Reversing Aging: Proinflammatory metabolite Prostaglandin E2 augments muscle regeneration

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Disclosure

REJUVENATION TECHNOLOGIES

Co-founder

MYOFORTE

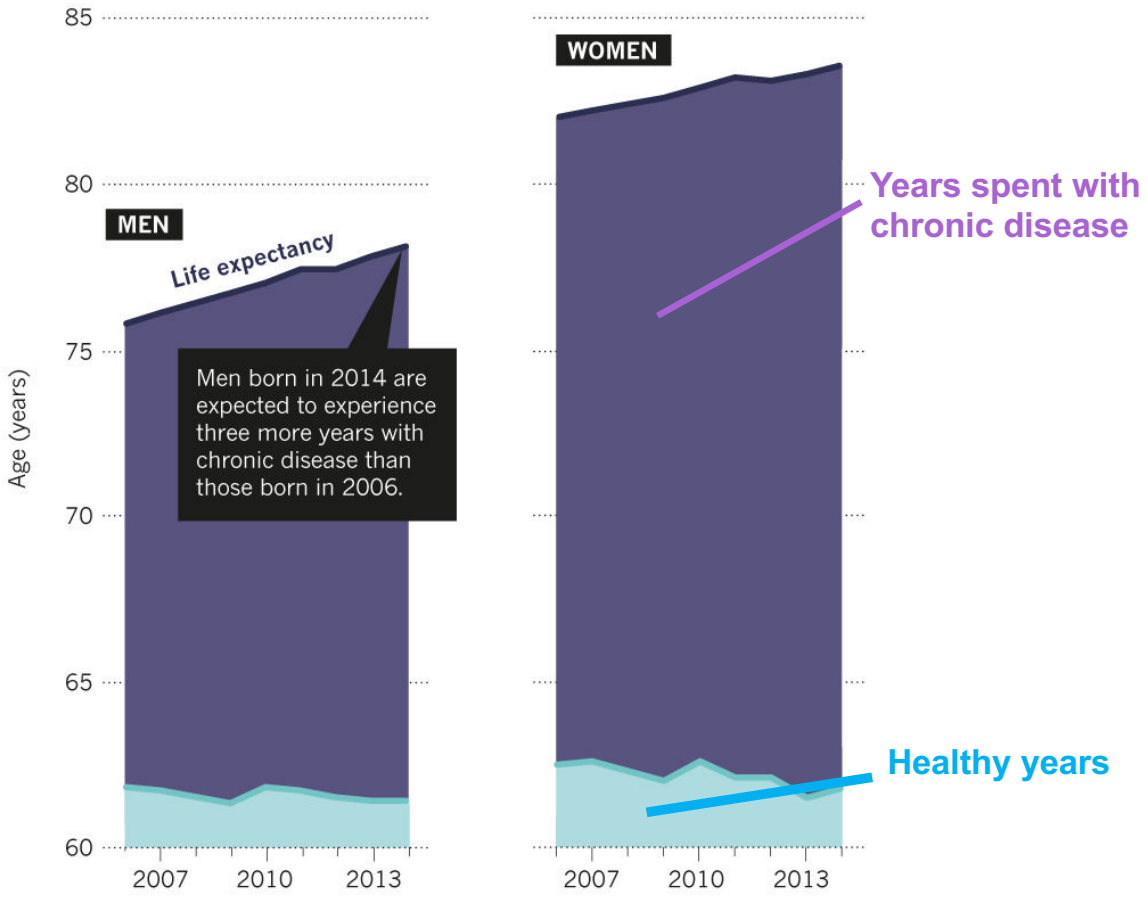
REJUVENATING MUSCLE

Co-founder

EPIRIUM

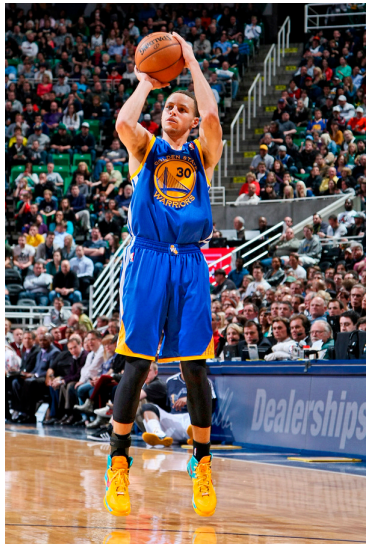
The Three Ages of Woman by Gustav Klimt

Aging: More years of what?

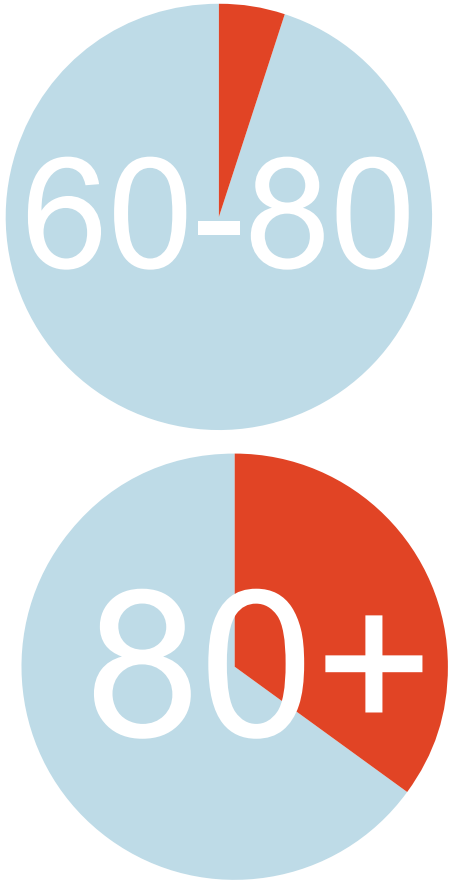


Bellantuono, *Nature,* 2018

Muscle is central to everything you do in life



Sarcopenia is loss of muscle mass and strength with aging



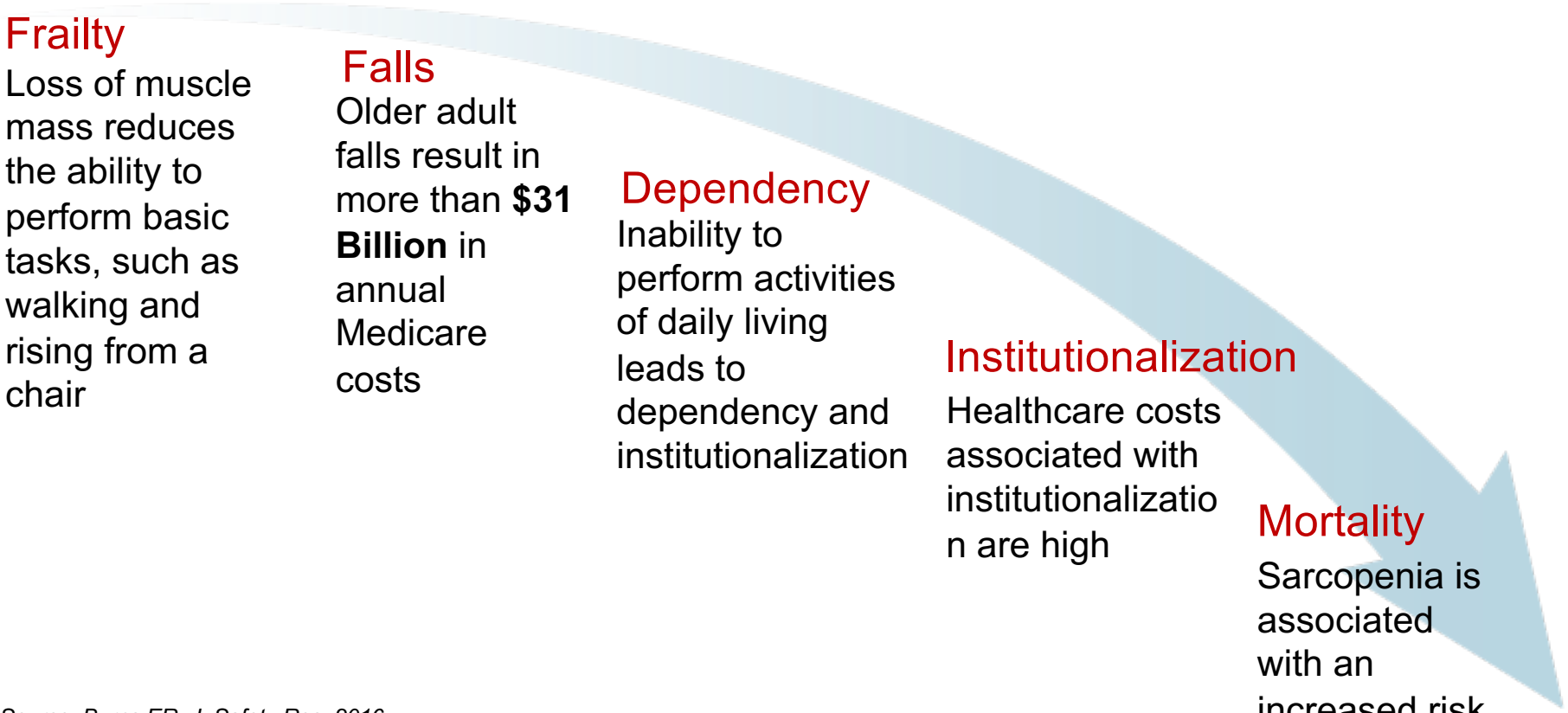
Humans lose 10% of muscle mass per decade after age 50yr

