

# Advances in Biogerontology: Clinical Promise and Ethical Pitfalls

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**Buck**



Division of  
Geriatrics  
Department of Medicine

**Live better longer**

A photograph of the Golden Gate Bridge in San Francisco, California, taken from a high vantage point on a hillside. The bridge's iconic orange-red towers and suspension cables are prominent on the right side of the frame. The bridge spans across the water towards the city skyline in the distance. The sky is a mix of soft orange and blue, indicating sunset or sunrise. The water is a deep blue-grey. In the foreground, there is a grassy hillside with some low-lying vegetation.

**Who Am I?**

**San Francisco, USA**

**Geroscience at Buck Institute:**

**Metabolic signals that regulate aging**

**Geriatrician at UCSF:**

**Hospital Medicine and Geriatrics**

**Additional materials and  
questions live on Twitter**

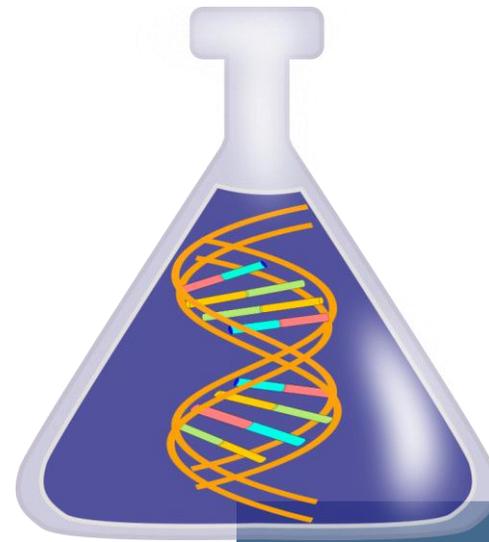


**@GerSciDoc**  
**#BiogerCUHK**

**Part 1: Aging Biology**

**Part 2: Clinical Trials**

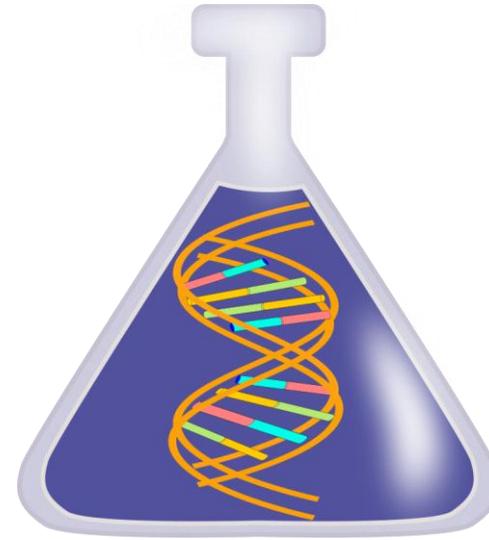
**Part 3: Questions**



**Part 1: Aging Biology**

**Part 2: Clinical Trials**

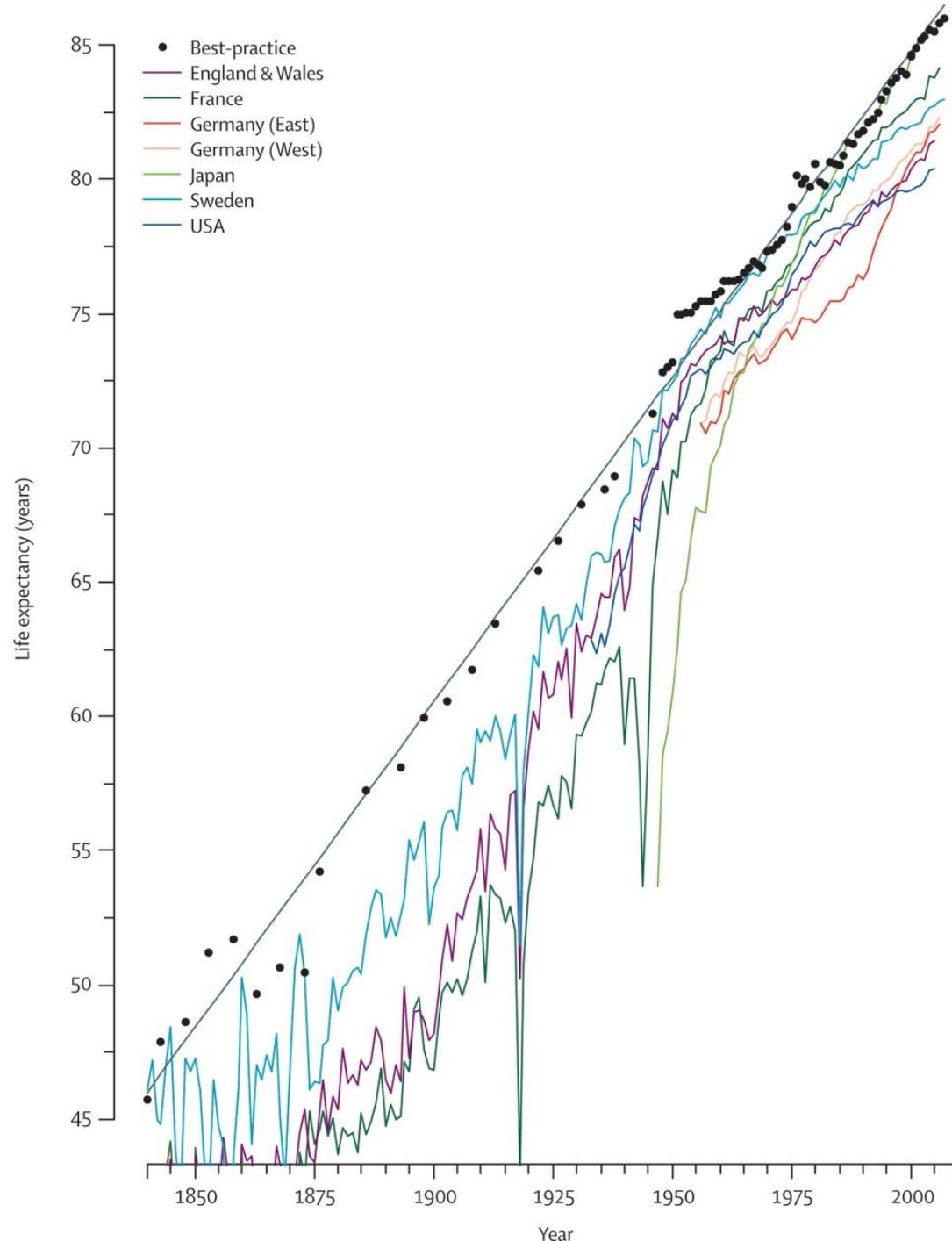
**Part 3: Questions**



# The Longevity Revolution: An old story!

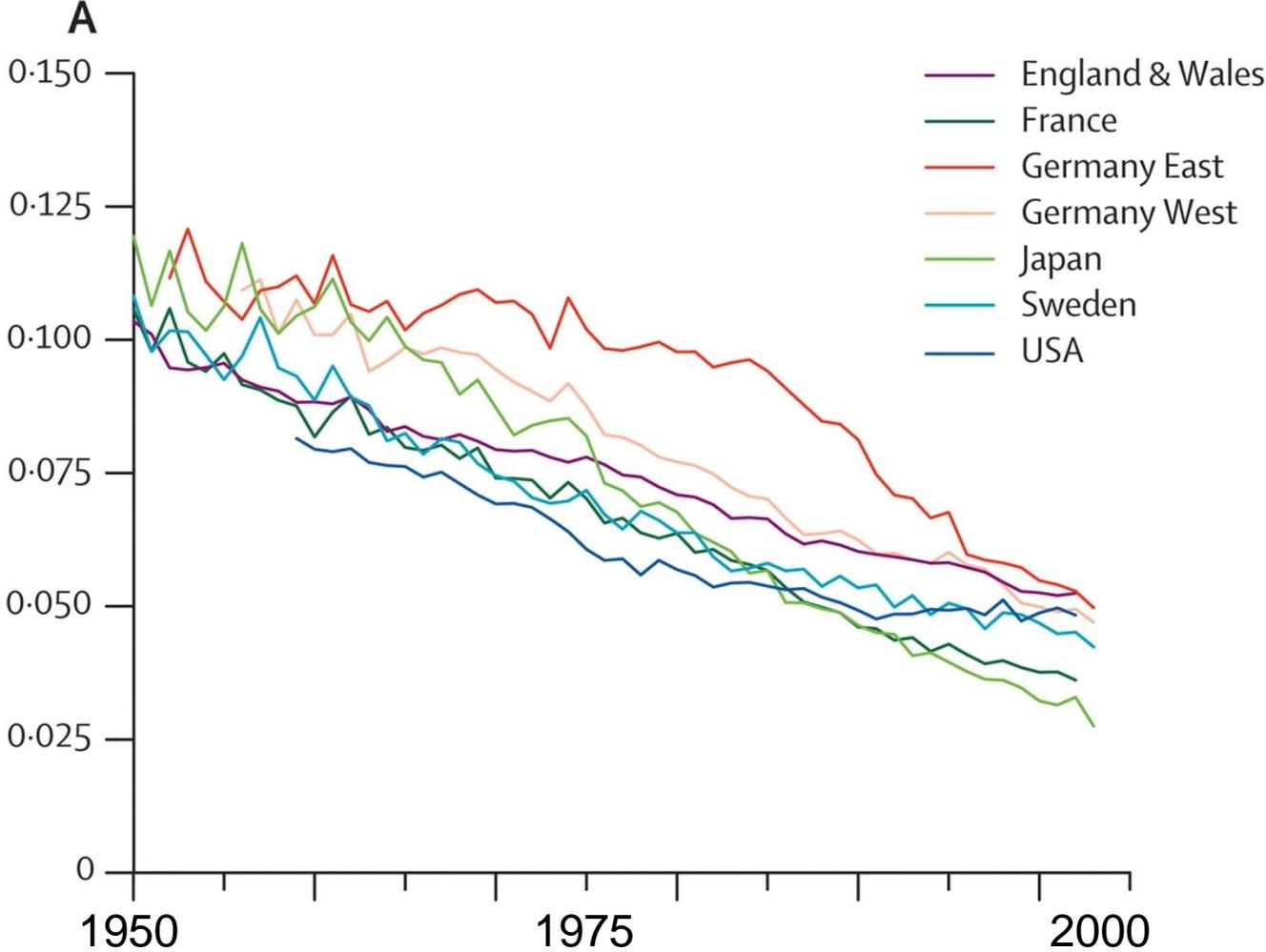
Since 1850,  
life expectancy has advanced  
by one year for every four  
("Christensen's Law"?)

