUM Reductions Consistent with ~20% improvement in muscle force in sarcopenia mouse model
- PGE₂ Increases consistent with that following eccentric exercise in humans (~60%)

Placebo-adjusted PGE-MUM Change from Baseline



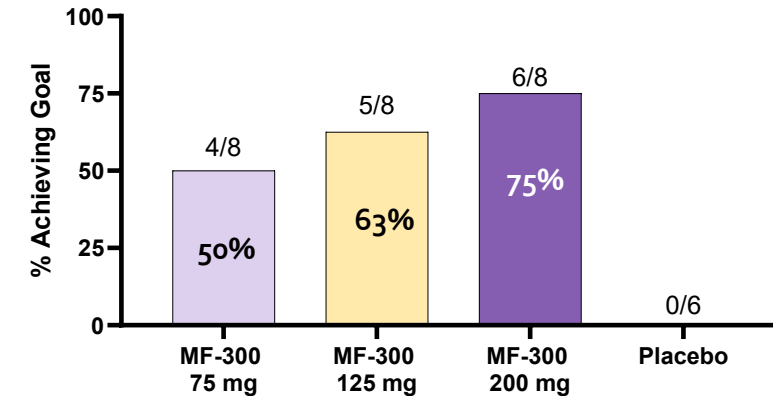
*p<0.05 versus placebo (95% CI does not include 0)

Placebo-adjusted PGE₂ Change from Baseline



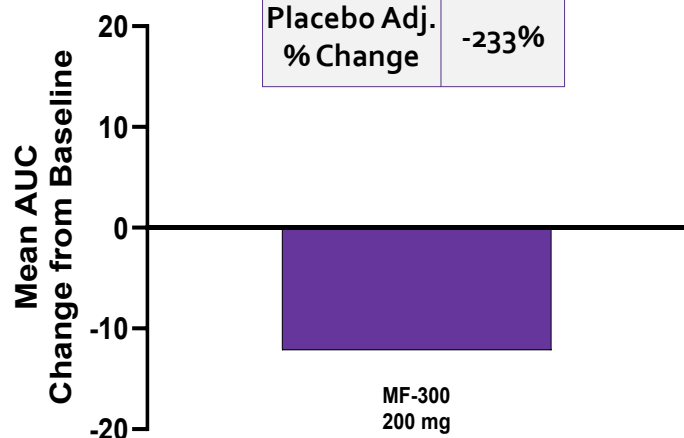
Note: Two outlier subjects in the 75 mg group, with markedly greater PGE₂ responses due to low baseline values, were excluded from analysis, including the two subjects = 614% increase in MF-300 75 mg dose group.

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



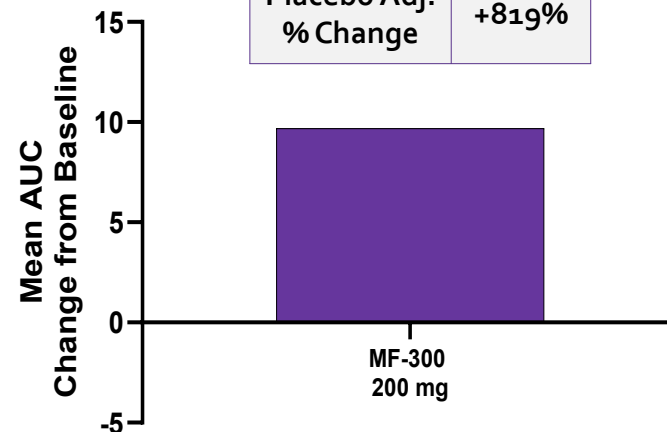
Placebo-adjusted PGE-MUM Change from Baseline