5% of people age 60 – 70yr are affected by sarcopenia

30% of people age 80 or older are affected by sarcopenia

Source: Center For Disease Control

Loss of muscle mass has severe consequences



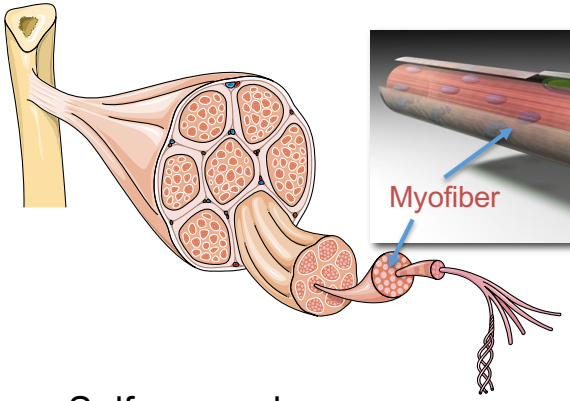
Source: Burns ER, J. Safety Res. 2016

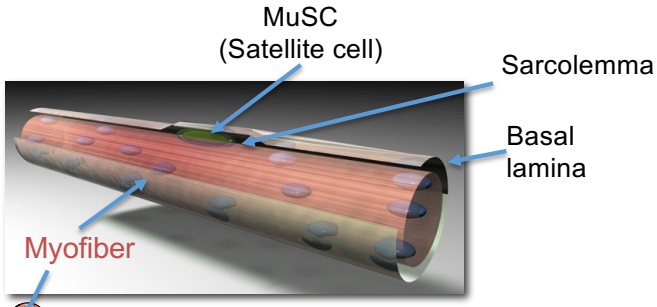
Approaches to combatting muscle aging

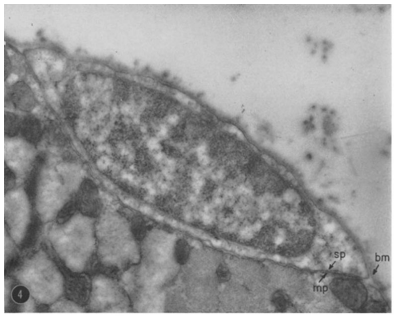
1) Muscle stem cell stimulation to enhance regeneration

2) Muscle myofiber rejuvenation

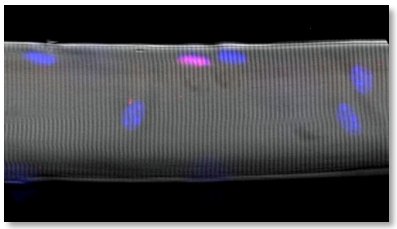
Muscle stem cells (MuSCs) are essential to muscle regeneration



