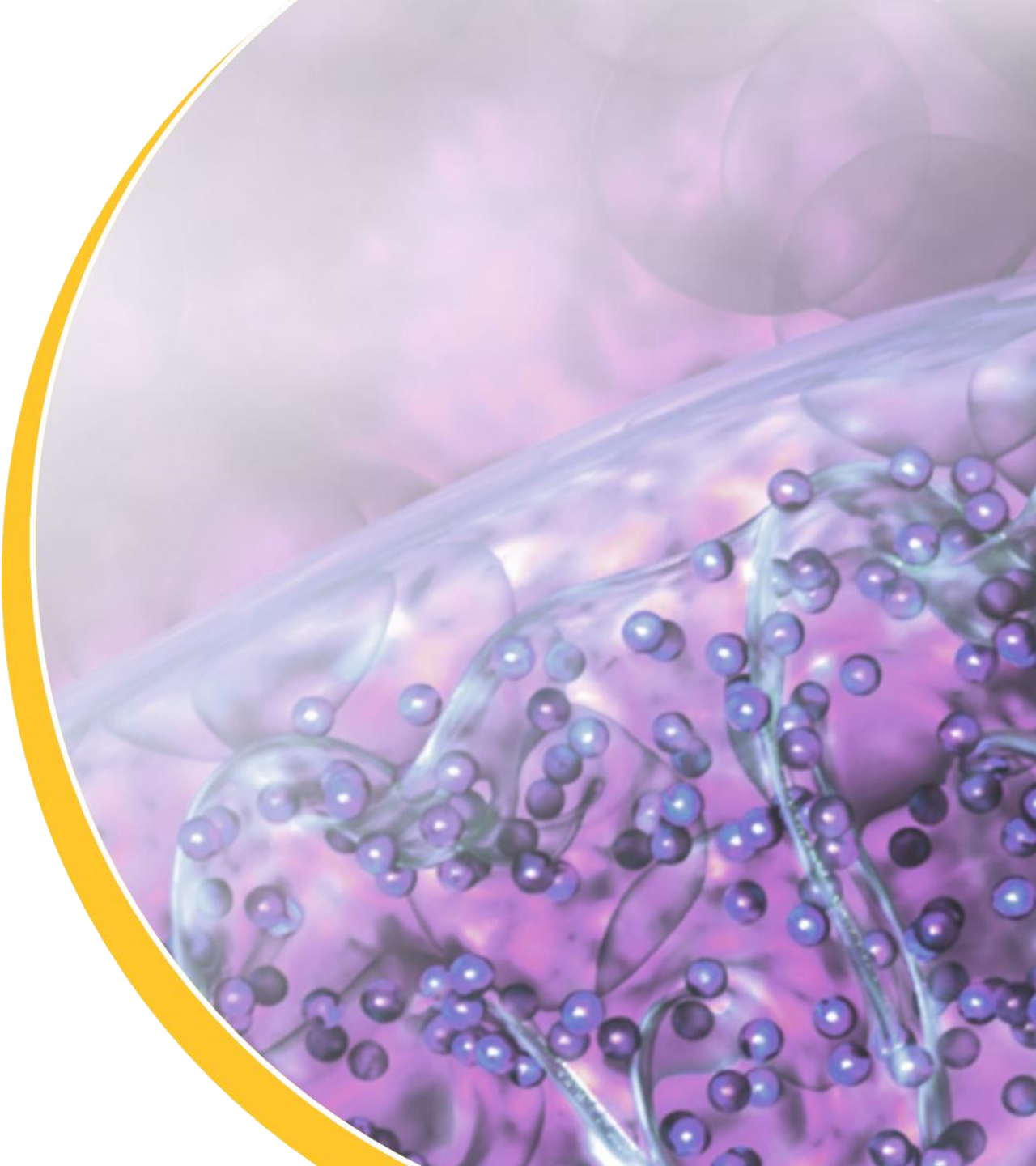




**Oral 15-PGDH Inhibitor Platform:**  
Leveraging PGE<sub>2</sub> Signaling To Treat  
Sarcopenia, Neuromuscular &  
Inflammatory Diseases (IBD):

- MF-300, lead oral small molecule,  
Phase 2b 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)



### Eric Miller, CFO

Head Finance, Synthorx (acq. Sanofi)

Corp. Controller & Head FP&A, Acadia Pharm.

Cadence Pharm. (acq. Mallinckrodt)



### Micah Webster, Ph.D. Sr. Director, TS

Ph.D. in Cellular and Molecular Biology, JHU

Scholar Rock, Associate Director, Translational Science

Discovery programs & Biomarker Strategy for apitegromab

## Key Consultant Advisors



### Leigh MacConell, Ph.D. Clinical Development

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



### 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



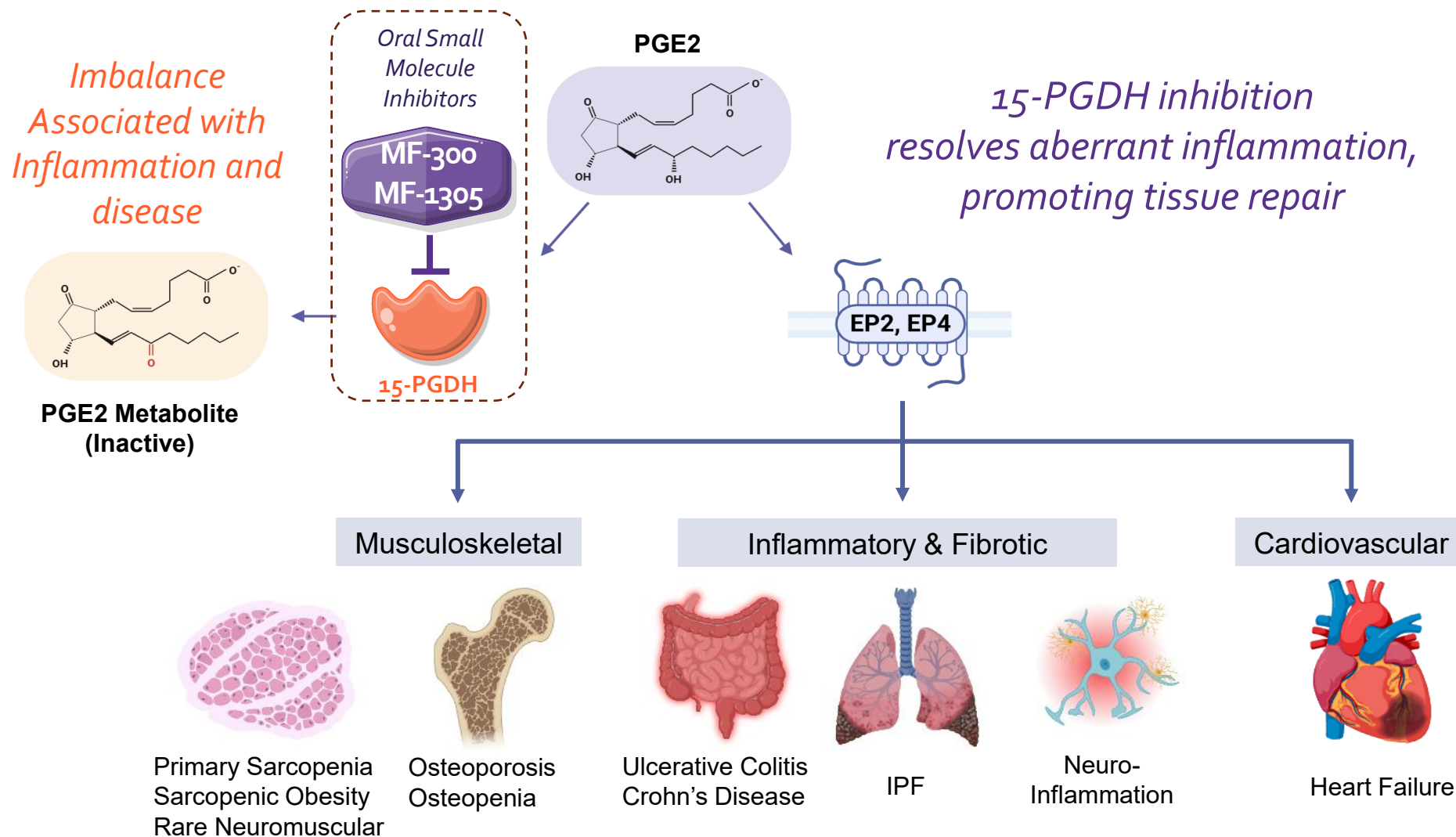
### Roger Fielding, Ph.D. Professor of Medicine

