Biology of resilience: predicting mouse aging?

Adam Salmon, PhD

Barshop Institute and Dept of Molecular Medicine, UTHSCSA

GRECC, South Texas Veterans Health Care System

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San Antonio Claude D. Pepper Older Americans Independence Center

San Antonio Nathan Shock Center

UT Health San Antonio

Sam & Ann Barshop Institute for Longevity & Aging Studies

Short-term Measurements of Physical Resilience as a Predictor of Healthspan in Mice: RFA-AG-17-040

- *"The goal of this Funding Opportunity Announcement (FOA) is to develop a panel of tests to measure resilience in young or middle-aged animals that can be used to predict: 1) individual future health outcomes, and 2) whether an intervention might result in increased longevity and/or healthspan in an animal model as a population."*

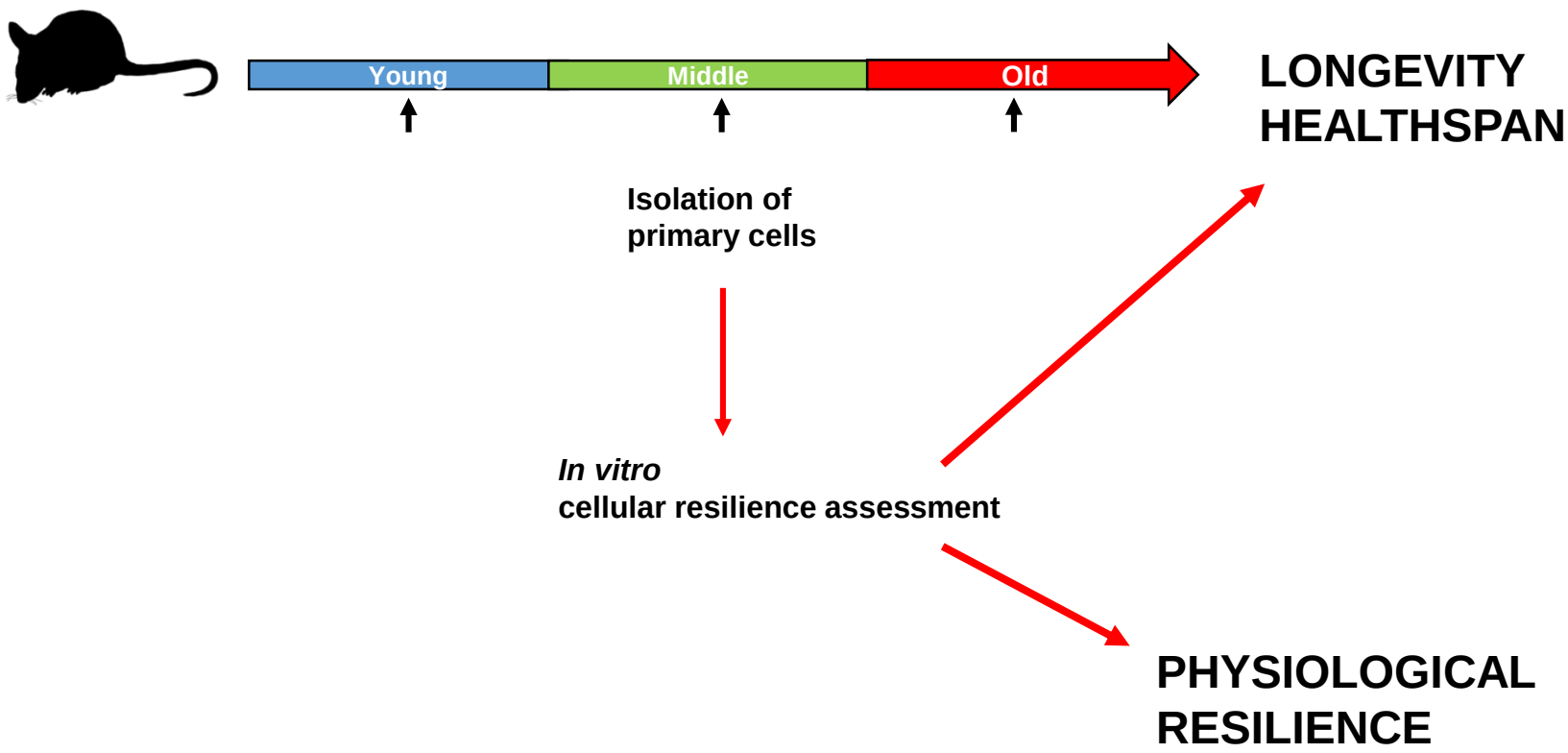
CHALLENGE

- What physical challenges or stresses and return to cellular, tissue and/or organismal homeostasis would have limited effect on future health outcomes?