MF-300 (mg)	200
Placebo Adj. % Change	-233%

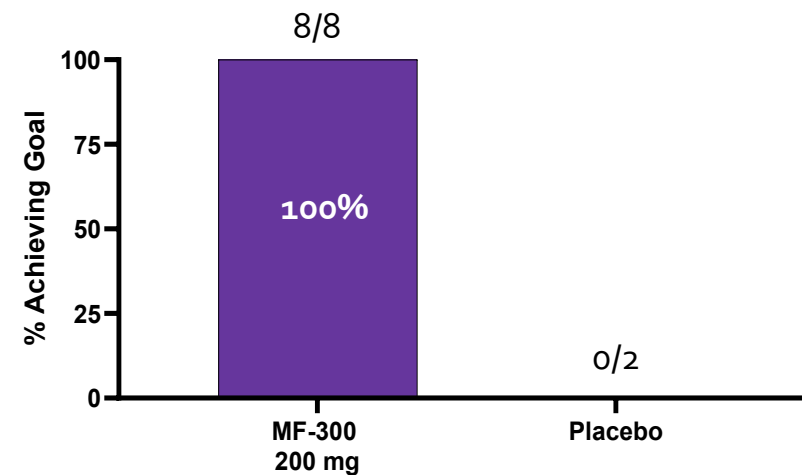


Placebo-adjusted PGE₂ Change from Baseline

MF-300 (mg)	200
Placebo Adj. % Change	+819%

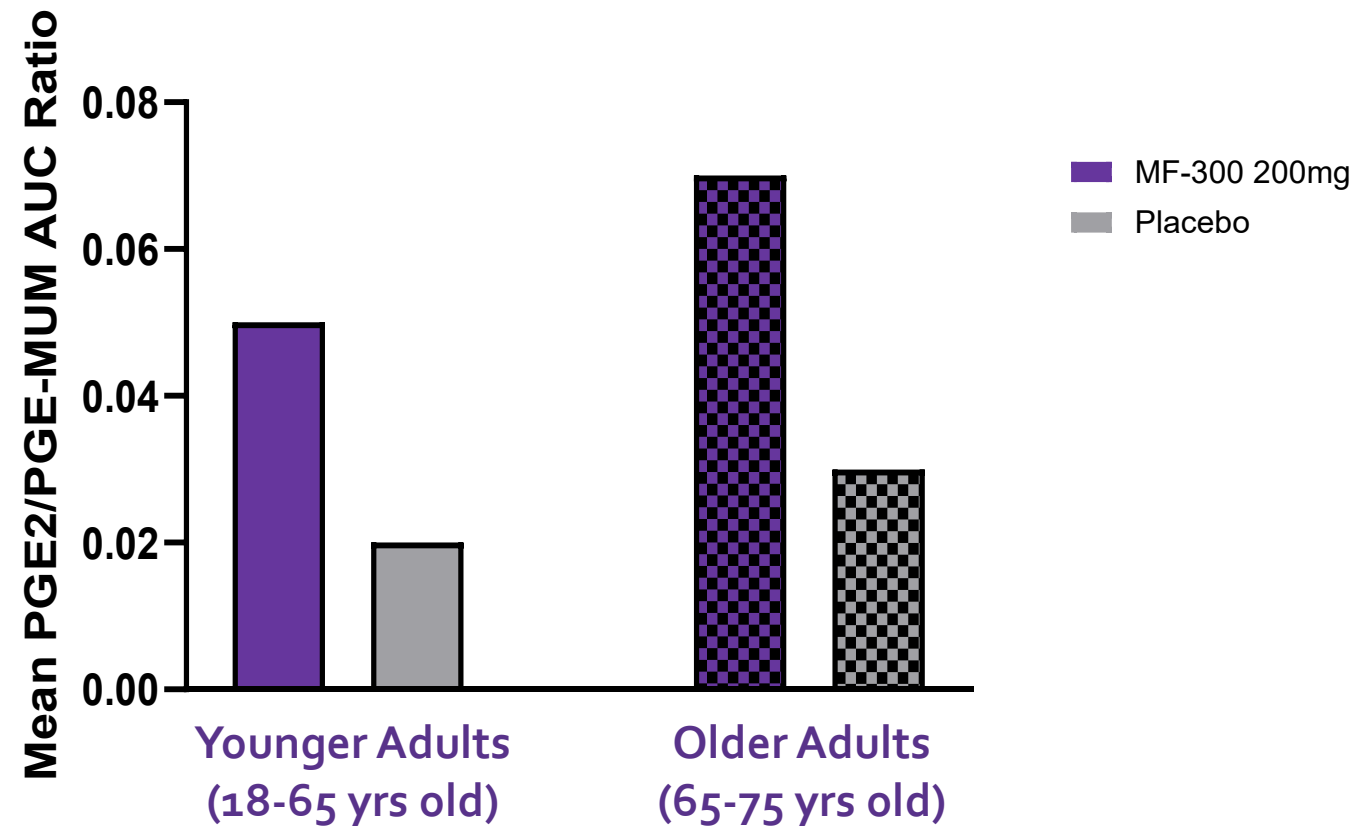


% Subjects with $\geq 50\%$ decrease in PGE-MUM & $\geq 60\%$ Increase in PGE₂

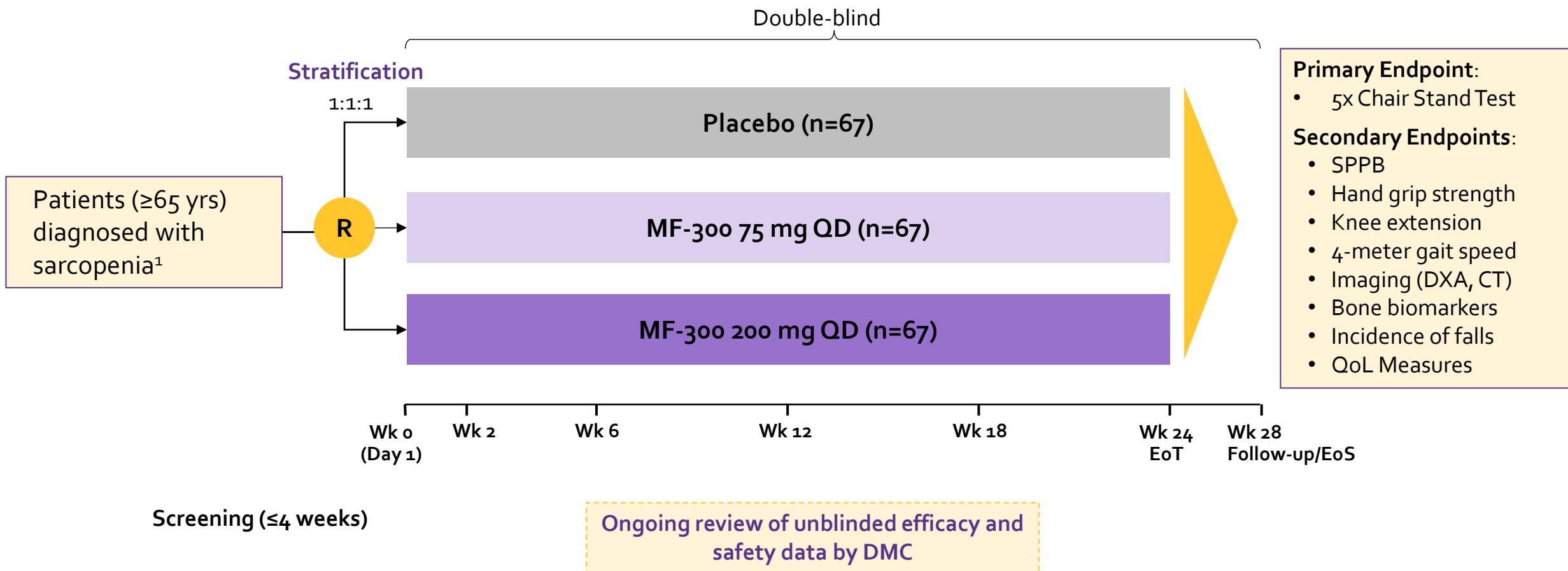


MF-300 Increases the Ratio of PGE₂/PGE-MUM Consistent with Reduced PGE₂ Catabolism in Both Age Groups

2-fold increase in PGE₂/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

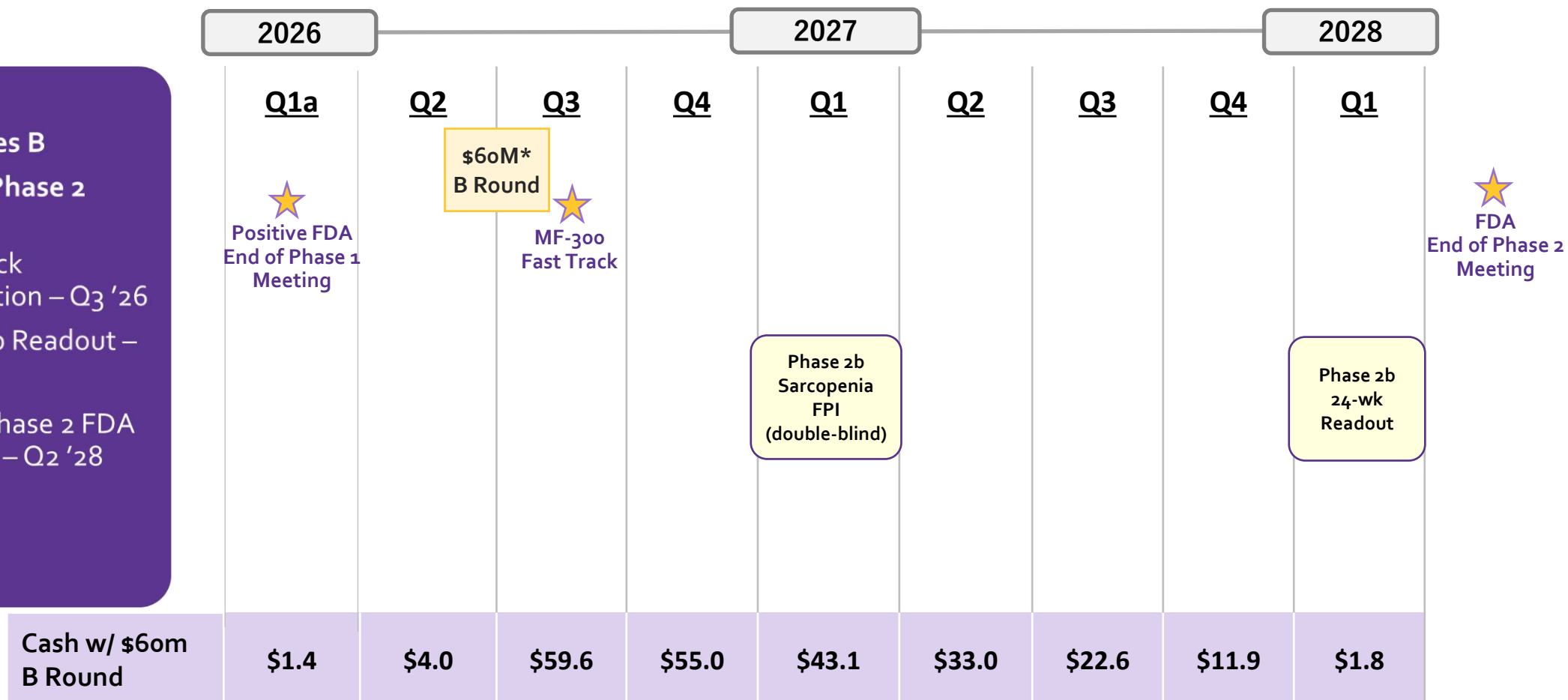
- Supports advancement of MF-300 to a Phase 2b study
- Phase 3 endpoint strategy is conditionally endorsed – regulatory risk around endpoints is reduced
- Fast Track, if accepted, will allow greater access to FDA during development and enable priority review, potentially accelerating development timelines