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

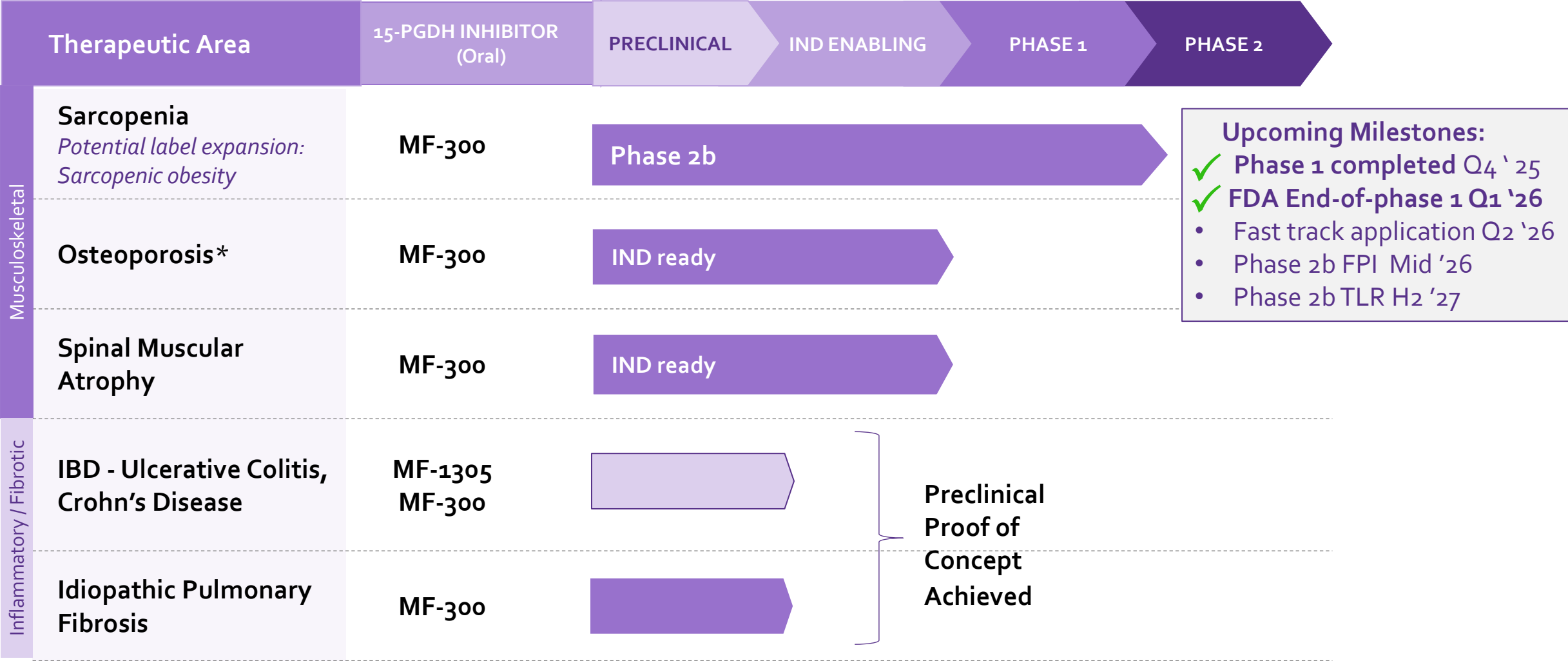
Published over 200 per-reviewed papers and 8,000 citations

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

Inhibiting 15-PGDH to leverage the potential of PGE<sub>2</sub> signaling in restoring tissue homeostasis: rebalancing inflammation, stimulating regeneration, reducing fibrosis



# 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

## Epirium MF-300 Lead Program in Sarcopenia:

- Unmet Need
- Scientific Rationale
- Preclinical Muscle Force & Biomarker Results



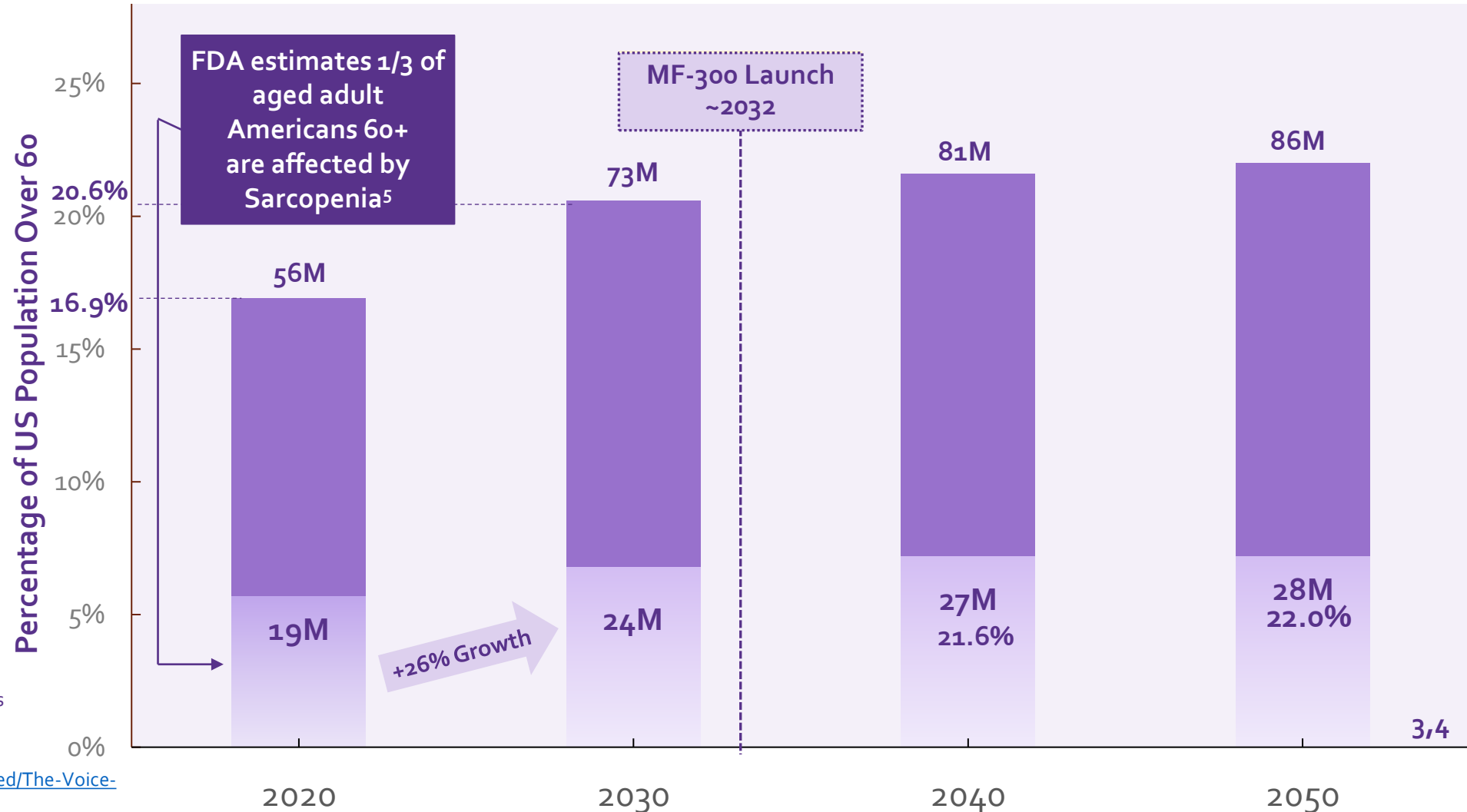
# Sarcopenia: Large and Growing Unmet Medical Need w/ No FDA Approved Therapy

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.

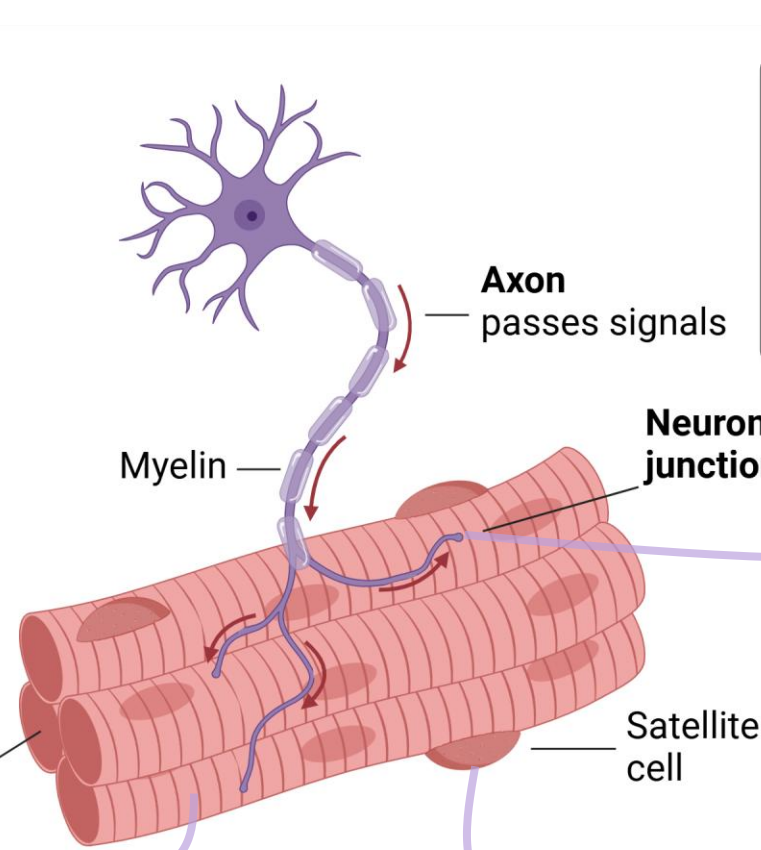
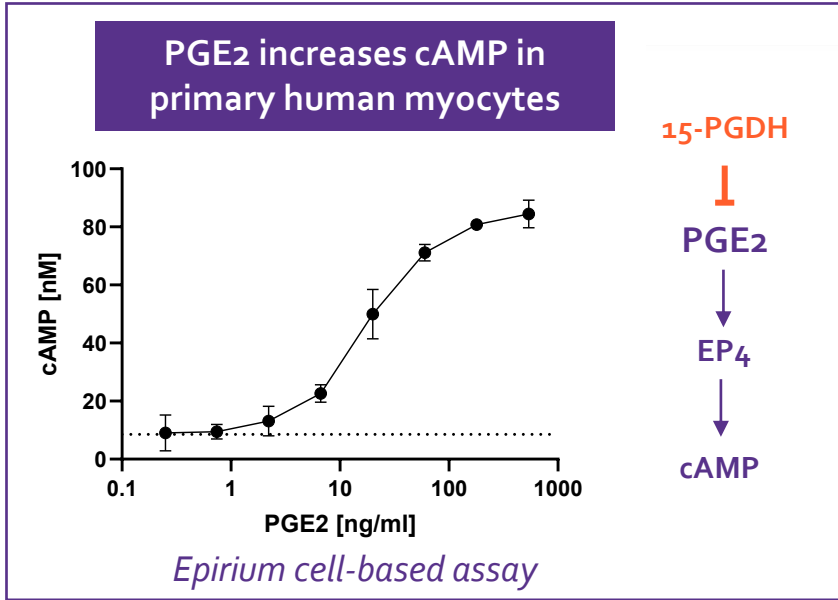
2. [www.agingresearch.org](http://www.agingresearch.org). Sarcopenia Facts and Figures

