## RESEARCH ON TAP The Biology of Aging

Wednesday, March 26 | 4-6 pm

#### bu.edu/research/events



## Agenda

#### **Opening Remarks**

#### **Presentations**

Funding Opportunities & Closing Remarks Ana Fiszbein Brianne Connizzo Thomas Perls

Tom Perls Stacy Andersen George Murphy Stefano Monti Brianne Connizzo Samuel Beck LaDora V. Thompson Ana Fiszbein Jeroen Eyckmans Daniel Dempsey Slava Labunskyy Vladimir Botchkarev Hadi T. Nia Tristan Barako

#### **Foundation Relations** Tristan Barako Katharine Canfield



### A Natural Model of Exceptional Health Span and Longevity

## Thomas Perls MD, MPH

Professor

Department of Medicine, Chobanian and Avedisian and School of Medicine

BOSTON UNIVERSITY

## **The New England Centenarian Study**

## Our NIH-NIA Funded Projects



Stefano Monti (CAM)



Longevity

Centenarian Project





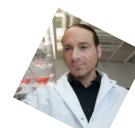






Daniel Segrè (CRC)

Rhoda Au (CAM)



George Murphy (CREM)



#### **Key Underlying Premise**



- People age differently from one another but at ages beyond 100, at older and older ages, they are more and more alike.
- About 90% of centenarians are disability-free up through their early nineties. "the older you get, the healthier you've been"!
- ▶ 15% are "Escapers". At age100, escaped aging-related diseases
- Supercentenarians: 70% "escapers" at 100 and live independently until 106 years old!

#### Nature v. Nurture?

- ► To live to age 90, 75% of how we age is due to our health behaviors. To live to age 106+ years, 75% due to about 200 protective genes
- ▶ They are so alike, so need sample size of 500-1000
- ▶ They have protective genes. They don't lack disease genes







## **Data and Biological Samples We Collect**

#### Data

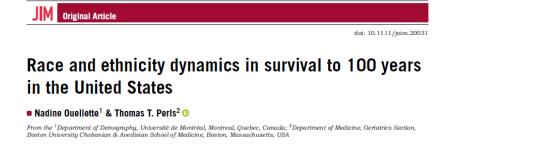
- Careful and detailed cognitive function
- 1 week's worth of physical and sleep function data
- Family pedigree data
- Medical and dental history
- Dietary habits and intake
- Brain MRIs



- Blood
- Fecal samples
- Blood for creating induced pluripotent stem cells (iPSCs)
- Brain donation









#### A longevity-specific bank of induced pluripotent stem cells from centenarians and their offspring

Todd W. Dowrey, Smuel F. Cranston, Nicholas Skvir, Yvonne Lok, Brian Gould, Bradley Petrowitz, Daniel Villar, Jidong Shan, Marianne James, Mark Dodge, Anna C. Belkina, Richard M. Giadone, Sofiya Milman, Paola Sebastiani, Thomas T. Perls, Stacy L. Andersen, George J. Murphy

Article

## **Cell Reports**

Metabolite signatures of chronological age, aging, survival, and longevity

Volume 43, Issue 11 November 26, 2024



## **Current Directions**

- Enhance diversity (different paths to 100+ years)
- Generate longitudinal omics (e.g. genetics, metabolites, microbiome, proteomics etc) data from our centenarian and offspring participants
- Enroll and study cognitive superagers (people with the cognitive function norms of people 30 years younger)
- Dr. Andersen:
  - Preclinical markers of cognitive decline v. resilience
  - Markers of rate of cognitive aging
- Dr. Murphy
  - iPSCs, differentiated lines and functional studies
  - Clocks
- Dr. Monti
  - Network Models, Pathways, Candidate Interventions



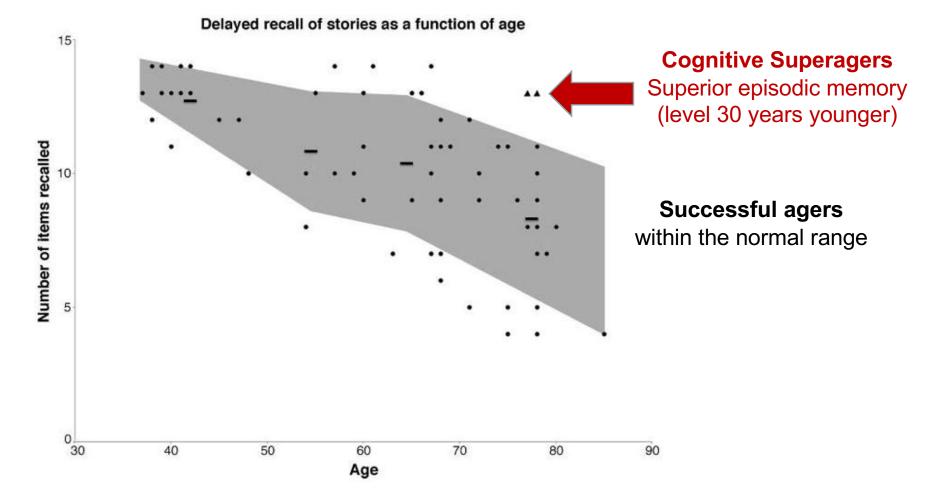
Insights into Alzheimer's Disease from Longevity Studies

## Stacy Andersen, PhD

Assistant Professor Dept of Medicine, Chobanian & Avedisian School of Medicine

> BOSTON UNIVERSITY

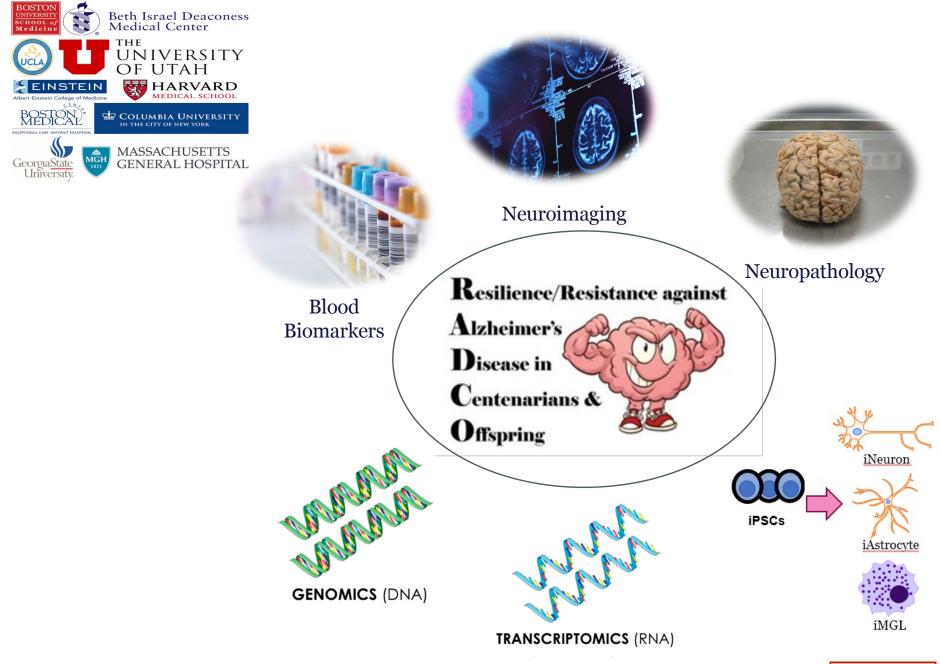
## Cognitive Superagers Youthful episodic memory function



Boston University Office of Research

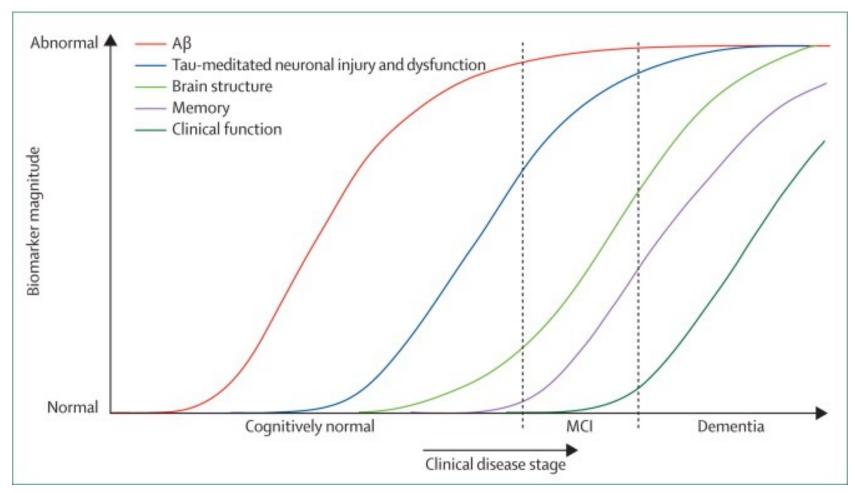
Rogalski et al. J Cogn Neurosci, 2013; 25(1):29-36.







