Geroscience

Aging

XP and Potential Therapeutics

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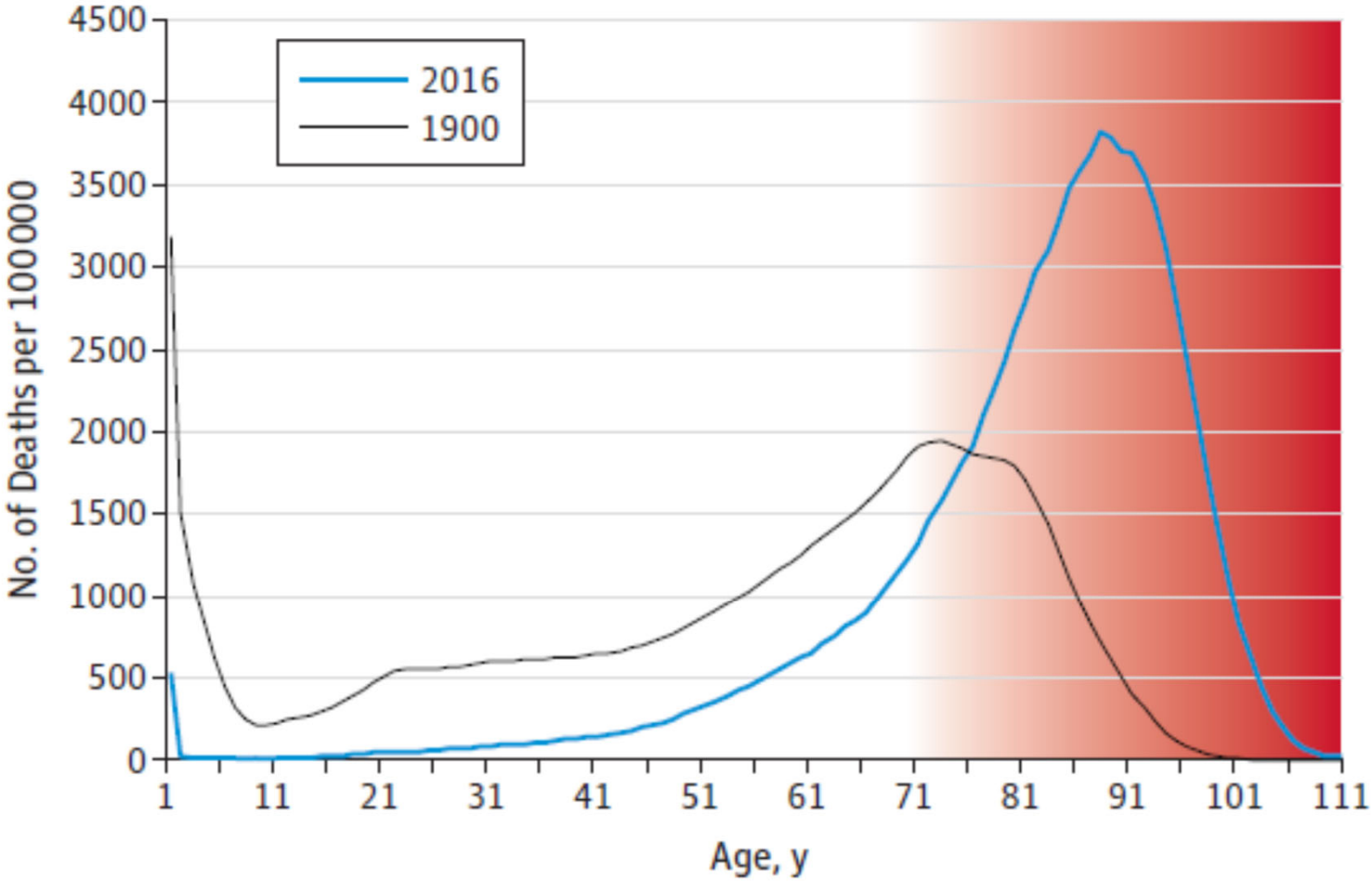
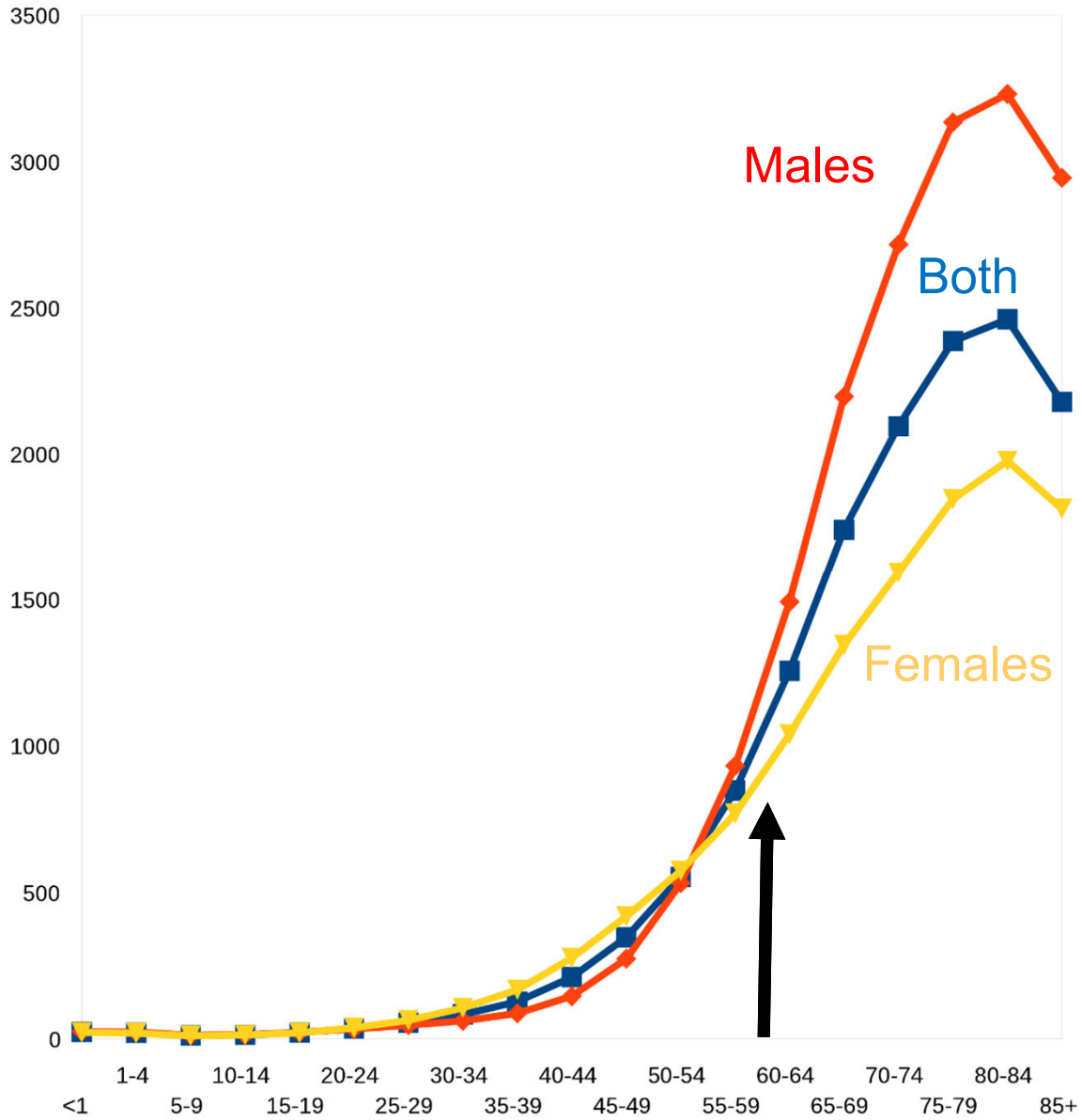
How we got here: an aging success story