\$60M Series B Achieves Phase 2 Readouts – Multiple Value Inflection Points



\$60M Series B Achieves Phase 2 Readouts:

- Fast-Track Designation – Q3 '26
- Phase 2b Readout – Q1 '28
- End of Phase 2 FDA meeting – Q2 '28



- 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) ICOPE¹ & EWGSOP²

- **Strong predictor of clinical outcomes**

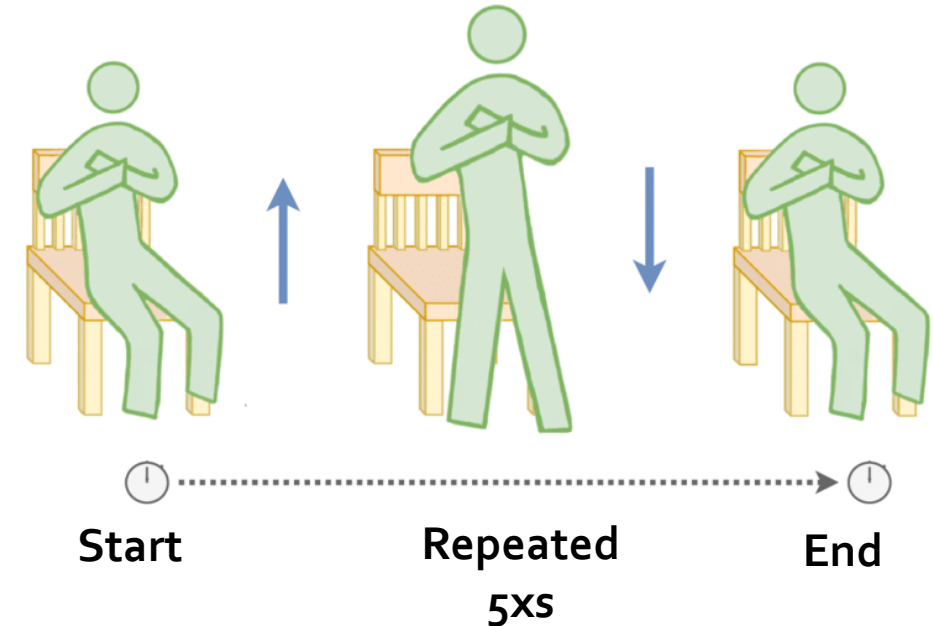
- Activities of daily living
- Fall Risk
- All-Cause Mortality