3. Burns ER, J Safety Res. 2016.

4. Papadopoulou SK. Nutrients. 2020.

5. <https://www.fda.gov/files/about%20of%20fda/published/The-Voice-of-the-Patient--Sarcopenia.pdf>

# 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. Bakooshi<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

PNAS

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

Andrew T. V. Ho<sup>1\*</sup>, Adelaida R. Palla<sup>1</sup>, Matthew R. Blake<sup>6</sup>, Nora D. Yucel<sup>6</sup>, Yu Xin Wang<sup>9</sup>, Klas E. G. Magnusson<sup>10</sup>, Colin A. Holbrook<sup>9</sup>, Peggy E. Kraft<sup>9</sup>, Scott L. Delp<sup>5</sup>, and Helen M. Blau<sup>1,2</sup>

<sup>†</sup>Baxter Lab, Stanford Sci Systems, Linn Stanford Un

Cell Stem Cell

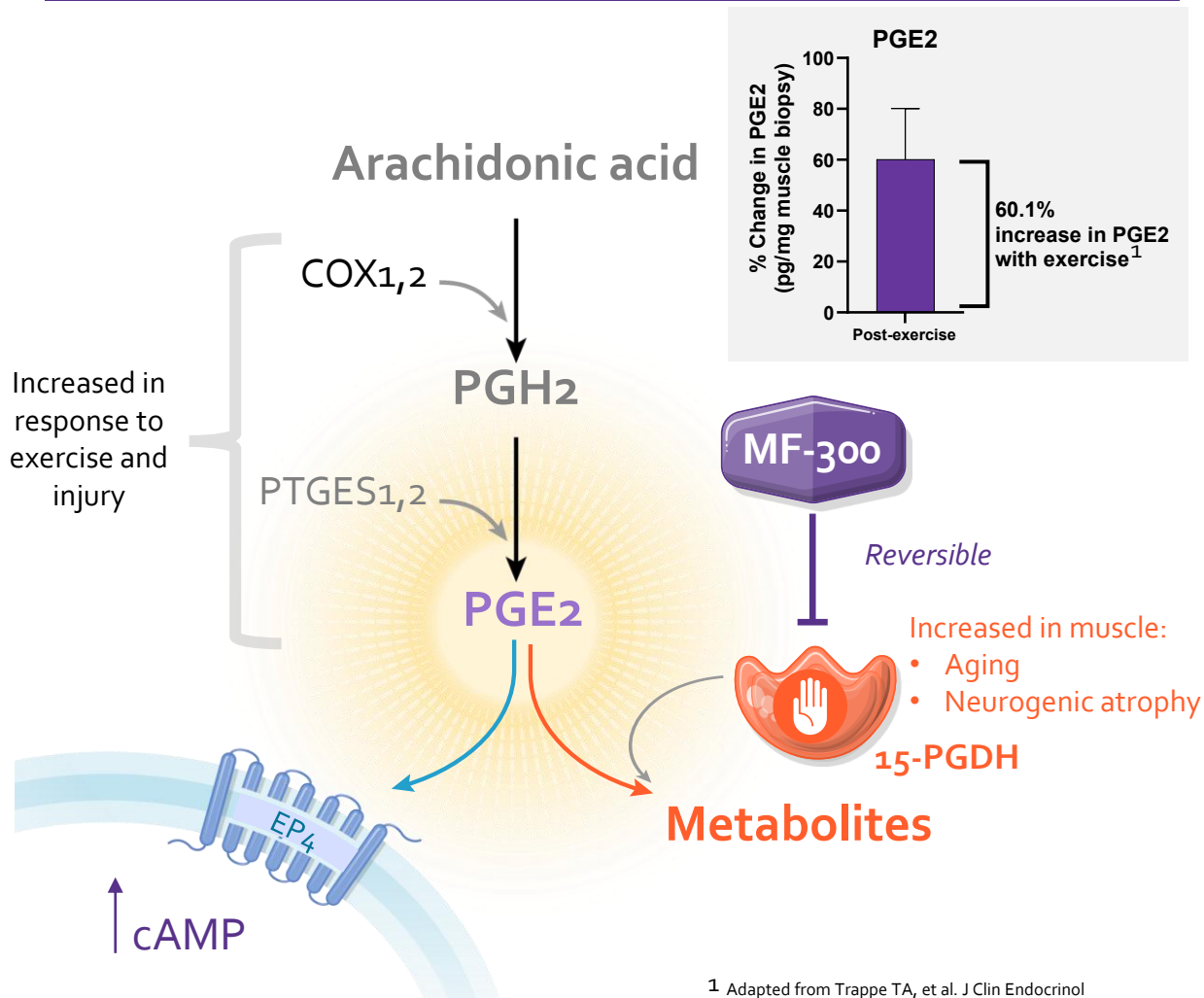
Article

**Multiomic profiling reveals that prostaglandin E2 reverses aged muscle stem cell dysfunction, leading to increased regeneration and strength**

Yu Xin Wang<sup>1,2,12</sup>, Adelaida R. Palla<sup>1,12</sup>, Andrew T.V. Ho<sup>1,8,12</sup>, Daniel C.L. Robinson<sup>1</sup>, Meenakshi Ravichandran<sup>1</sup>, Glenn J. Markov<sup>1</sup>, Thach Mai<sup>1</sup>, Chris Still<sup>11,12</sup>, Akshay Balasubramani<sup>1,2</sup>, Surag Nair<sup>4</sup>, Colin A. Holbrook<sup>1</sup>, Ann V. Yang<sup>1</sup>, Peggy E. Kraft<sup>1</sup>, Shiqi Su<sup>1,2</sup>, David M. Burns<sup>1,11</sup>, Nora D. Yucel<sup>1</sup>, Lei S. Qi<sup>5,7,8</sup>, Anshul Kundaje<sup>10</sup>, and Helen M. Blau<sup>1,3,5</sup>

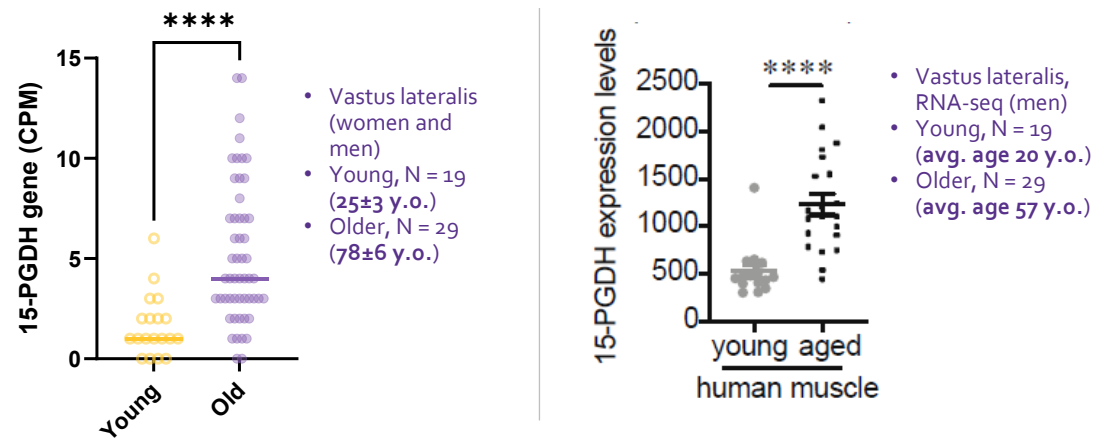
# 15-PGDH, a Gerotherapeutic Target that Reduces PGE2 Levels, is Upregulated in Aged Muscle

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

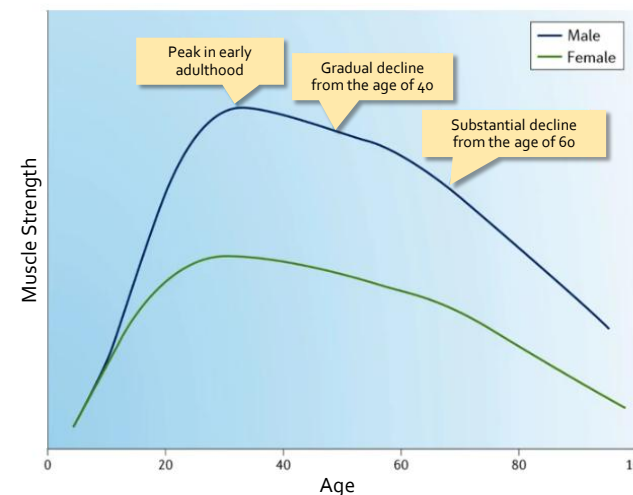


<sup>1</sup> Adapted from Trappe TA, et al. J Clin Endocrinol Metab. 2001;86(10):5067-5070

