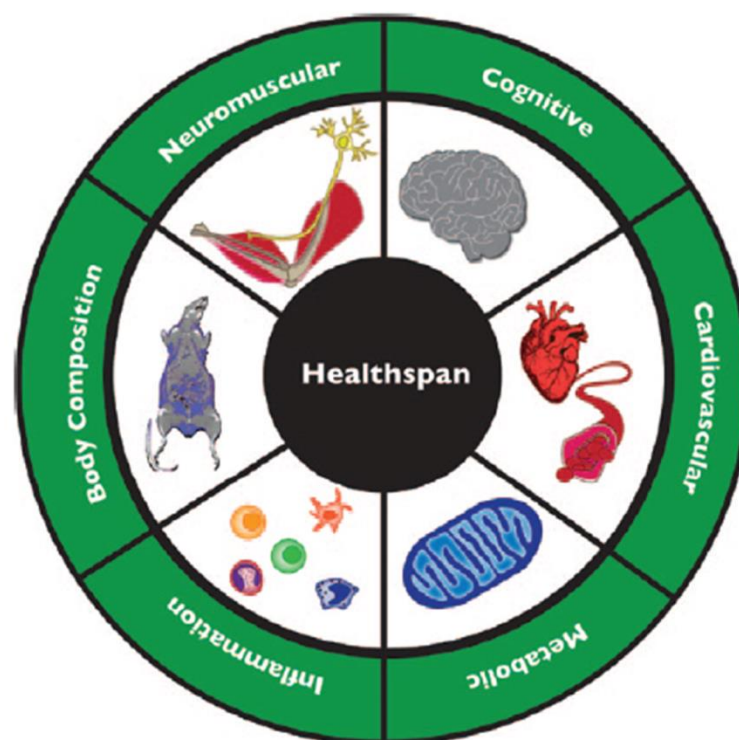


Special Issue: Moving Geroscience into Uncharted Waters: Perspective

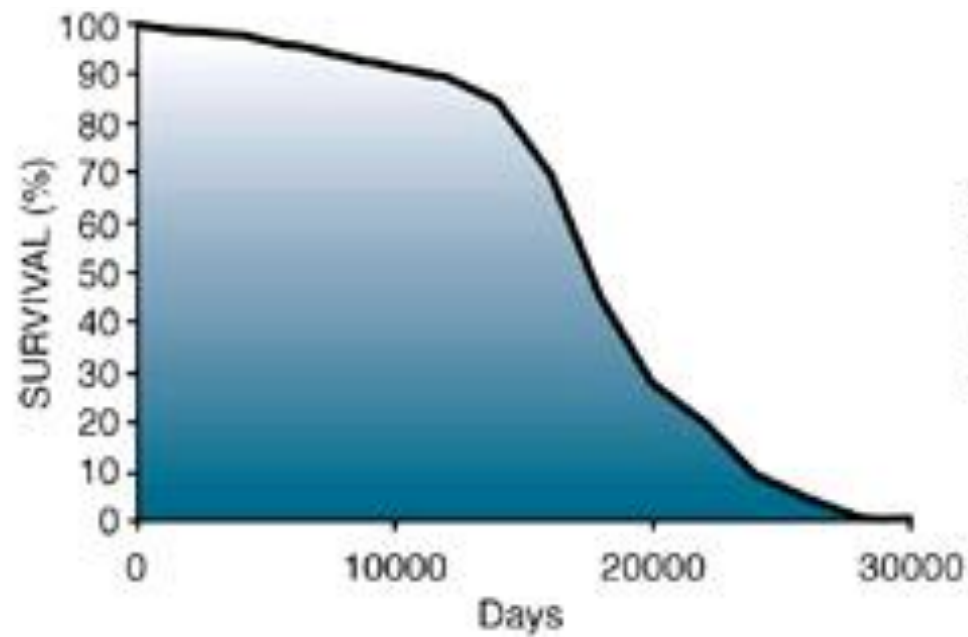
Evaluating Health Span in Preclinical Models of Aging and Disease: Guidelines, Challenges, and Opportunities for Geroscience

Derek M. Huffman,¹ Jamie N. Justice,² Michael B. Stout,³ James L. Kirkland,³ Nir Barzilai,¹ and Steven N. Austad⁴

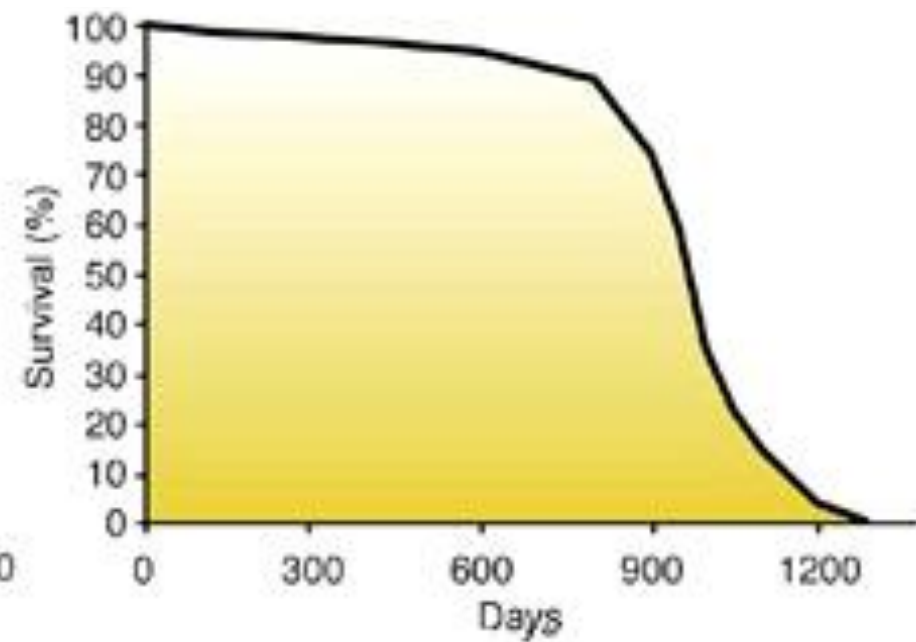


Universality of aging

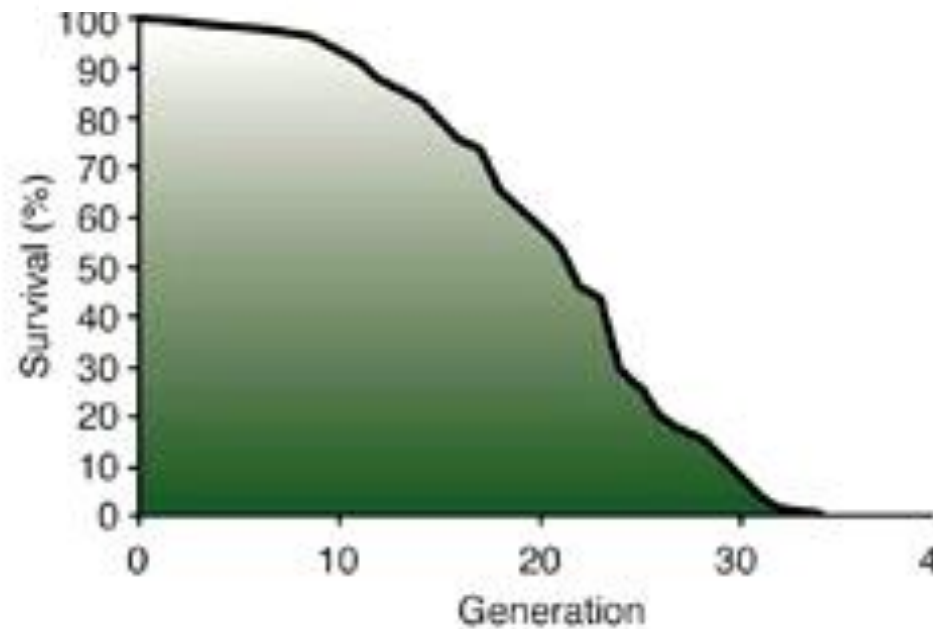
Human



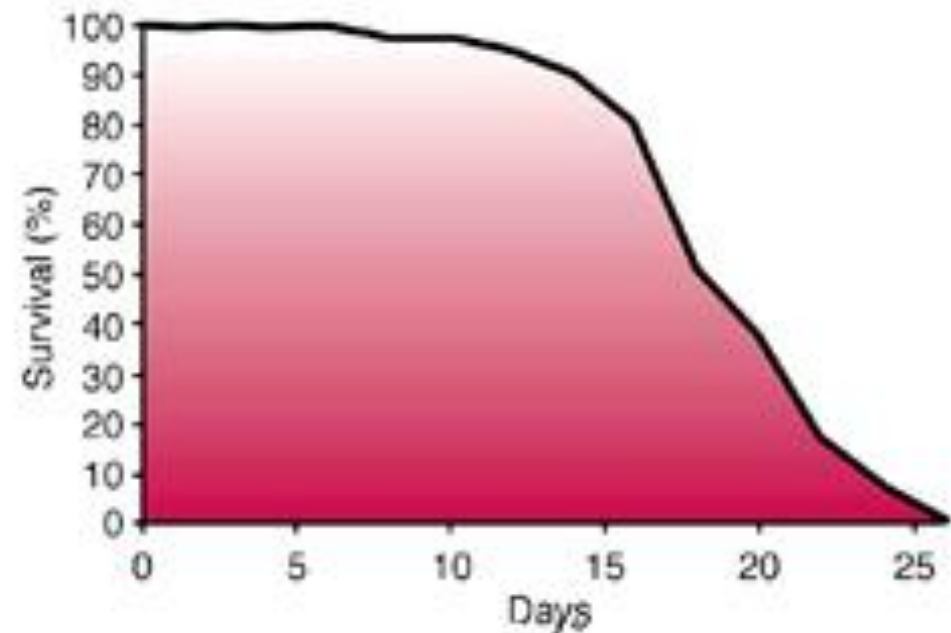
Mouse



Yeast

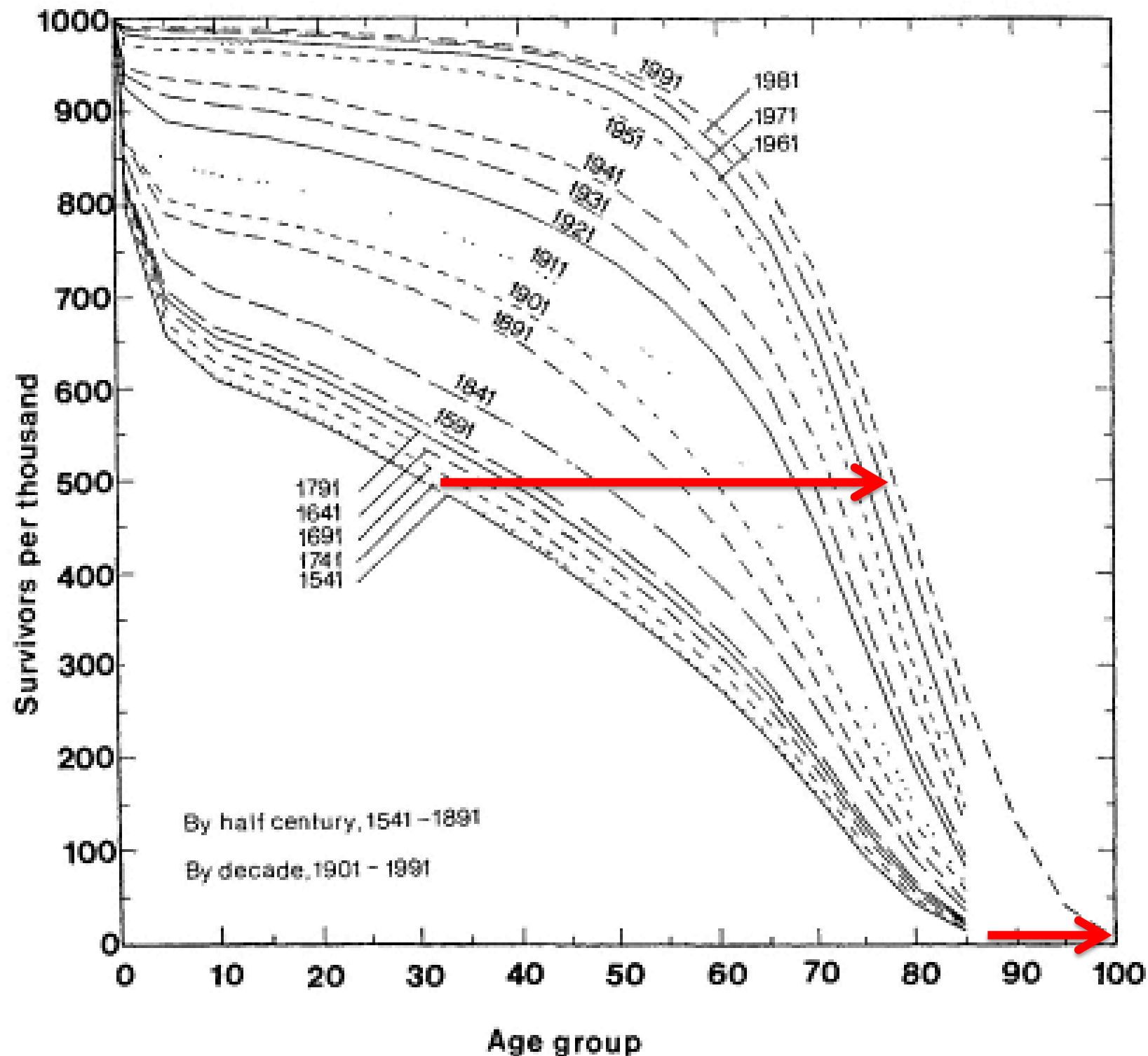


Worm

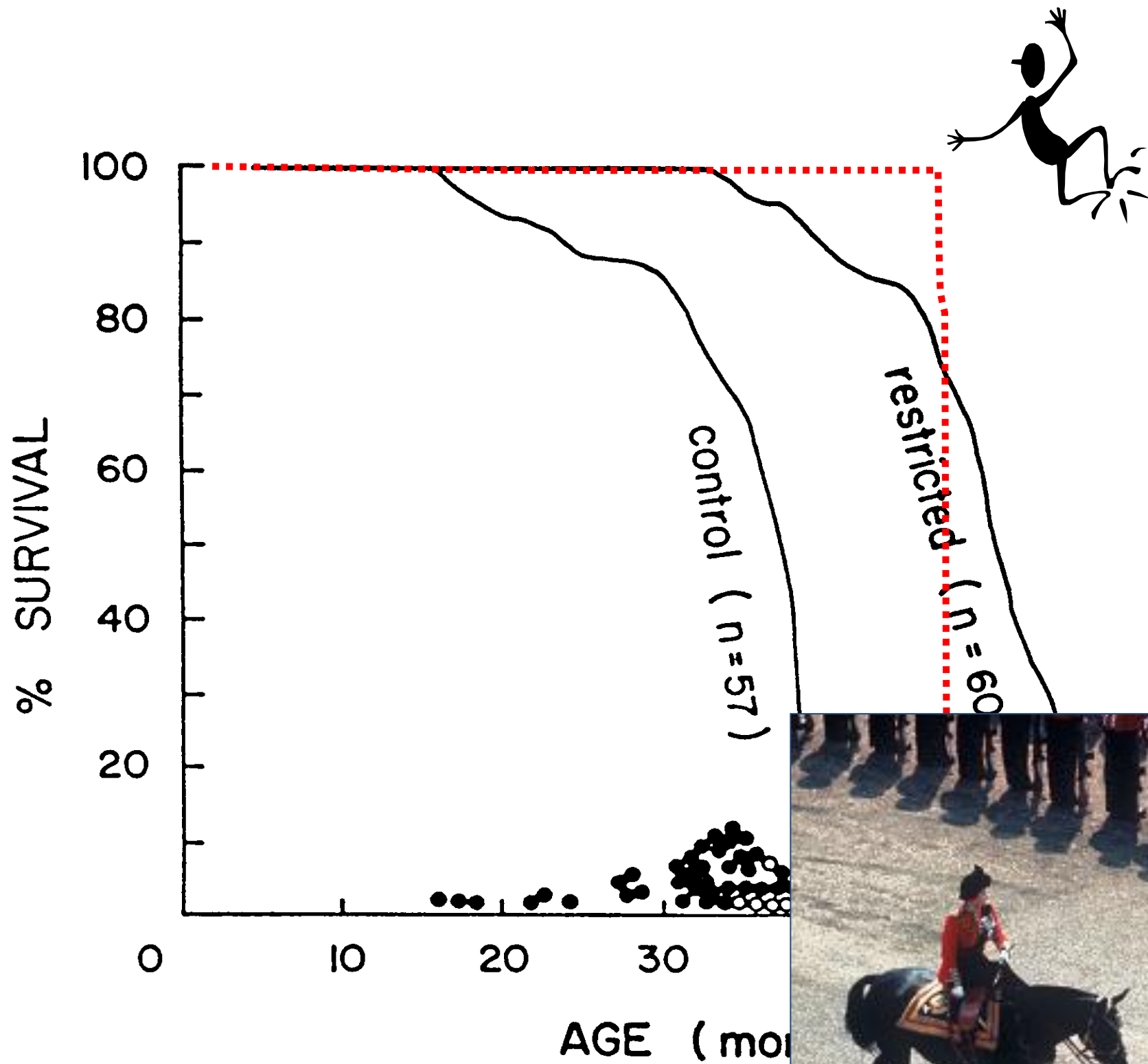


Squaring the survival curve in human populations

Trajectories of Human Lifespan



Caloric restriction



C3B10RF₁ mice

TIME

CAN WE STOP AGING?

There are

NO!!!!!!

NO LONGER HAVE CO...

Afghanistan: Racing to Save Lives
Toyota: The Fall of An Icon

T

The Science of Living Longer

SPECIAL 22-PAGE HEALTH SECTION



THREE GENERATIONS
Laila, 7; mother

Ma, 65

TIME

THE LONGEVITY ISSUE

The Alzheimer's Pill

A radical new drug could change old age
By Alice Park

- Plus**
How to be wealthy at 100 *p92*
- Three daily habits to change now *p80*
- Long-life secrets from a clam *p74*



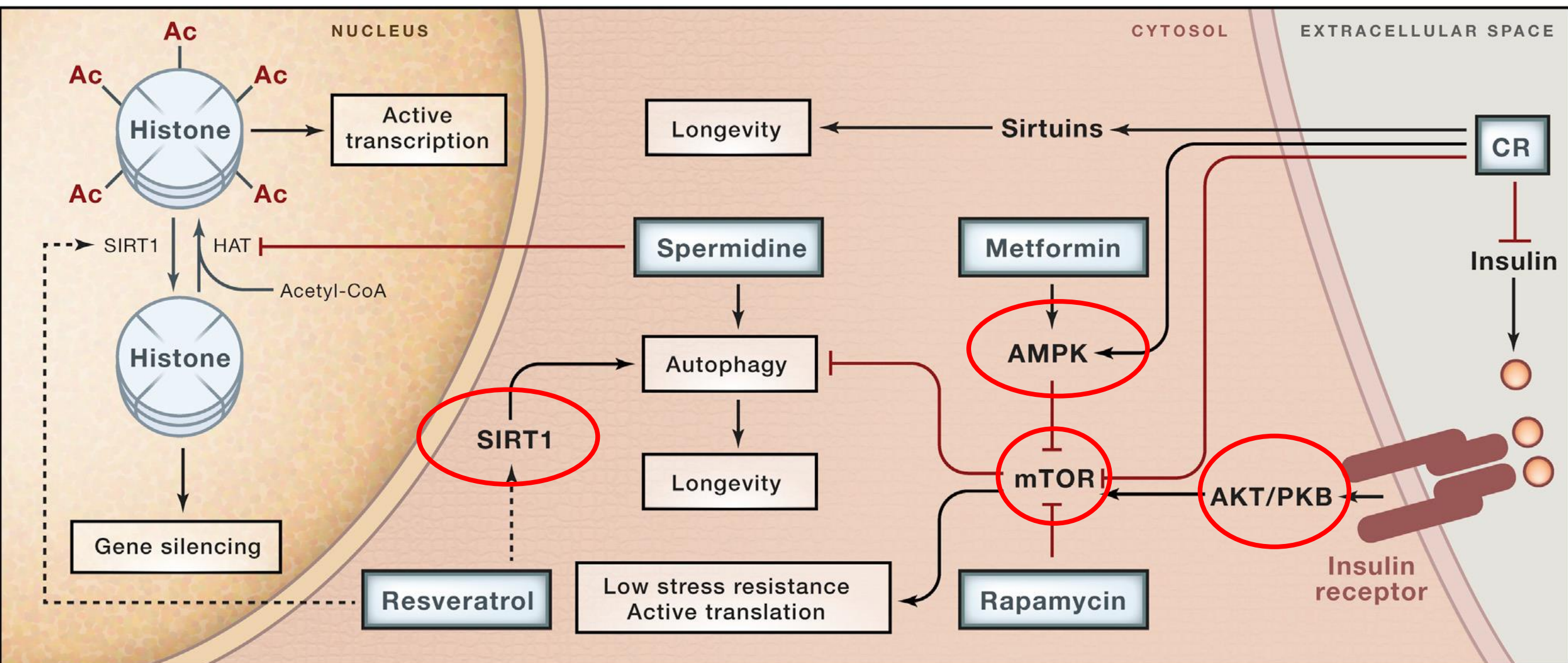
1992

University of Berkeley, 1992 and 1944

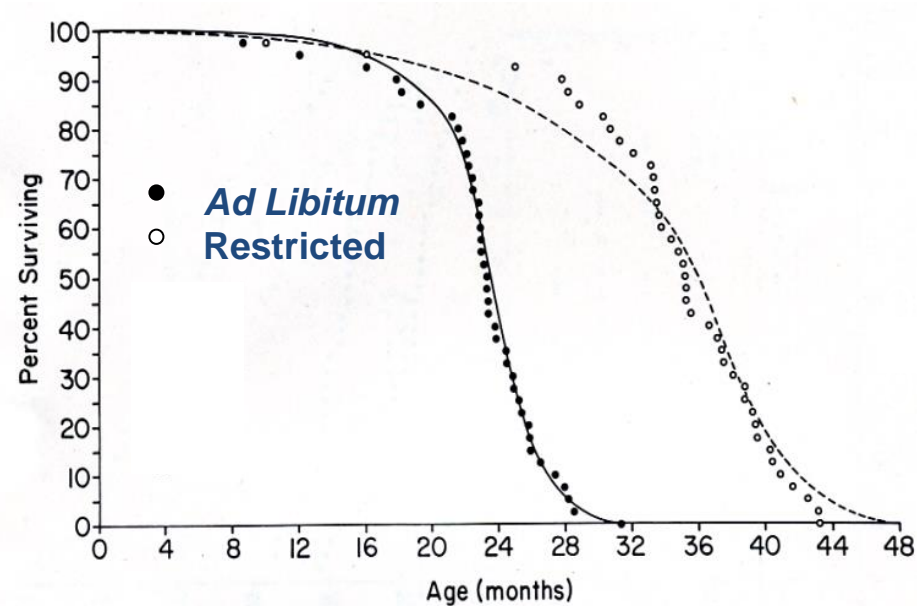
2010

2016

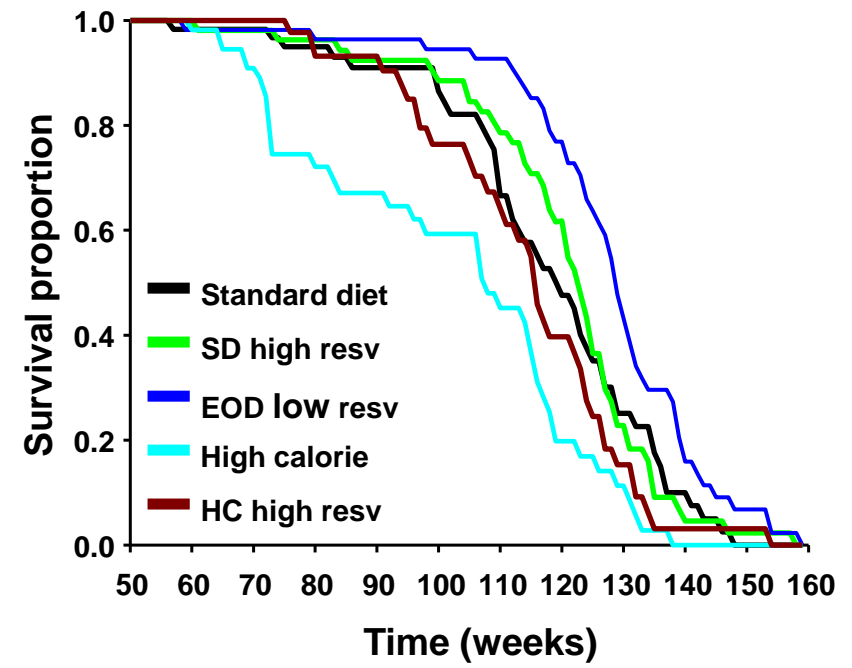
Molecular Targets for Caloric Restriction and Pharmacological Interventions For Healthy Aging



