

ANIMAL MODELS

of physical resilience

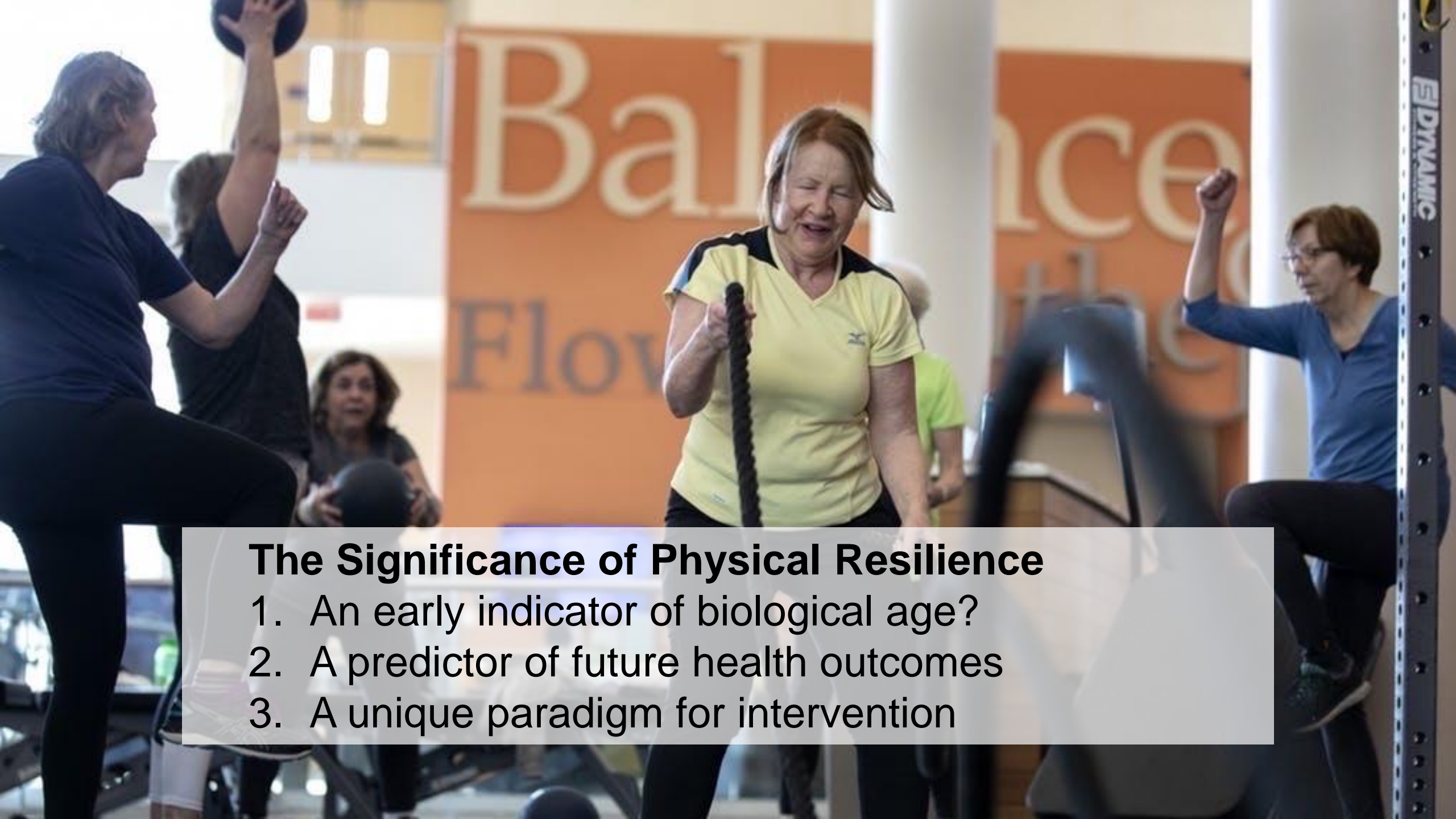
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Department of Physical Medicine & Rehabilitation