RATIONALE OF OUR STUDY

- If there are biological mechanisms of resilience, they should exist throughout the organism

Predicting longevity & functional resilience from cellular resilience



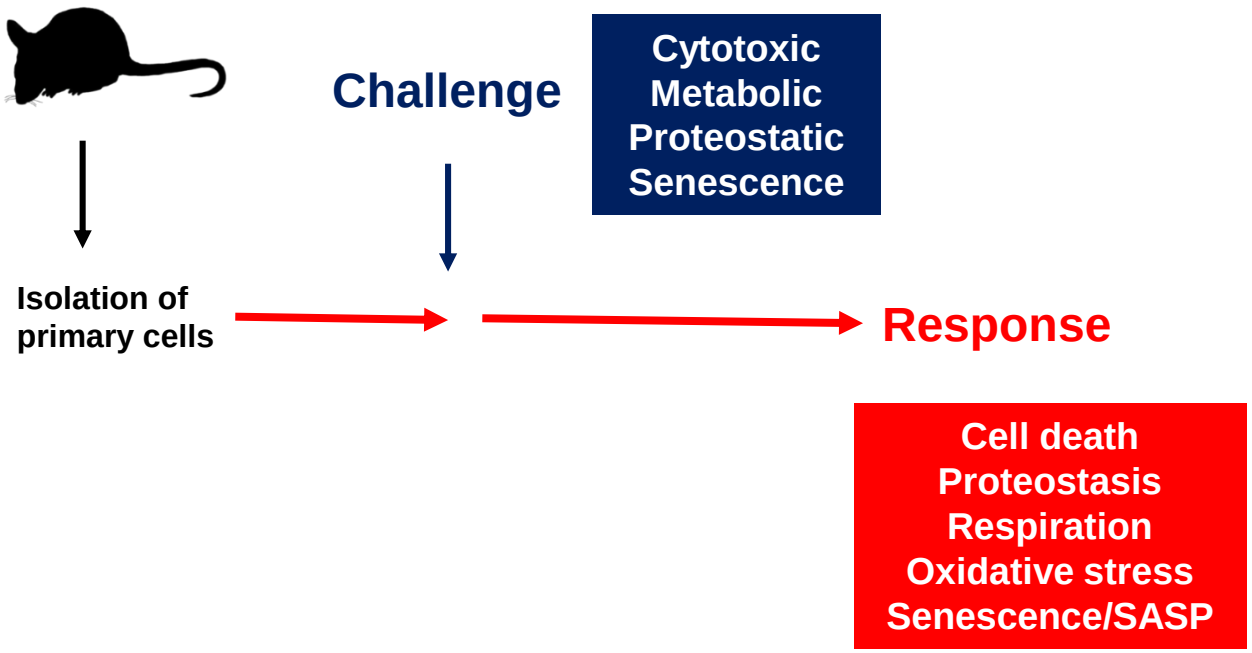
Selection of primary cells (fibroblasts) as a model?

- Minimally invasive biopsy collection (tail snip); can be repeated
- Readily expandable in culture; multiple assessments from a single cell “line”
- Primary fibroblasts retain “in vivo” characteristics even after growth and expansion in culture
  - Fibroblasts from long-lived mutant mice (*i.e.,* dwarf mice, GHR-knockout) are resistant to multiple forms of cellular stress
  - Fibroblasts from long-lived species tend to be stress resistant compared to those from short-lived species
  - Cellular resilience to one form of stress predicts resilience to others

