The Mystery of Human Aging:

Why are we aging, what did we learn and where are we going?

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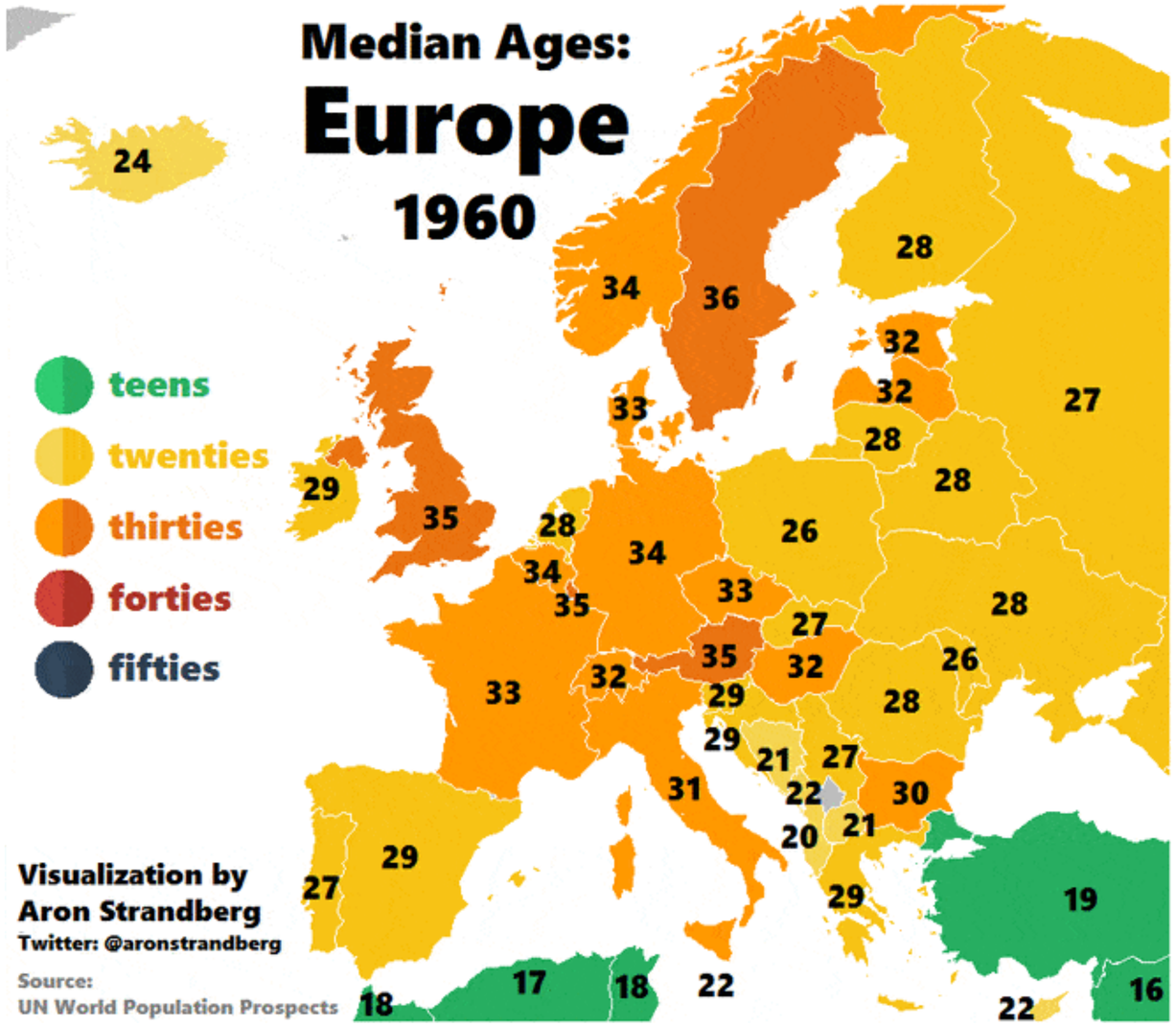
The demographic change in Europe