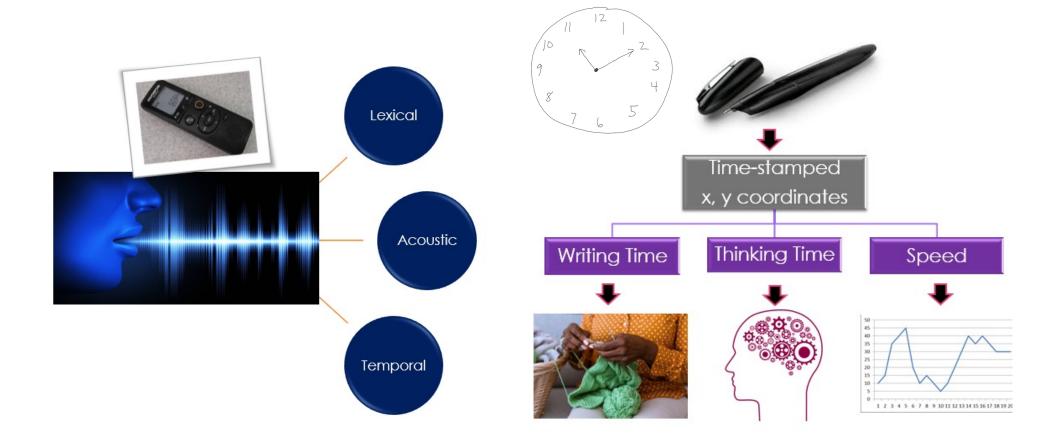
### **Early detection of Alzheimer's Disease**



Jack et al., 2010. Lancet Neurology



## **Preclinical detection of cognitive impairment** The power of digital technologies





## Uncovering the Molecular Mechanisms of Exceptional Longevity through iPSC-based Modeling of Resiliency

## George J. Murphy Associate Professor of Medicine Co-Founder Center for Regenerative Medicine (CReM) Chobanian & Avedisian School of Medicine

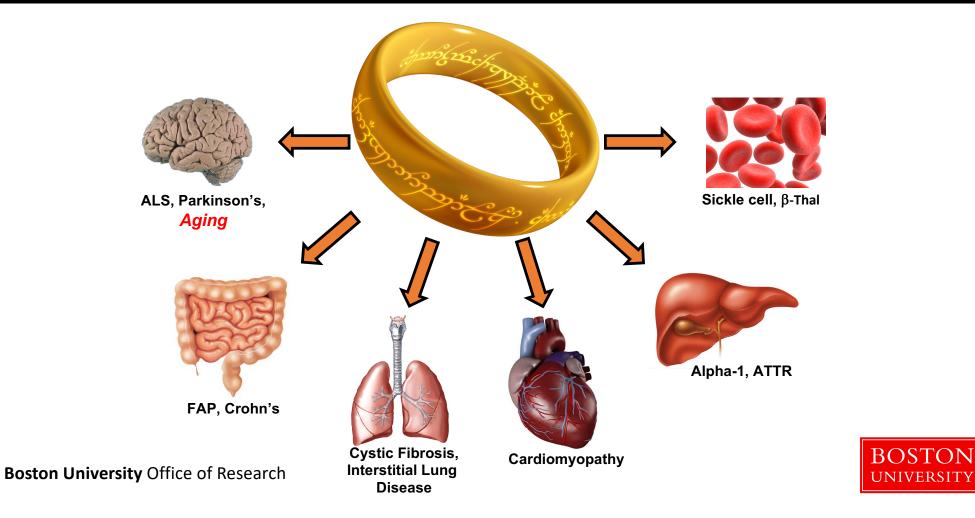






XCEPTIONAL CARE. WITHOUT EXCEPTION

## Pluripotent Stem Cells: One Cell to Rule Them All



## A longevity-specific bank of induced pluripotent stem cells from centenarians and their offspring

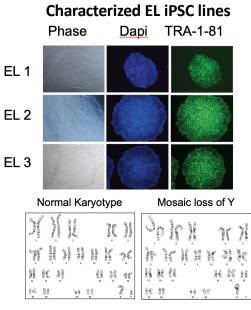
#### **Exceptional Longevity (EL) Bank**

Age	Sex	PBMC Collected	iPSC Generated
100-104	Male	13	1
100-104	Female	18	2
105-109	Male	7	6
	Female	8	5
110+	Male	0	0
	Female	2	2
EL	Male	18	1
Offspring	Female	31	3
Non-EL	Male	5	0
controls	Female	2	0
Total		104	20

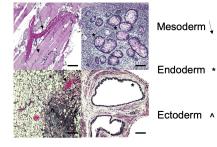
#### **Clinical history of EL subjects**

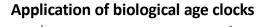
- Cognitive status (superager, normal, impaired)
- Disease, hospitalization
- Medications
- Quality of life (independence, fitness)

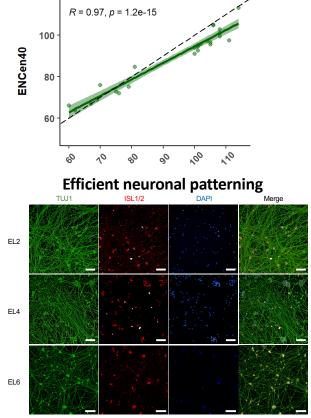
- Frailty index



#### Teratoma assay

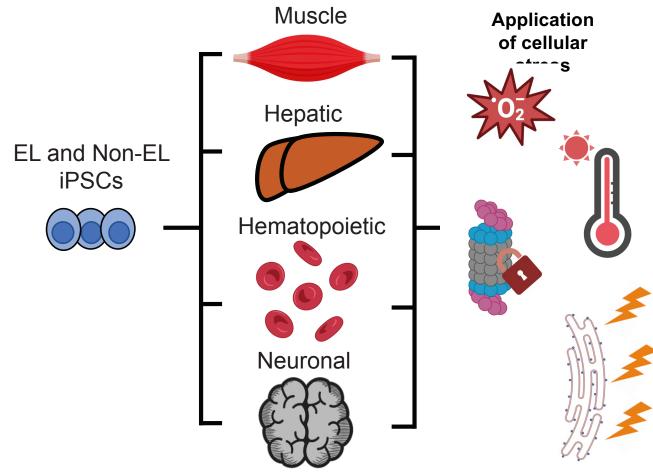




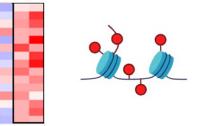


Dowrey et al., Aging Cell 2024

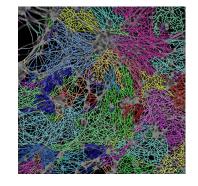
## Establishing stress signatures in EL iPSC-derived cells



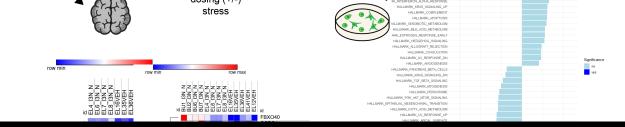
## Transcriptional and epigenetic profiling



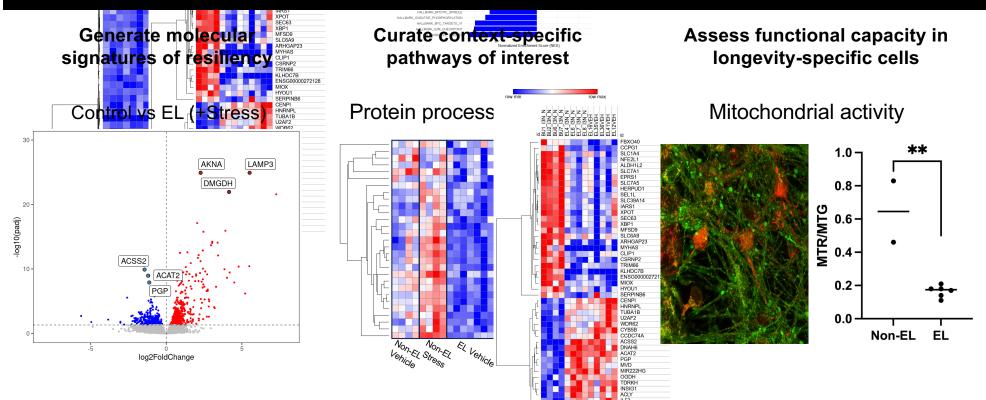
#### **Functional readouts**







## Application of resiliency signatures in discovery and validation

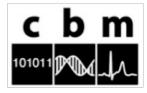


EL subjects maintain a molecularly and functionally guieter" landscape while maintaining the ability to productively and robustly respond to stress





**Chobanian & Avedisian School of Medicine** Department of Medicine



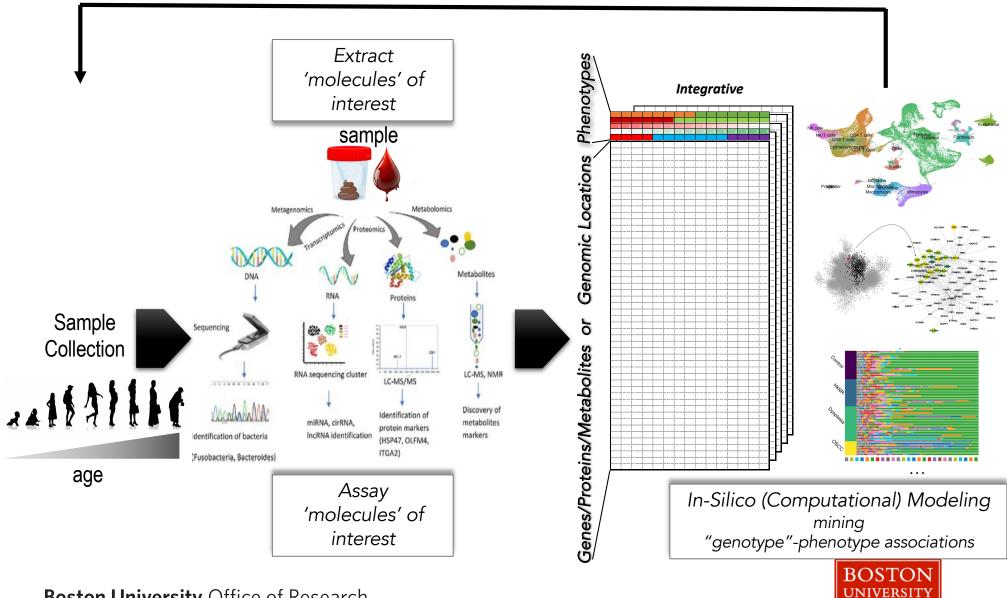
## Multi-Omics Modeling to Study Healthy Aging and Exceptional Longevity (EL)