- **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

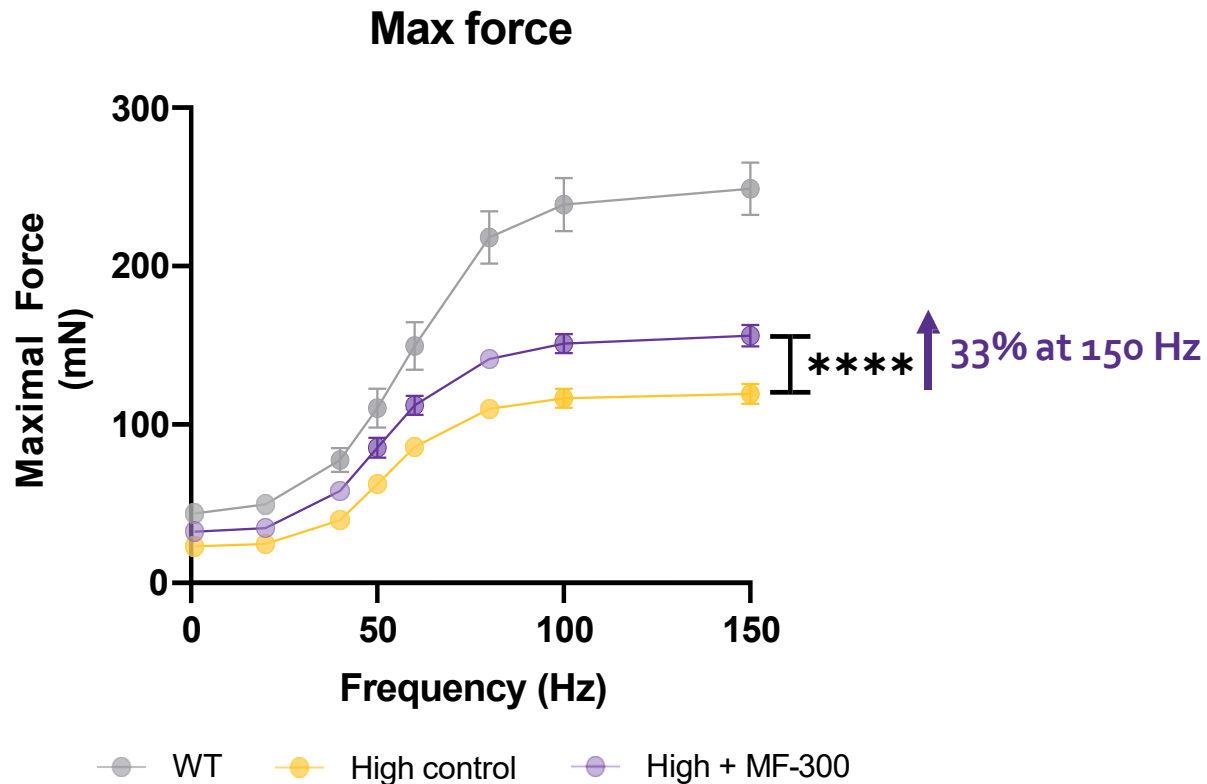
5xs Chair Stand Test



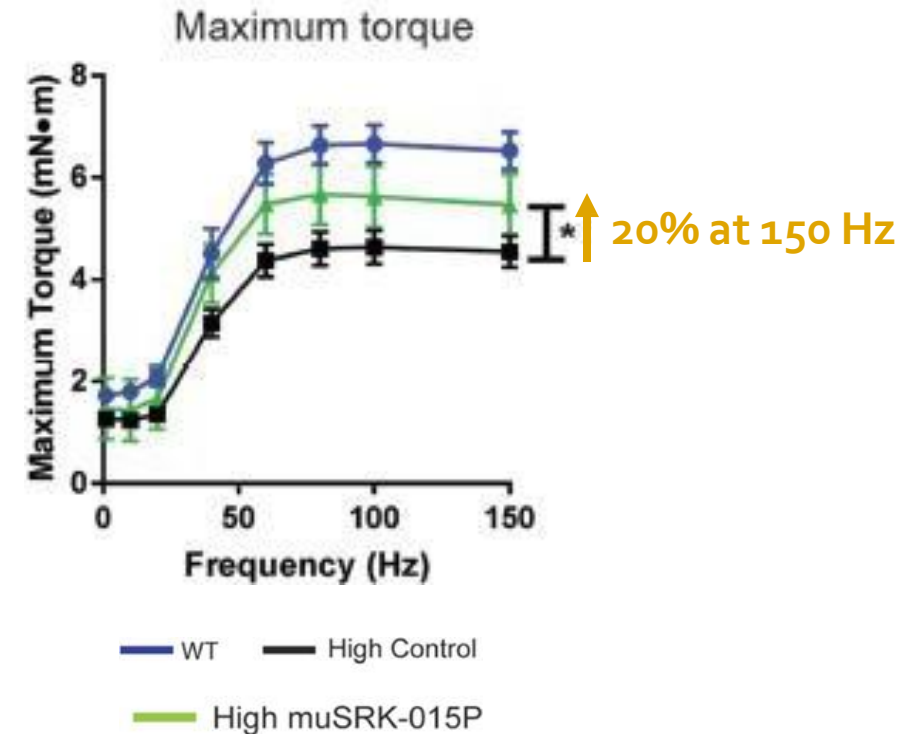
1. ICOPE=Integrated Care for Older People ([9789240103726-eng.pdf](https://www.who.int/publications/i/item/9789240103726-eng))

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 Δ 7 High/High Male mice



mSRK-015P in mouse Δ 7 High/High Male and female mice

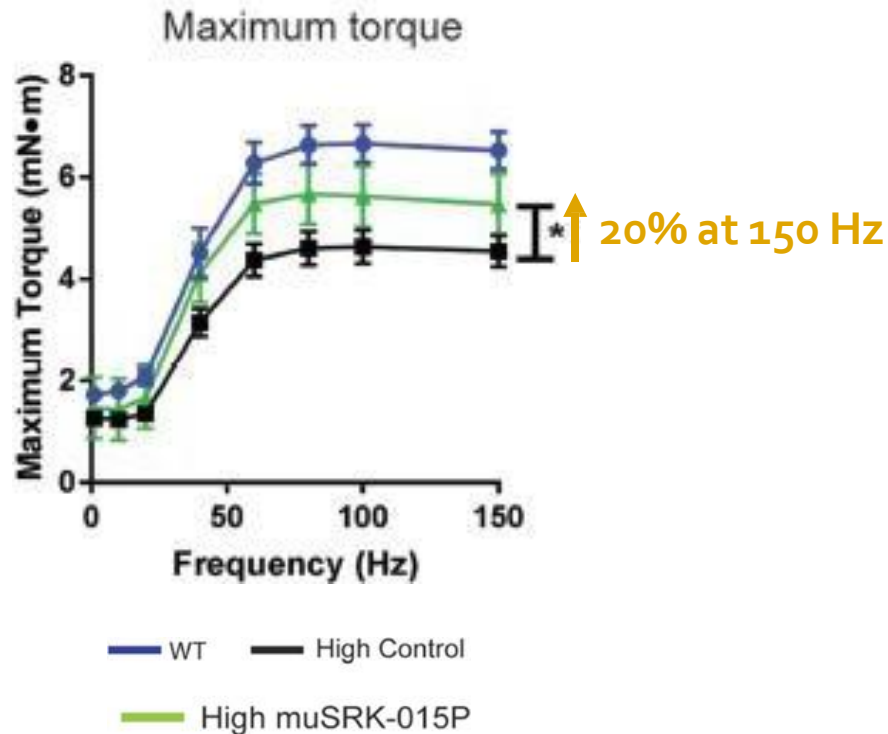


Force = Torque

MYOLOGICA

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

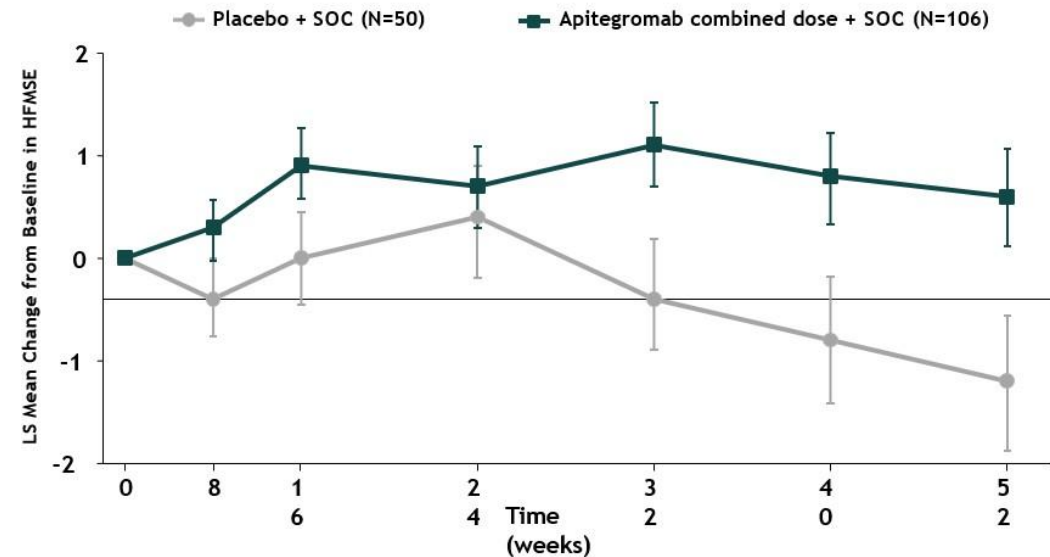
mSRK-015P in mouse $\Delta 7$ High/High



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

Apitegromab in SMA + SOC (Ph 3 SAPPHERE)

