Perspectives on Cancer & Aging

ARTI HURRIA MEMORIAL WEBINAR SERIES

APRIL 9, 2020

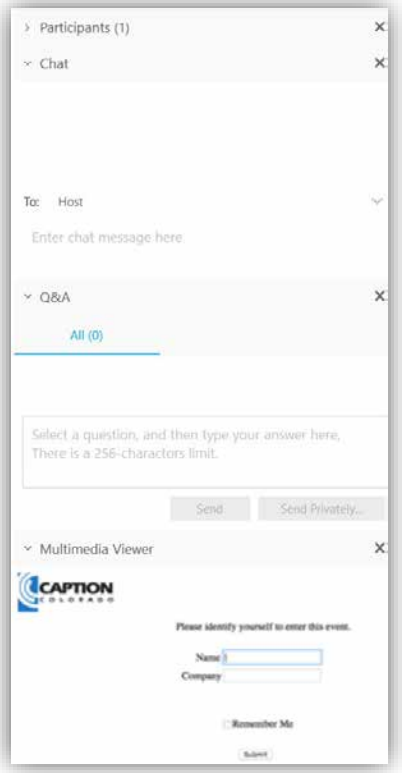
Cancer and Aging: Biological and Phenotypic Measures of Aging

A WEBINAR TRIBUTE TO DR. ARTI HURRIA

Luigi Ferrucci, M.D., Ph.D.
Morgan Levine, Ph.D.
Cancer & Aging Research Group

NIH NATIONAL CANCER INSTITUTE

Using WebEx and webinar logistics



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- Submit questions at any time during the presentation by typing into the Q&A feature on the right-hand side of the WebEx interface.
  - Select Host and a moderator will ask the questions on your behalf
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- This webinar is being recorded

Today's speakers:

Luigi Ferrucci, M.D., Ph.D.
Geriatrician and Epidemiologist
Scientific Director
National Institute on Aging

Morgan Levine, Ph.D.
Assistant Professor
Department of Pathology
Yale School of Medicine

April 9th 2020
Perspectives on Cancer and Aging Webinar

"Connecting the biological and phenotypic manifestations of aging: the case of muscle aging".

Luigi Ferrucci - National Institute on Aging

NIH Intramural Research Program
Our Research Changes Lives

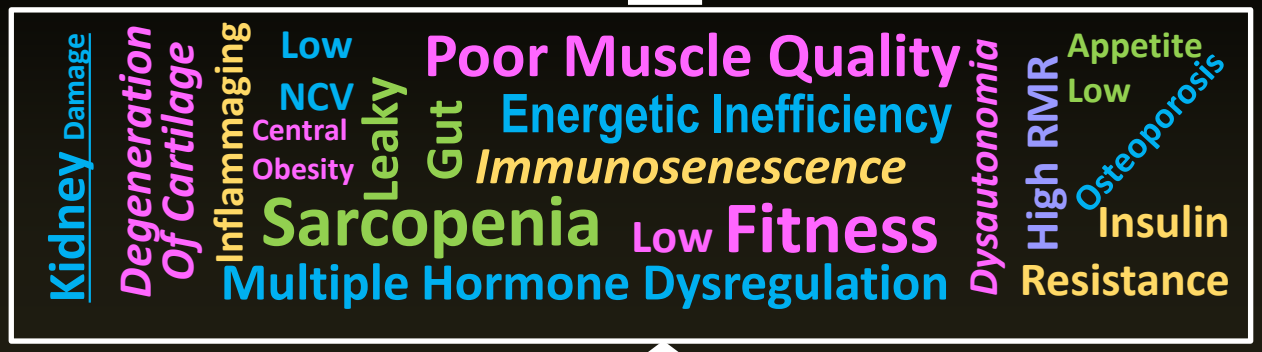
The Metrics of Aging

Functional Aging *(impact on daily life)*

- Cognitive Function
- Physical Function
- Mood
- Mental Health

Phenotypic Aging *(phenotypes that change)*

- Body Composition
- Energetics
- Homeostatic Mechanisms
- Brain health



Biological Aging *(root mechanisms)*

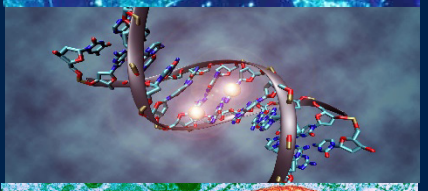
- Molecular damage
- Defective repair
- Energy exhaustion
- Signal/noise reduction

Genomic Instability

The Accumulation of Somatic Mutations with Aging

Cellular Senescence

Trade-off Between Cancer and Aging

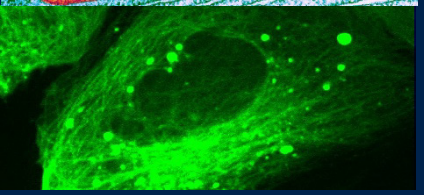


Epigenetics (methylation)

The “Epigenetic Clock”

Mitochondrial Dysfunction

The Power Plant

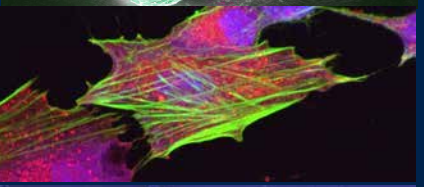


Proteostasis (autophagy)

Repair, Recycle or Trash?

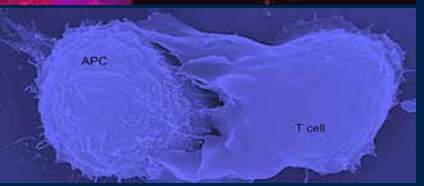
Telomere Length

Protecting the DNA During Replication



Stem Cell Exhaustion

Templates for Cells Restoration



Cell to Cell Communication

Accuracy and Context in the Flow of Information

The Hallmarks of Aging
Carlos Lopez-Otın et al.

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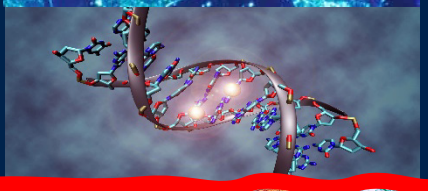

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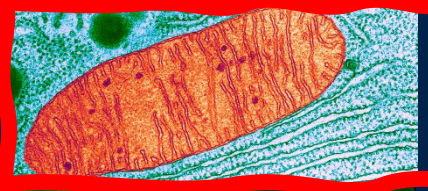
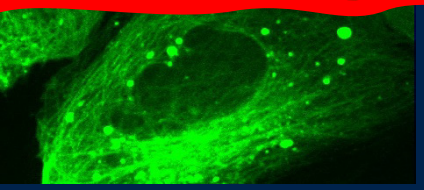


Mitochondrial Dysfunction

The Power Plant



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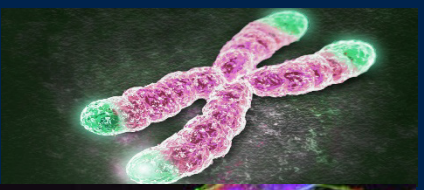

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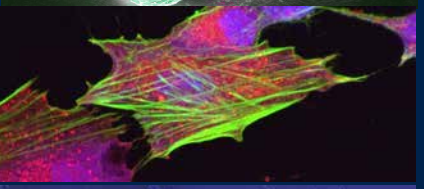

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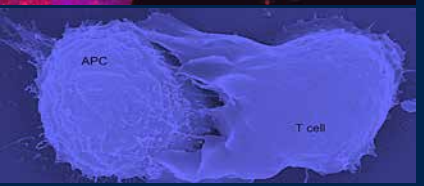

Cell to Cell Communication

Accuracy and Context in the Flow of Information

The Hallmarks of Aging
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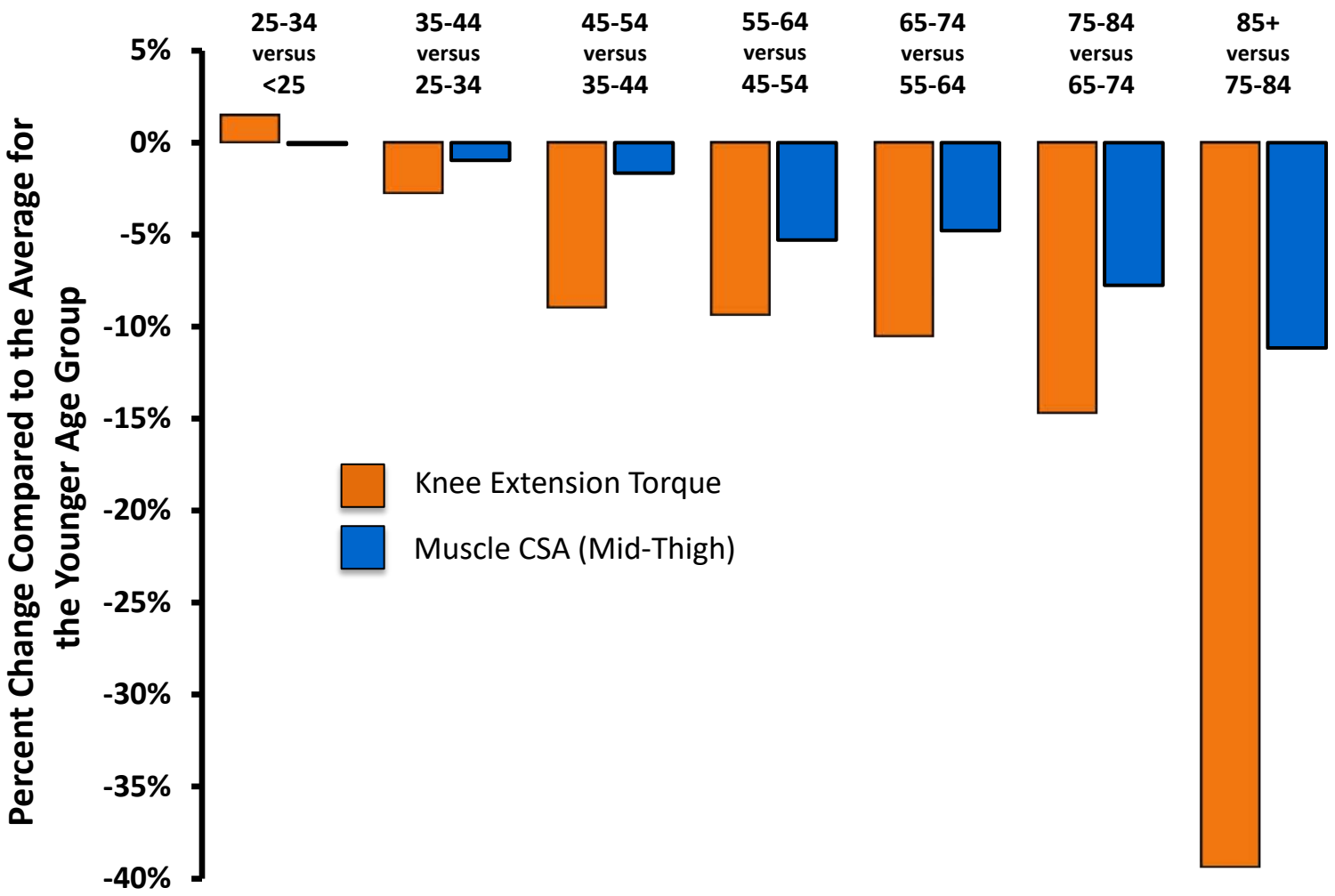
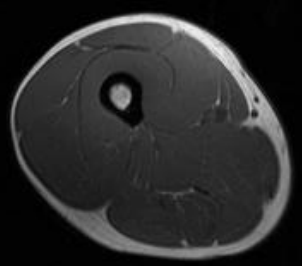
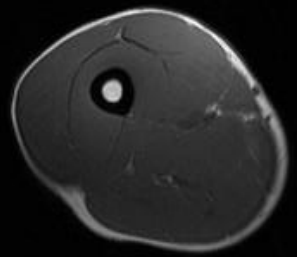
Muscle

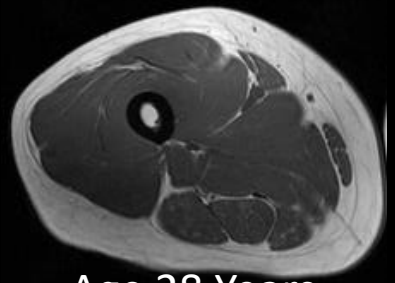
Strength/ Mass Ratio in BLSA Participants 60-70 yrs Old

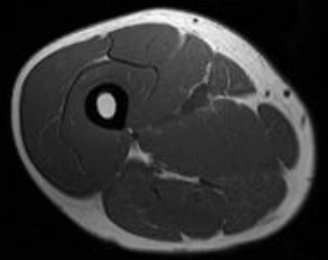


Mid-thigh T1w MRI Images (Men; GESTALT)