Christensen et al.,  
Lancet 2009



# The Longevity Revolution: An old story!

Chance of dying  
while age 80



Mortality is falling throughout life,  
even among the very oldest

Christensen et al.,  
Lancet 2009



# Healthspan

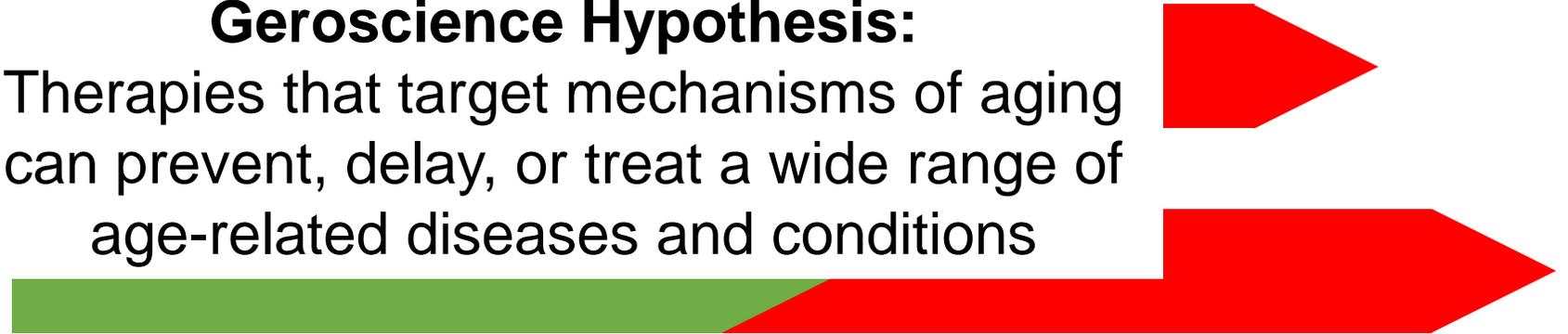
Healthy life

Illness and disability

## Geroscience Hypothesis:

Therapies that target mechanisms of aging can prevent, delay, or treat a wide range of age-related diseases and conditions

Extend lifespan



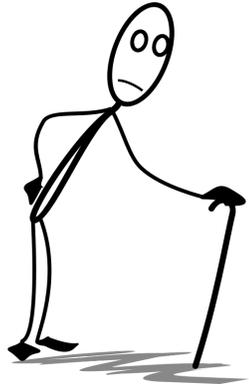
Extend healthspan



Extend both

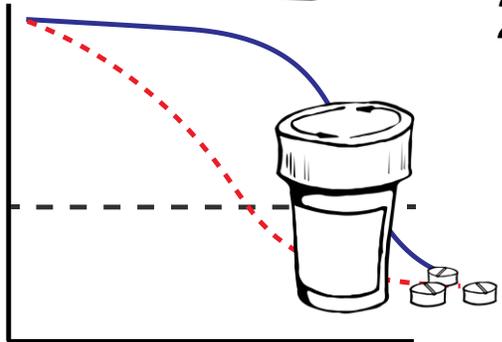


# How to study “Aging”



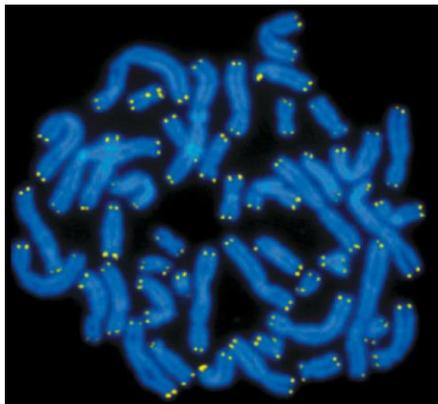
## 1. Describe it

Gradual, progressive, universal loss of function beginning after maturation



## 2. Define it

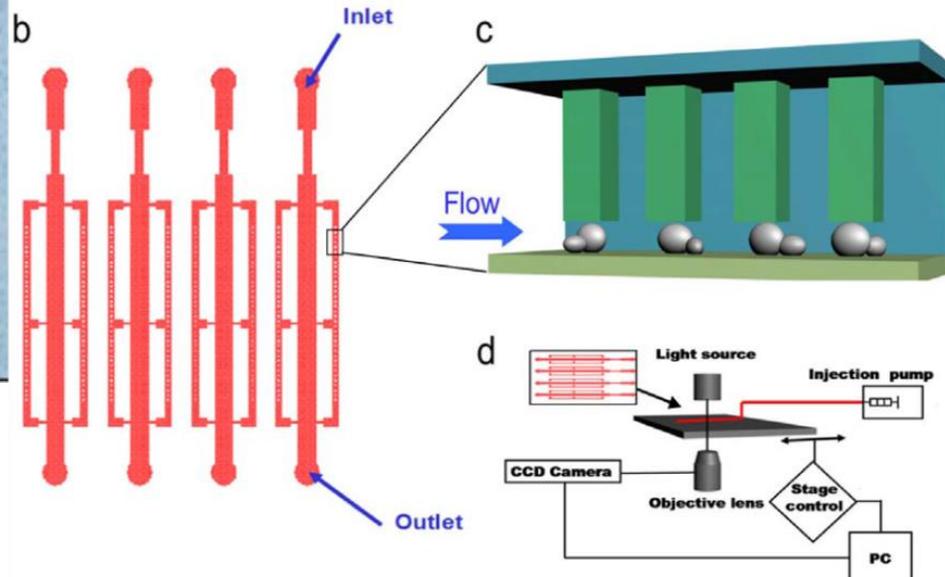
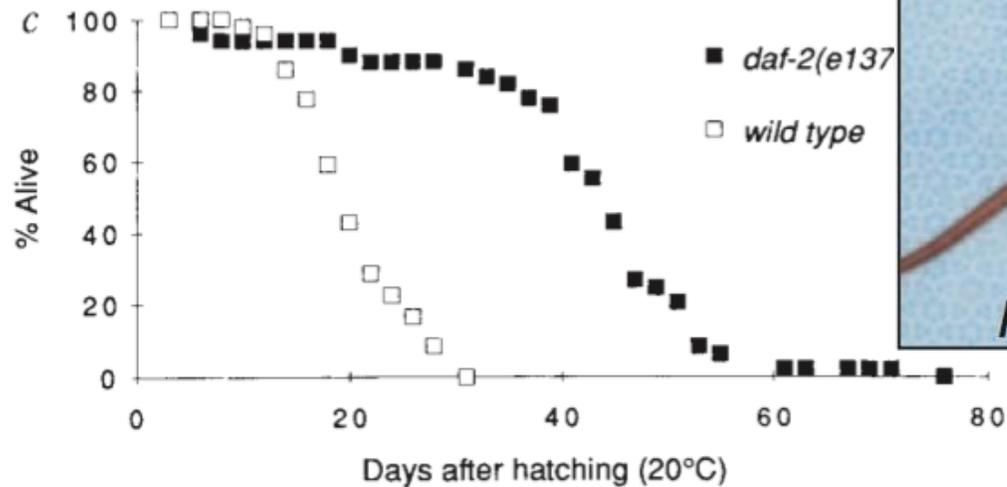
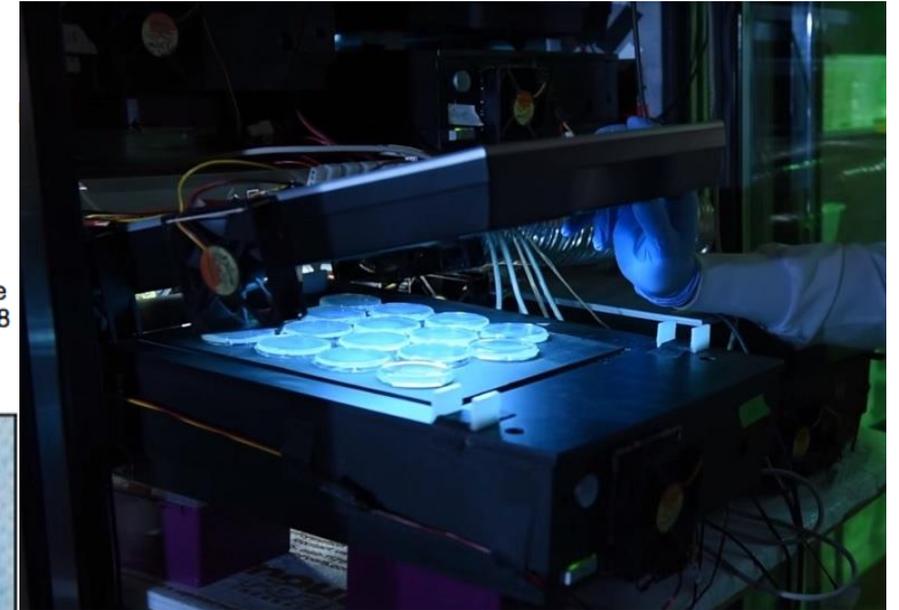
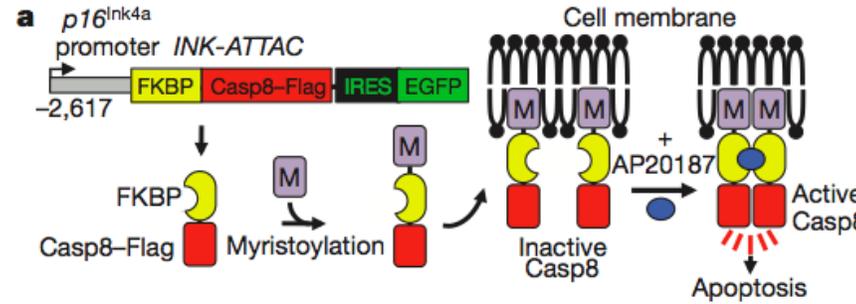
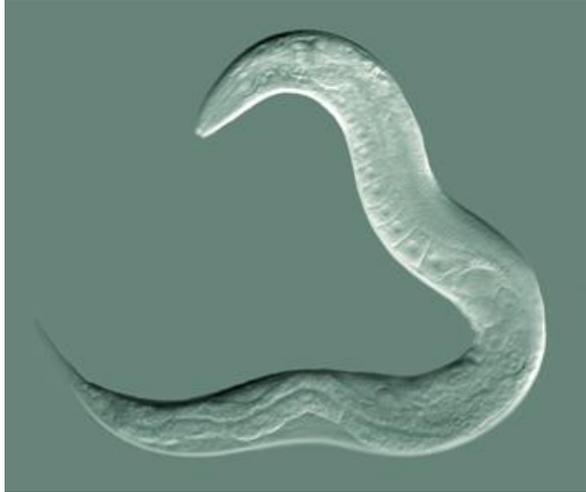
Susceptibility to disease  
Increasing probability of death  
Loss of resilience to stressors  
Loss of reproduction capacity