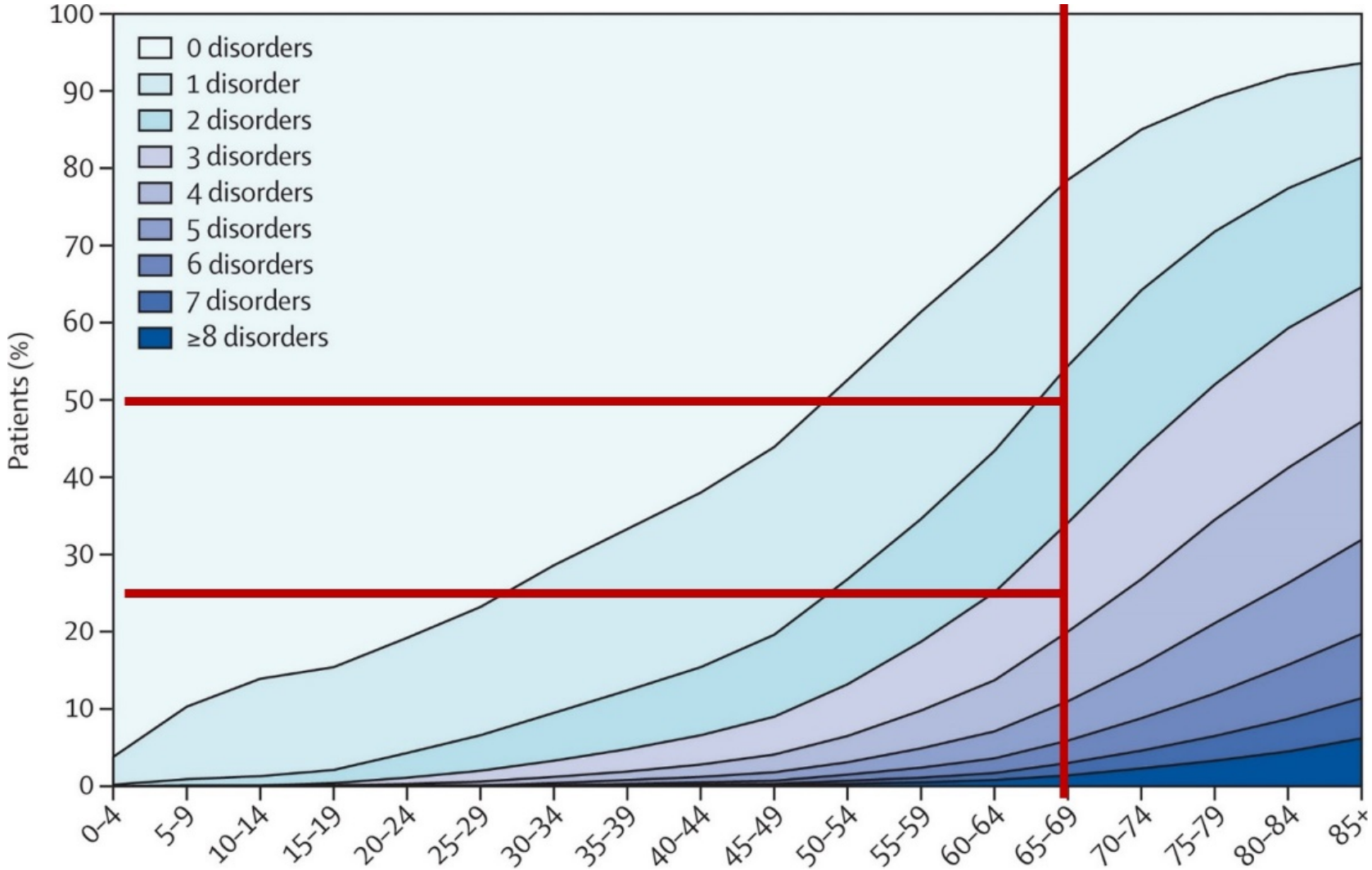
Jay Olshansky 2018 JAMA

Exponential increase in disease risk after 60



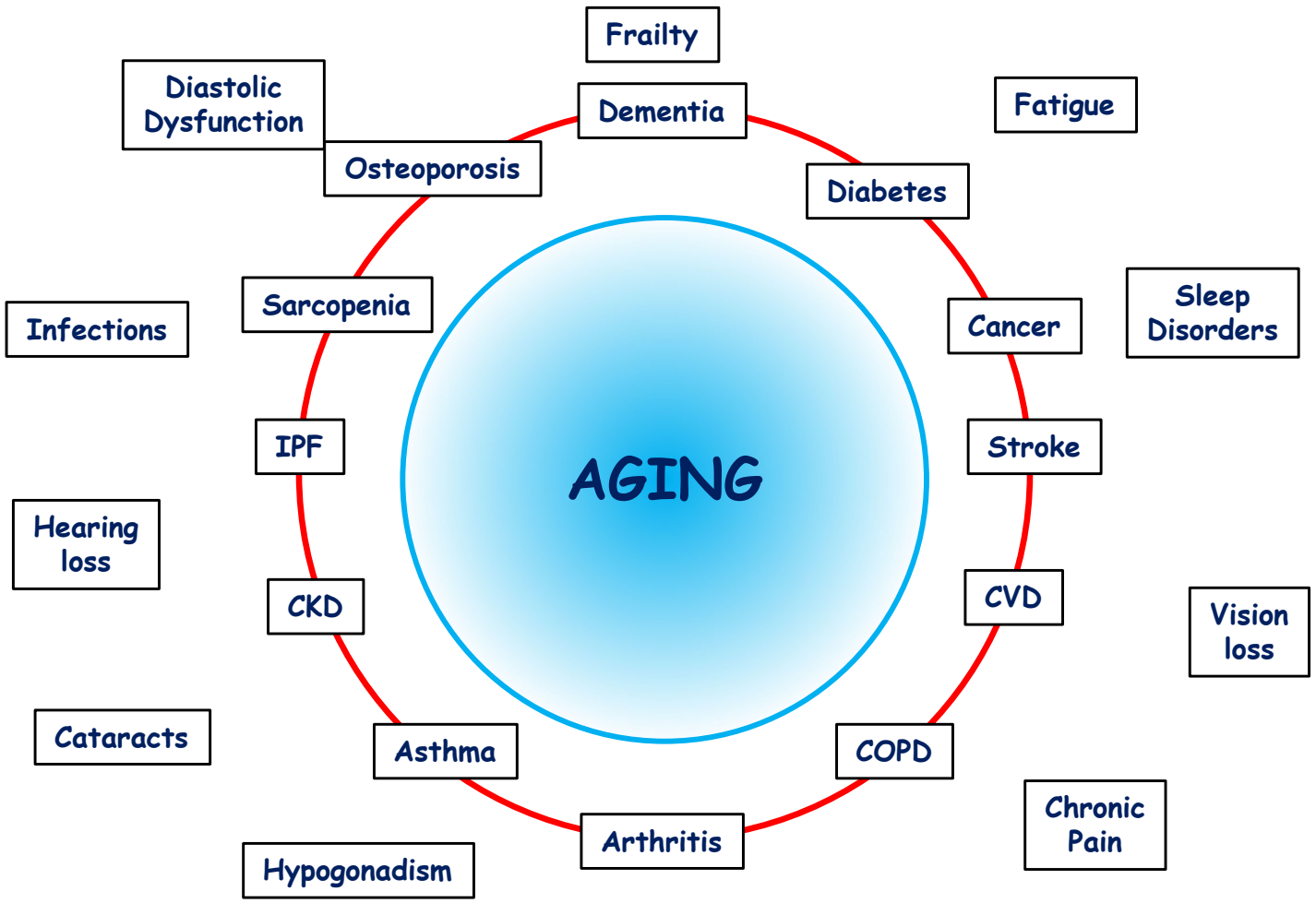
- osteoporosis
- cardiovascular disease
- neurodegenerative diseases
- osteoarthritis
- type II diabetes
- cancer
- macular degeneration