Department of Physiology & Biomedical Engineering





The Significance of Physical Resilience

1. An early indicator of biological age?
2. A predictor of future health outcomes
3. A unique paradigm for intervention

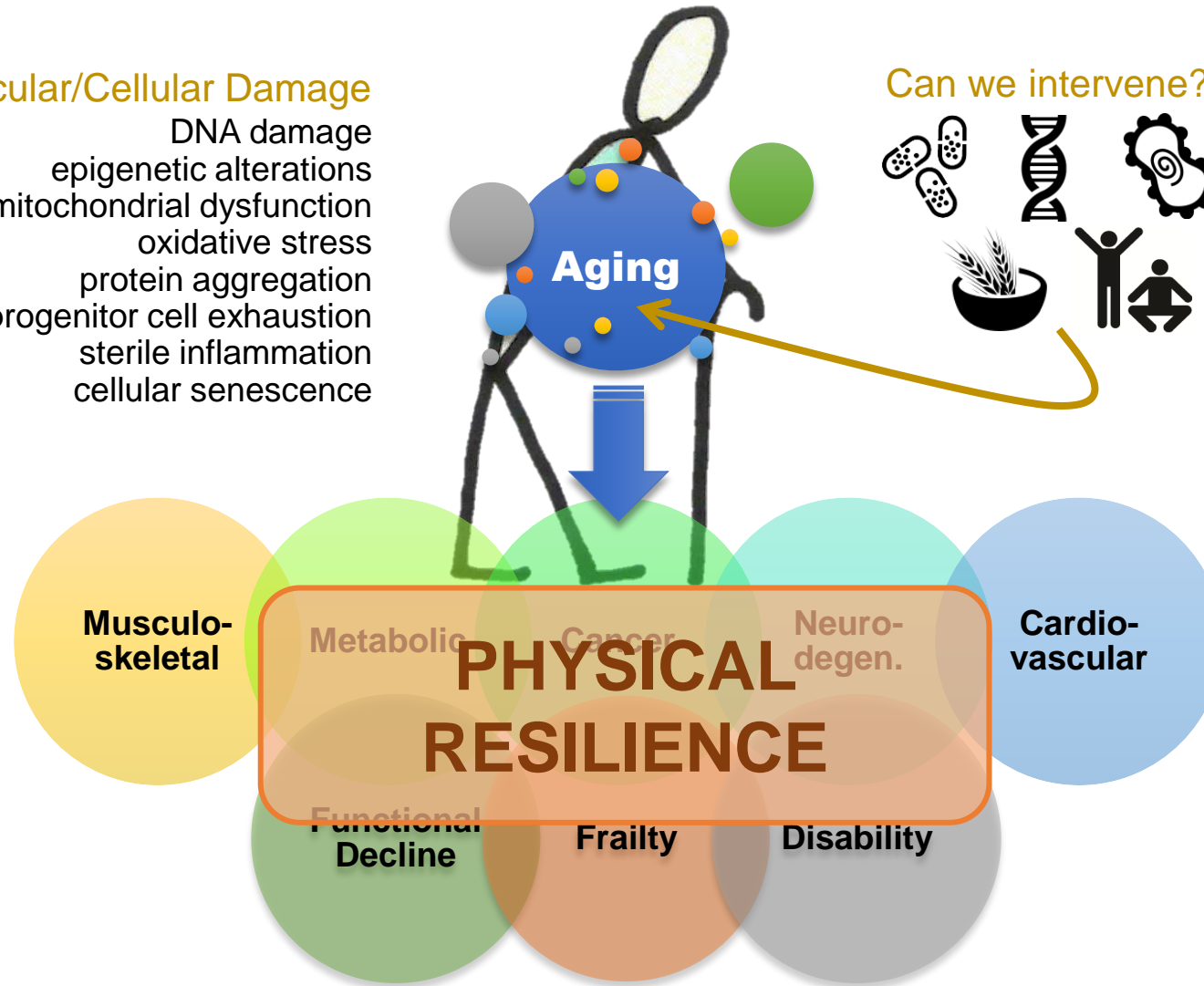
Targeting the Biology of Aging

Not science fiction, but science now

Molecular/Cellular Damage

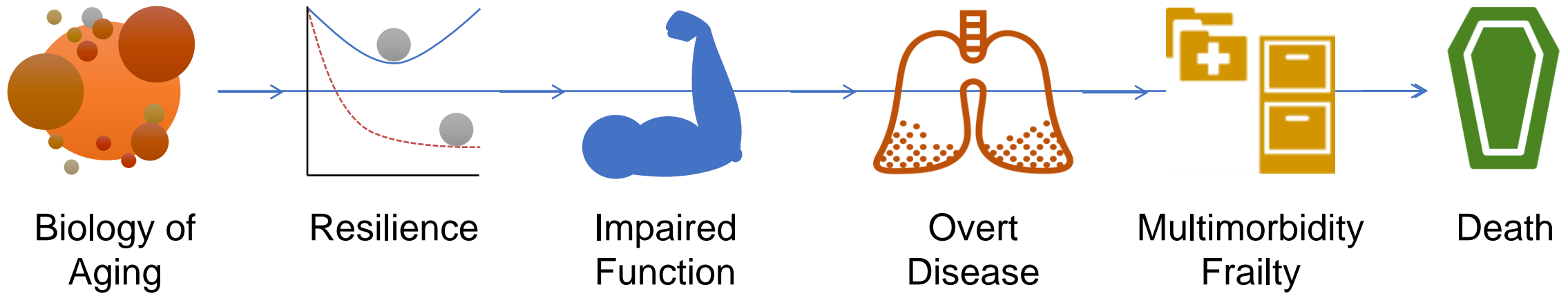
- DNA damage
- epigenetic alterations
- mitochondrial dysfunction
- oxidative stress
- protein aggregation
- progenitor cell exhaustion
- sterile inflammation
- cellular senescence

Can we intervene?



Extending Human Healthspan
Compressing morbidity

Aging and Physical Resilience



Physical Resilience and Healthy Aging

Clinical challenges

Measures of Resilience

Molecular

Physiological

Clinical

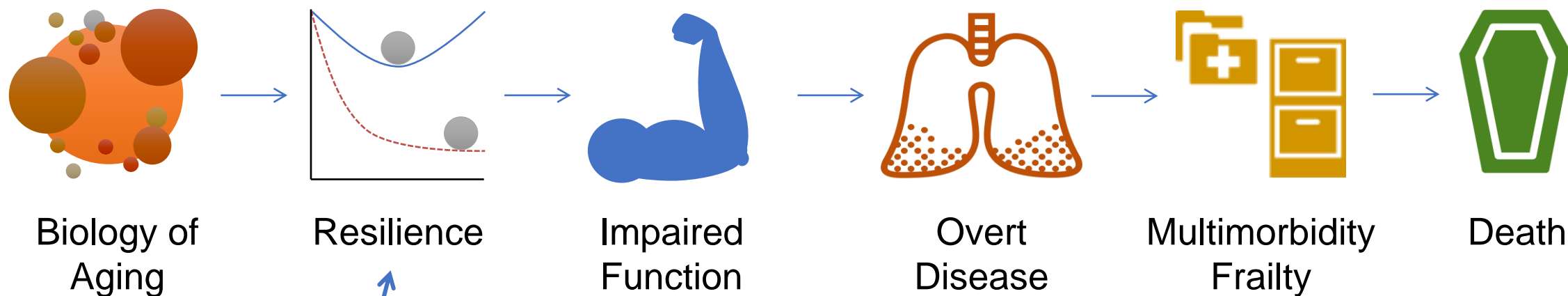
Subjective

Socioeconomic



Targeting the Biology of Aging

Paradigms for **Reverse** Translation



Can we develop preclinical models to test resilience?