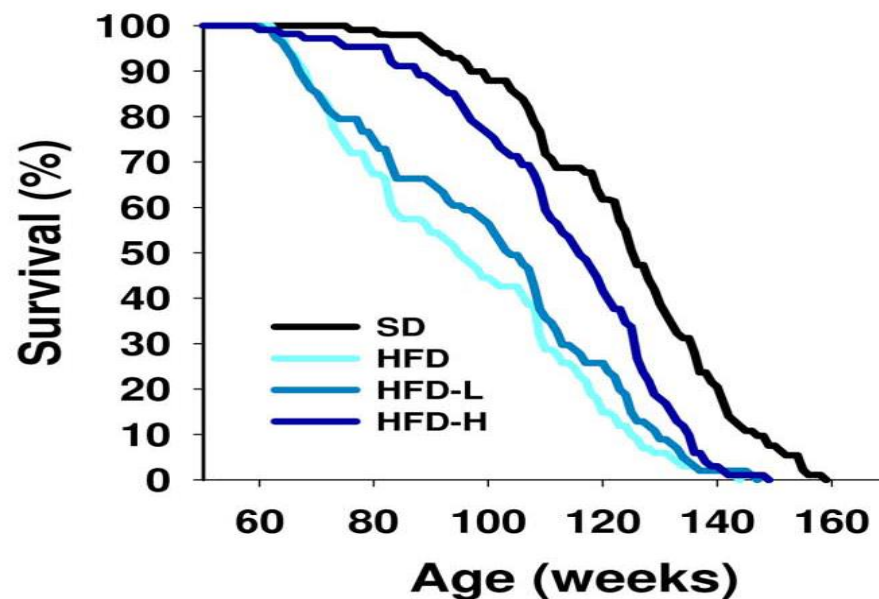
Non-genetic extension of lifespan



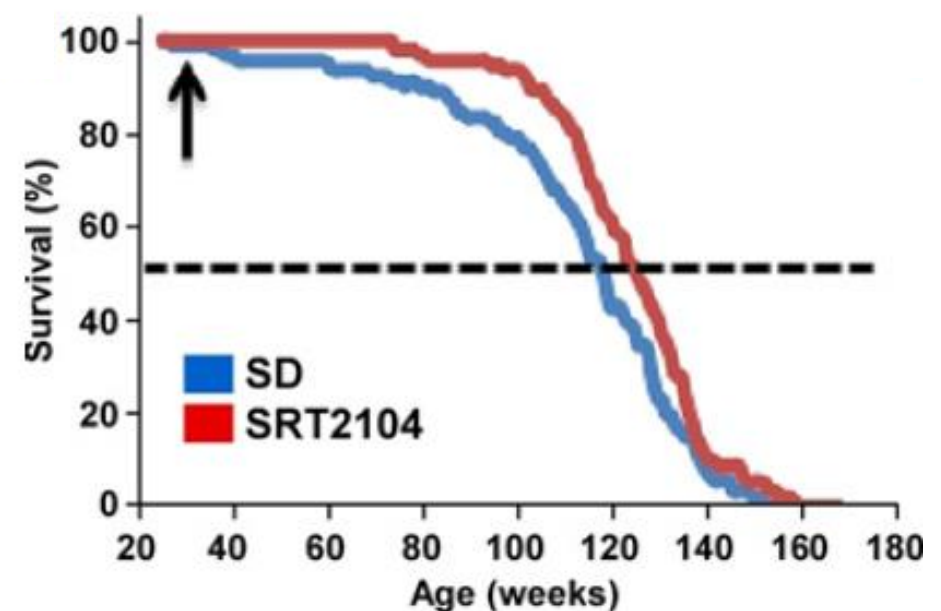
Calorie Restriction



Resveratrol

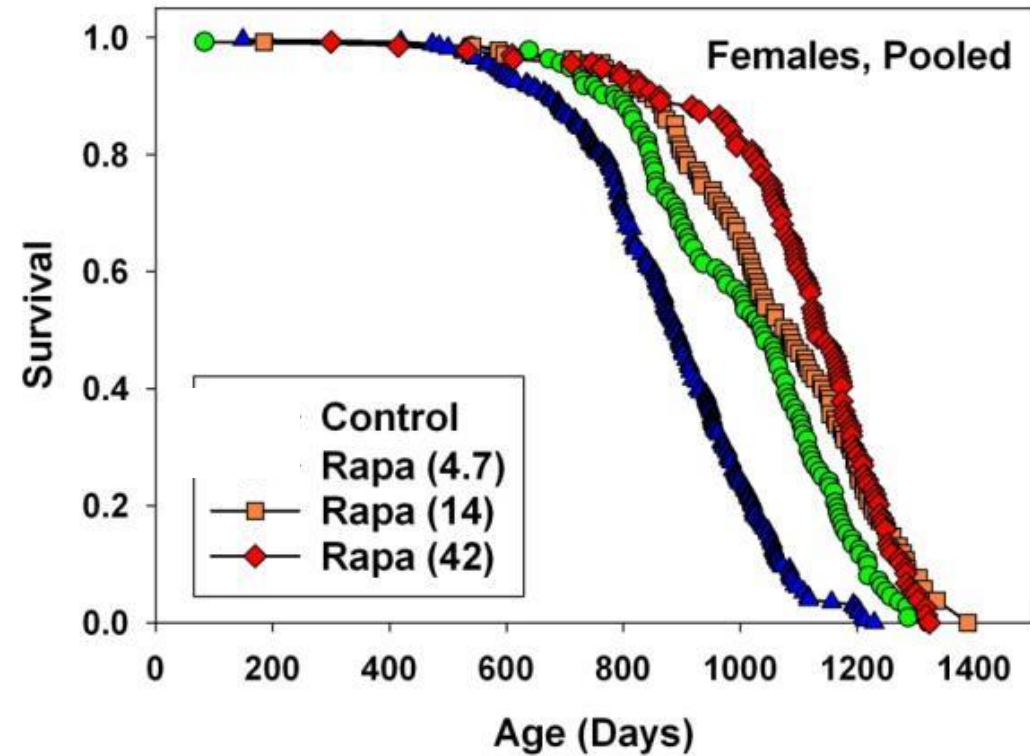
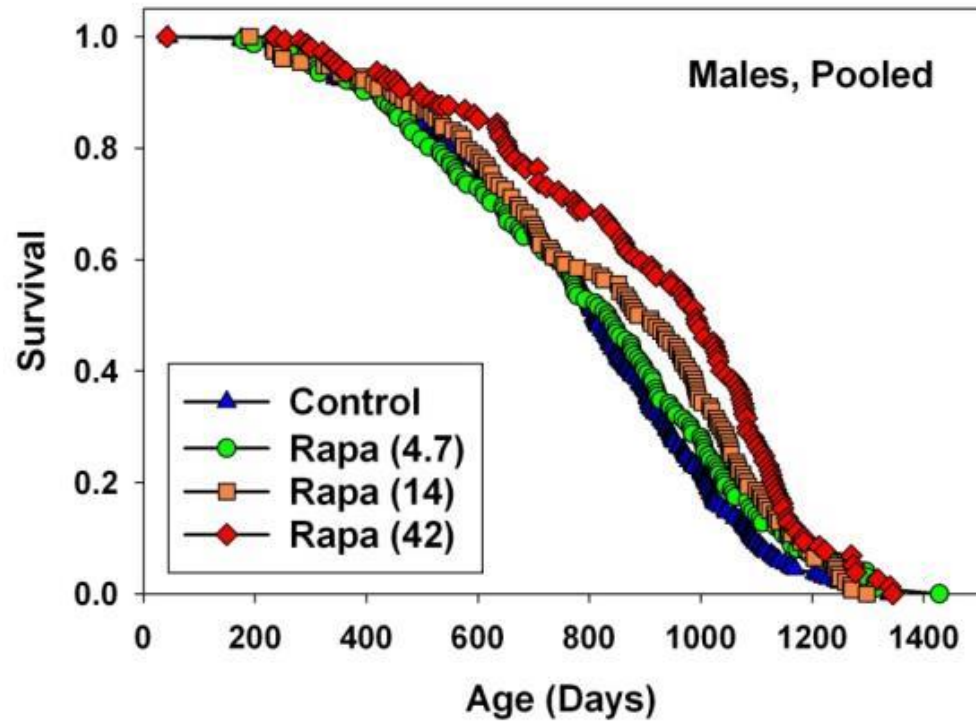


SRT1720



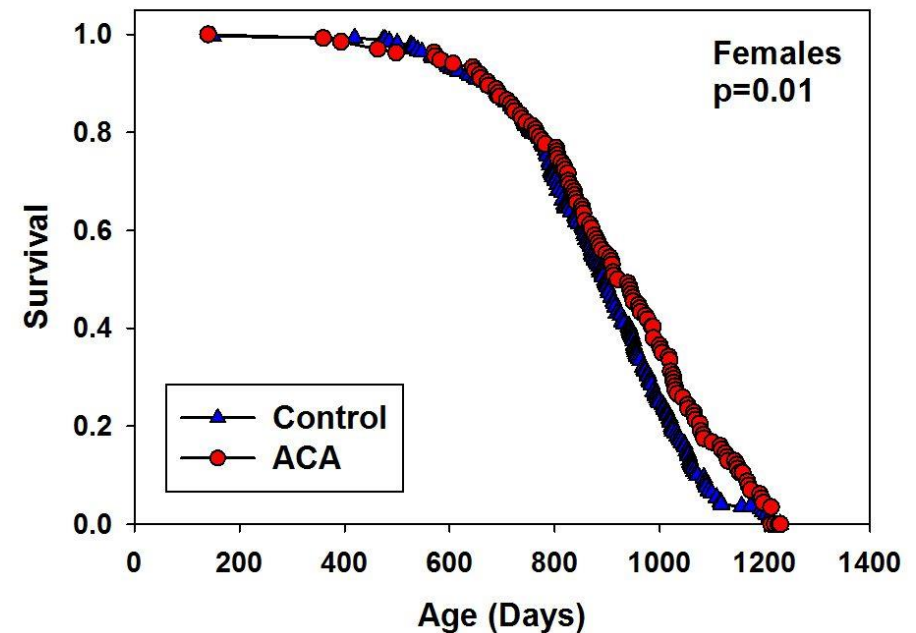
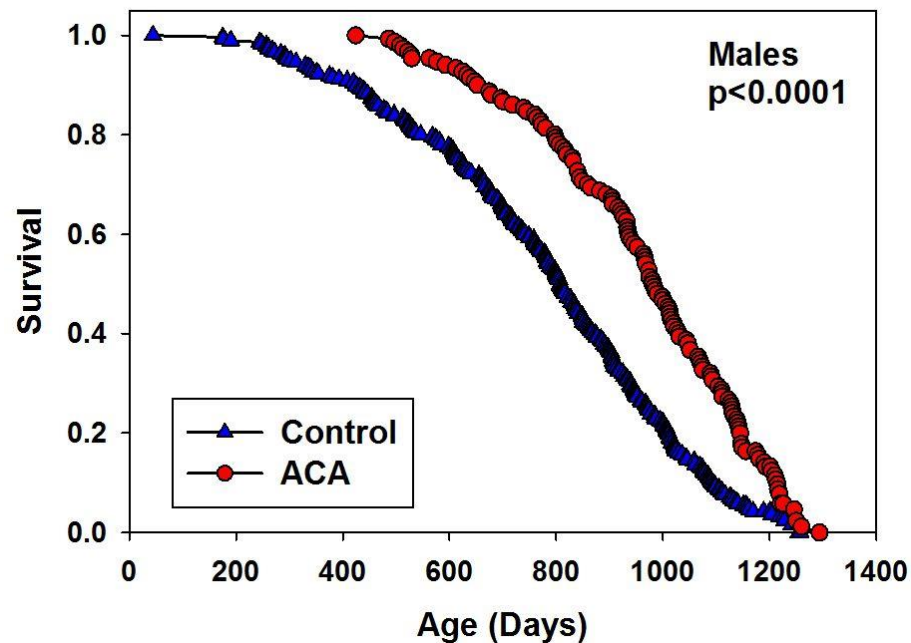
SRT2104

Rapamycin: Females better than Males



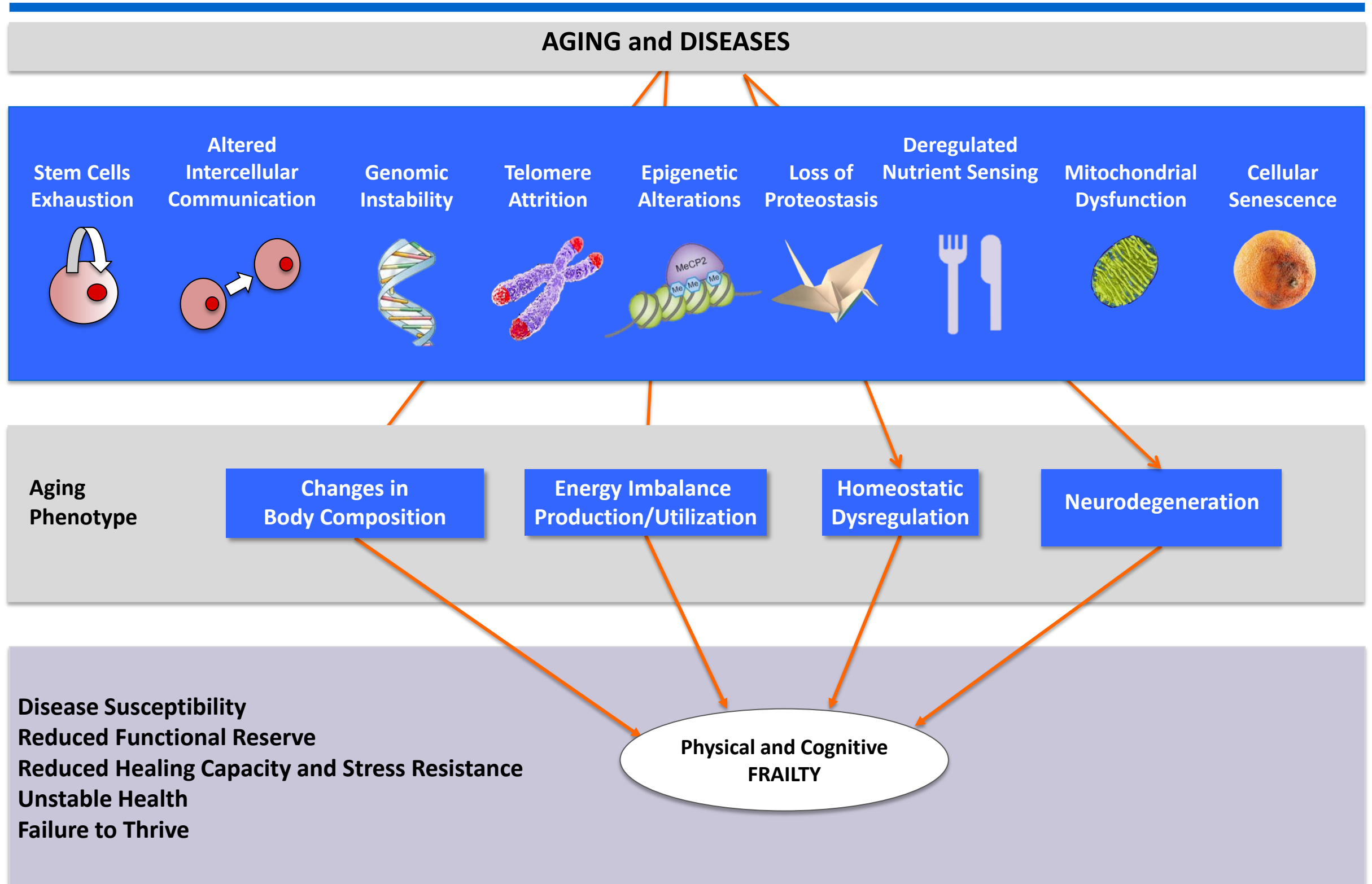
Miller et al., Aging Cell, In Press

Acarbose: Longevity Effect Greater in Males



Harrison et al. (Aging Cell, 2014)

What are the mechanisms behind aging and disease That affect aging phenotypes and longevity?



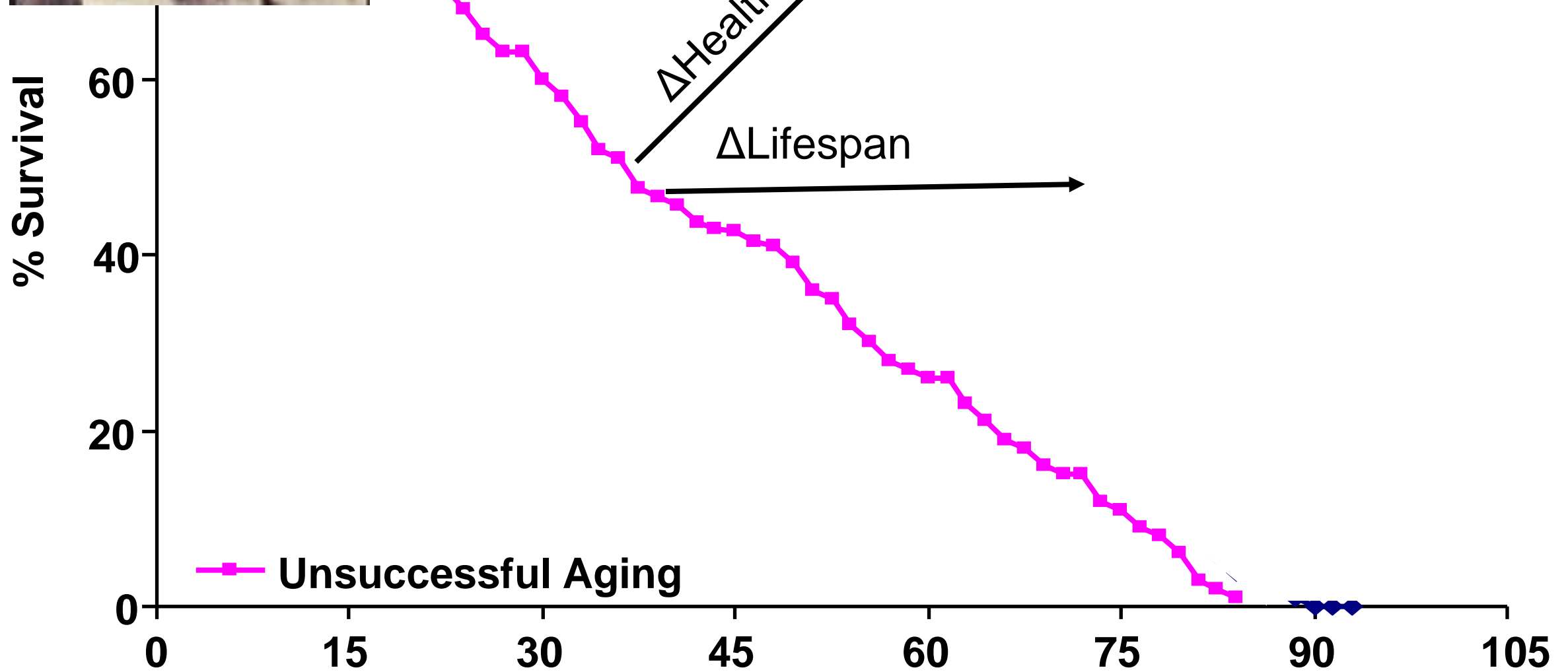
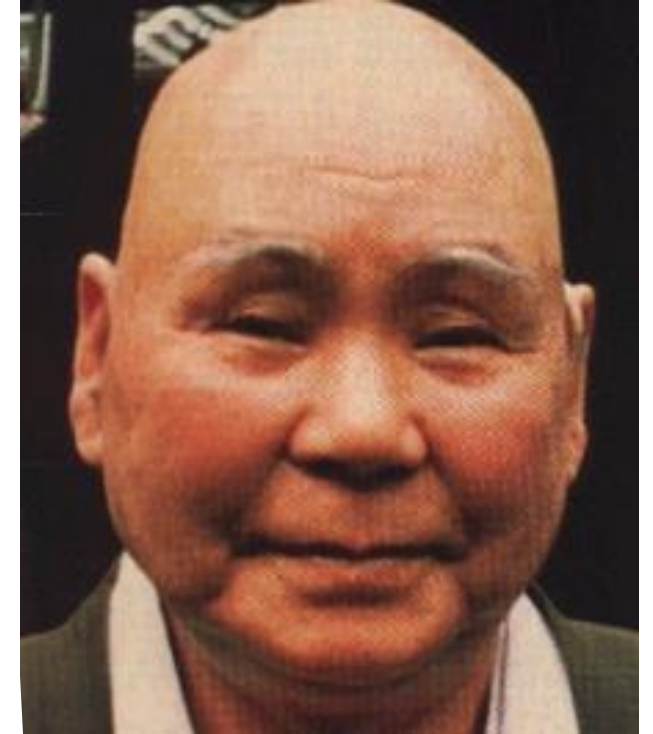
Unsuccessful Aging