## 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>

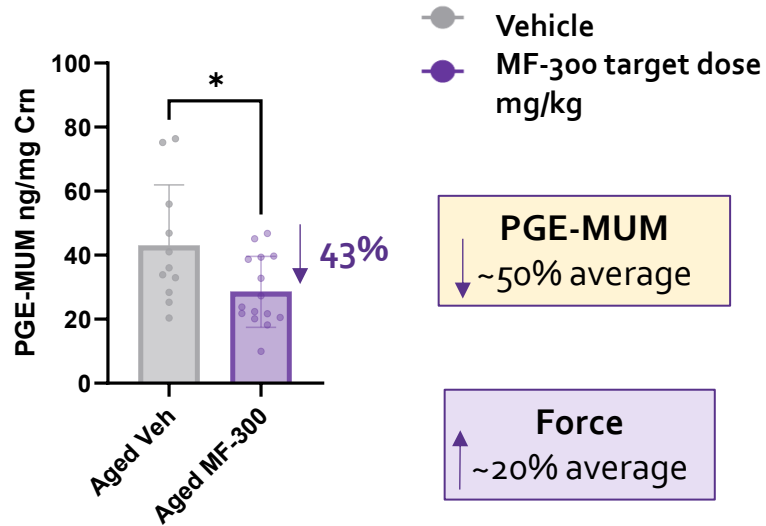


<sup>3</sup> GEO167186, <sup>4</sup> Raue et al., J Appl Physiol 2012 (published in Palla et al., Science 2021), <sup>5</sup> Dennison et al., Nat Rev Rheum 2017

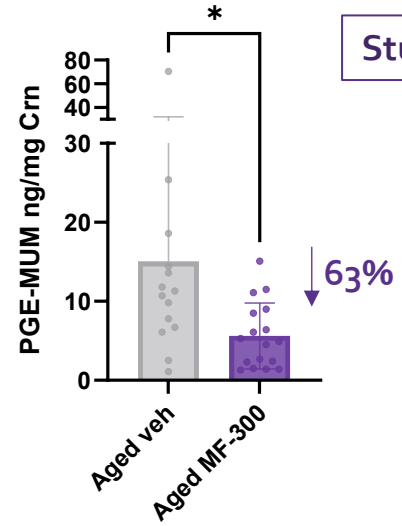
## Preclinical Sarcopenia Studies

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

Study 1

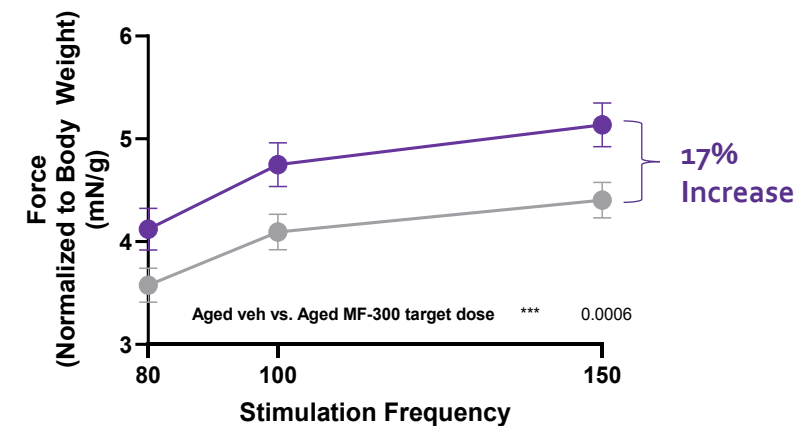
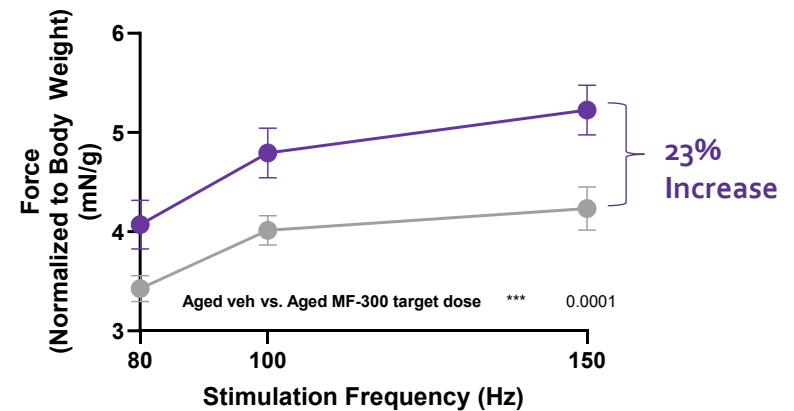


Study 2



### Target Engagement Biomarker

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



# Phase 1 Proof of Mechanism Study

**Objectives:** Assess the safety, tolerability, pharmacokinetics and pharmacodynamics of MF-300 following single ascending doses (SAD) and multiple ascending doses (MAD)

**Populations:** Adult healthy volunteers  $\geq 18$  -  $\leq 65$  years of age & Healthy elderly cohort  $>65$  -  $\leq 75$  years of age

**Doses:** SAD explored 5 doses ranging from 75mg to 800mg; MAD explored 3 doses of 75mg, 125mg, and 200mg

## Part 1a SAD

- N=8 per cohort (2 pbo, 6 MF-300)
- Doses: 75, 125, 250, 500, & 800mg

Single Ascending Dose  
5 non-elderly cohorts, 1 elderly cohort

## Part 1b Food Effect

- N=12 (all MF-300)
- 500mg 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
- Doses: 75mg, 125mg, 200mg

Multiple Ascending Dose  
3 non-elderly cohorts & 1 Elderly cohort

- All predefined Phase 1 success criteria across Safety, PK, and PD were achieved
- Enabling 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 (PGE<sub>2</sub> metabolite) w/ substantial proportion of subjects achieving  $\geq 50\%$  reduction in PGE-MUM
- ✓ Evidence of mechanism-increased PGE<sub>2</sub> levels
- ✓ Clear dose/response relationship defining therapeutic range, supportive of Phase 2b dose selection

## MF-300's Safety Profile Supportive of Continued Development

### Safe and well tolerated across the evaluated dose ranges

- No deaths, SAEs, or discontinuations due to AEs
- Maximally tolerated dose not identified up to 800 mg (therapeutic range 75-200mg)

### Adverse Events: No dose-limiting Toxicities

- No maximally tolerated dose identified, majority of adverse events mild, resolved with intervention. No dose-response in frequency or severity of AEs.
- With repeat dosing (MAD): No difference in overall AE incidence between MF-300 and placebo.
- **Most common AE:** Mild diarrhea: 30% overall incidence in SAD, single event in MAD; transient (resolving w/in 1-2 days)

### Laboratory / Vital Signs / ECGs: No clinically meaningful trends in labs, vital signs, or ECGs

- Fasting glucose remained stable
- Some fluctuations in blood pressure and heart rate consistent with placebo
- No QTc prolongation or hemodynamic concerns

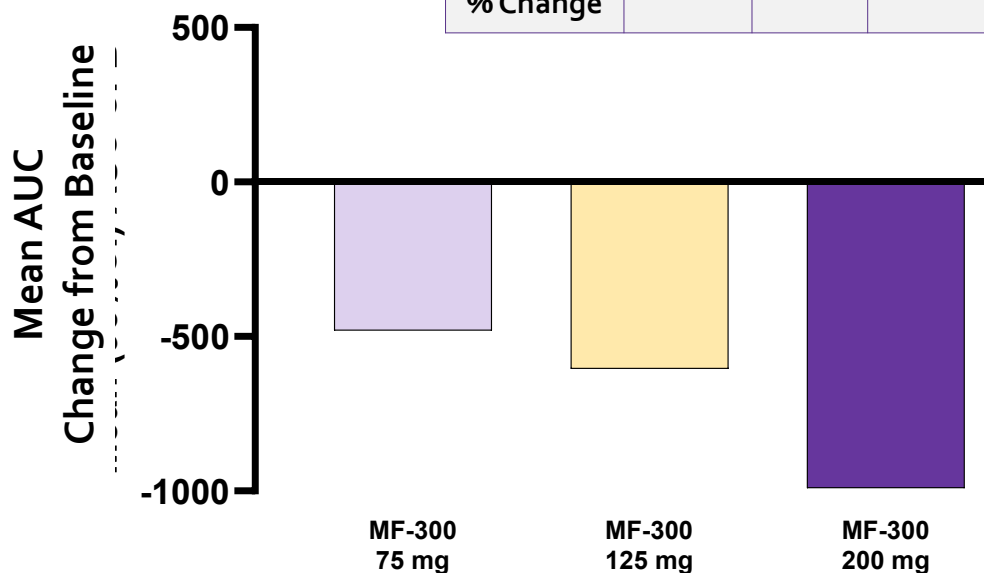
*No additional monitoring required beyond standard Phase 2b assessment*

# Increased PGE<sub>2</sub> Levels with MF-300 Demonstrates Proof of Mechanism

- Reductions in PGE-Major Urinary Metabolite (PGE-MUM) are consistent with those associated with ~20% improvement in muscle force in sarcopenia mice model
- Increases in urinary PGE<sub>2</sub> are consistent with those in muscle following eccentric exercise in humans