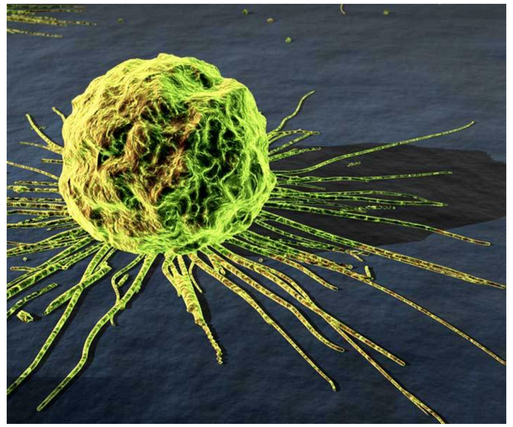


Long life comes at the expense of age-related disease

Dementia

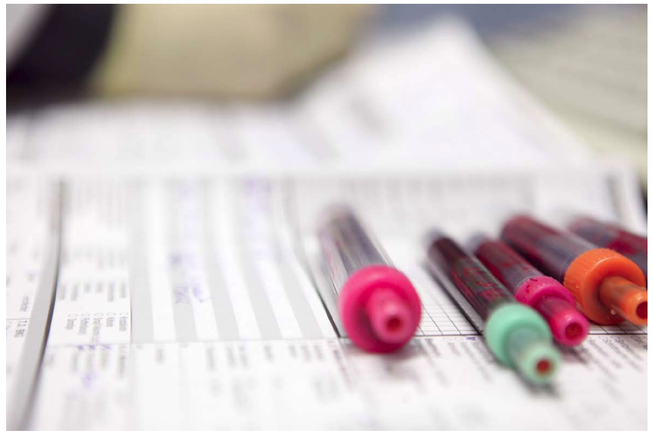
Chronic kidney disease

Cancer



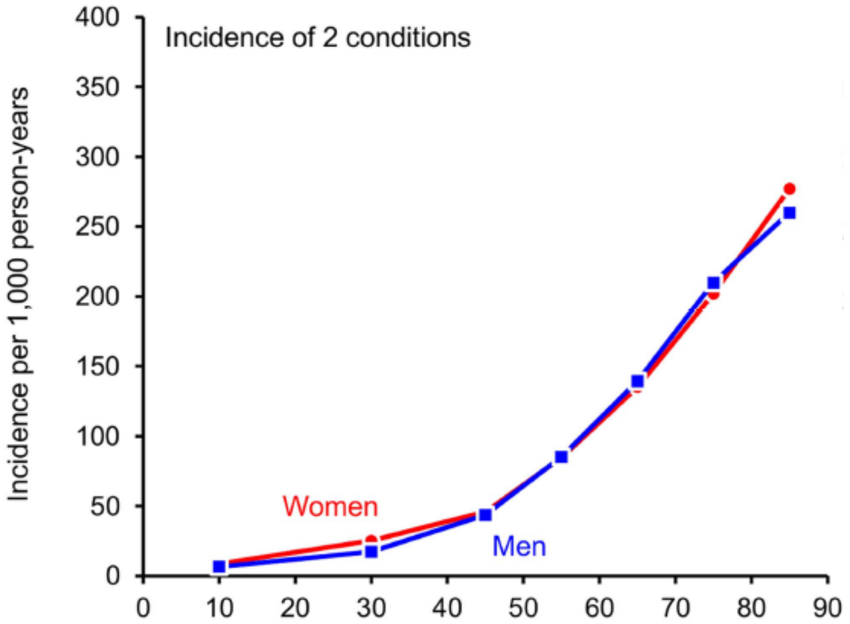