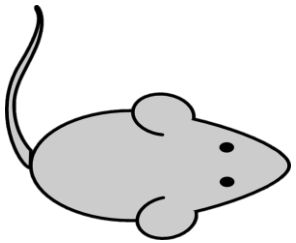
NIA initiative (Sierra and Macchiarini) in partnership with Austad, Huffman, Ladiges, Richardson, and Salmon

Modeling Resilience in Mice

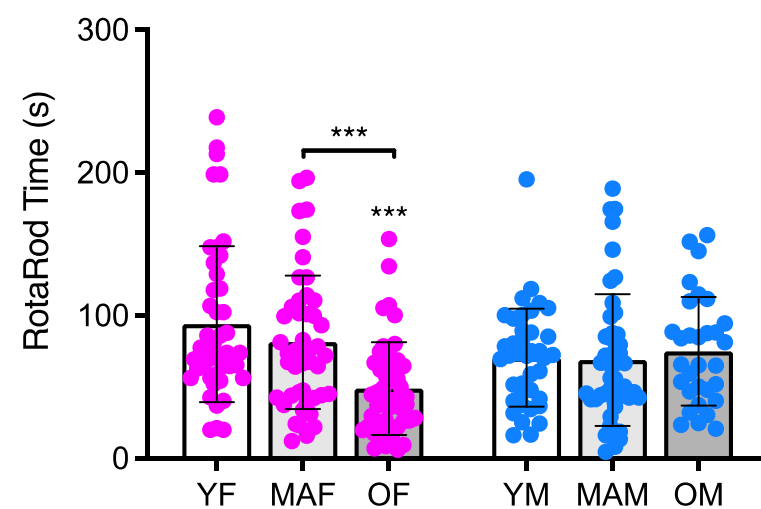
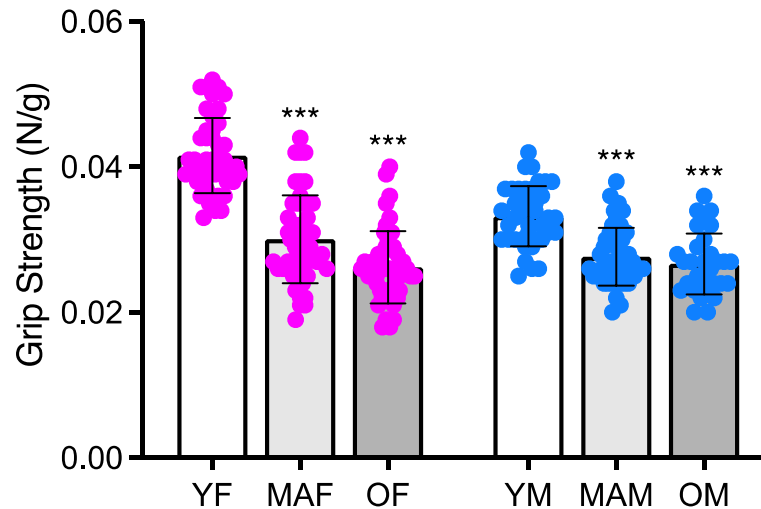
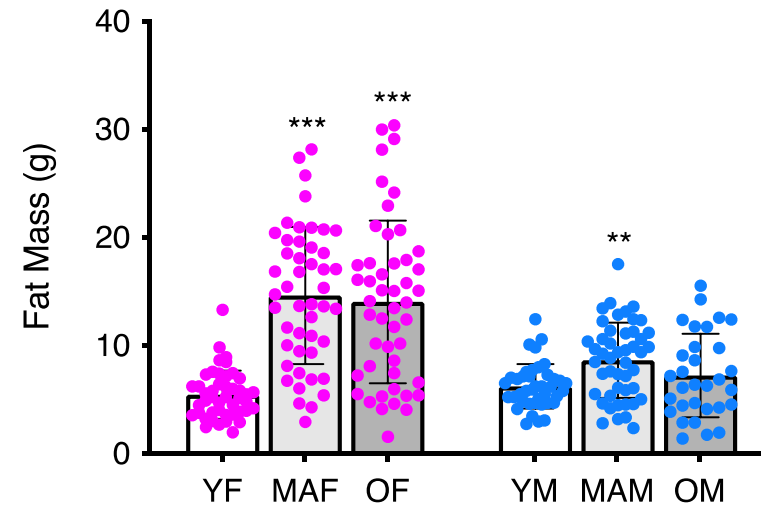
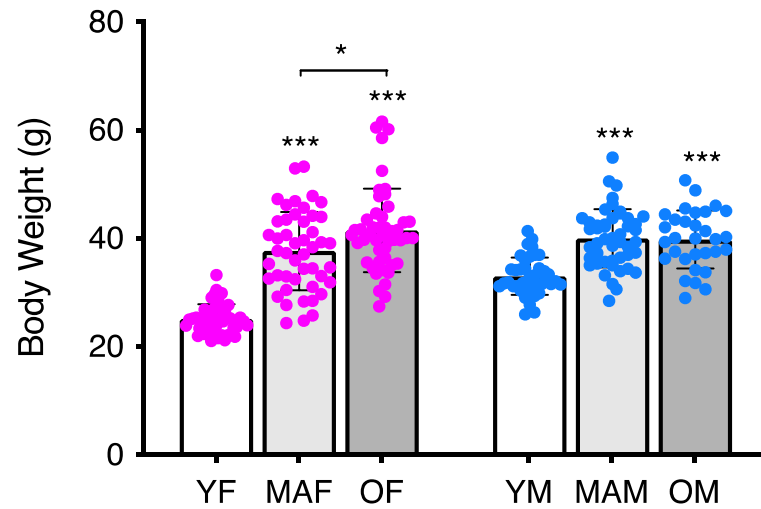
- Relatively **simple**
- Burden **multiple** physiological system
- Expose differences as **a function of age** and **between mice of similar age**
- Clinically **relevant/** **translatable**



Phenotypes of Younger (6 mo), Middle-Aged (12 mo), and Older (20 mo) 4-way Cross Mice