Successful Aging



AGE 62

AGE 91



Heterogeneity of male B6 mice



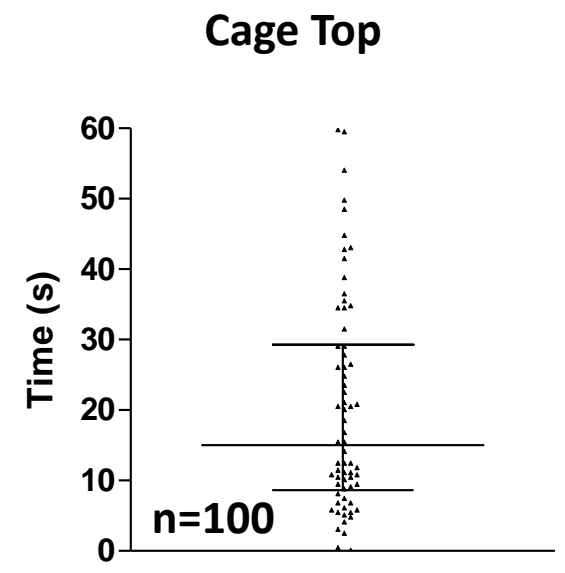
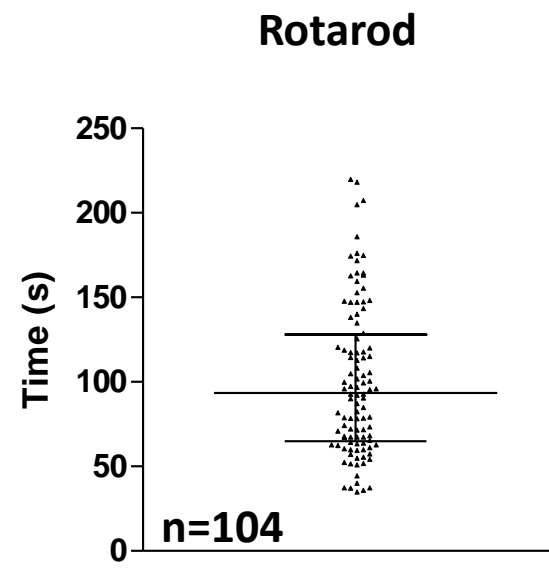
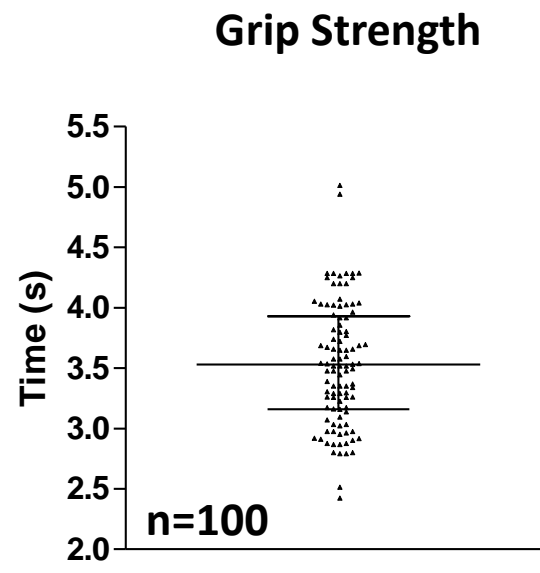
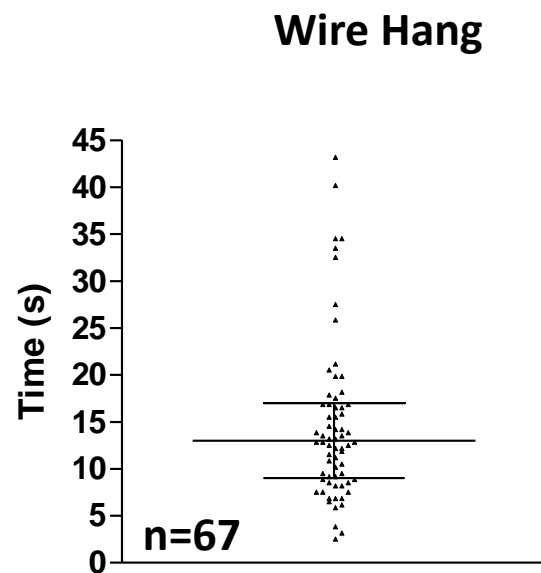
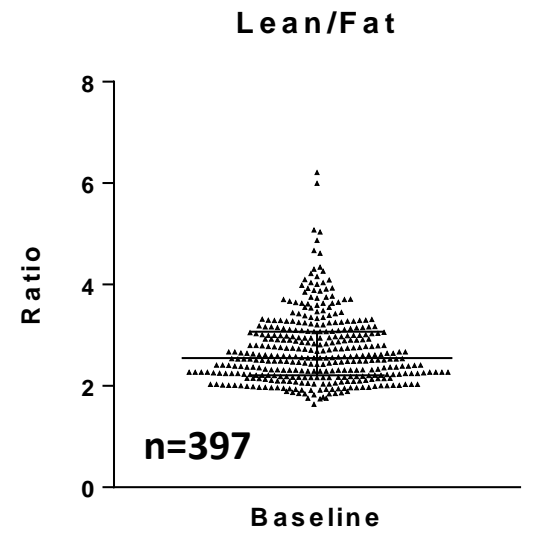
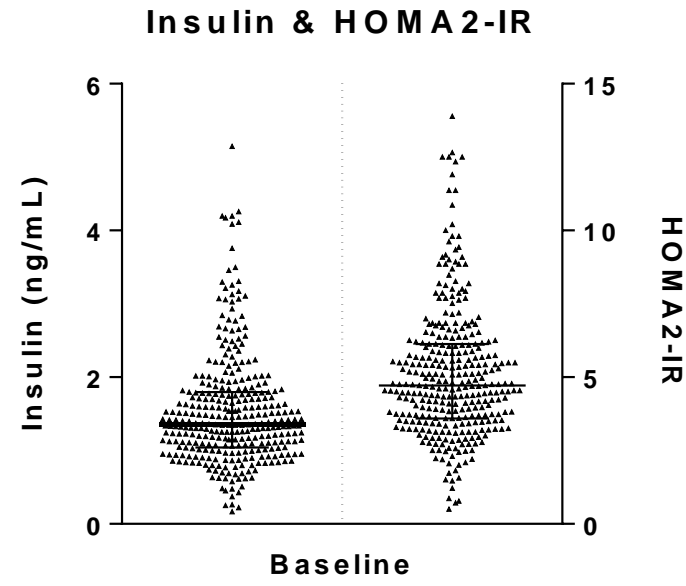
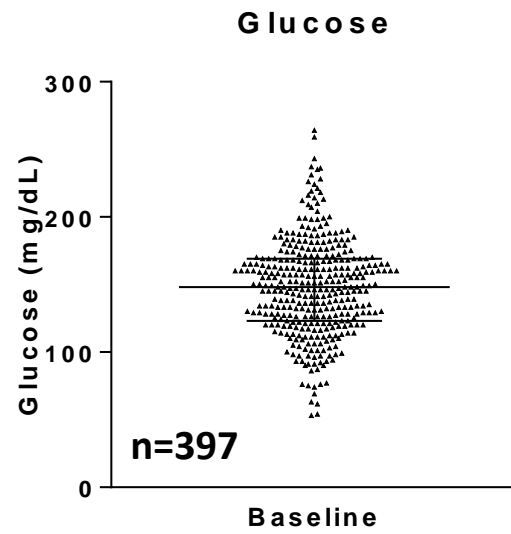
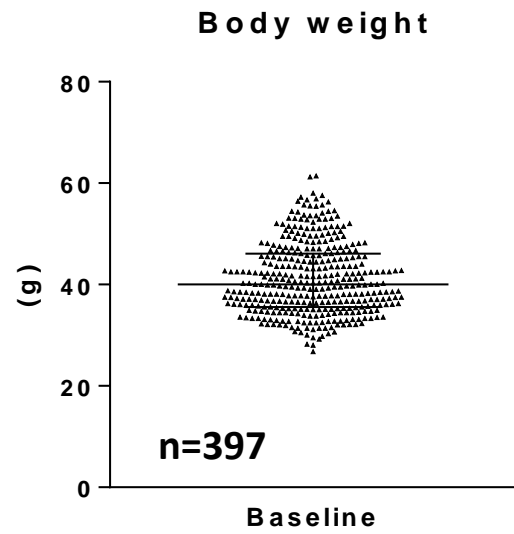
C57BL/6J

Male

n = 400

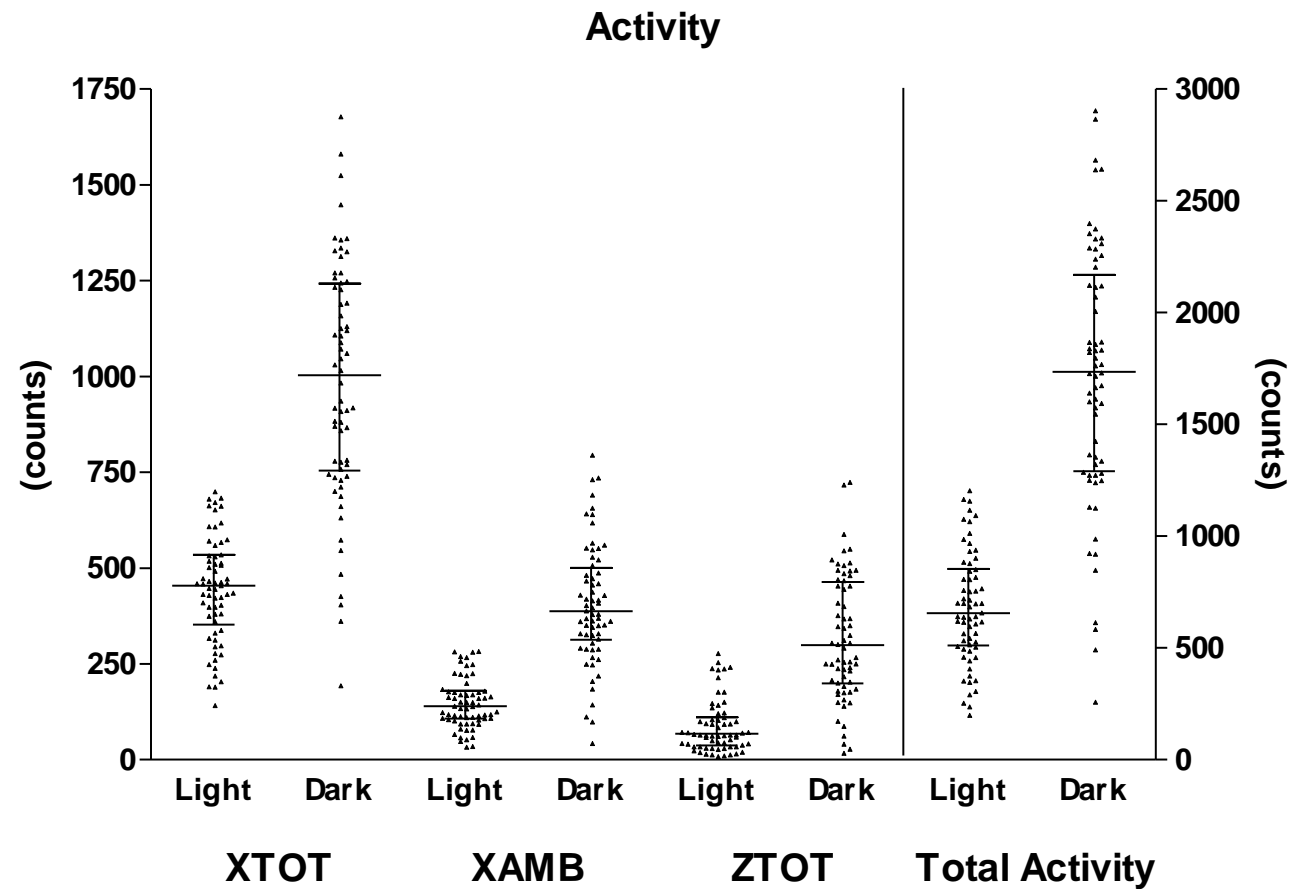
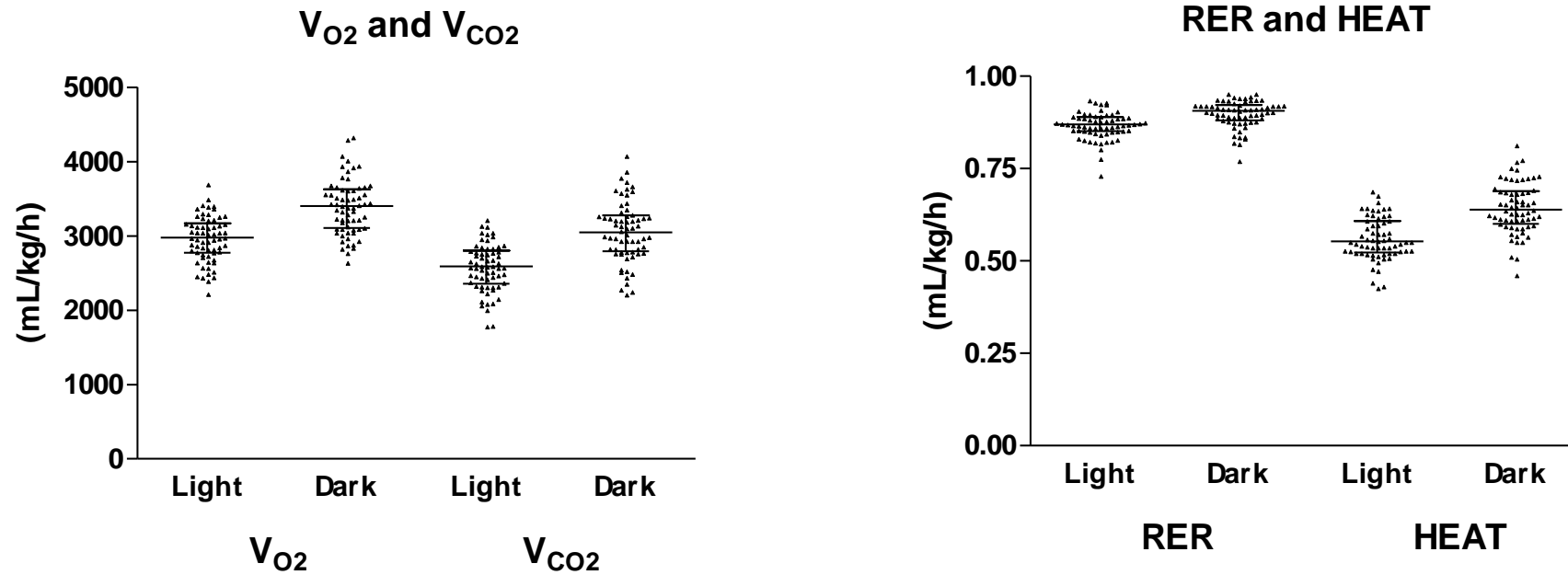
Old: 23-24 months old

Baseline Data



Metabolic cages

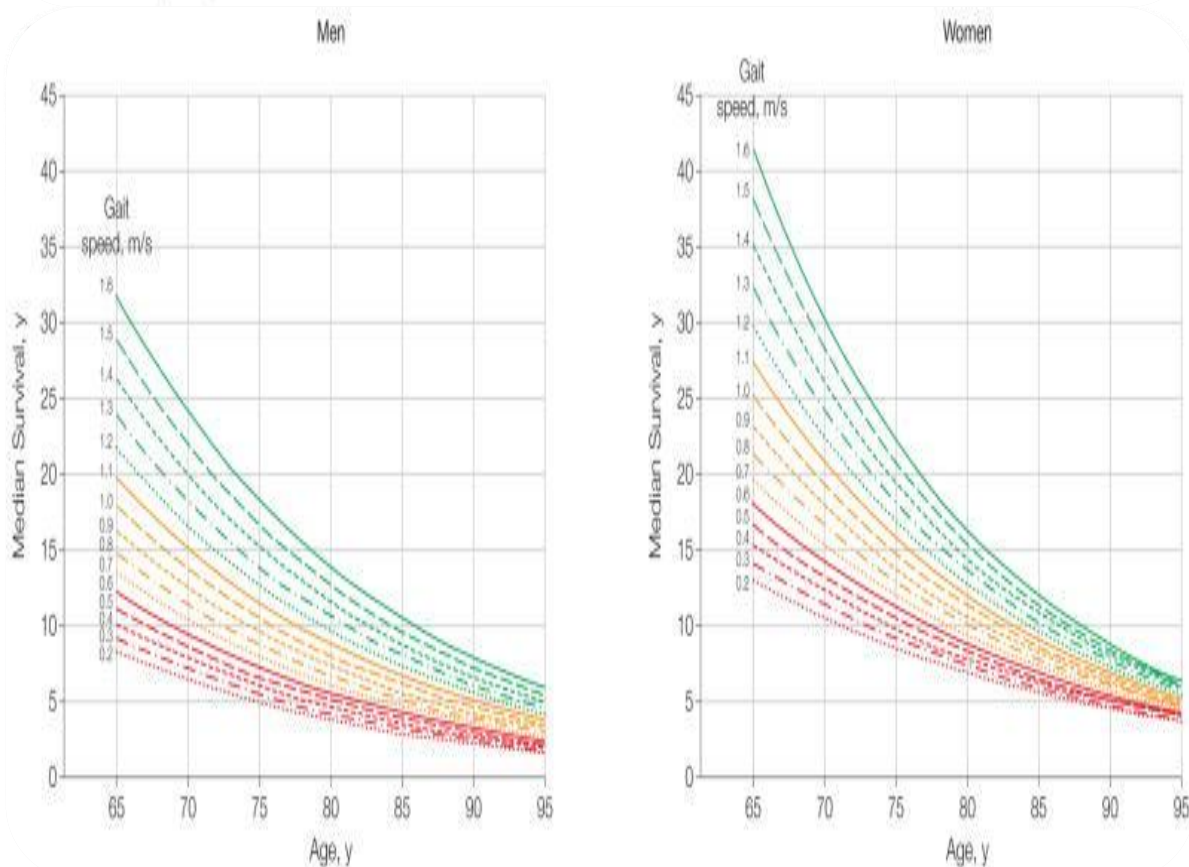
n = 64



Original Contribution | January 5, 2011

Gait Speed and Survival in Older Adults

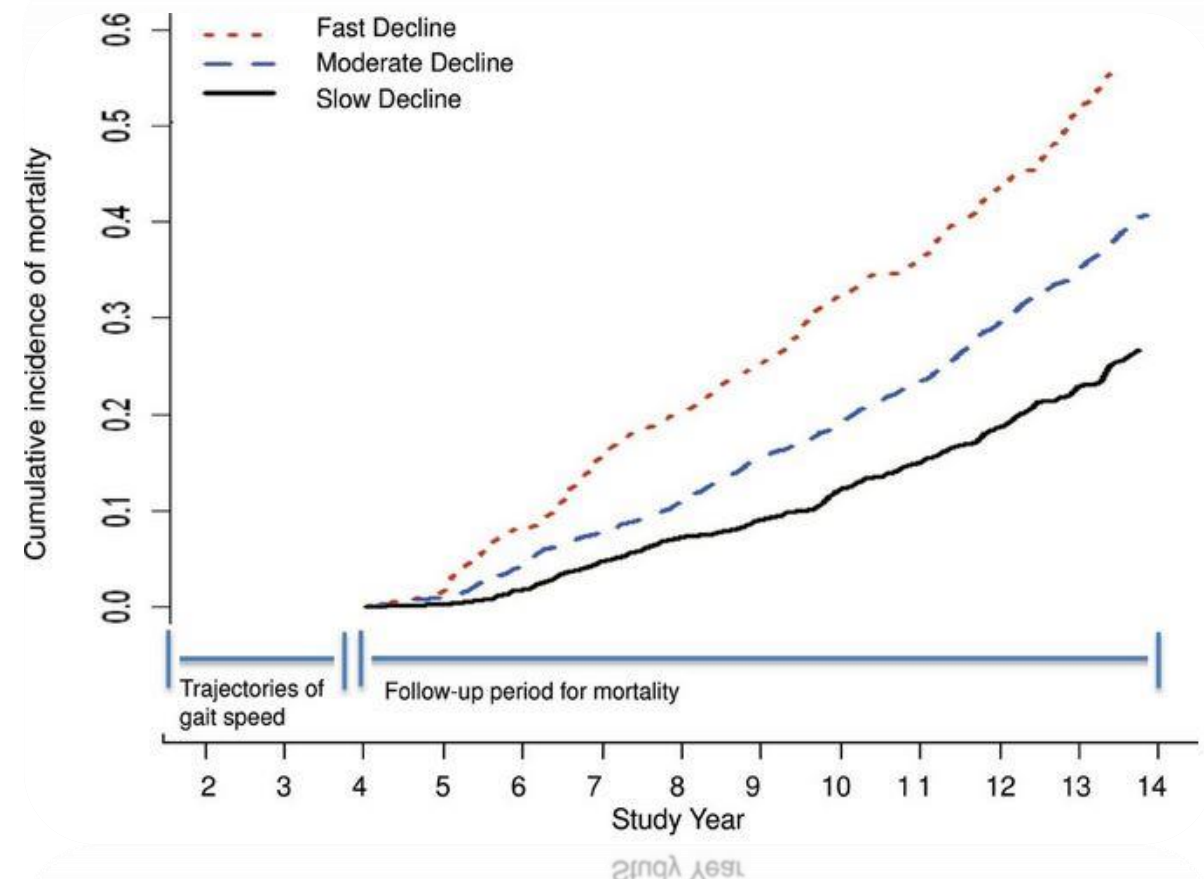
Stephanie Studenski, MD, MPH; Subashan Perera, PhD; Kushang Patel, PhD; Caterina Rosano, MD, PhD; Kimberly Faulkner, PhD; Marco Inzitari, MD, PhD; Jennifer Brach, PhD; Julie Chandler, PhD; Peggy Cawthon, PhD; Elizabeth Barrett Connor, MD; Michael Nevitt, PhD; Marjolein Visser, PhD; Stephen Kritchevsky, PhD; Stefania Badinelli, MD; Tamara Harris, MD; Anne B. Newman, MD; Jane Cauley, PhD; Luigi Ferrucci, MD, PhD; Jack Guralnik, MD, PhD