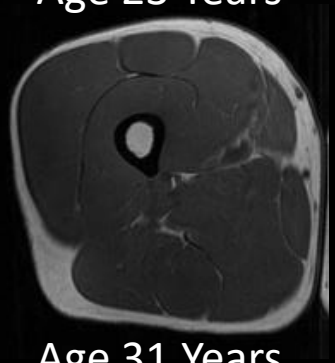

Age 23 Years

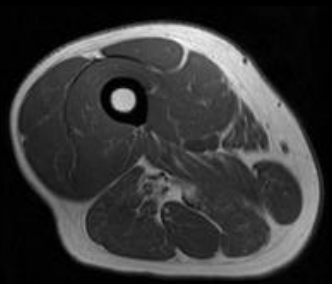

Age 26 Years

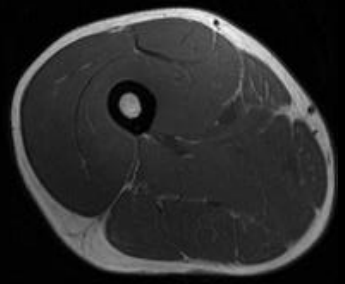

Age 28 Years

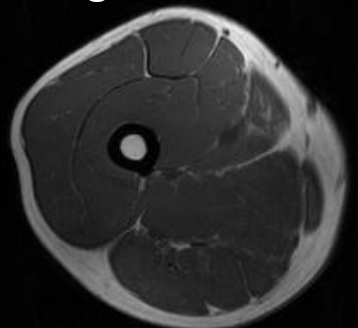

Age 31 Years

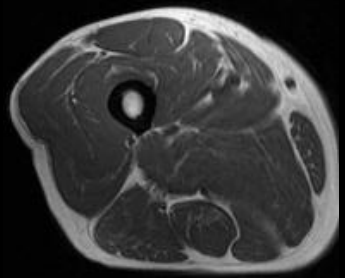

David Reiter

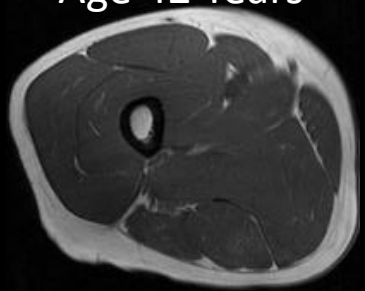

Age 31 Years

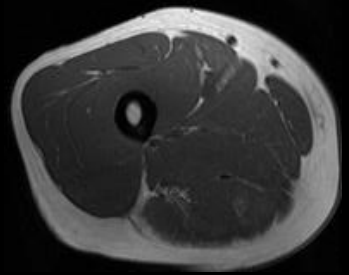

Age 42 Years

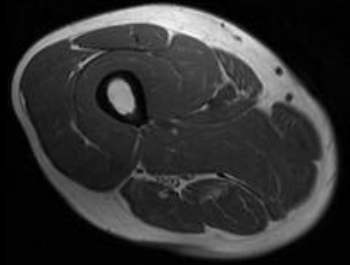

Age 45 Years

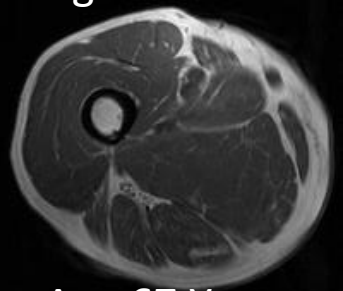

Age 45 Years

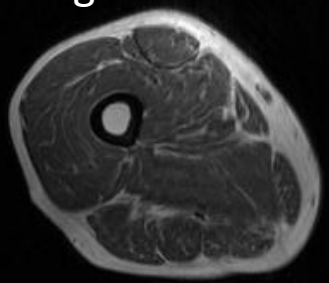

Age 51 Years

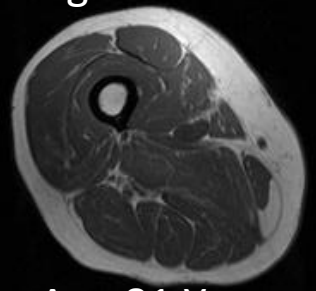

Age 52 Years

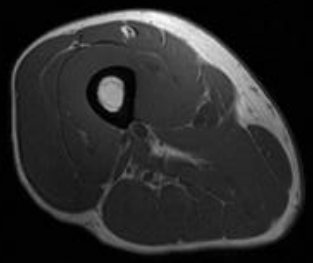

Age 57 Years


Age 60 Years


Age 67 Years


Age 72 Years


Age 81 Years


Age 83 Years

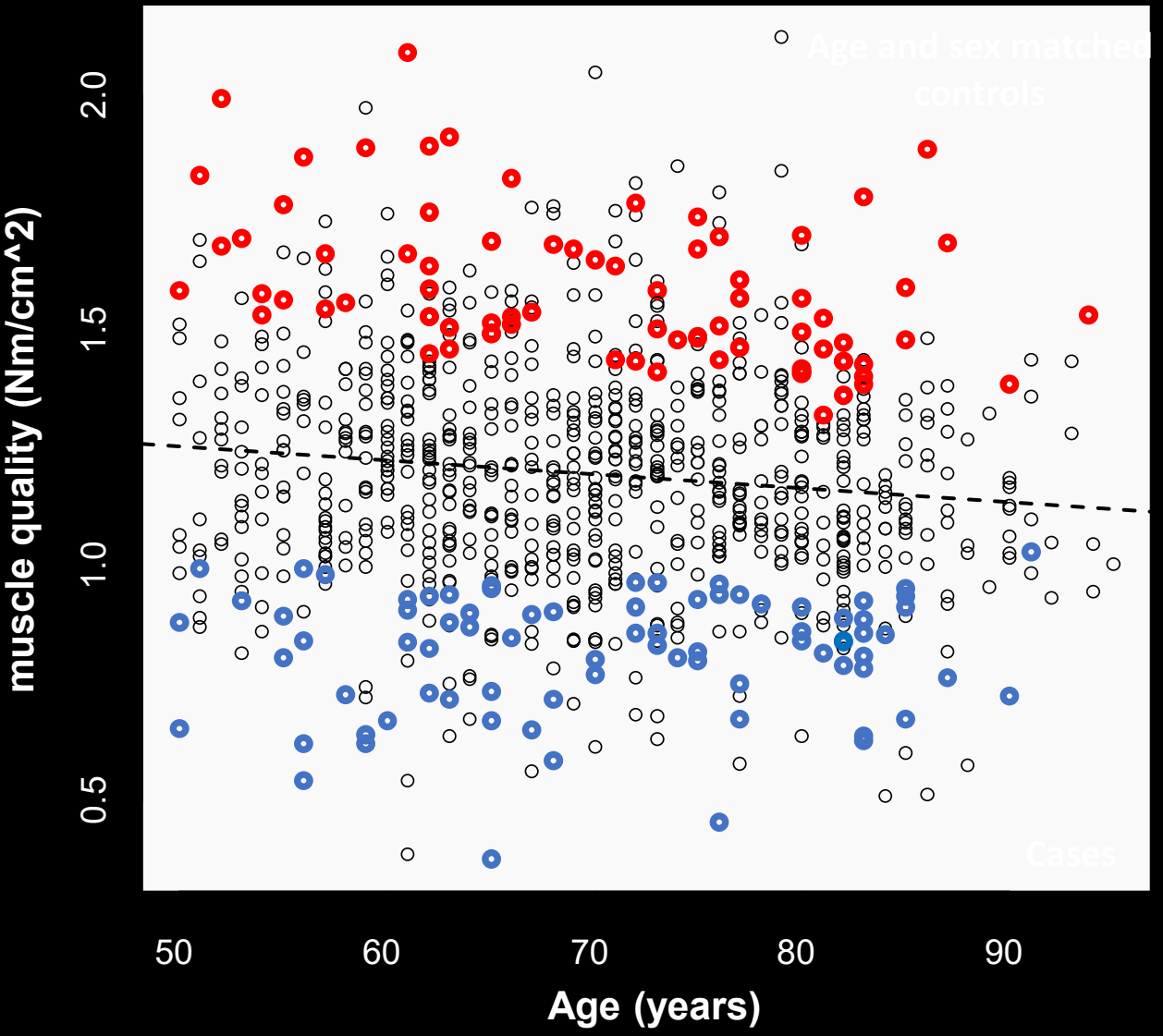
NESTED CASE-CONTROL STUDY in BLSA

Selection of 79 pairs of cases (low muscle quality) and controls (high muscle quality), matched by age (±2.5 years), sex, and height (±1.5cm). Muscle quality defined as knee extension torque/mid-thigh muscle cross-sectional area.

Moaddel R et al. J Gerontol A Biol Sci Med Sci. March 2016. doi:10.1093/gerona/glw046

Ruin Moaddel

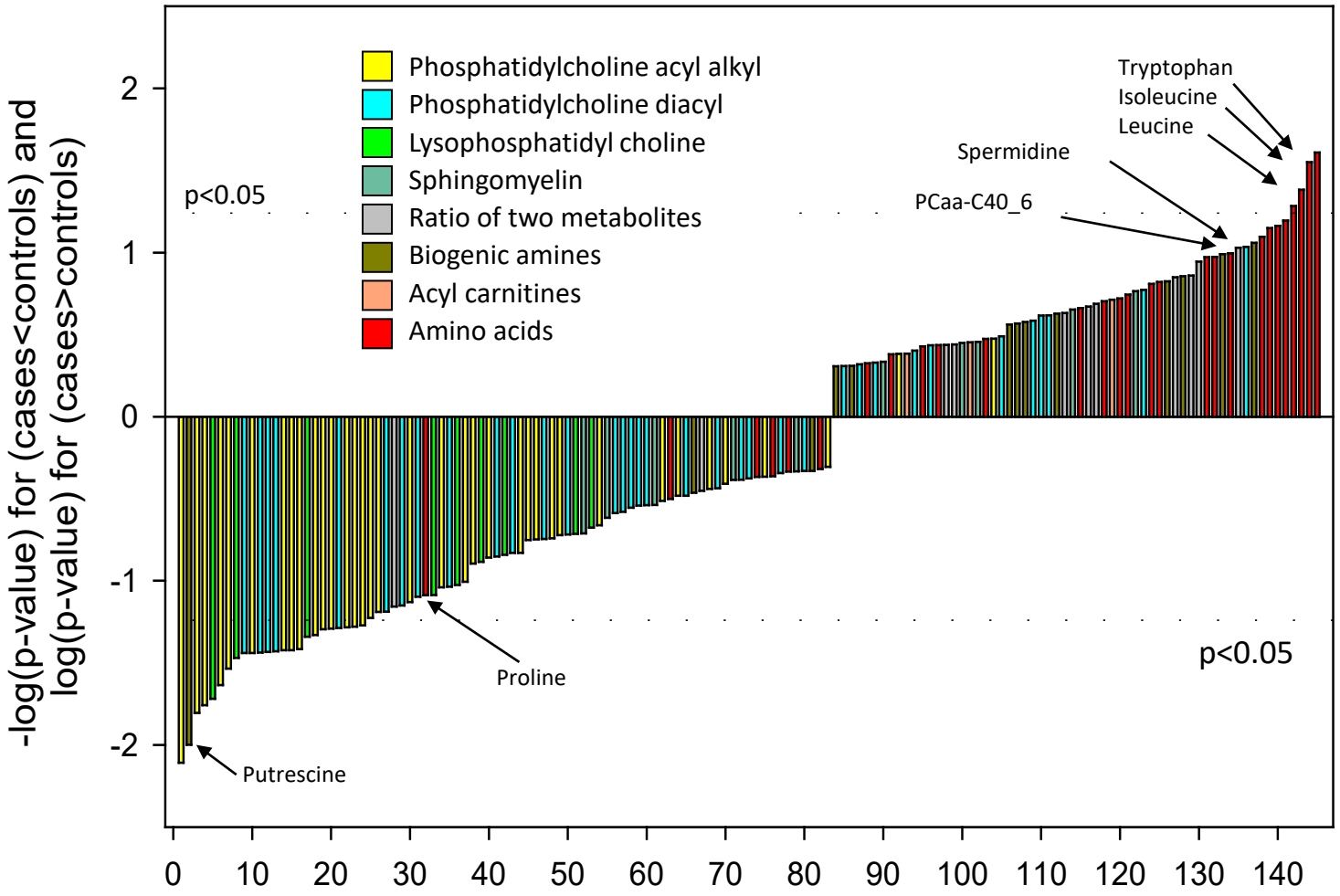
Elisa Fabbri



NESTED CASE-CONTROL STUDY in BLSA

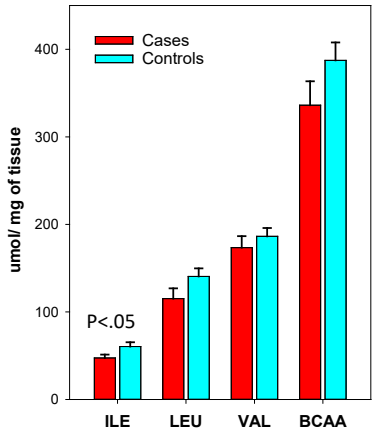
126 Metabolites according to down-regulation or up-regulation in cases (low muscle quality) compared to controls (high muscle quality)

Moaddel R et al. J Gerontol A Biol Sci Med Sci. March 2016. doi:10.1093/gerona/glw046

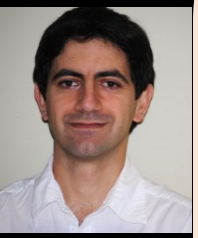


Metabolites ordered by expression differences between cases and controls

Metabolomics on Muscle Biopsies



BCAAs stimulates energy production and protein synthesis



BCAT = Branched chain aminotransferase
BCKDH = Branched-chain alpha-keto acid dehydrogenase

BCAAs
extracellular

SNAT2

LAT1

Gln

Protein
Breakdown

BCAAs
intracellular

SIRT-1

PGC-1α
HIF-1α

mTOR
(TORC1)

Myocyte

4E-BPs

eIF4E

P70
S6 Kinase

Protein
Synthesis
Cascade

Muscle
Protein
Synthesis

Mitochondrial
Biogenesis

Mitochondrion

BCAAs

Ala (to liver)

α-KG

BCAT

Pyr

Glu

glucose

BCKAs

BCKDH
Kinase

Inactive

P

BCKDH

BCKDH

Active

BCKDH
Phosphatase

R-CoA
(IB-CoA, MB-CoA, IV-CoA)

Succinyl-CoA

Acetyl-CoA

Acetoacetate

TCA Cycle

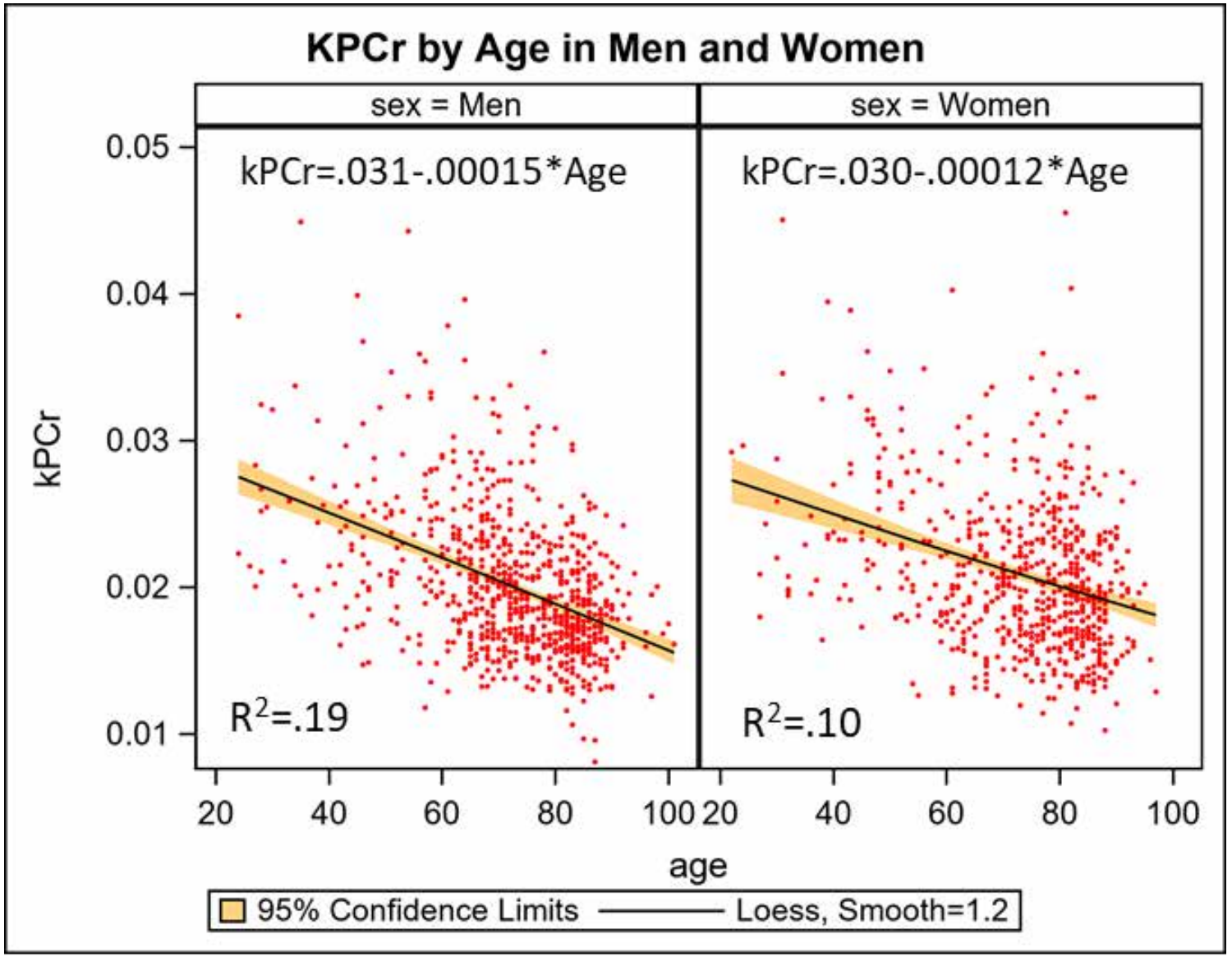


Figure 1. Skeletal muscle oxidative capacity, a proxy marker of mitochondrial function, declines with aging both in men (n=400) and women (n=331). BLSA 2020 limited to first measures.

Muscle Strength Mediates the Effect of Mitochondrial Function on Walking Performance.