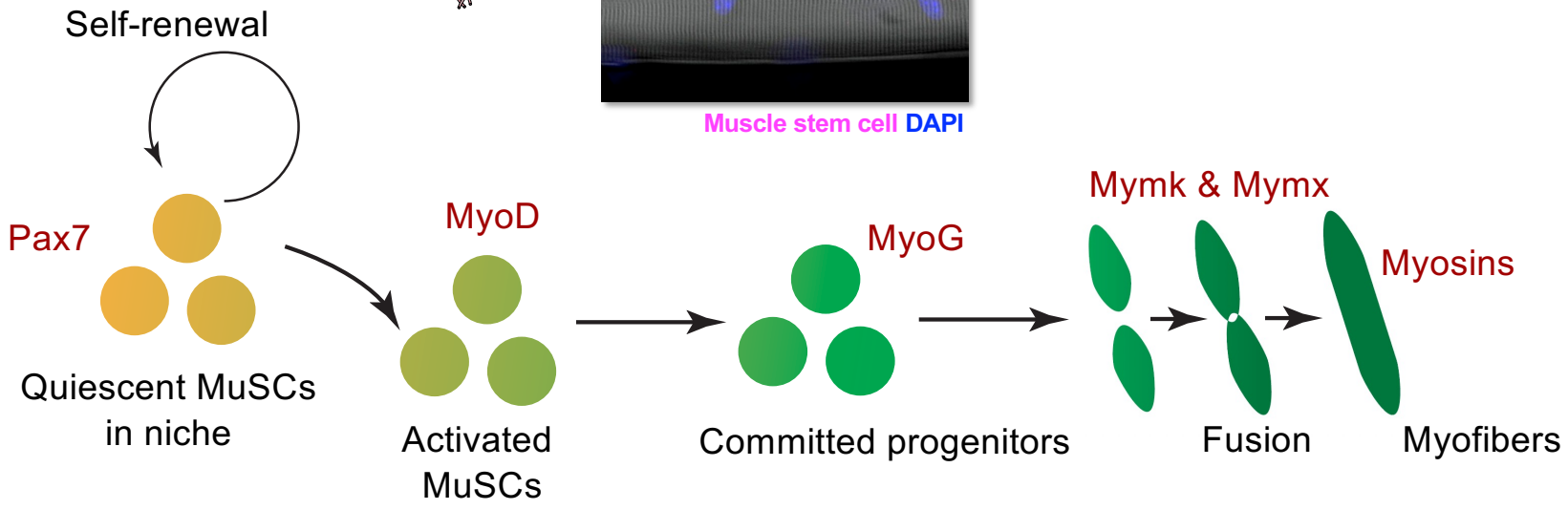




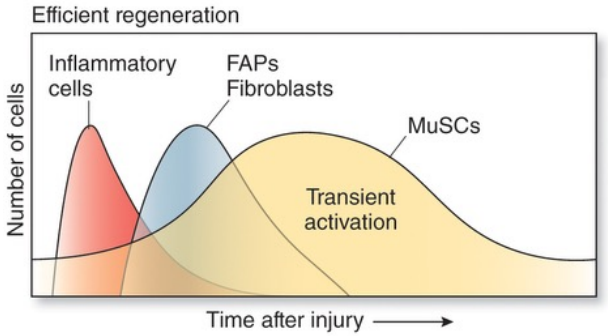
Mauro A, 1961



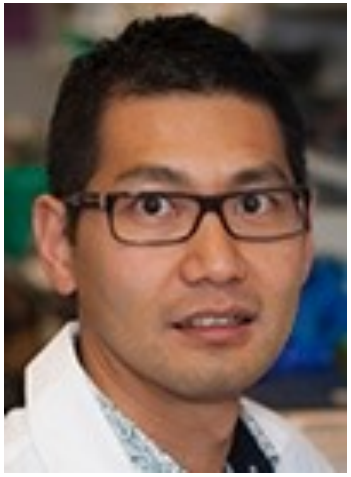
Muscle stem cell DAPI



PGE2: natural inflammatory mediator that stimulates muscle stem cell function



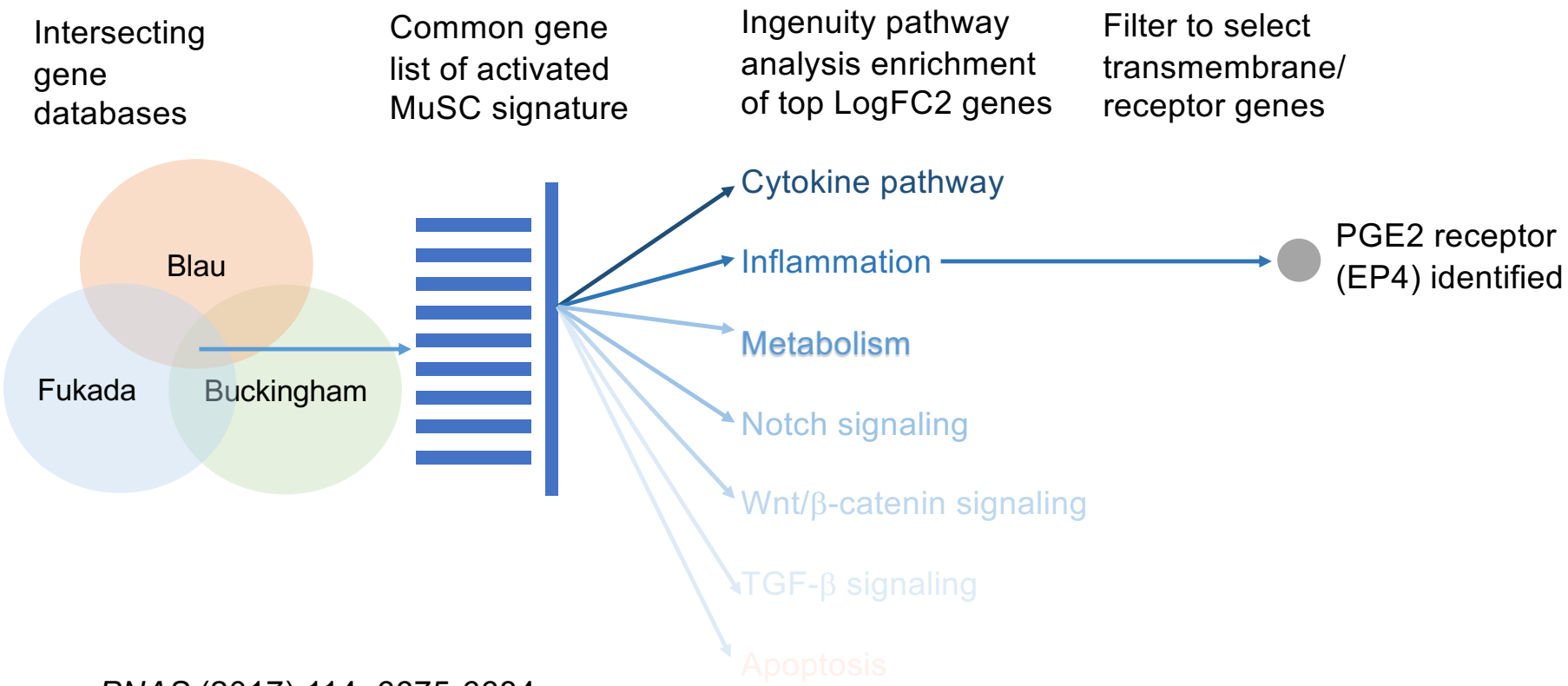
Blau et al., *Nature Med.*, 2015



Andrew Ho

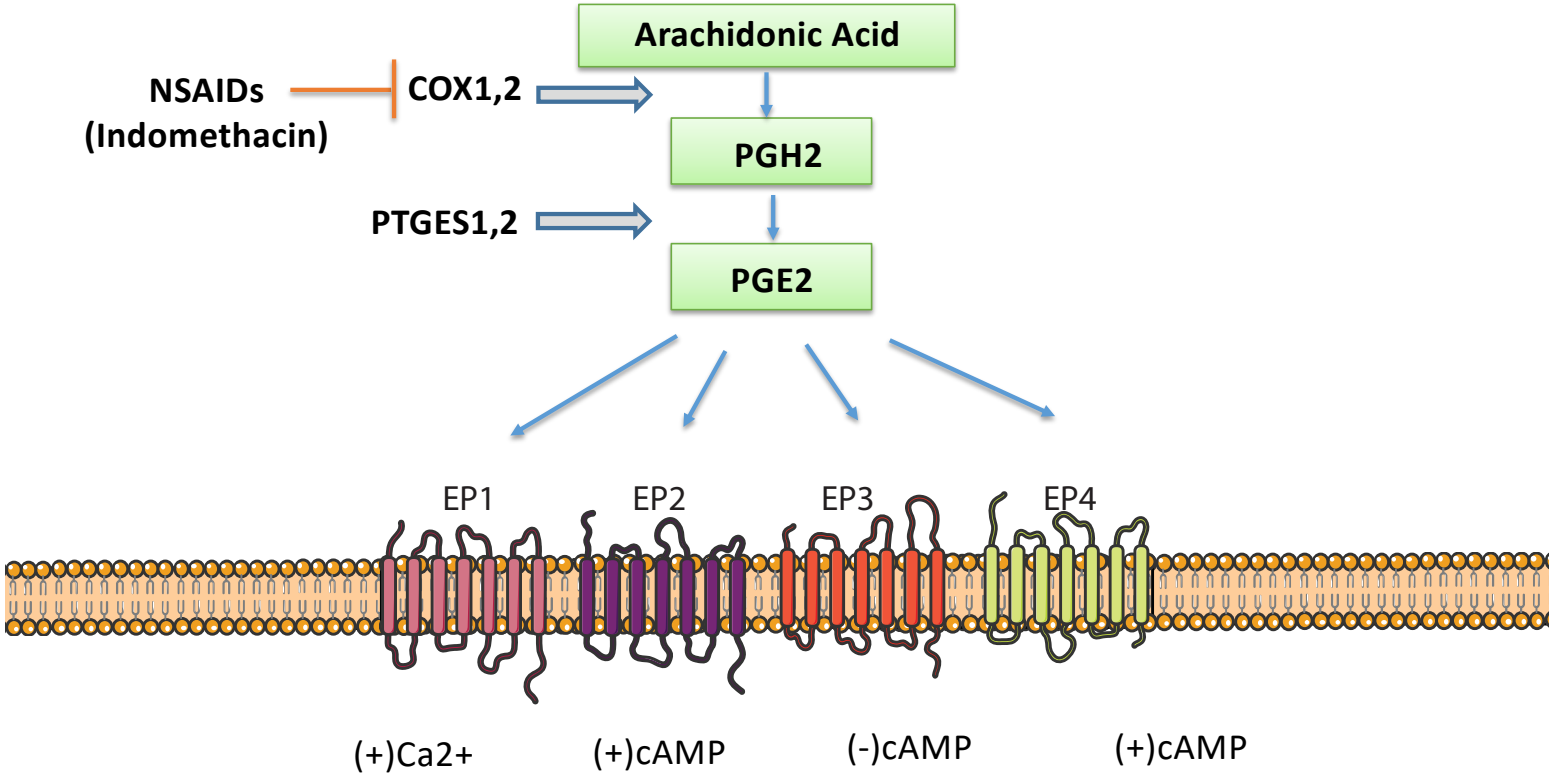
Adelaida Palla

Bioinformatic analysis implicates key inflammatory mediator as MuSC regulator



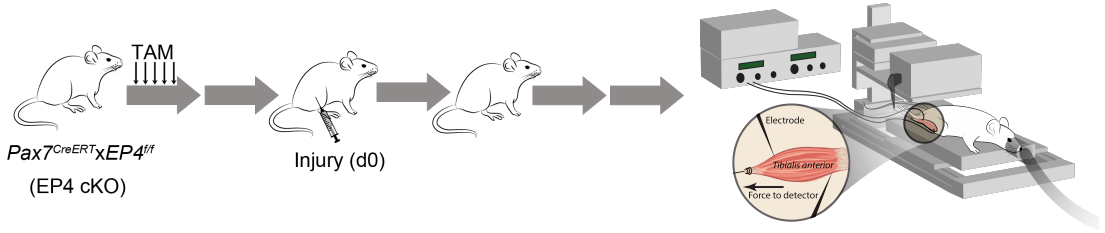
PNAS (2017) 114: 6675-6684

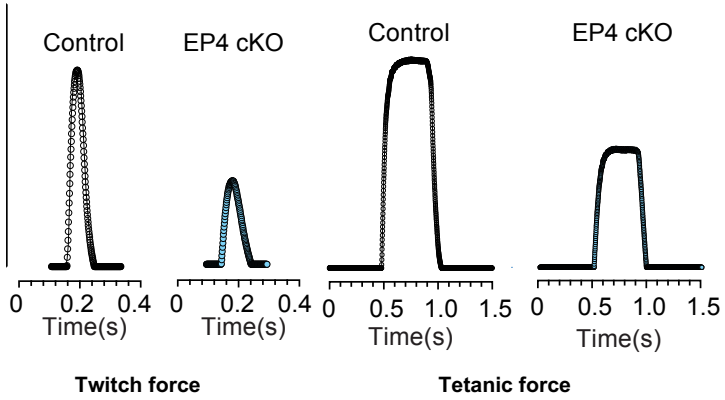
Prostaglandin E2 (PGE2) is a metabolite that stimulates MuSC function

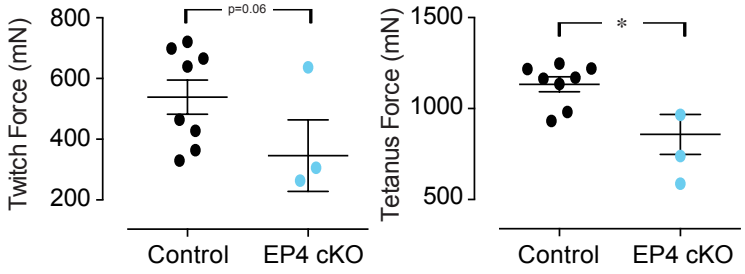


Loss of PGE2 signaling in MuSCs impairs regeneration and recovery of strength

Conditional MuSC-specific EP4 deletion

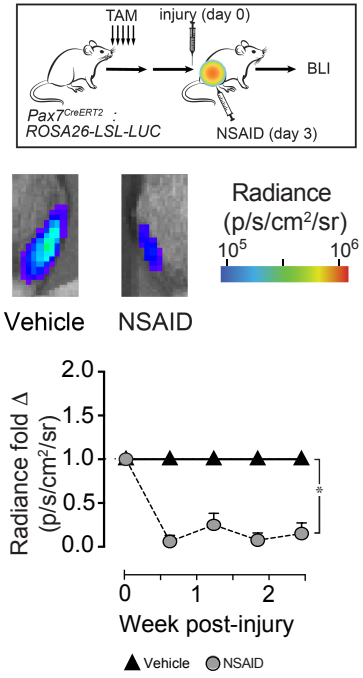


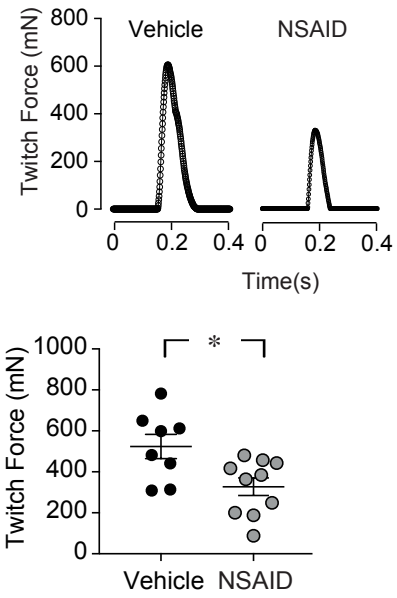




Young mice get weaker

Loss of endogenous PGE2 signaling after injury due to NSAIDS (ibuprofen) impairs strength





No pain, no gain!