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

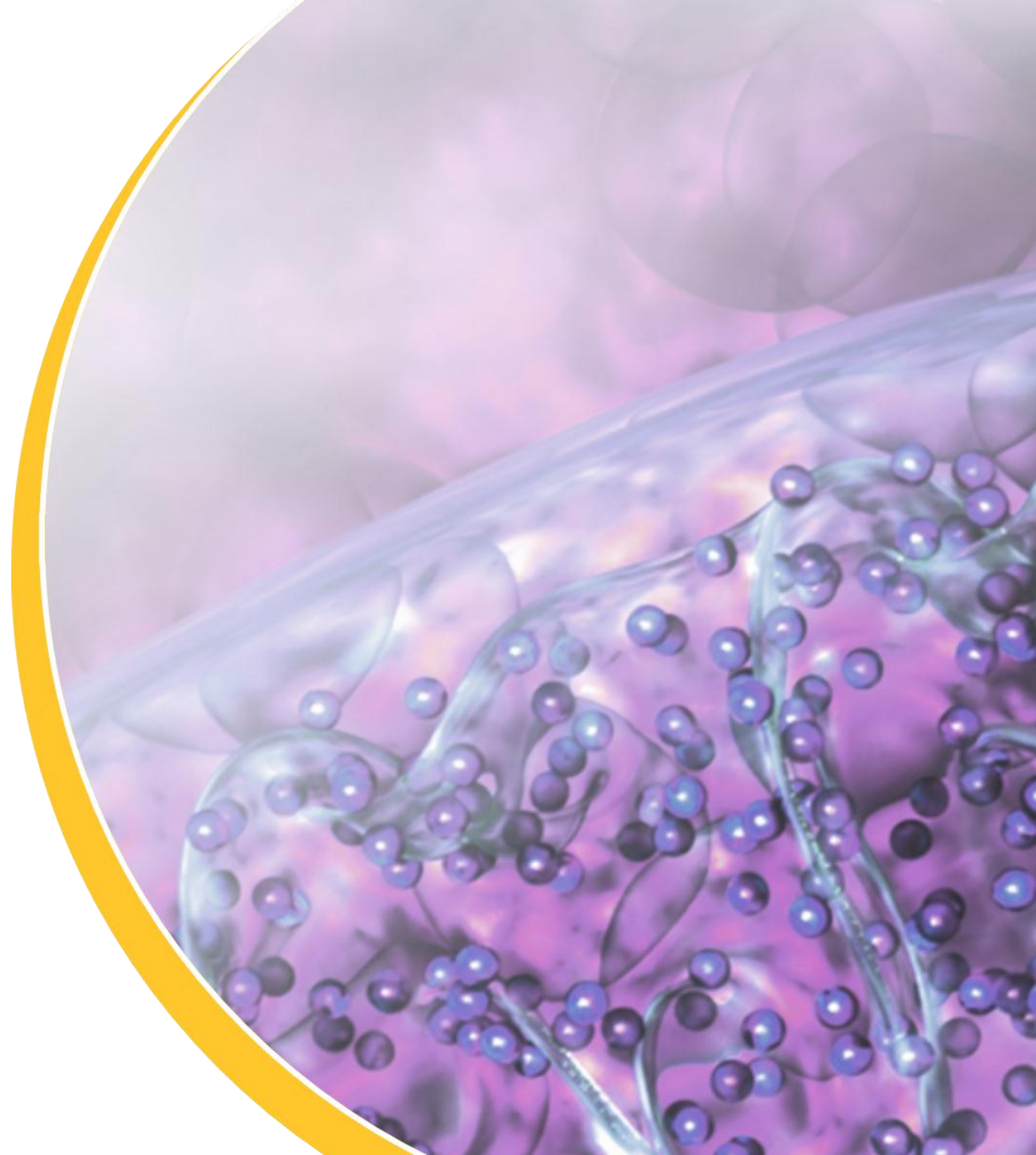
Fmr. FDA, Deputy Dir. Endocrinology Division

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



Epirium's 15-PGDH inhibitor platform:

- IBD Preclinical Efficacy: Mucosal Healing in DSS induced Colitis
- Poster Presentation DDW May '26



Proven Mechanistic Rationale for the Treatment of IBD: Inhibiting 15-PGDH to Increase Physiological PGE₂

The PGE₂/EP₄ axis
improves outcomes in DSS
colitis models

15-PGDH



PGE₂



EP₄



↓ Inflammation

↑ Mucosal protection/healing

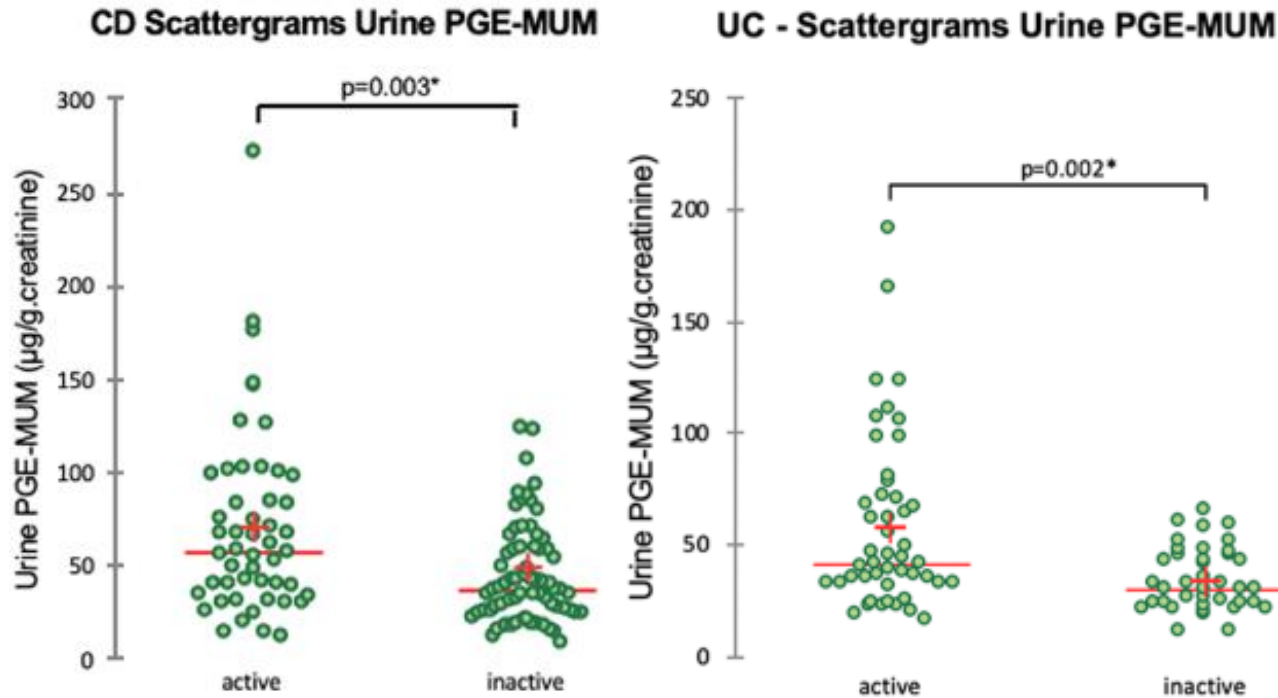
Intervention / genetic model	Species & colitis model	Key outcomes	Reference
SW033291 (15-PGDH inhibitor, IP)	Mouse, DSS colitis	<ul style="list-style-type: none"> Reduced % ulcerated colon area Improved disease activity Reduced pro-inflammatory cytokines Increased crypt cell proliferation 	Zhang et al., 2015
HW201877 (15-PGDH inhibitor, PO)	Mouse, DSS colitis	<ul style="list-style-type: none"> Improved DAI Improved colon length Improved histological measures 	Li et al., 2025
<i>Hpgd</i> knockout (15-PGDH gene)	Mouse, DSS colitis including older mice	<ul style="list-style-type: none"> Minimize weight loss Improved colon length & histology scores 	Zhang et al., 2015; Ho et al., 2022
AGN205203 (EP ₄ agonist)	Mouse, DSS (and DSS+indomethacin) colitis	<ul style="list-style-type: none"> Improved DAI Improved histology: preserved epithelium, reduced epithelial apoptosis, preserved goblet cells, enhanced epithelial regeneration 	Jiang et al., 2007
ONO-AE1-329 (EP ₄ agonist)	Rat & Mouse DSS colitis	<ul style="list-style-type: none"> Reduced erosion/ulceration Suppressed mucosal damage and inflammation <i>EP₄ KO & EP₄ antagonist worsened colitis</i> 	Kabashima et al. (JCI) 2002; Nitta et al. 2002
KAG-308 (EP ₄ agonist)	Mouse, DSS colitis	<ul style="list-style-type: none"> Suppressed DSS colitis onset Promoted histological mucosal healing Reduced TNFα production <i>EP₄ antagonist increased mortality</i> 	Watanabe et al., 2015
PGE ₂ (Exogenous)	Mouse, DSS colitis	<ul style="list-style-type: none"> Alleviated mucosal injury Promoted epithelial protection/healing 	Peng et al. 2017

