Therapeutic approaches to aging

Laura Niedernhofer, M.D., Ph.D.
Director, Institute on the Biology of Aging and Metabolism
Medical Discovery Team Biology of Aging
Professor of Biochemistry, Molecular Biology and Biophysics

UNIVERSITY OF MINNESOTA

Medical Discovery Teams

Addiction

Rural & American Indian Health

Biology of Aging

Optical Imaging & Brain Science

UMN
Institute on the Biology of Aging and Metabolism

Paul Robbins

Senescence
Drug development

Christina Camell

Inflammasome
Immunology

Xiao Dong

Somatic mutations
Single cell; Bioinformatics

Matt Gill

Endocrine and lipid signaling
C elegans

Lei Zhang

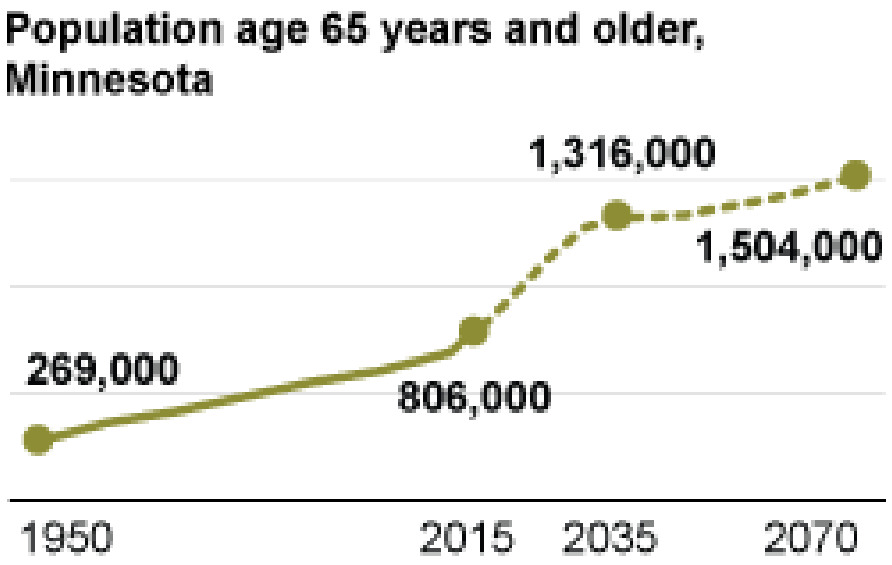
Epigenetics
Single cell; Comparative biology

iBAM Mission

To improve the health, and thereby the quality of life, for the elderly in the state of Minnesota and beyond, through:

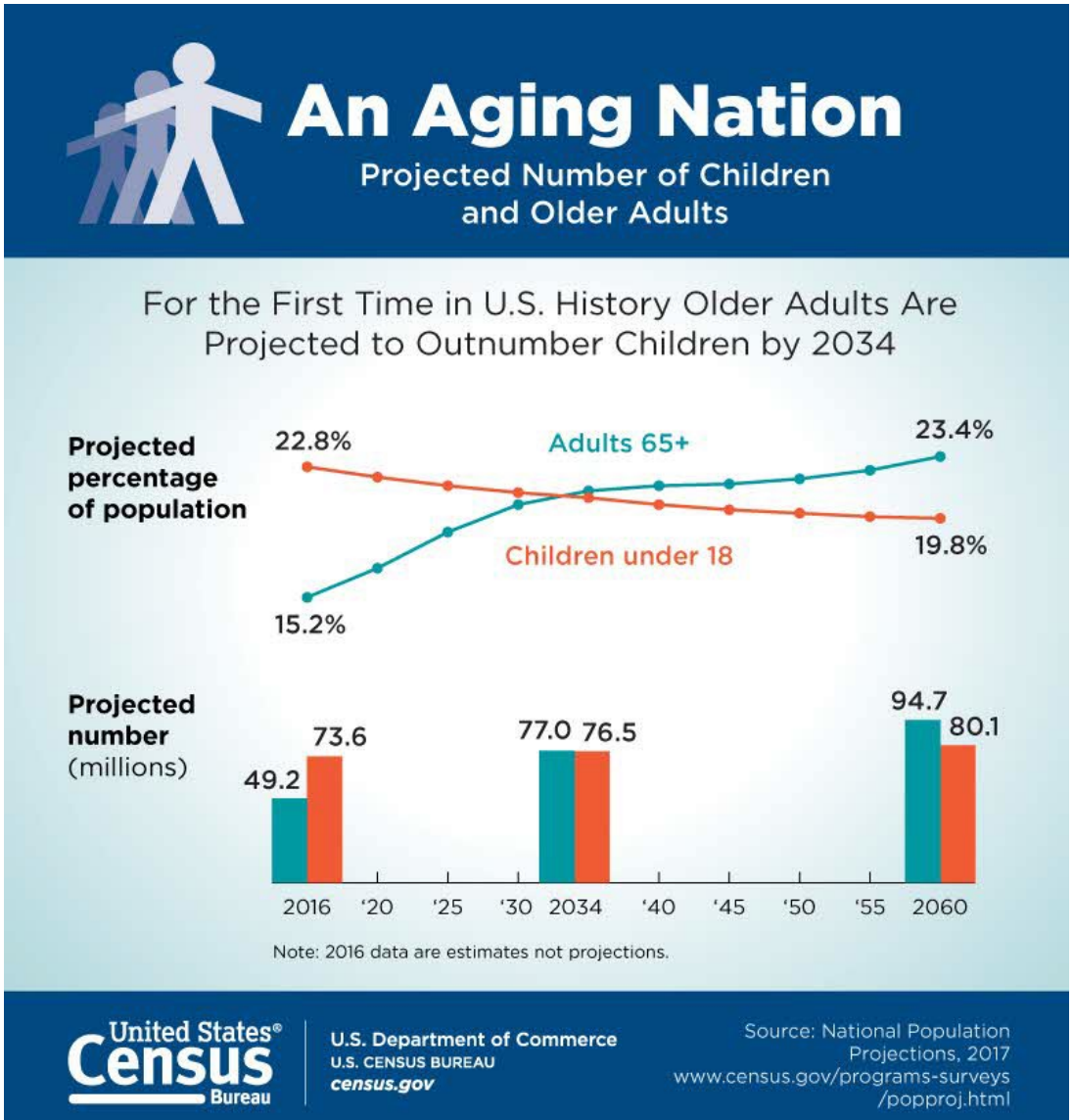
- discovery of fundamental mechanisms that drive aging, the number one risk factor for the majority of debilitating chronic diseases.
- drug development targeting these fundamental processes.
- augmenting emerging approaches to clinically test therapeutics aimed to extend health span of the elderly.
- educating the next generation of basic and clinical scientists dedicated to this mission.