REMINDER

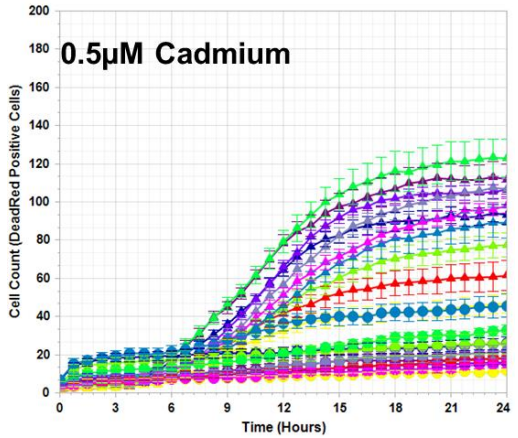
If there are biological mechanisms of resilience, they should exist throughout the organism (i.e., they should be agnostic to cell type, origin or role in physiology)

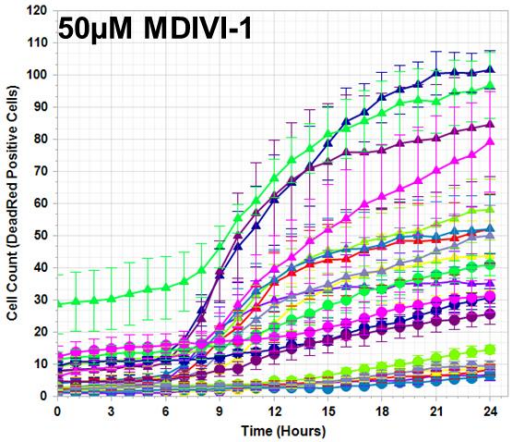
What is cellular resilience and how can it be leveraged?

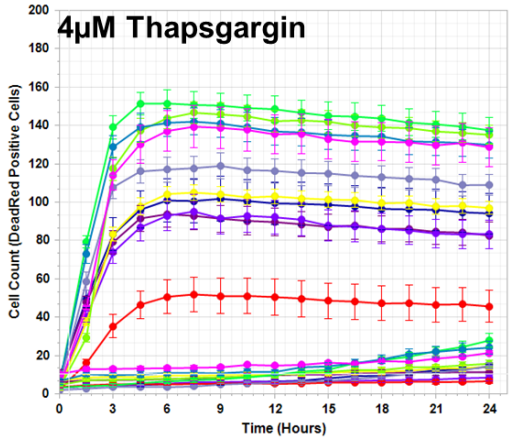


Variability (*predictive power*) among mice in cellular resilience

Live cell imaging (Incucyte)