Trajectories of Gait Speed Predict Mortality in Well-Functioning Older Adults: The Health, Aging and Body Composition Study

Daniel K. White, Tuhina Neogi, [...], and Yuqing Zhang

[Additional article information](#)



Cross-sectional design



C57BL/6J

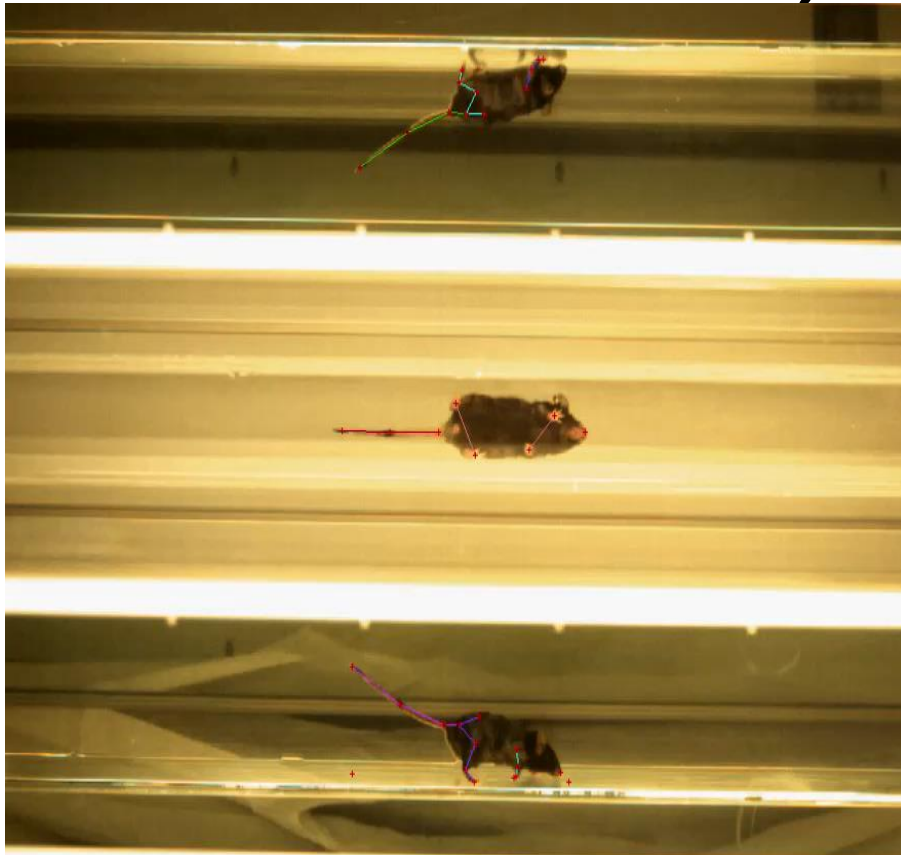
Male

n = 100

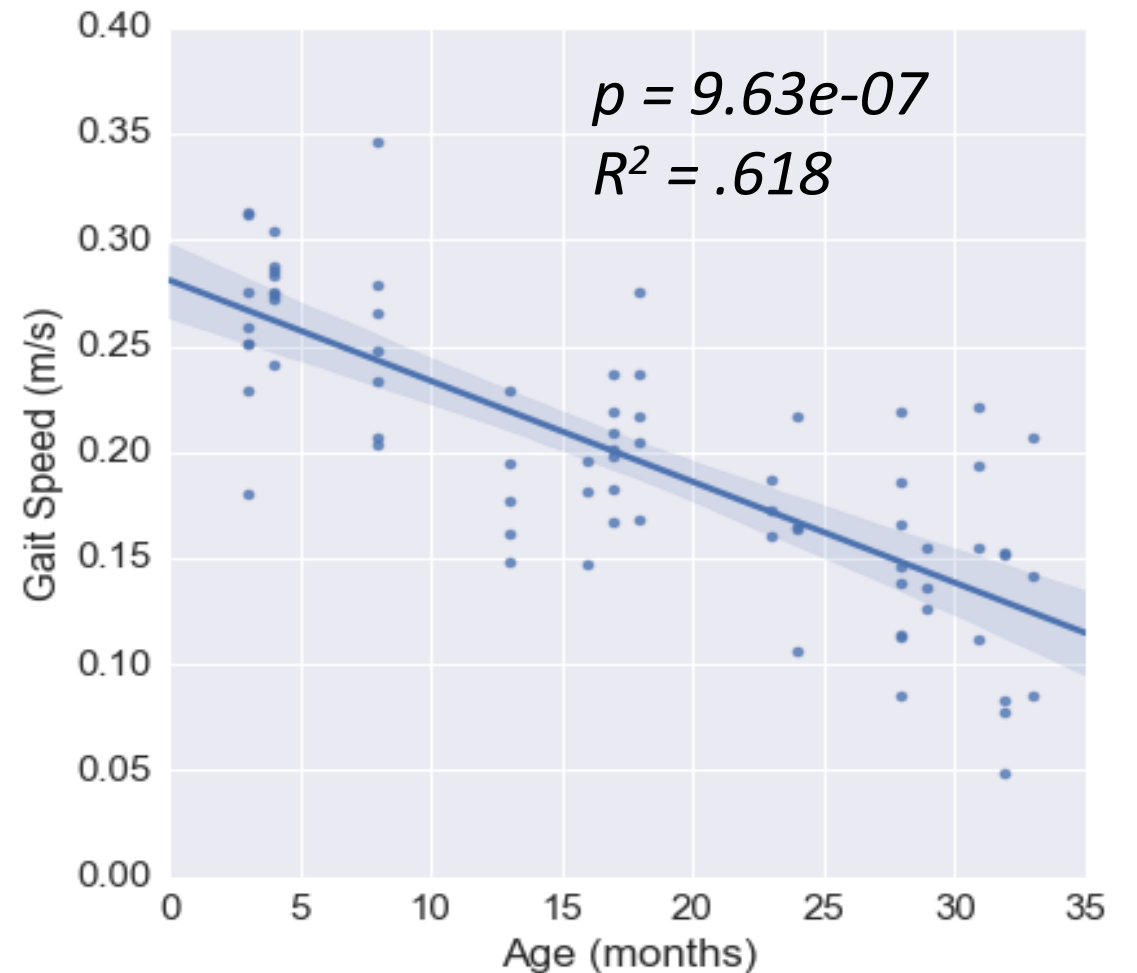
Young, Middle Aged and Old

Gait Analysis

MotoRater (TSE Systems) for *fine motor kinematic analysis*



Gait speed



Gait speed, Cadence, Tail Height, Stride

Frailty

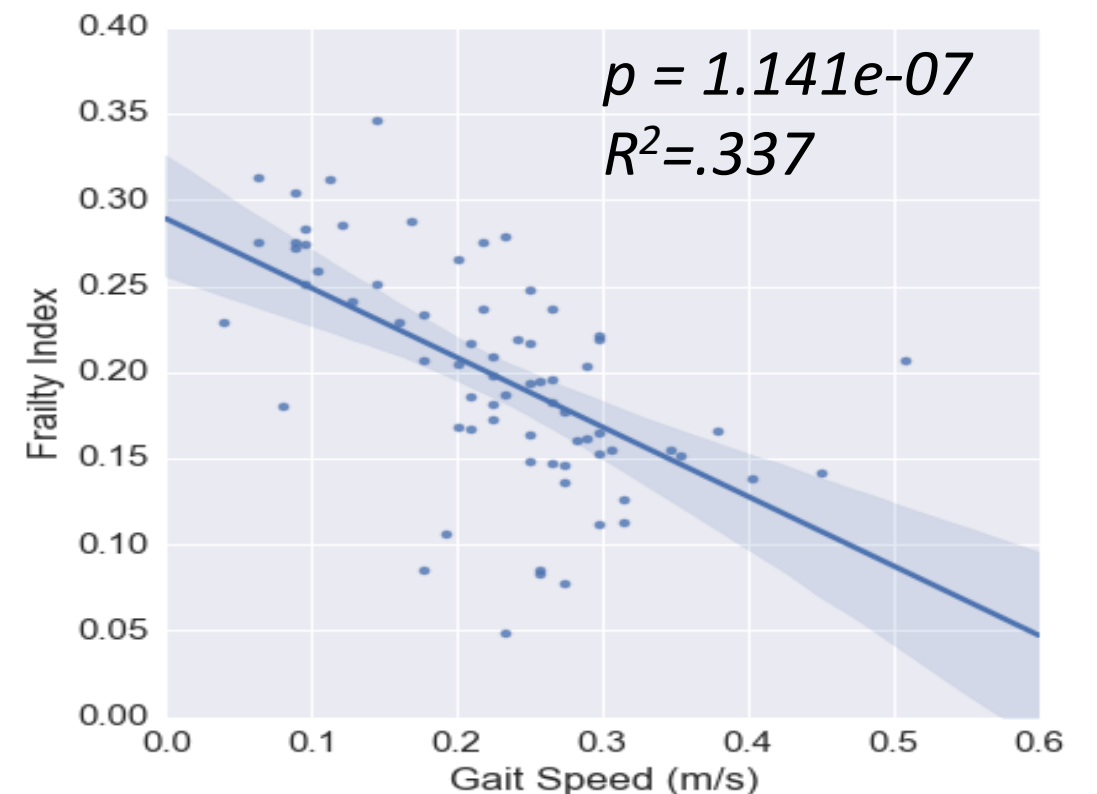
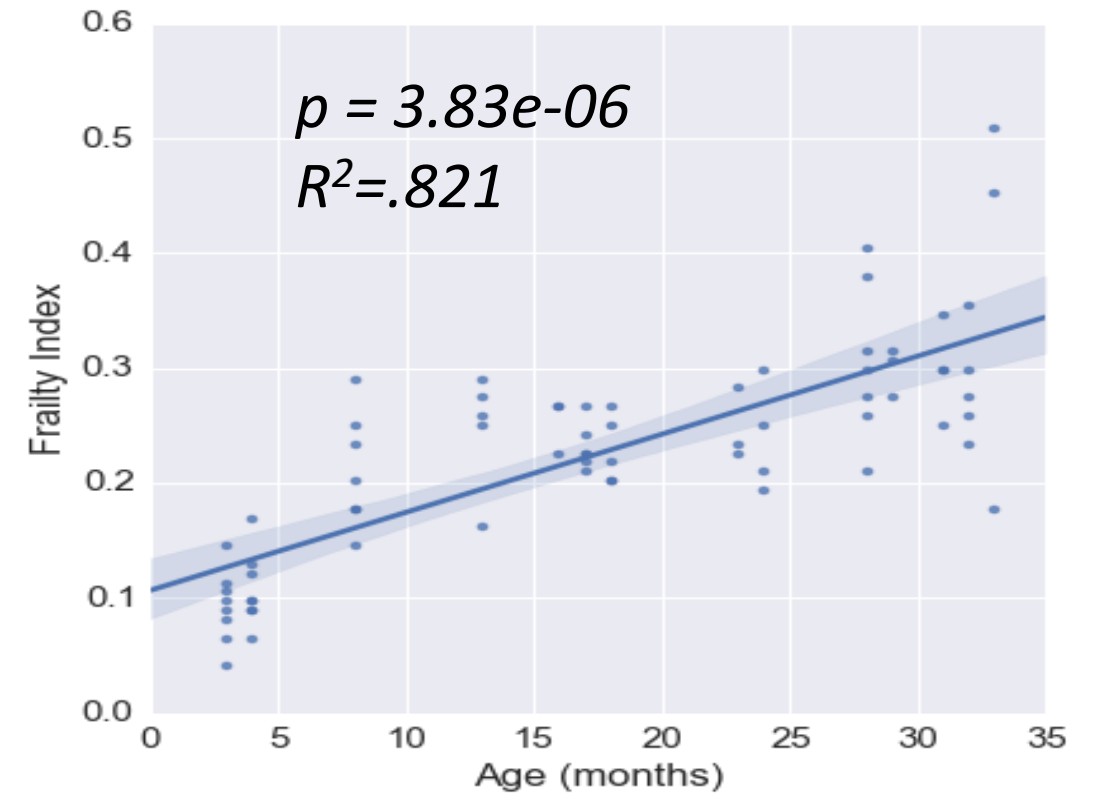
Date: _____

Mouse #: _____ Date of Birth: _____ Sex: F M
 Body weight (g): _____ Body surface temperature (°C): _____

Rating: 0 = absent 0.5 = mild 1 = severe

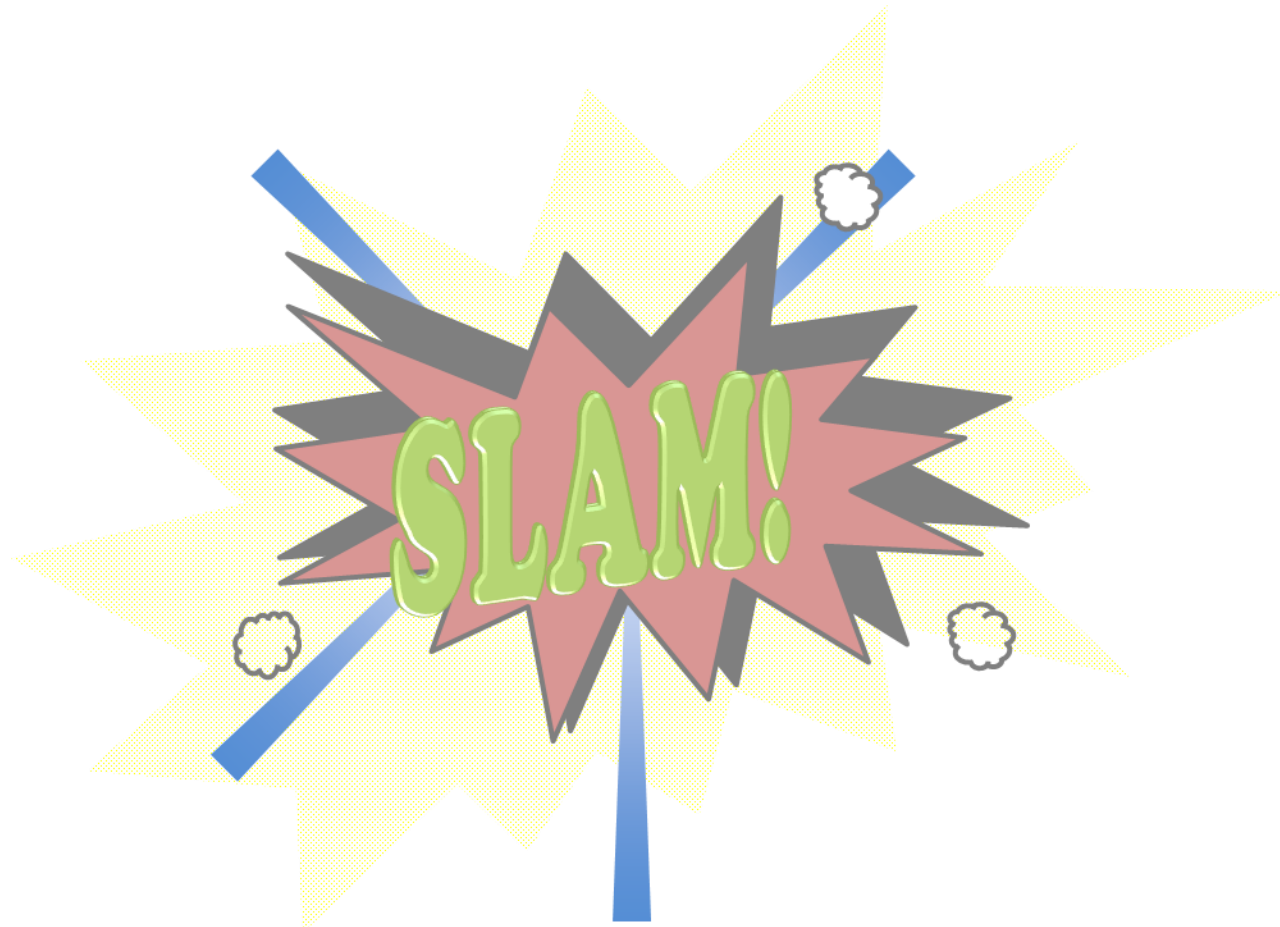
➤ Integument:			NOTES: _____ _____ _____ _____	
❖ Alopecia	0	0.5		1
❖ Loss of fur colour	0	0.5		1
❖ Dermatitis	0	0.5		1
❖ Loss of whiskers	0	0.5		1
❖ Coat condition	0	0.5	1	
➤ Physical/Musculoskeletal:			_____ _____ _____ _____ _____ _____ _____ _____ _____ _____	
❖ Tumours	0	0.5		1
❖ Distended abdomen	0	0.5		1
❖ Kyphosis	0	0.5		1
❖ Tail stiffening	0	0.5		1
❖ Gait disorders	0	0.5		1
❖ Tremor	0	0.5		1
❖ Forelimb grip strength	0	0.5		1
❖ Body condition score	0	0.5		1
➤ Vestibulocochlear/Auditory:				_____ _____
❖ Vestibular disturbance	0	0.5	1	
❖ Hearing loss	0	0.5	1	
➤ Ocular/Nasal:			_____ _____ _____ _____ _____ _____ _____ _____	
❖ Cataracts	0	0.5		1
❖ Corneal opacity	0	0.5		1
❖ Eye discharge/swelling	0	0.5		1
❖ Microphthalmia	0	0.5		1
❖ Vision loss	0	0.5		1
❖ Menace reflex	0	0.5		1
❖ Nasal discharge	0	0.5		1
➤ Digestive/Urogenital:			_____ _____ _____ _____	
❖ Malocclusions	0	0.5		1
❖ Rectal prolapse	0	0.5		1
❖ Vaginal/uterine/penile prolapse	0	0.5		1
❖ Diarrhoea	0	0.5	1	
➤ Respiratory system:			_____ _____	
❖ Breathing rate/depth	0	0.5	1	
➤ Discomfort:			_____ _____ _____	
❖ Mouse Grimace Scale	0	0.5		1
❖ Piloerection	0	0.5		1
❖ Temperature score: _____				
❖ Body weight score: _____				

Total Score/ Max Score: _____



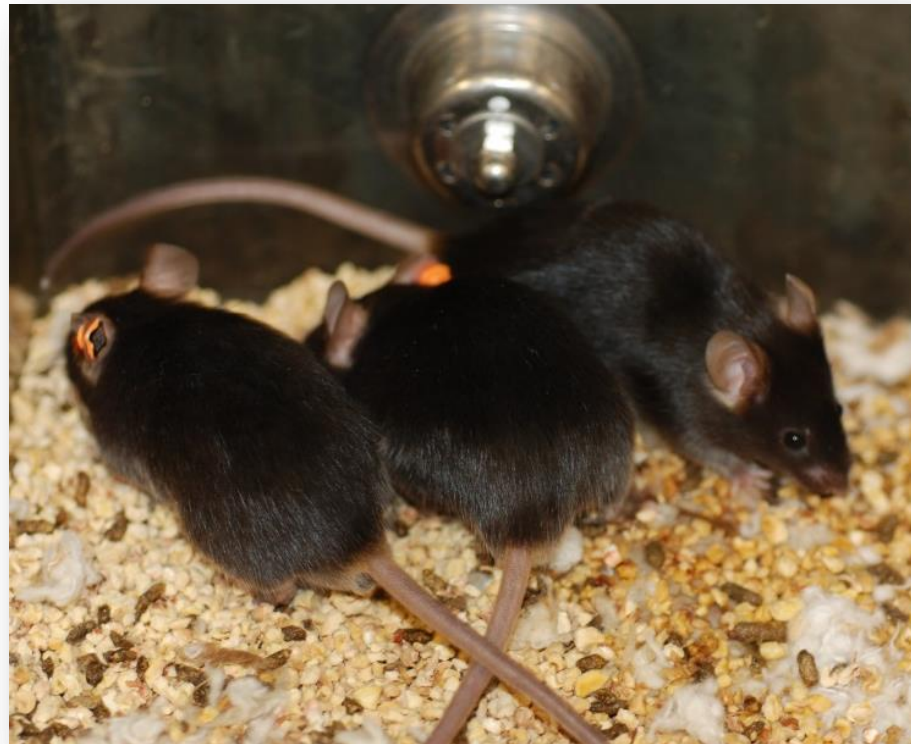
STUDY OF LONGITUDINAL AGING IN MICE

Multi PI study at the NIA Baltimore



C57BL/6J

Genetically homogeneous



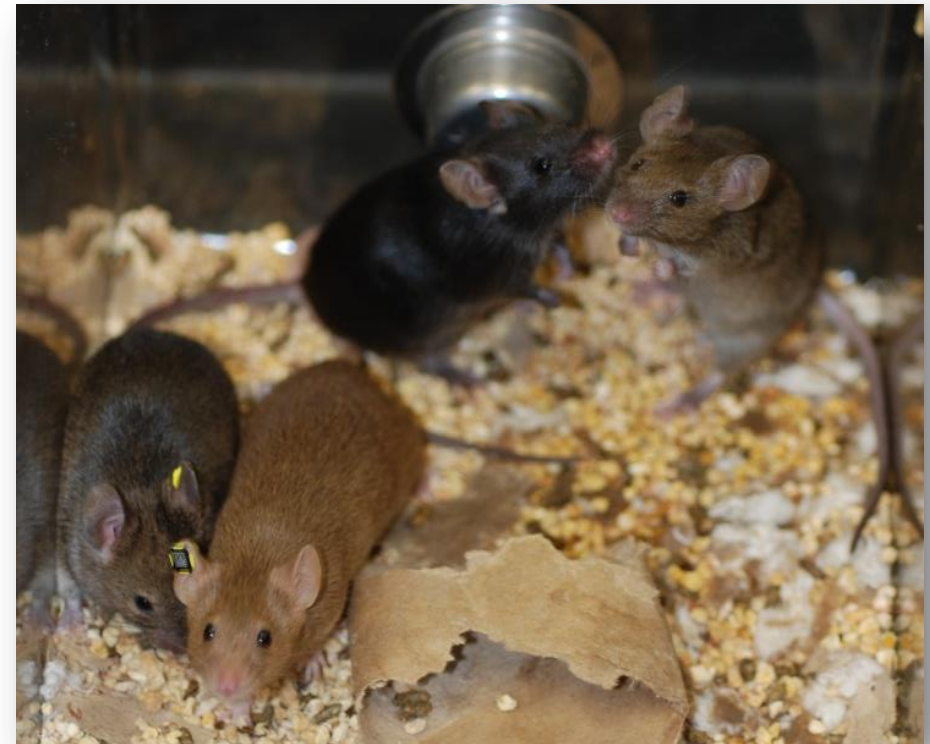
n = 400



n = 400

UM-HET3 (CByB6F1 x C3D2F1)