## Placebo-adjusted PGE-MUM Change from Baseline (95% CI)

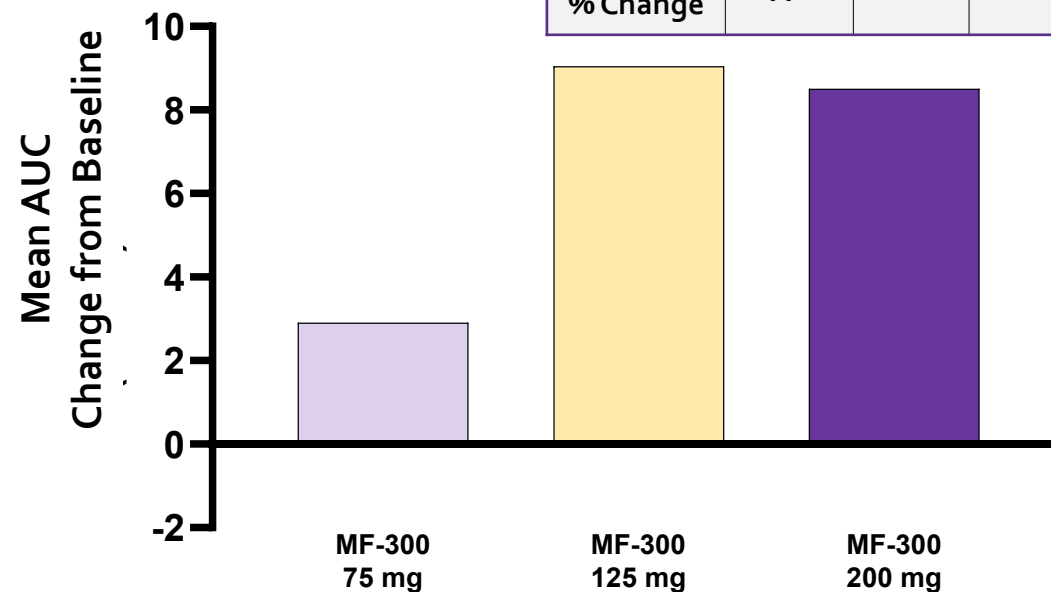
MF-300 (mg)	75	125	200
Placebo Adj. % Change	-64%	-64%	-83%*



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

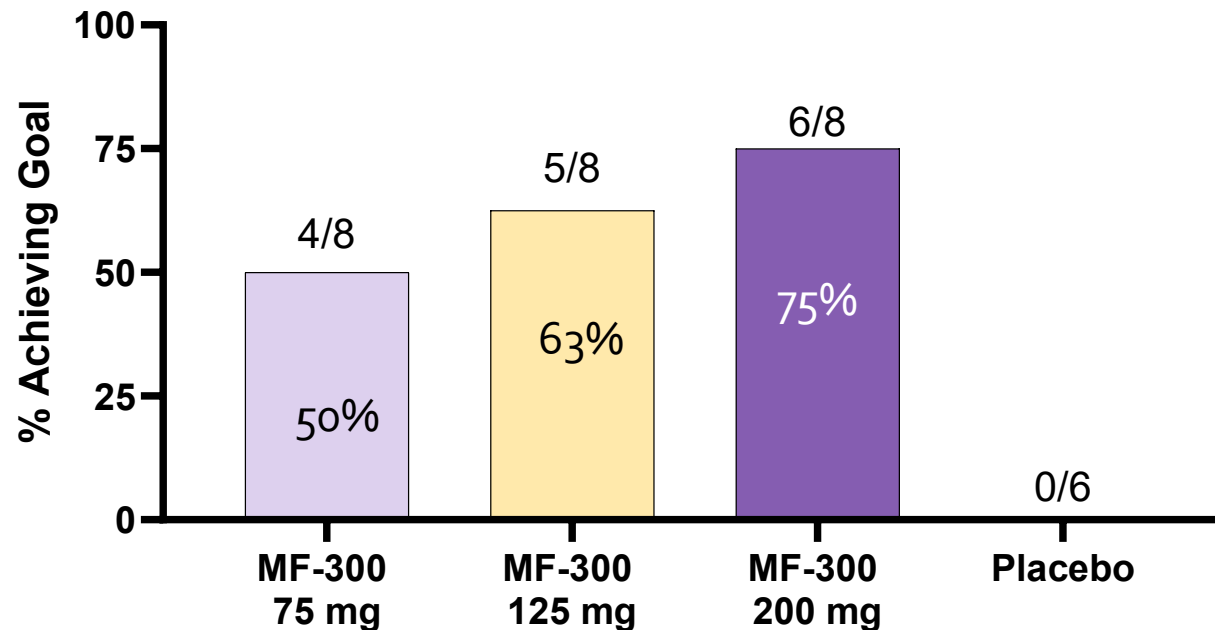
## Placebo-adjusted PGE<sub>2</sub> Change from Baseline (95% CI)

MF-300 (mg)	75	125	200
Placebo Adj. % Change	+77%	+116%	+128%



Note: Two outlier subjects in the 75 mg group, with markedly greater PGE<sub>2</sub> responses due to low baseline values, were excluded from analysis, including the two subjects = 614% increase in MF-300 75 mg dose group.

## Proportion of Subjects Achieving Targeted % decrease in PGE-MUM & 60% Increase in PGE<sub>2</sub>



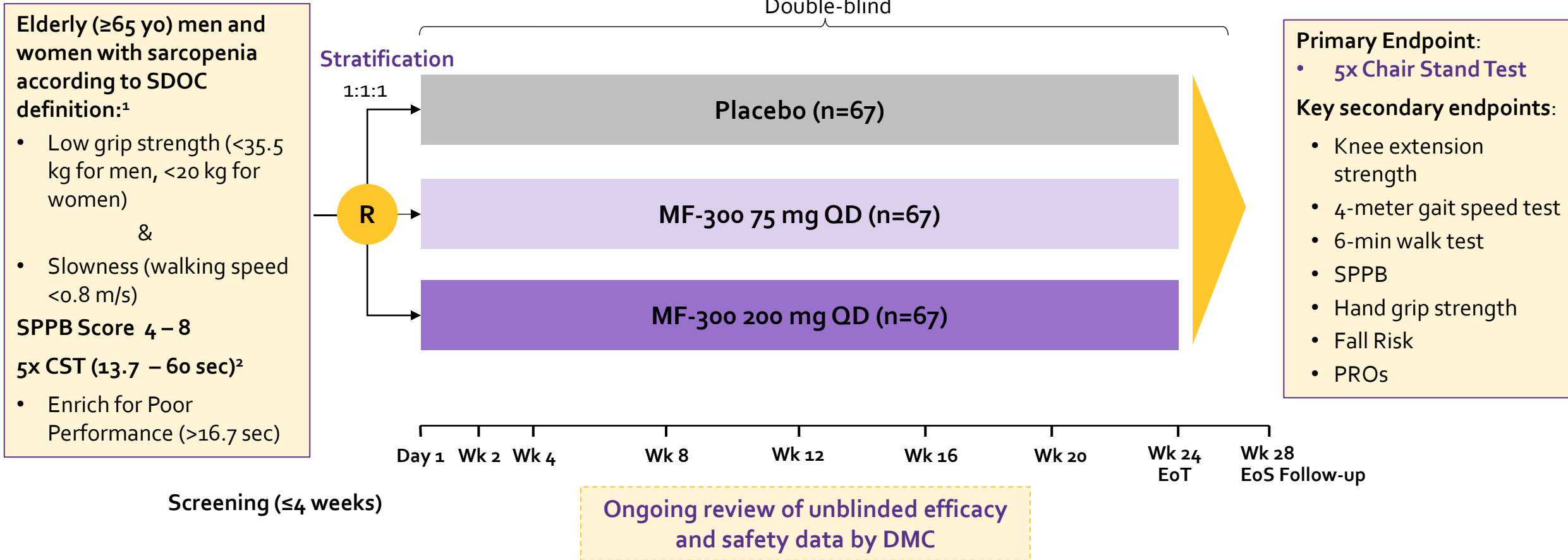
### Rationale for targets:

- ~Targeted % reduction in PGE-MUM is associated with ~20% improvement in muscle force
- ~60% increase in muscle following eccentric exercise in humans<sup>1</sup>

Subjects were counted only once with their maximum improvement at any timepoint (Day 1-5).

<sup>1</sup>Trappe et al., *J Clin Endo Met* 2001

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



\*The study provides ~80% power to detect a 15% difference between the active and placebo groups

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.

- **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**

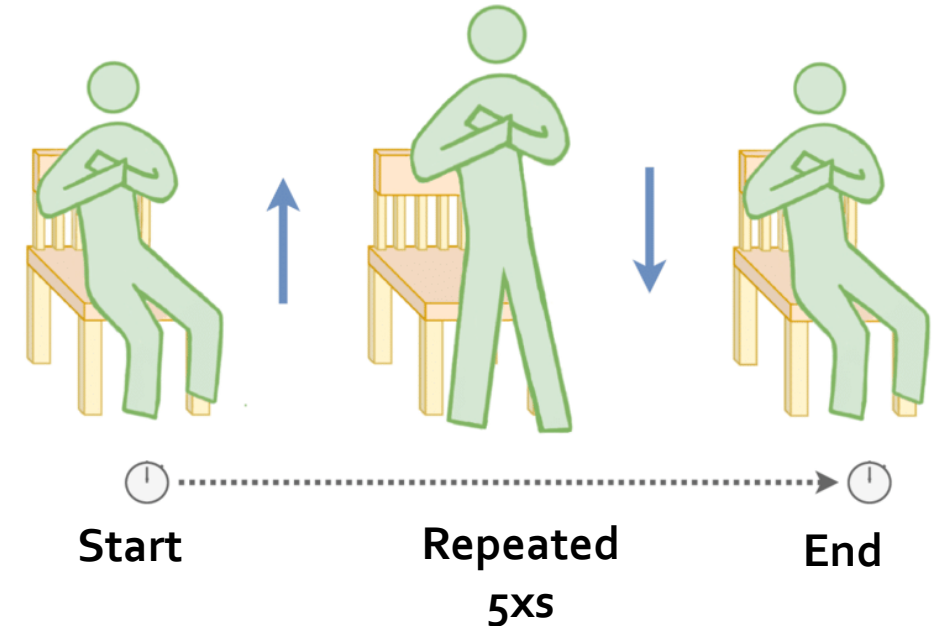
- Activities of daily living
- Fall Risk
- All-Cause Mortality