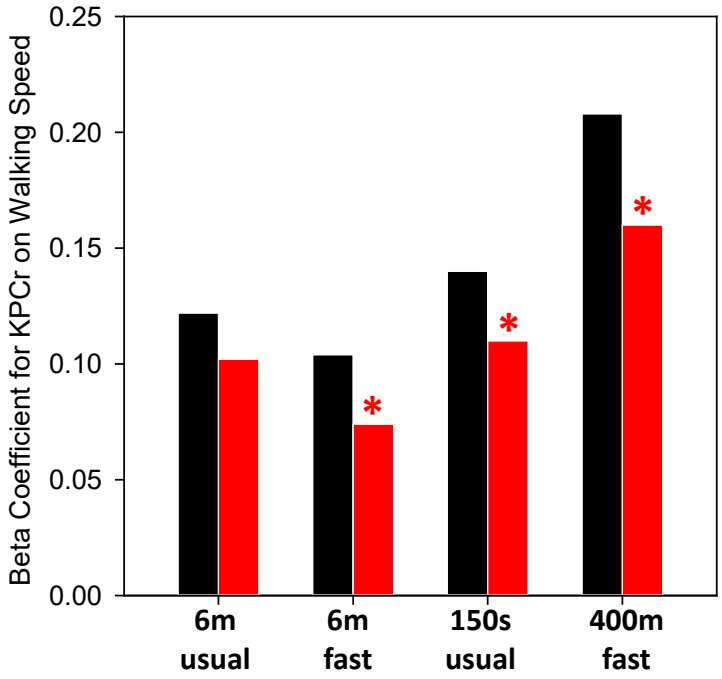
Mitochondrial Function
(KPCr)

Muscle Strength

Beta Coefficient

0.102 (-16%)	6m Usual Pace
0.074 (-29%)	6m Fast Pace
0.110 (-27%)	150s Usual Pace
0.160 (-23%)*	400m Fast Pace

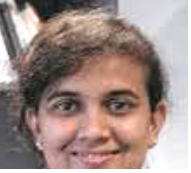
Walking Speed



* Sobel Test (mediation): P<.05

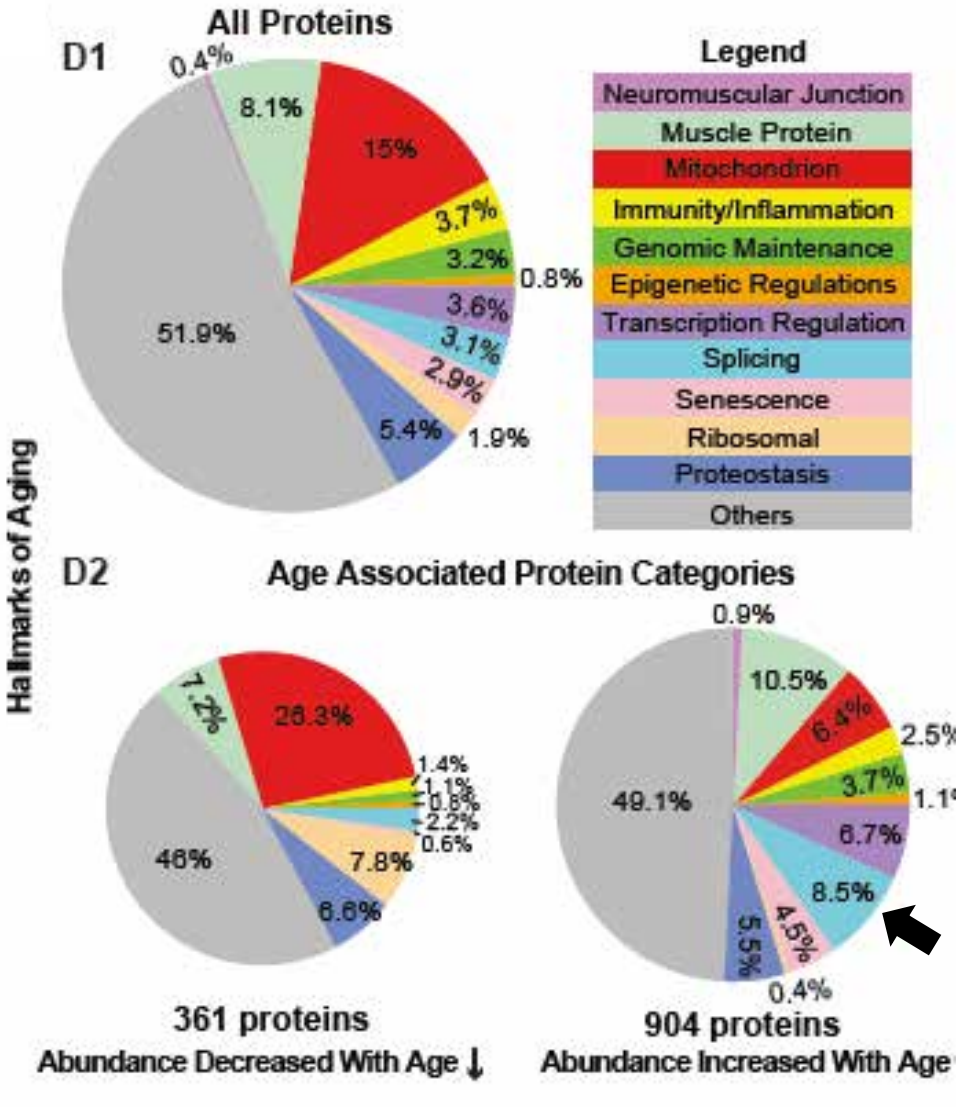
All models adjusted for sex, height, weight, and %PCr depletion; * P<.05; ** P<.01

Zane A et al. Aging Cell 2016



Classification of Age-associated Proteins In Skeletal Muscle

Proteins associated with Aging



Ubaida-Mohien C et al. eLife 2019

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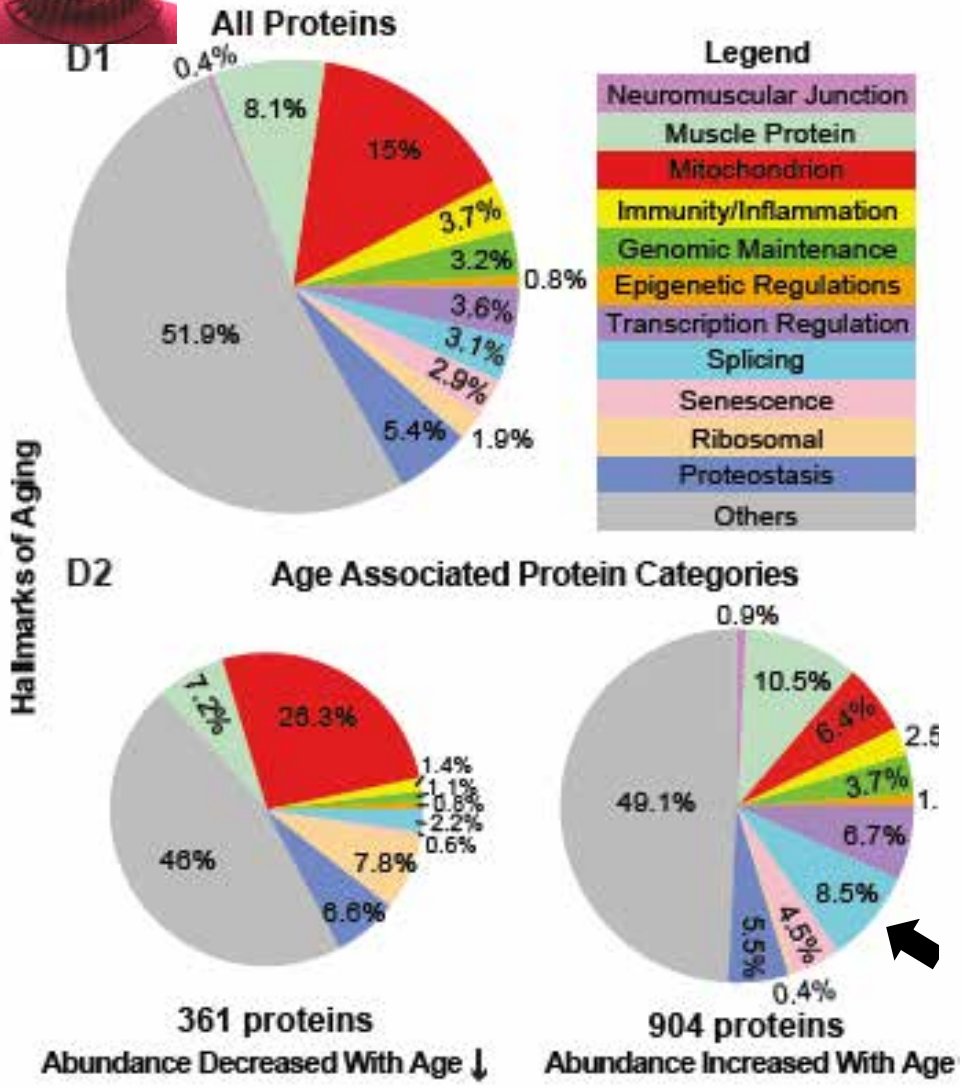
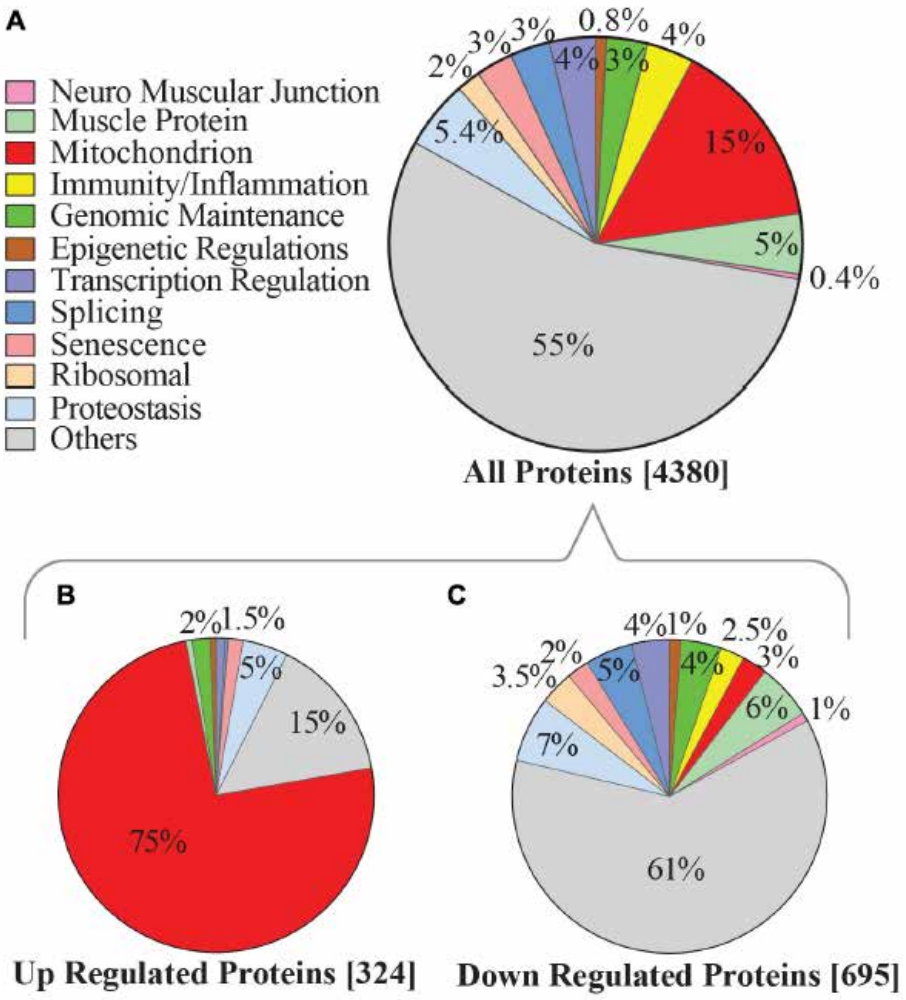


Proteins associated with Physical Activity



Ubaida-Mohien C et al. eLife 2019

Ubaida-Mohien C et al. Frontiers Physiol 2019

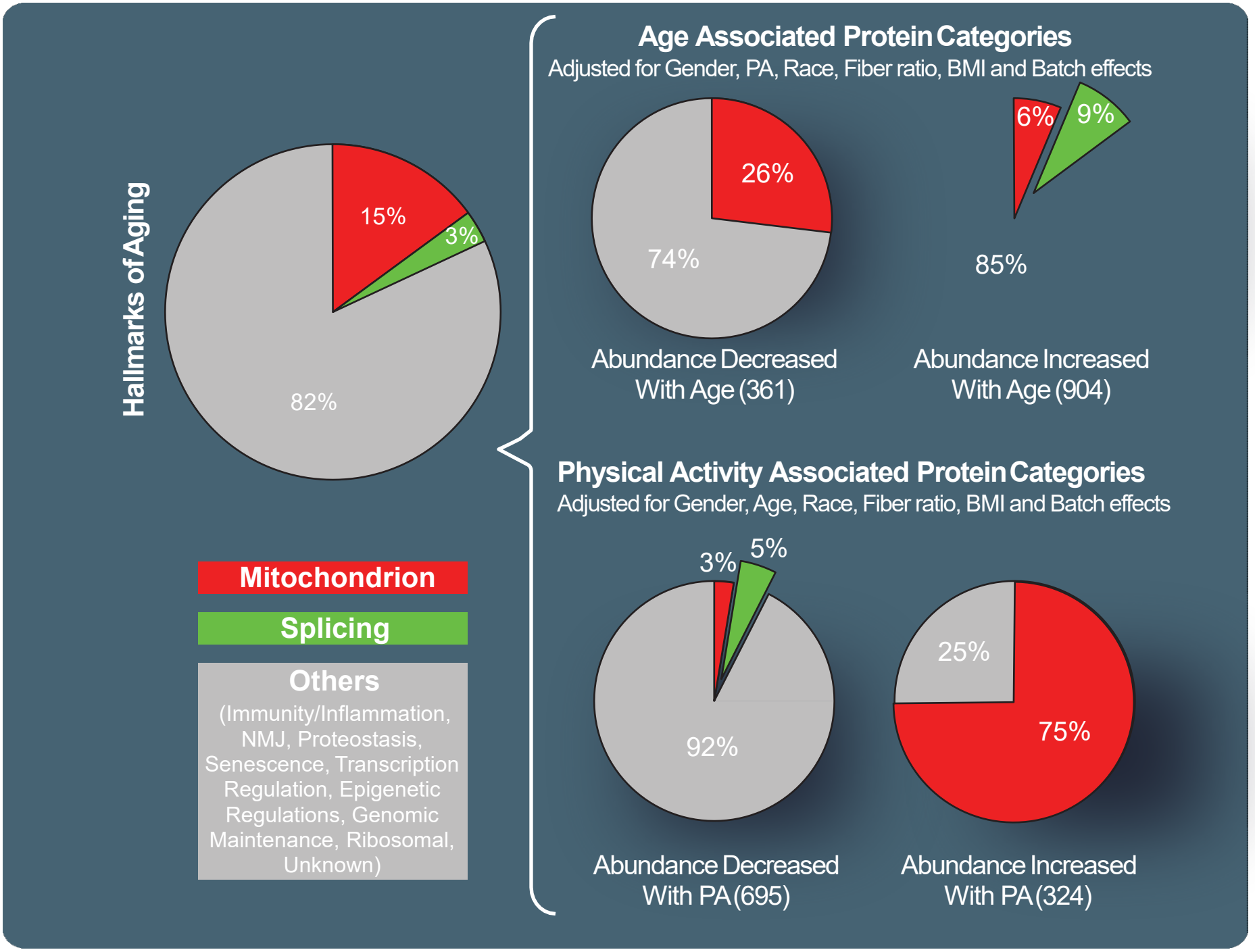

Hallmarks of Aging
15%
3%
82%
Mitochondrion
Splicing
Others
(Immunity/Inflammation, NMJ, Proteostasis, Senescence, Transcription Regulation, Epigenetic Regulations, Genomic Maintenance, Ribosomal, Unknown)
Age Associated Protein Categories
Adjusted for Gender, PA, Race, Fiber ratio, BMI and Batch effects
26%
74%
Abundance Decreased With Age (361)
6%
9%
85%
Abundance Increased With Age (904)
Physical Activity Associated Protein Categories
Adjusted for Gender, Age, Race, Fiber ratio, BMI and Batch effects
3%
5%
92%
Abundance Decreased With PA (695)
25%
75%
Abundance Increased With PA (324)