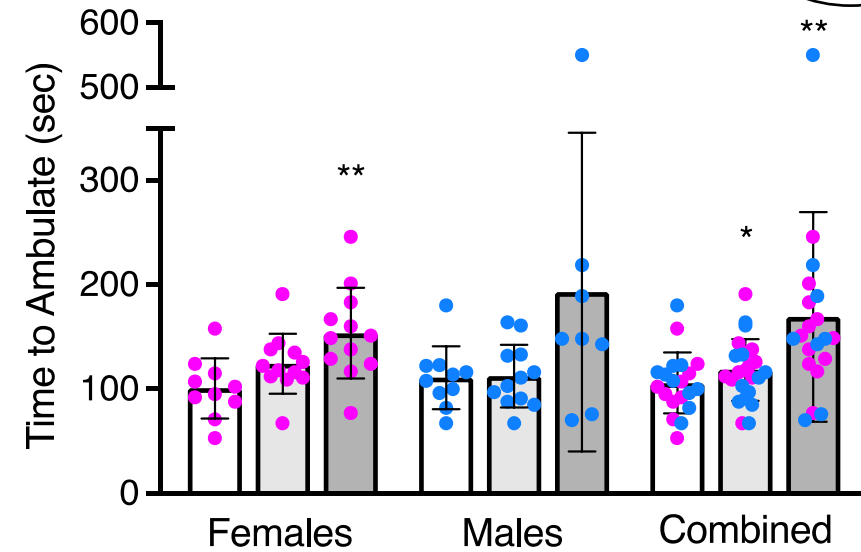
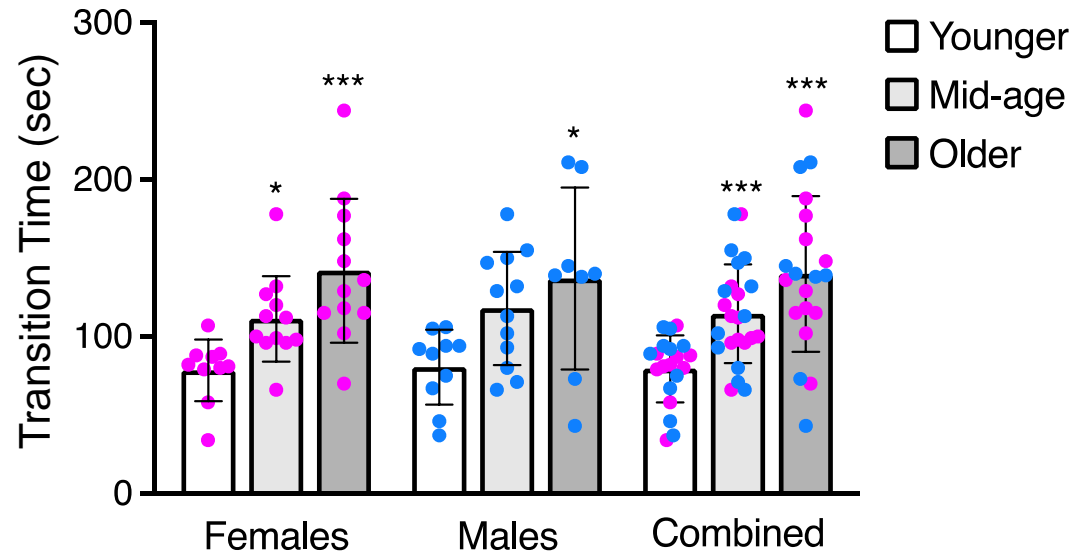
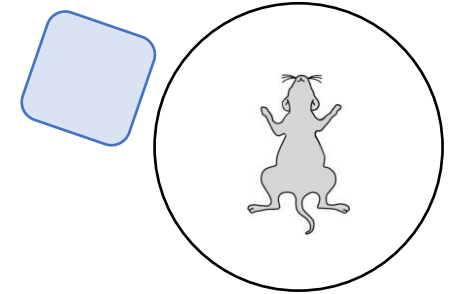
CB6F1 ♀ x C3D2F1 ♂



Brown, Mazula, R. Miller, J. Miller, et al...unpublished

Anesthesia Challenge

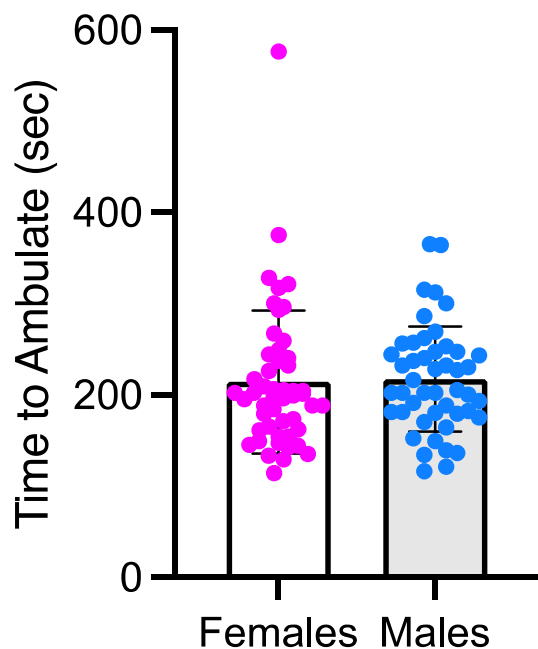
Anesthesia Challenge: 5 minutes exposure to 4% isoflurane.
Time to transition from supine to prone or ambulate to safe harbor in younger, middle-aged, and older female (●) and male (●) mice.



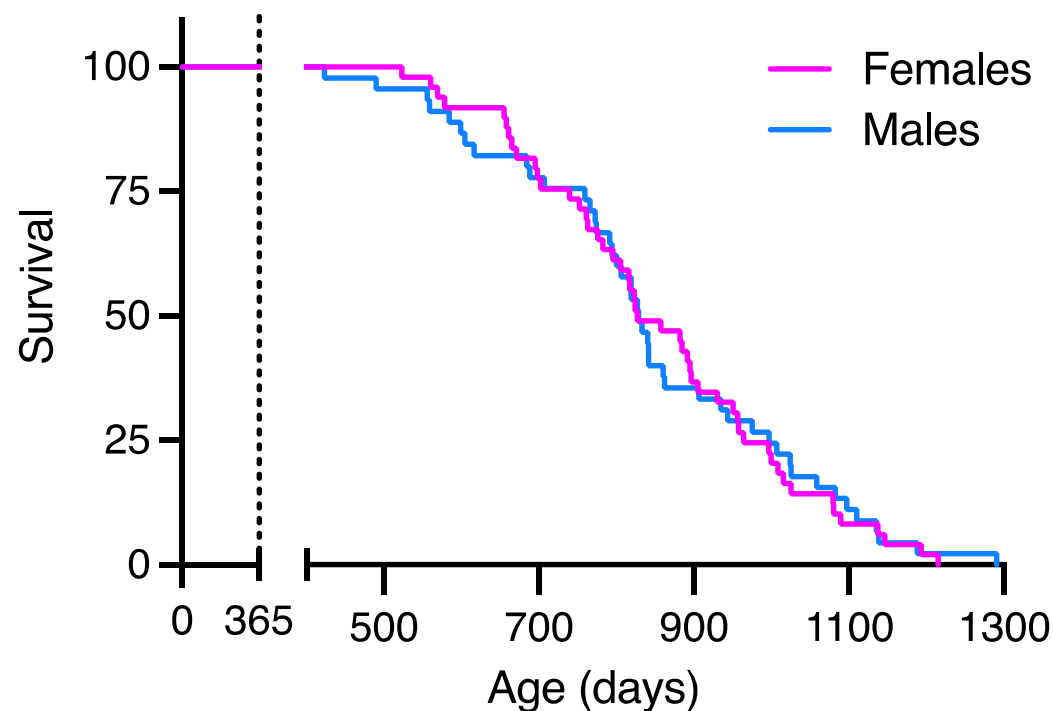
Simple. Age-sensitive. Higher variability in older mice.