Stefano Monti Section of Computational Biomedicine @ BUSM Department of Biostatistics @ BSPH Bioinformatics Program @ CDS smonti@bu.edu https://www.bumc.bu.edu/compbiomed/labs/monti/

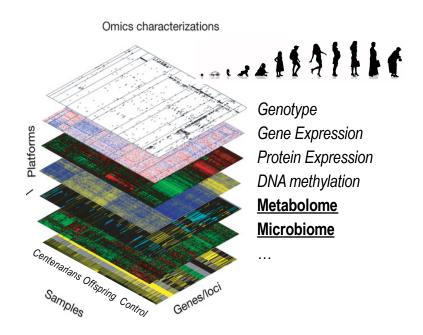
Boston University Office of Research

**Boston University** Interdisciplinary Programs Bioinformatics

#### From Experiments to (Multi-Omics) Data molecular epidemiology of age



### **Integrative Multi-Omics** The Study of Healthy Aging & Longevity



#### Collaboration with

- Tom Perls, Paola Sebastiani, Stacy Andersen-Toomey
- New England Centenarian Study (NECS)
- George Murphy, et al.

#### Several Consortia

- Longevity Consortium (Schork et al.)
- Long Life Family Study (LLFS) (Province et al.)
- Integrative Longevity Omics (ILO) (Perls et al.)

#### **Exciting Challenges**

- Analysis of "new" omics layers (Metabolomics, Metagenomics, ...)
- **Integrative Analysis of Multi-Omics**



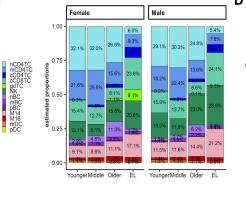
**Boston University** Office of Research

Sebastiani

Province

et al

#### Single Cell Transcriptomics



LLFS

n=2764; 24 to 110 yrs

~8 vears

(a) Single Proteins

		U	Middle v. Younger	Older v. Younger	EL v. Younger	Female v. Male
		cCD4TC	***	***	***	***
	5.4%	gdTC		***	***	***
4.8%	7.8%	M14		*	*	***
	6.0%	nCD4TC			***	***
	24.1%	mCD4TC			***	***
3.6%	24.170	pBC			**	
2% 3.6% 3.1%	0.3%	mDC			***	***
).1%		pDC			***	***
3.0%	28.9%	nBC		***	***	•
	-0.00	mBC		***		**
5.2% 2%	9,2%	M16		***		***
4.4%	21.2%	cCD8TC				***
3%	7.6%	NK	**	***		***
Older	EL			age coef		-2 -1 0 1 2
						Bulk

Hallmark Pathways

> 15 years follow-up

www.thelancet.com Vol 90 April, 2023

Multi-modal profiling of peripheral blood cells across the human lifespan reveals distinct immune cell signatures of aging and longevity

Tanya T. Karagiannis,<sup>a,n,\*</sup> Todd W. Dowrey,<sup>b,n</sup> Carlos Villacorta-Martin,<sup>b</sup> Monty Montano,<sup>c,d</sup> Eric Reed,<sup>e</sup> Anna C. Belkina,<sup>f,g</sup> Stacy L. Andersen,<sup>h</sup> Thomas T. Perls,<sup>h</sup> Stefano Monti,<sup>i,j,k,n</sup> George J. Murphy,<sup>b,l,n</sup> and Paola Sebastiani<sup>a,m,n</sup>

#### Proteomics

aroup

Offspring 0.2 Centenarian markers

> down up

ORIGINAL ARTICLE Control



Protein signatures of centenarians and their offspring suggest centenarians age slower than other humans



#### **Bulk Metabolomics**

#### **Cell Reports**

Article

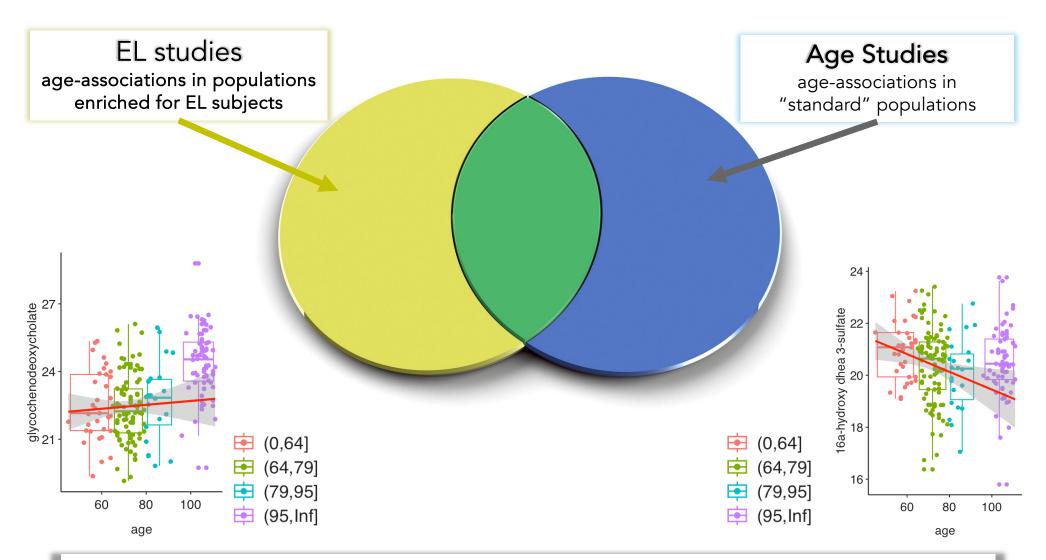
Metabolite signatures of chronological age, aging,

A08 lipid and polar metabolites survival, and longevity 308 152 associated predict Graphical abstract **Authors** with age nortality 258 changed 24 unique ir Paola Sebastiani, Stefano Monti, over time lonaevity LLFS Michael S. Lustgarten, ..., Noa Rappaport, > 15 years follow-up Integration n=2764; 24 to 110 yrs Thomas T. Perls, Gary J. Patti  $\underline{00310}$ Signatures Network Aging clock UNIVERSITY **Boston** 

many (multi-)omics studies in the pipeline (transcriptomics, metabolomics, metagenomics) ...

#### Looking for what is unique about EL subjects

"EL-only" vs. "Age-only" molecular features



#### Major Challenge

distinguishing End of Life (EoL) markers from Exceptional Longevity (EL) markers

# Improving musculoskeletal health to extend healthspan

## **Brianne Connizzo**

Assistant Professor Biomedical Engineering

> **BOSTON** UNIVERSITY

## **MOBILITY IS CRITICAL TO HEALTHY AGING**



## **Blood Pressure Disease Risk Stress & Anxiety**

## Strength Community Independence

HEALTH TUESDAY, JAN. 11, 2011 ••• THE NEWS JOURNAL D3

## Gait speed linked to longevity

In a study, older people who walked faster lived longer

By JANICE LLOYD USA Today

Want to know how long you or your aging parents will live? One simple indi-that goes beyond diseases." health problems, she said, and in many cases the re-

talization.

vide doctors with an inex-"My hope is that we pensive, safe and simple begin to think about ways way of measuring performto reflect the health and ance that can help identify

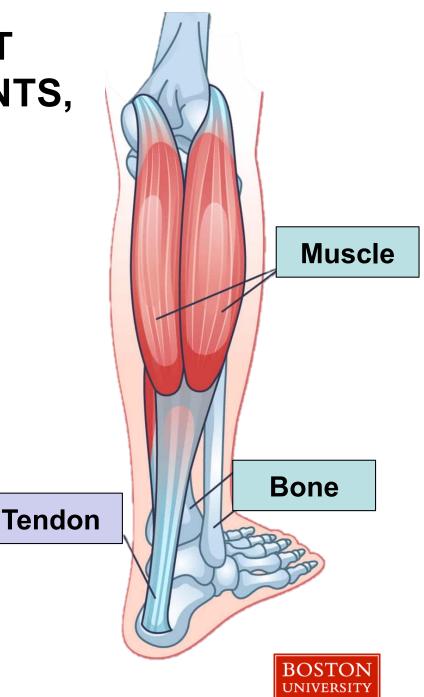


## EFFICIENT MOVEMENT REQUIRES HEALTHY JOINTS, AND TENDONS!

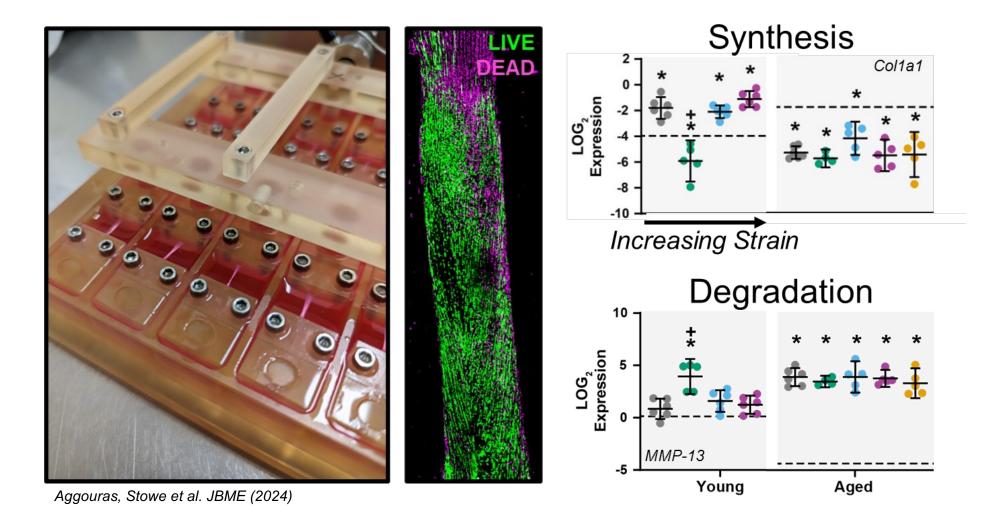
Required for Joint Stability and Efficient Movement