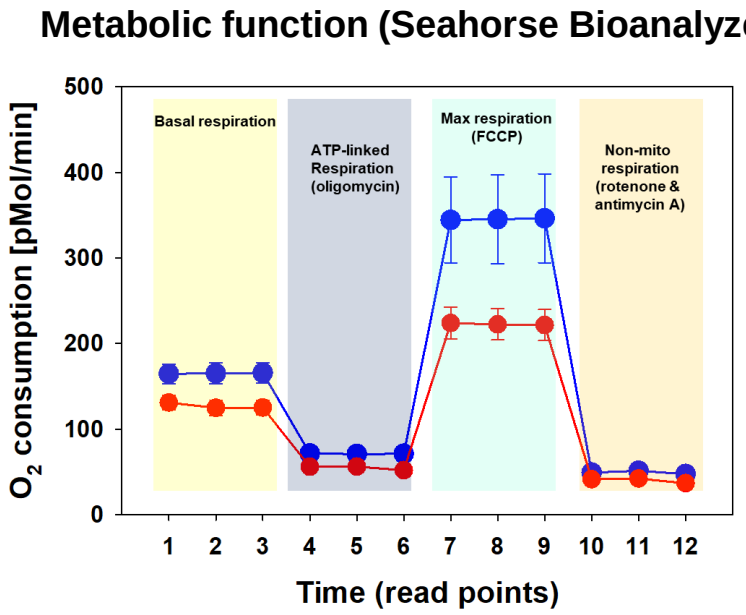


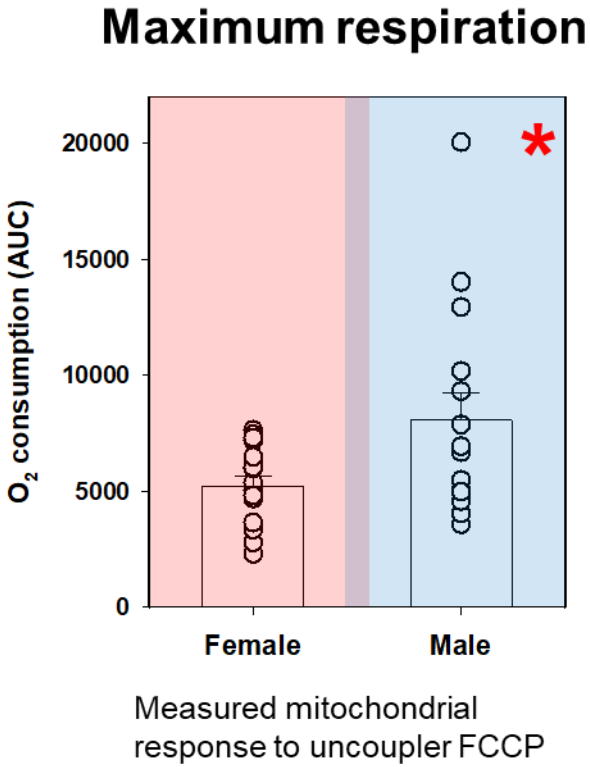




Cell death
Autophagy
Respiration
Oxidative stress
Senescence/SASP

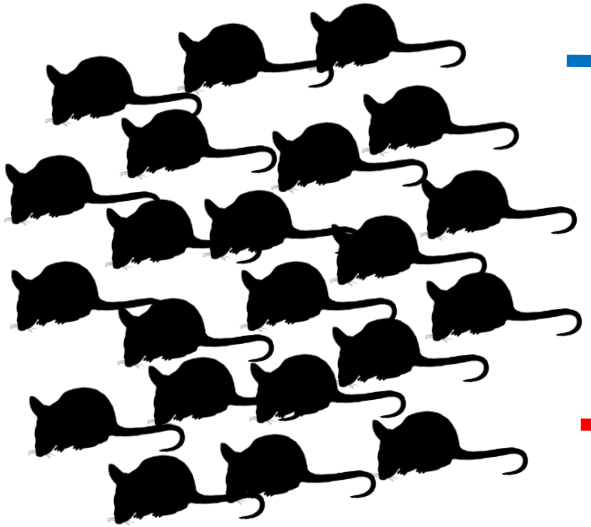
Variability (*predictive power*) among mice at cellular level





Measured mitochondrial response to uncoupler FCCP

Can cellular resiliency predict longevity or healthspan in normally aging mice?



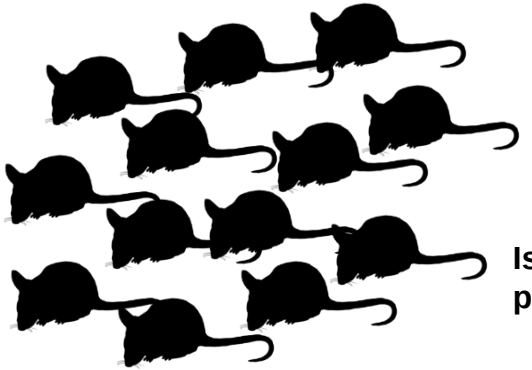
LONGEVITY
HEALTHSPAN

Cell Resilience

~260 UM-HET3 mice; M/F
Tail biopsy @ 6, 18 mo.

Genetic heterogeneity (*i.e.,* not inbred)
Grand-offspring of 4 different inbred lines (C57BL/6, DBA/2, C3H, BALB/C)
Males and females; testing at different ages

Can cellular resiliency predict physiological resilience?