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

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

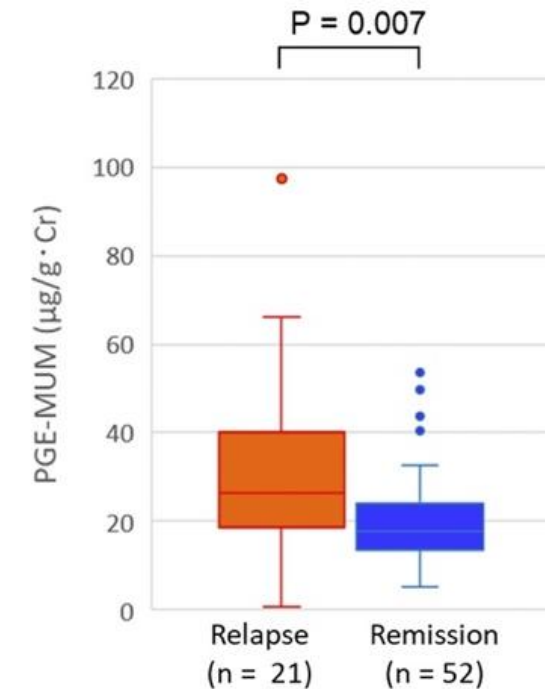
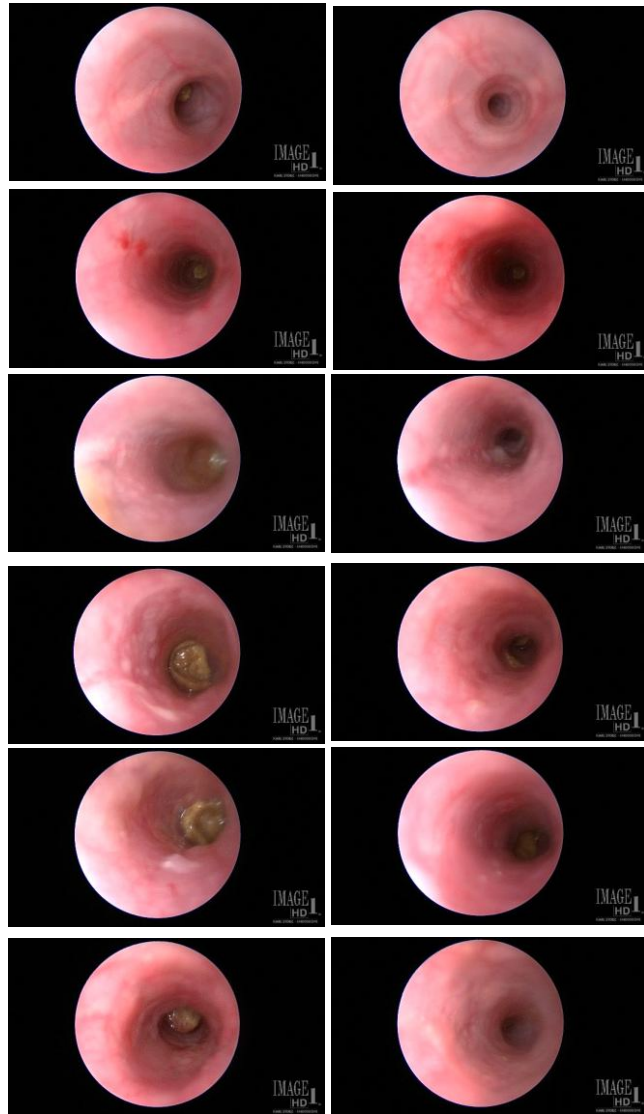


Figure from Ishida et al. *Clin Transl Gastroenterol*. 2022;13;7

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: At Day 19 Endoscopy, All MF-300 Doses Significantly Reduced Colitis Severity, Comparable to Anti-p40 Positive Control