- **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

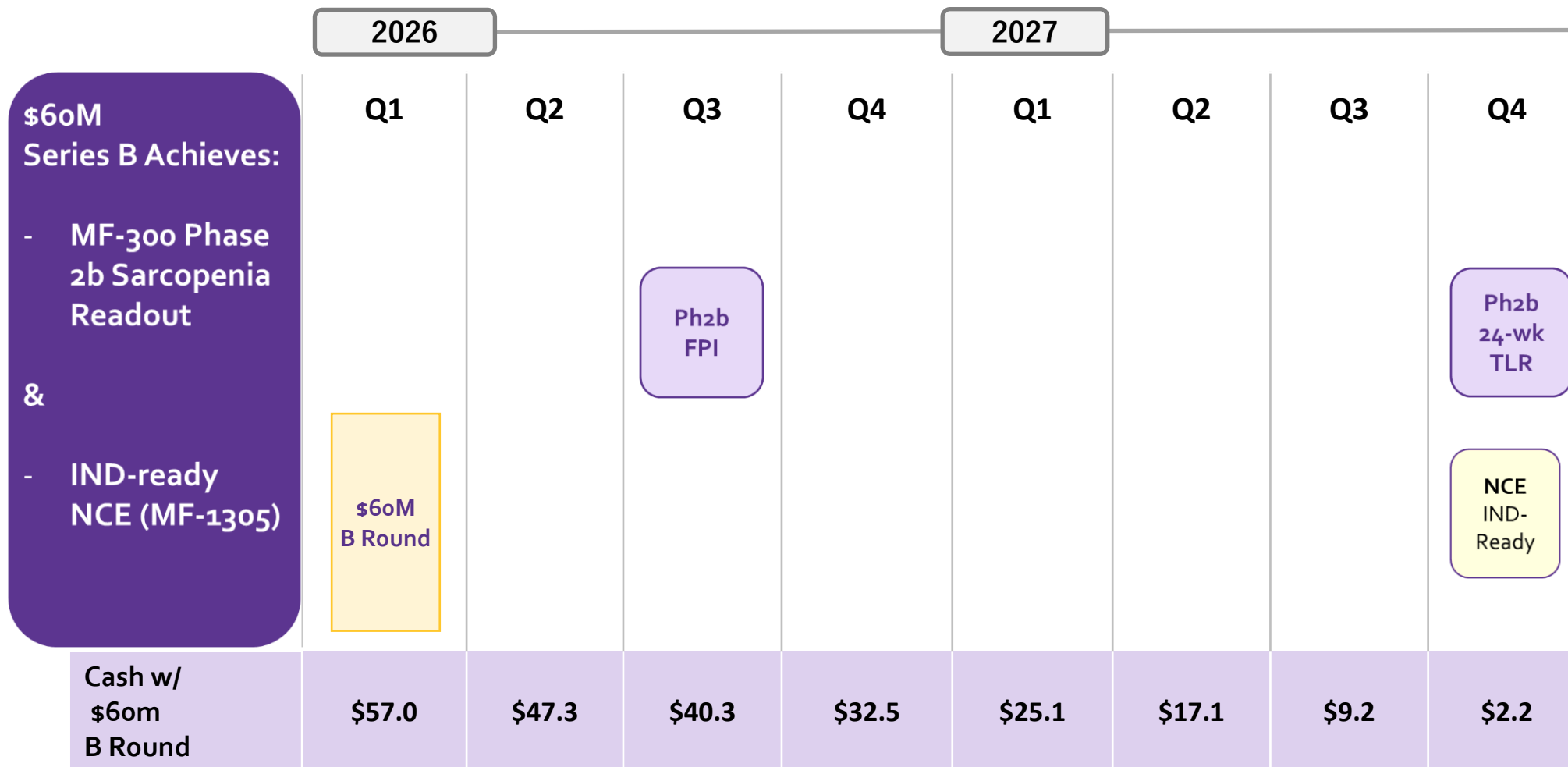
## 5xs Chair Stand Test



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).

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



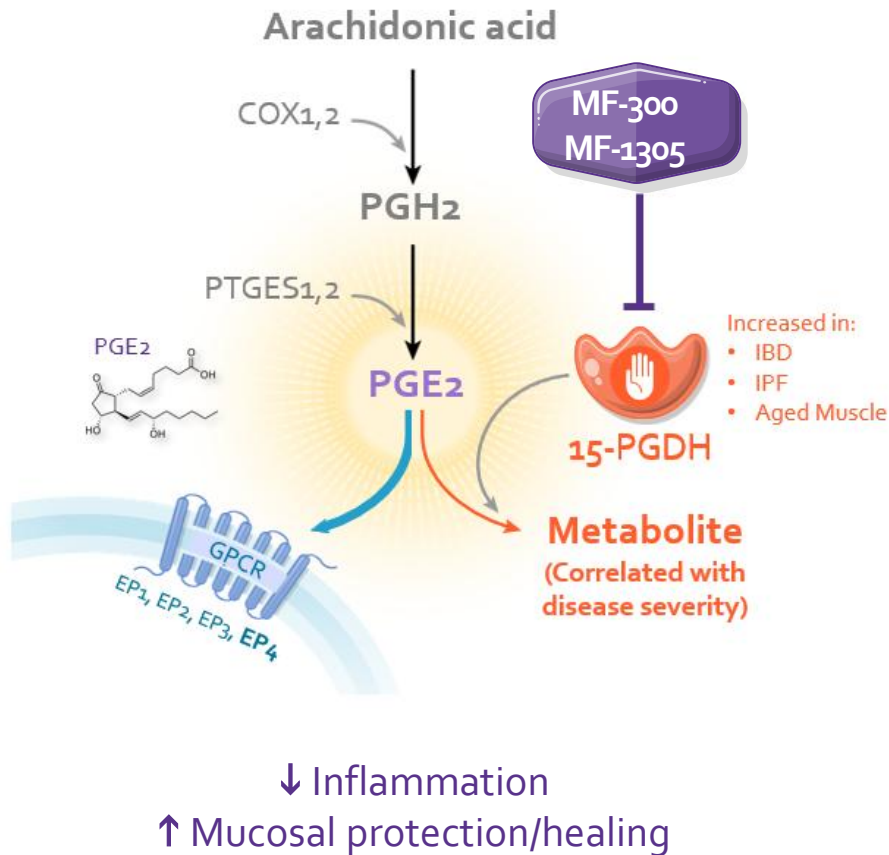
*Additional \$25M (\$85M raise) enables Phase 3 CMC commencement bringing forward MF-300 Commercial Launch 6 months to 1H 2032*

## Positive IBD Results: MF-1305 DSS Mouse IBD Colitis Study

- Supportive Scientific Rationale
- Detailed Treatment Study Results

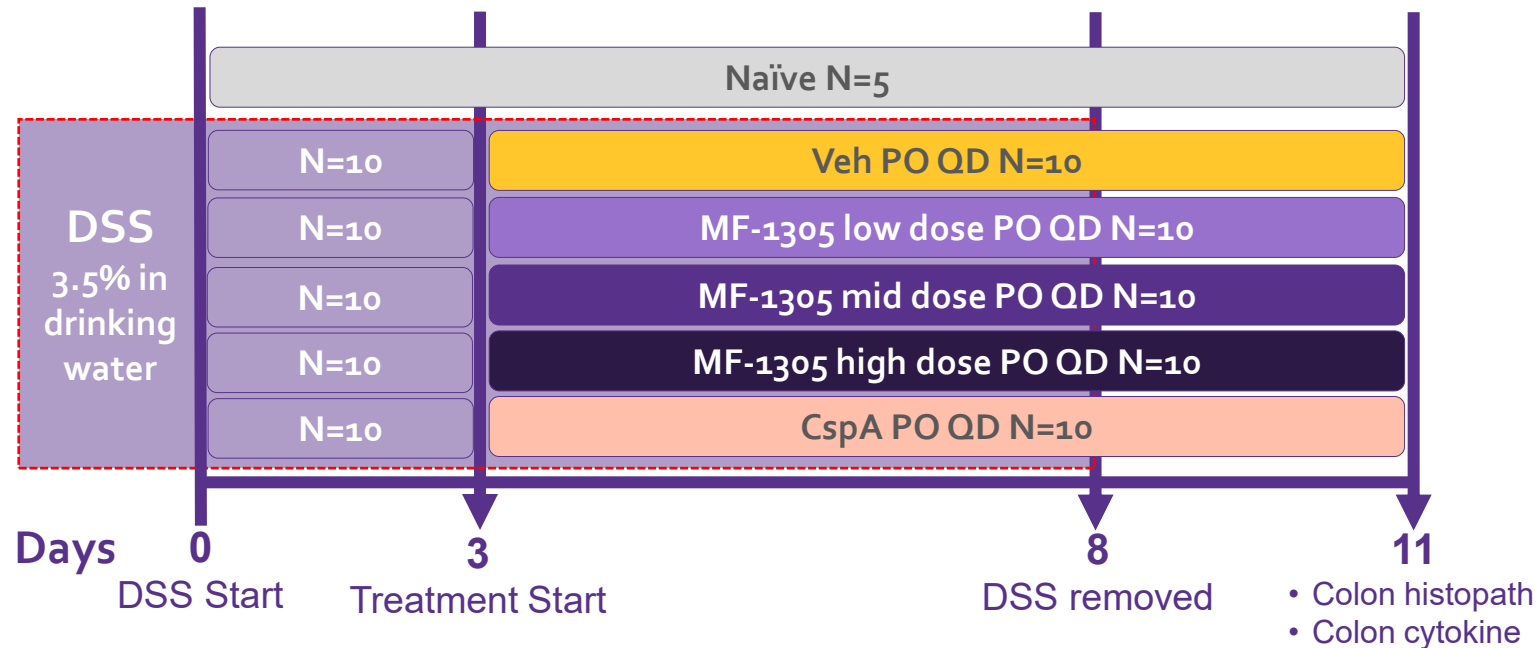
# Inhibiting 15-PGDH with an Oral Small Molecule to Increase Physiological PGE<sub>2</sub>: Proven Mechanistic Rationale for the Treatment of IBD