Ho et al., *PNAS*, 2017

Is it possible to globally increase muscle function with PGE2?

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

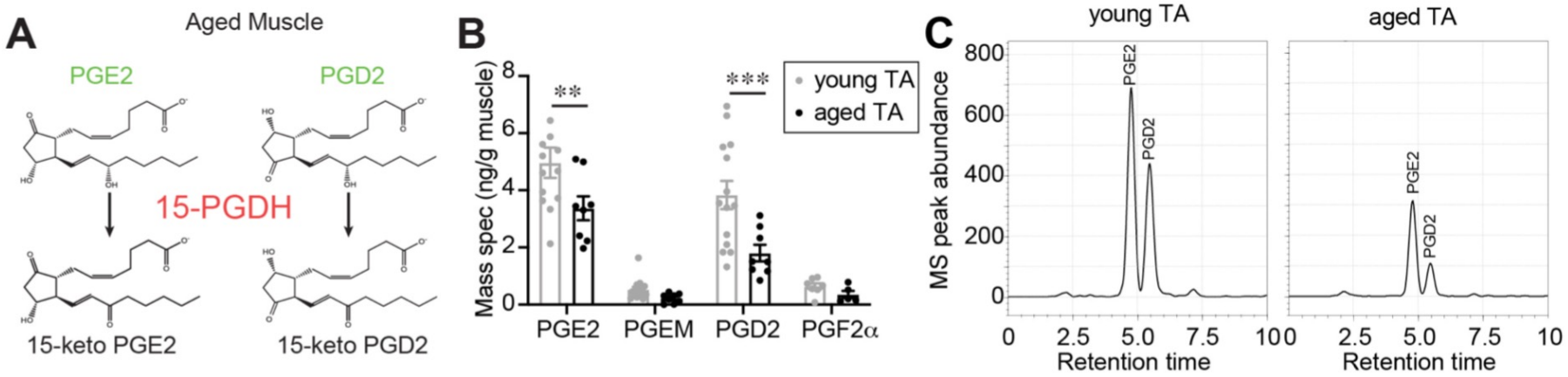
Adelaida Palla

Meenakshi Ravichandran

Yu Xin (Will) Wang

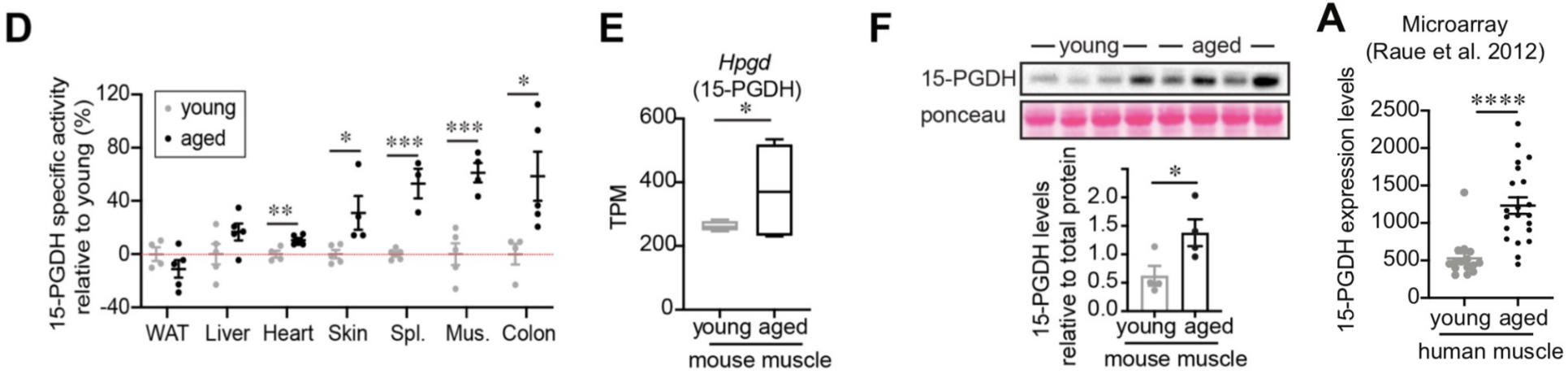
Palla et al, Science, 2020

PGE2 and PGD2 are reduced in aged muscles



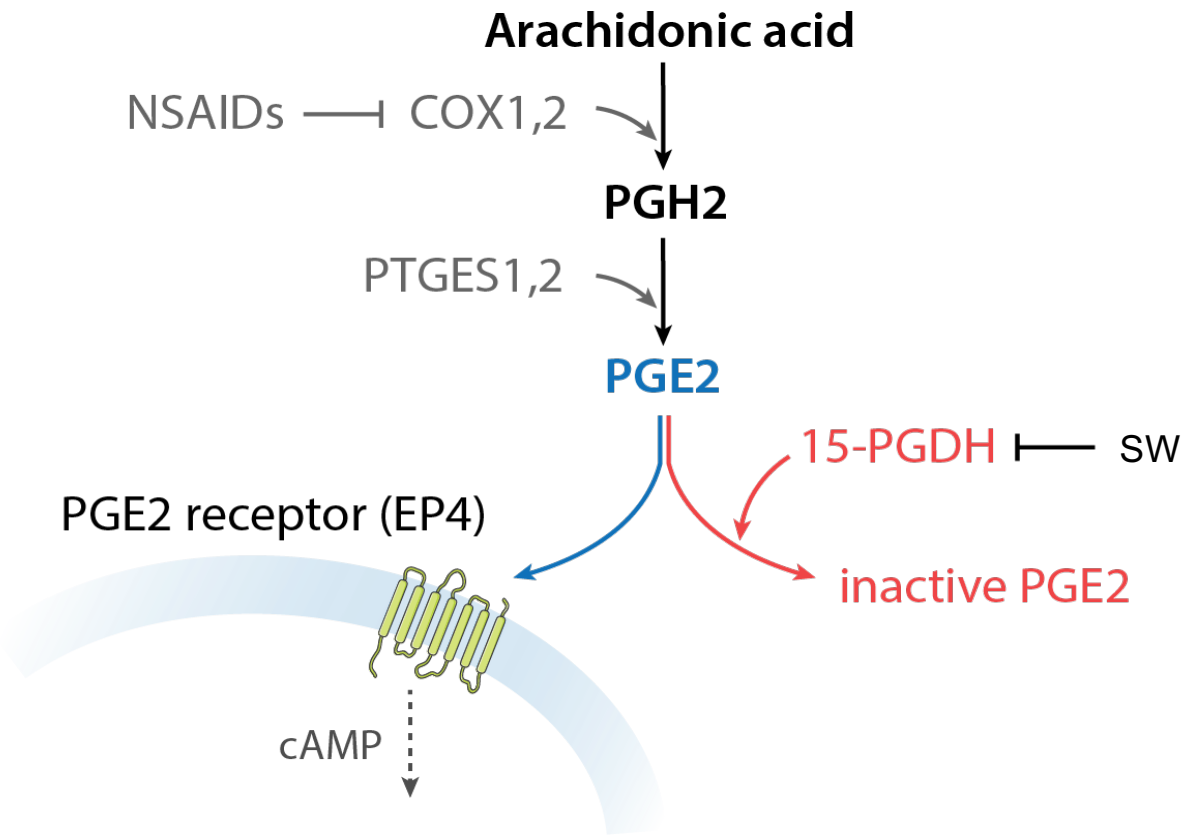
Palla et al., *Science,* 2020

15-PGDH levels are elevated in aged mouse and human muscles

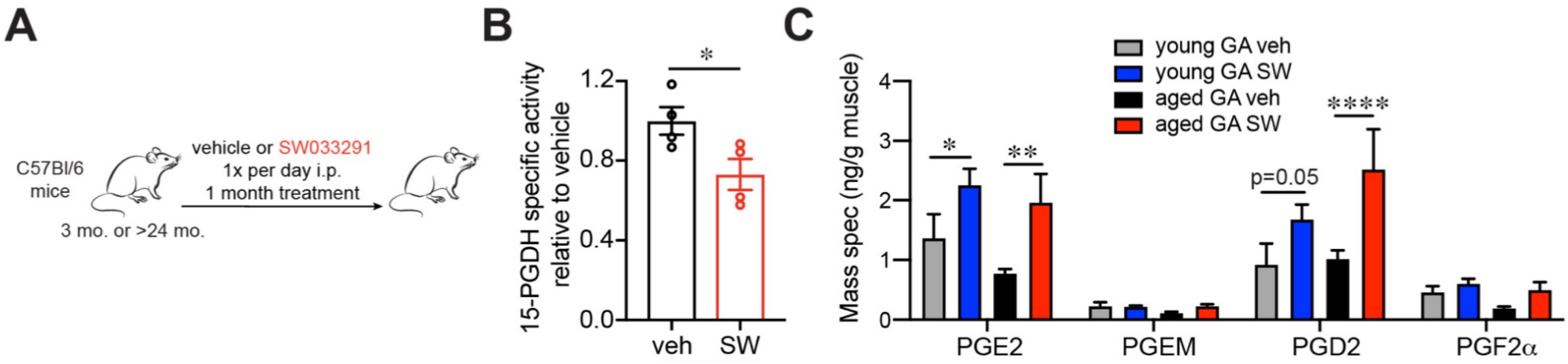


Palla et al., *Science,* 2020

Inhibition of 15-PGDH increases PGE2 signaling to augment muscle stem cell and muscle fiber function