The number of older adults in MN will double by 2035

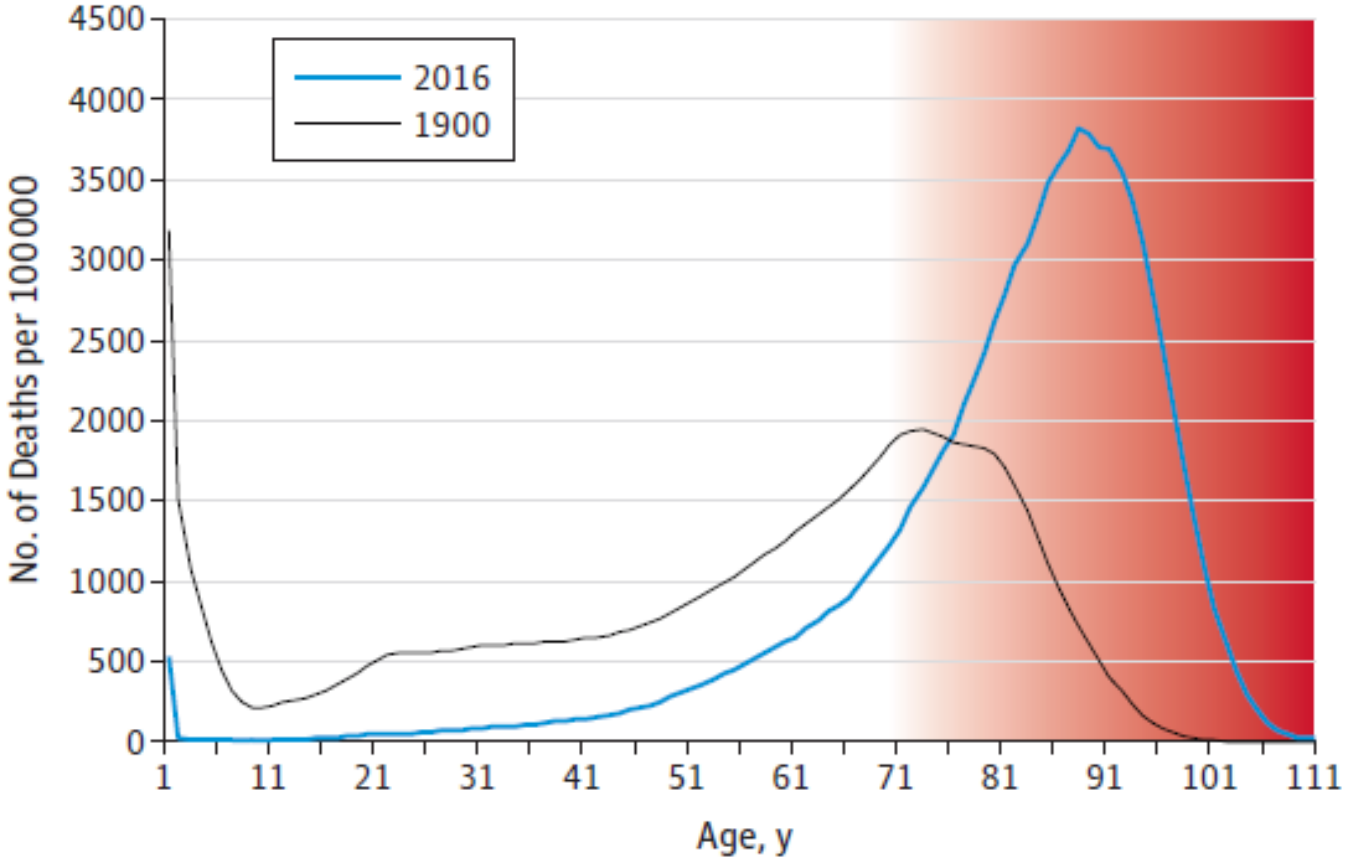


https://www.mncompass.org/trends/insights/

Older adults will soon outnumber minors in the USA

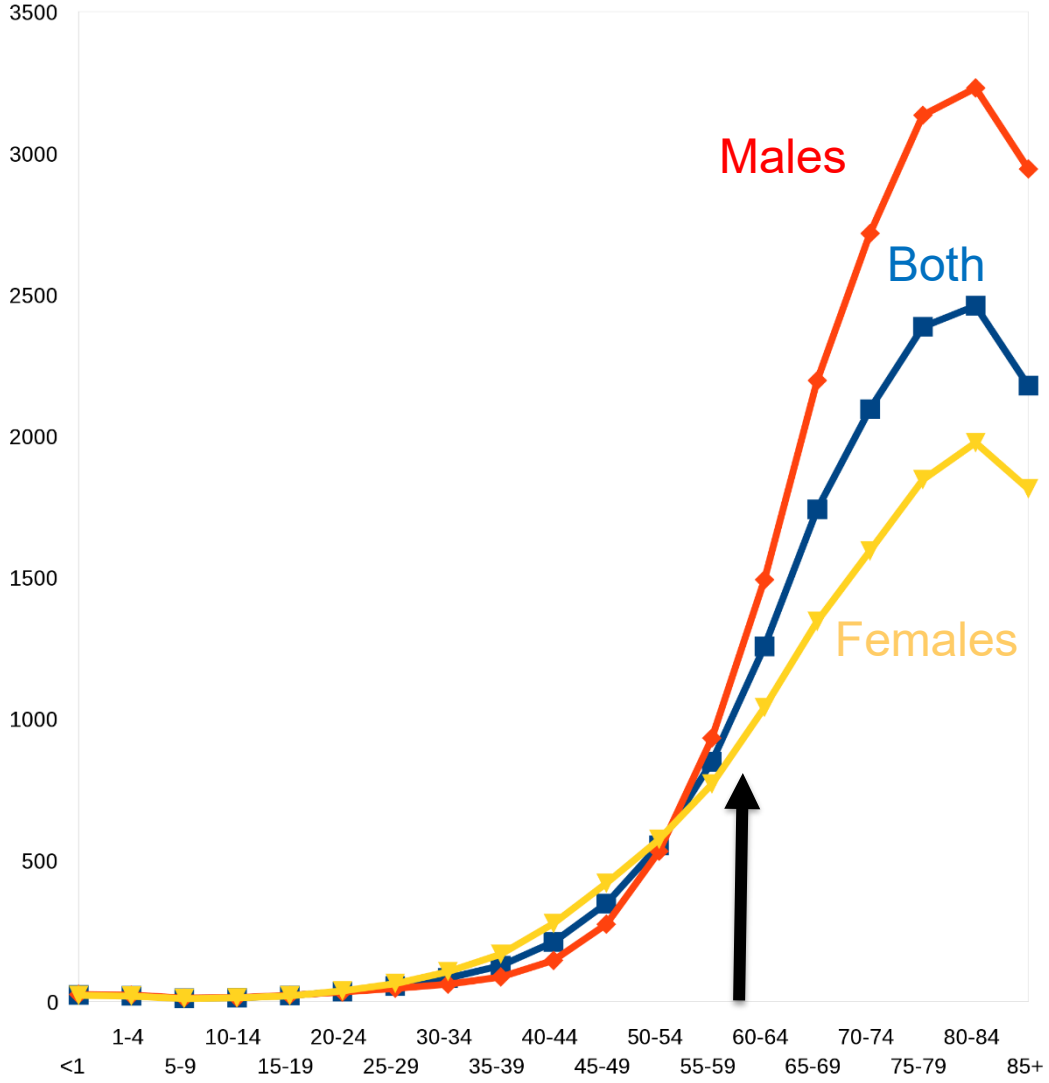


Why is this happening?
A biomedical success story



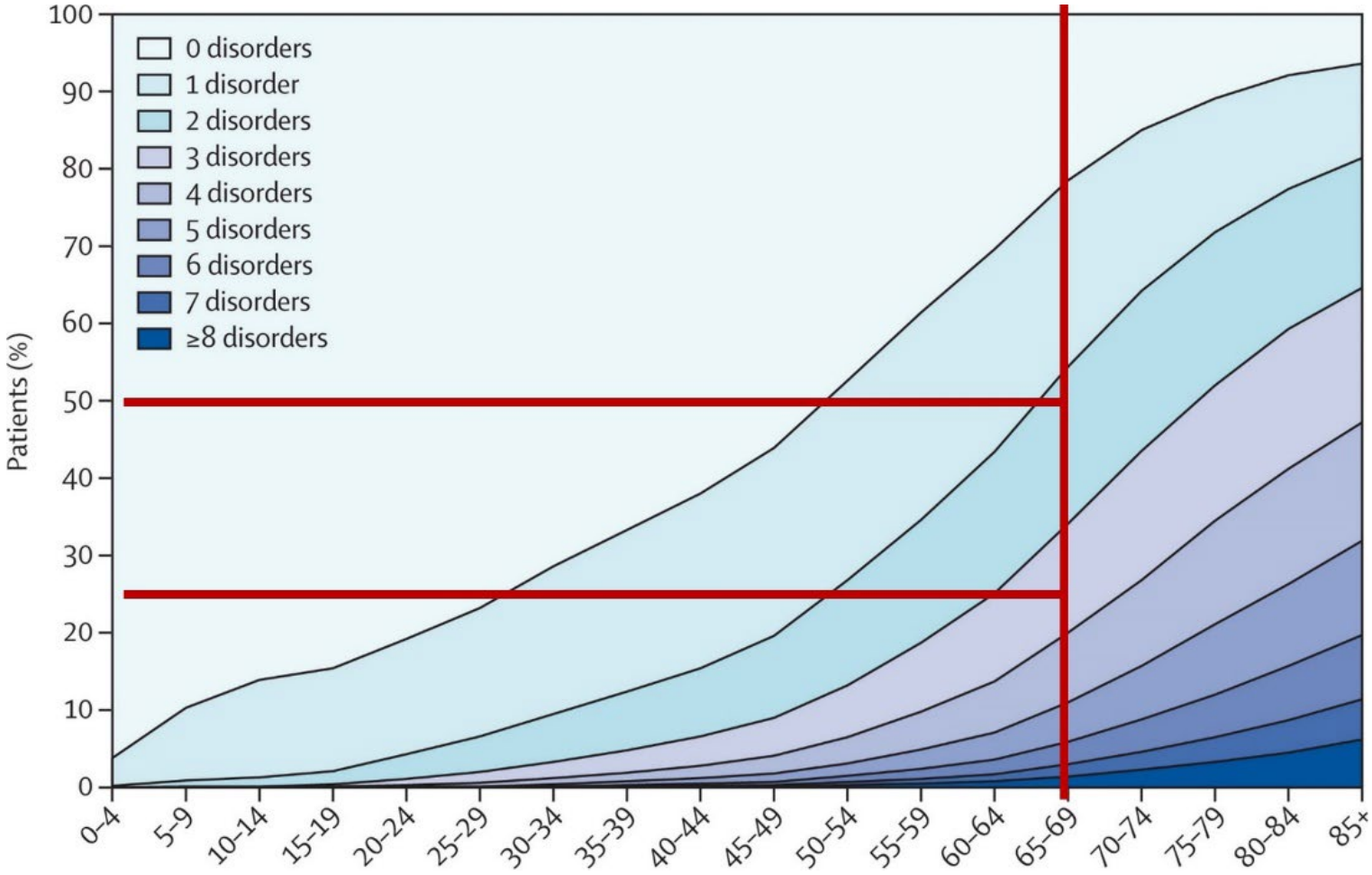
Jay Olshansky 2018 JAMA

Exponential increase in disease incidence in people over 60



- osteoporosis
- cardiovascular disease
- neurodegenerative diseases
- osteoarthritis
- type II diabetes
- cancer
- macular degeneration
- intervertebral disc degeneration
- hearing loss

Most older adults have >1 disease



Many chronic diseases (or their treatment) can accelerate aging

Xeroderma **Pigmentosum**: A Model for Human Premature **Aging**.