Figure 3 Functional Decline of Mitochondrial Proteins with Age

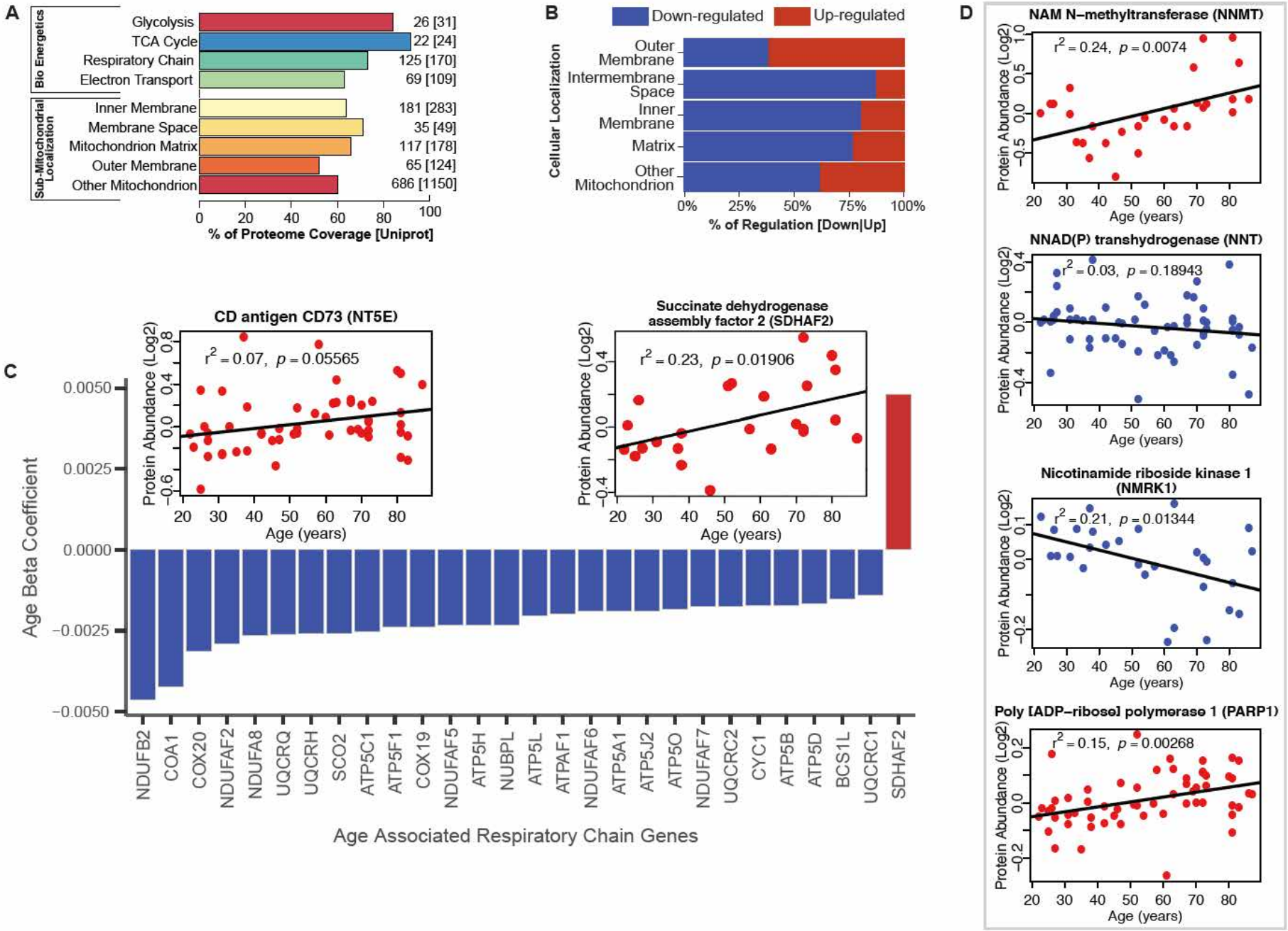
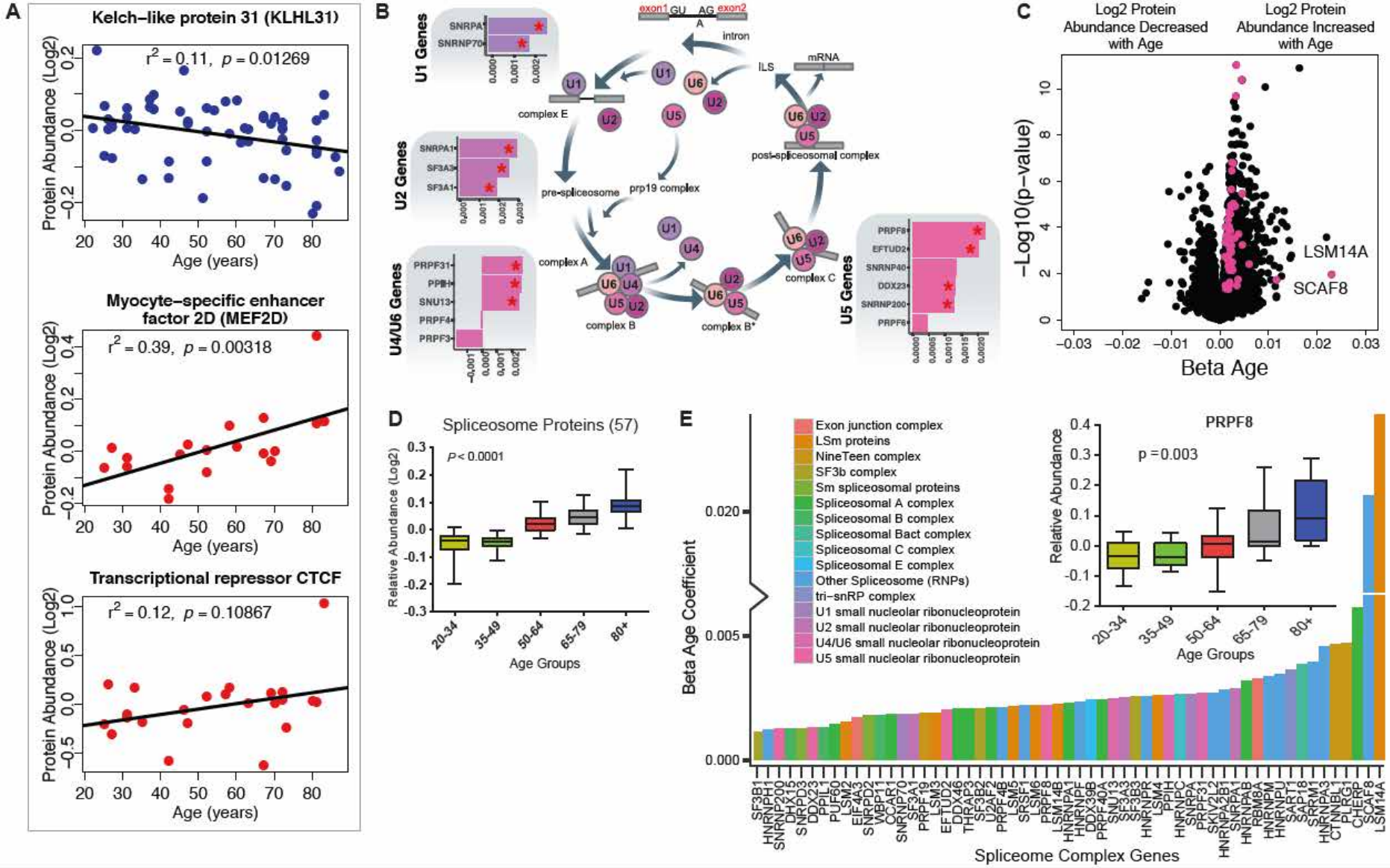
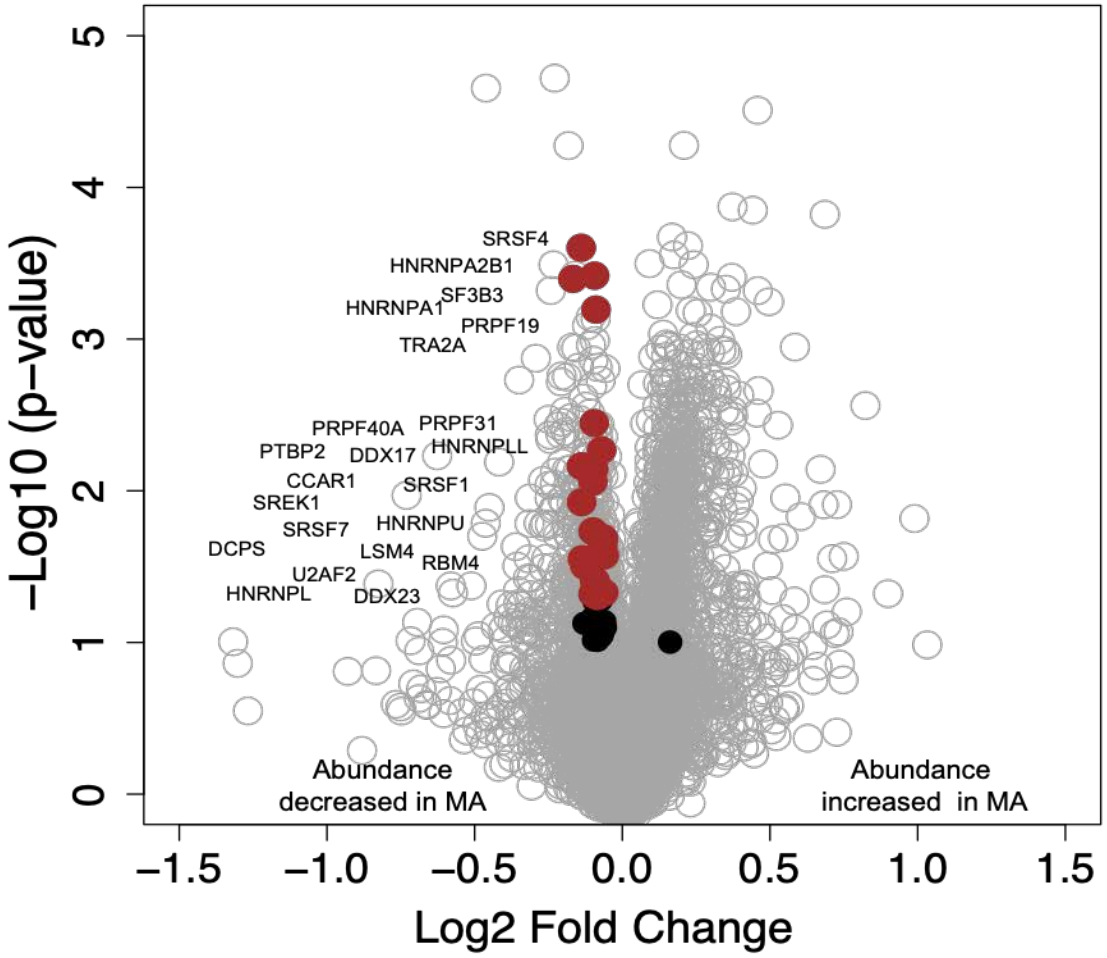


Figure 4 Implications of Proteins that Modulate Transcription and Splicing



Relative Abundance of Spliceosome Proteins in Master Athletes Compared to Age-Matched Controls

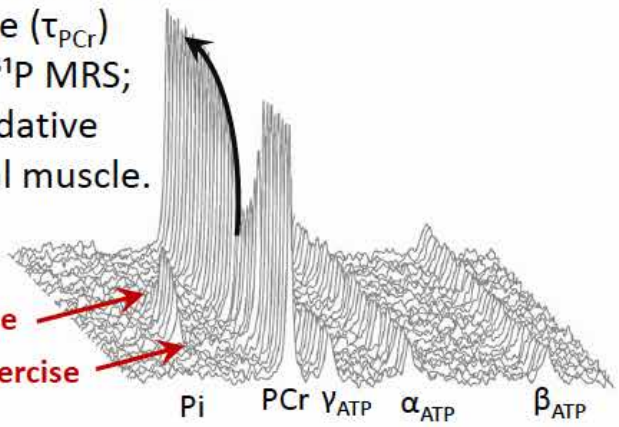
Collaboration with Russel Hepple, PhD (University of Florida)



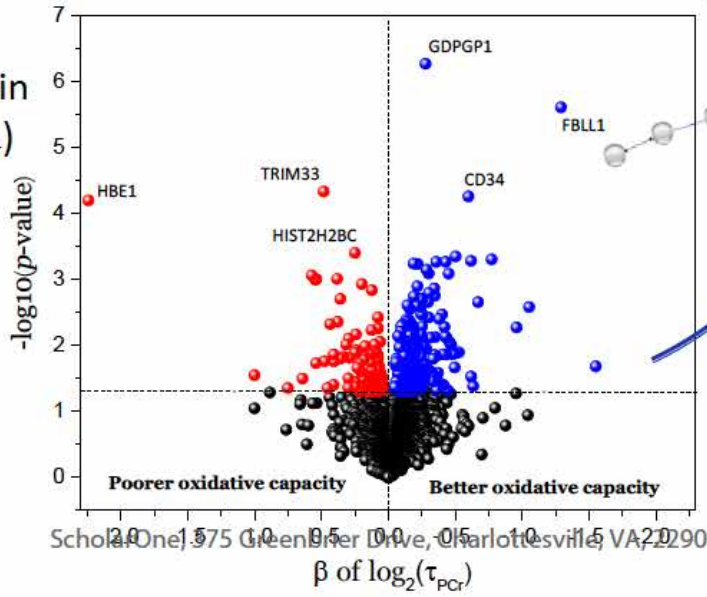
Discovery proteomics on muscle biopsies quantified using TMT and LC-MS methods. Overall, 132 spliceosome pathway proteins were quantified. Of these, 122 were underrepresented in master athletes compared to controls, and for 22 of them the difference was significant.

Adjusting for Age and Physical Activity, Up-Regulation of the Splicing Machinery is Associated with Better Mitochondrial Function

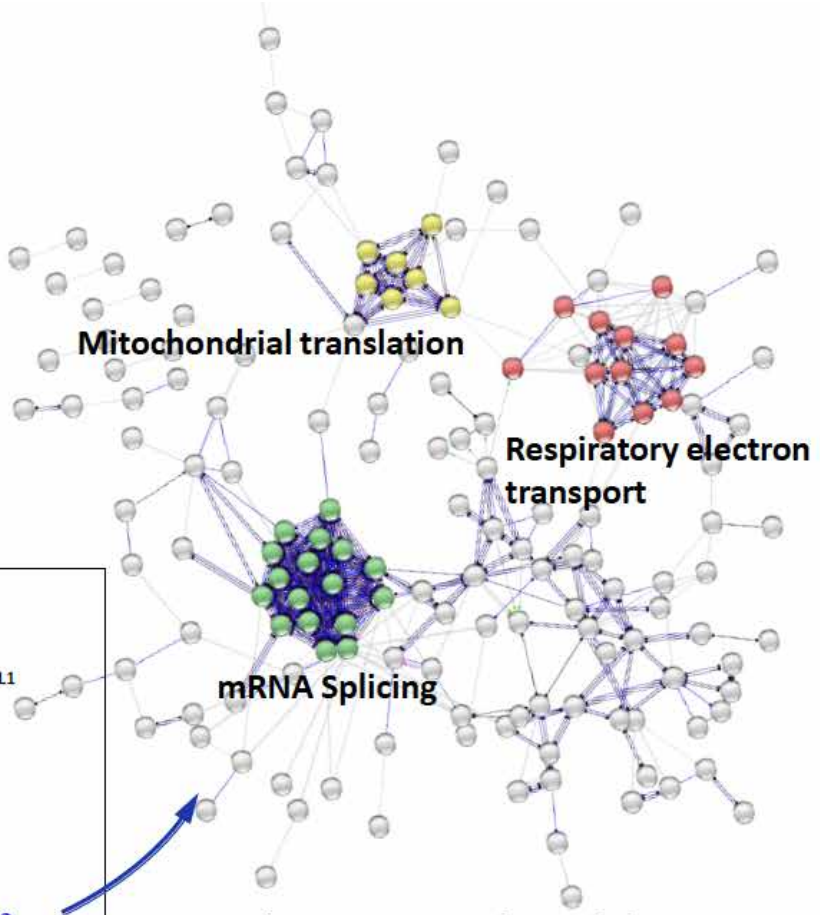
Post-exercise phosphocreatine (PCr) recovery time (τ_{PCr}) measurement by ^{31}P MRS; reflects *in vivo* oxidative capacity of skeletal muscle.