ECM-Rich Tissue with Few Cells

Relatively Quiescent But High Capacity for Adaptation

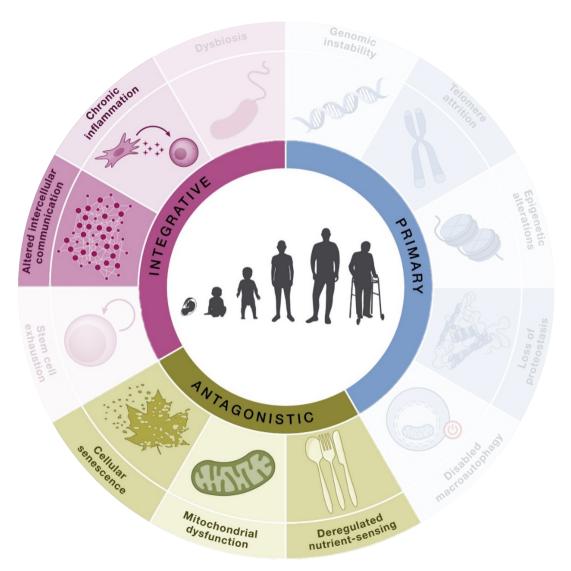


## ADAPTATION TO CHANGING FUNCTION IS LOST WITH AGING





## WHAT CAUSES DYSFUNCTIONAL ADAPTATION? HOW CAN WE PREVENT OR REVERSE IT?



## Adaptive remodeling is lost in aging

Aggouras, Stowe et al. JBME (2024) Mlawer et al. (In Prep) Stowe et al. (In Prep)

## Senescence disrupts ECM remodeling

Stowe et al. Aging Cell (2024)

## Intertissue signaling is disrupted

Kalĉo et al. (In Prep)

## Nutrient sensing + processing is altered

Mlawer et al. BioRxiv (2025)



Beyond Epigenetics: Leveraging Big Data for Breakthrough Anti-Aging Therapies

## Samuel Beck, PhD

Assistant Professor Department of Dermatology, Chobanian & Avedisian School of Medicine

> **BOSTON** UNIVERSITY

#### Question: Changes in chromatin architecture during aging

## Cytoplasm

Euchromatin

**Nucleus** 

--- Nuclear envelope

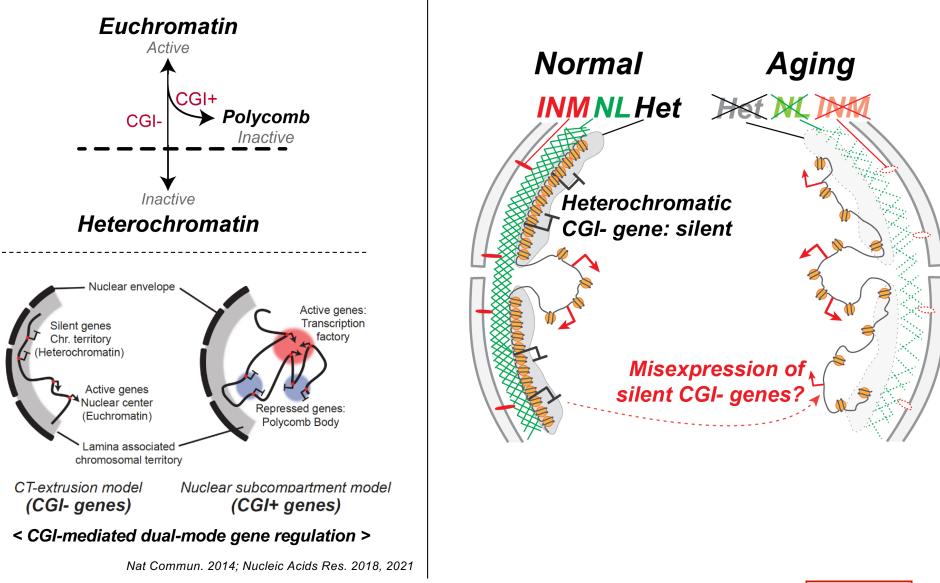
Inner nuclear membrane (INM) proteins (LBR, LAP1, LAP2, Emerin) Nuclear lamina (A & B-type lamin)

<sup>•</sup>*Heterochromatin* (H3K9me2/3, HP1α)

	Normative aging		Premature aging		
	Aged cells	Senescence	Progeria	Werner syndrome	
Cause	Normative aging	Telomere shortening, oncogene induction	LMNA mutation	WRN mutation	
INM protein	Loss of LAP2β / LBR	Loss of LBR	Loss of LAP2 $\alpha$	Loss of LAP2β / LBR	
Nuclear lamina	Loss of Lamin A, Progerin accumulation	Degradation of Lamin B1	Progerin accumulation	Lamin B1 mislocalization	
Heterochromatir	Global decondensation of heterochromatin, Degradation of HP1α				

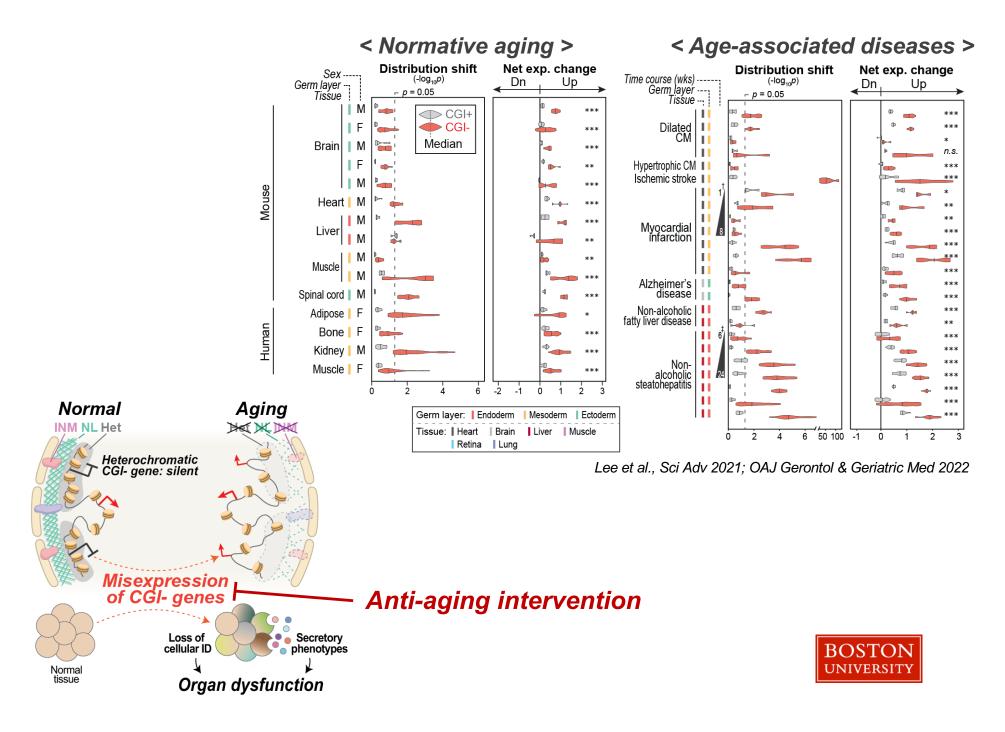


#### Hypothesis: Does aging cause uncontrolled expression of CGI- genes?

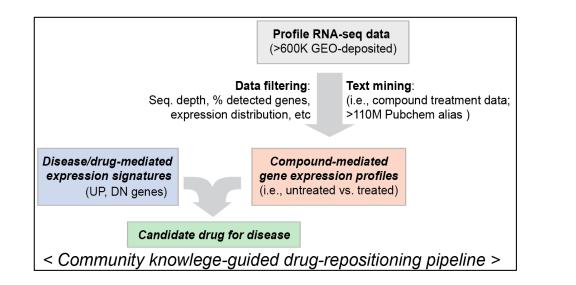


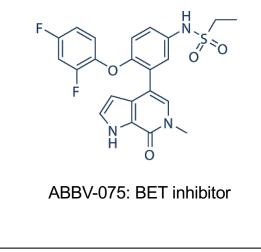


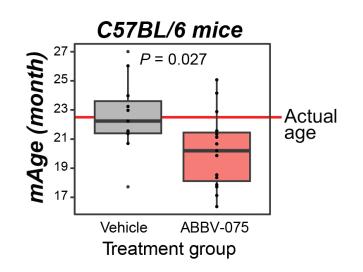
#### Global misexpression of CGI- genes in aging and diseases