Rizza ERH, DiGiovanna JJ, Khan SG, Tamura D, Jeskey JD, Kraemer KH.

J Invest Dermatol. 2021 Apr;141(4S):976-984. doi: 10.1016/j.jid.2020.11.012. Epub 2021 Jan 9.

Fanconi Anemia: A DNA repair disorder characterized by **accelerated** decline of the hematopoietic stem cell compartment and other features of **aging**.

Brosh RM Jr, Bellani M, Liu Y, Seidman MM.

Ageing Res Rev. 2017 Jan;33:67-75. doi: 10.1016/j.arr.2016.05.005. Epub 2016 May 17.

Premature **aging** in childhood **cancer survivors**.

Kruseova J, Zichova A, Eckschlager T.

Oncol Lett. 2022 Dec 13;25(2):43. doi: 10.3892/ol.2022.13629. eCollection 2023 Feb.

Cellular Senescence in **Diabetes Mellitus**: Distinct Senotherapeutic Strategies for Adipose Tissue and Pancreatic β Cells.

Murakami T, Inagaki N, Kondoh H.

Front Endocrinol (Lausanne). 2022 Mar 31;13:869414. doi: 10.3389/fendo.2022.869414. eCollection 2022.

Cellular Senescence in **Obesity** and Associated Complications: a New Therapeutic Target.

Narasimhan A, Flores RR, Camell CD, Bernlohr DA, Robbins PD, Niedernhofer LJ.

Curr Diab Rep. 2022 Nov;22(11):537-548. doi: 10.1007/s11892-022-01493-w. Epub 2022 Oct 14.

Donor cord blood **aging accelerates** in recipients after **transplantation**.

Onizuka M, Imanishi T, Harada K, Aoyama Y, Amaki J, Toyosaki M, Machida S, Kikkawa E, Yamada S, Nakabayashi K, Hata K, Higashimoto K, Soejima H, Ando K.

Sci Rep. 2023 Feb 14;13(1):2603. doi: 10.1038/s41598-023-29912-2.

Chronologic age is the greatest risk factor for heart disease (x 1000)

Geroscience Hypothesis:
Treat aging biology

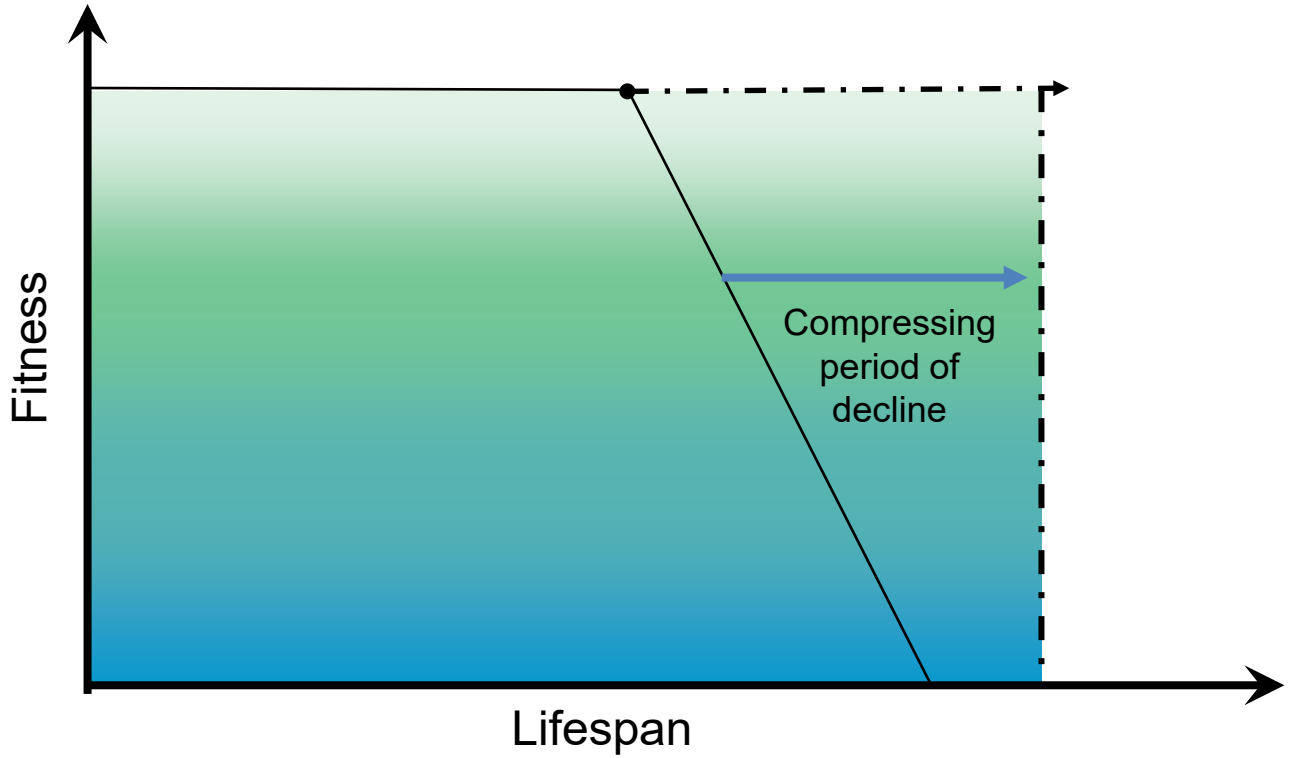
+ prevent, delay or ameliorate multiple debilitating, chronic degenerative diseases

+ avoid spending the rest of your life with “ologists”