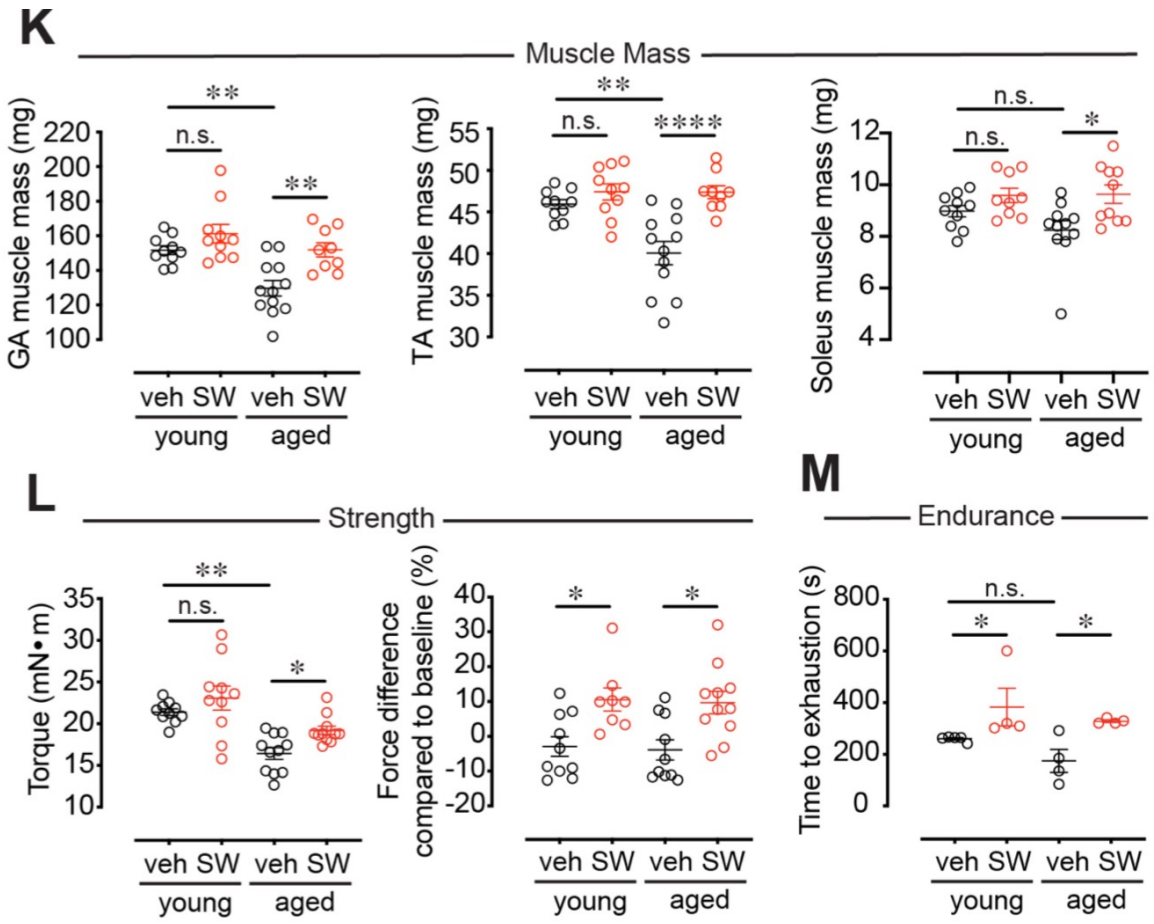


15-PGDH pharmacological inhibition increases PGE2 and PGD2 levels



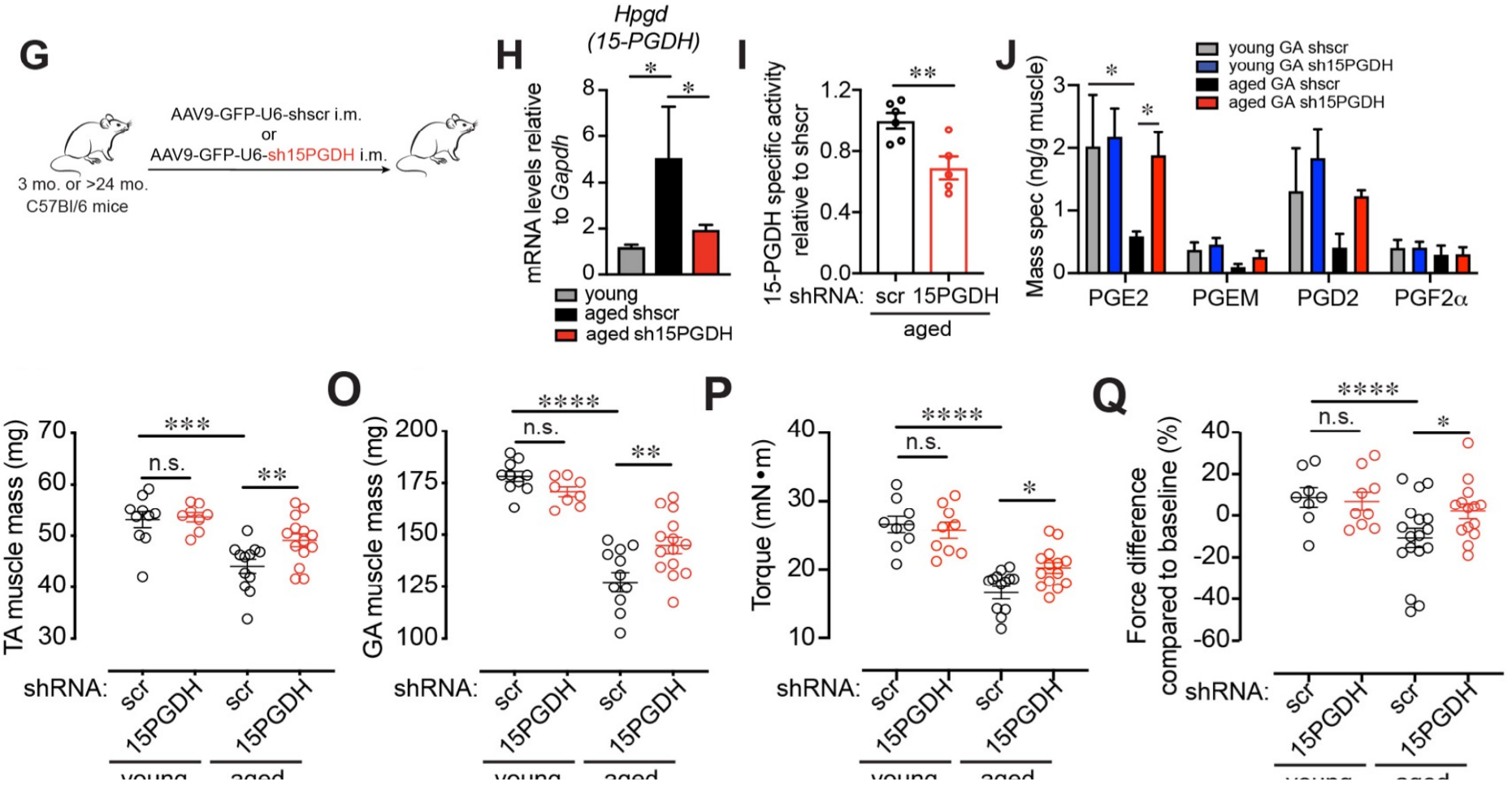
Palla et al., *Science*, 2020

15-PGDH pharmacological inhibition augments aged muscle mass, strength and endurance