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



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>EP<sub>4</sub> KO &amp; EP<sub>4</sub> antagonist worsened colitis</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>EP<sub>4</sub> antagonist increased mortality</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

- Mouse strain: C57Bl/6
- Sex/Age: Female/10-12 weeks



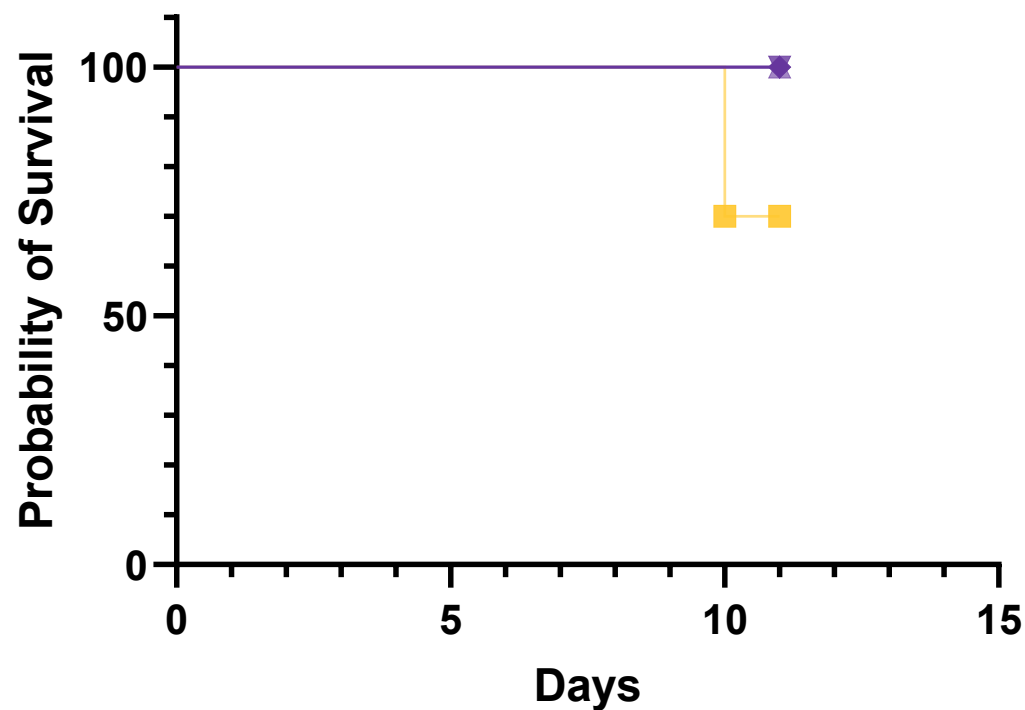
## In life:

- Disease Activity Index (daily)
  - Body weight
  - Fecal blood
  - Stool consistency

## Endpoints:

- Colon
  - Cytokines
  - Histology

## Survival proportions: Survival of DSS



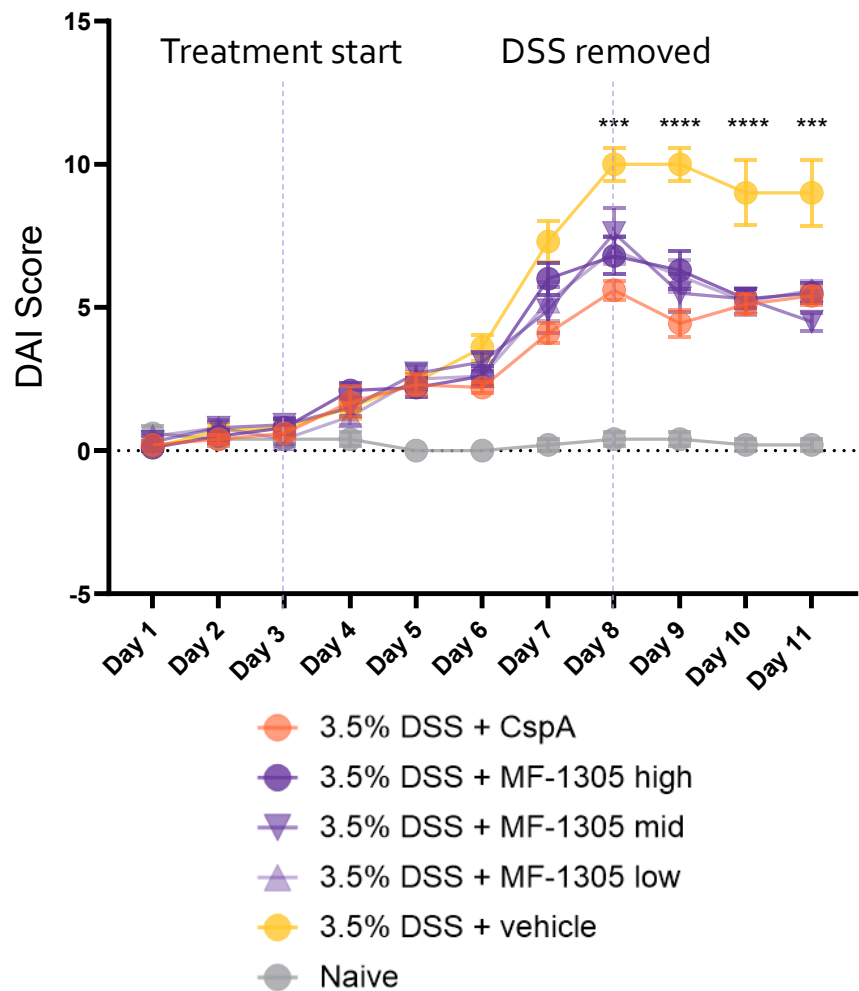
- ▲ DSS MF-1305
- ▼ DSS MF-1305
- ◆ DSS MF-1305
- DSS Veh

Log-rank (Mantel-Cox) test	
P value	0.0235
P value summary	*
Are the survival curves sig different?	Yes

N = 3 animals from the DSS Veh group were euthanized on Day 10.  
 Naïve and DSS CspA group, not included in survival analysis – both groups 100% survival.

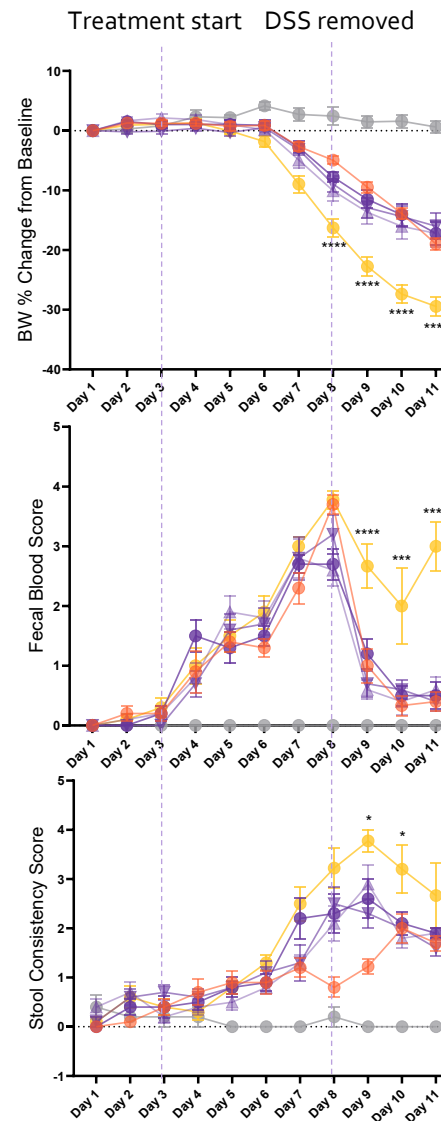
# MF-1305 Significantly Improved Disease Activity Index (DAI) & Survival

MF-1305 improved DAI



Two-way ANOVA; Dunnett's test for multiple comparisons  
 \* $p \leq .0239$ , \*\*\* $p \leq .0004$ , \*\*\*\* $p < .0001$  for all MF-1305 doses compared to DSS + veh