Resilience as an early indicator of biological age

*Is midlife resilience to anesthesia predictive of **lifespan**?*



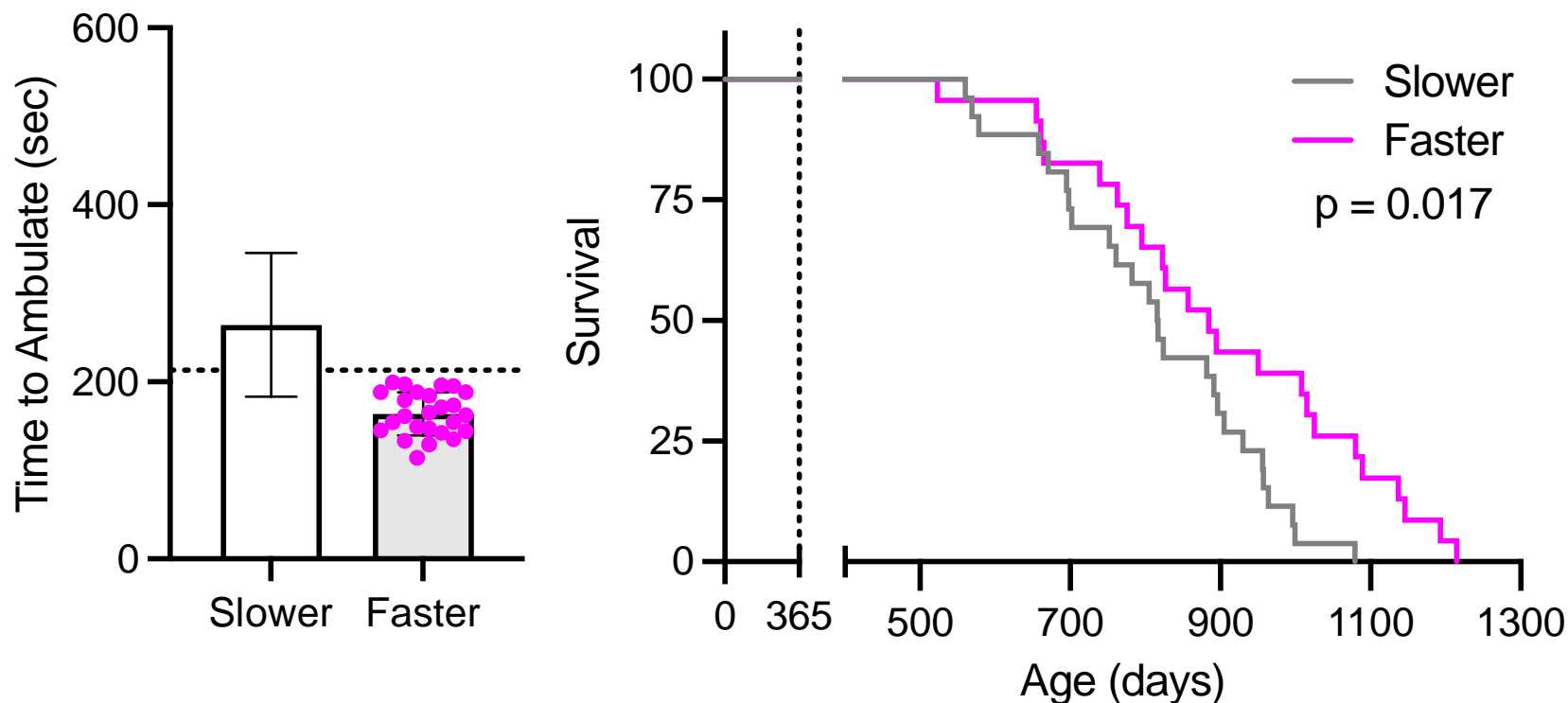
**12-month-old
4-way cross mice**
(50 female, 47 male)



University of Michigan Cohort: Lifespan
Rich Miller, Lori Roberts, Suja Kumar

Resilience as an early indicator of biological age

*Is midlife resilience to anesthesia predictive of **lifespan**?*



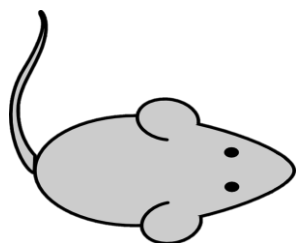
*Female mice that recover **FASTER** at 12 months of age live **LONGER***
(No difference in males!)