## 3. Operationalize it for studies

Cell divisions  
Lifespan  
Multimorbidity

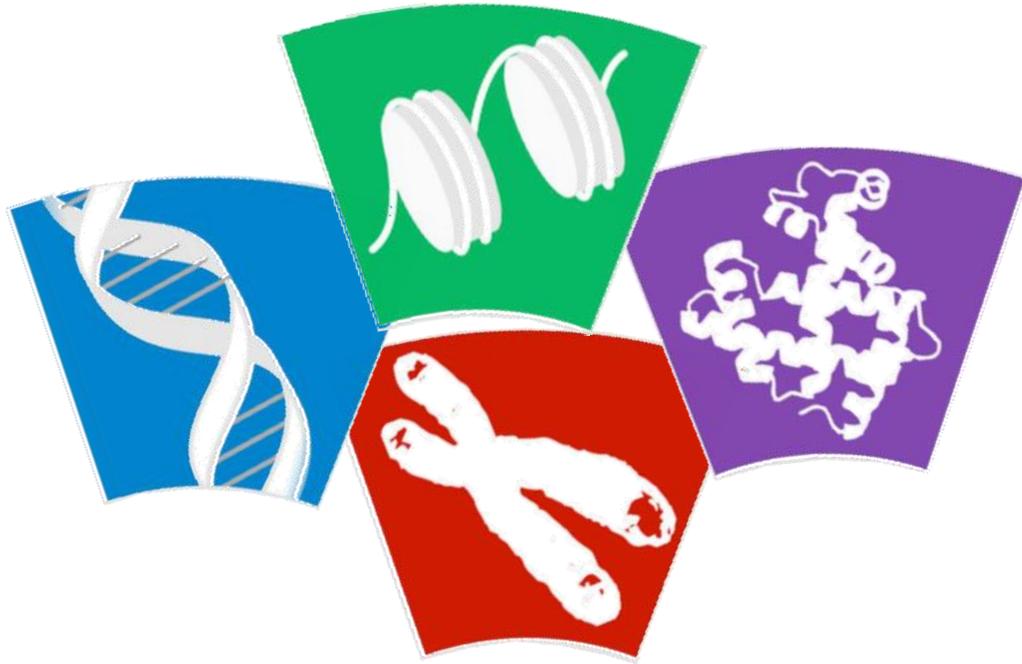
# Aging: Just another biological process



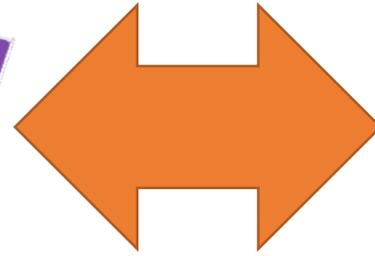
# Hallmarks Of Aging...



# Damage



DNA damage  
Protein damage and misfolding  
Epigenetic damage  
Telomere damage

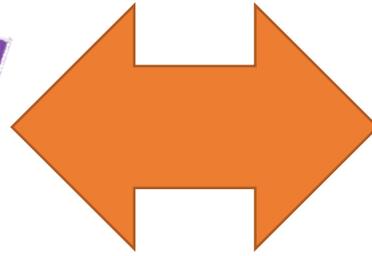
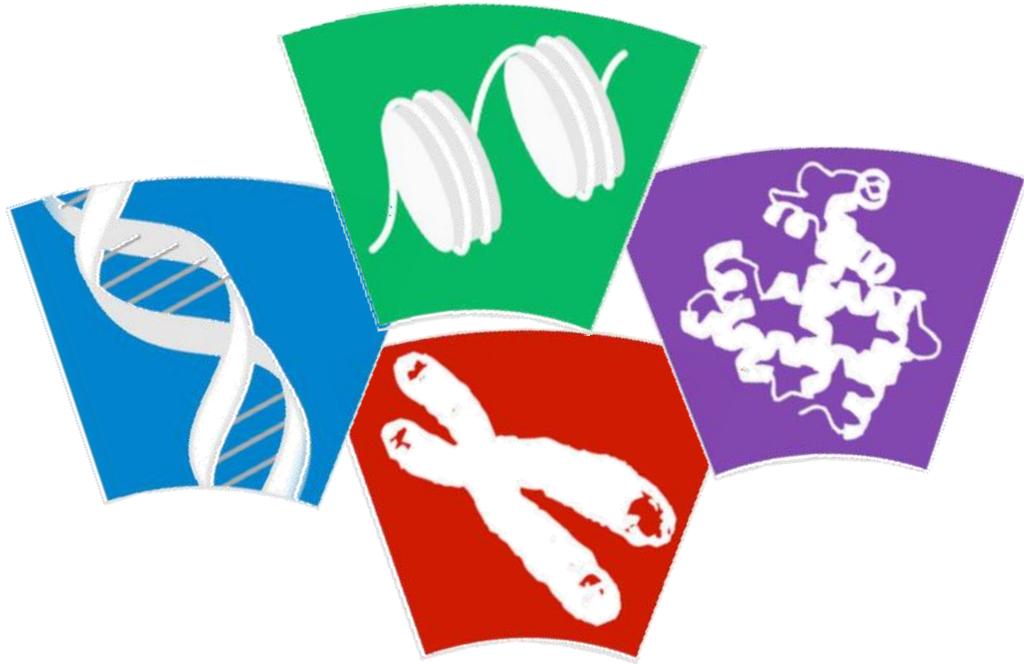


# Consequences



Senescent cells  
Stem cell exhaustion  
Mitochondrial dysfunction  
Chronic inflammation

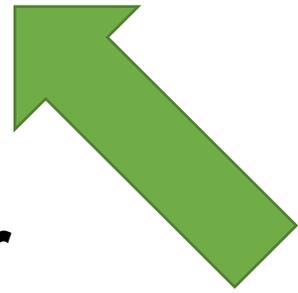
# Damage



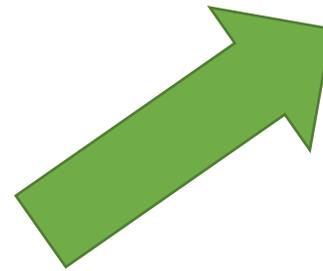
# Consequences



**Repair  
Damage**

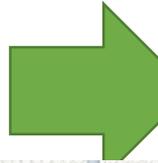


**Stop  
Consequences**



# Metabolic signals and stress response

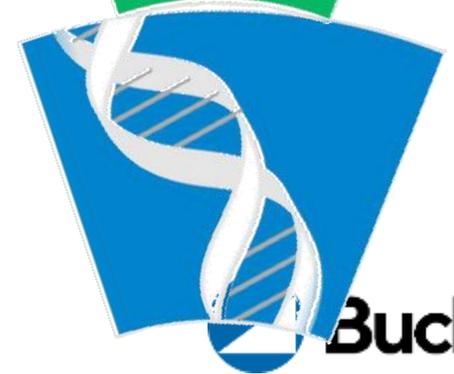
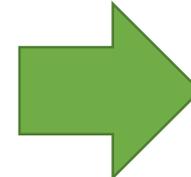
Less  
Nutrients



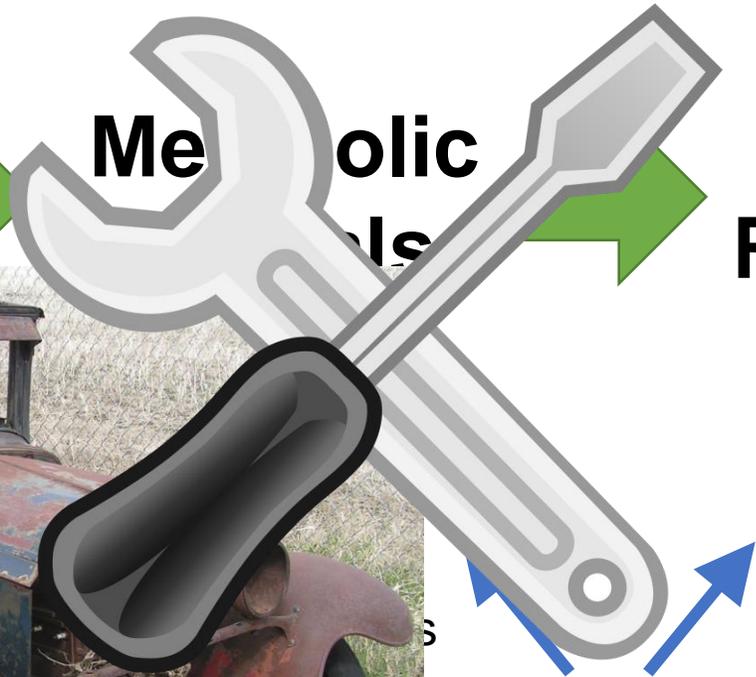
Metabolic  
Signals



Stress  
Response



Buck



**DRUGS:**  
Metformin  
Rapamycin

...

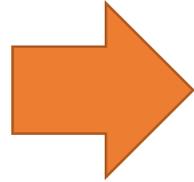
FOXO3  
Sirtuins  
Autophagy  
Mitophagy

D  
P  
Met

# Senescent cells and senolytics

## Damage

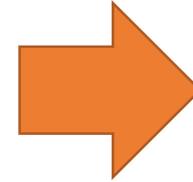
DNA damage  
Short telomeres



## Senescence



Stop dividing =  
no cancer  
"Zombie cell"