Skeletal muscle protein association with (τ_{PCr})



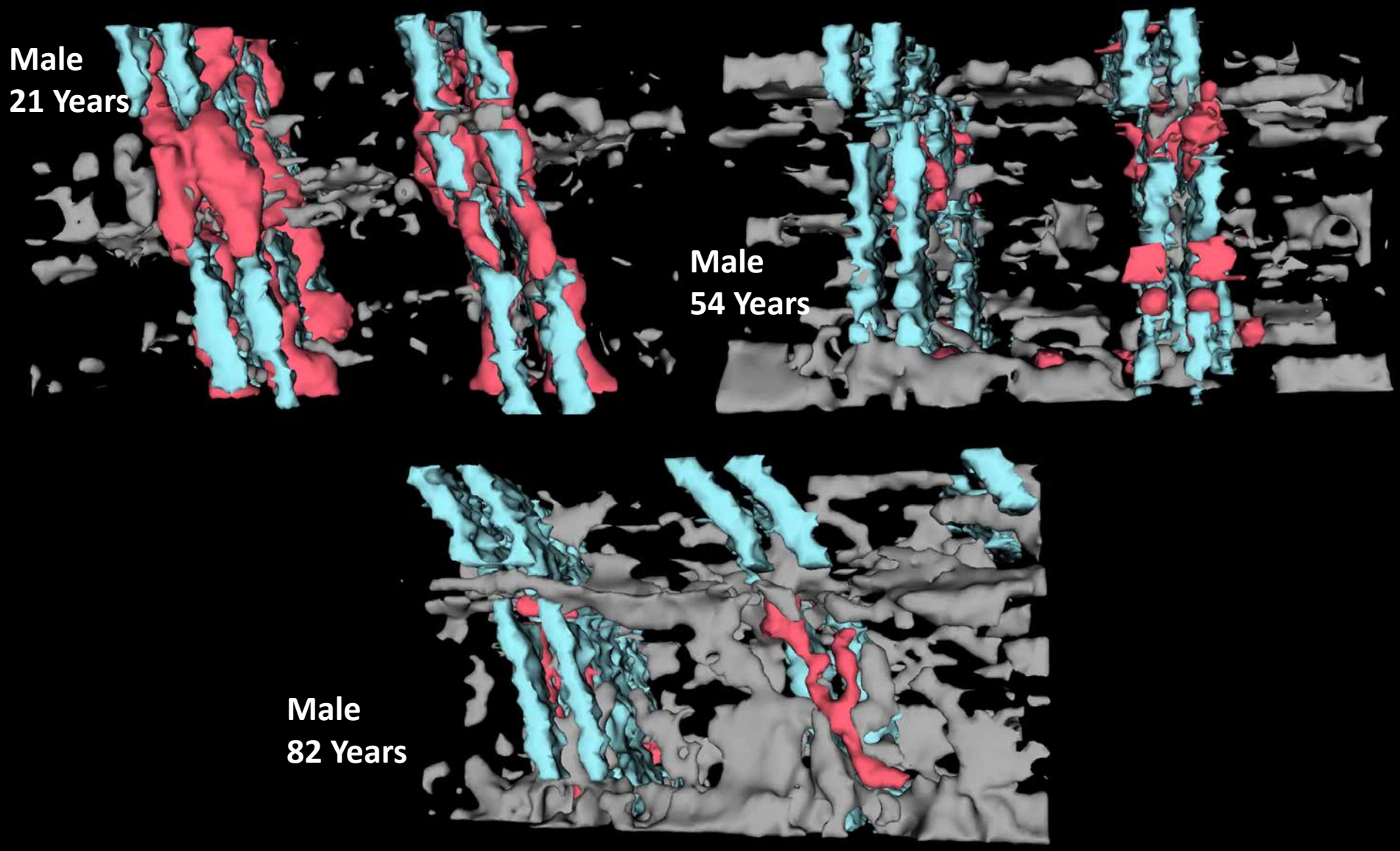
Fatemeh Adelnia



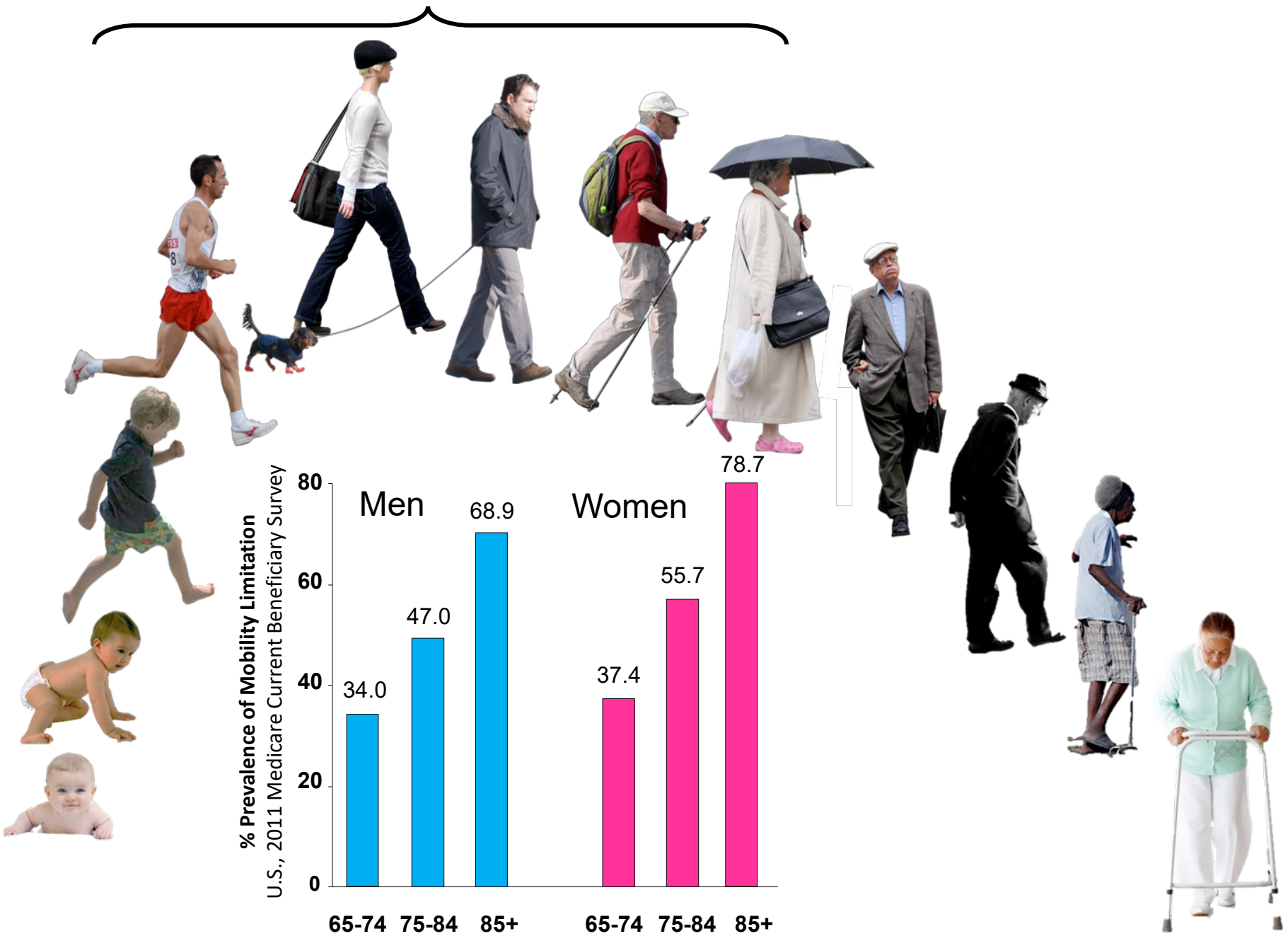
Network representation of the 253 proteins associated with better muscle oxidative capacity

Adelnia F. et al. Submitted to Aging Cell

3D Reconstructions of FIB-SEM images in 3 different age groups. Mitochondria are pink, Z-bands are cyan, and voided areas are gray.

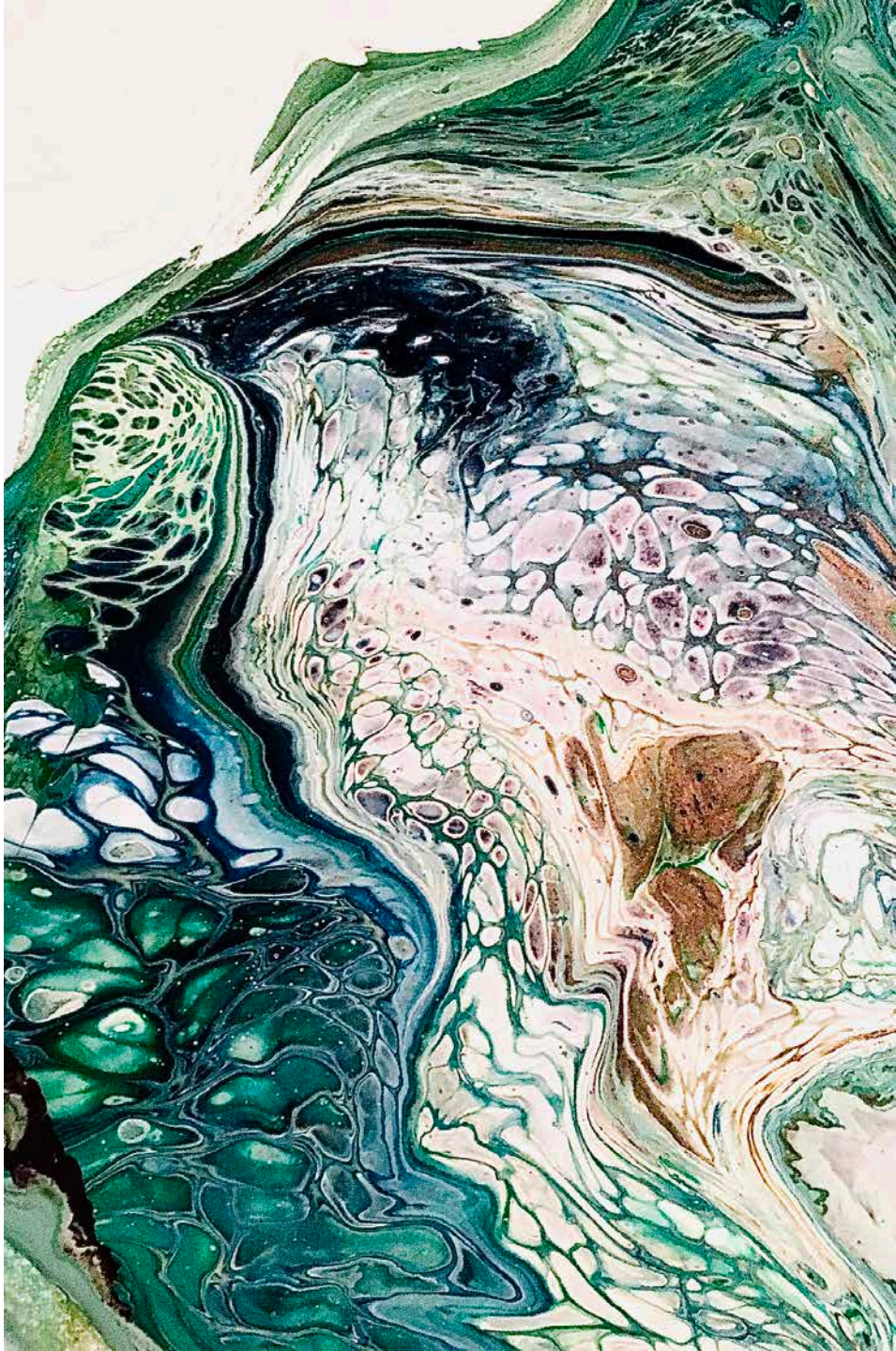


Geroscience anticipates secondary prevention



DNA Methylation Landscapes in Aging & Disease

Morgan Levine
Assistant Professor
Department of Pathology
Yale University School of Medicine



Cancer Risk

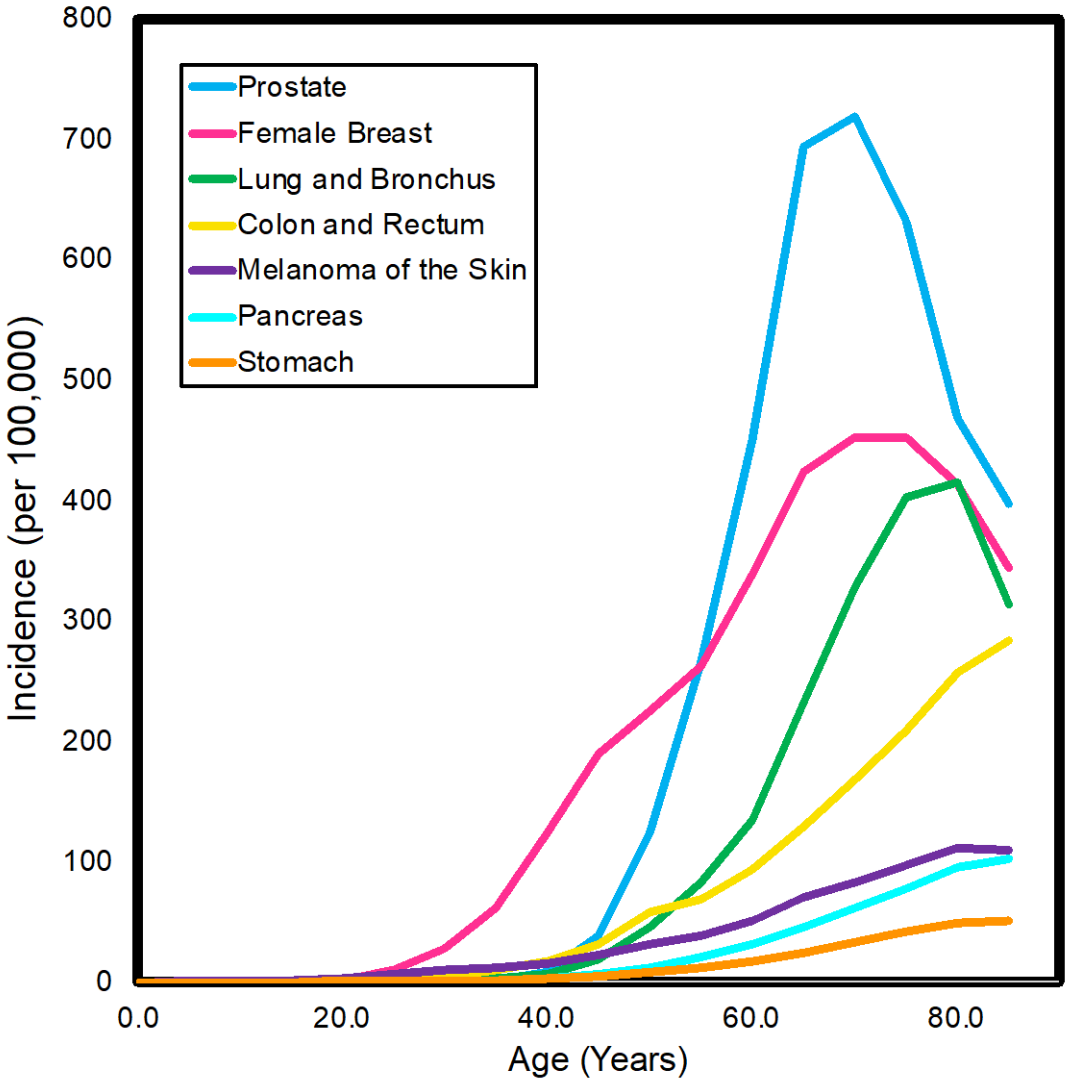
What is the biggest risk factor for lung cancer?

Smoking increases lung cancer incidence and death by 15 to 30 fold

1 in 200k chance for ages 25-29, nearly 400 in 100k chance ages 75-79

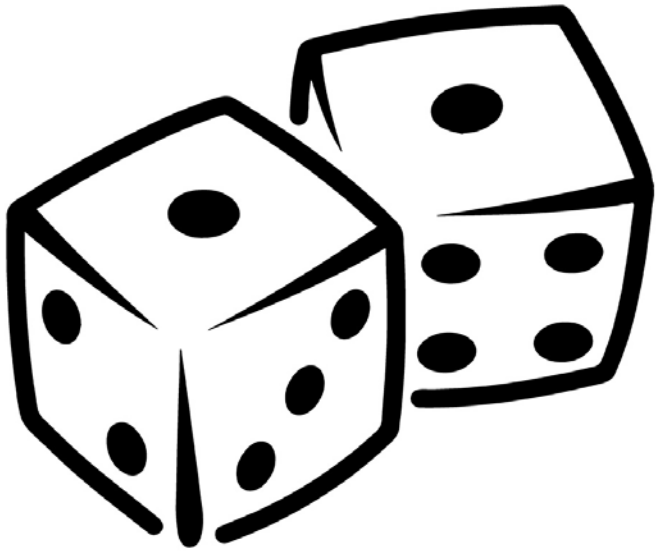
Geroscience

The aging process is thought to play a causal role in the etiology of most major chronic diseases.



Cancer Risk & Age

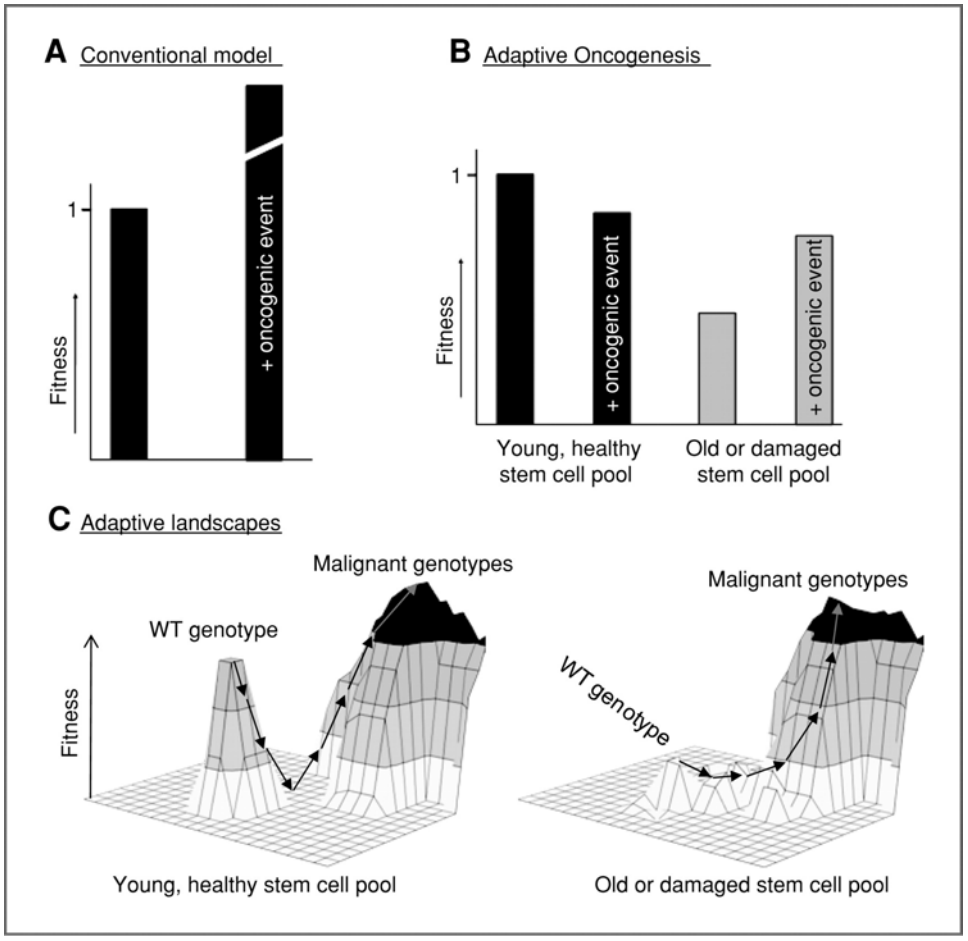
Is aging causal or consequential in cancer?