- intervertebral disc degeneration
- hearing loss

Most elderly individuals have >1 disease



Risk factors for heart disease

Geroscience Hypothesis



Geroscience: Treat aging biology

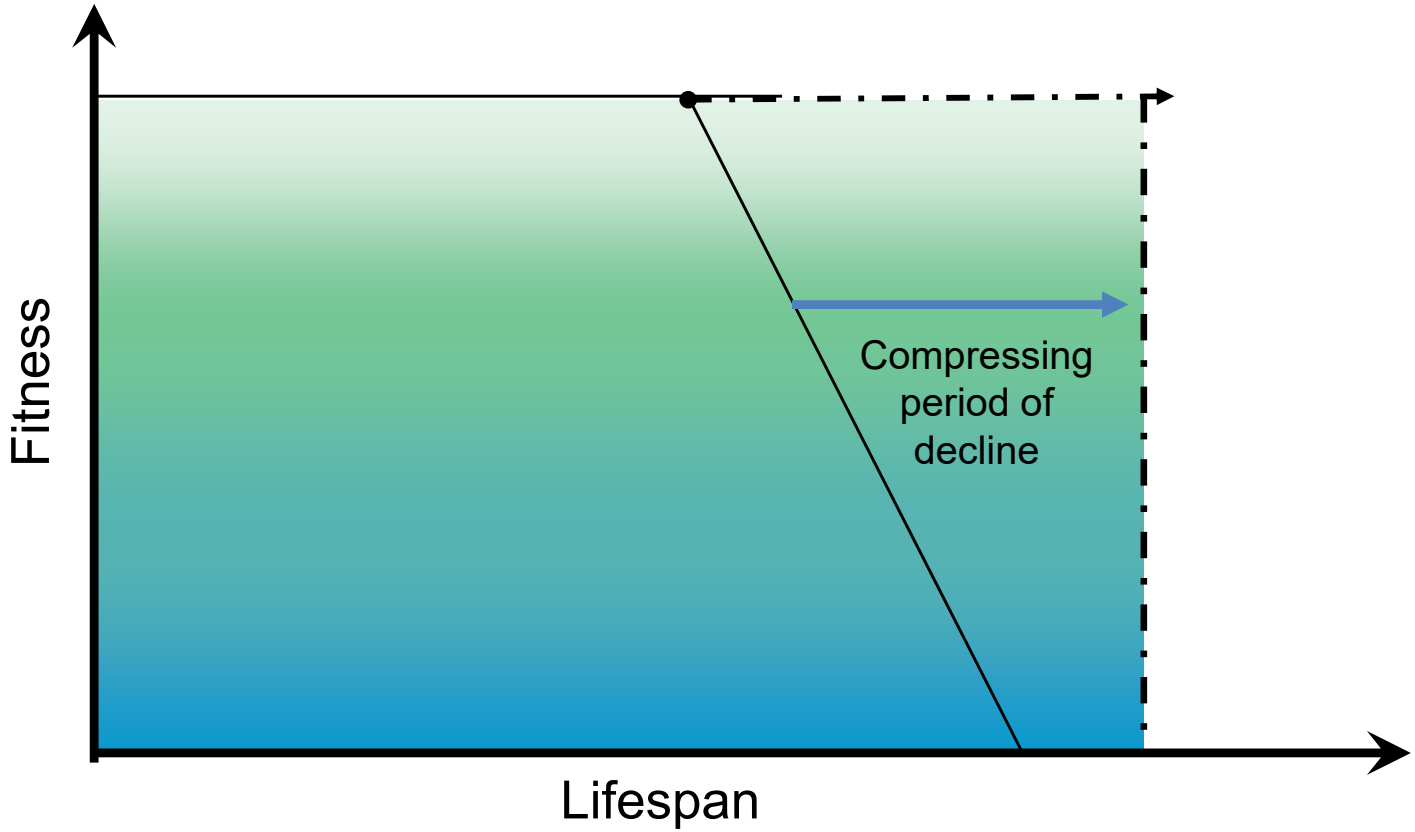
+ prevent, delay or ameliorate multiple debilitating, chronic degenerative diseases