+ avoid polypharmacy

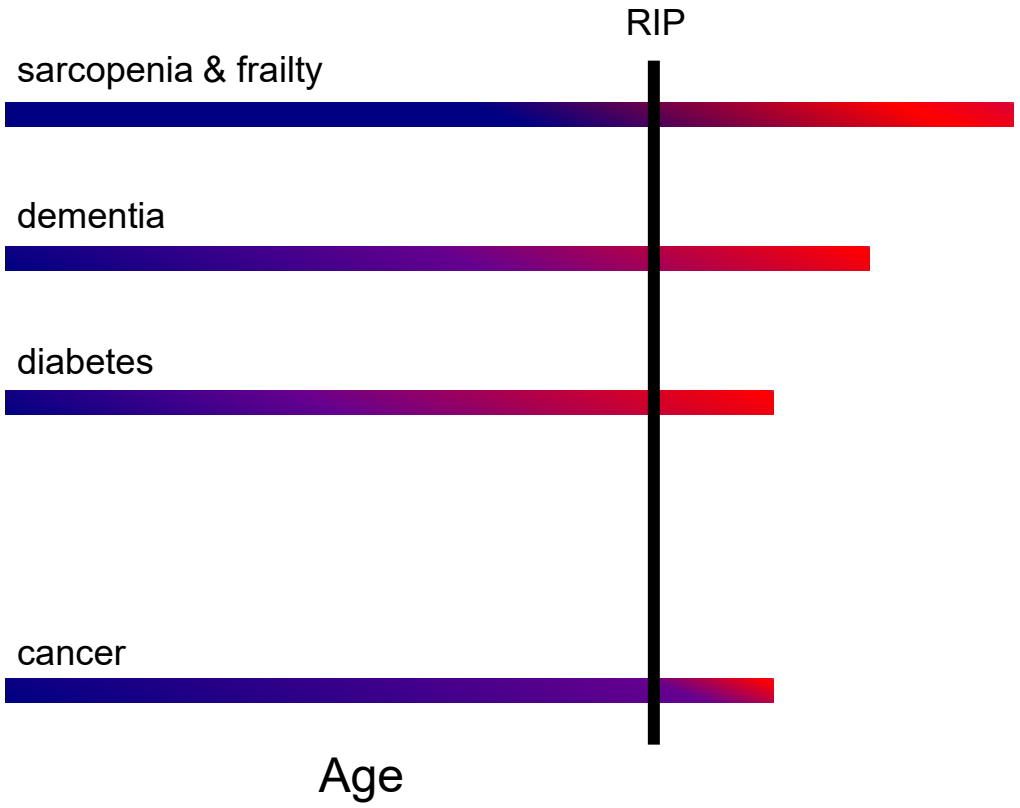
+ reduce healthcare costs

Goal:
increase healthspan, not lifespan

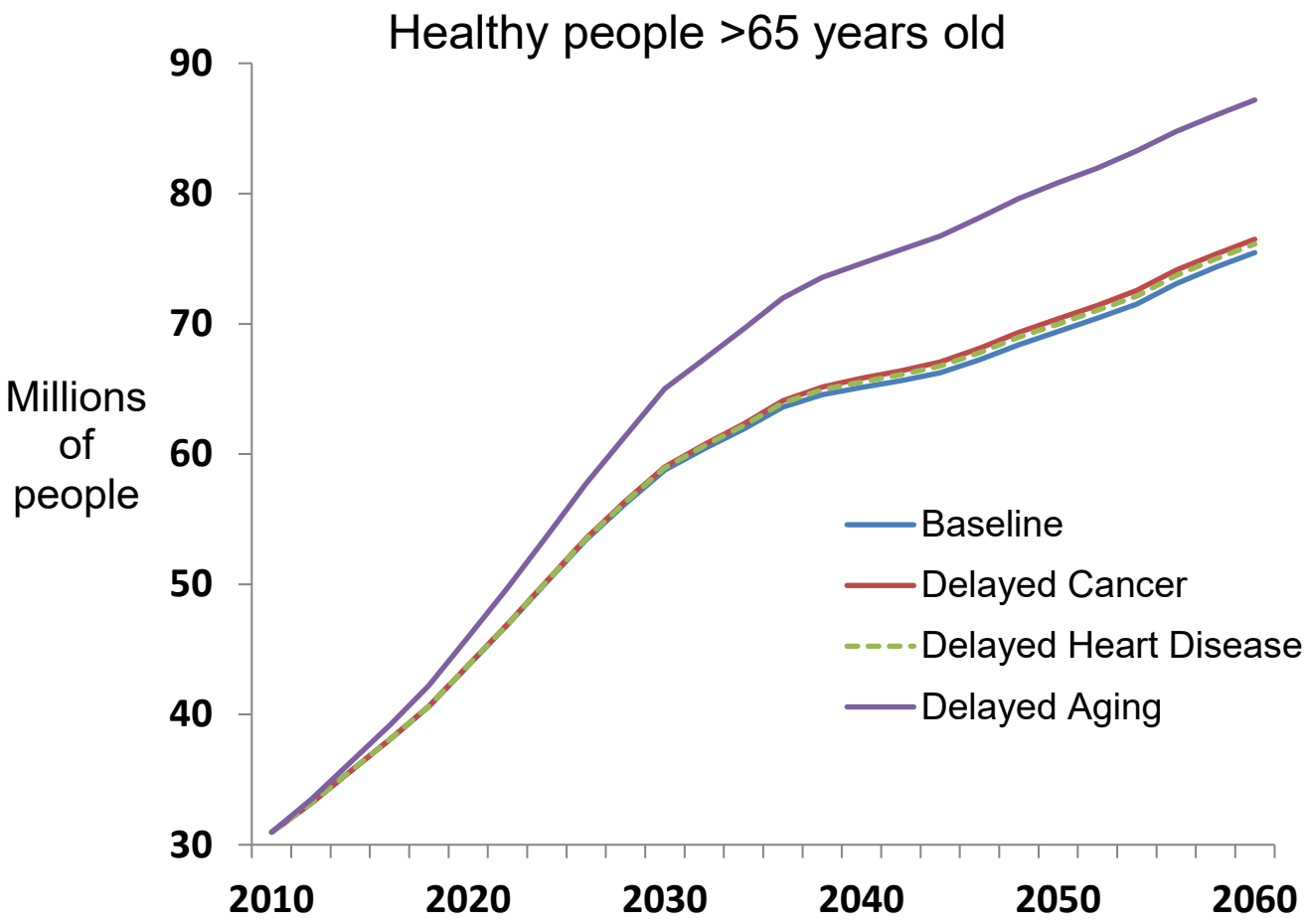


Impact on an individual's trajectory

Time dependent
onset of
age-related disease



Impact on a population's trajectory



$38T

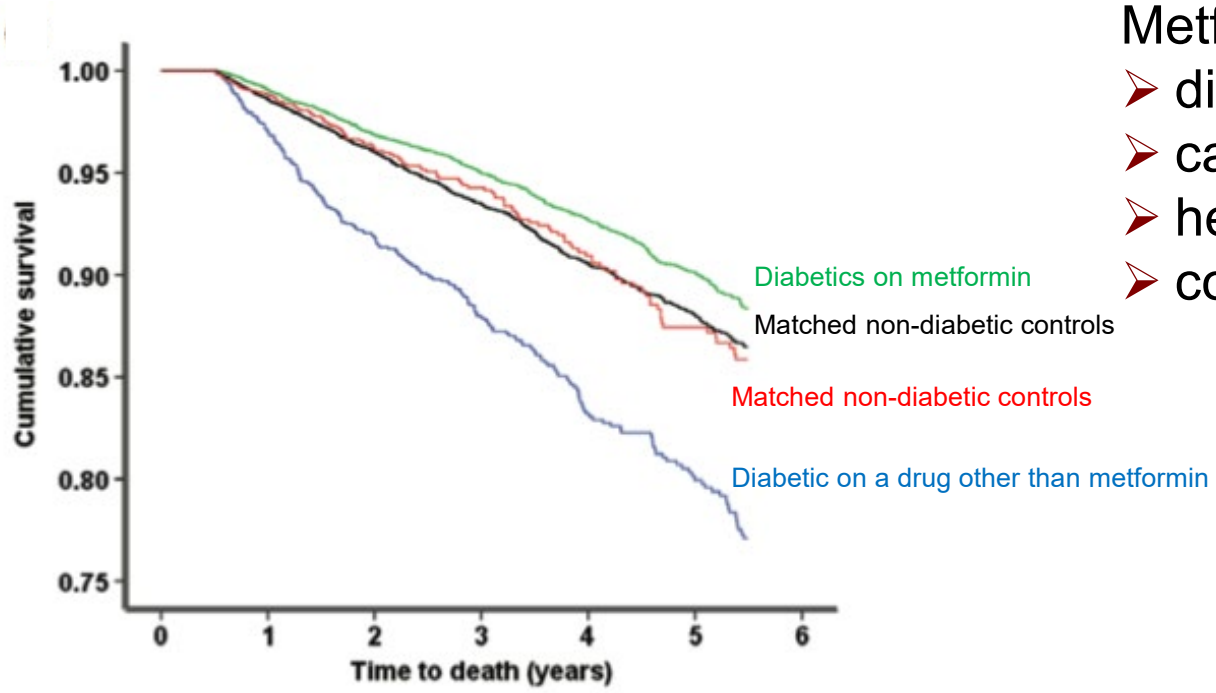
Bannister et al., 2014 Diabetes, Obes, Metab

Centenarians: evidence that healthy longevity is possible

2.5X↓ in health care $ in last 2 years of life

20+ more years of disease-free survival

Metformin: evidence it's pharmacologically possible to stave off multiple diseases with 1 pill

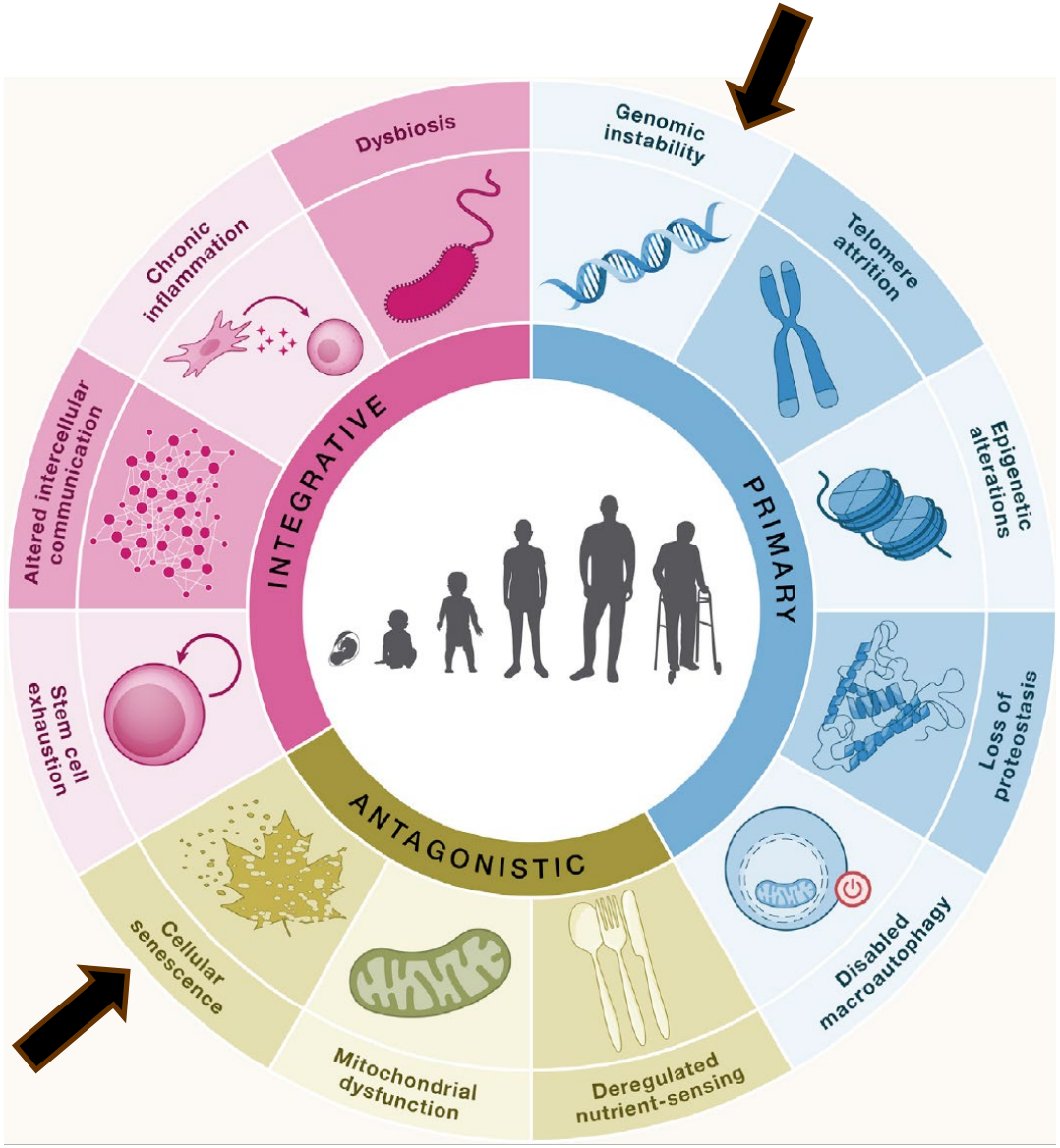


Metformin reduces the risk of:

- diabetes
- cancer
- heart disease
- cognitive decline

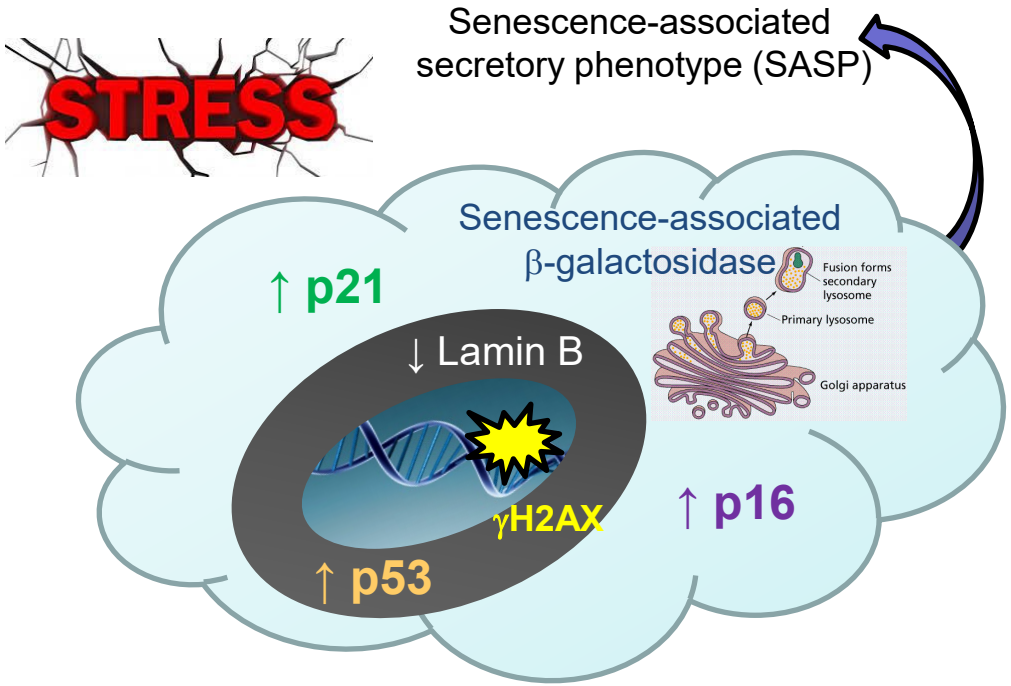
Bannister et al., 2014 Diabetes, Obes, Metab

What about aging biology can we therapeutically target?



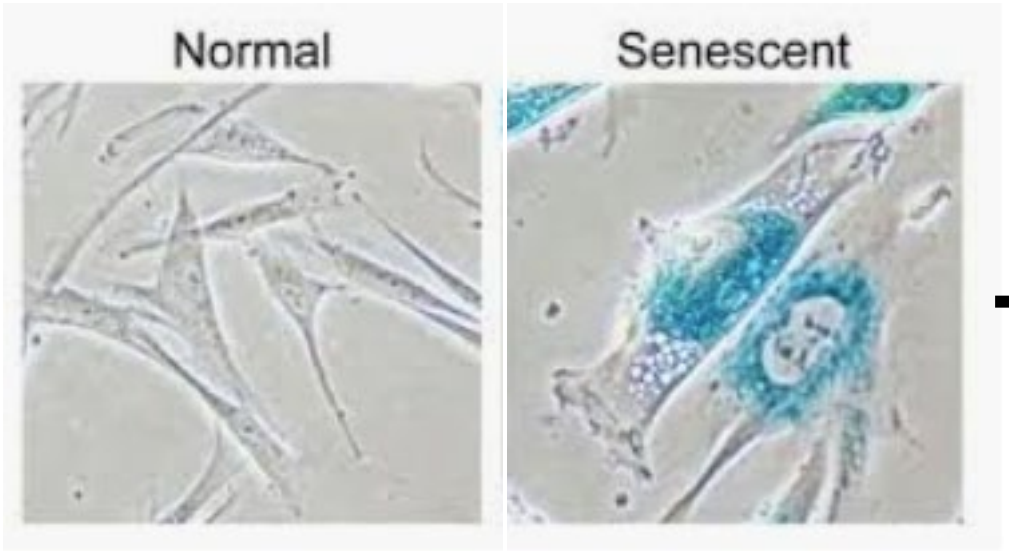
Lopez-Otin *et al*
2023 *Cell*

What are senescent cells?