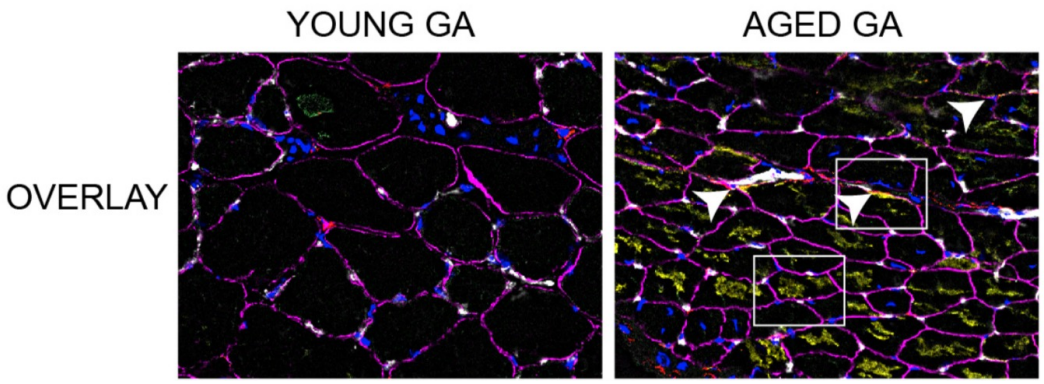


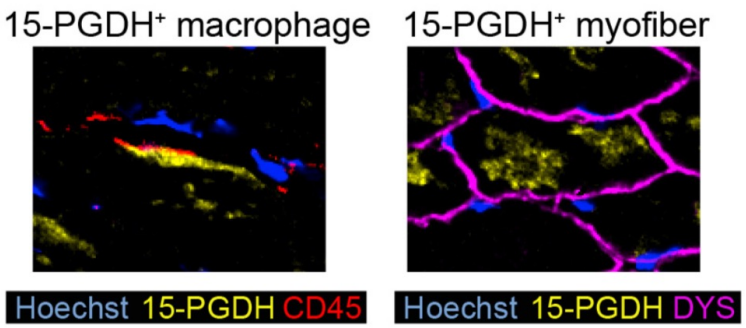
Palla et al., *Science*, 2020

15-PGDH knockdown improves aged muscle function and establishes specificity



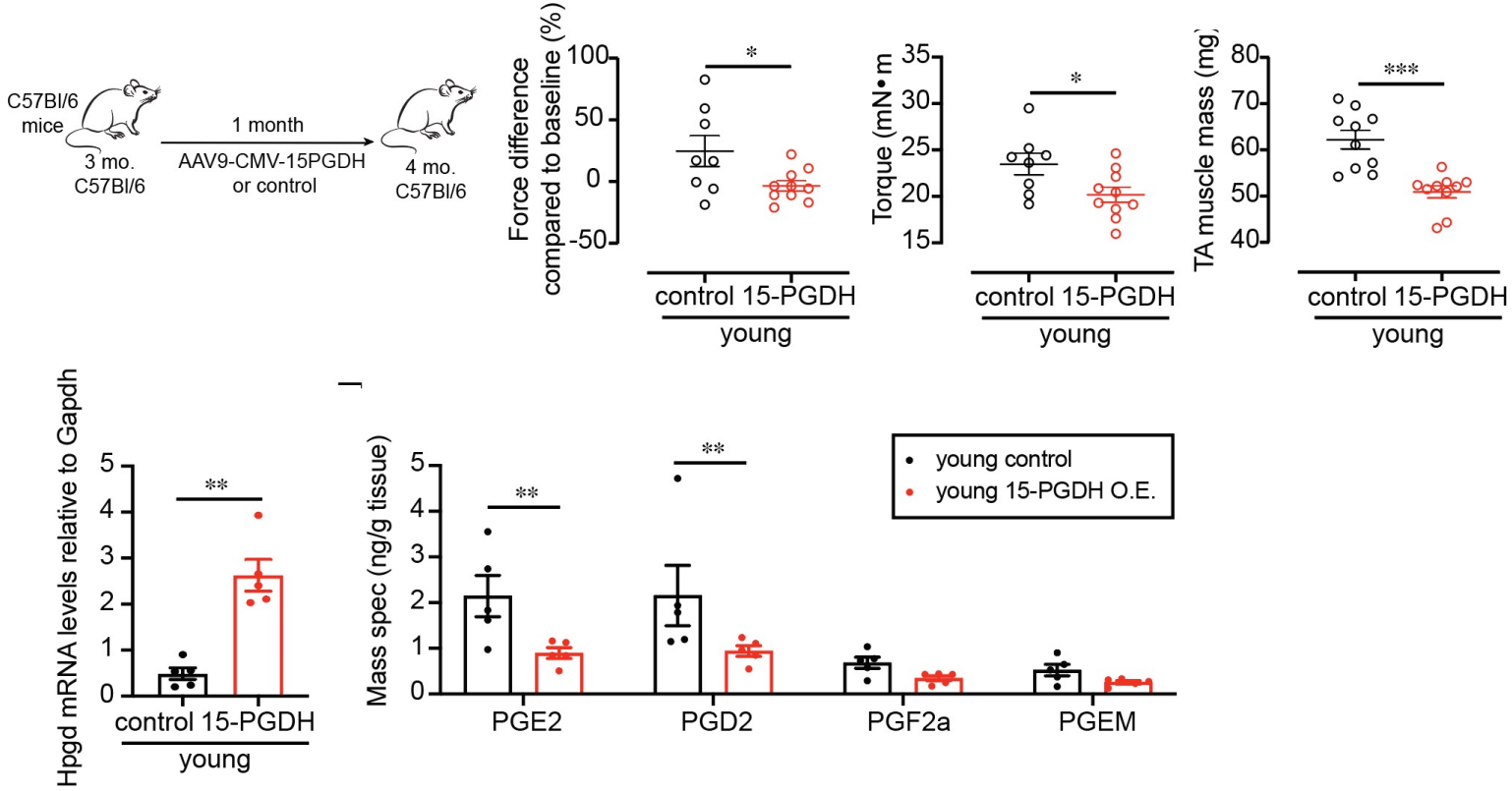
CODEX imaging reveals myofibers and macrophages as a 15-PGDH source in aging





Palla et al., *Science,* 2020

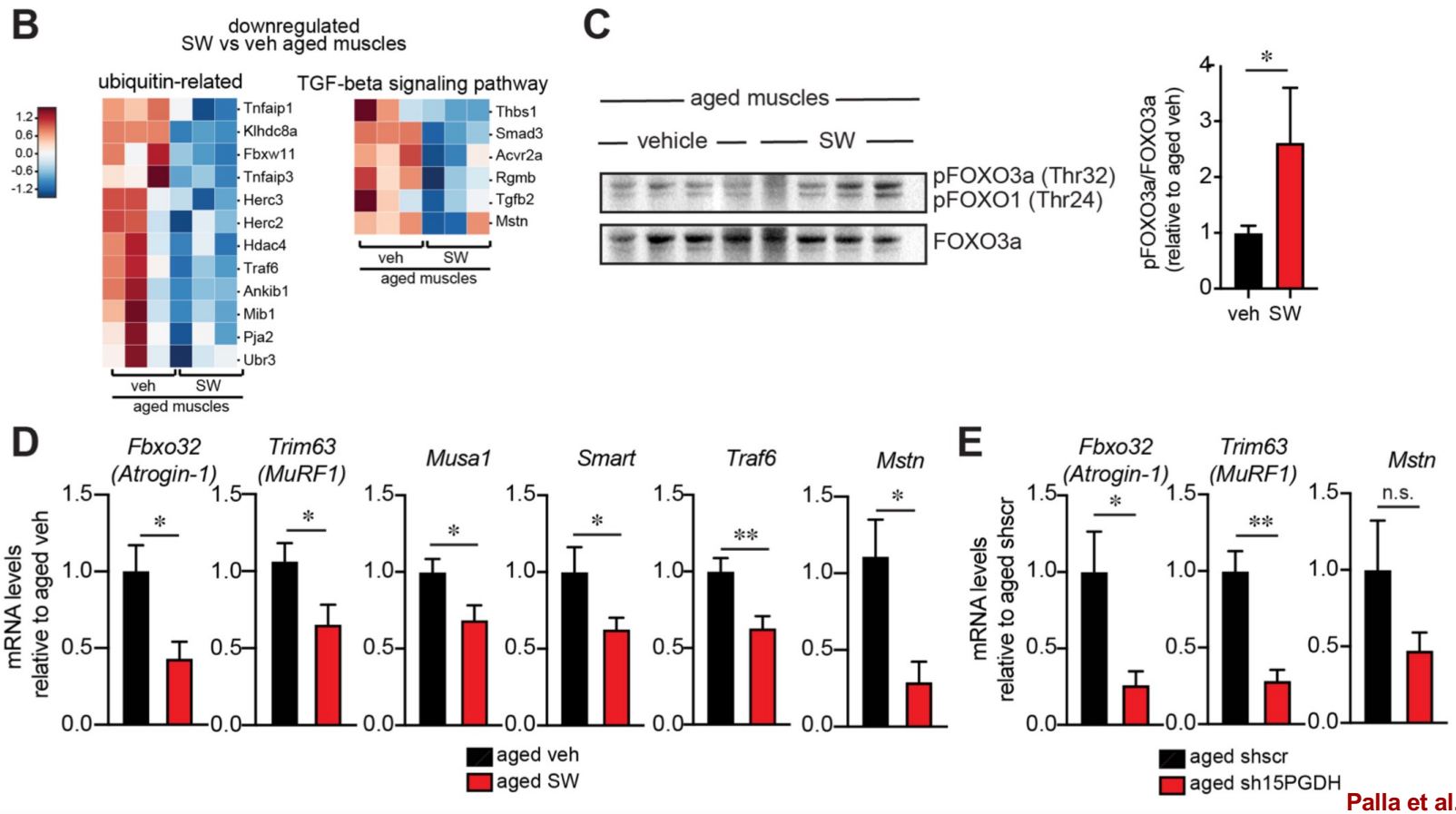
15-PGDH overexpression in young mice leads to muscle atrophy and loss of strength