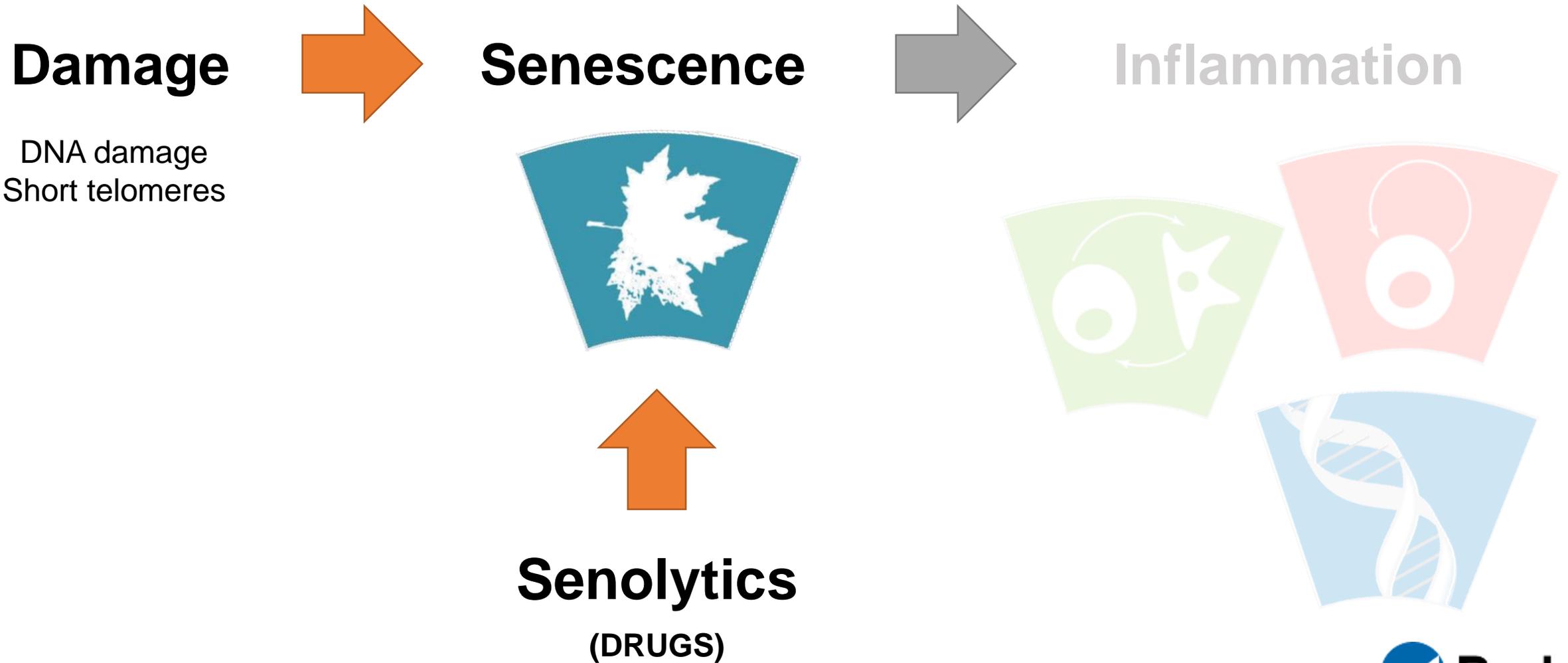
## Inflammation



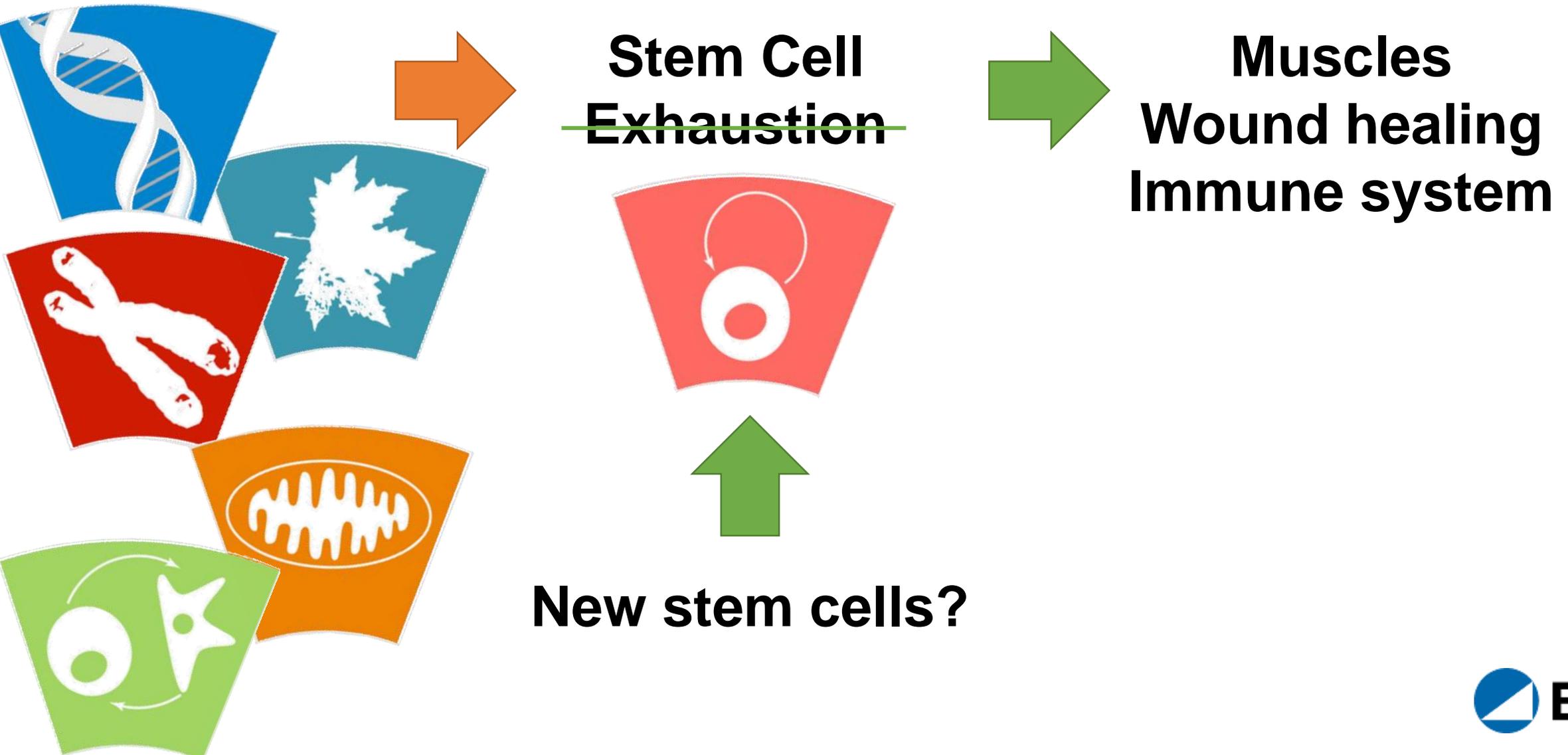
Damage nearby cells  
Promote cancer



# Senescent cells and senolytics



# Senescent cells and senolytics



# Potential Interventions



## Metabolic therapies

Metformin  
Rapamycin  
Acarbose  
NAD supplements (NR, NMN)  
Sirtuin activators (SRT2104,  
SRT1720)  
Novel TOR inhibitors  
CD38 inhibitors  
Ketone esters

Blood factors  
Myostatin inhibitors

## Senolytics

Navitoclax  
Dasatanib  
Quercetin  
HSP90 inhibitors (17-AAG,  
17-DMAG)  
Other BCL-activators

Dietary  
Caloric restriction  
Protein restriction  
Methionine restriction

## Other drugs

Aspirin  
17 $\alpha$ -estradiol  
NDGA  
ACEI/ARBs

Procedures  
Young mesenchymal stem  
cell infusion  
Young plasma infusion

**Part 1: Aging Biology**

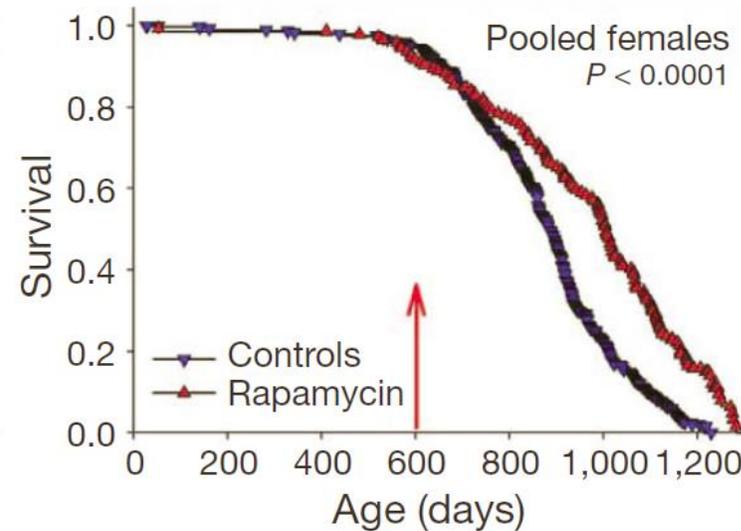
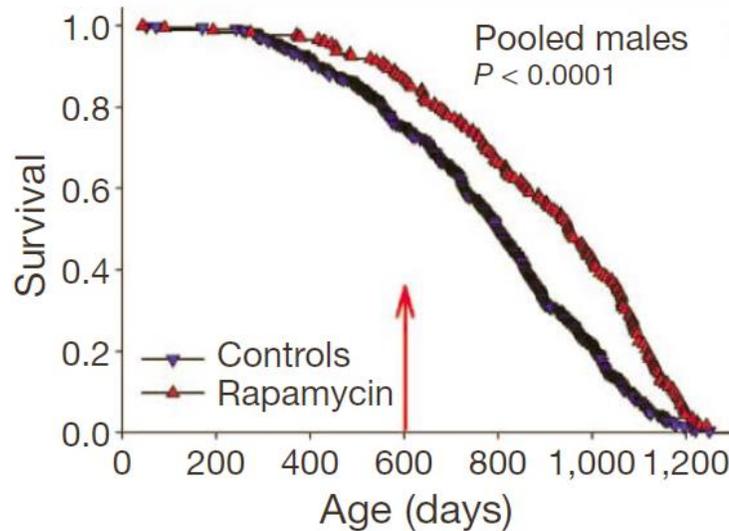
**Part 2: Clinical Trials**

**Part 3: Questions**





# Studies in laboratory animals: Rapamycin was the first aging therapy



US National Institute on Aging  
Interventions Testing Program  
Multicenter "Clinical Trial" for mice

Harrison, Nature 2009



# How to test aging interventions in humans?

Healthy life

Illness and disability



# How to measure aging in humans?

Healthy life

Illness and disability

Extend healthspan



**“Age” is not a number:  
Calendar age  
*versus*  
Physiological age**

(If you’ve seen one 80 year old  
you’ve seen one 80 year old)