Resilience as an early indicator of biological age

*Is midlife resilience predictive of **healthspan**?*

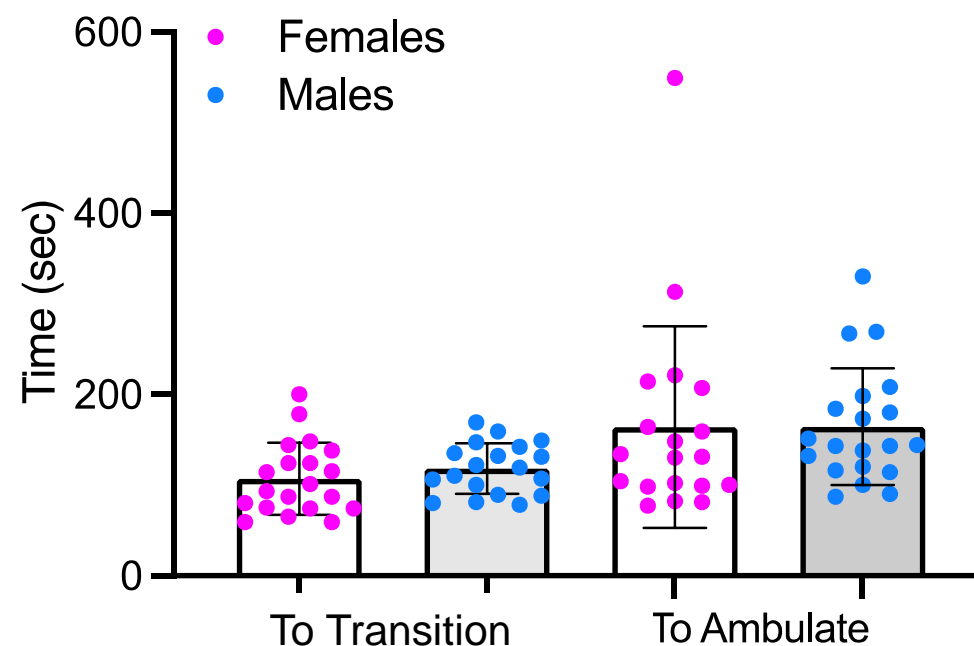
Mayo Clinic Cohort

12-month-old mice
(20 Female, 20 Male)



CB6F1 ♀ x C3D2F1 ♂

Anesthesia Challenge @12 months



Healthspan Outcomes

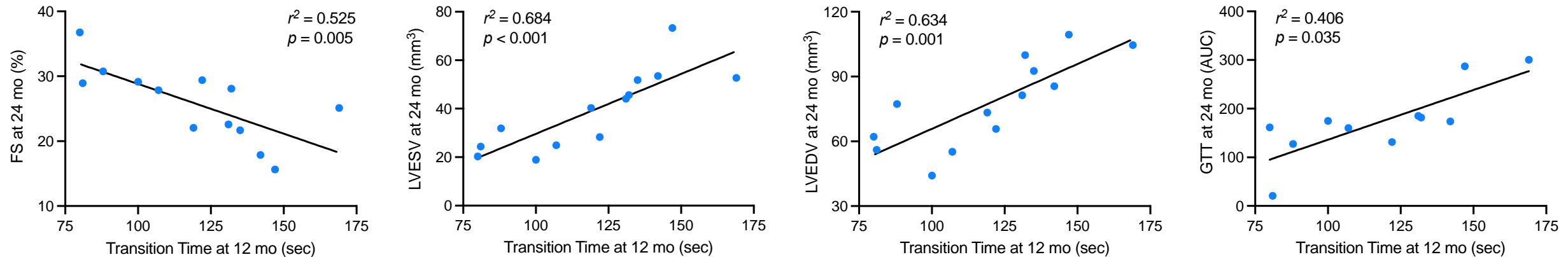
@18 and 24-months

- Physical function
- Cardiovascular function
- Metabolic function
- Cognitive function

Jordan Miller, Ashley Brown,
Dan Mazula, Vessa Pearsall,
Carolyn Roos

Resilience as an early indicator of biological age

*Is midlife resilience predictive of **healthspan**?*

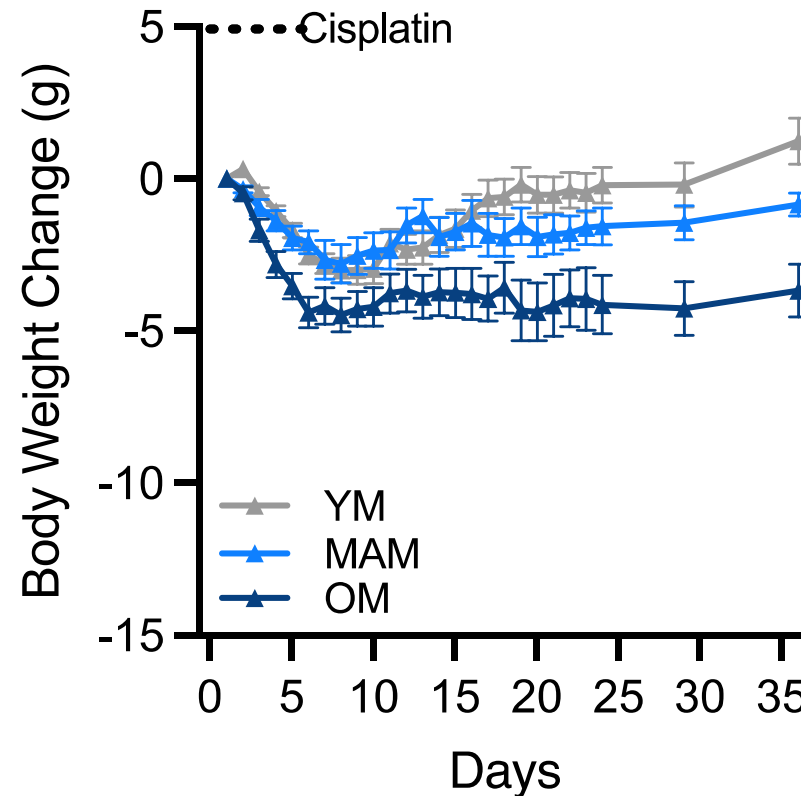
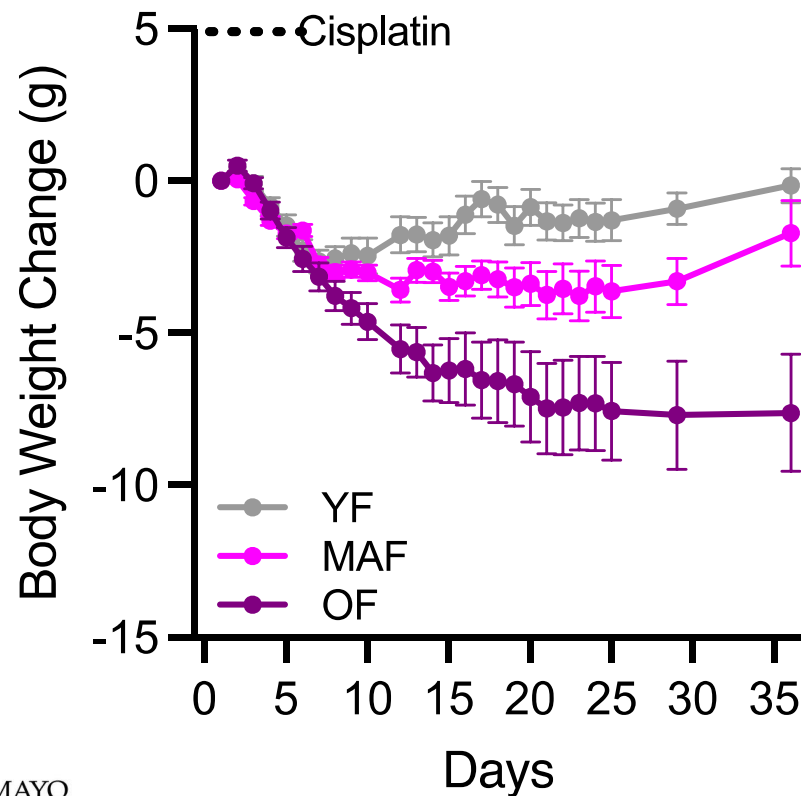