The more times you roll the dice (function of chronological time) the more likely your chances?

Cancer Risk & Age

Is aging causal or consequential in cancer?



Adaptive Oncogenesis Model

Dr. James DeGregori

Roughly half of all mutations occur before full body maturation

Context matters!

system-level dynamics that change with age alter the fitness landscape

Biomarkers of Aging

Useful proxies that estimate aging (or agedness) of a sample.

Should Answer:

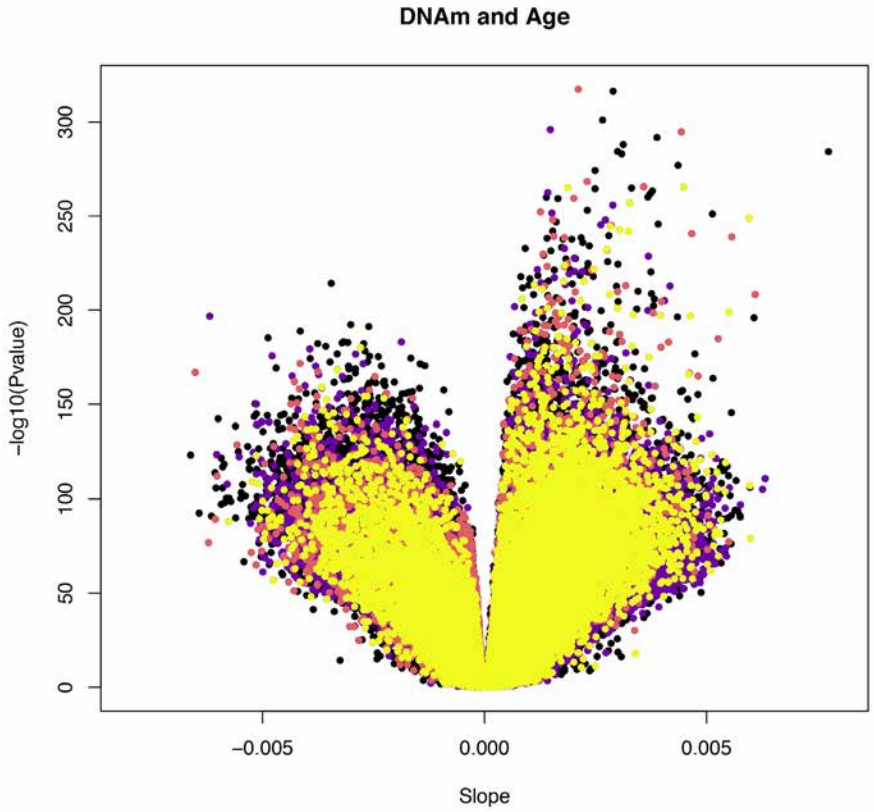
Biologically, what differentiates the average 20 year old from the average 80 year old?

What differentiates a healthy 80 years old from an unhealthy 80 year old?

Epigenetics: Molecular OS

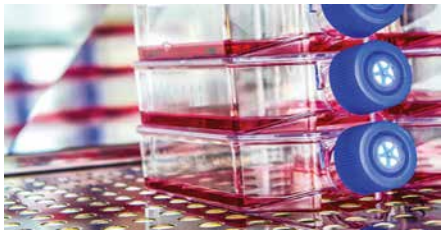
DNA Methylation (DNAm)

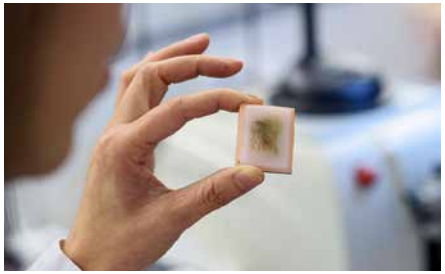
Involved in cell proliferation/differentiation, transcriptional repression, genomic imprinting, organization of chromatin.

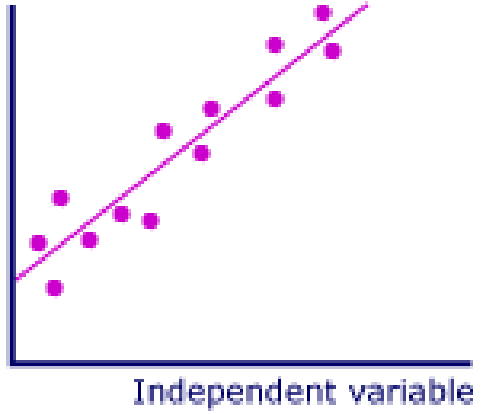


Epigenetic Clocks

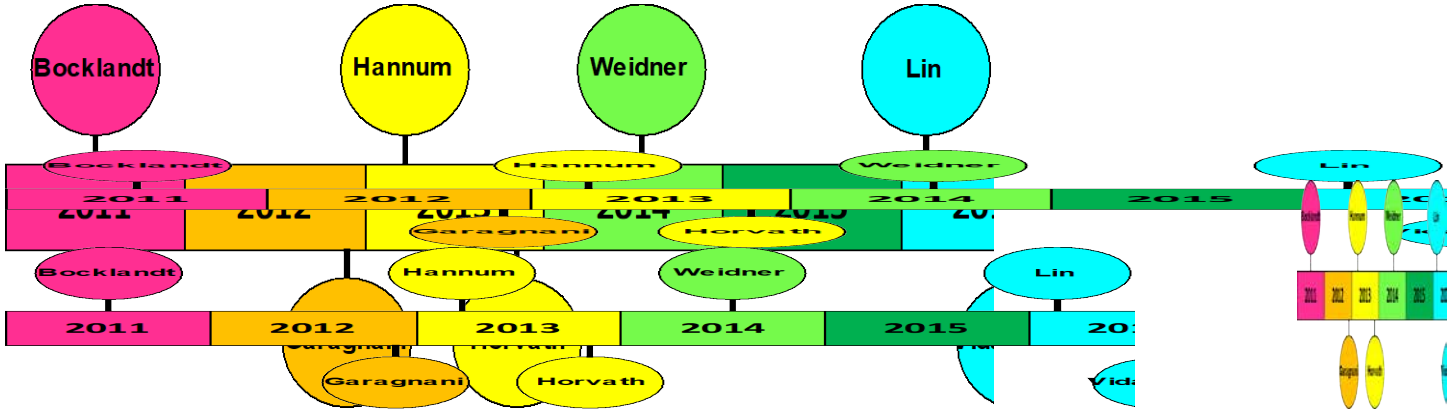
**Because of the precise age changes,
we can use machine learning to predict "the age"
of a sample based on its DNAm levels.**

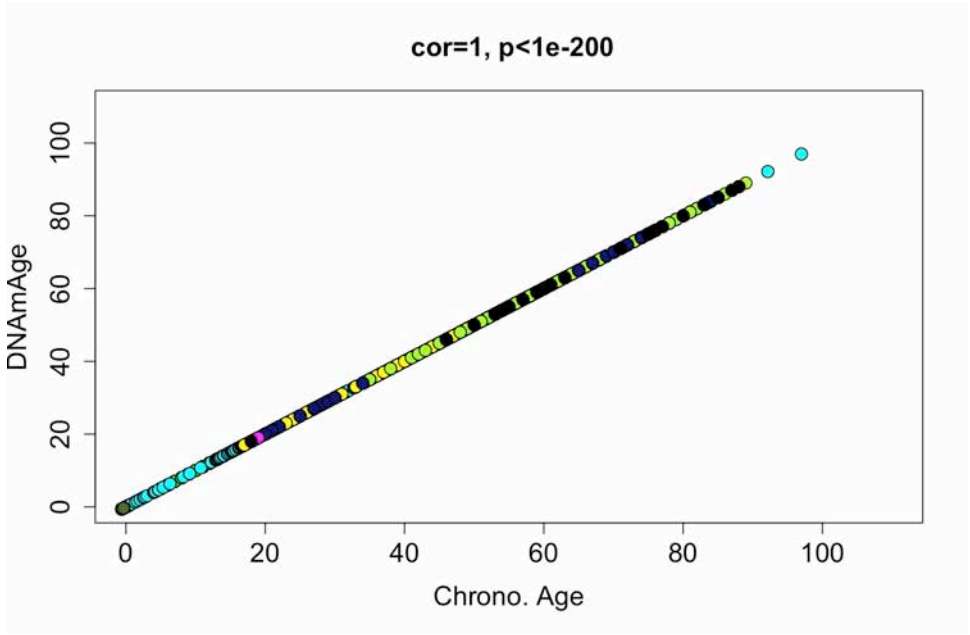






Epigenetic Clocks

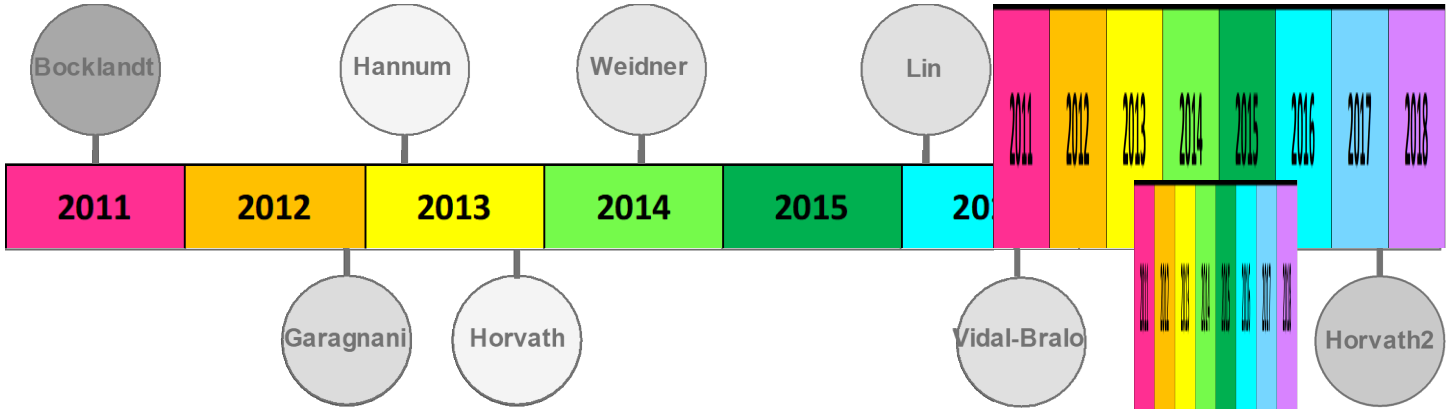


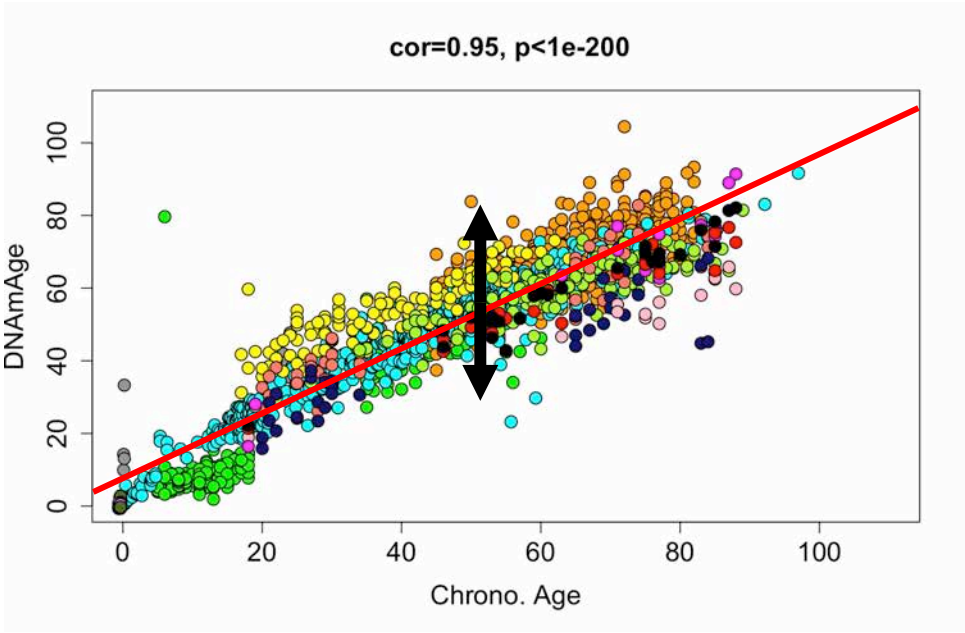


1st Generation:
Age Predictors

Supervised machine learning to predict age from hundreds of CpGs

Epigenetic Clocks

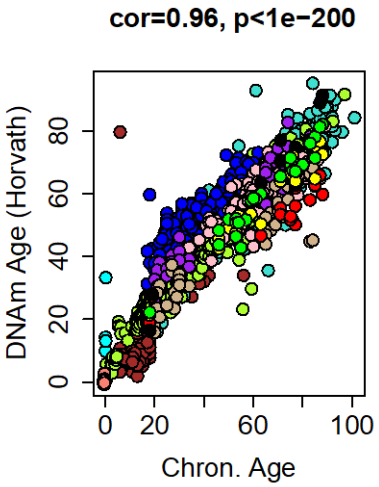


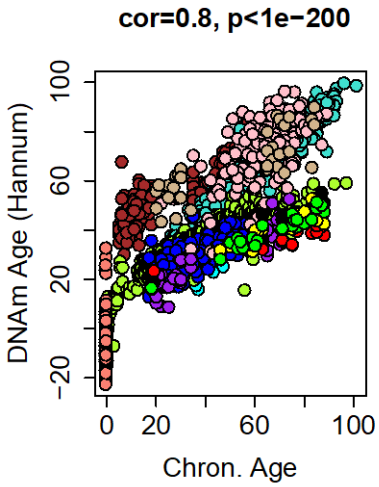


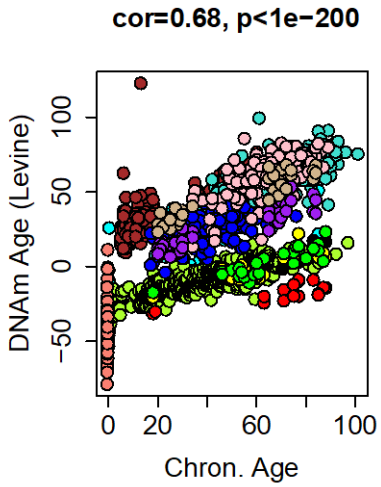
2nd Generation:
Aging Outcome Predictors

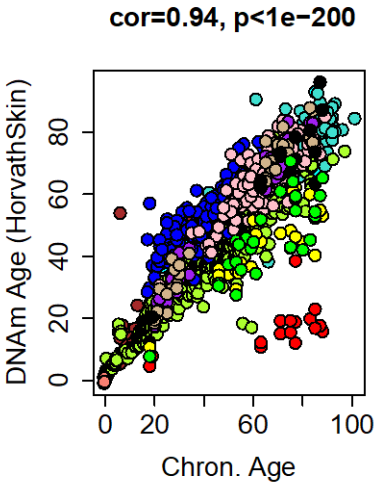
Supervised machine learning to predict age-related outcomes from hundreds of CpGs