Palla et al., *Science*, 2020

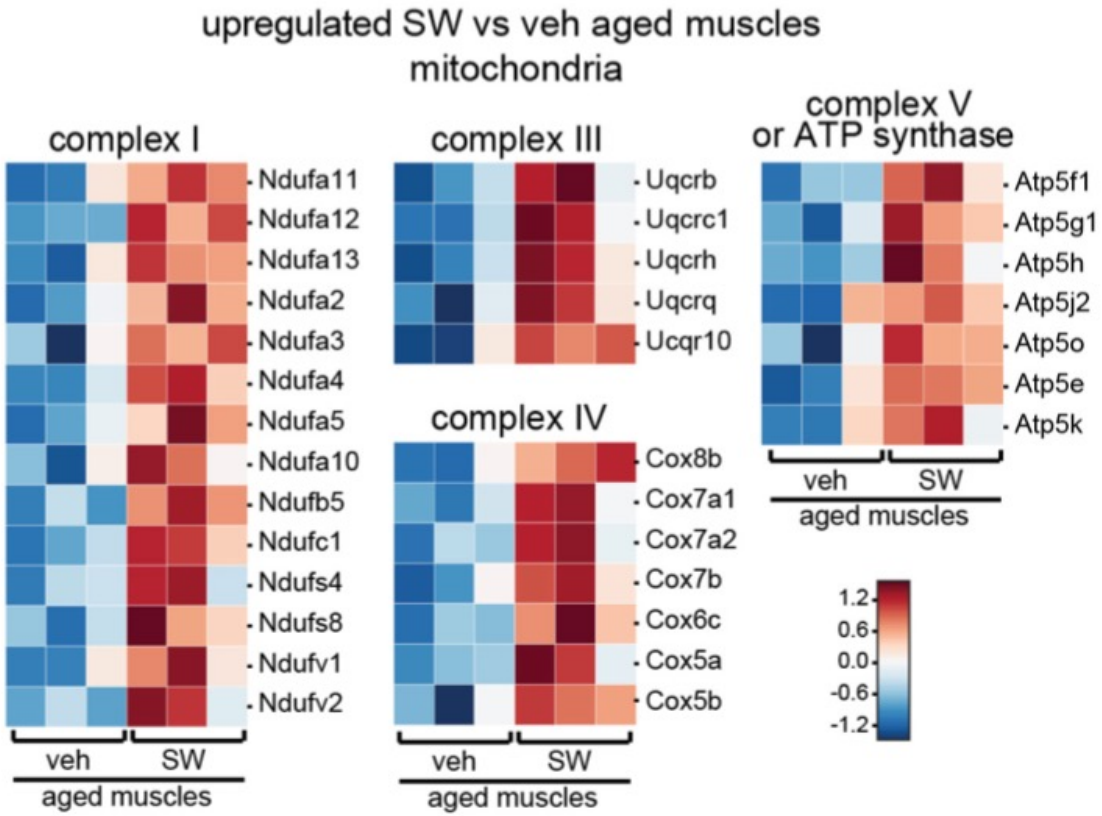
What is the mechanism of action
of 15-PGDH inhibition
that leads to increase in muscle function?