**Multimorbidity: chronic diseases**

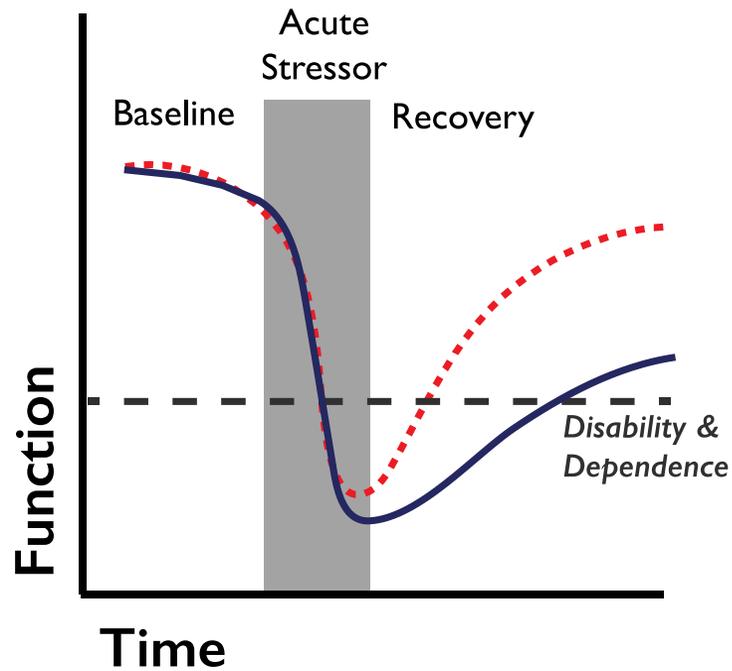
**Geriatric Syndromes**

- Frailty
- Falls
- Functional Decline
- Delirium

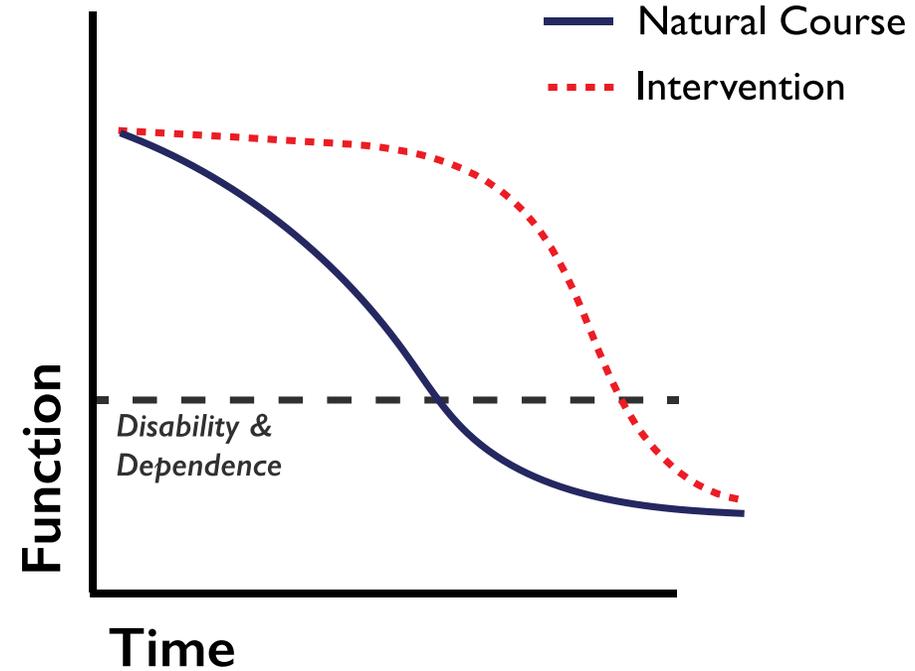
**Loss of resilience to acute stress**

# Designing Clinical Trials for Aging

## Functional Reserve or “Resilience”



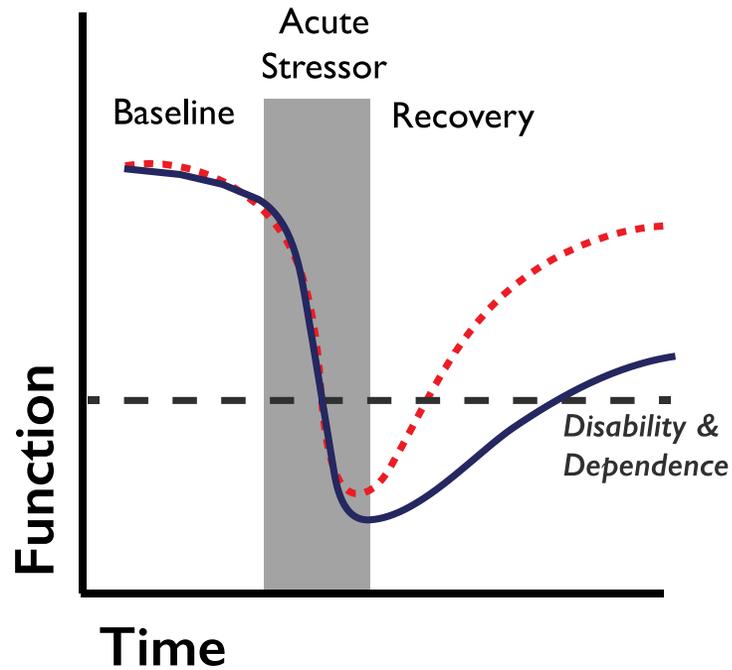
## “Healthspan”: Multimorbidity or geriatric syndromes



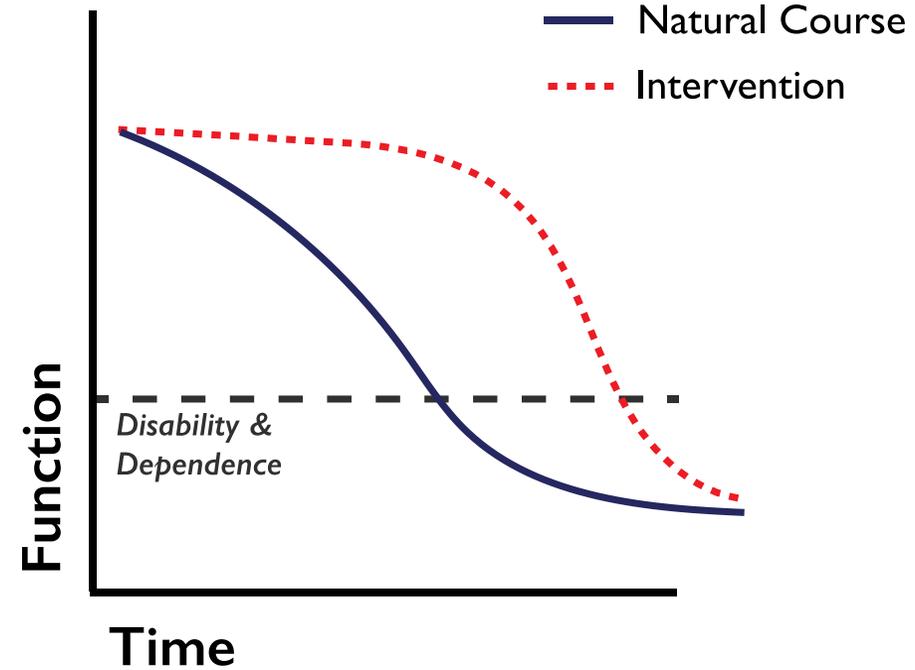


# Designing Clinical Trials for Aging

Geriatric specialty  
hospital wards

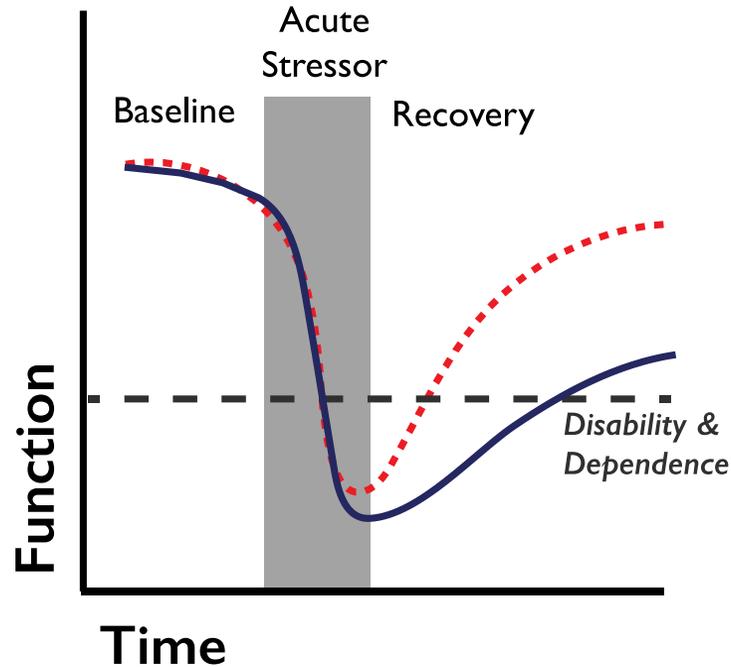


Exercise for  
improving frailty



# Health stress or hospitalization

Functional Reserve  
or “Resilience”



**Rapamycin improves influenza  
vaccine effect**  
(Novartis, Science Trans Med 2014)

**Rapamycin plus cardiac  
rehabilitation in the elderly**  
(Mayo Clinic)

**Metformin with resistance  
exercise training in the elderly**  
(U. Kentucky, U. Alabama)

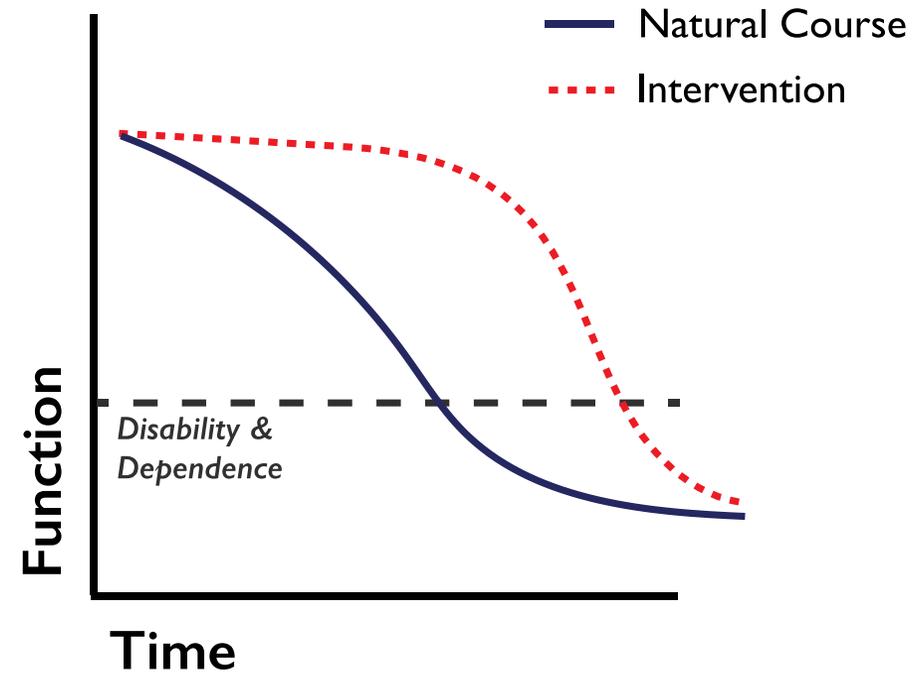
# Multimorbidity or Geriatric Syndromes

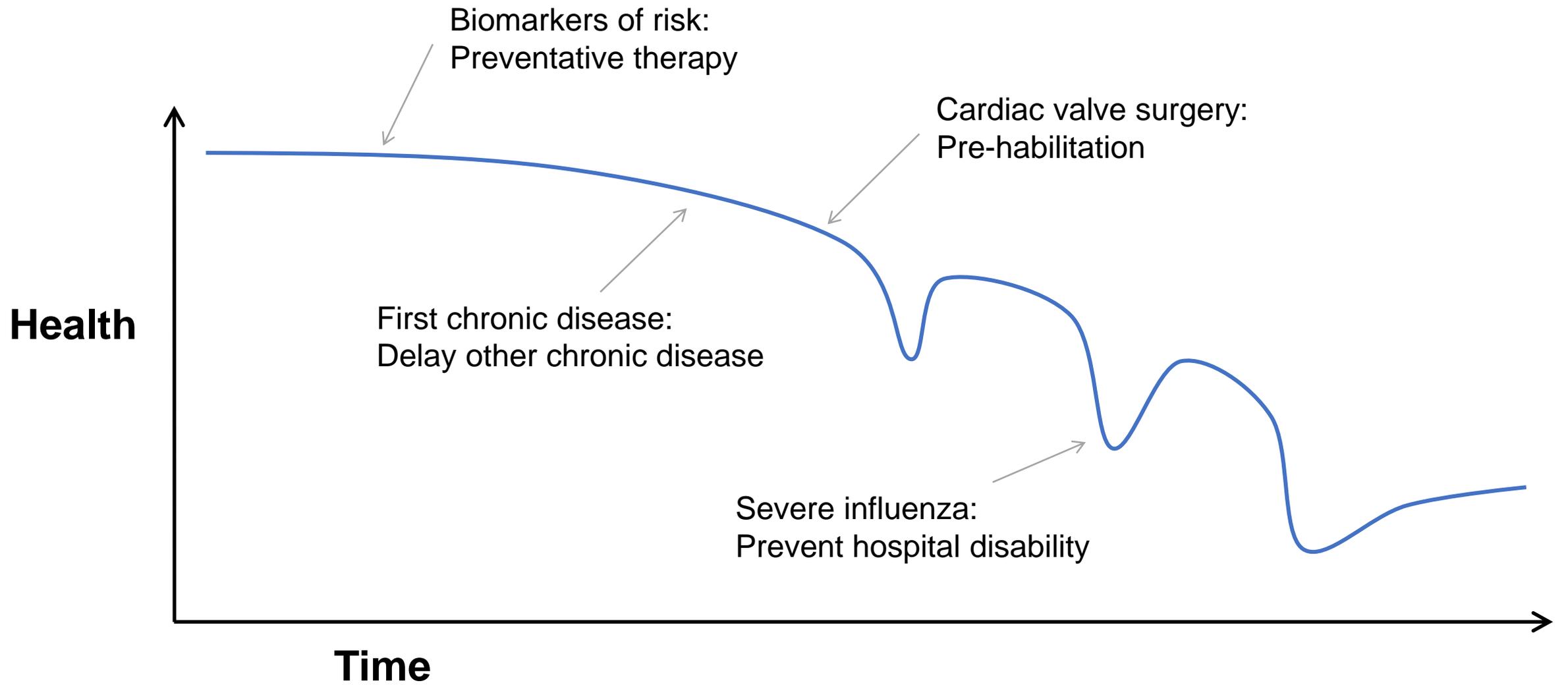
**Rapamycin for preventing respiratory infections in frail elderly**  
(PureTech/resTORbio)