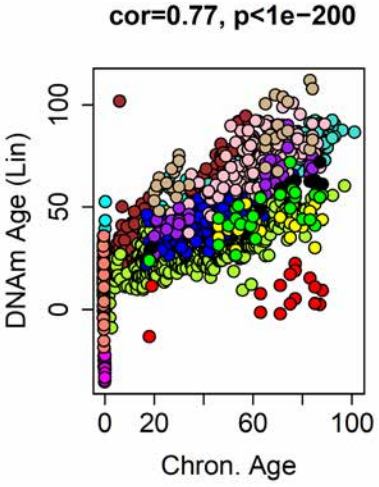
Epigenetic Clocks

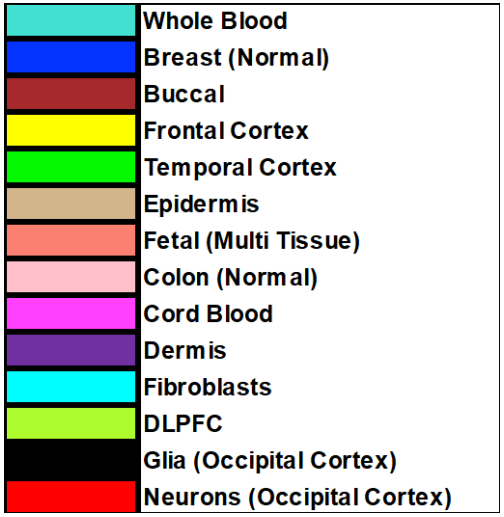








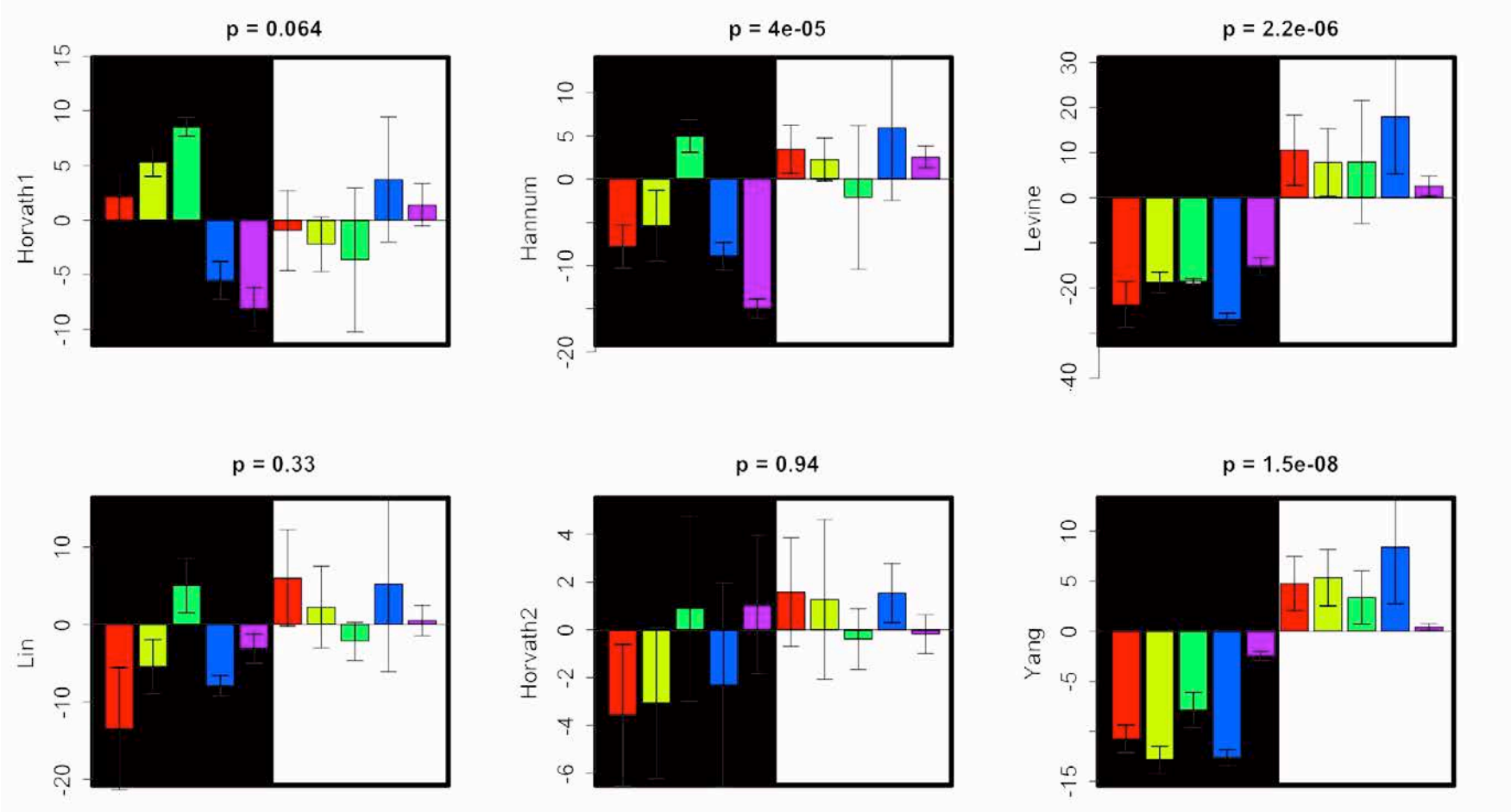




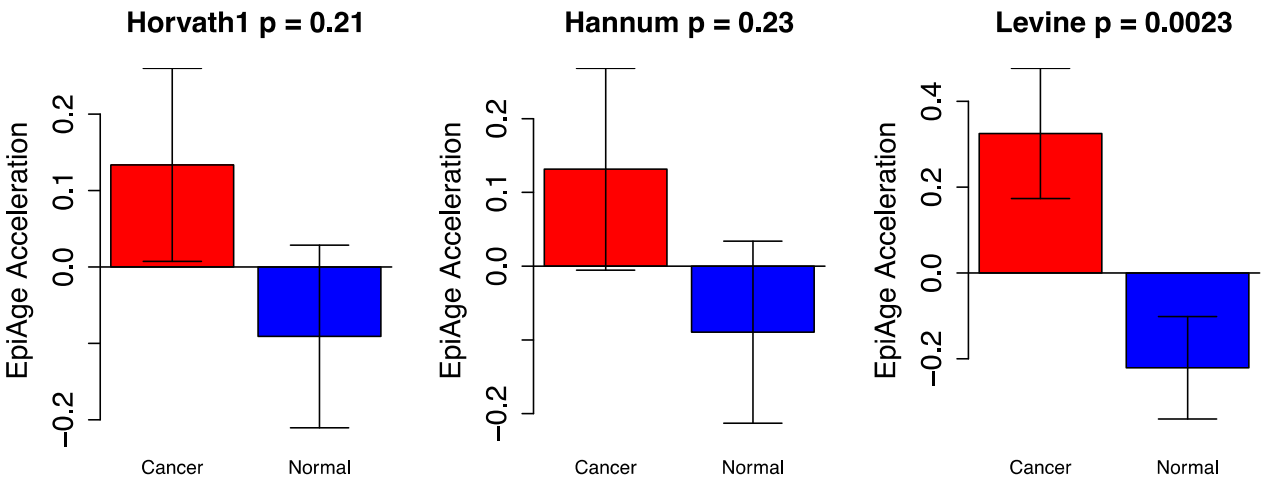
Epigenetic Clocks

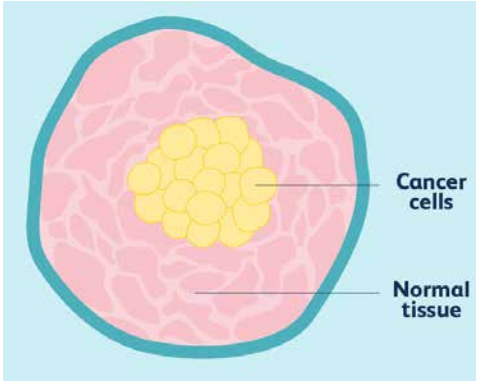
Normal Tumor

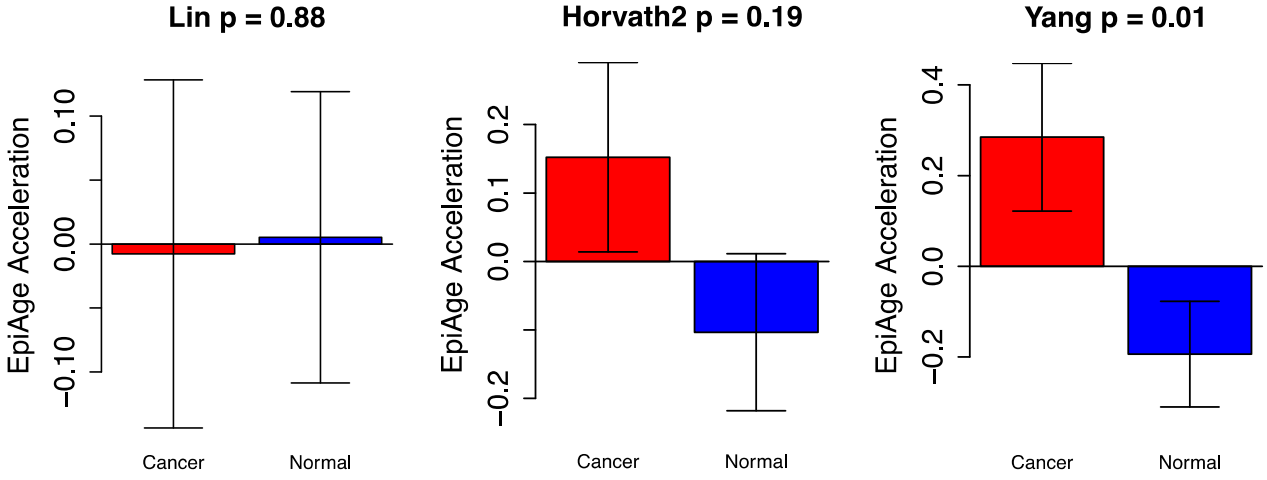
breast, colon, lung, pancreas, thyroid



Epigenetic Clocks







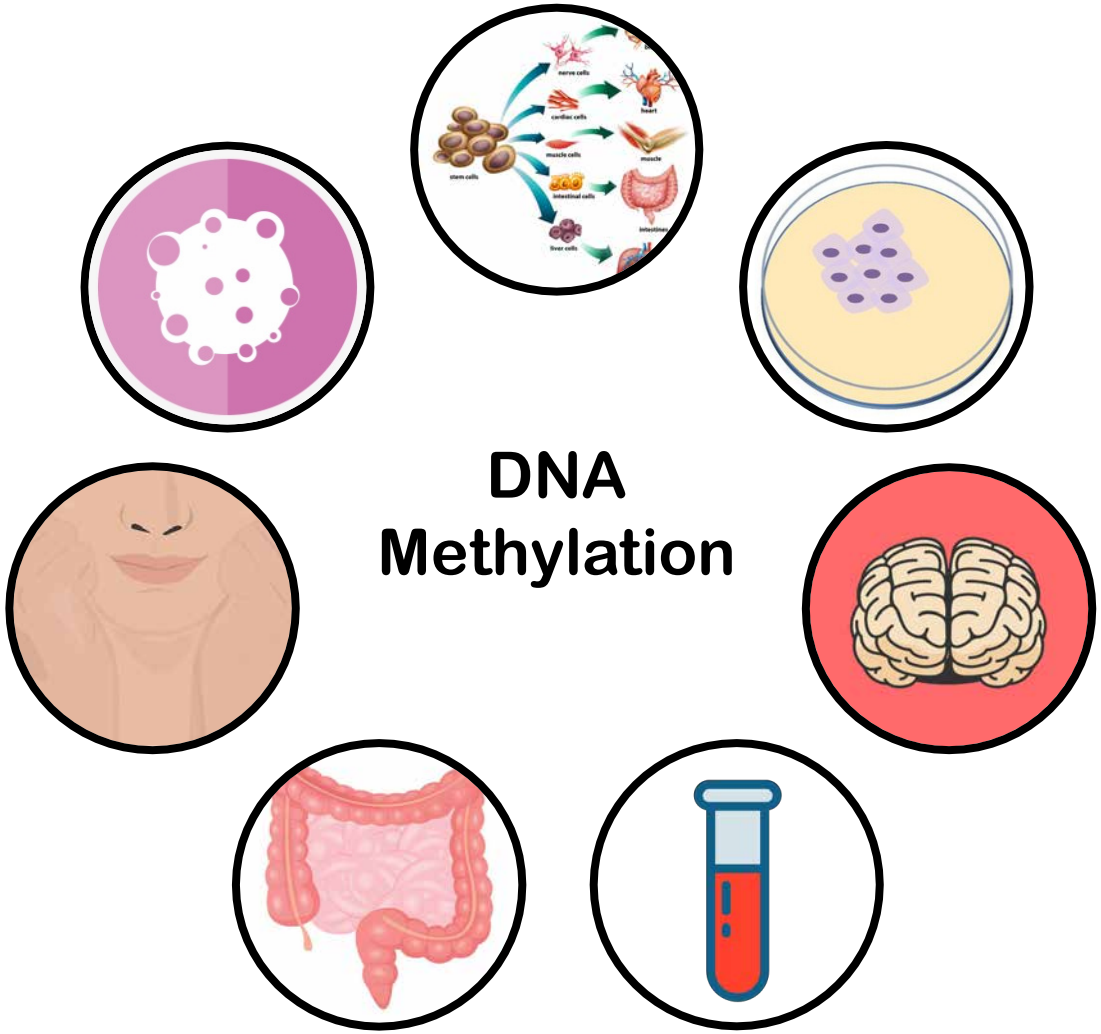
Epigenetic Clocks

DNAm can capture a lot of cellular/molecular changes.

What are the core signals (parts) being captured by the clocks?

Are there shared signals across aging phenomena and/or tissues?

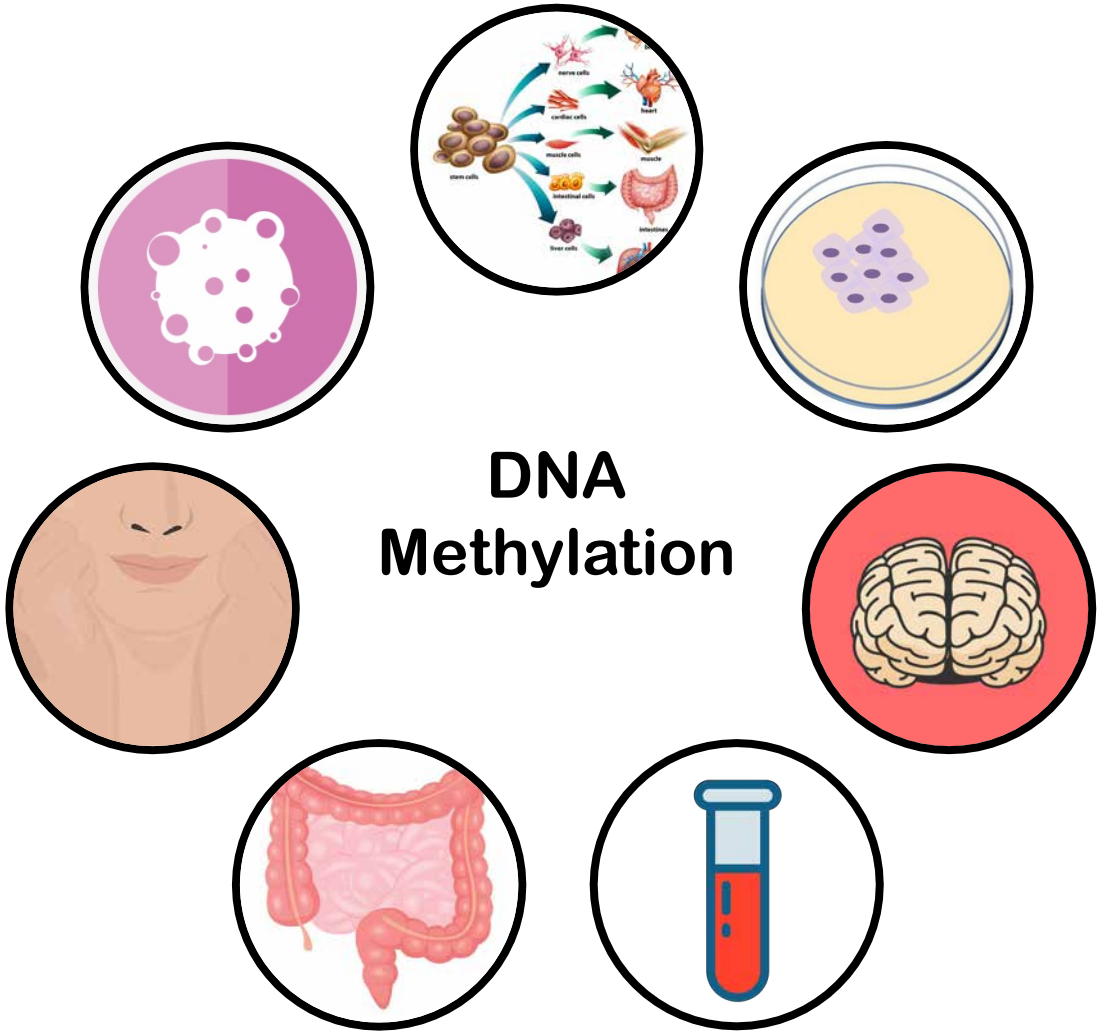
Shared DNAm Signals



PCA in 9 Datasets

Whole blood
Adult Brain
Developmental Brain
Dermis
Epidermis
Senescence
iPSC/Reprogramming
Tumor/Normal