Genetically heterogeneous



n = 400

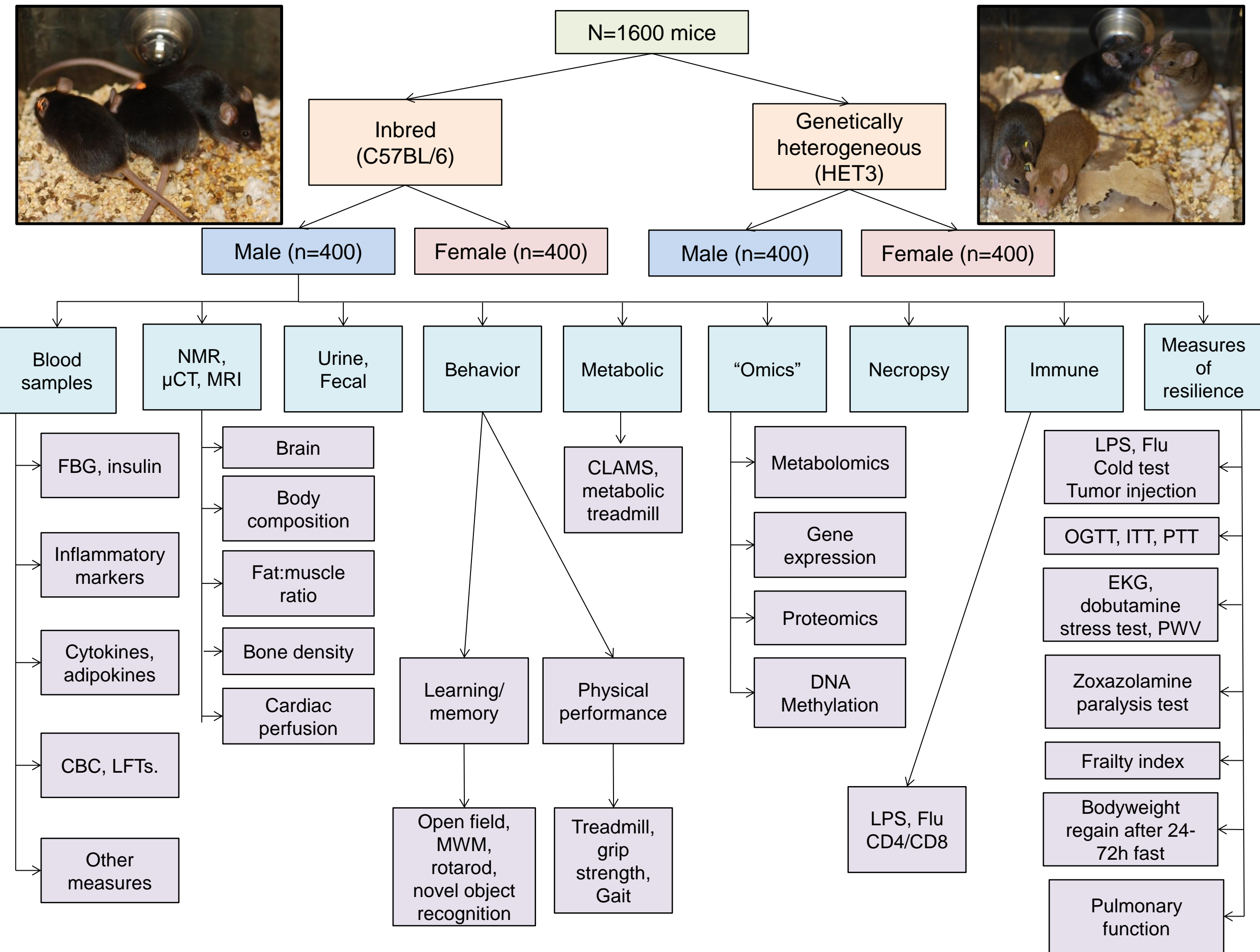


n = 400

Diet: irradiated NIH-31

Mice

- 2 strains:
 - C57BL/6 males and females
 - 4-waycross (HET3) males and females
- $n = 1600$ ($n = 400/\text{strain}/\text{sex}$)
- Starting age: 4-mo old (arrival at our vivarium when they are 3-4 weeks old)
- Diet: NIH31
- Mice will be received in 8 cohorts from JAX every 3 months ($n=50/\text{sex}/\text{strain}$)

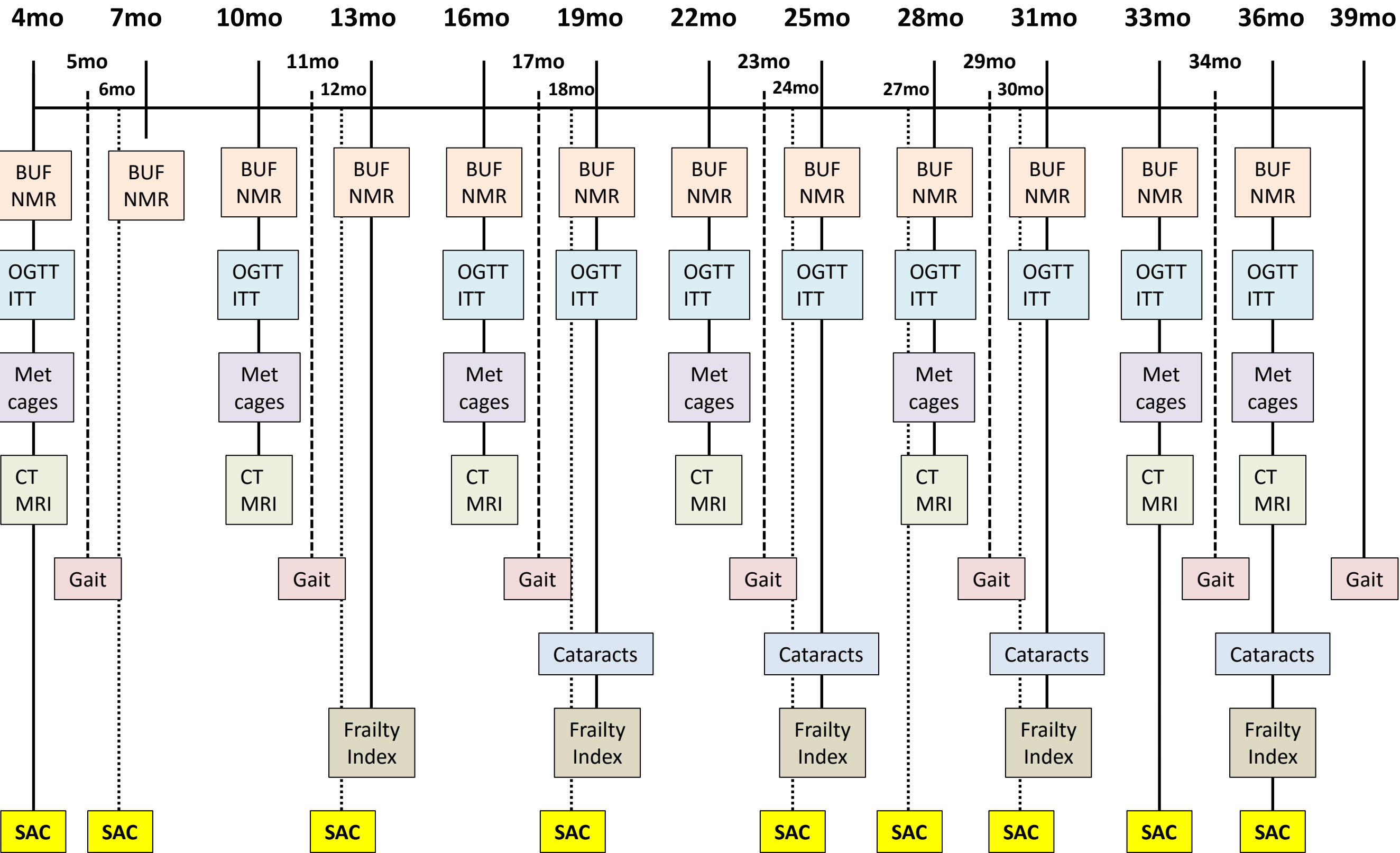


Lifespan time points

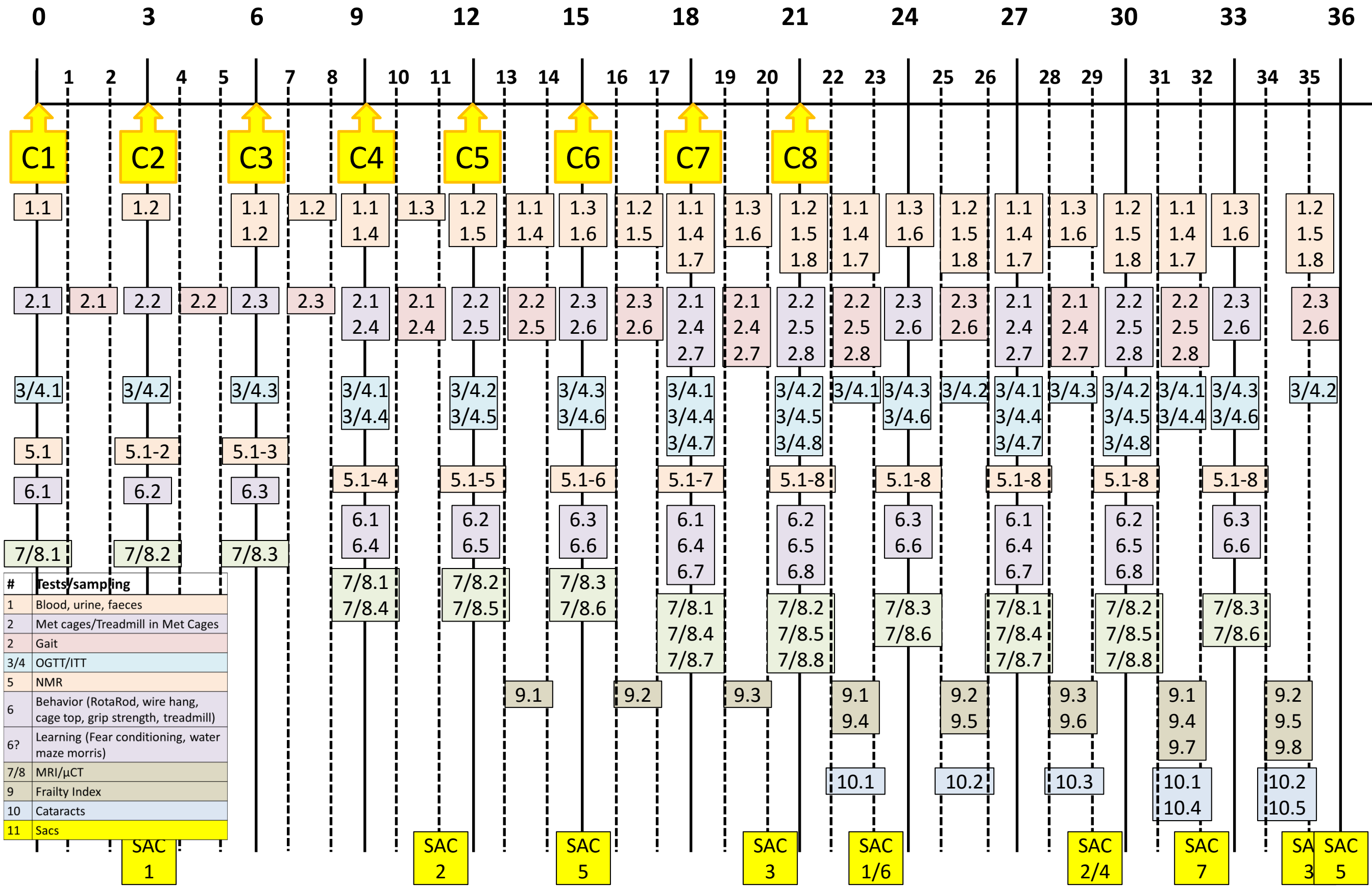
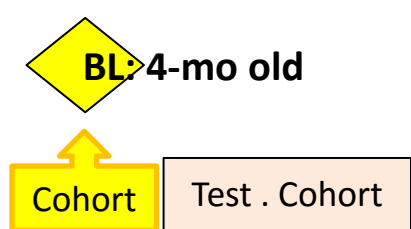
BUF: blood, urine, faeces