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

+ avoid polypharmacy

+ reduce healthcare costs

Goal:
increase healthspan, not lifespan



Extension of Healthspan/Lifepan is feasible

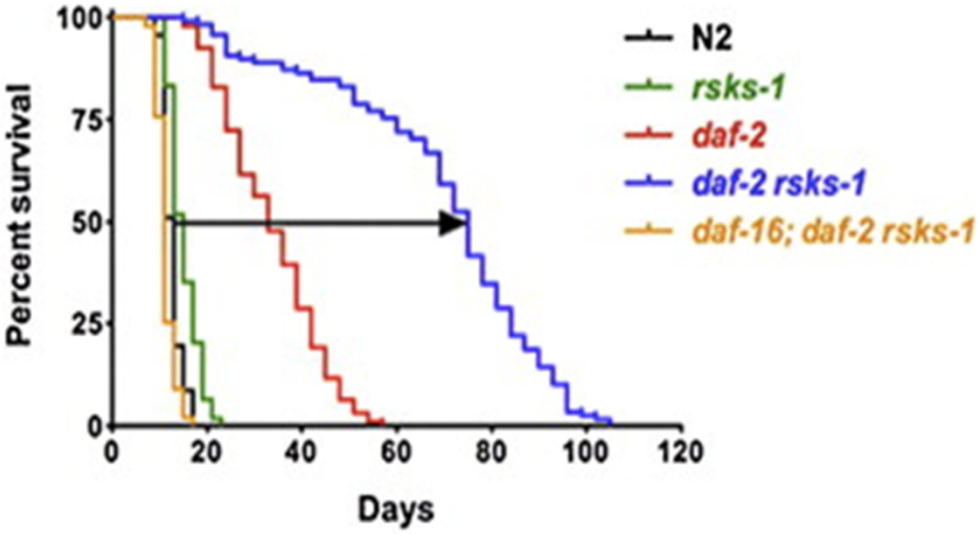
Naked mole rat: 30 years