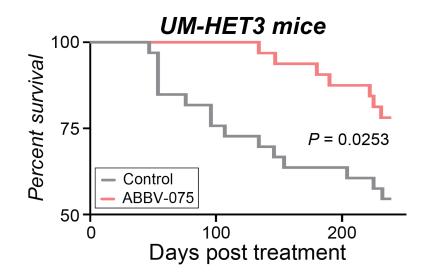


#### Crowdsourced drug discovery and validation











Boston University Office of Research

US Patent:18022948

## Living Longer, Healthier, and Better (Can aging be cured?)

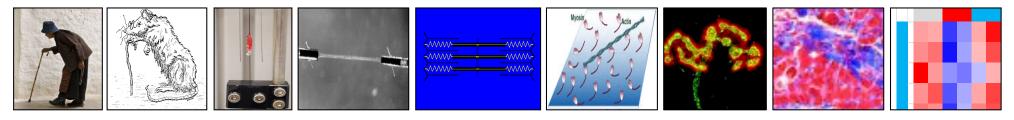
## LaDora V. Thompson, PhD, PT, FAPTA

Travis M Roy Endowed Professor of Rehabilitation Sciences Physical Therapy, Sargent College

> BOSTON UNIVERSITY

## Mission, Vision & Values

The Thompson research team is hard at work trying to understand what causes aging and how to help people stay healthy longer. Her research uses cutting-edge technologies to reveal the intricacies of muscle aging, which sparks research to slow it, or even reverse it.



<u>We strive</u> to make the world a better place by answering essential questions at the intersection between the biology of aging and healthy aging.

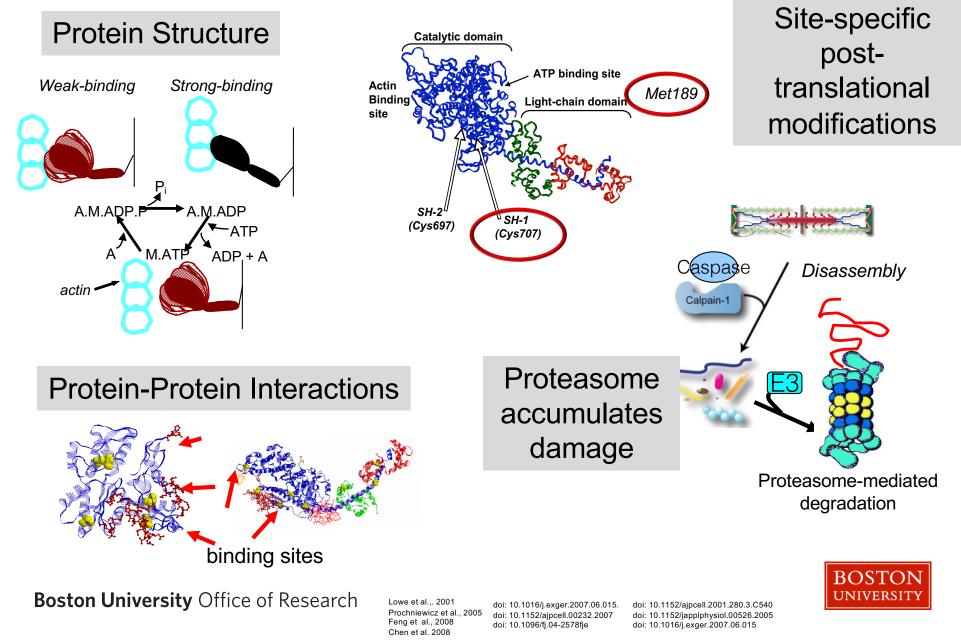
<u>We believe</u> that our discoveries will lead to fundamental new insights on how the muscle system adapts to stress to improve human health and combat disease.

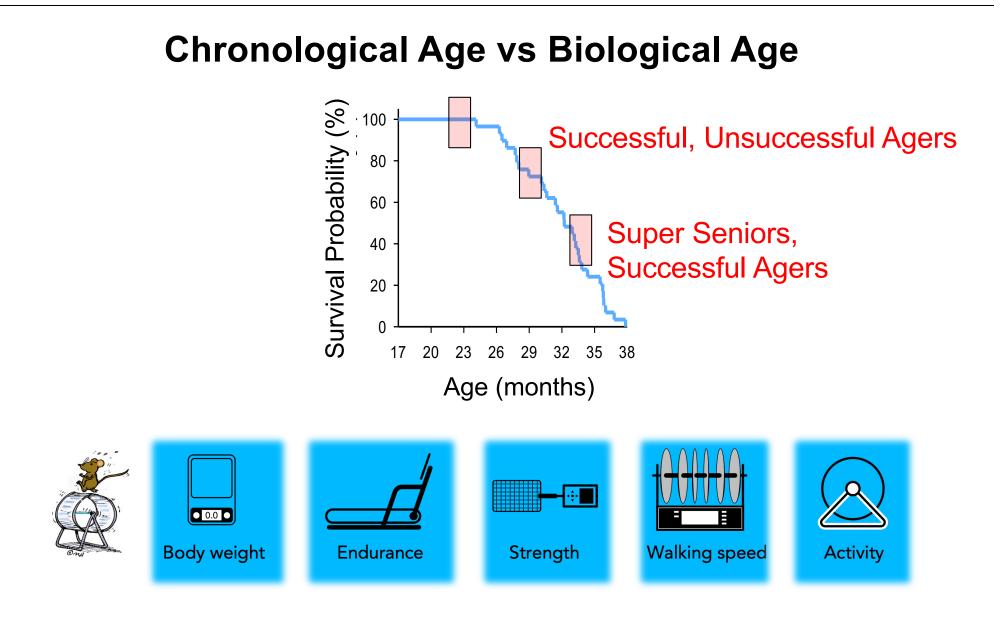
<u>We commit</u> to the core principles of rigor in science, objective evaluation, ethical conduct, collaboration, and honesty.

<u>We foster an inclusive, constructive, and respectful training</u> environment to educate the next generation of scientists and thinkers.



## Mechanisms Contributing to Impaired Contractile Quality with Aging (weakness)







### Exercises

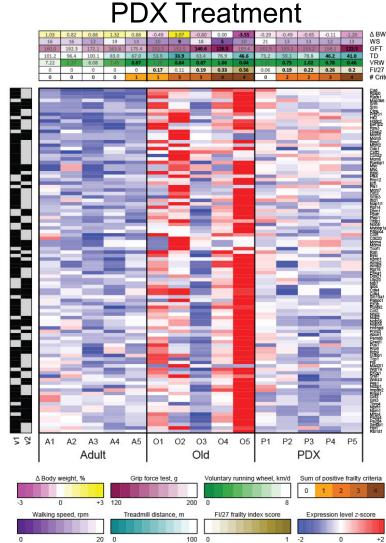


**Precision Exercise** 

Pharmacological therapies



Inflammaging & senescence



**Therapeutics** 

<u>Collaborators</u> Paola Divieti-Pajevic, MD, PhD Brianne Connizzo, PhD Chao Zhang, PhD Beth Bragdon, PhD

#### THOMPSON LAB MEMBERS PAST AND PRESENT

<u>Funding</u> NIA/NIH Hevolution Foundation MHet BU ARC Travis M Roy Endowed Professorship



## Tracking alternative gene boundaries in aging

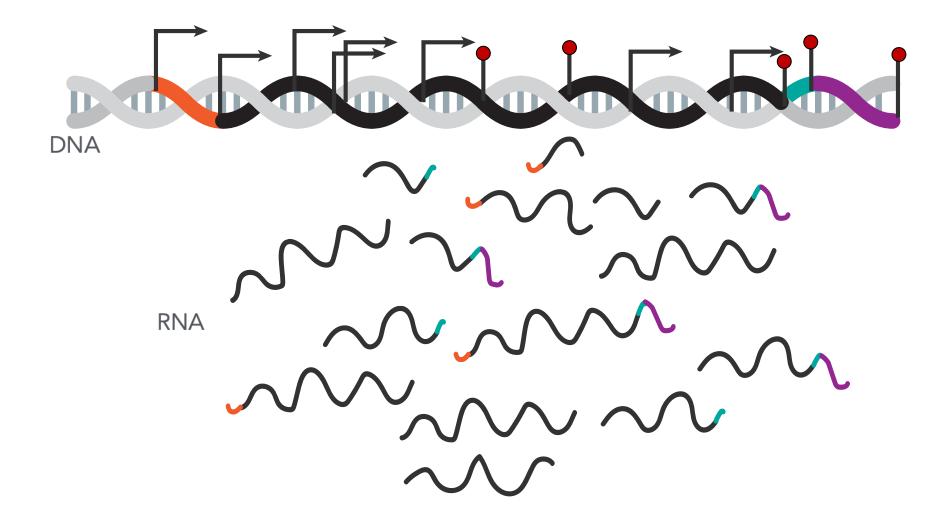
## Ana Fiszbein

Assistant Professor Biology Department, Computing & Data Sciences College of Arts and Sciences