Shared DNAm Signals

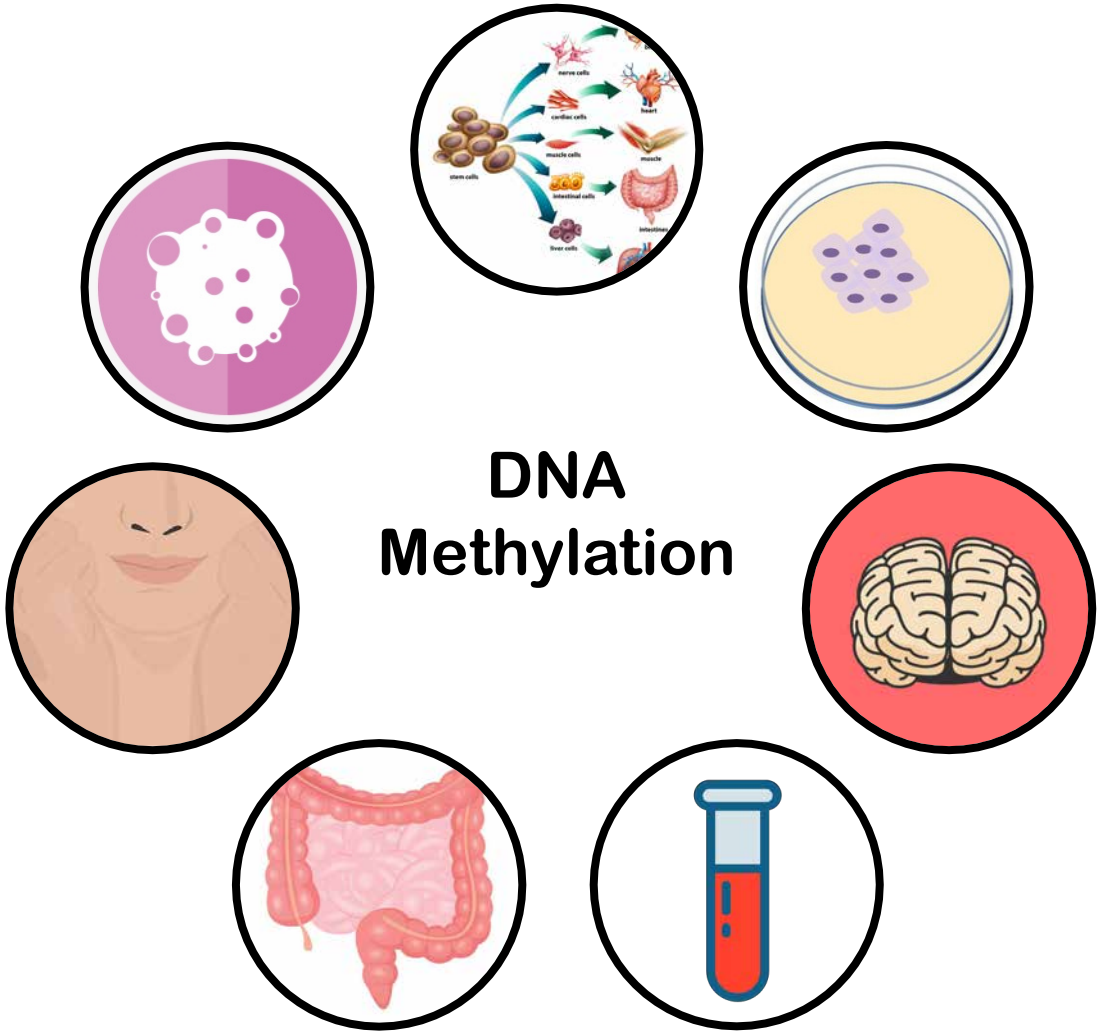


PCA in 9 Datasets

Whole blood
Adult Brain
Developmental Brain
Dermis
Epidermis
Senescence
iPSC/Reprogramming
Tumor/Normal

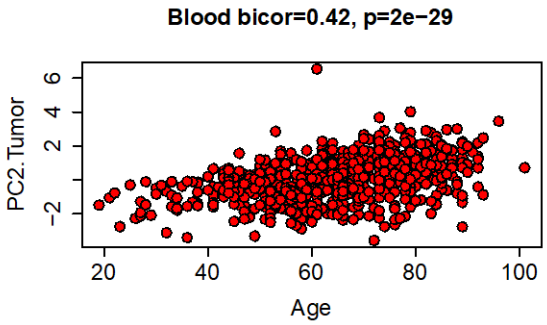
Estimate top 10 PCs in all datasets (n=90 variables in each dataset)

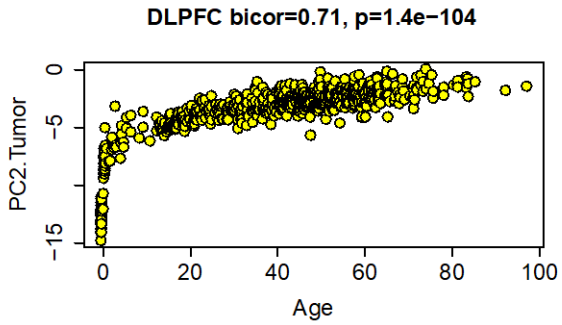
Shared DNAm Signals

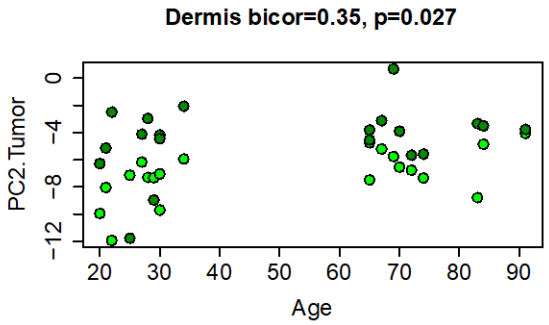


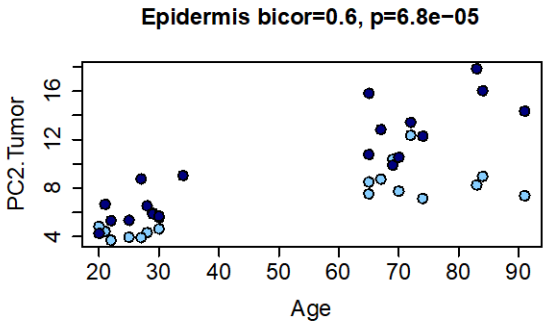
10 of the 90 PCs had consistent age and/or aging-outcome associations across all 9 datasets

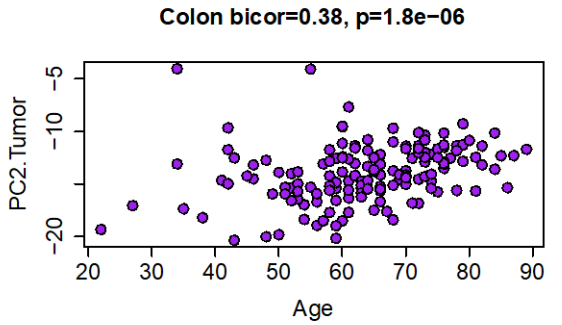
Shared DNAm Signals

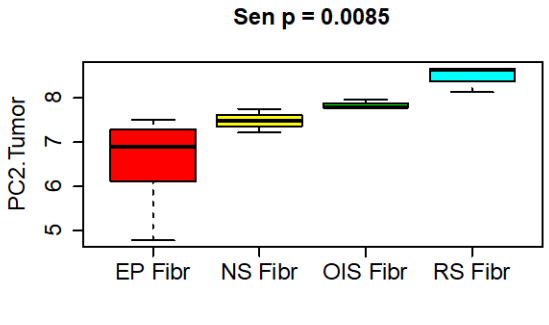


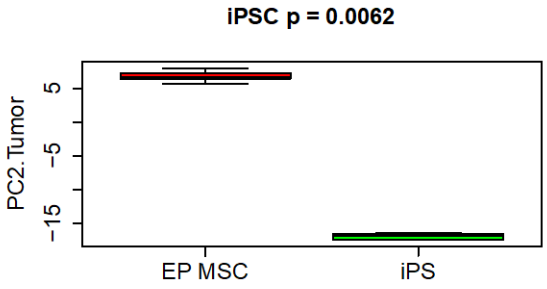


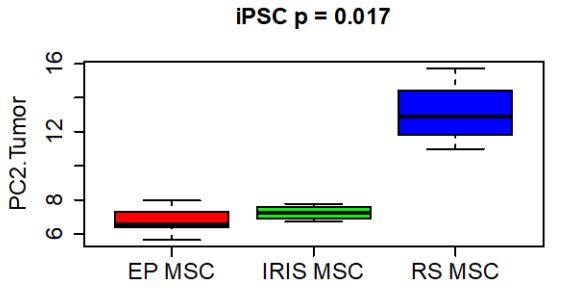


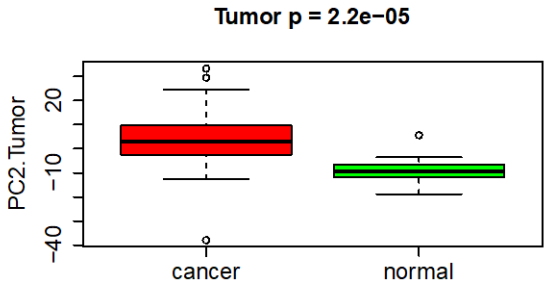




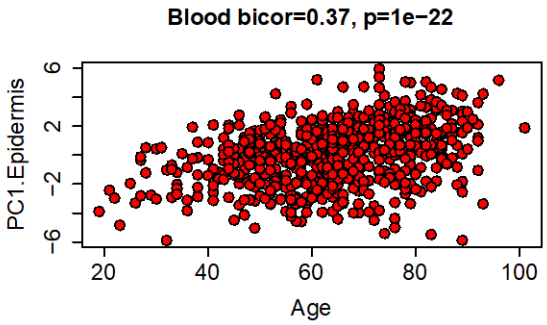


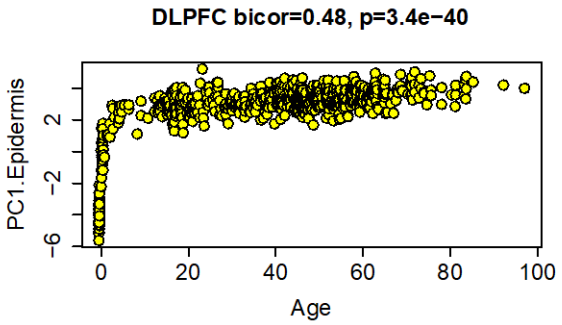


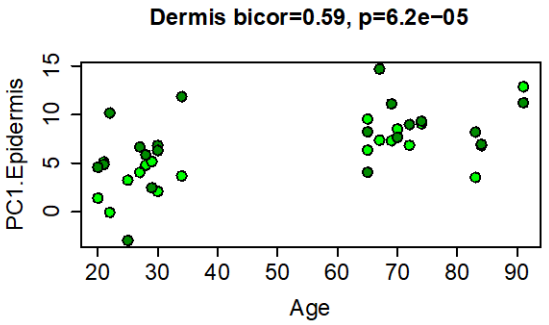


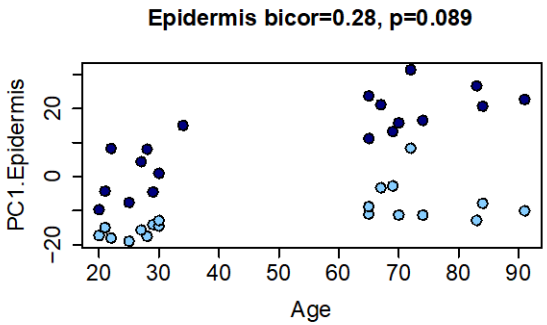


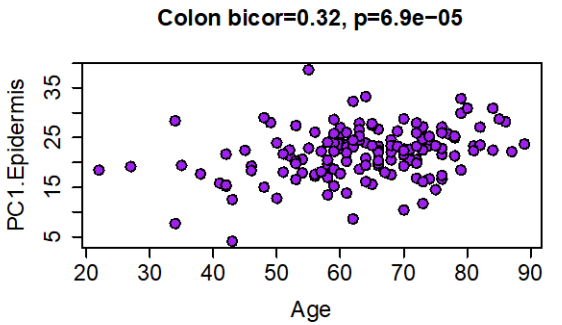
Shared DNAm Signals

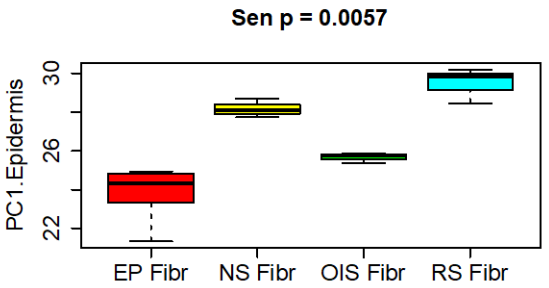


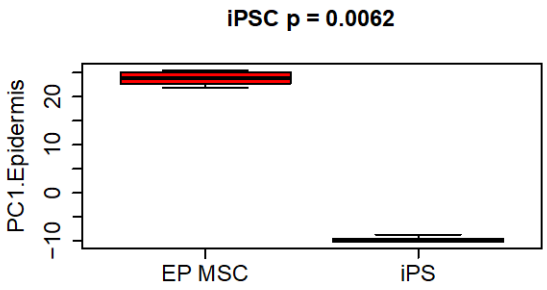


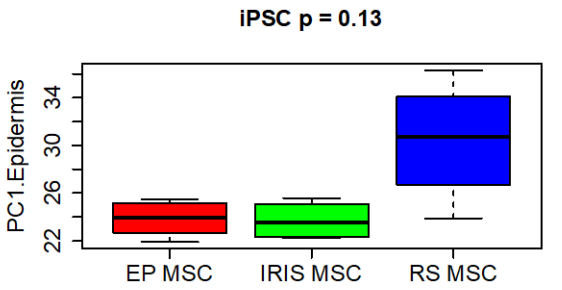


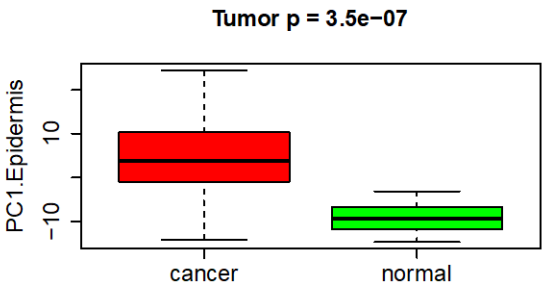












Conclusions

Does biological aging in a tissue predispose it to tumorigenesis?

- Aging/Cancer: probability with time vs. causal driver

Preliminary Evidence for Aging → Cancer

1. One can estimate "aging" in various tissues using DNAm.
2. For most clocks, tissues show different rates of aging.
3. DNAmAge can differentiate tumor versus normal tissue (acceleration in cancer).
4. DNAmAge can differentiate normal breast tissue in women with history of breast cancer versus controls.
5. DNAm patterns in cancer apply to other tissues.
    1. Correlate with age in blood, brain, skin, colon
    2. Accelerated in skin exposed to sun
    3. Accelerated in senescent cells (oncogene induced and replicative)

Acknowledgements

A L
I S

Laboratory for
AGING IN LIVING SYSTEMS

Current Members
Kyra Thrush (PhD Student Computational Biology)
Albert Higgens-Chen (Post Doc)
John Gonzalez (PhD Student in Molecular Medicine)
Margarita Meer (Assistant Research Scientist)
Diana Leung (PhD Student Computational Biology)
Chris Minteer (PhD Student in Molecular Medicine)

Former Members
Zuyun Liu (Former Post Doc)

NIH National Institut on Aging

Human Immunology Project Consortium

ELYSIUM

GLENN FOUNDATION FOR MEDICAL RESEARCH

Yale Claude D. Pepper Older Americans Independence Center

Q&A

Save the date for the next webinar:

- September 14, 1-2 p.m. ET
  - Speakers: Dr. Hyman Muss and Dr. Grant Williams

- Send speaker suggestions and other feedback to:
  NCIDCCPSagingwebinar@mail.nih.gov

www.cancer.gov www.cancer.gov/espanol