Diabetes

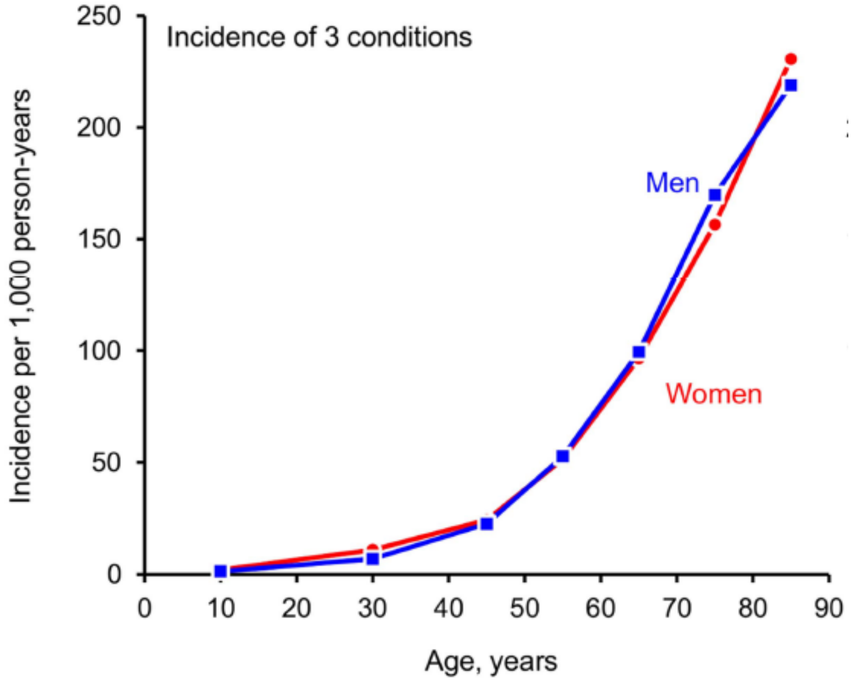
Stroke



Osteoporosis

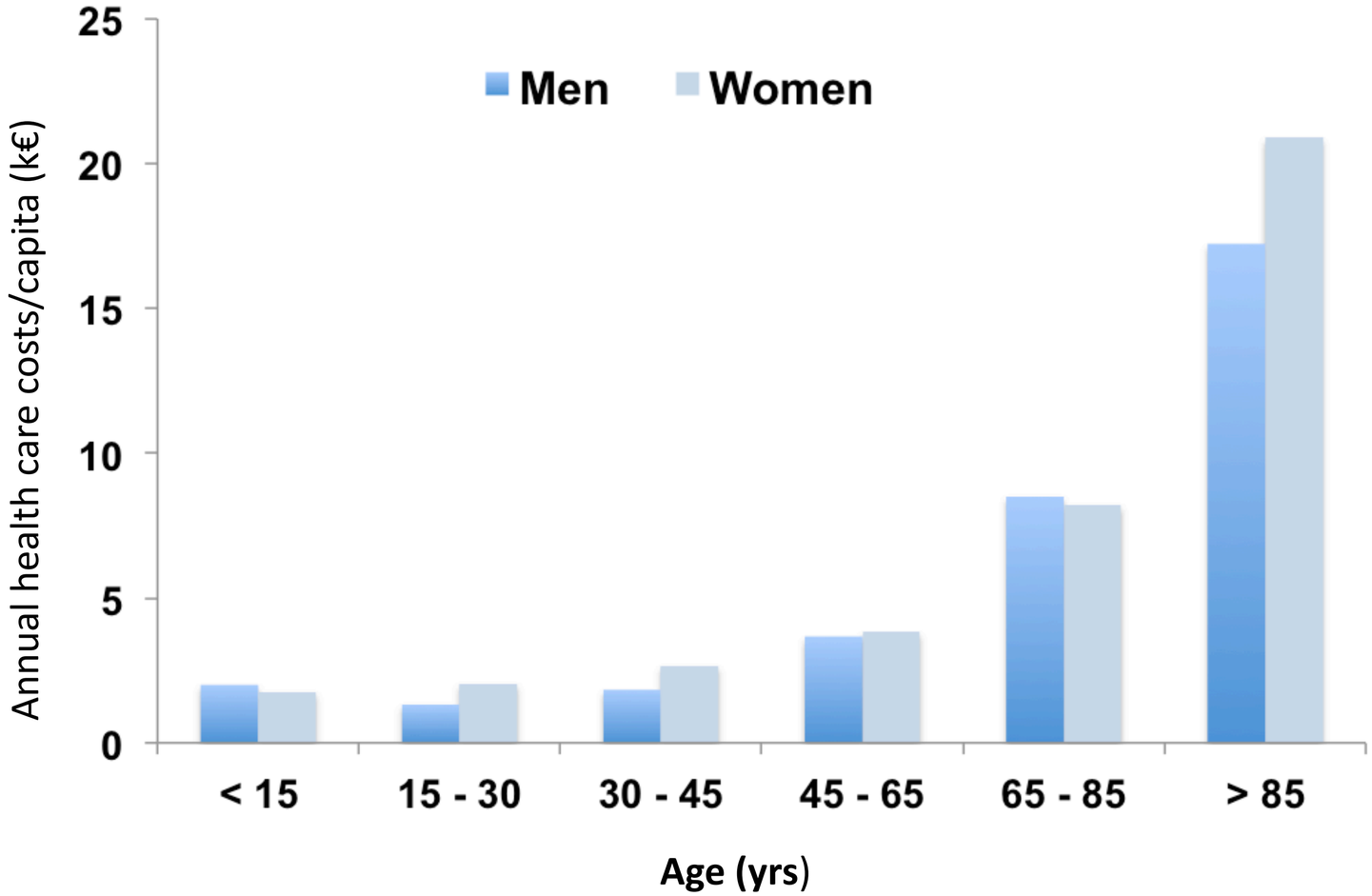
Multimorbidity: Incidence of two or more chronic conditions increases exponentially in the 50+