# Gene expression controls cell identity DNA RNA Protein

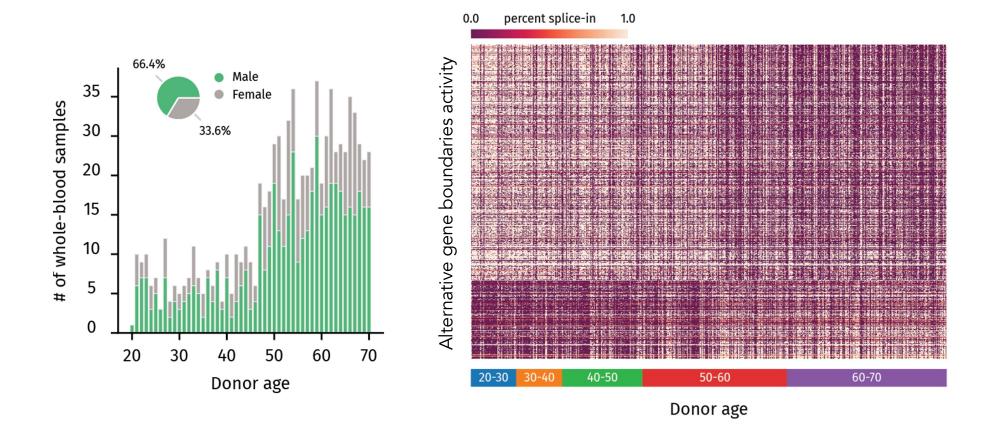
### Human genes have alternative boundaries



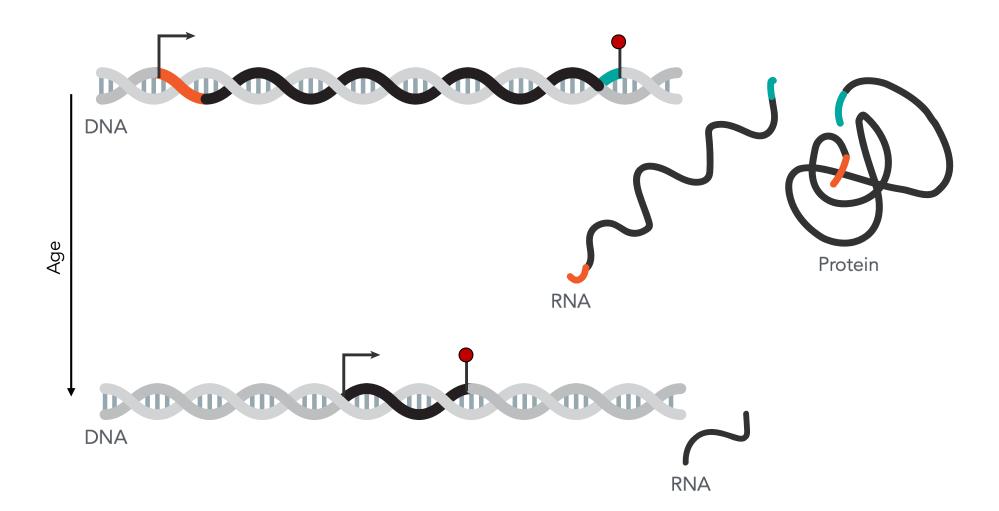
>>> Protein



## Gene boundaries change during aging



## Aberrant gene isoforms are activated during aging









## **Deconvolving Aged Wound Healing**

## Jeroen Eyckmans

Research Assistant Professor Biomedical Engineering, School of Engineering

Eyckmans@bu.edu



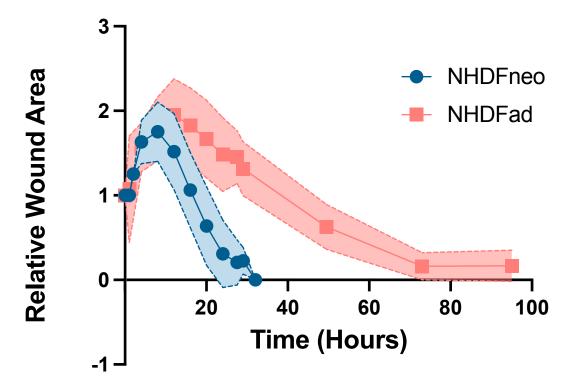
## **Wound Healing and Tissue Repair**



Hemostasis & Inflammation

BOSTON

### Wound-on-Chip Model

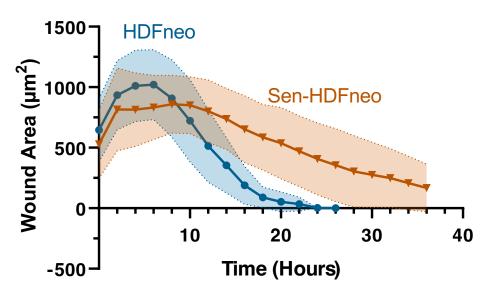




## Senescent Cells and ECM Delay Gap Closure



Anish Vasan

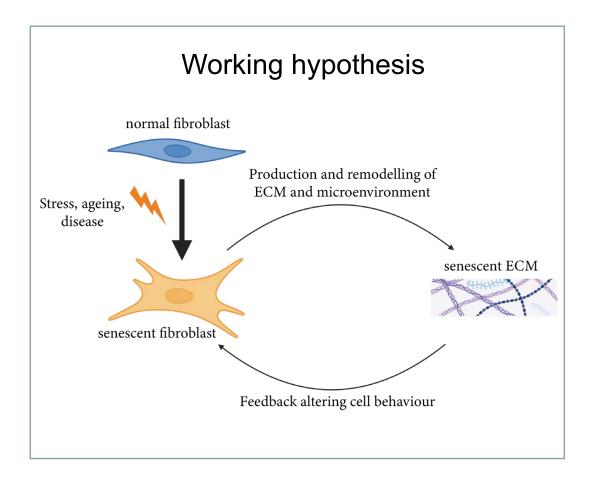


Wound Area vs. Time



## Modulating the ECM to Increase Resilience to Injury

Max Relative Area \* 6-**Relative Wound Area** sci collan 0 sci nai **HDFneo** sen-HDFneo





## Unlocking the secrets of the ubiquitinproteasome system and its role in age-related diseases

Daniel Dempsey

**Assistant Professor** 

Departments of Pharmacology, Physiology, & Biophysics, and Dermatology Boston University Chobanian and Avedisian School of Medicine

> **BOSTON** UNIVERSITY

#### **Mission statement**

The mission of our lab is to understand the basic biological mechanisms of proteins that are essential to human health and disease. We use protein chemistry, biophysical, and cellular approaches to elucidate mechanisms of how chemical changes to proteins regulate their function. We are also interested in advancing new chemical strategies to investigate how proteins function and the regulatory purpose of these chemical changes.

#### Research area 1

Unlocking the secrets of the ubiquitin-proteasome system and its role in in age-related diseases

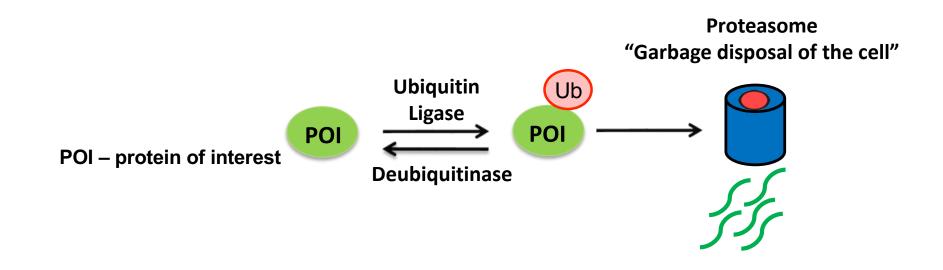
Research area 2

Elucidate how protein modifications regulate RNA biology



### Unlocking the secrets of the ubiquitin-proteasome system and its role in agerelated diseases

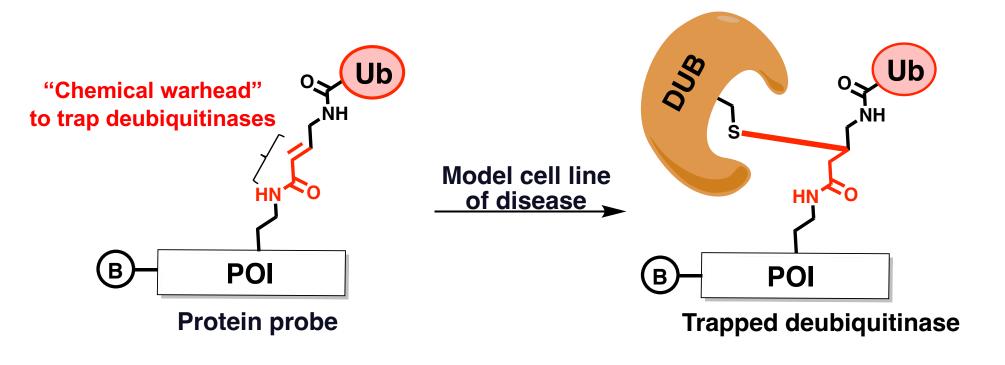
Research goal – Identify vulnerabilities in the ubiquitin-proteasome system (UPS) to target with novel therapeutics.



### Can we leverage this system to destabilize proteins that drive agerelated diseases?



Development of protein traps to discover deubiquitinases that stabilize disease causing proteins



### Future goals of research program

- Advance innovative chemical approaches to identify and characterize deubiquitinases that target proteins that cause disease.
- 2. Evaluate the contribution of deubiquitinases to the pathogenesis of the disease.
- 3. Assess other protein substrates of the deubiquitinases.
- 4. Begin screening and designing selective inhibitors of the deubiquitinases.