**Metformin to delay the onset of multiple chronic diseases**  
("TAME: Targeting Aging with Metformin", public consortium)

**Young mesenchymal stem cell infusion to treat frailty**  
(Longeveron, U. Miami)

"Healthspan":  
Multimorbidity, function,  
or geriatric syndromes





**Part 1: Aging Biology**

**Part 2: Clinical Trials**

**Part 3: Questions**



**Aging is universal**

**Is "Aging" a disease?**

**It happens to everyone!**

**If not, what does a drug company or regulatory agency do?**



**Large clinical trials of frail, vulnerable, elderly people?**

**First to harm, last to help...**

**We test cancer drugs in patients with cancer...**

**We need more clinical trials in the elderly anyway!**

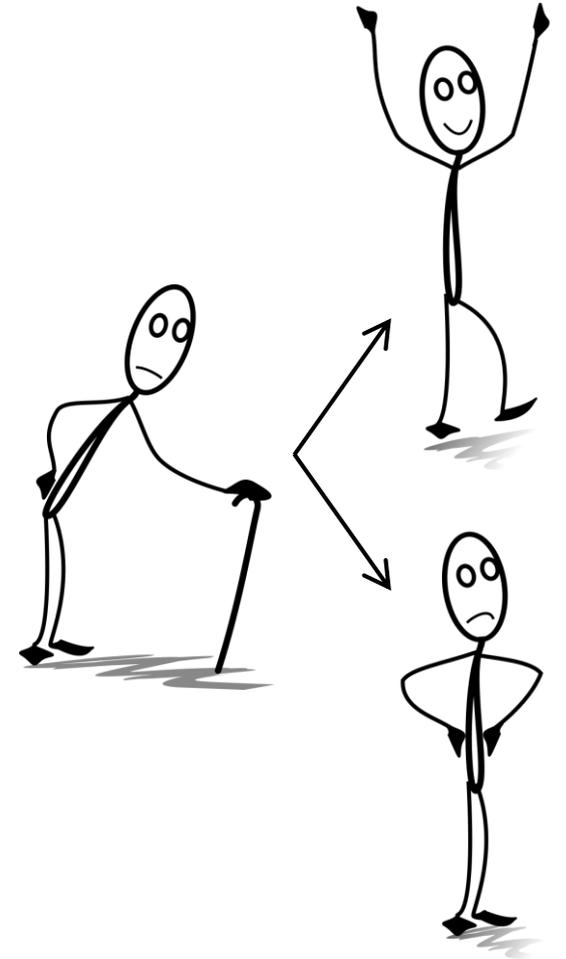


**Who will get these treatments?**

**Everyone, right? Right?**

**What if it's expensive?**

**What if it's rare?**



# Expensive Treatments

**Expensive by choice:** Novel senolytics

Hepatitis C cures

**Expensive by design:** Aging-factor blocking antibodies

Antibody-based drugs

**Expensive by technology:** Autologous organoids or stem cells

CAR-T, Dialysis

**Expensive by scarcity:** Young blood/cell infusion

Transfusion, organ transplant

## **Aside: Frankenstein medicine**

**“Replacement parts” approach to medicine does not work**

**Transplants, dialysis, LVADs, etc etc – it’s never just one thing. The whole person is old and frail.**

**What if aging therapies change that?**

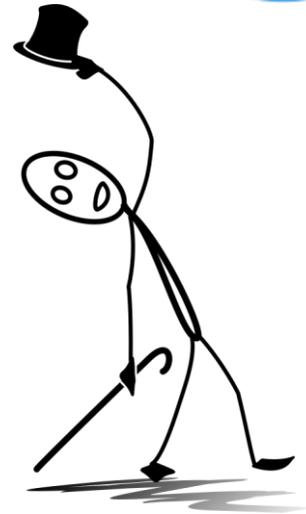


**Who will benefit?**

**Everyone, right? Right?**

**Fancy health care can exacerbate disparities**

**But it's easier to fix what's broken – who is most affected by aging now?**



**Will aging therapies exacerbate or reduce health disparities?**

**Rich already live longer – less room to improve**

**Poor and disadvantaged have vicious cycle of health problems, accelerated aging, and geriatric syndromes**

# Therapies for “aging” are on the way



# Thank you!

**[jnewman@buckinstitute.org](mailto:jnewman@buckinstitute.org)**

**@GerSciDoc**

**Buck Institute**

**National Institute on Aging**

**American Federation for Aging Research**

**UCSF Division of Geriatrics**

**US Veterans Health Administration**

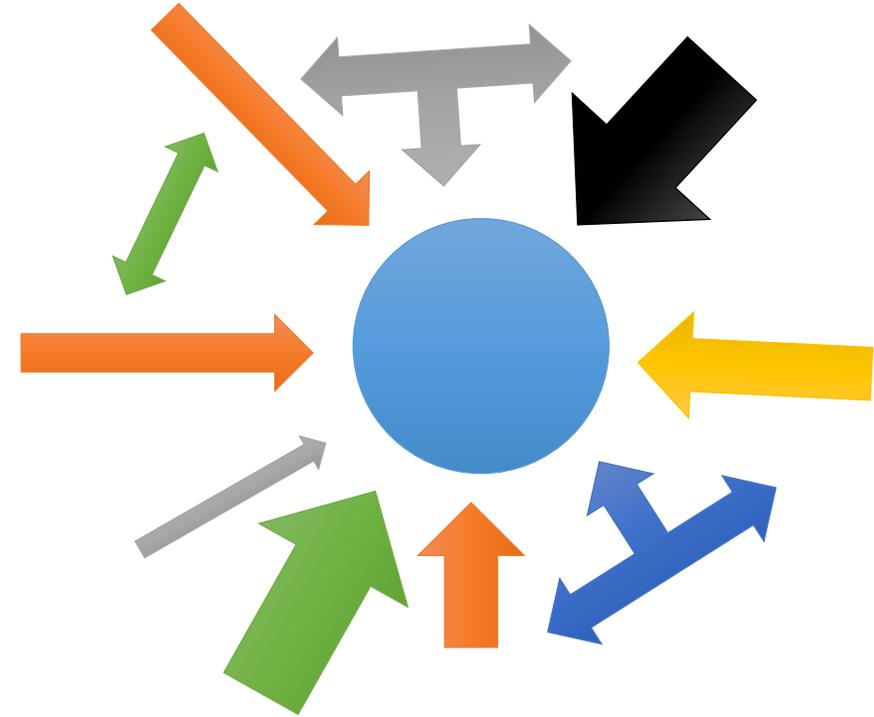
Graphics from [openclipart.org](https://openclipart.org) and [wikimedia](https://commons.wikimedia.org)