Red sea urchin: 200 years

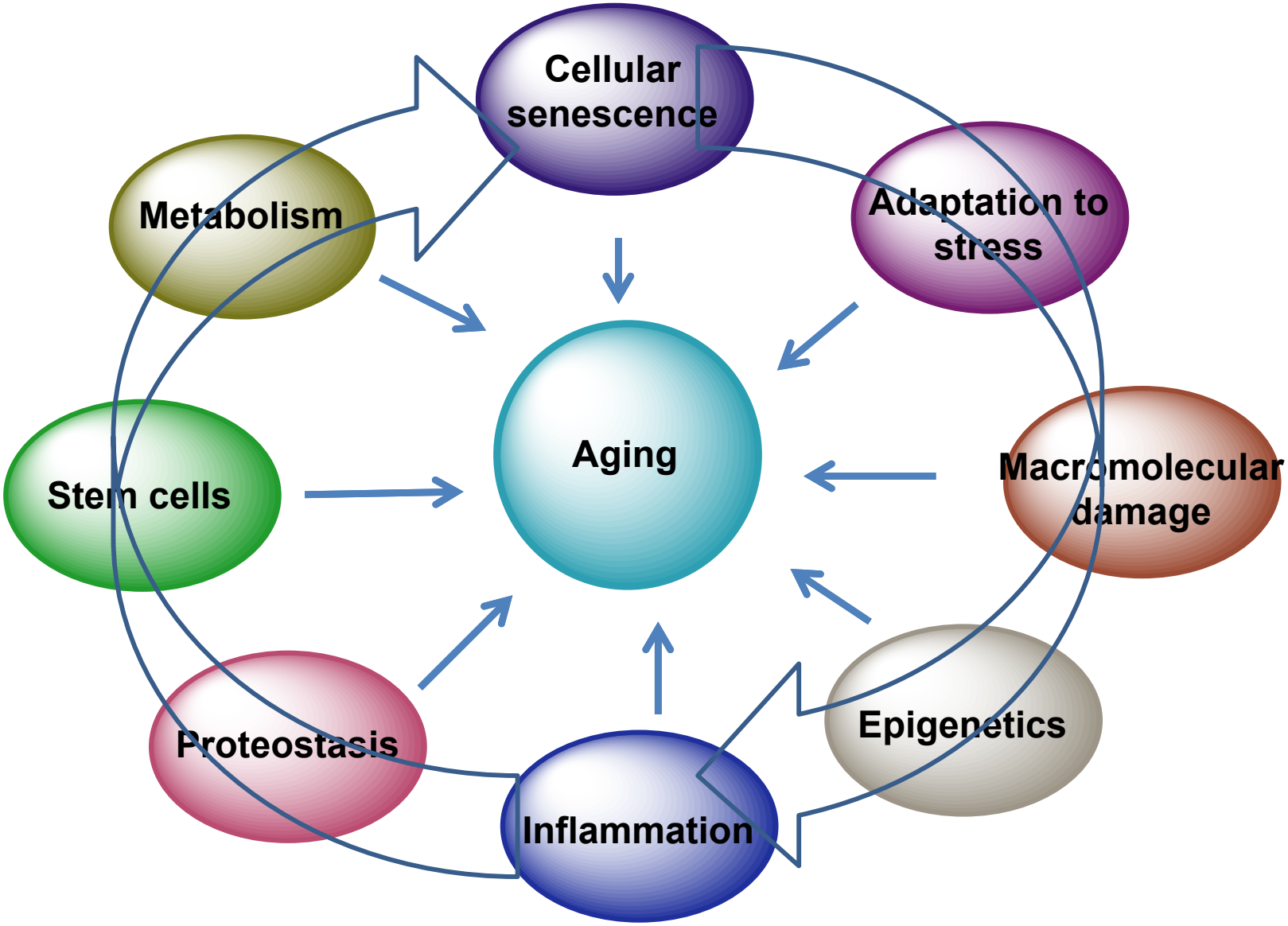
Bowhead whale: >200 years

Quahog clam: >507 years

C. elegans: < 3 weeks



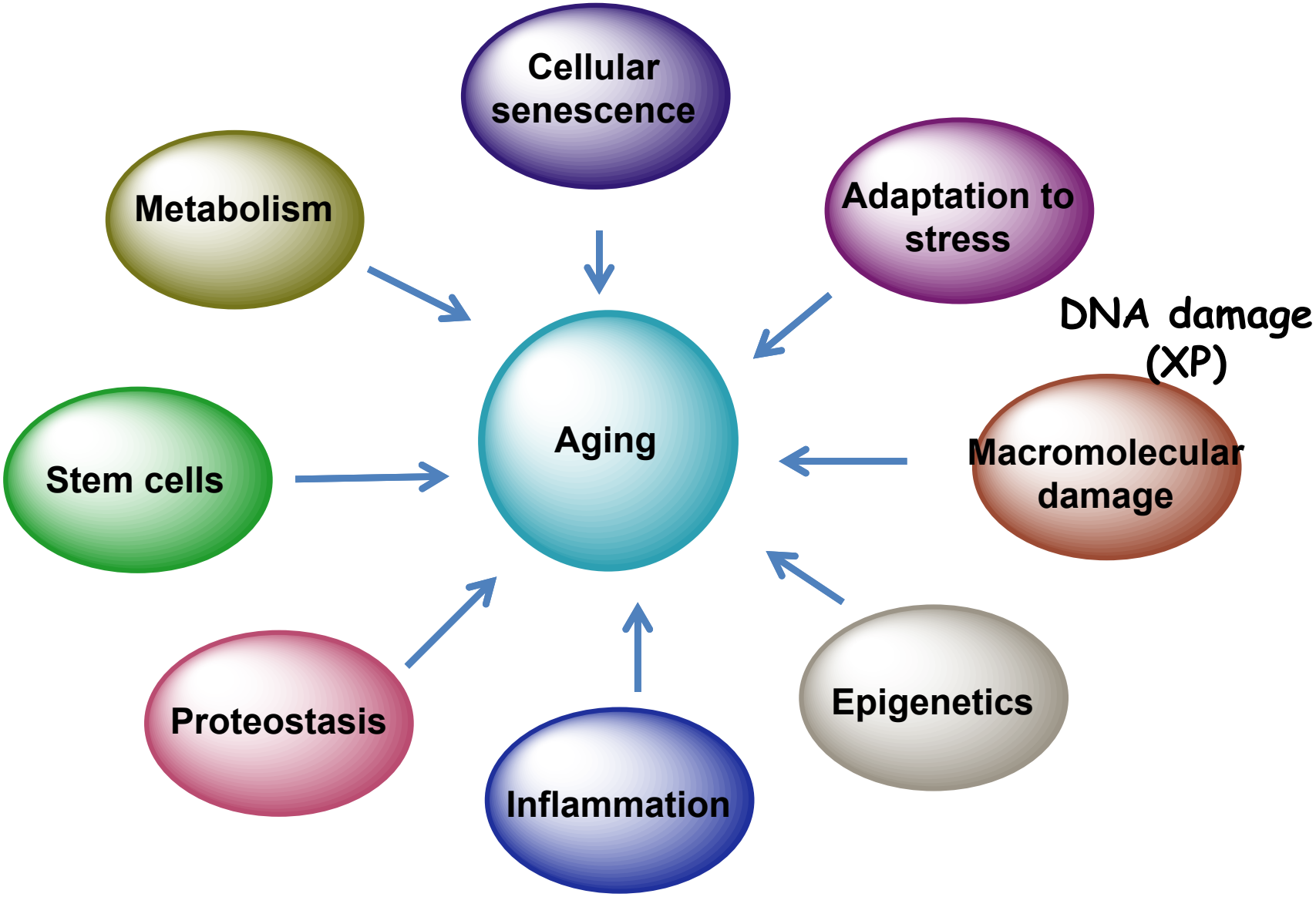
What about aging can we therapeutically target?