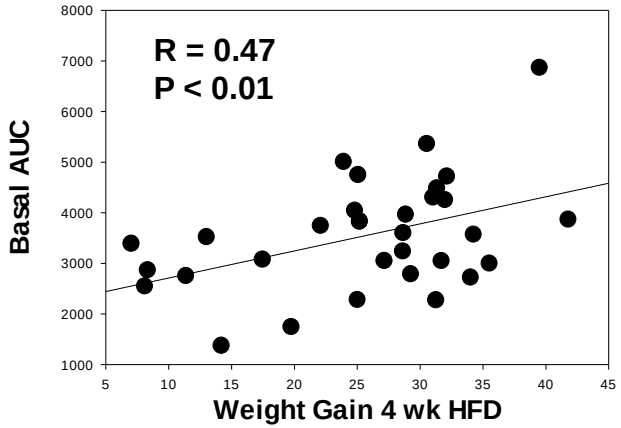


HIGH FAT DIET

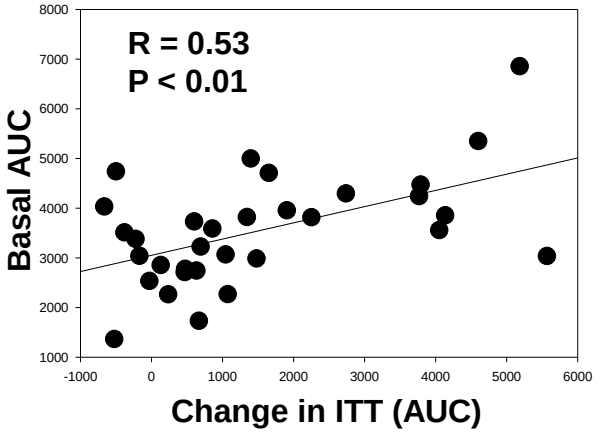
METABOLIC RESILIENCE

Isolation of primary cells

Basal resp VS weight gain



Basal resp VS ITT change



Harnessing cellular variability in resilience

PROTEOSTATIC

CELL GROWTH

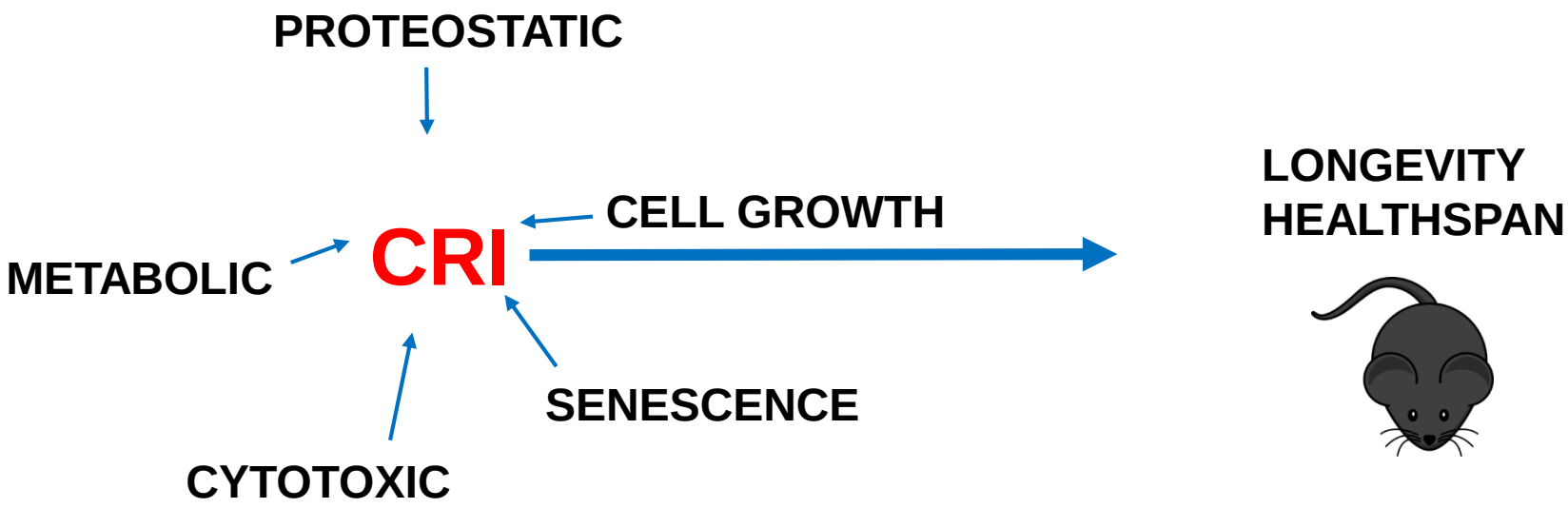
METABOLIC

SENESCENCE

CYTOTOXIC

LONGEVITY
HEALTHSPAN

Harnessing cellular variability in resilience



CRI: Cellular Resilience Index

Translational opportunities?

- Can we identify Cellular Resilience Index across species?
  - Non-human primates (marmosets, baboons), humans
- Can cellular resilience be modified?
- Does cellular resilience exist across cell types?
  - How do tissue-derived cells compare to blood cells?
- Personalized medicine?

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