# Geriatrics: Care for older adults

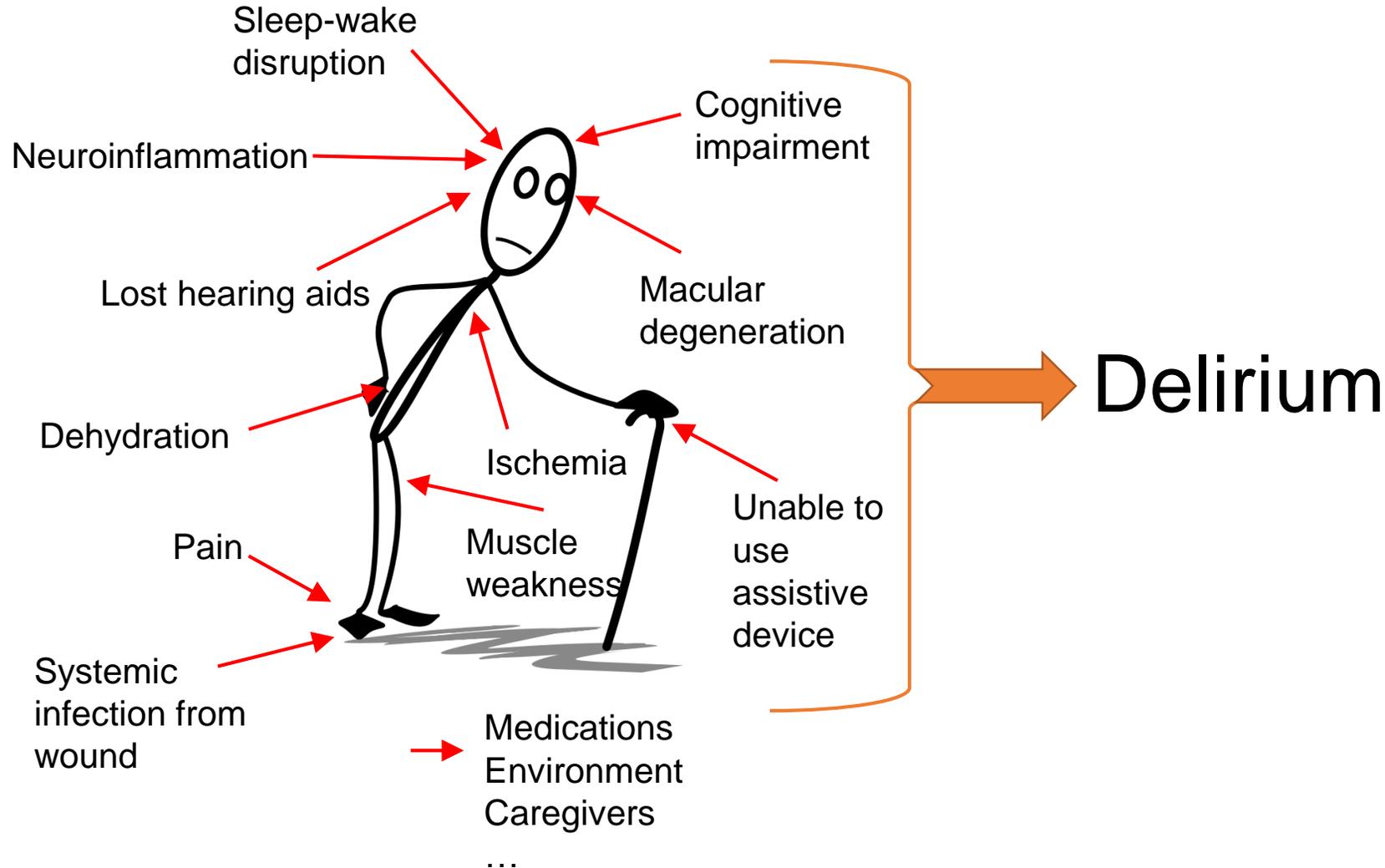


Big-picture goals,  
Whole-person



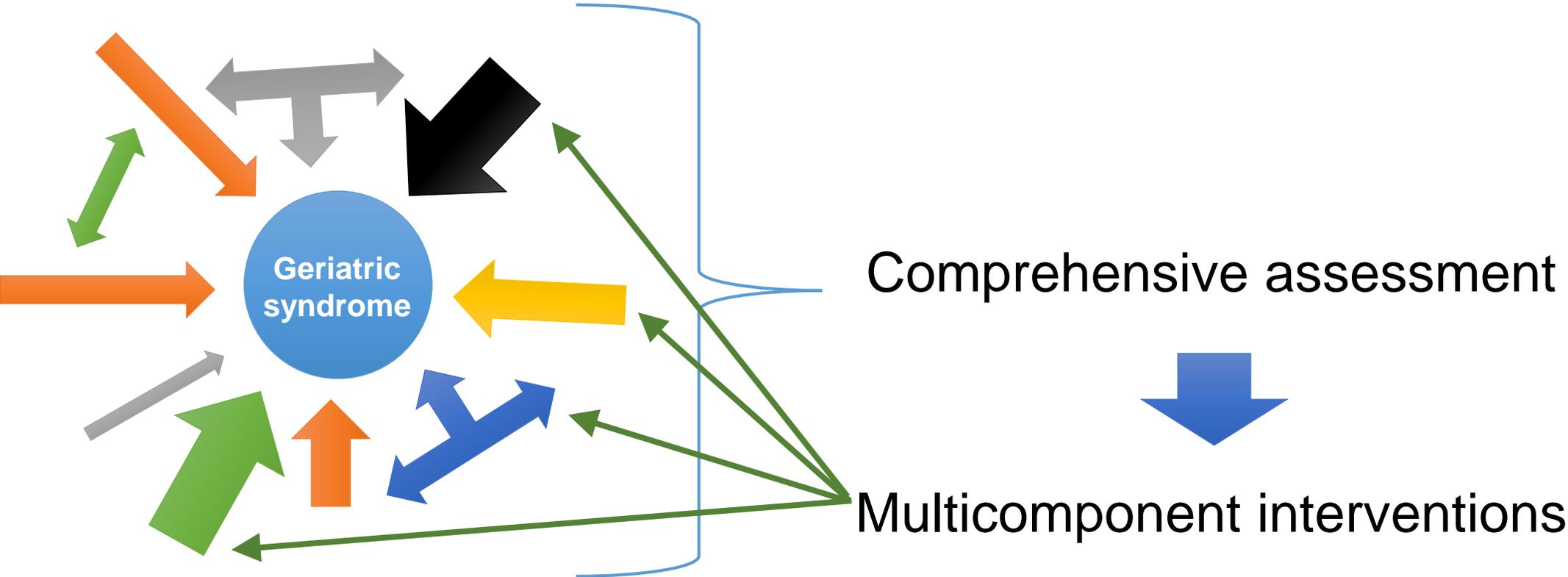
Complexity:  
“Everything affects  
everything else”

# Why do we get delirium?

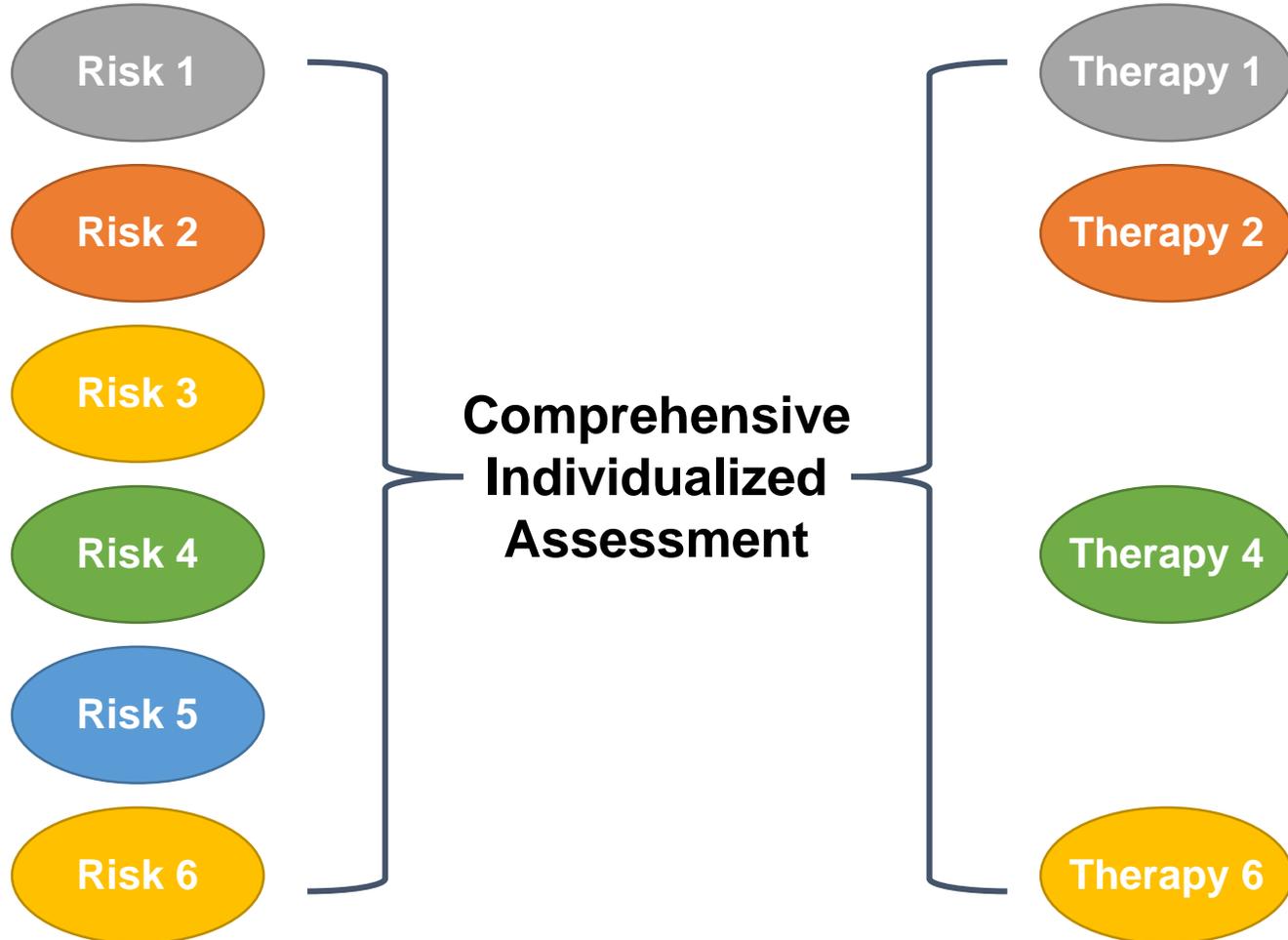


Geriatric syndrome:  
Multifactorial  
Multisystem  
Age-related  
Integrative outcome