Gait: MotoRater

BL

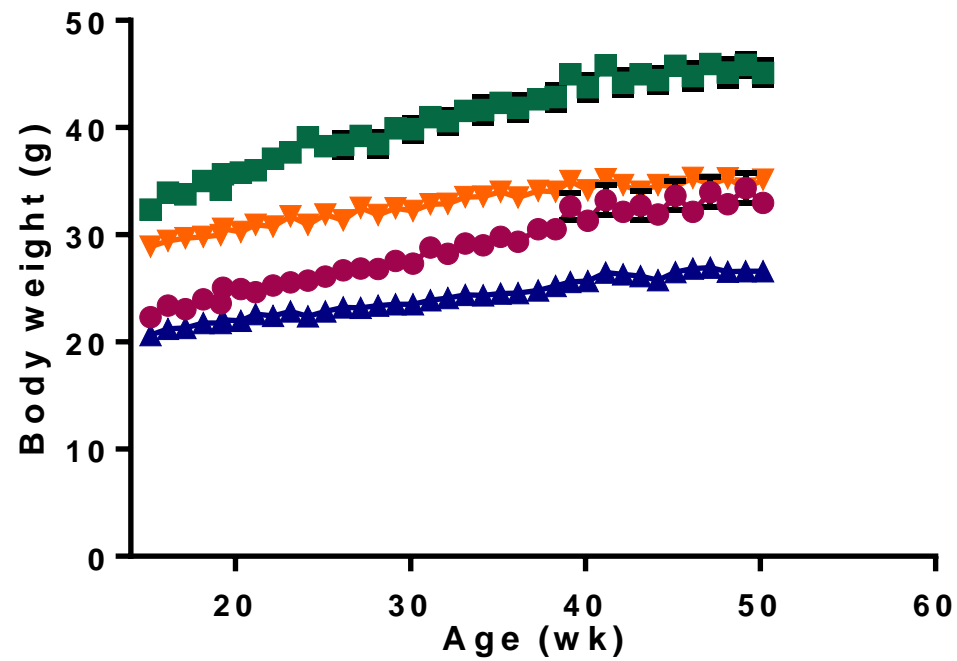


Staggered plan – first 36 mo

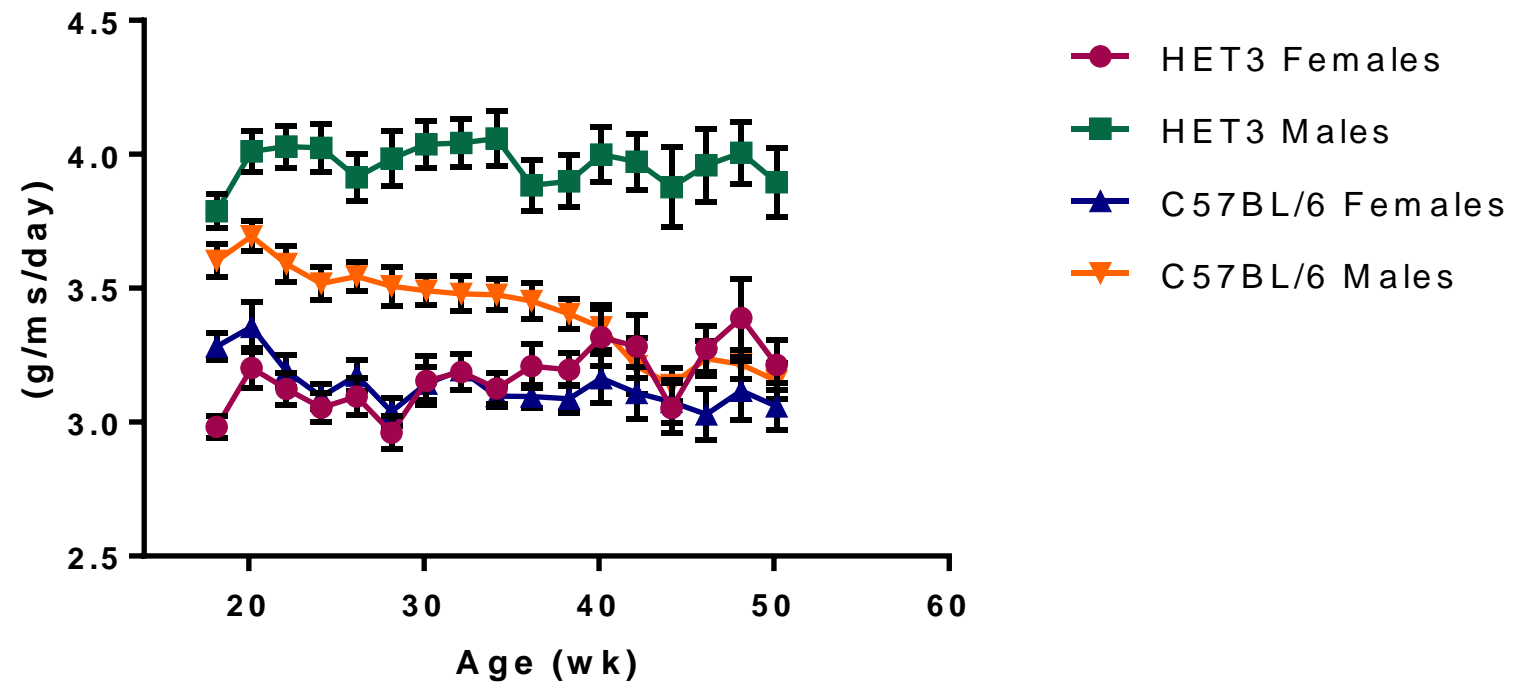


Body weight and food consumption

Body weight

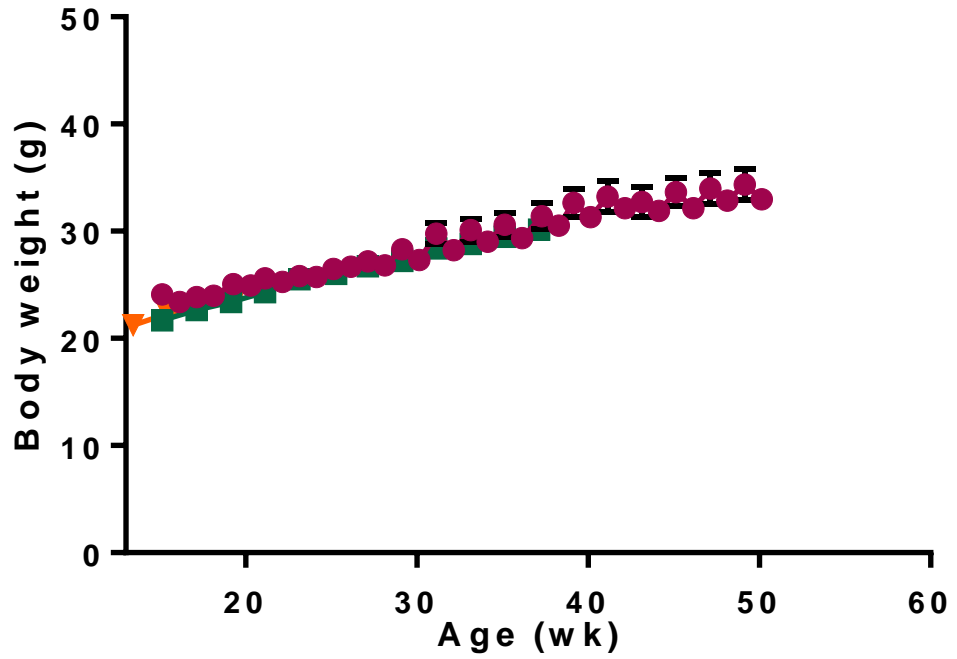


Food consumption

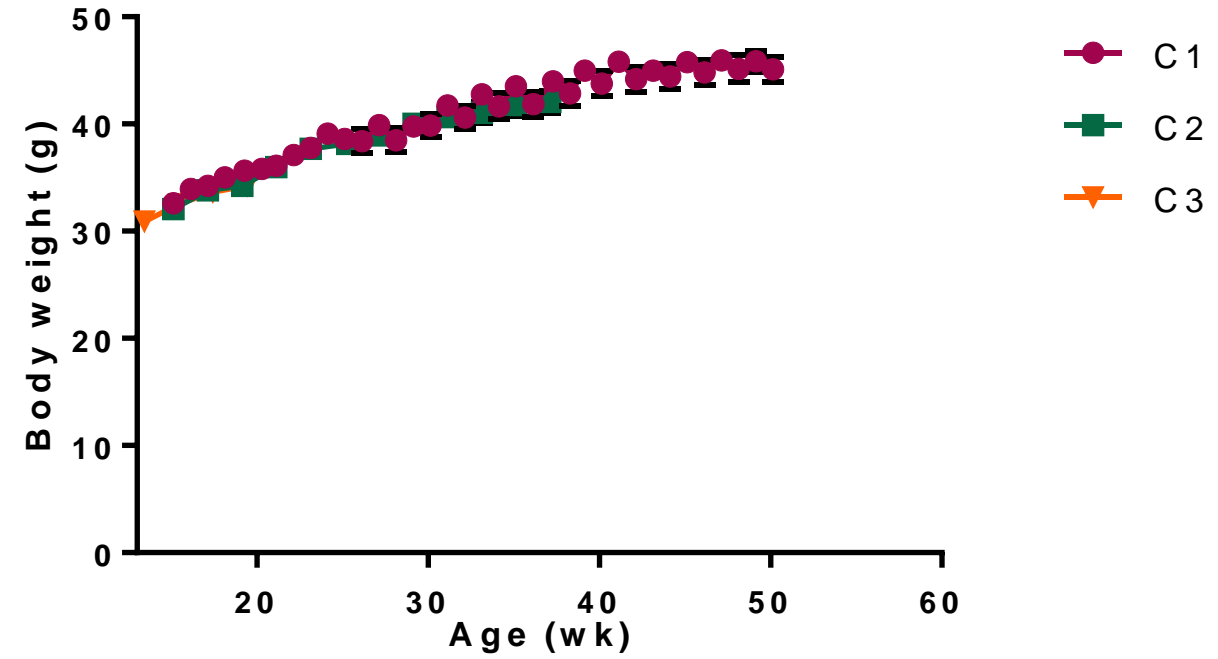


BW

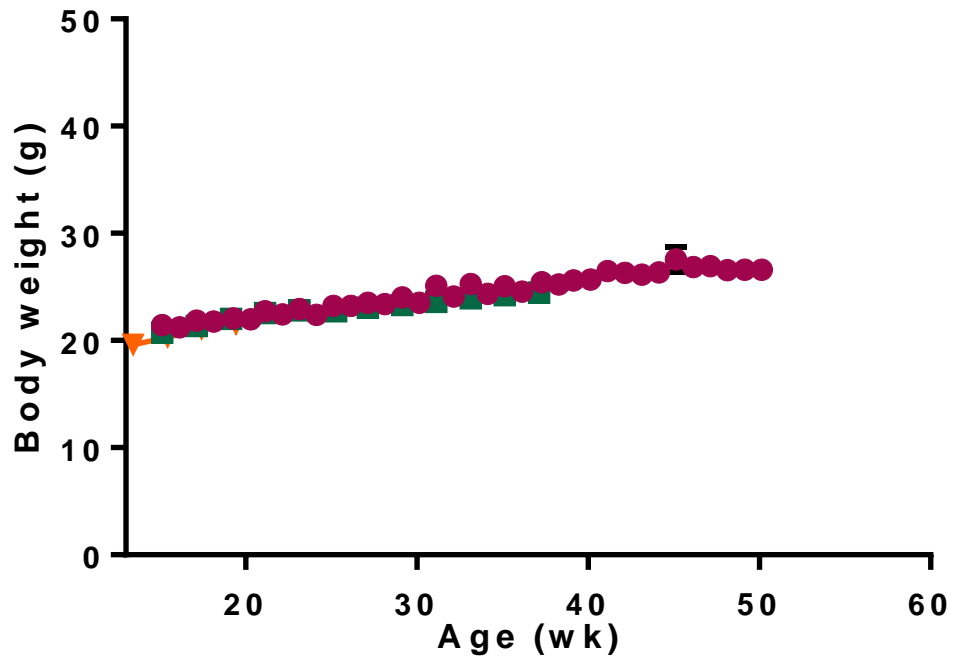
HET3 Females



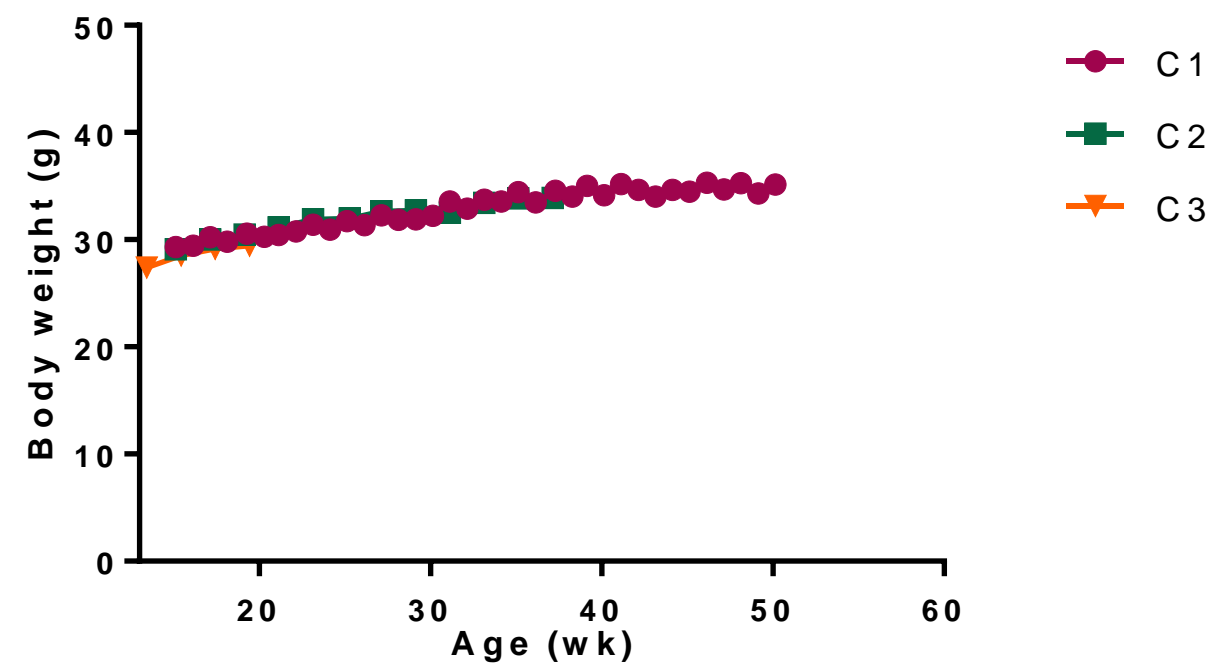
HET3 Males



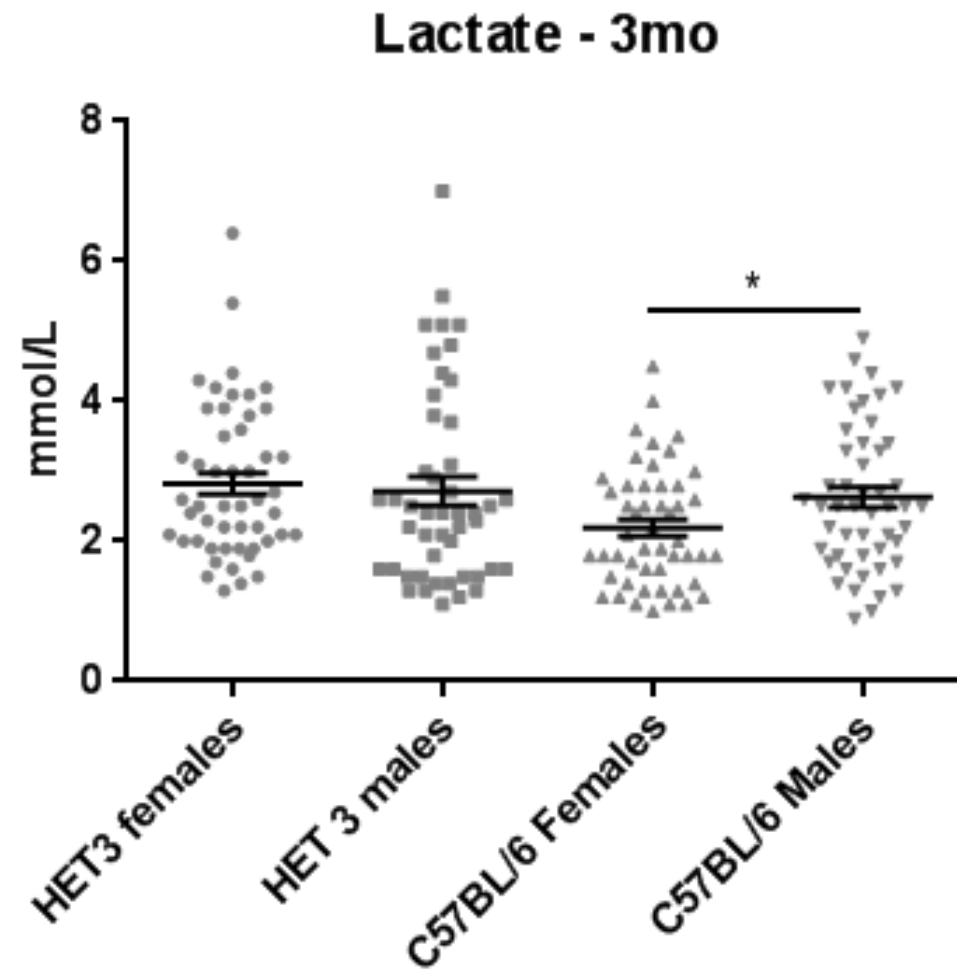
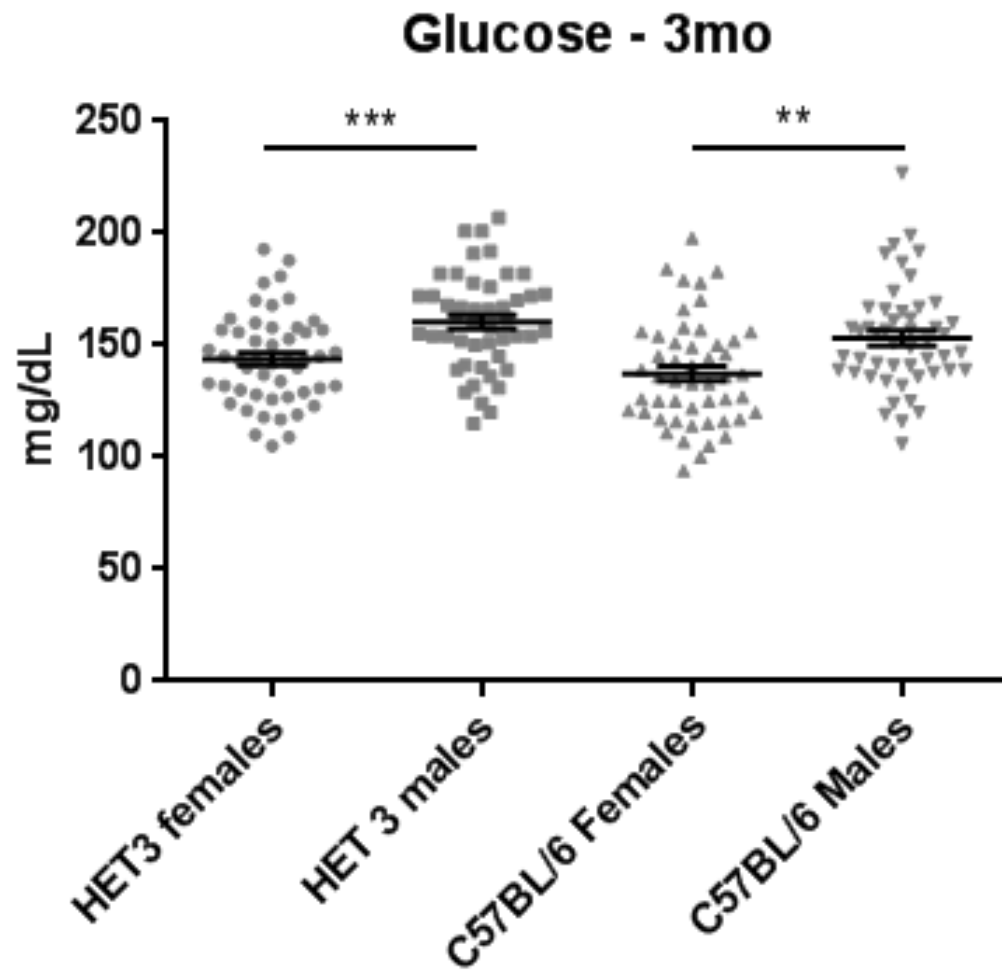
C57BL/6 Females



C57BL/6 Males

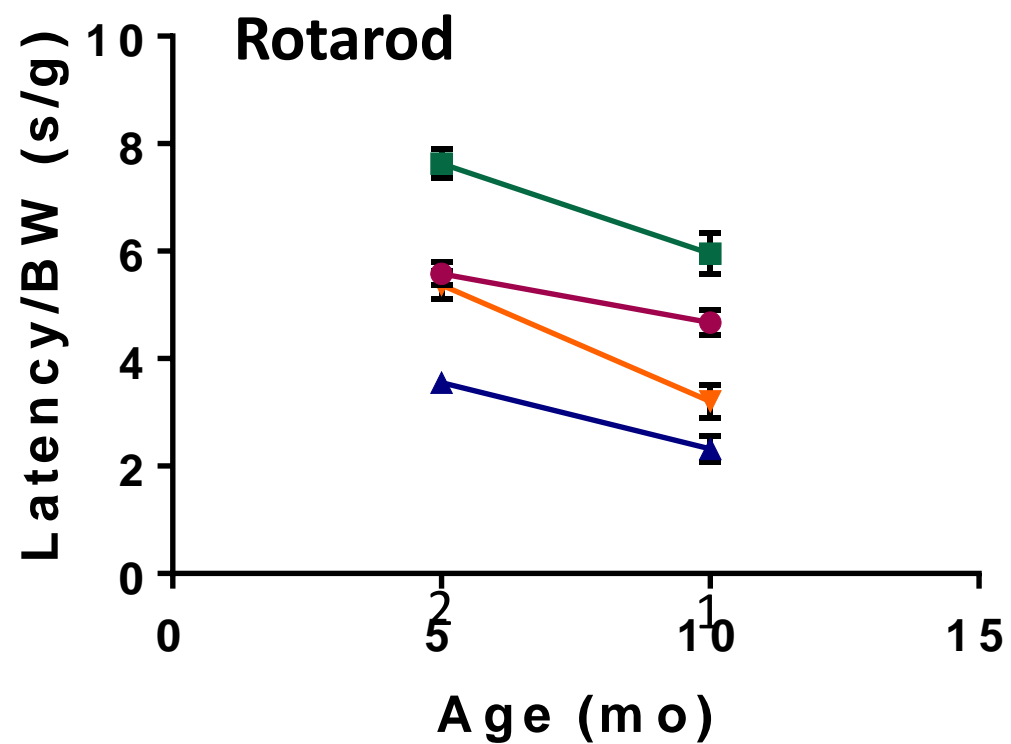
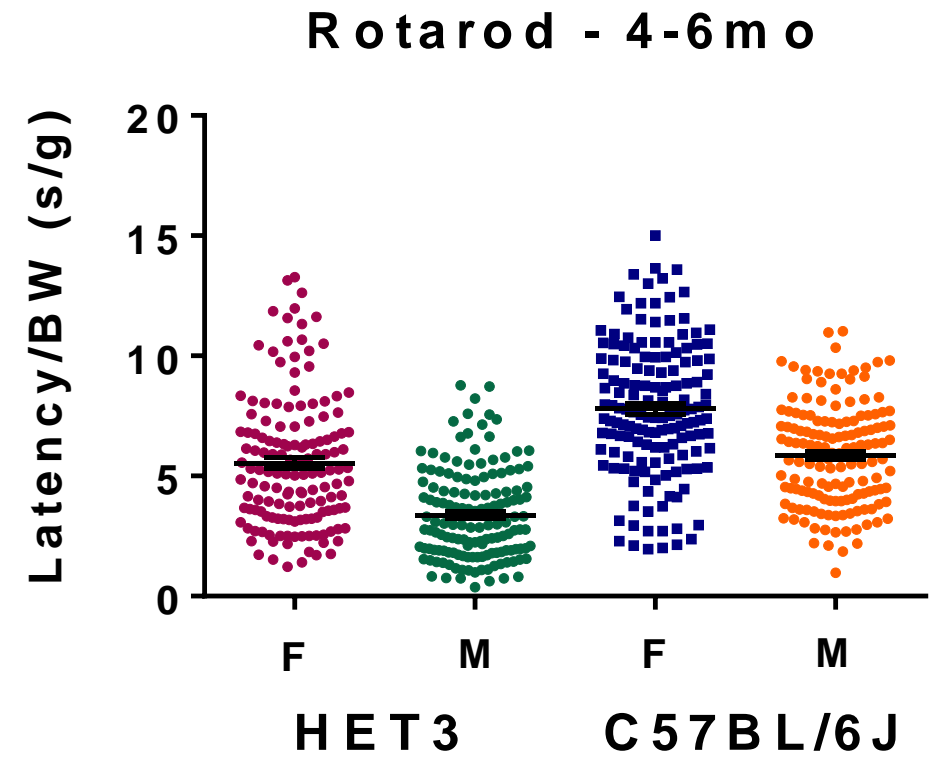
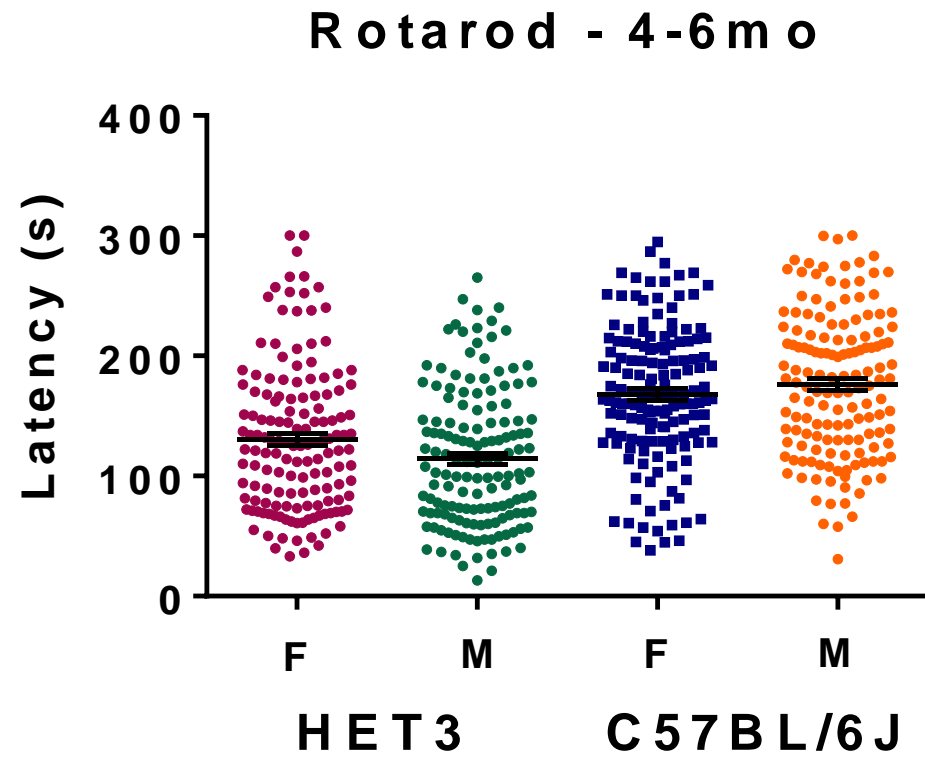


Glucose and Lactate

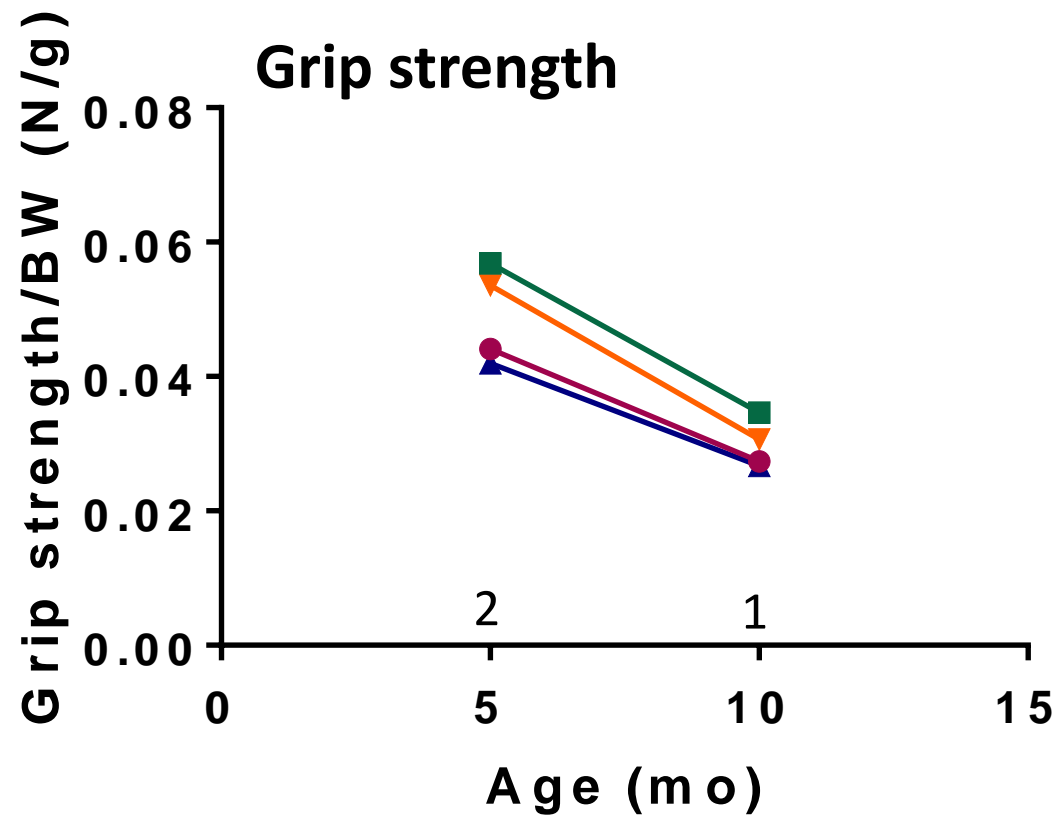
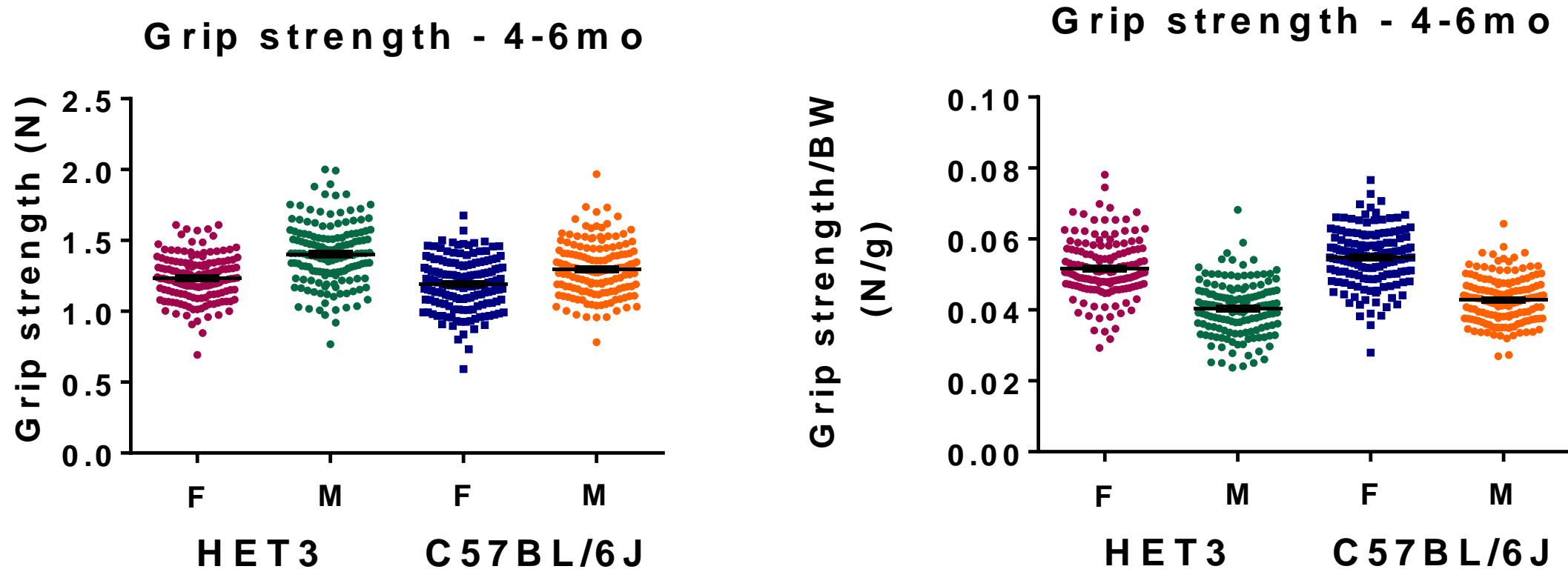