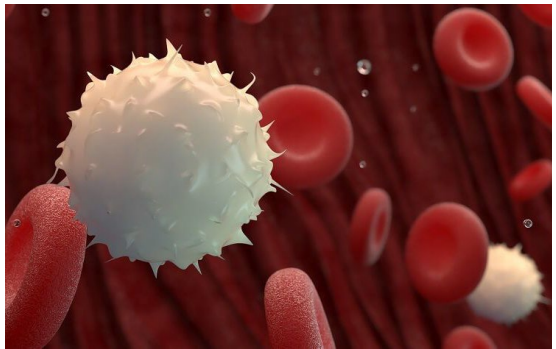


Annual Rev Pharm Toxicol 2020

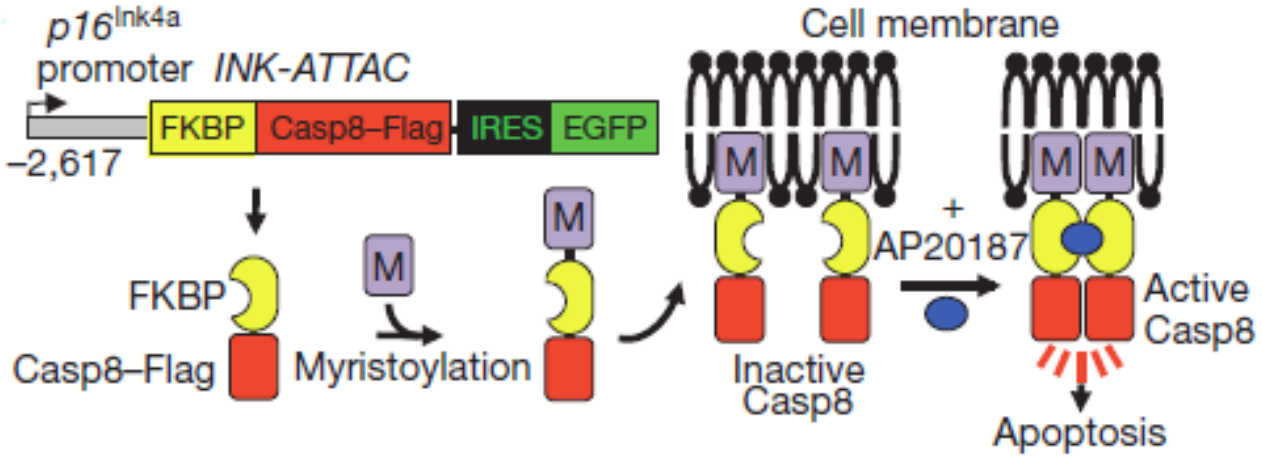
Senescent cells are pro-inflammatory

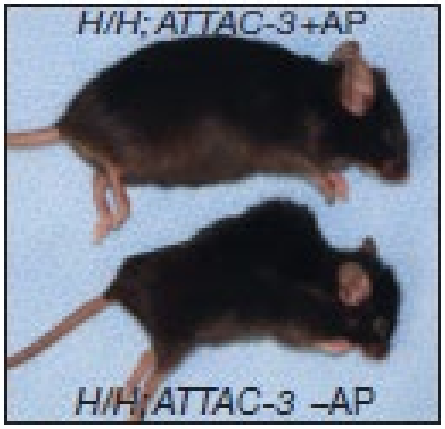


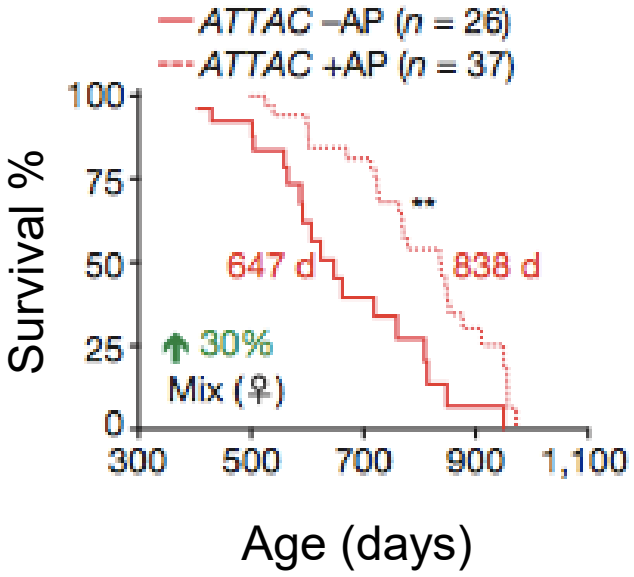
Inflammatory proteins



Senescent cells play a causal role in aging



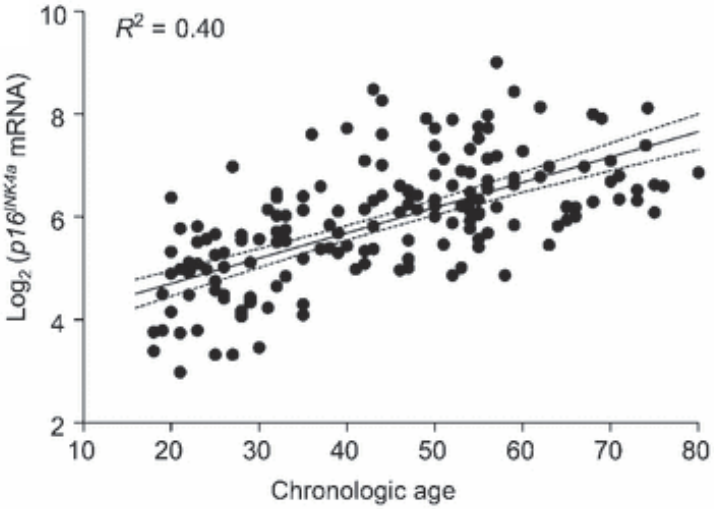


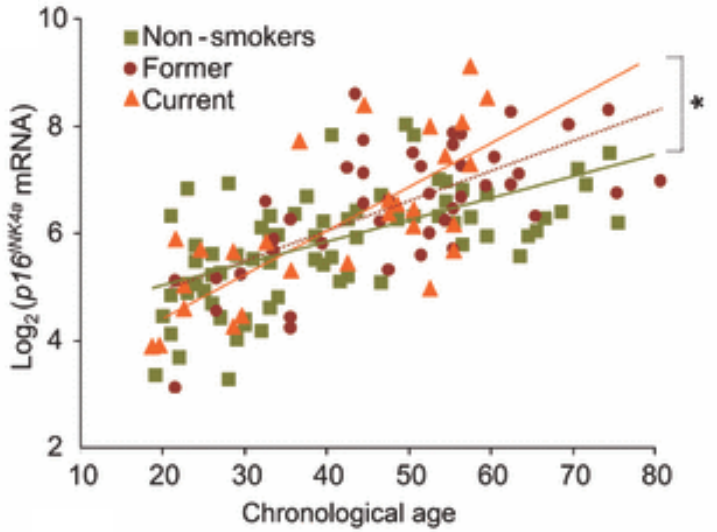


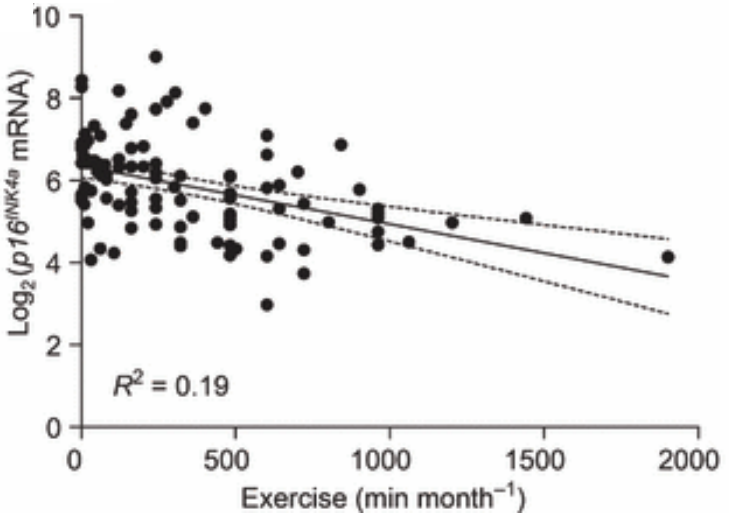
Baker et al, 2011. *Nature*

Baker et al, 2016. *Nature*

p16^{INK4a} expression in peripheral CD3^{+} cells is a marker of biological age





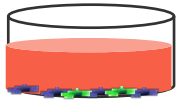


Aging Cell 8(4): 439-448 July 2009

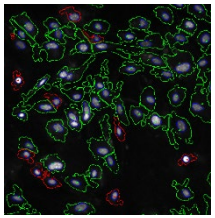
Development of drugs targeting senescent cells

Drug screening

Senescent cells



Drug screening

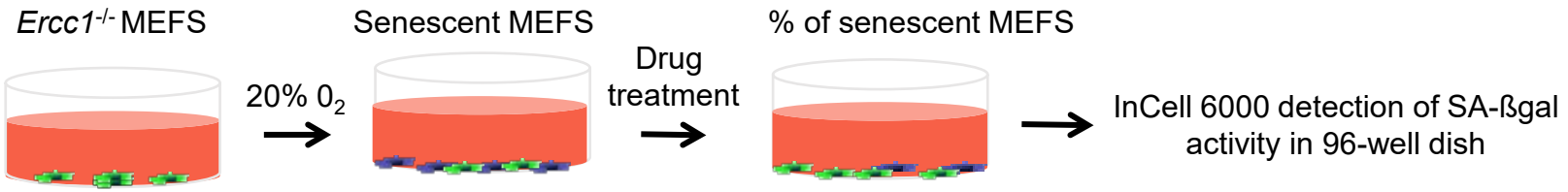


High throughput imaging

Preclinical testing

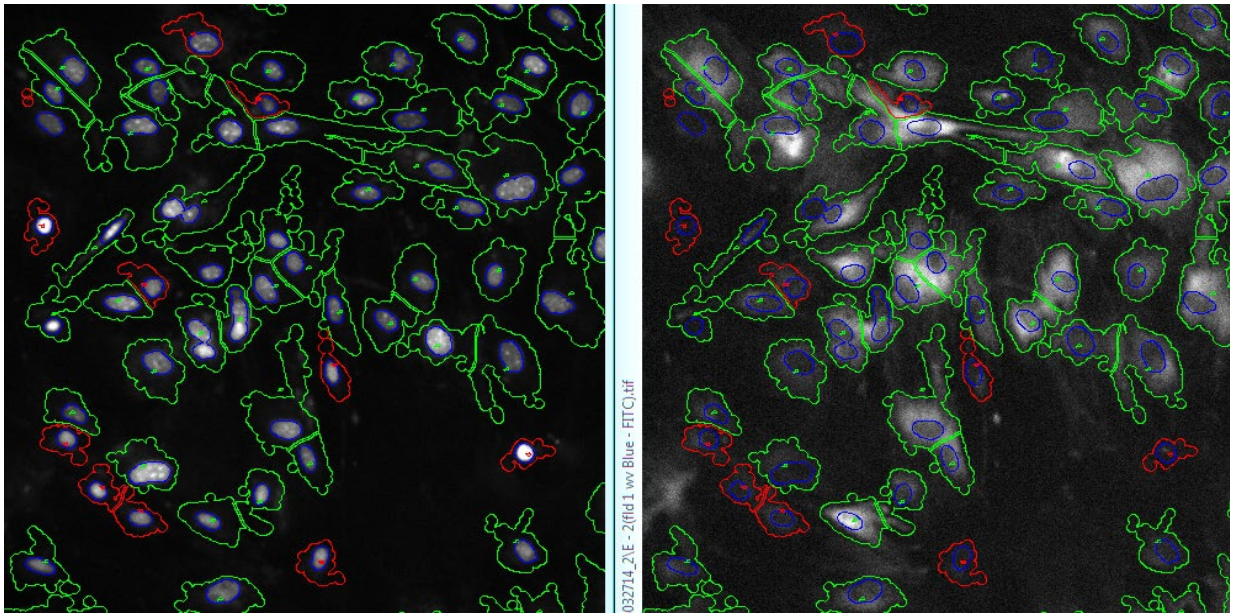
Clinical trials

Fluorescence-based assay to screen for senolytic drugs



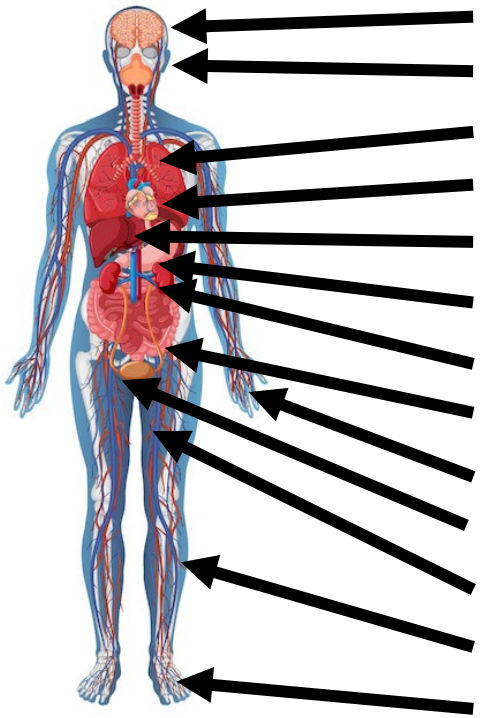
number of nuclei / field
= **# viable cells**