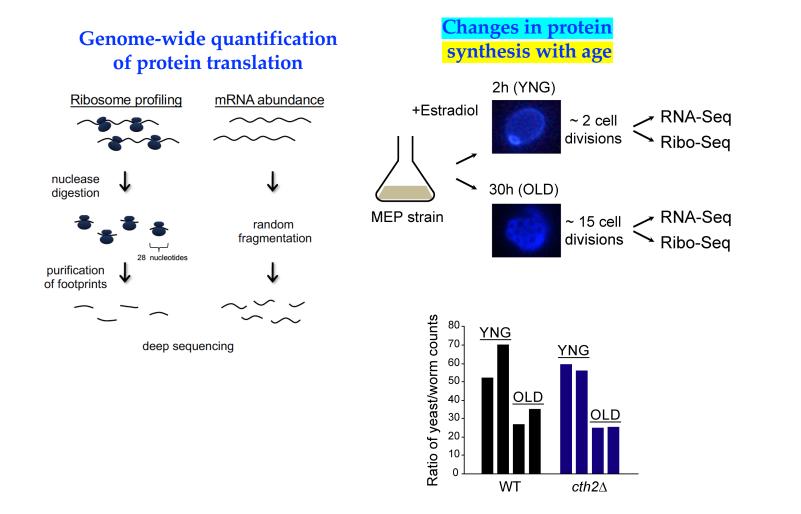
## Targeting iron homeostasis to promote healthy lifespan

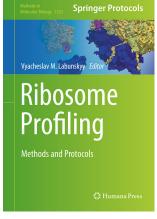
## Slava Labunskyy

Co-Director BUMC Center for Aging Research

> **BOSTON** UNIVERSITY

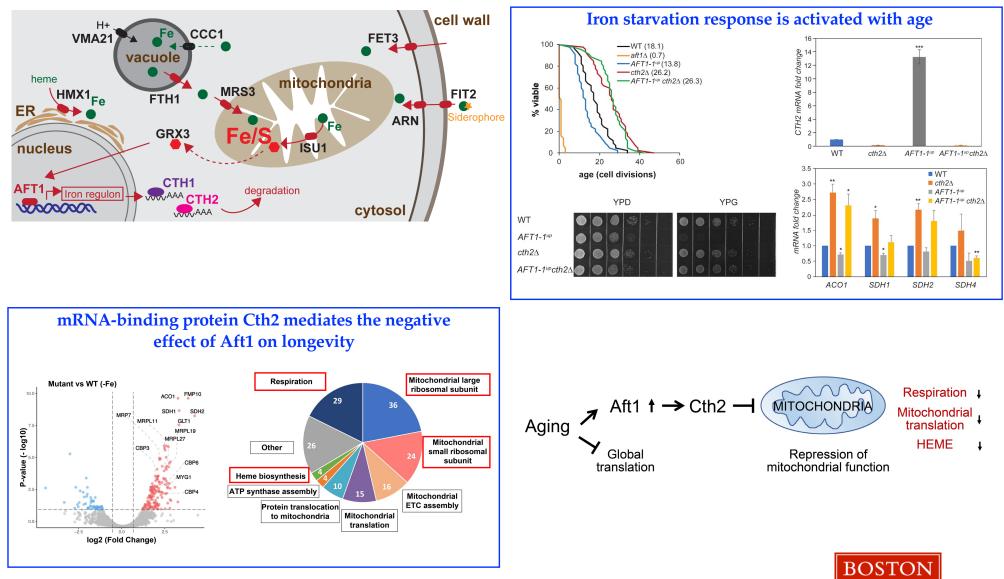
## **Systems Biology of Aging and Longevity**







## The Role of Iron Homeostasis in Aging



UNIVERSITY

## **BUMC Center for Aging Research**



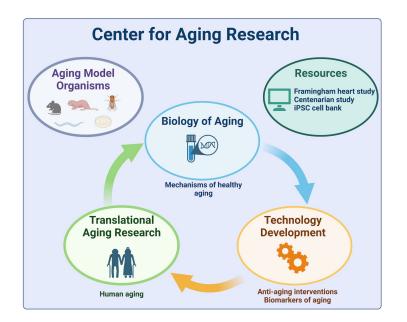
The **mission** of our Center for Aging Research is to advance our knowledge of basic mechanisms driving aging and to translate these discoveries to clinical practice, to promote healthy aging in humans.

The **long-term objectives** of the Center include:

- Establish BU as a leader in translational aging research
- Foster interdisciplinary research collaborations among BU faculty
- Provide university-wide access to new technologies and aging models
- <u>https://aging.bu.edu</u>



## **Uncovering the Mechanisms of Healthy Aging**



#### **Communicating longevity science**

- Monthly Seminar Series
- Annual Research Symposium
- Courses on Biology of Aging

#### **Building critical infrastructure**

- Aging Models
- Biomarkers of Aging



#### Bringing longevity innovations to people



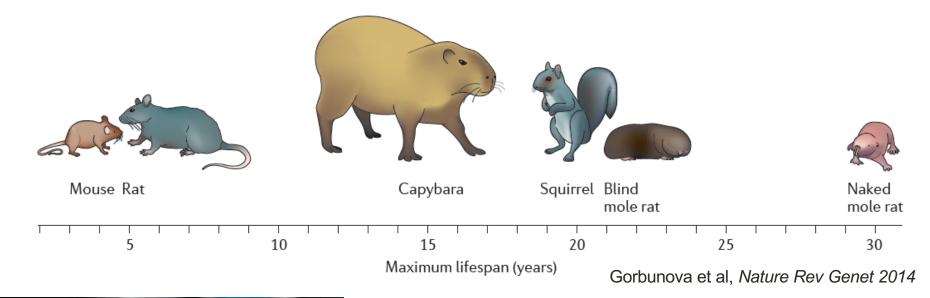
## Naked mole-rats as unique mammalian model for aging research

## Vladimir Botchkarev, MD, PhD, FRSB

Professor and Co-Director Center for Aging Research Department of Dermatology Chobanian and Avedisian School of Medicine



## Naked mole-rats are centenarians in a rodent world: live over 30 years, which is equivalent of 800+ human years



• Highly resistant to cancer

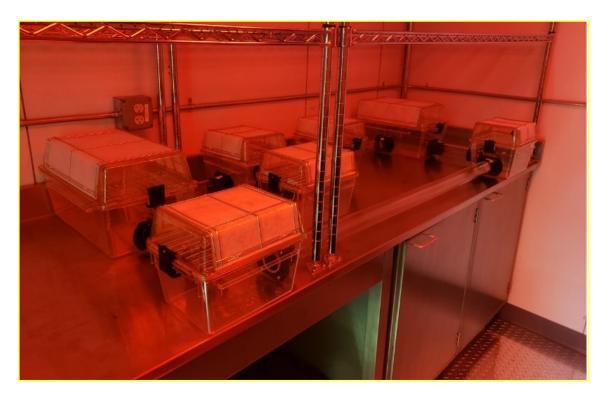
- Can survive without oxygen for 18 minutes
  - Can barely feel pain
  - Anaerobic metabolism





Boston University Office of Research

## Naked mole-rat facility at BUSM ASC is the only facility in New England harboring over 100 animals

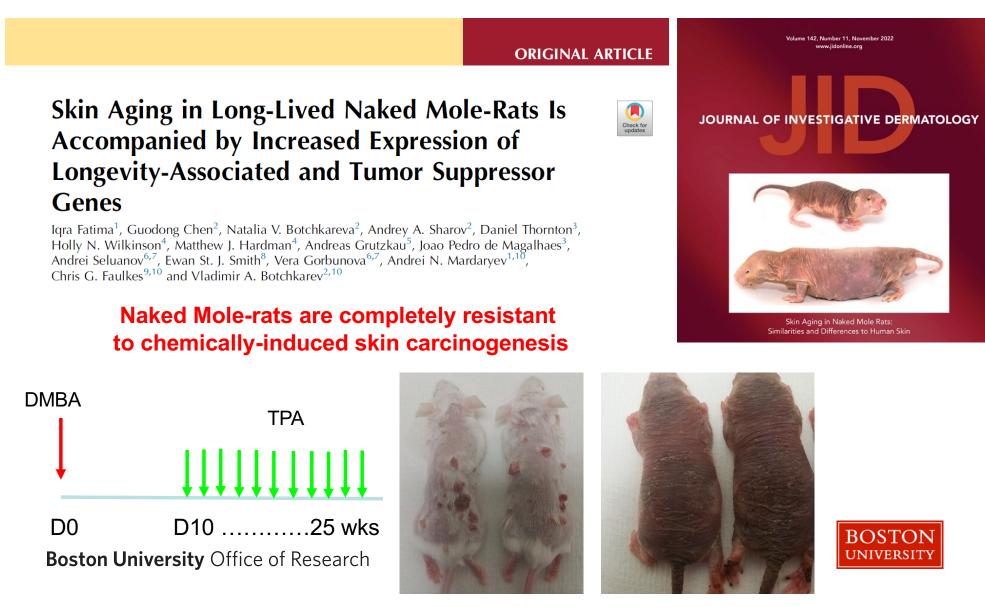


Quantity of produce per one room	
Sweet	5, medium size
Potato	
Apple	4 -5 , medium size
Corn	3 ears
Carrot	4-5, medium size
<b>Carrot tops</b>	1 medium bunch, tops
	and carrots together
Celery	4-5 sticks
Lettuce	1 medium bunch
Squash	1/3 of medium squash
White	5, medium size
potato	
Banana	3
Cucumber	2
Grapes	1 per animal
Turnip	1 per animal, cut in half 3-4, medium size
D	SIZE

High temperature (90F) Sensitive to noise & vibration Water-enriched food



## Skin aging in Naked mole-rats is accompanied by upregulation of anti-cancer genes



### Comparative biology helps in discovery of novel mechanisms underlying aging and disease resistance

Naked mole rat skin serves as innovative model for studying mechanisms of aging and cancer resistance

The power of comparative biology helps in identification of novel solutions for human medical problems by studying animals that naturally possess resistance to diseases



1R61AR078093

The skin of naked mole rats as a model for scar-free wound healing BOTCHKAREV (Contact PI), GORBUNOVA, SHAROV, VEVES (BIDMC)



Institutes

of Health



## **Crystal ribcage:**

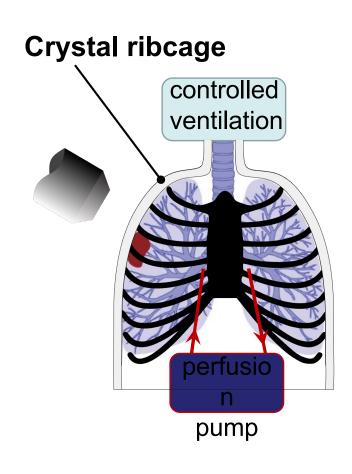
## A platform for probing the effect of aging on lung function in health and disease

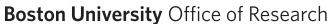
## Hadi T. Nia, Ph.D.