Hallmarks of Aging

Kennedy et al. 2014. *Cell*

DNA damage drives aging



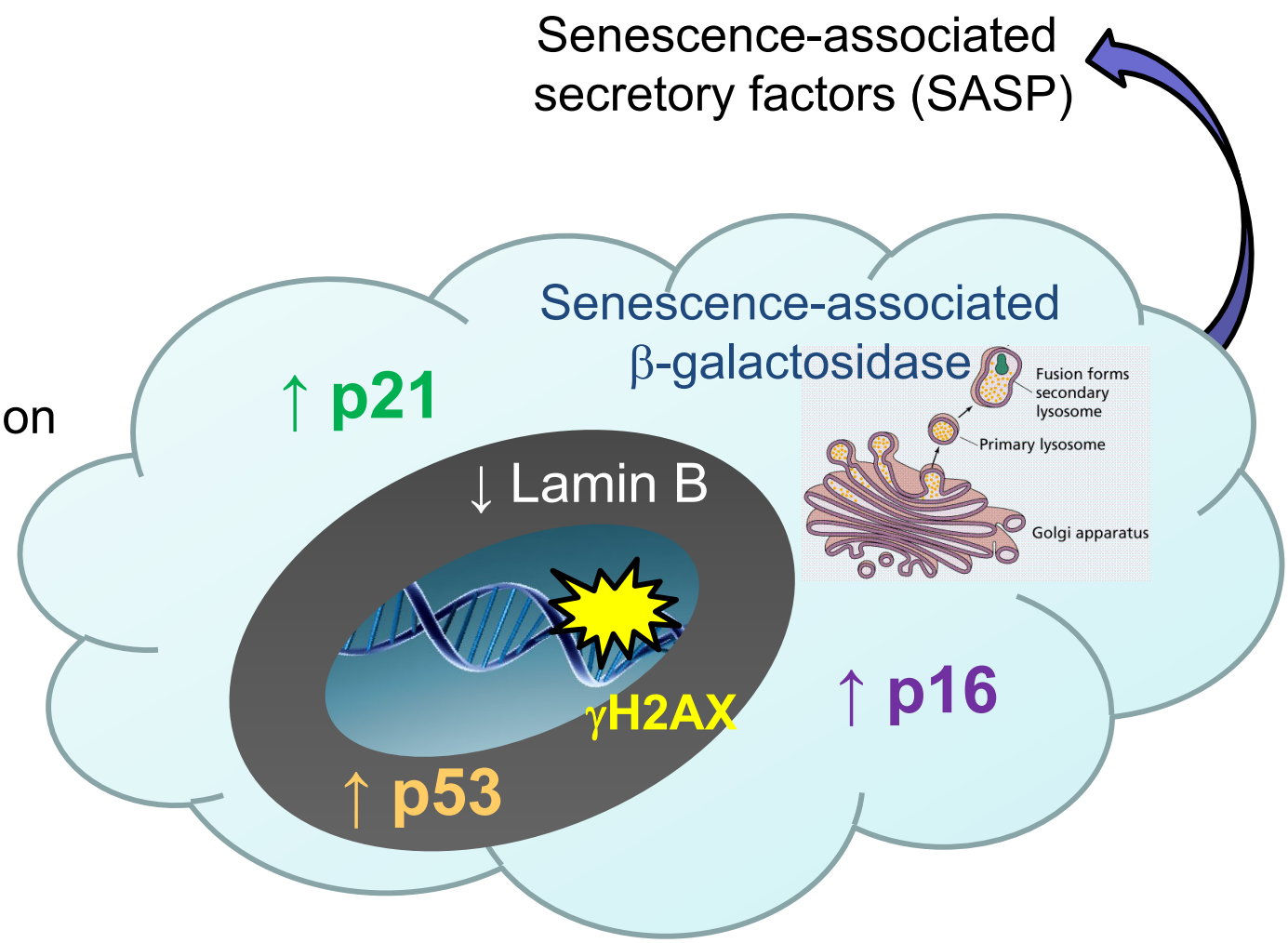
Hallmarks of Aging

Available therapeutics that target >1 hallmark of aging

Drug	Hallmark of aging impacted
LSD1 inhibitors	Epigenetics, senescence, inflammation
Acarbose	Inflammation, metabolism
Rapamycin	ROS & DNA damage, autophagy, stem cells inflammation, senescence, metabolism
Canagliflozin	Mitochondria, autophagy, metabolism
Metformin	ROS & DNA damage, mitochondria, autophagy inflammation, senescence, metabolism, stem cells
Senolytics	Senescence, inflammation, metabolism, stem cells
Aspirin	ROS & DNA damage, autophagy, inflammation, senescence, metabolism, epigenetics

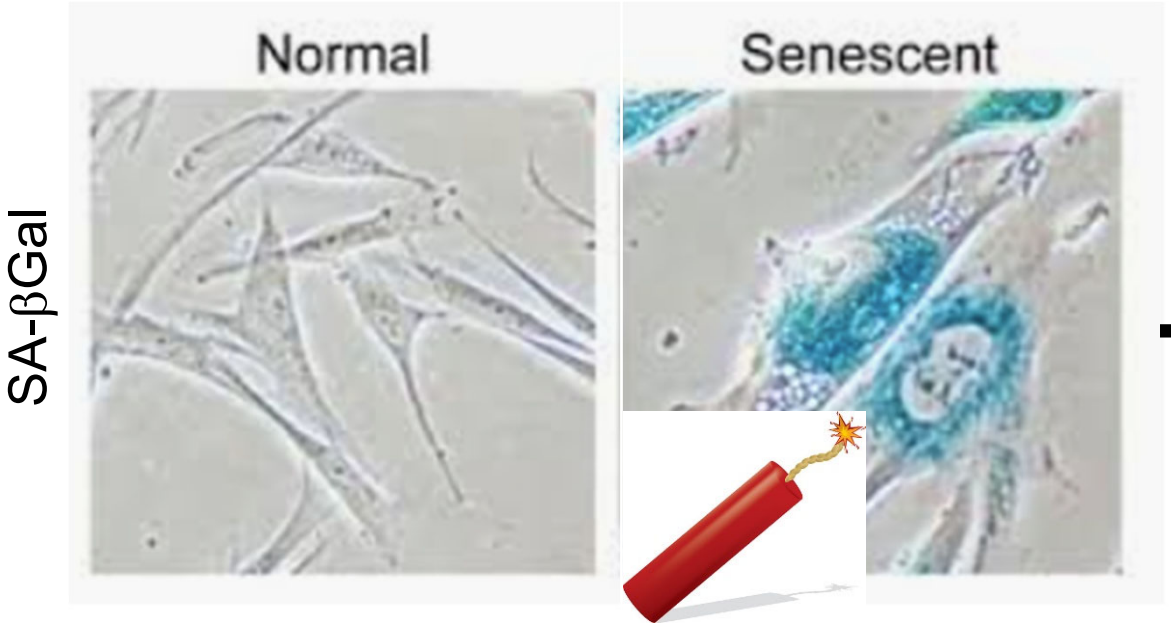
Senescent cells

Triggers:
mitotic stress
telomere erosion
DNA damage
epigenetic stress
oxidative stress
ER stress
mitochondrial dysfunction
proteotoxic stress
nucleolar stress
nutritional stress