number of fluorescent cells
= # **senescent cells**

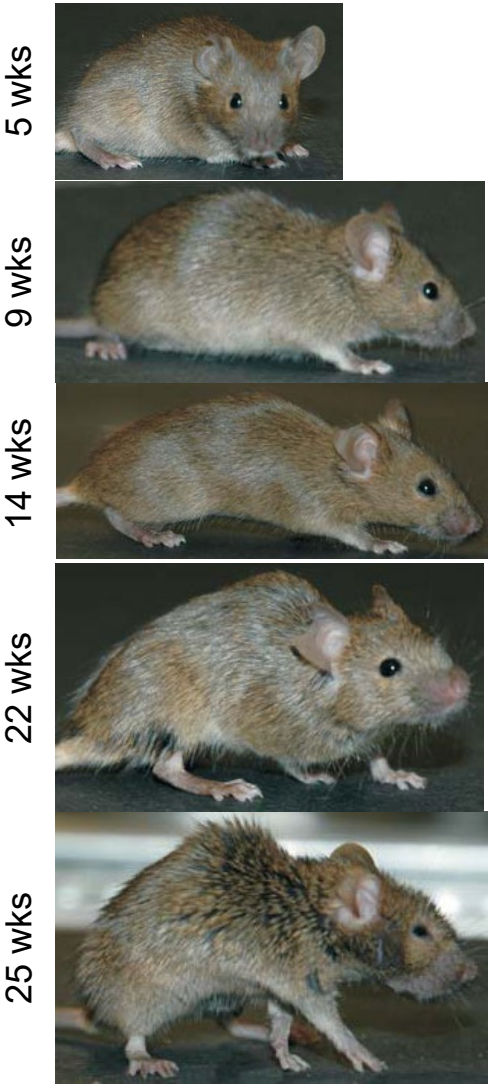


Aging Cell 2015
Aging Cell 2016
Nat Comm 2017
Lab News 2016
Nat Comm 2017
Redox Biol 2018
PLOS Biol 2018
Aging 2017
J Amer Ger Soc 2017
Nat Rev Drug Disc 2018

Ercc1$^{-/\Delta}$ mouse model of XFE progeroid syndrome



- cerebral atrophy with cognitive decline
- loss of vision and hearing
- pulmonary fibrosis
- heart failure
- hepatic fibrosis
- intervertebral disc degeneration
- chronic kidney disease
- osteoporosis
- loss of subcutaneous fat
- urinary incontinence
- fatty replacement of the bone marrow
- sarcopenia
- peripheral neuropathy



Natural product

Senomorphic

√ Cancer therapy

Senolytic

Senotherapeutics

First-generation senolytics: hypothesis-driven, mechanism-based discovery		
Agent		
Dasatinib	●	√
Quercetin		
Fisetin		
Luteolin		
Curcumin	★	
Curcumin analog EF24	★	
Navitoclax (ABT263)	●	√
A1331852	●	√
A1155463	●	√
Geldanamycin, tanespimycin, alvespimycin, and other HSP90 inhibitors		√
Piperlongumine		
FOXO4-related peptide	●	
Nutlin3a [although Nutlin3 can also cause senescence (87)]	●	
Cardiac glycosides such as ouabain, proscillaridin A, and digoxin	★	
Aspirin	★	
Second-generation senolytics: traditional and other drug discovery methods		
Method		
High-throughput compound library screens		
Vaccines		
Toxin-loaded nanoparticles preferentially lysed by Sncs		
Immunomodulators		
Cell-based therapies		

Aging Cell 2015 14(4):644

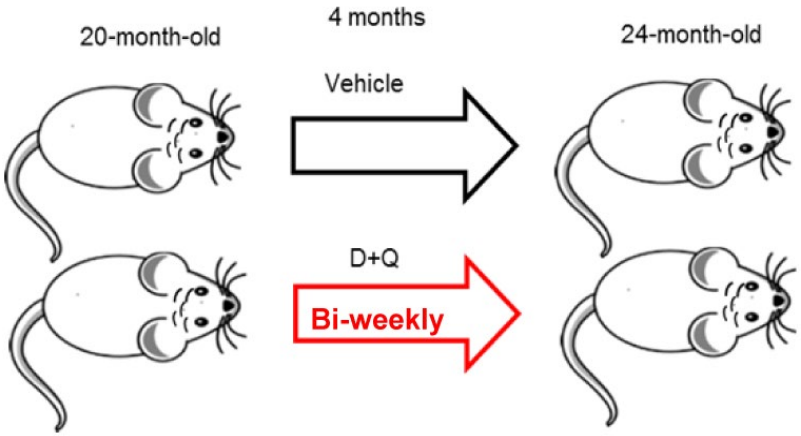
Nature Rev Drug Discovery 2018 17(5):377