# Geriatrics = Systems Biology of Medicine

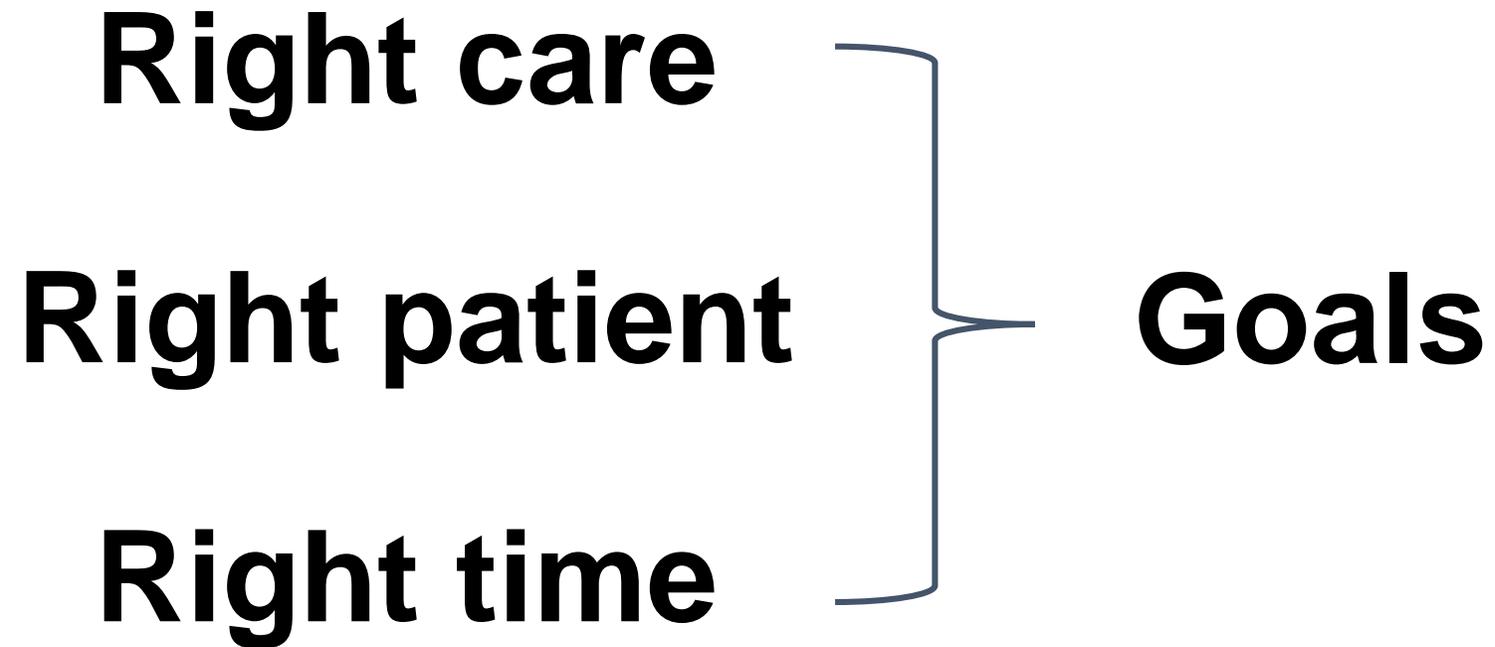


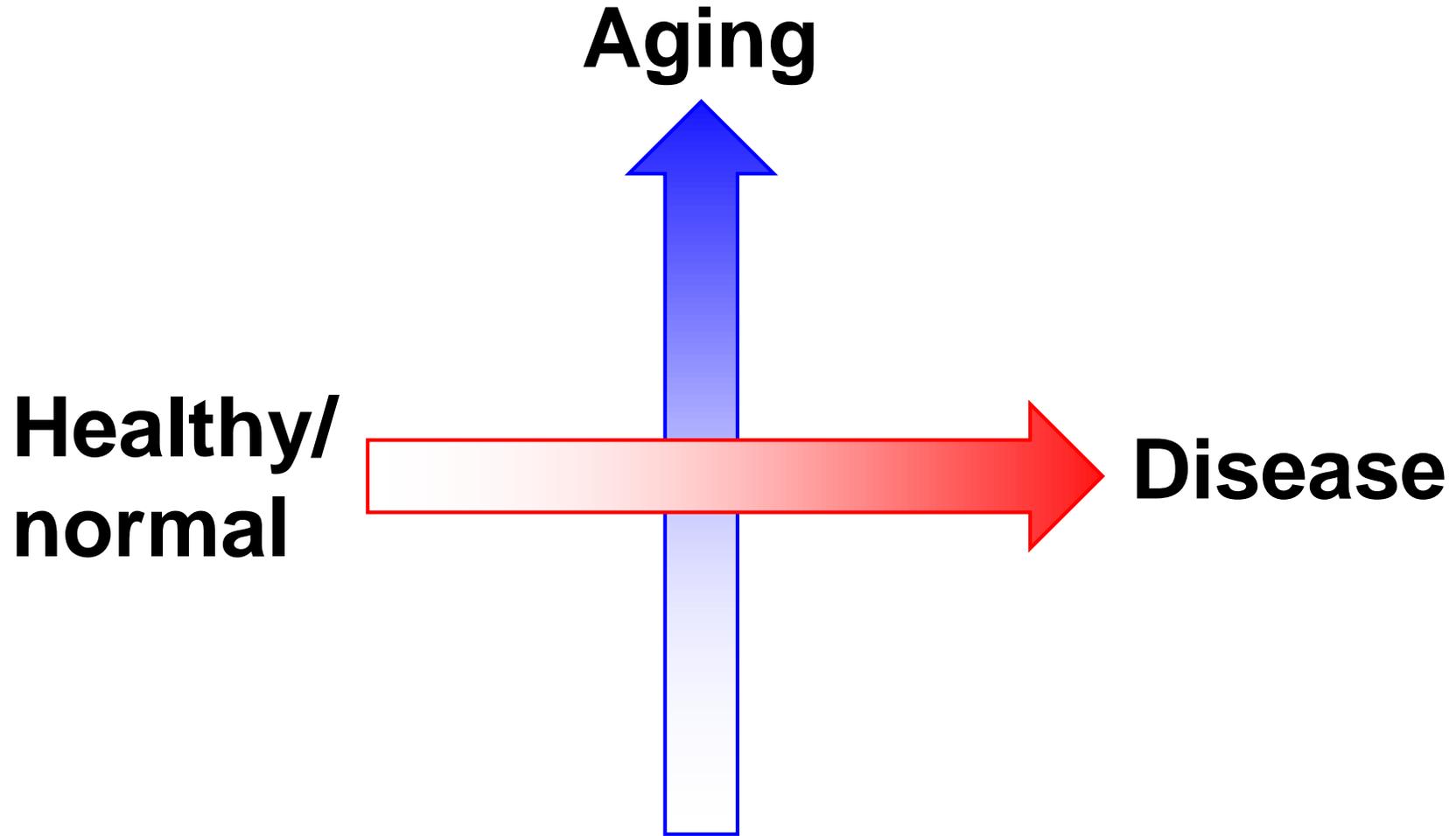
# Treating Geriatric syndromes



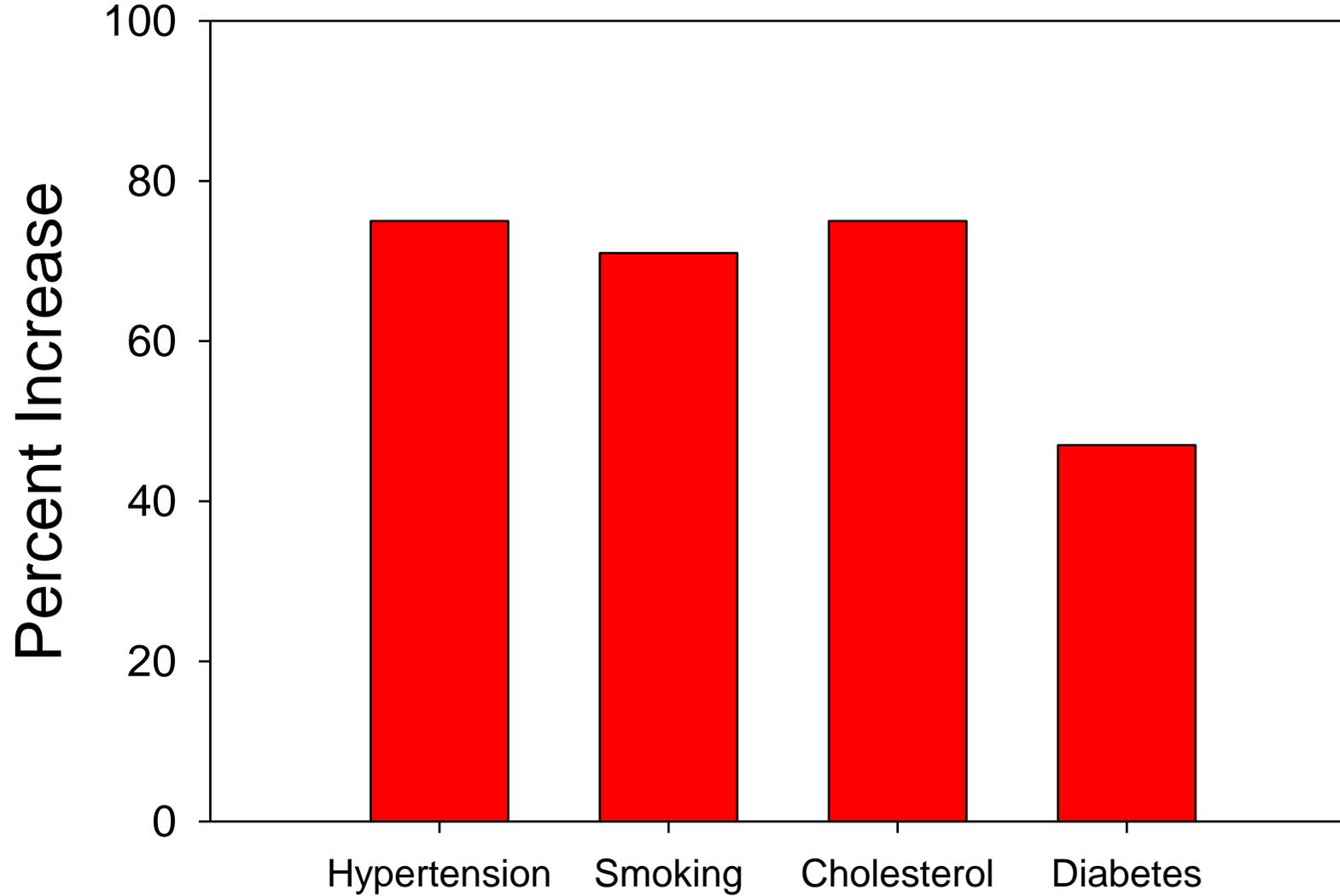
50% of delirium prevented with this approach

**Risk-Tailored  
Multicomponent  
Therapy**

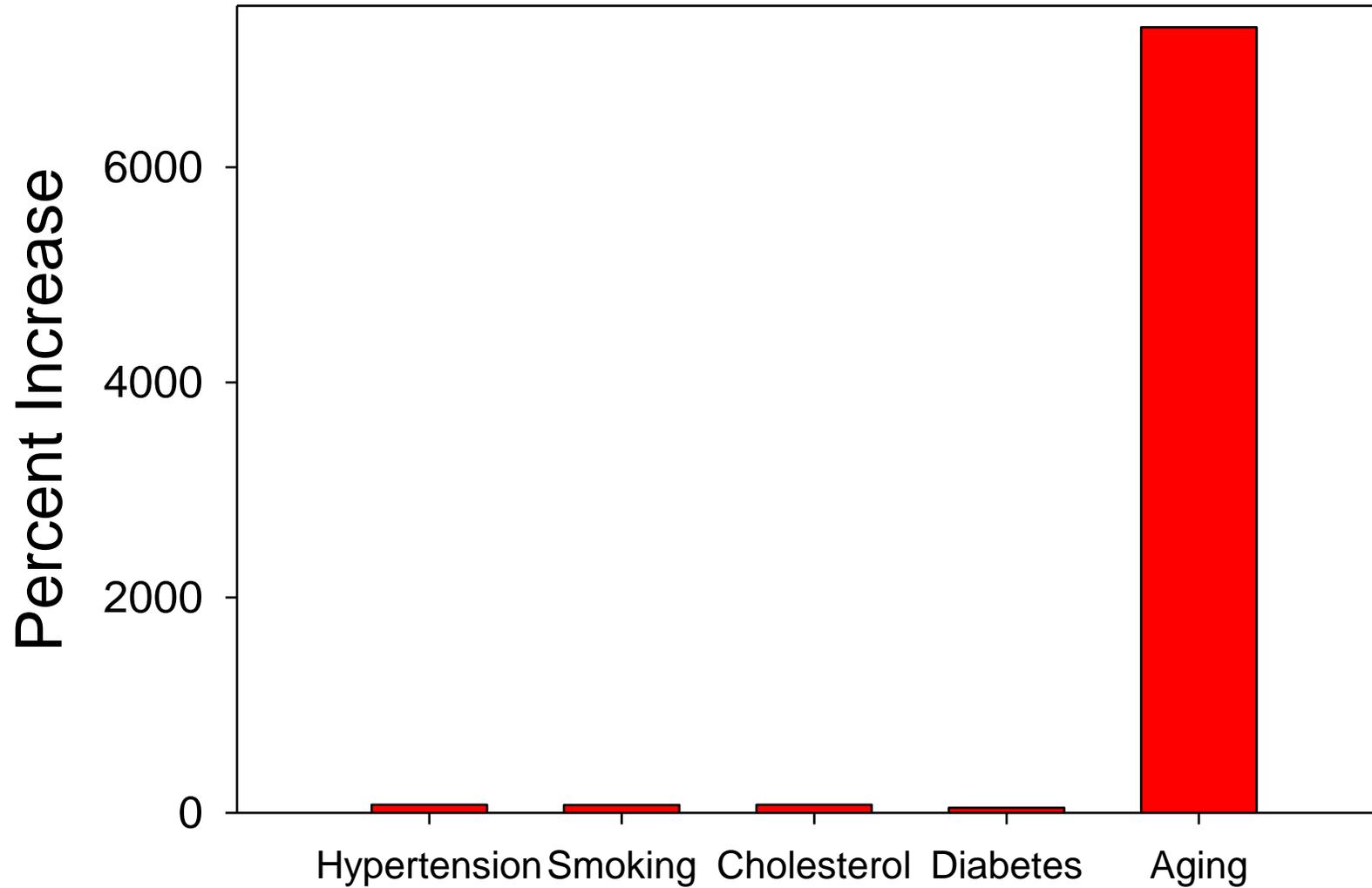




# Heart disease risk factors



# Heart disease risk factors



Steve Austad, University of Alabama