*Male mice that recover **FASTER** at 12 months of age have **BETTER CARDIAC AND METABOLIC FUNCTION** function at 24 months of age
(Very few differences in females!)*

Resilience as an early indicator of biological age

*Is midlife resilience to chemotherapy predictive of **lifespan**?*

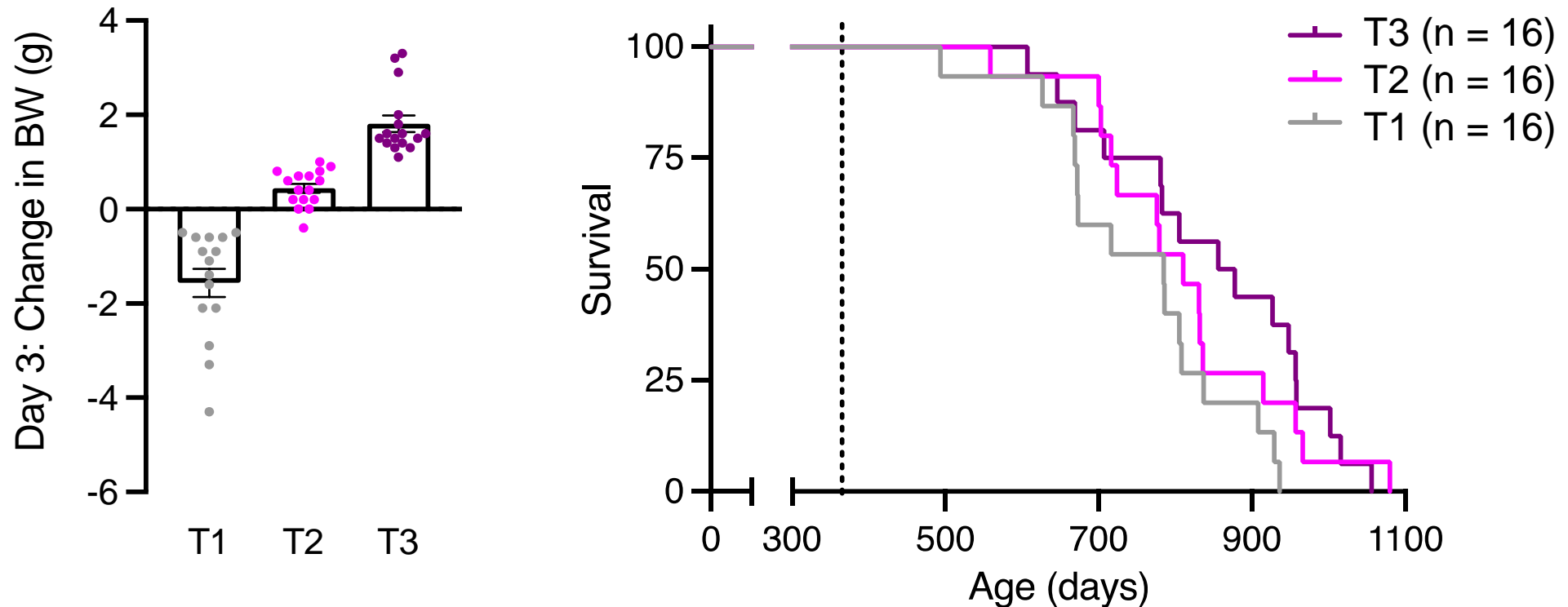
Cisplatin Challenge: One 5-day cycle of cisplatin (2 mg/kg/day). Changes in body weight and composition between baseline and 30-days after challenge in younger, middle-aged, and older mice.



*Simple-ish. Age-sensitive.
Higher variability in
older mice (AUC, max weight
loss...).*

Resilience as an early indicator of biological age

*Is midlife resilience to chemotherapy predictive of **lifespan**?*



*Female mice that are **resistant** to acute body weight loss at 12 months of age live **LONGER**.
However, associations with late-life health in females and males were underwhelming.*

Work in Progress

Surgery challenge and healthspan

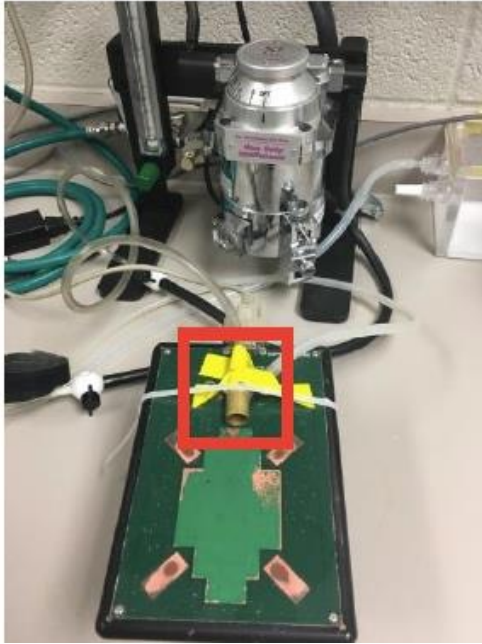
Heated anesthesia
platform

Surgical procedure
Body temp

Sternal recumbence
Time to ambulate

Younger
Day 0 Day 1 Day 8

Older
Day 0 Day 1 Day 8



Brown, Mazula, J. Miller, Roos, B. Zhang...*unpublished*

Murine Models of Physical Resilience

- Potential for anesthesia, chemotherapy, and surgical challenges based on:
 - **Age-related changes** in select measures of resilience
 - Higher **variability in older mice**, indicative of more and less resilient
 - Translatability
 - Disease agnostic-ity; **integrate multiple physiological systems**
 - Relative simplicity, scalability
- Aspects of mid-life resilience may be **predictive of lifespan** and parameters of **healthspan!**
 - More data to crunch
 - Sex differences are intriguing
- Can interventions targeting biology of aging **improve** later-life resilience? **Stay tuned....**
 - **Rapamycin/Rapalogs**. Mannick et al., *STM* 2014 & 2018, *Lancet Healthy Longevity*, 2021
 - **Senotherapeutics**. Camell et al., *Science*, 2021