n = 47-50/strain/sex

Rotarod

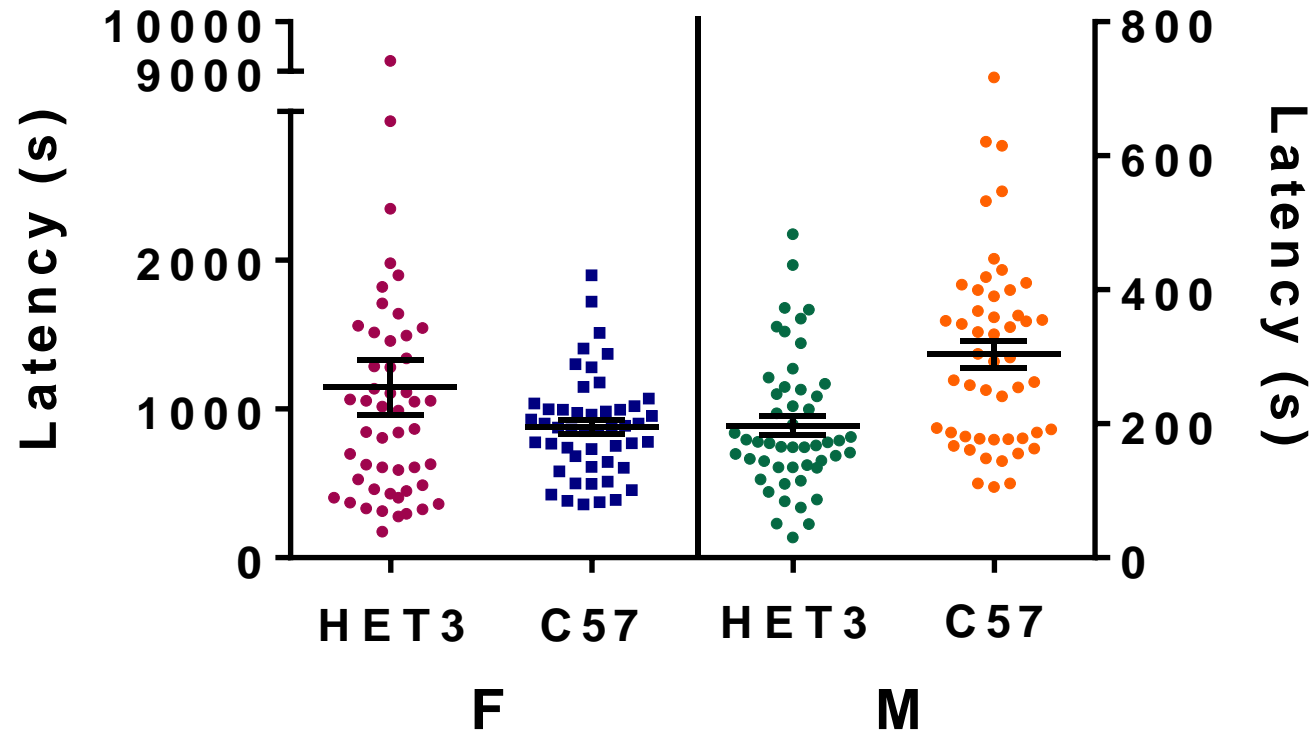


Grip strength

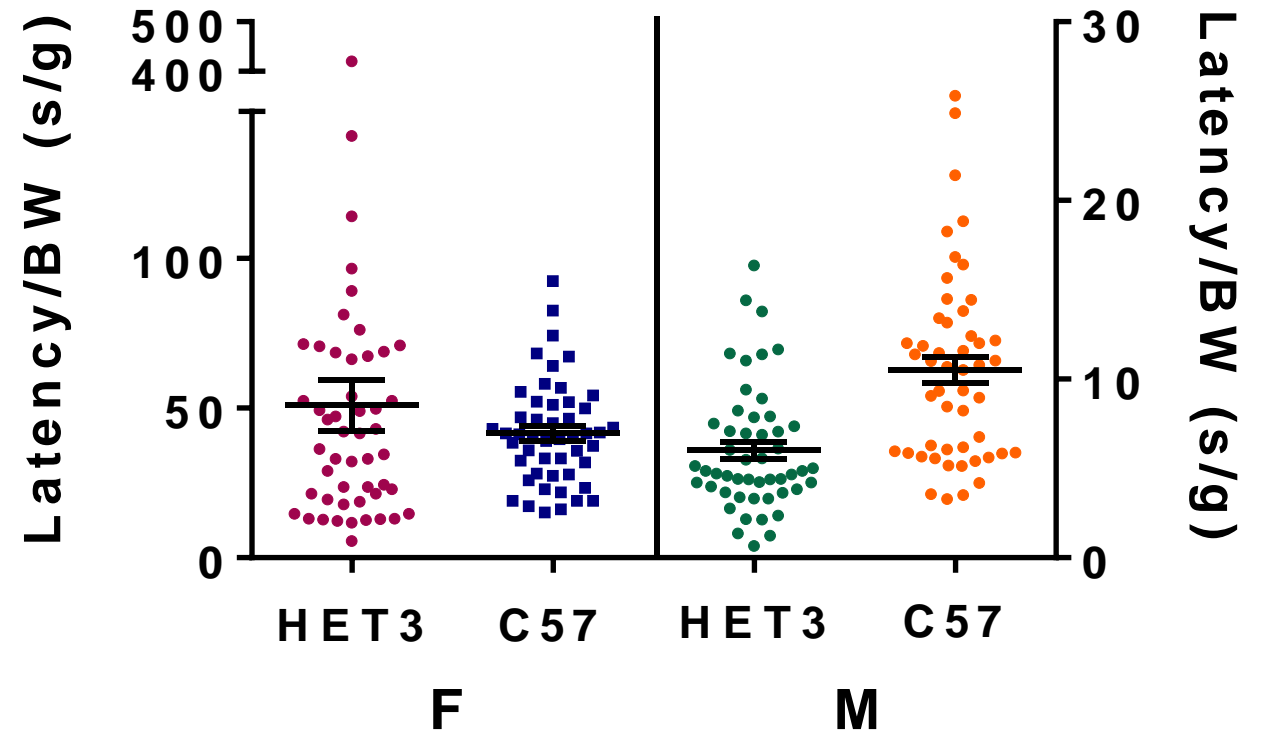


Cage top - max

C3 - Cage top



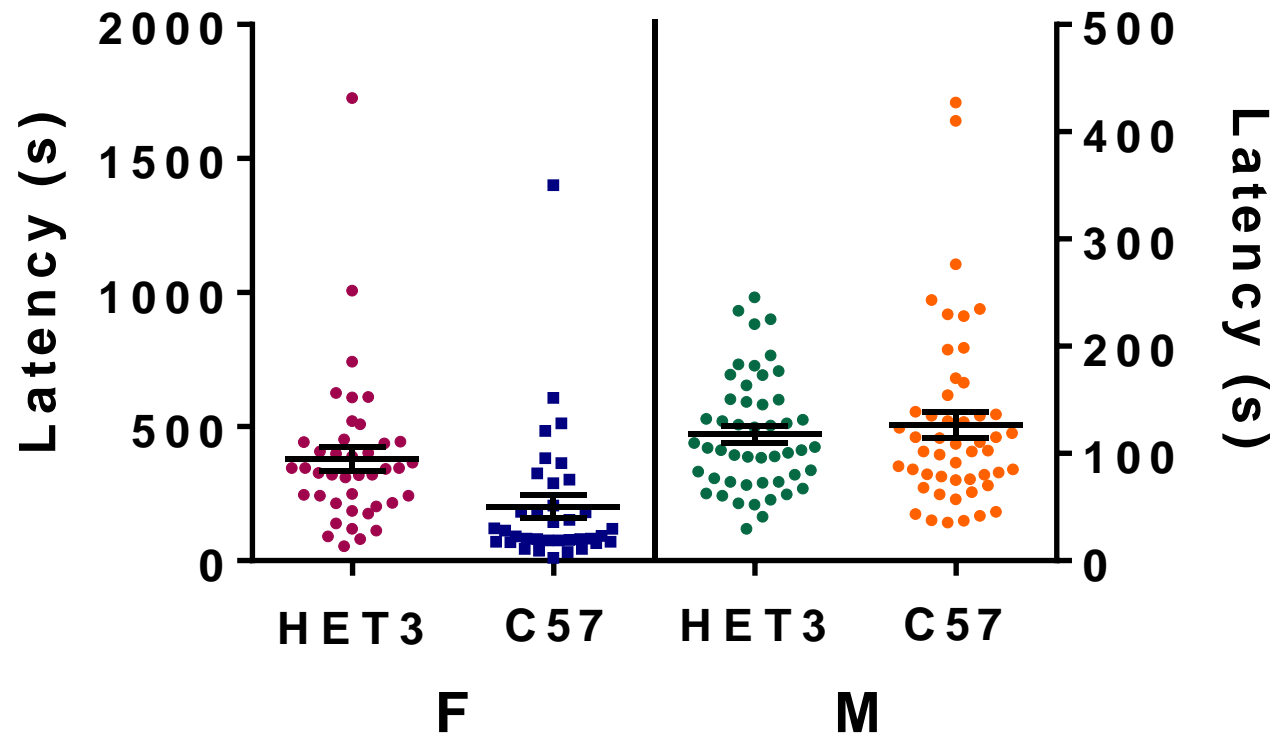
C3 - Cage top



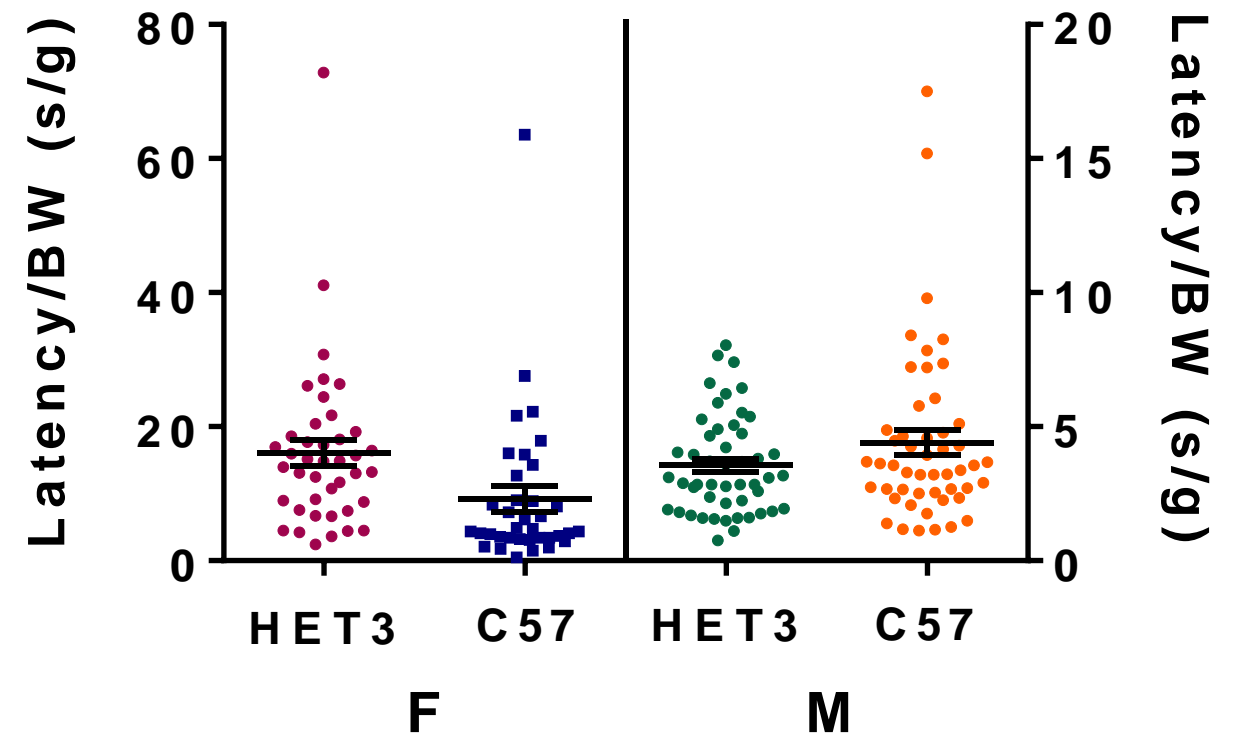
4 mo old
N=50/strain/sex

Wire hang - max

C3 - Wire hang



C3 - Wire hang

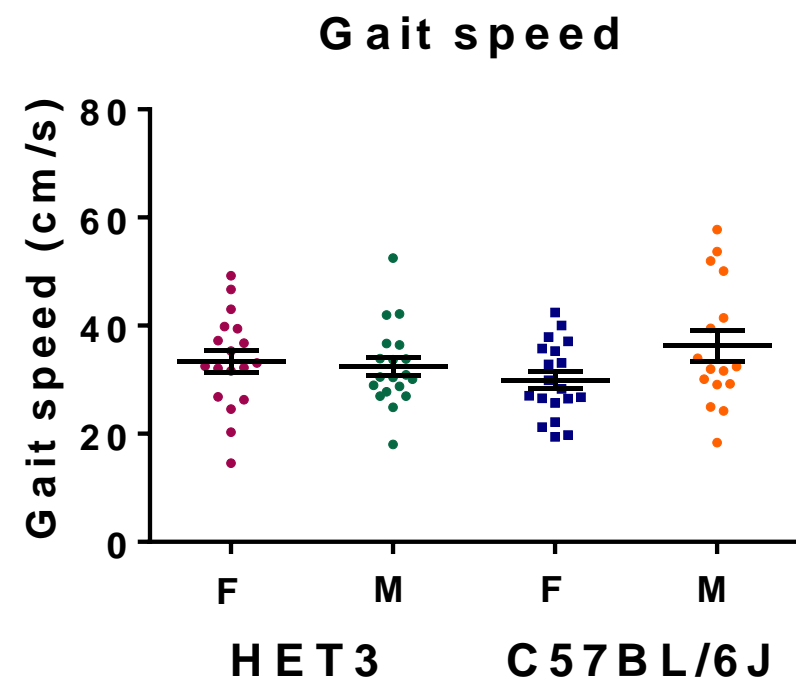
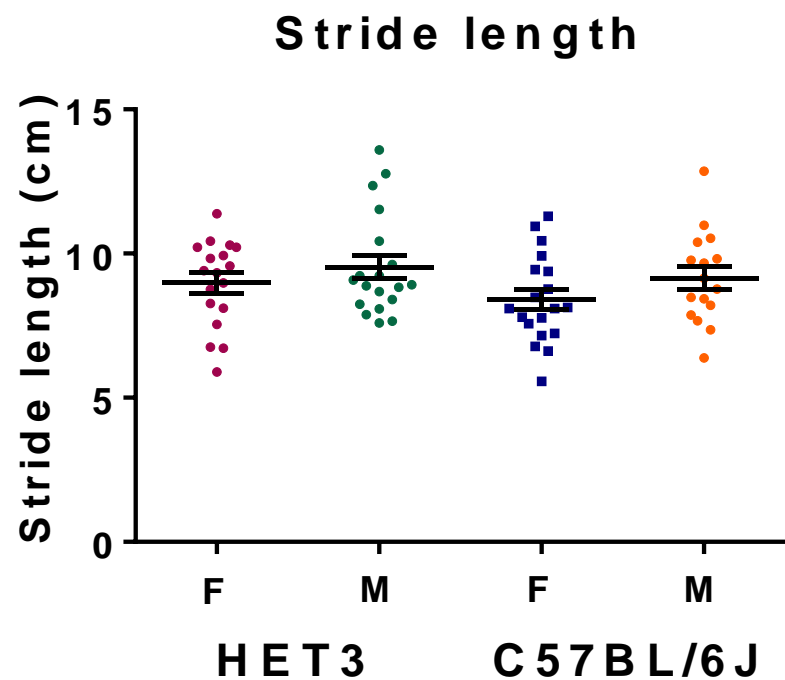
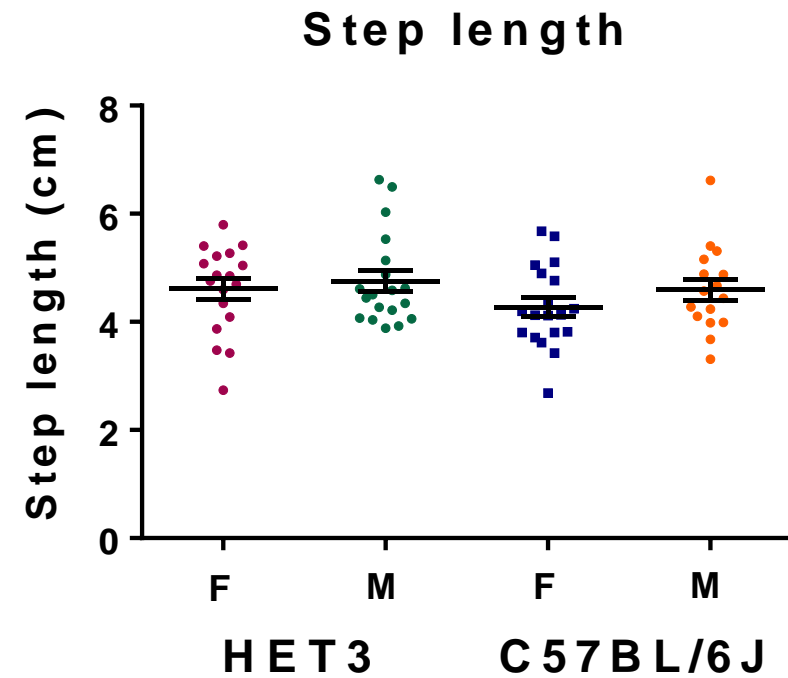
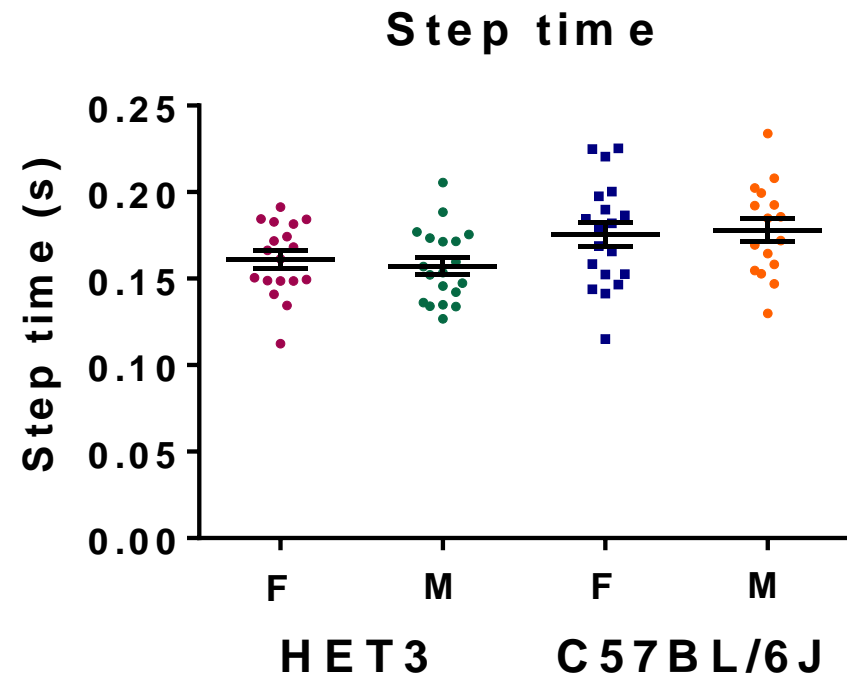