Naive
Mean endoscopy score: 0.20

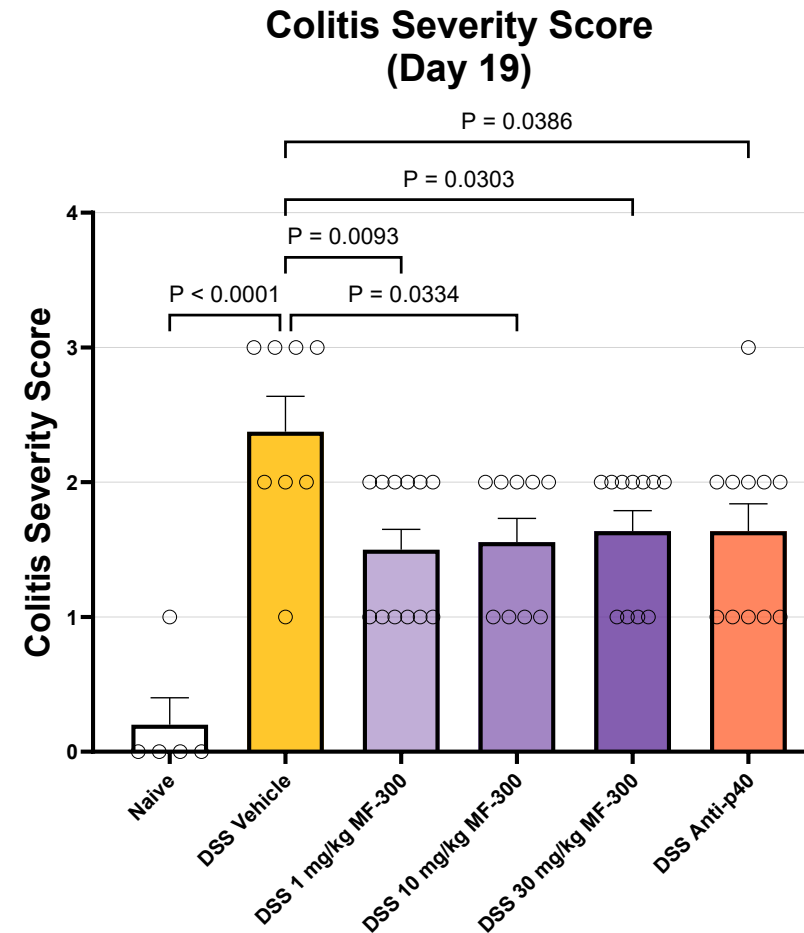
DSS Vehicle
Mean endoscopy score: 2.38

DSS 1 mg/kg MF-300
Mean endoscopy score: 1.50

DSS 10 mg/kg MF-300
Mean endoscopy score: 1.56

DSS 30 mg/kg MF-300
Mean endoscopy score: 1.64

DSS Anti-p40
Mean endoscopy score: 1.73



• 2way ANOVA w/ Holm-Šídák's multiple comparisons test

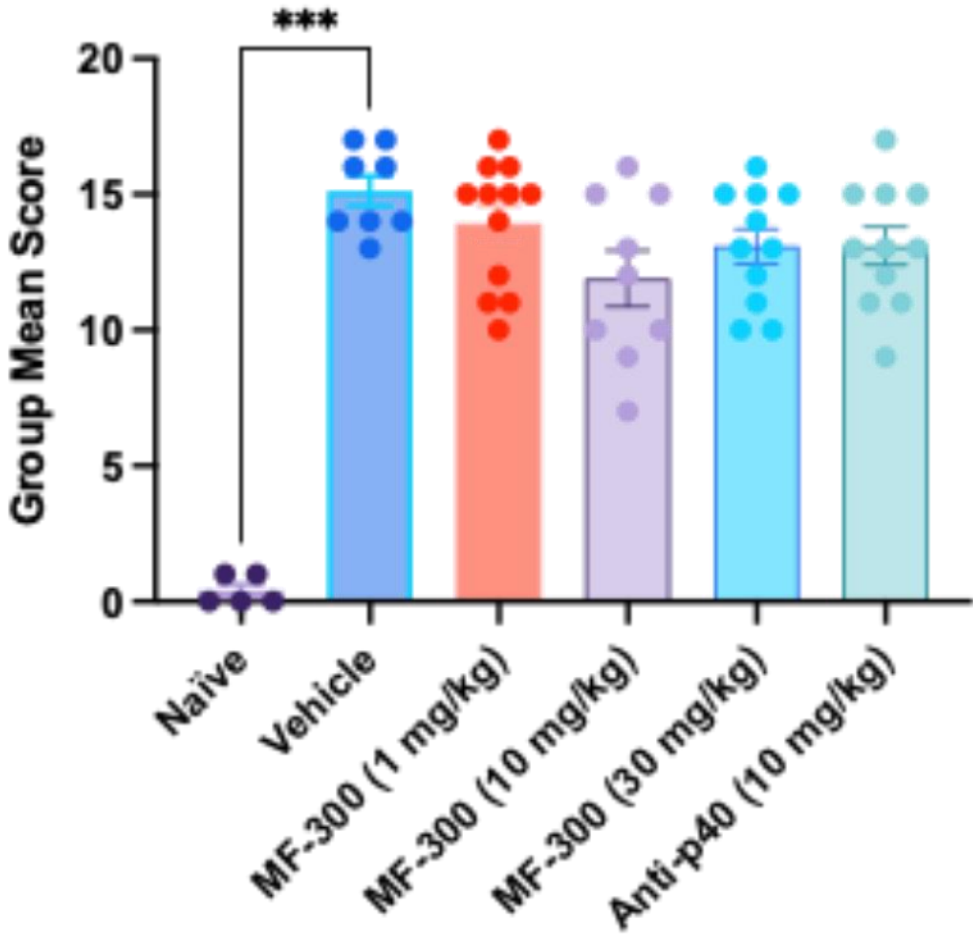
Colitis Severity Score % Change Relative to Vehicle	
	Day 19
Naive	-92%
Vehicle	--
1 mg/kg MF-300	-37%
10 mg/kg MF-300	-35%
30 mg/kg MF-300	-31%
anti-p40*	-27%*

*Feedback from BioModels (CRO): Consistent with maximal effect for anti-p40 in this DSS model

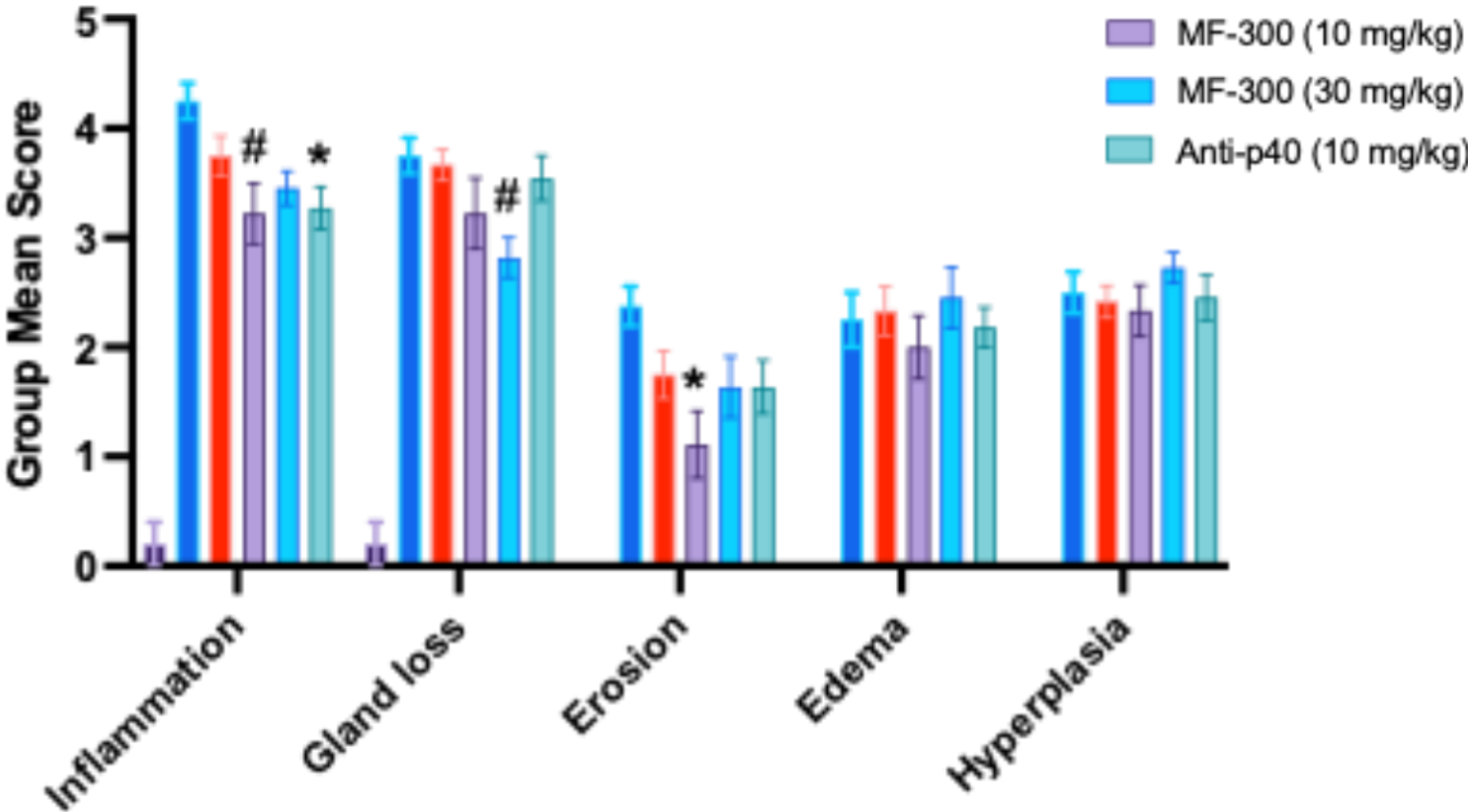
Study #3: MF-300 Drives Broad Histological Improvement Across Multiple Disease Markers in DSS Colitis Equivalent or Better Than Anti-P40