## Assistant Professor Department of Biomedical Engineering Boston University

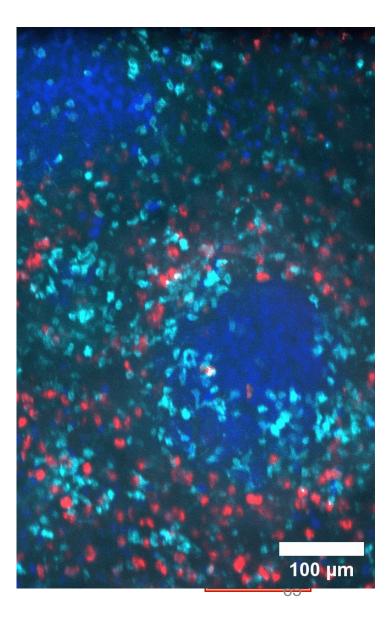


## Proposed solution: Developing crystal ribcage to open the black box of the lung to optical microscopy

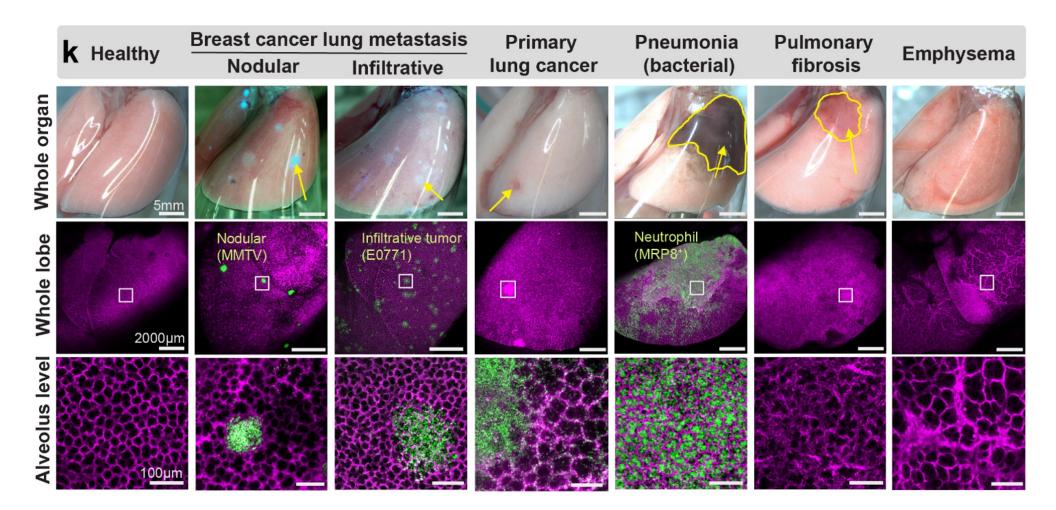








## Crystal ribcage to probe nearly any pulmonary disease with parenchymal presentation

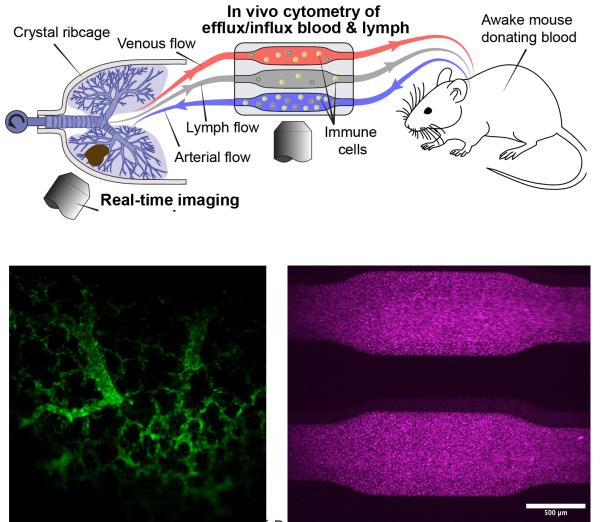


• R. Banerji\*, G. Grifno\*, ..., H. Nia, Nature Methods, 2023 \*: equal contribution

UNIVERSIT

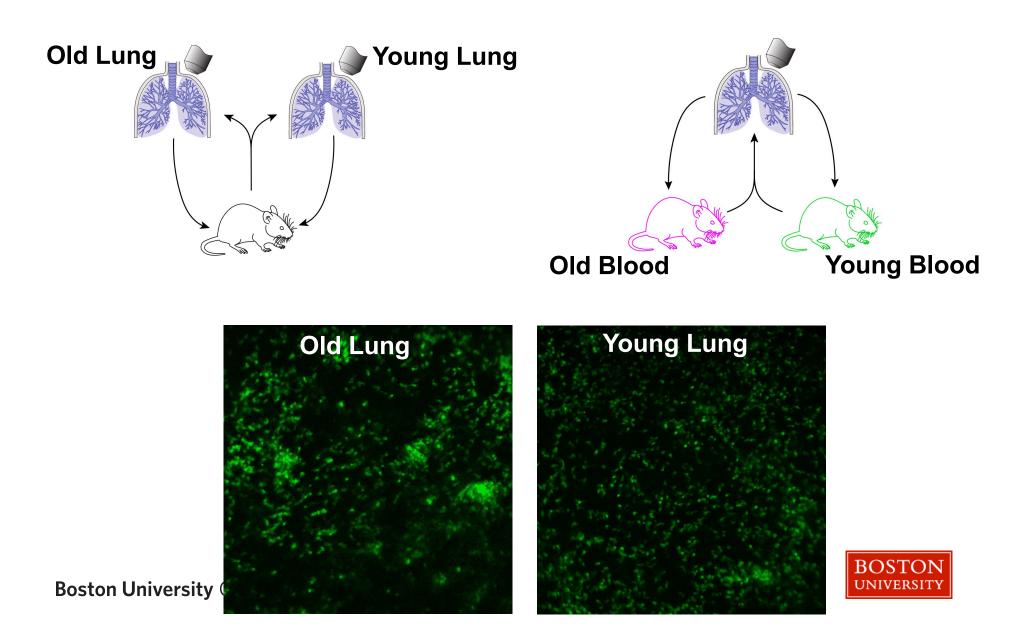
• Bost Than Birsity High Resture Biomedical Engineering, 2023

## Crystal ribcage and cross-circulation of aged vs young mice





## Decoupling the effect of aging on the resident vs circulatory factors during pneumonia progression



## **Closing Remarks:**

### **Glenn Foundation Centers in the Biology of Aging Research**

- Goal: support centers of excellence in basic research into biology of aging and extension of healthspan with lifespan
- Funding: \$4M over 4-5 years
- **Key people**: Kevin Lee, PhD, Senior Scientific Advisor; funded PIs (see next)
- Centers:
  - Buck Institute: mechanisms of aging, relationship to chronic conditions of aging; E. Verden, M. Hansen; 2016-
  - Harvard: molecular basis of normal aging and age-related physiological decline; B. Yanker, M. Haigis; 2006-
  - Mayo: senescent cells' mechanistic contributions to aging-related decline, disease; D. Baker, N. LeBrasseur; 2013-
  - Michigan: multiple projects; R. Miller, S. Pletcher; 2014-
  - Princeton: quantitative aging: tools, techniques to measure phenotypes that change with age; C. Murphy; 2012-
  - Salk: genetic analysis, stem cell biology, metabolism; J. Karlseder, G. Shadel; 2009-
  - Stanford: biological processes that drive aging, w/ emphasis on stem cell; A. Brunet, K. Cimprich, J. Frydman; 2011-

Previously: Albert Einstein (2012-20); MIT (2008-22); Berkeley/UCSF (S. Prusiner, A. Dillon; 2014-17)

• Next steps: network in; confirm process



## OFFICE OF RESEARCH Upcoming Events

## **Research on Tap**

4/2 Tackling Cancer ThroughMultidisciplinary Research, BUMC4/16 Al and the Humanities, CRC

## **Research How-to**

**3/31** Research Meets Policy: Engaging with Federal Lawmakers, Virtual

**4/3** From Insight to Impact: Crafting Op-Eds That Amplify Your Expertise, Virtual



### bu.edu/research/events