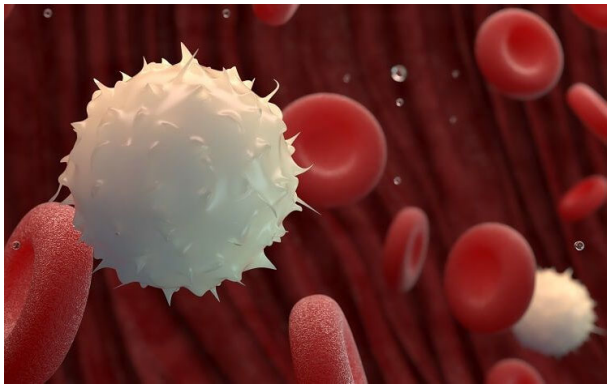


Annual Rev Pharm Toxicol 2020

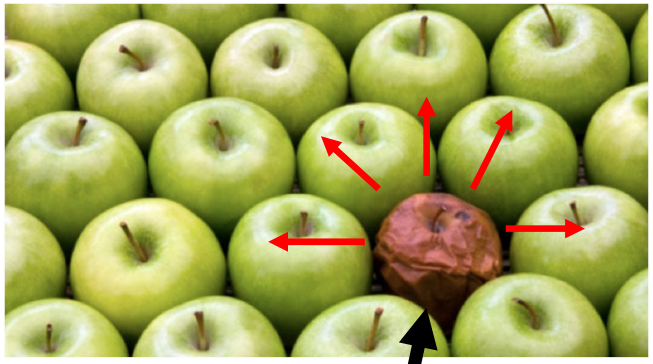
Senescent cells are pro-inflammatory



Inflammatory proteins



Rotten apples



Senescent cell

A few bad apples can spoil a whole bushel

Damaged tissue

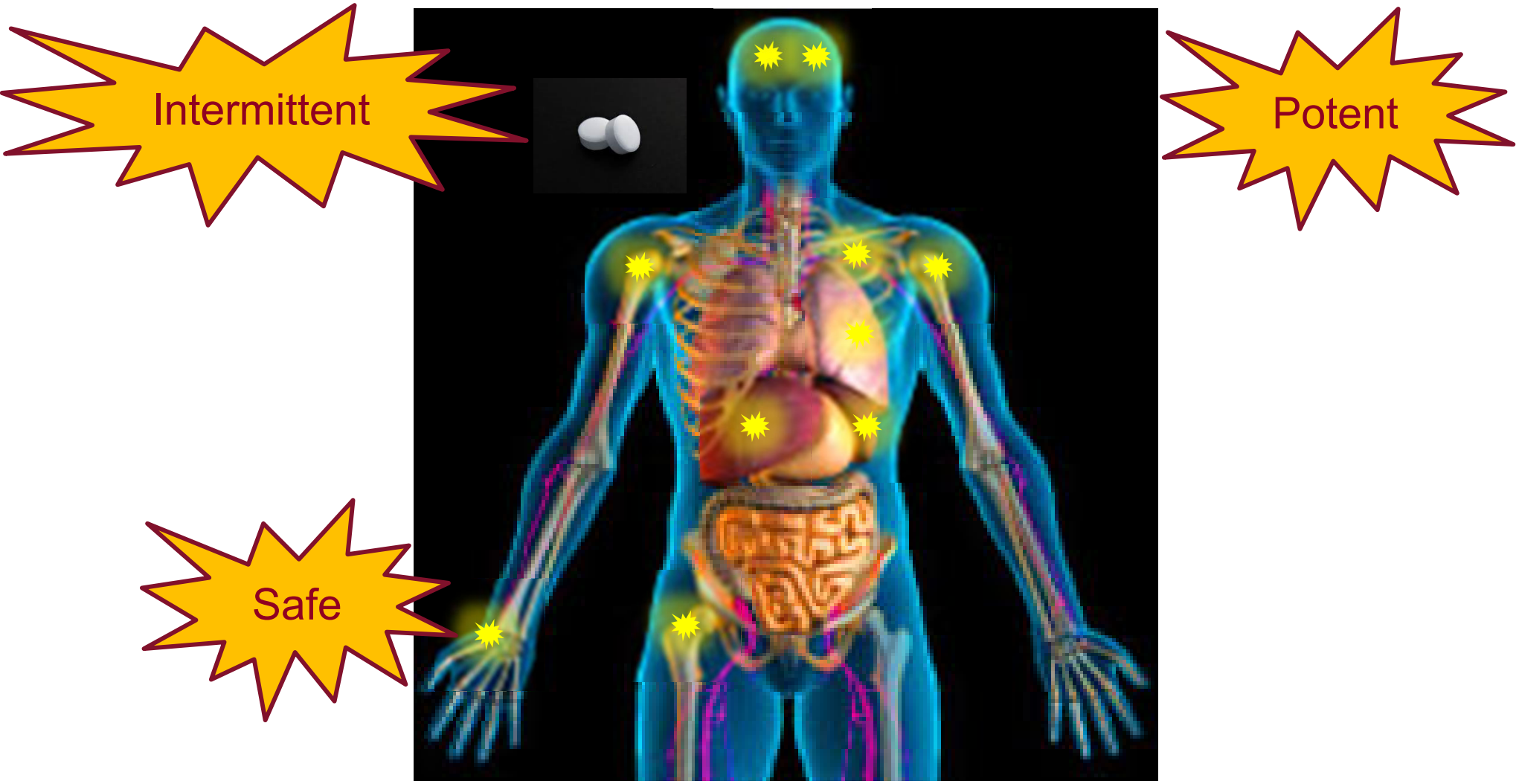
A few senescent cells can cause inflammation and tissue destruction