15-PGDH inhibition impacts multiple pathways to improve aged muscle function



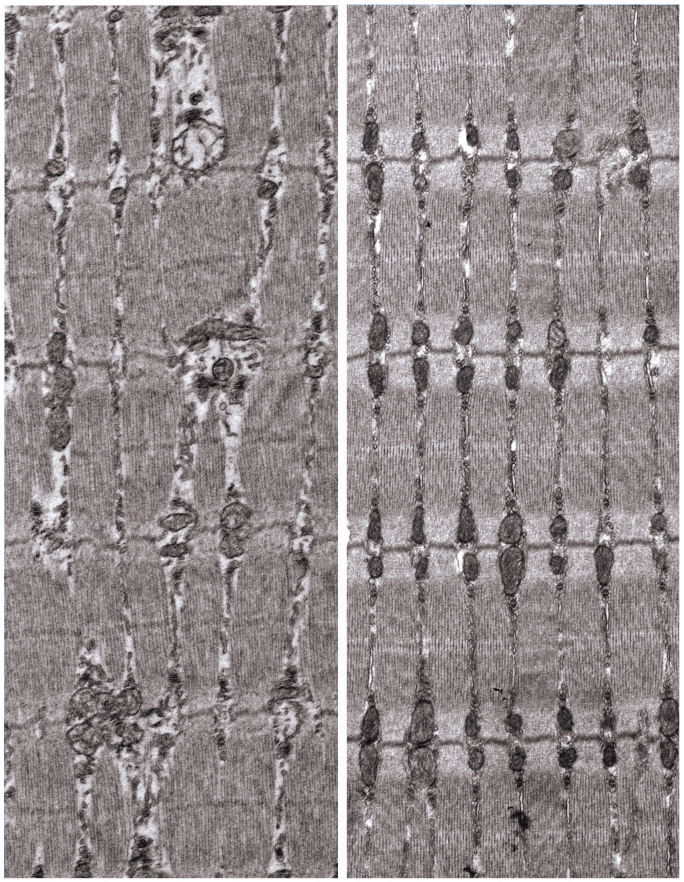
Palla et al., *Science*, 2020

15-PGDH inhibition upregulates mitochondria related genes in aged muscles

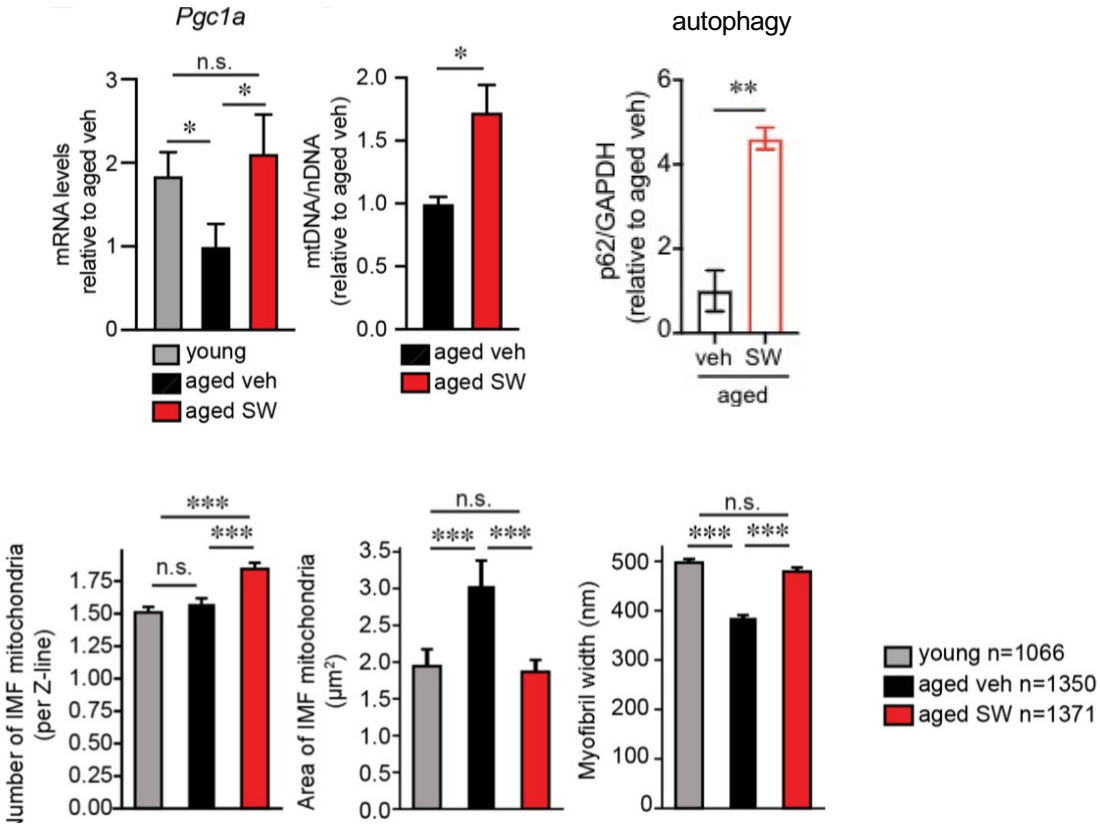


Palla et al., *Science,* 2020

15-PGDH inhibition promotes mitochondria biogenesis in aged muscles

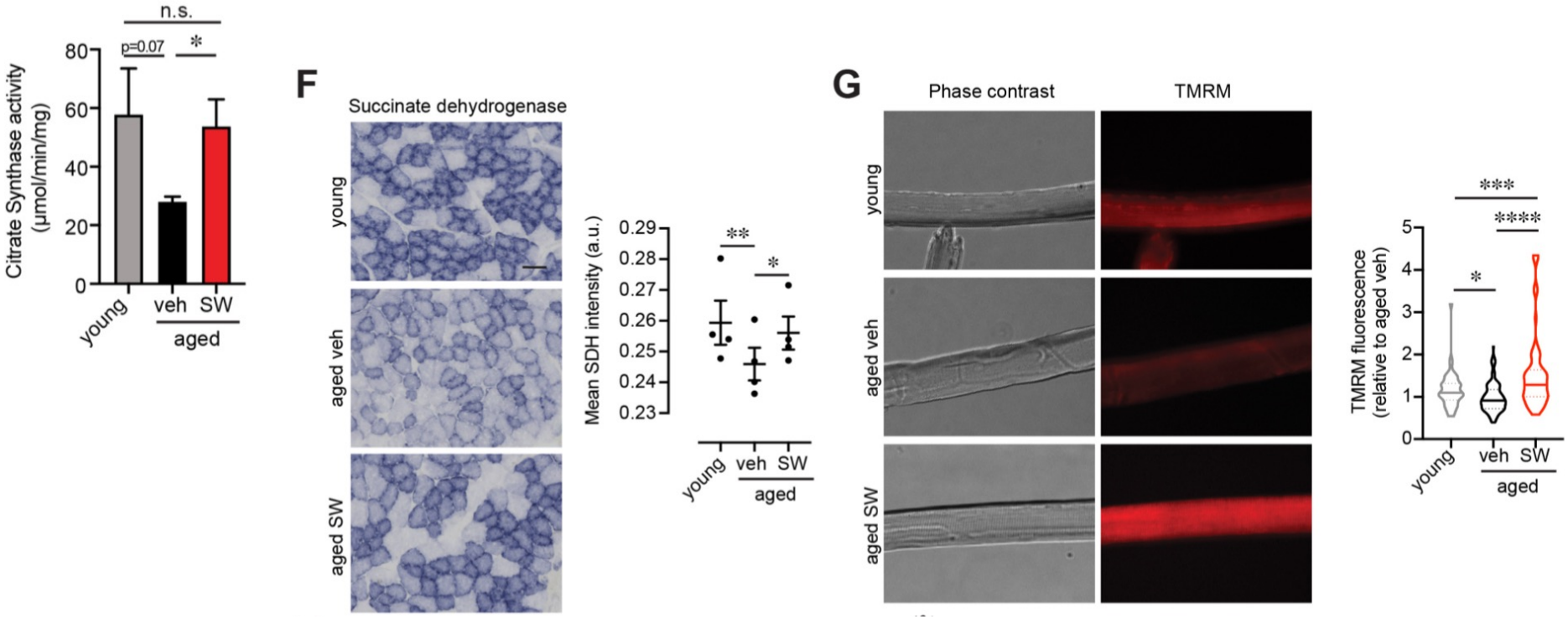


Aged Aged SW



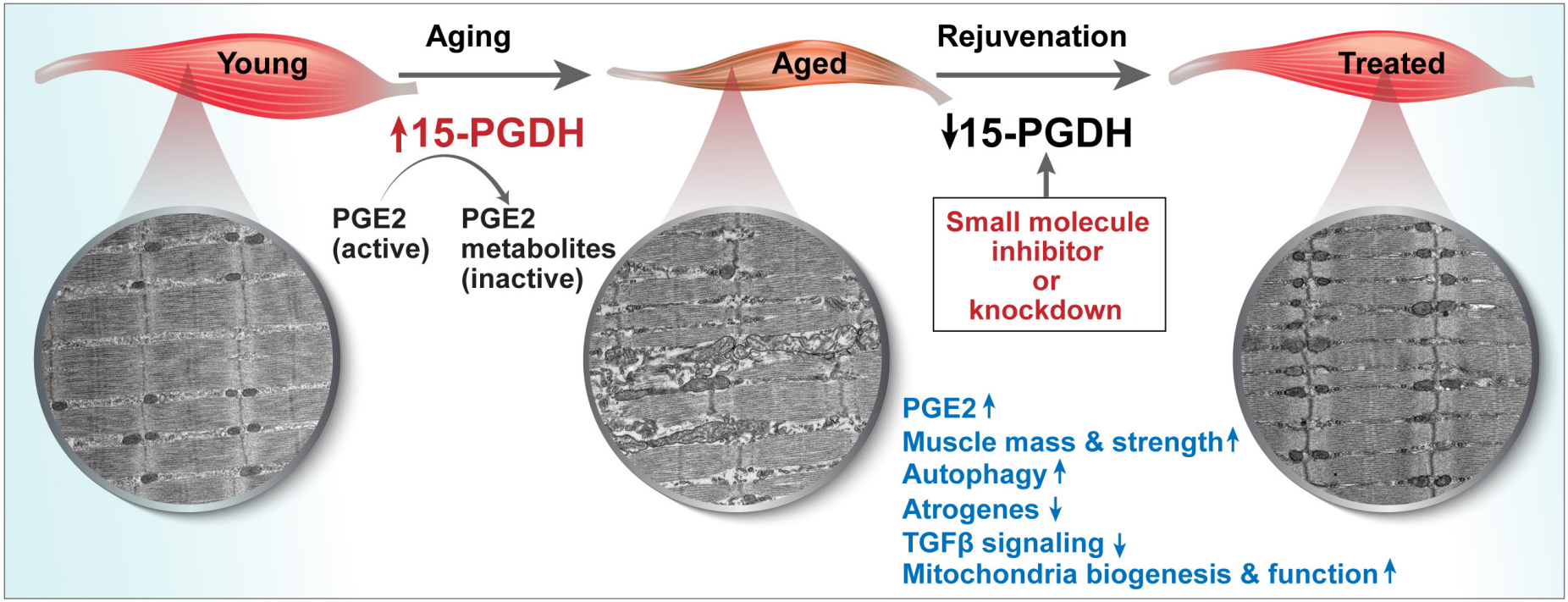
Palla et al., *Science*, 2020

15-PGDH inhibition leads to increased mitochondrial function in aged muscles



Palla et al., *Science,* 2020

Inhibition of prostaglandin degrading enzyme 15-PGDH increases muscle strength in sarcopenic aged mice



Palla et al., *Science,* 2020

SUMMARY: Prostaglandin signaling is critical for muscle maintenance, regeneration, and rejuvenation

PGE2 augments MuSC function:

- PGE2 is an essential inflammatory metabolite for muscle regeneration – body's natural healing mechanism
- PGE2 is required and sufficient for muscle stem cell (MuSC) expansion and engraftment
- PGE2 heritably alters MuSC function – epigenetic modifications

PGE2 augments muscle fiber function:

- 15-PGDH degrades PGE2 and is a novel hallmark of aged muscles and other aged tissues
- Benefit derives from physiologic modulation of "pro-inflammatory" metabolite to youthful level
- Targeting pivotal regulator of muscle aging, 15-PGDH, may be a therapeutic strategy to counter sarcopenia

Acknowledgements

Current members

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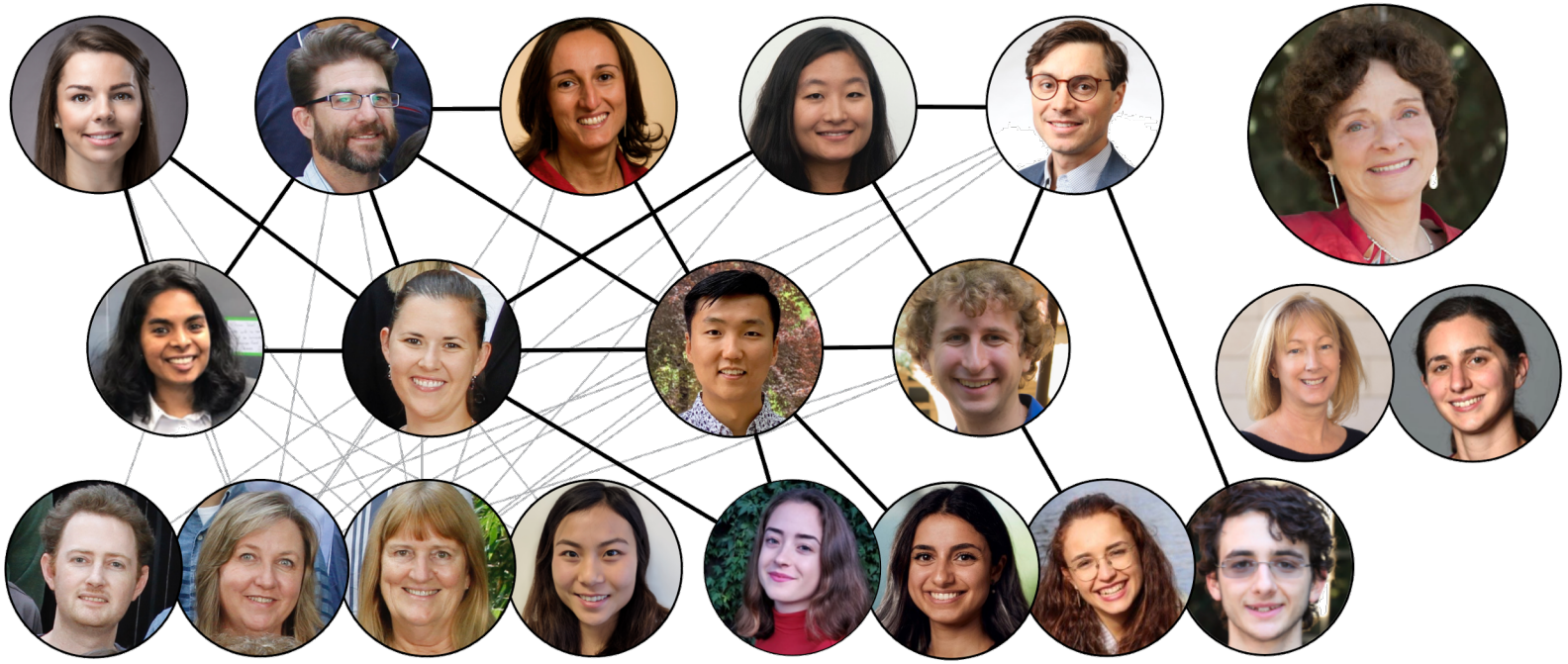

Stanford Collaborators

Scott L. Delp
Sebastian Thrun
Stanley Qi
Garry Nolan
Peter Jackson
Anshul Kundaje

NIH National Institutes of Health
American Heart Association.
Baxter
CIRM California Institute for Regenerative Medicine The State Stem Cell Agency
LI KA SHING FOUNDATION 李嘉誠基金會
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SPARK