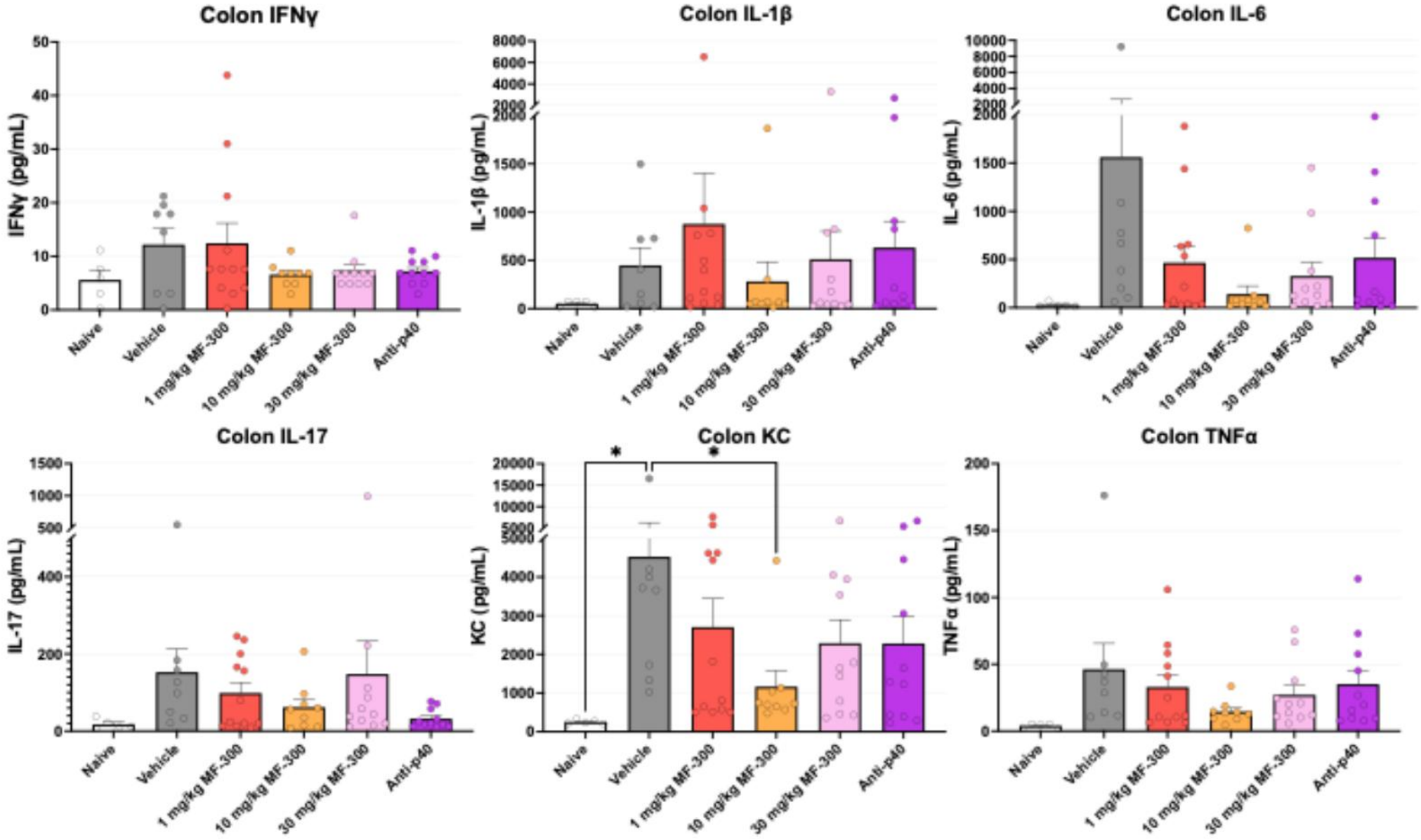
Mouse Distal Colon Mean Sum Scores



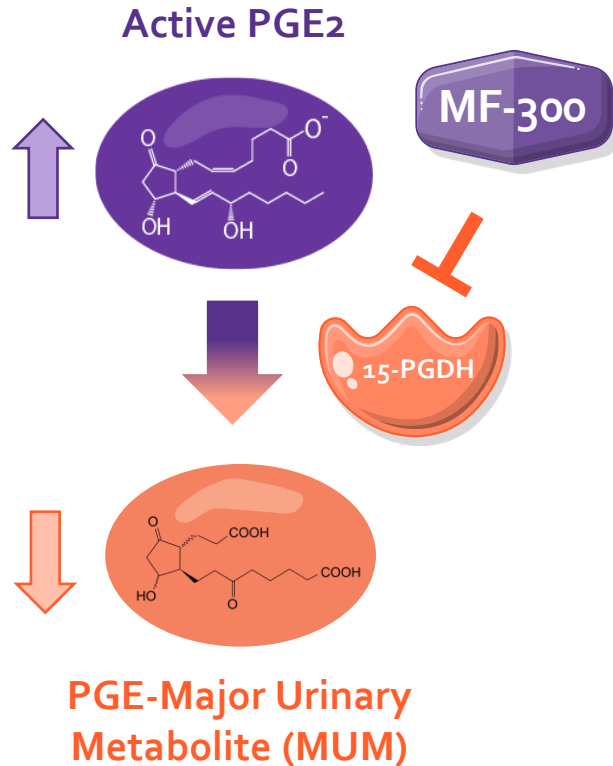
Mouse Distal Colon Mean Histopathology Scores



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 PGE₂ metabolite^{1,2}
- ✓ Elevated in active UC & CD; tracks to disease activity^{3,4,5}
- ✓ Detects mucosal healing during clinical remission⁶
- ✓ Reflects CD endoscopic activity⁷
- ✓ Predicts relapse in long duration UC⁸
- ✓ Combination with fecal calprotectin may improve inflammation profiling in UC and CD⁹

¹ Miyamoto et al., 2024

² Gross et al., 2005

³ Arai et al., 2014

⁴ Arai et al., 2016

⁵ Fujiwara et al., 2000

⁶ Sakurai et al., 2022

⁷ Ishida et al., 2025

⁸ Ishida et al., 2022

⁹ D'Inca et al., 2025

- **PGE-MUM** is a stable downstream metabolite of PGE₂
- **Target engagement & disease biomarker hypothesis for IBD:** Reduced PGE-MUM will demonstrate inhibition of 15-PGDH and stabilization of therapeutic PGE₂ levels in the diseased intestine