MF-1305 improved each composite score of the DAI

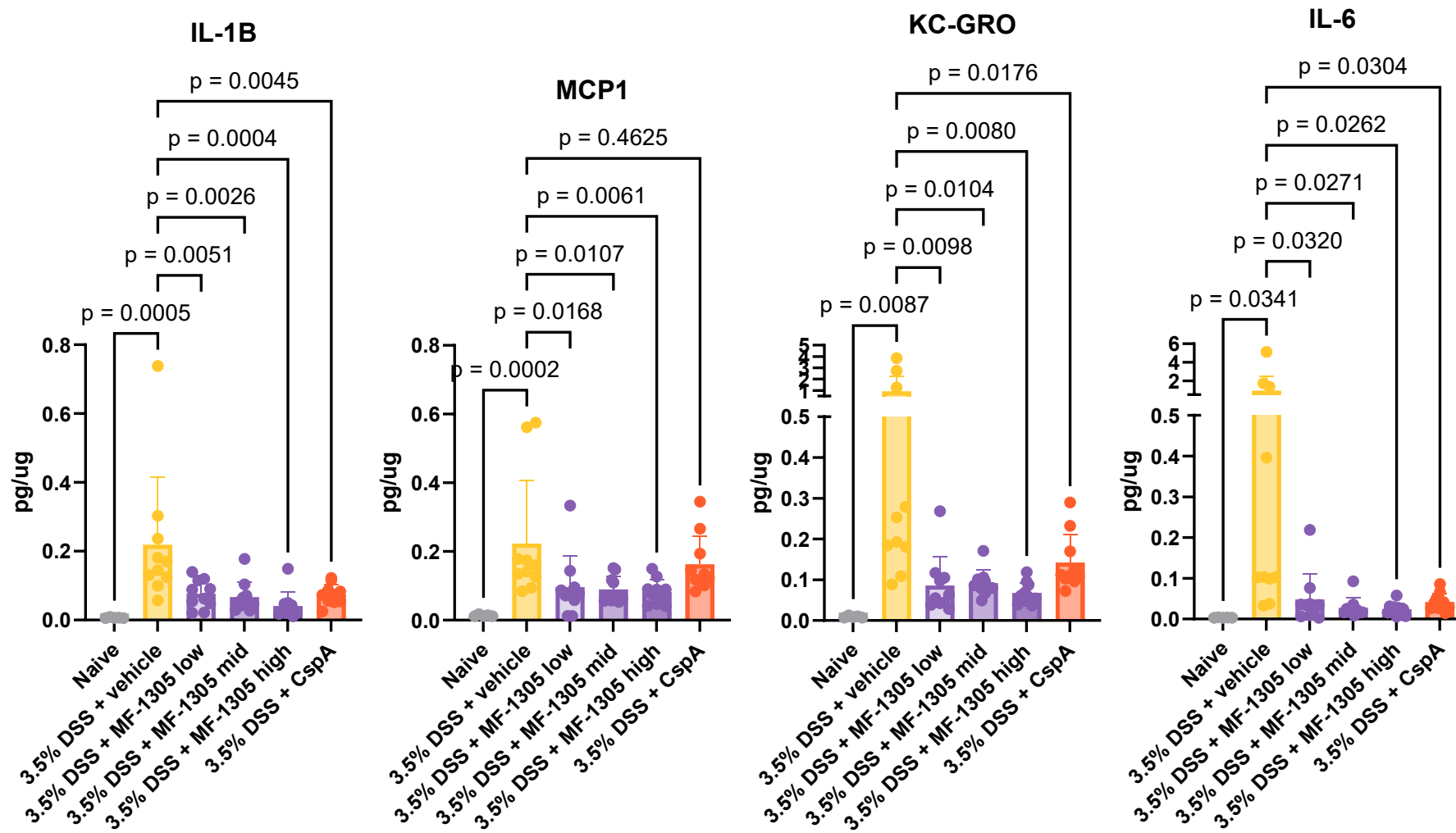


MF-1305 preserved body weight

MF-1305 reduced fecal blood content

MF-1305 improved stool consistency

# MF-1305 Significantly Reduced Colon Cytokines



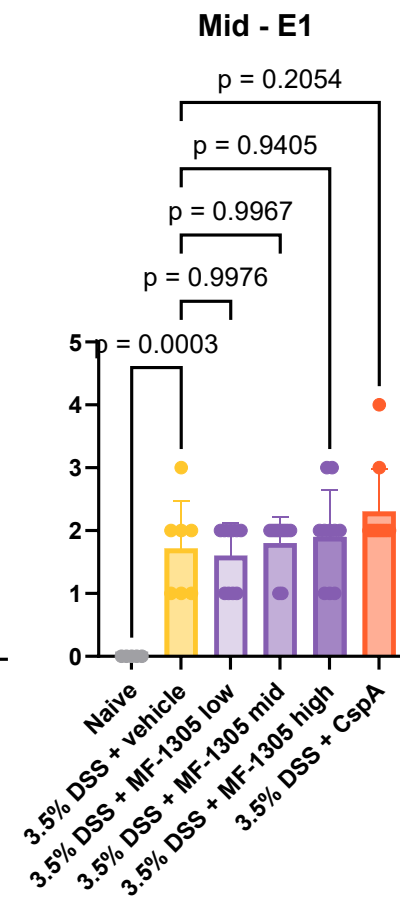
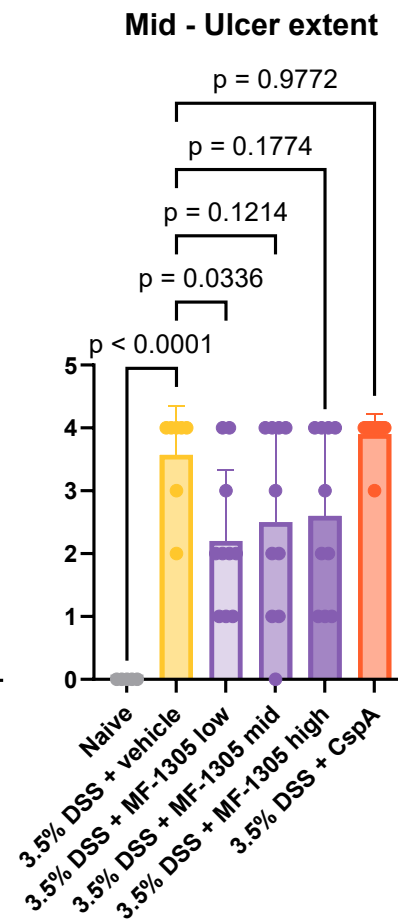
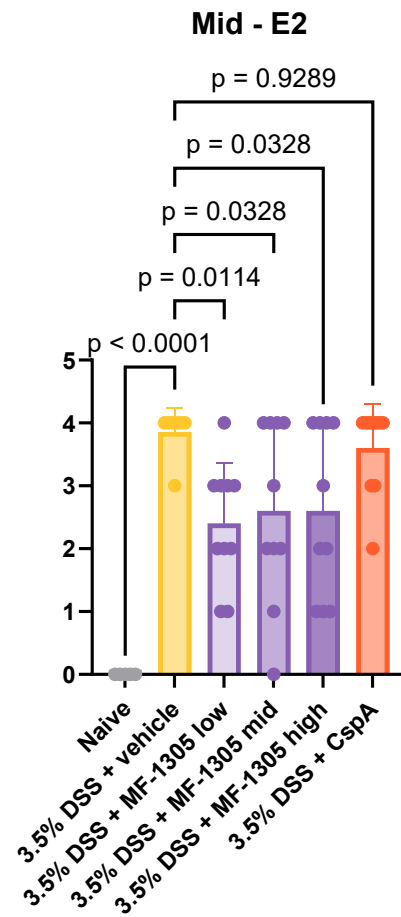
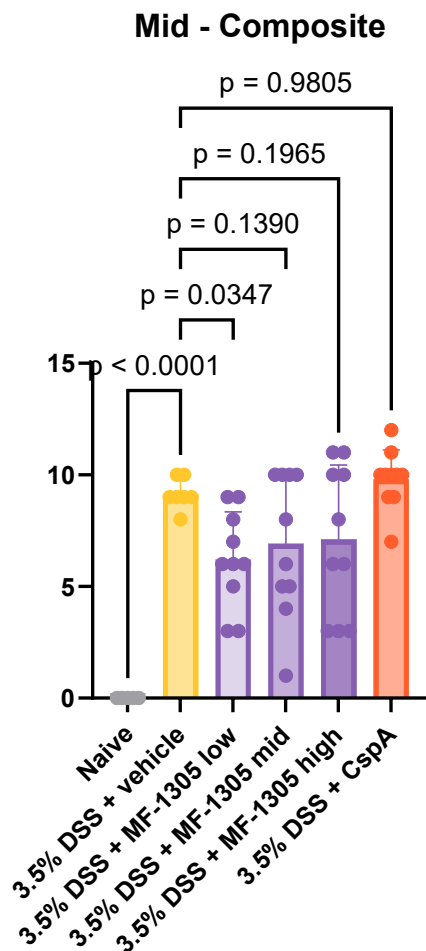
Two-way ANOVA, Dunnett's multiple comparisons test  
 N = 3 DSS Veh group samples collected on Day 10 excluded from graphs  
 TNF- $\alpha$  – high rate of BQL results, not included here

# MF-1305 Significantly Improved Histological Disease in Mid-Colon

Benefits observed on tissue architecture (i.e., E2) and ulcer extent

Overall Ulcer Extent Score:	
0	normal
1	<10%
2	10-19%
3	20-29%
4	>30%
E1: % of section affected by any inflammatory changes	
0	normal
1	1 - 25%
2	26 - 50%
3	51 - 75%
4	76 - 100%
E2: % of section affected by severe inflammatory changes with obliteration of normal architecture, erosion/ulceration and/or crypts abscesses	
0	normal
1	<10%
2	10-19%
3	20-29%
4	>30%

Adapted from Burich, 2001 and Hausmann, 2007



Two-way ANOVA, Dunnett's multiple comparisons test  
 N = 3 DSS Veh group samples collected on Day 10 excluded from graphs

- MF-1305 significantly improved Disease Activity Index (DAI): body weight, fecal blood, and stool consistency.
- MF-1305 improved survival
- MF-1305 significantly reduced colon cytokine levels.
- MF-1305 significantly improved histological disease including ulceration and tissue architecture in colon mid-section.