Targeting the Biology of Aging and Resilience

Paradigms for Translation

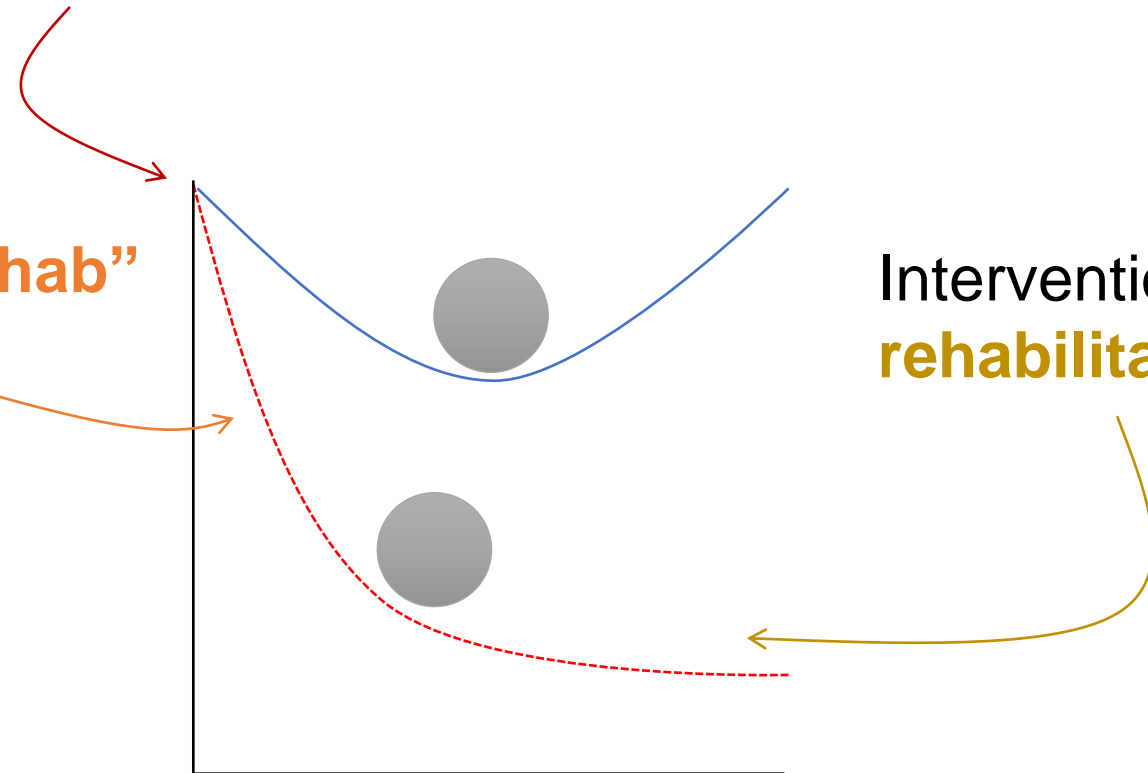
Biological age as a **predictor** of resilience

(ICSFR Task Force, *JNHA*, 2021;
Schafer, *JCI Insight*, 2020)

Interventions as **boosters “prehab”**

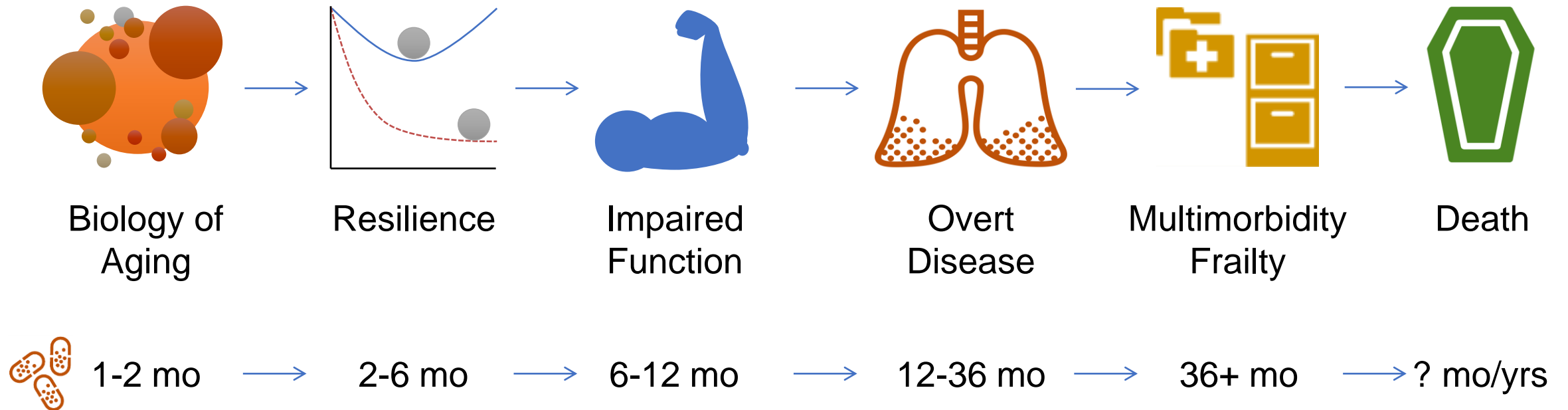
- **Exercise.**
- **Rapamycin/Rapalogs.**
Mannick et al., *STM* 2014
& 2018, *Lancet Healthy Longevity*, 2021
- **Senotherapeutics.**
Camell et al.,
Science, 2021

Interventions as **rehabilitators**



Targeting the Biology of Aging

Paradigms for Translation



Acknowledgements



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