4 mo old

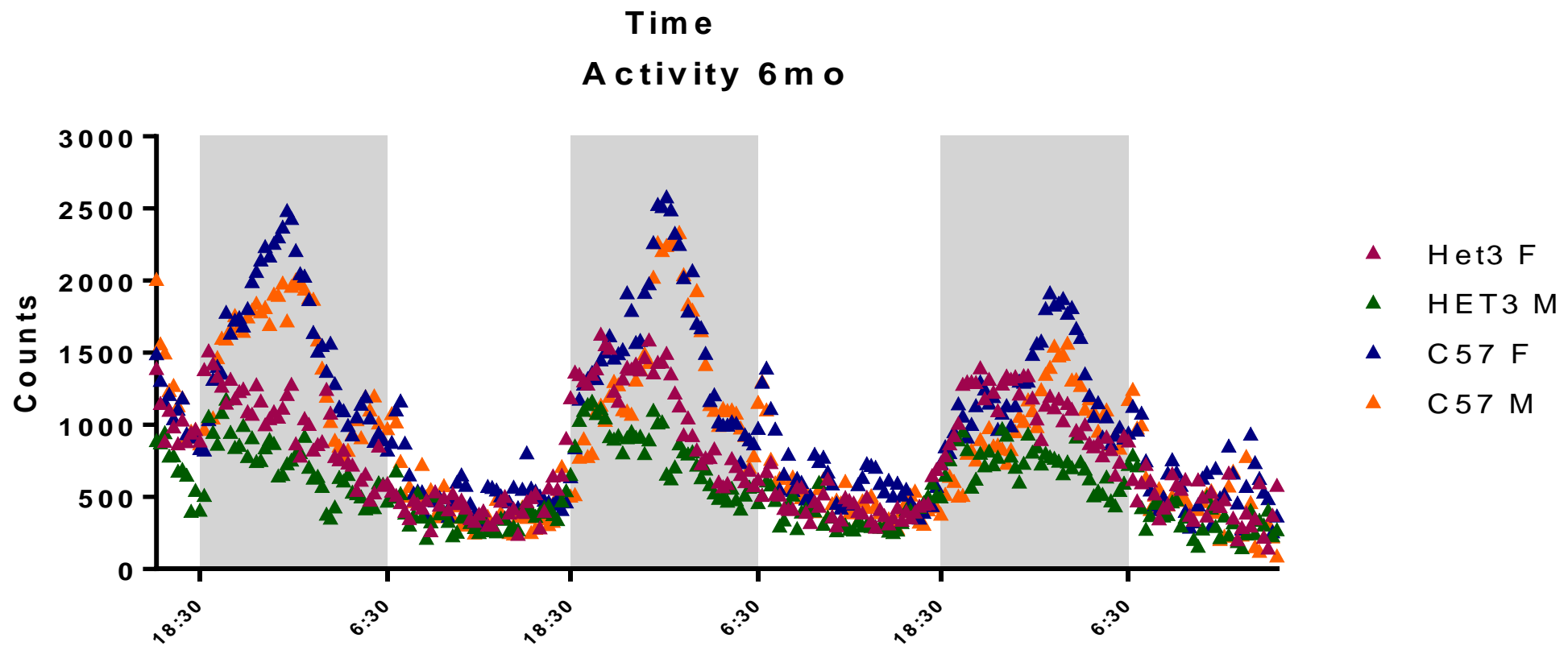
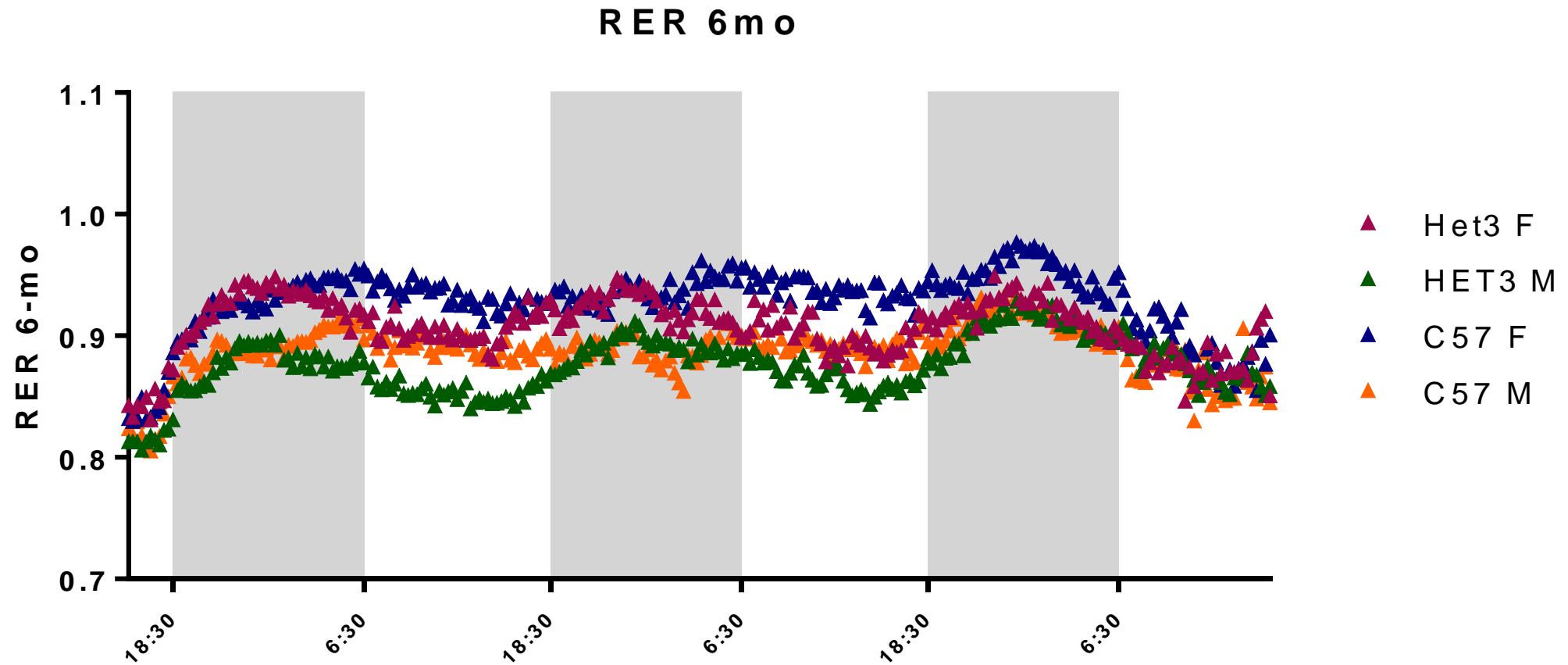
Gait analysis

Only C1 first time point.

We have the videos and we are analyzing C1 2nd time point and C2 first time point.



Metabolic cages

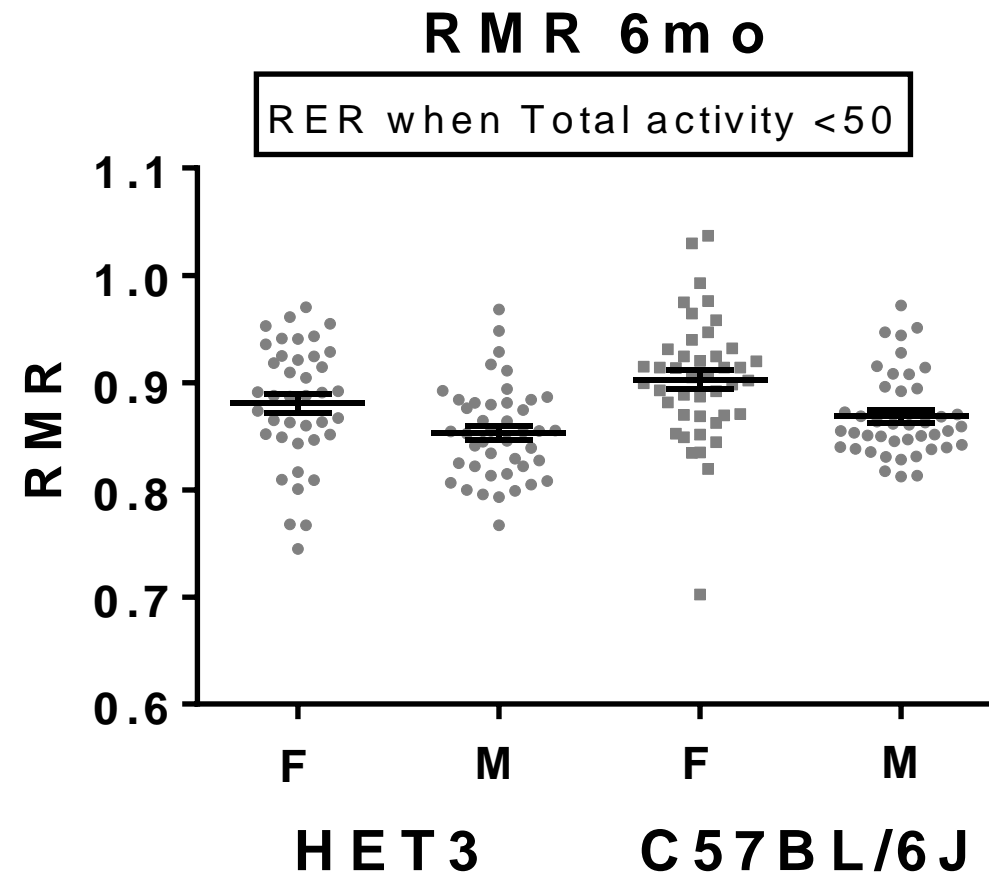


Metabolic cages – RMR

RMR is defined as average RER when **Total Activity <50**

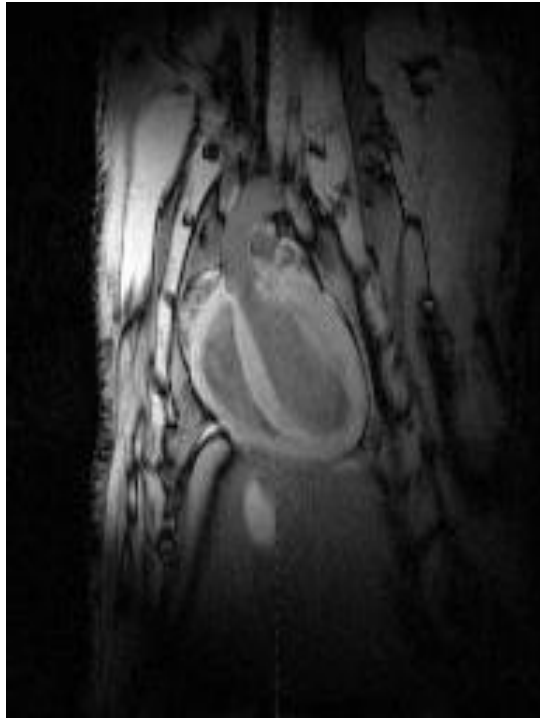
Also, $VO_2 > 1000$, $VCO_2 > 1000$, $0.6 < RER > 1.1^*$

*to avoid weird values due to power blips or other problems



Ongoing MR imaging examples

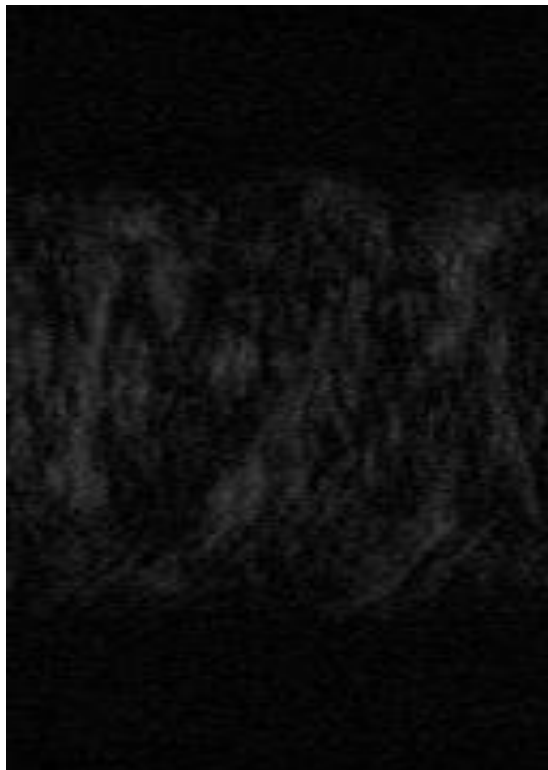
heart



brain



fat

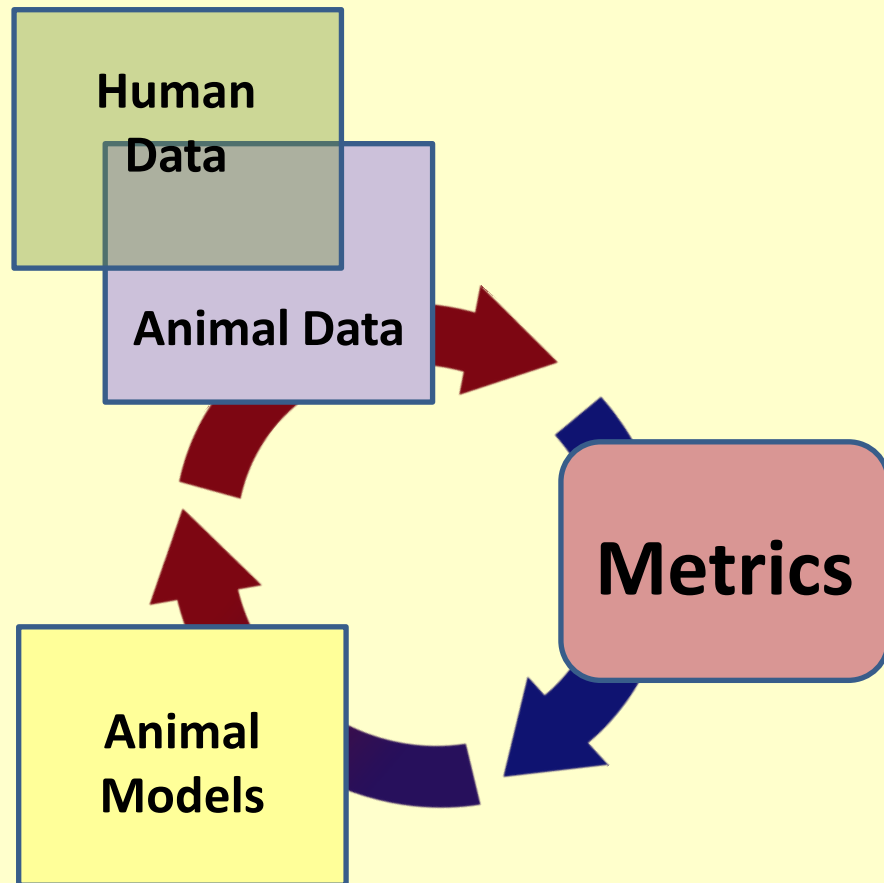


liver



SO....what is the THE BIG PICTURE

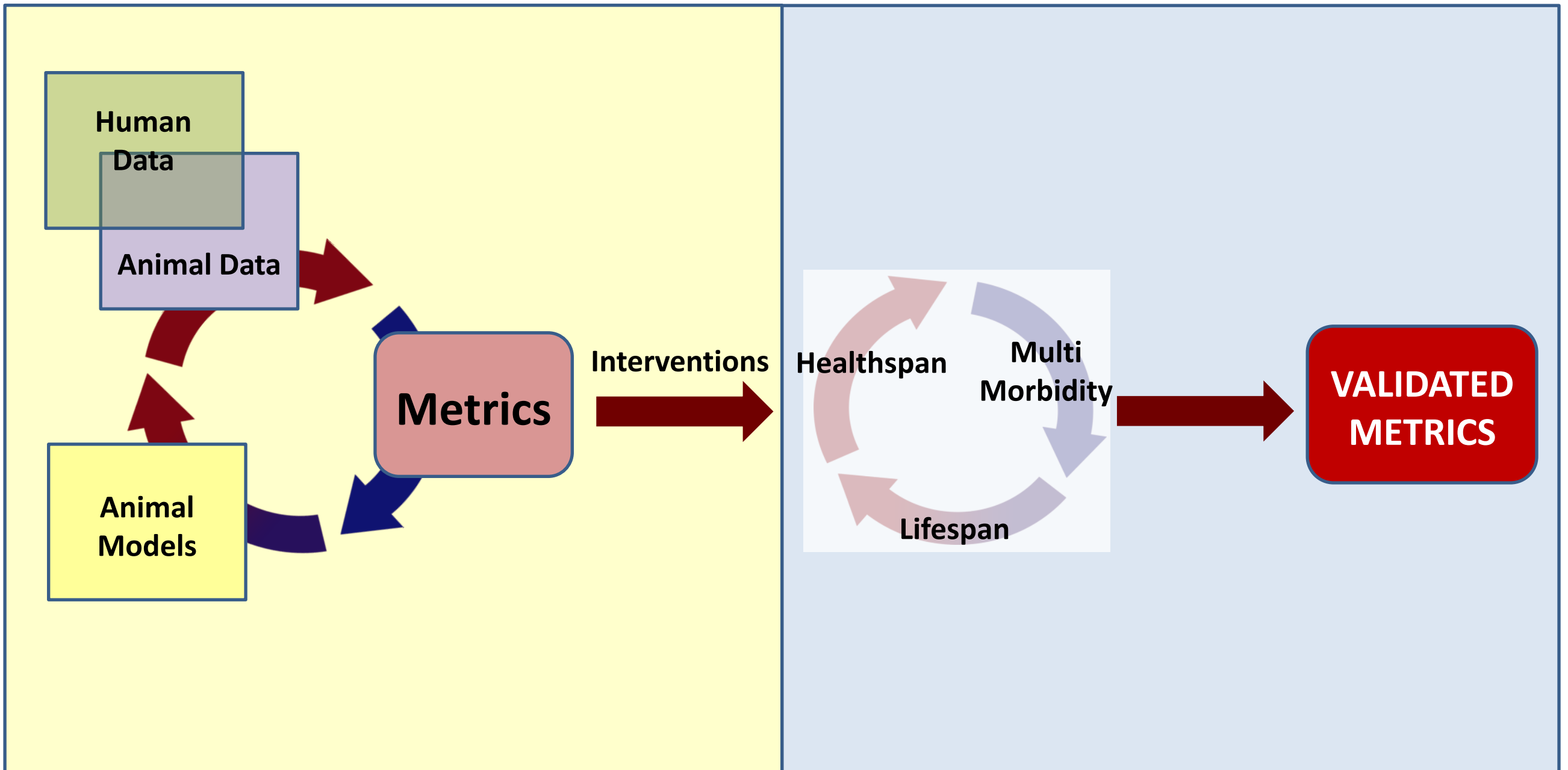
Identification of Predictive Targets



THE BIG PICTURE

Identification of Predictive Targets

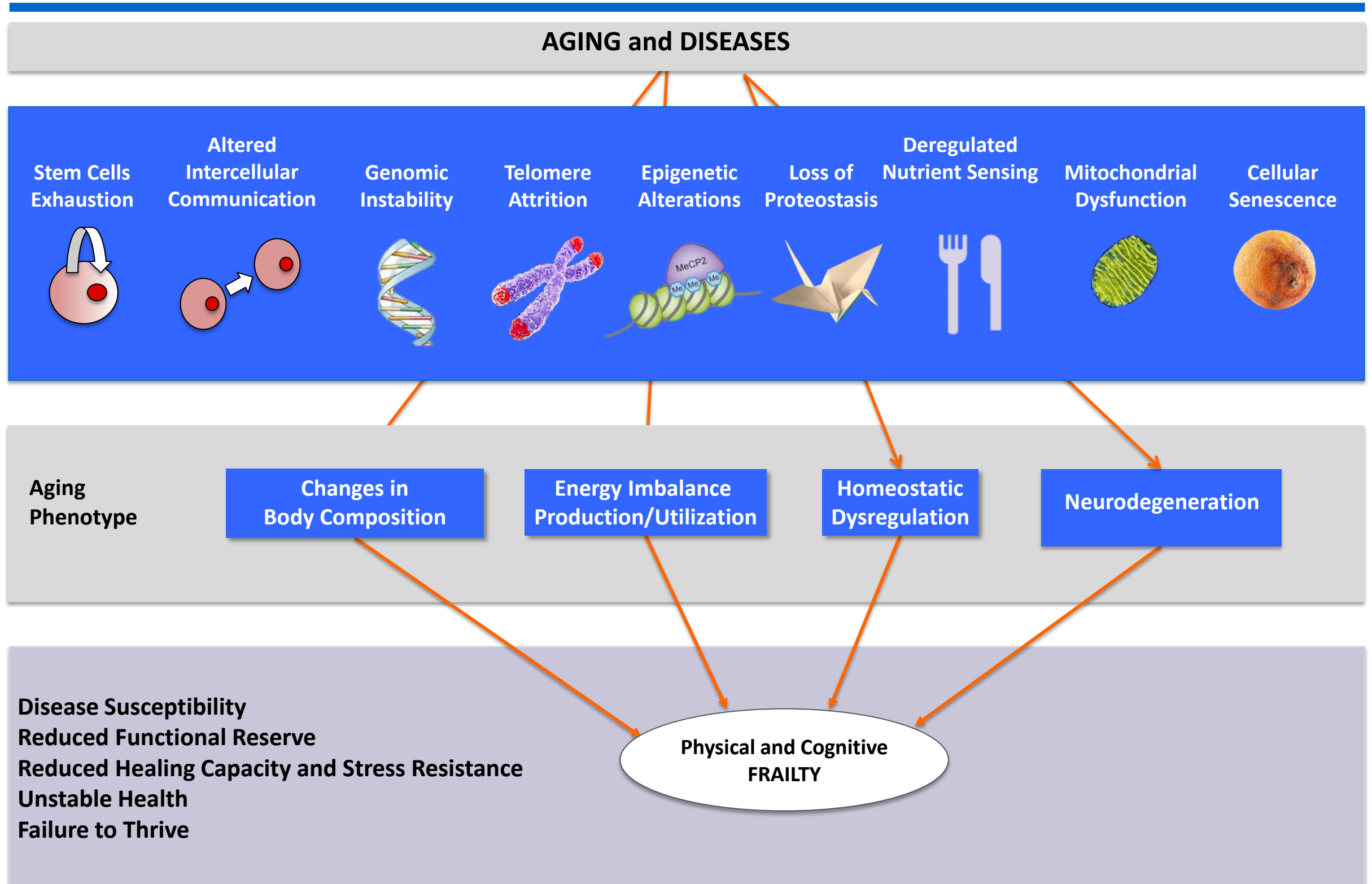
Target Engagement And Validation



Predictive Mechanism-Related Markers for Aging-Related Outcomes

Felipe Sierra

What are the mechanisms behind aging and disease That affect aging phenotypes and longevity?



Acknowledgements

Office of the Scientific Director
Translational Gerontology Branch



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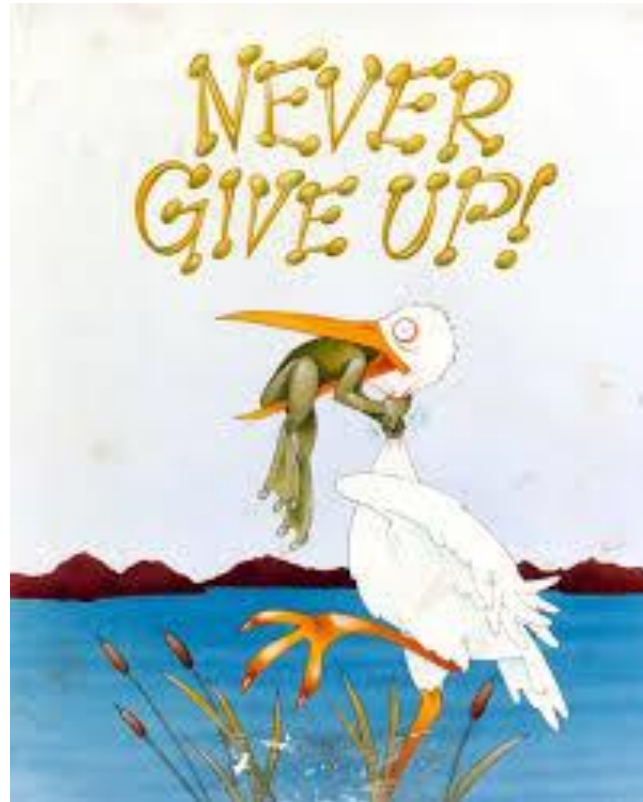
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THANKS!

**We are always happy to share and collaborate!
STUDY OF LONGITUDINAL AGING IN MICE (SLAM)**

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