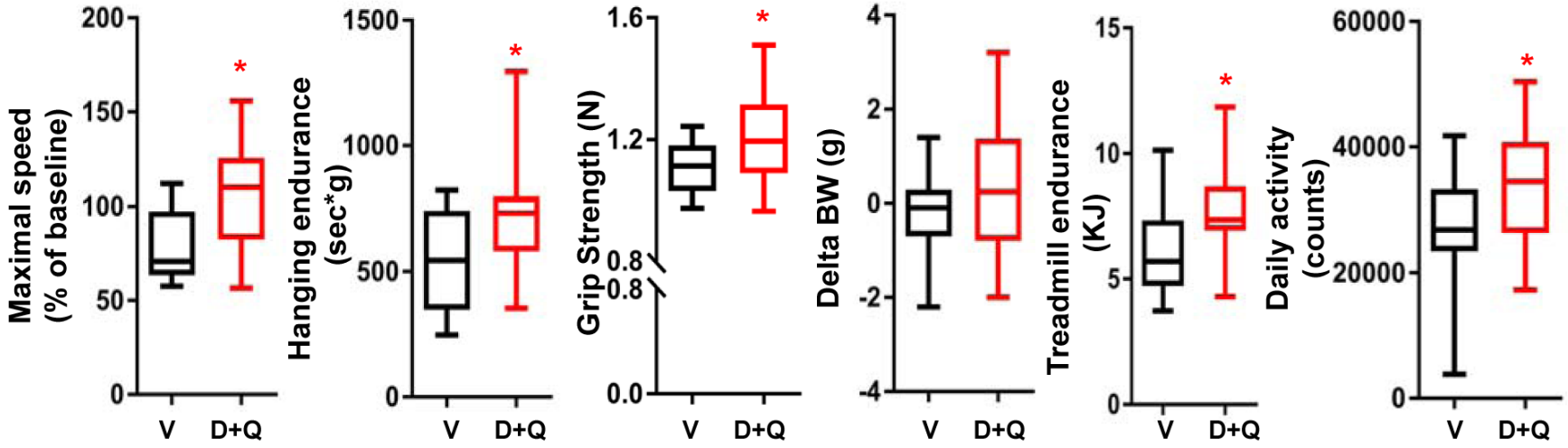
Cell 2019 179(4):813

Annual Rev Pharmacol Toxicol 2020

JNCI 2021

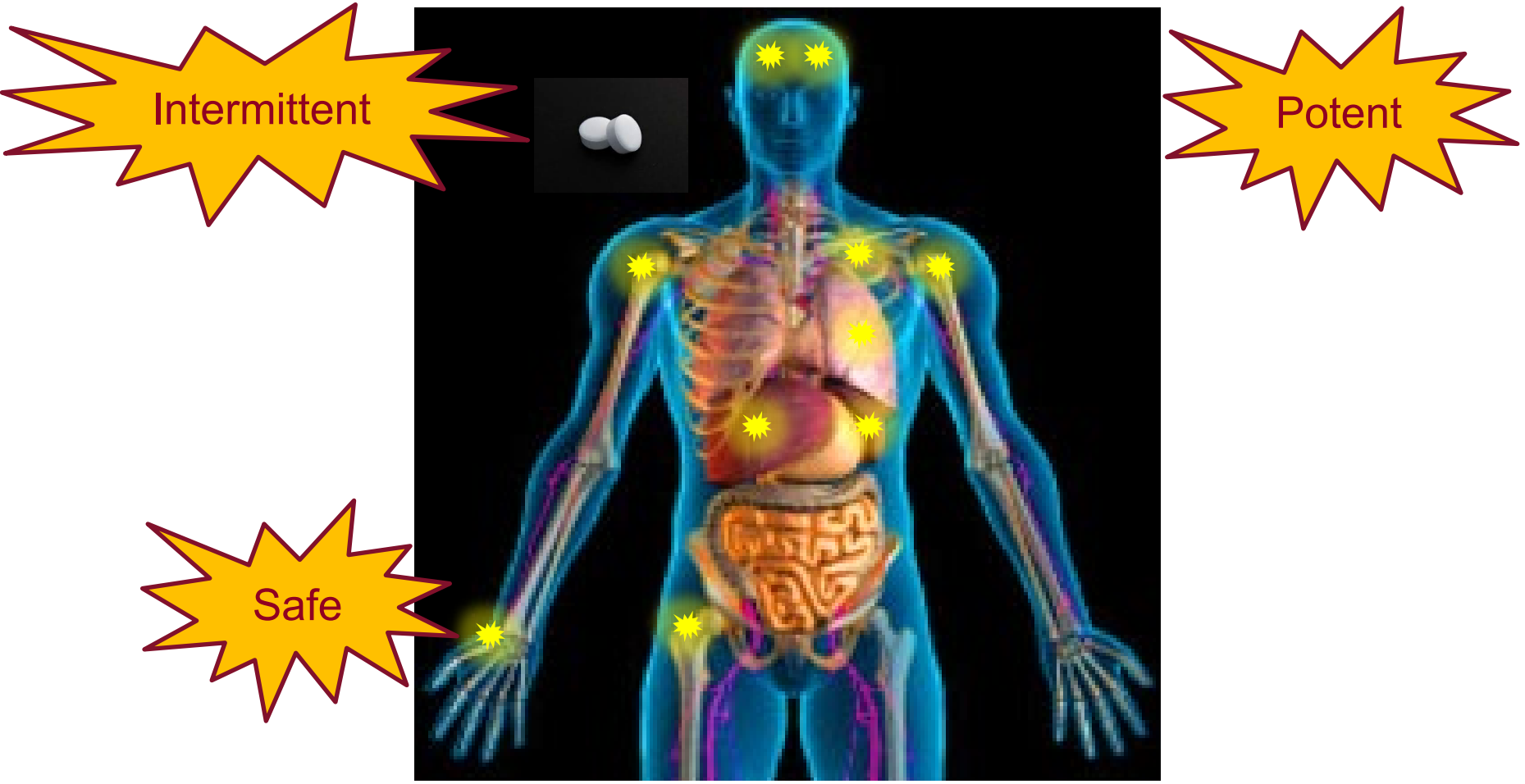
Senolytics improve physical function when administered in old age





Xu *et al.*, *Nat. Med.*, 2018

How senolytics are envisioned to work



Diseases in which senolytics work (in mice)

- Neuromuscular dysfunction
- Tauopathy (Alzheimer's disease)
- Pulmonary fibrosis
- AV fistulae
- Steatosis
- Hepatic fibrosis
- Osteoporosis
- Osteoarthritis
- Atherosclerosis
- Kidney disease
- Cardiovascular disease
- Frailty
- COVID-19

2015 → 2018 → 2024

Senolytics first described

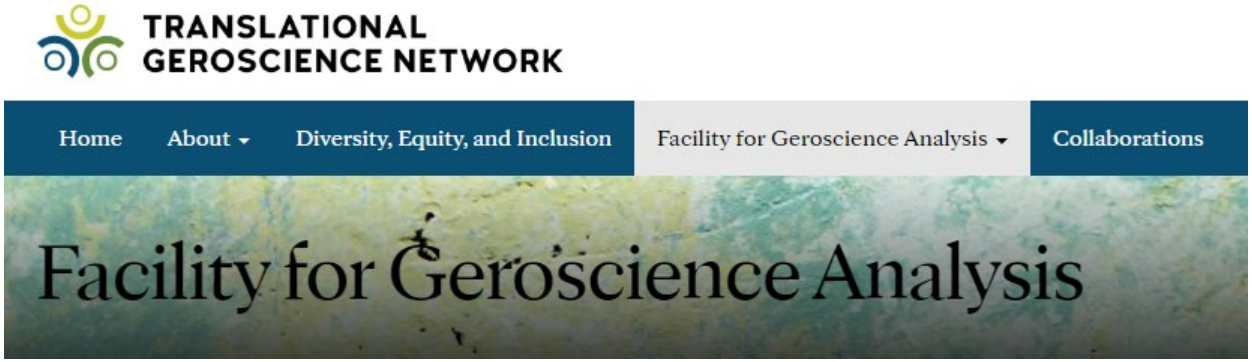
First clinical trial

>40 clinical trials

SenNet Consortium

https://sennetconsortium.org/

https://www.gerosciencenetwork.org/



https://www.gerosciencenetwork.org/

FDA-approved drugs that could be repurposed as Gerotherapeutics

Drug	Organs affected in humans	Affects in humans	Organs affected in mice	Affects in preclinical models	Hallmark of aging impacted
SGLT2i	Pancreas CV Renal	Healthspan Lifespan	CV Pancreas Liver, Renal	Lifespan (Healthspan)	Mitochondria Autophagy Metabolism
Metformin	Pancreas Liver CV, CNS	Healthspan Lifespan	Bone/cartilage CNS Muscle	(Lifespan) Healthspan	ROS, DNA damage, Mitochondria, Autophagy Inflammation, Senescence, Metabolism, Stem cell
Acarbose	Pancreas CV	Healthspan	CNS Renal Pancreas CV	Lifespan Healthspan	Inflammation Metabolism
Rapamycin	Immune	(Healthspan)	CNS, Eye, CV, Liver ♀ Reproductive Muscle	Lifespan Healthspan	ROS, DNA damage, Autophagy Inflammation, Senescence, Metabolism Stem cell
Methylene blue	CV	Healthspan	CNS	Lifespan (Healthspan)	ROS Mitochondria Senescence
ACEi & ARBs	Pancreas, CV, Renal CNS, Pulmonary Bone, Muscle	Healthspan Lifespan	Muscle CV	Lifespan Healthspan	Autophagy ROS
Fisetin or D+Q	Pulmonary Renal Muscle	n/a	CNS, Muscle, Bone, CV Pulmonary, ♀ Reproductive Liver, Pancreas	Lifespan Healthspan	Senescence Inflammation Metabolism Stem cell
Aspirin		n/a	CNS CV	Lifespan Healthspan	ROS, DNA damage, Autophagy Inflammation, Senescence, Metabolism, Epigenetics
N-acetyl- cysteine		n/a	CNS	(Lifespan) (Healthspan)	ROS

Kulkarni et al. Aging Cell 2022

Longevity Landscape

Commercial:	Altos
	Cambrian
	Juvenescence
	Life Biosciences
	Elysium
	Unity Biologics
Granting organizations:	AFAR
	Astera Institute
	Impetius
	VitaDAO
Social catalysts:	The Academy for Healthspan and Lifespan Research
	Ondeck Longevity Fellowships
	Beyond Aging
	SENS
	A4LI
Mega Foundations:	The Milkyway Foundation
	Hevolution
	Longevity Science Foundation
Industry vehicles:	Longevity Biotechnology Association
	The Alliance for Longevity Initiatives

Congress of the United States

House of Representatives

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

2321 RAYBURN HOUSE OFFICE BUILDING

WASHINGTON, DC 20515–6301

(202) 225–6375

www.science.house.gov

No, we won't defeat aging!

However, by studying aging, we hope to postpone disease, frailty, and disability

Niedernhofer Lab


Linshan Shang
Ph.D.


Vinal Menon
Ph.D.


Carolina
Soto-Palma, Ph.D.


Chathurika
Henpita, Ph.D.


Akilavalli
Narasimhan, Ph.D.


Beth Thompson
Ph.D.


Sara McGowan
B.S.


Peter Gullikson
B.S.


Luise Angelini
B.S.


Ryan O'Kelly
B.A.


Mackenzie Plummer
B.S.


Vicky Usina
B.S.


Mickayla DuFresne-To
B.S.


Sam Peters
B.S.


Hector Martell
Martinez, B.S.


Josh Carey
B.S.


Joe Robin
B.S.


Jiayi Hu
Grad student

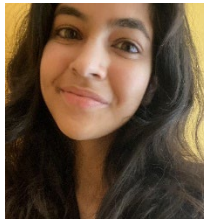

Tra Kieu
Grad student

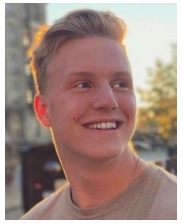

Rahagir Salekeen
Grad student


Karah Shirley
undergrad


Caeden Windschitl
undergrad

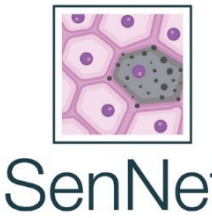

Alexa Soto
undergrad


Mehek Jahan
B.S.


Brittan Burns
B.S.

Funding


NIH
National Institute
on Aging


SenNet


NIH
The Common
Fund


MERCK SHARP & DOHME


UNIVERSITY OF MINNESOTA
FOUNDATION


asap
Aligning Science
Across Parkinson's


Pfizer


NIH
NIEHS