Senotherapeutics

Natural product
Senomorphic
√ Cancer therapy
Senolytic
XP mouse model

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				

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
- XP

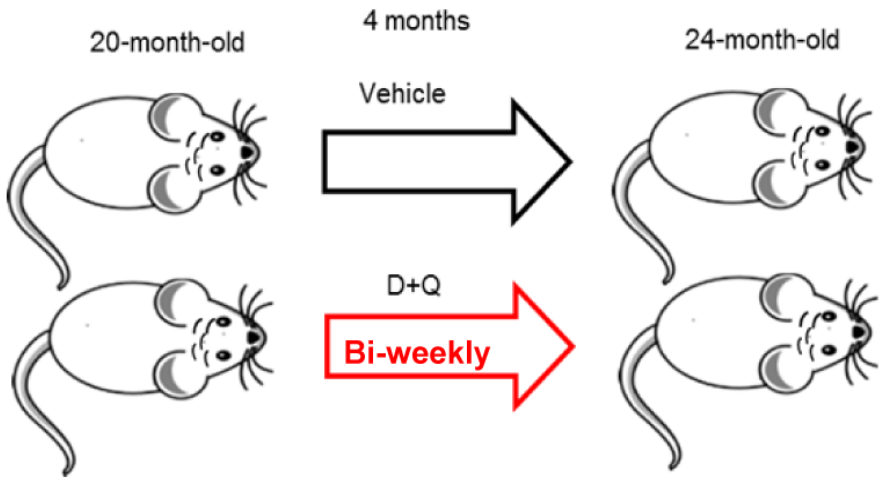
2015 → 2018 → 2021

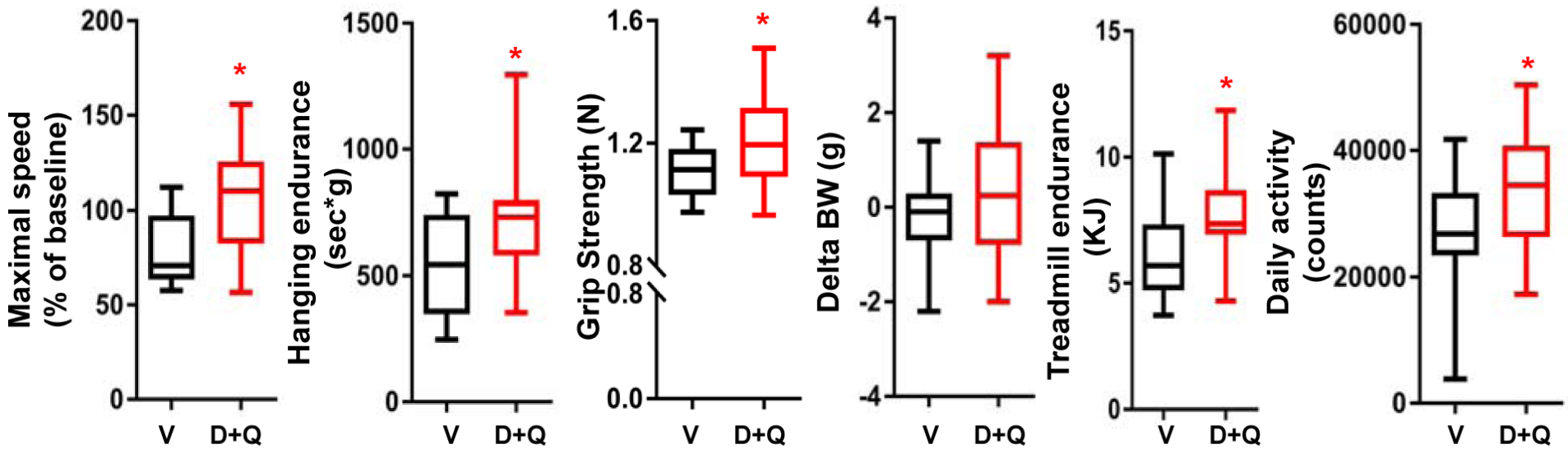
Senolytics first described

First clinical trial

>20 clinical trials

Senolytics improve physical function when administered in old age

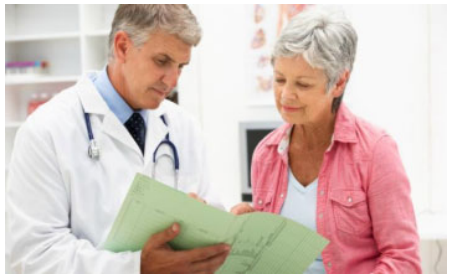




Xu *et al.*, *Nat. Med.*, 2018

Senolytic Clinical Trials

Phase I/II underway or planned
based on UMN/Mayo pre-clinical data



- Idiopathic pulmonary fibrosis (NCT028749819)
- Age-related osteoporosis (NCT04313634)
- Osteoarthritis (NCT04210986)
- Frailty (NCT03675724)
- Bone marrow transplant survivors (NCT02652052)
- Alzheimer's disease (NCT0463124)
- Diabetic chronic kidney disease (NCT02848131)
- Childhood cancer survivors (NCT04733534)
- Improving outcomes after transplanting organs from old donors
- Reducing mortality in elderly Covid-19 patients (NCT04476953, NCT04537299, NCT04771611)

Laura’s team at work on the skin biopsies

Biomarkers related to Hallmarks of Aging

Hallmark of aging	Measure	Sample
Mitochondrial function	Cell mitochondrial content	Skin fibroblasts/keratinocytes - stain
Autophagy	p62 mRNA	PBMC - RNA qPCR
Metabolism	NAD+	Blood drop dip stick
ROS	4-HNE	PBMC protein lysate - ELISA
DNA damage	γH2AX foci and 8-oxo-dG	PBMC and skin fibroblasts/keratinocytes - stain
Inflammation	SASP	Plasma - ELISA
Senescence	SA-ßGal Senescence & SASP biomarkers	Skin fibroblasts/keratinocytes and PBMC - qPCR RNA
Stem cell function	Differentiation	
Epigenetics	GrimAge clock	PBMC DNA