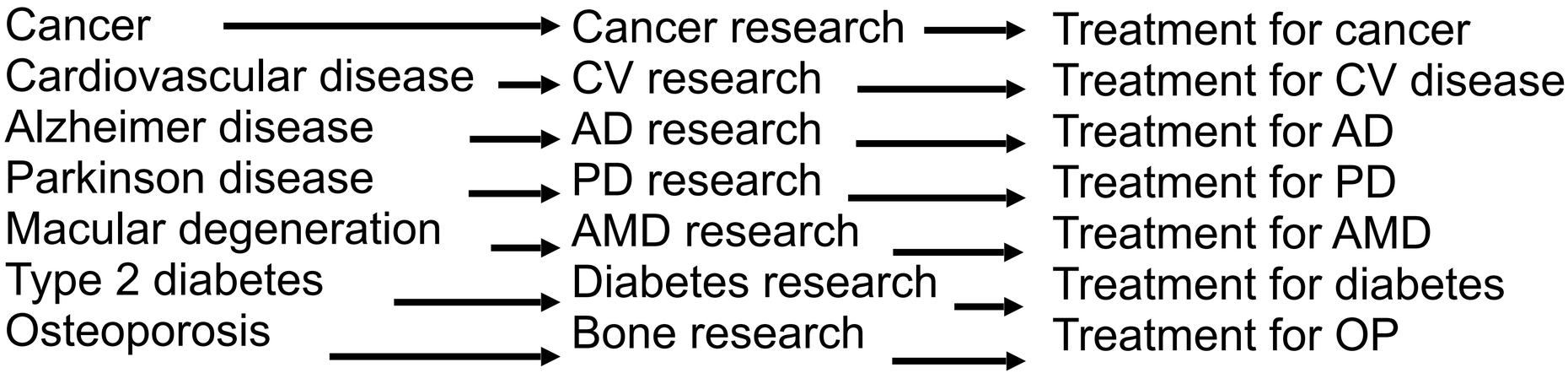
St Sauver *et al. BMJ Open* 2015

Annual healthcare costs increase with age

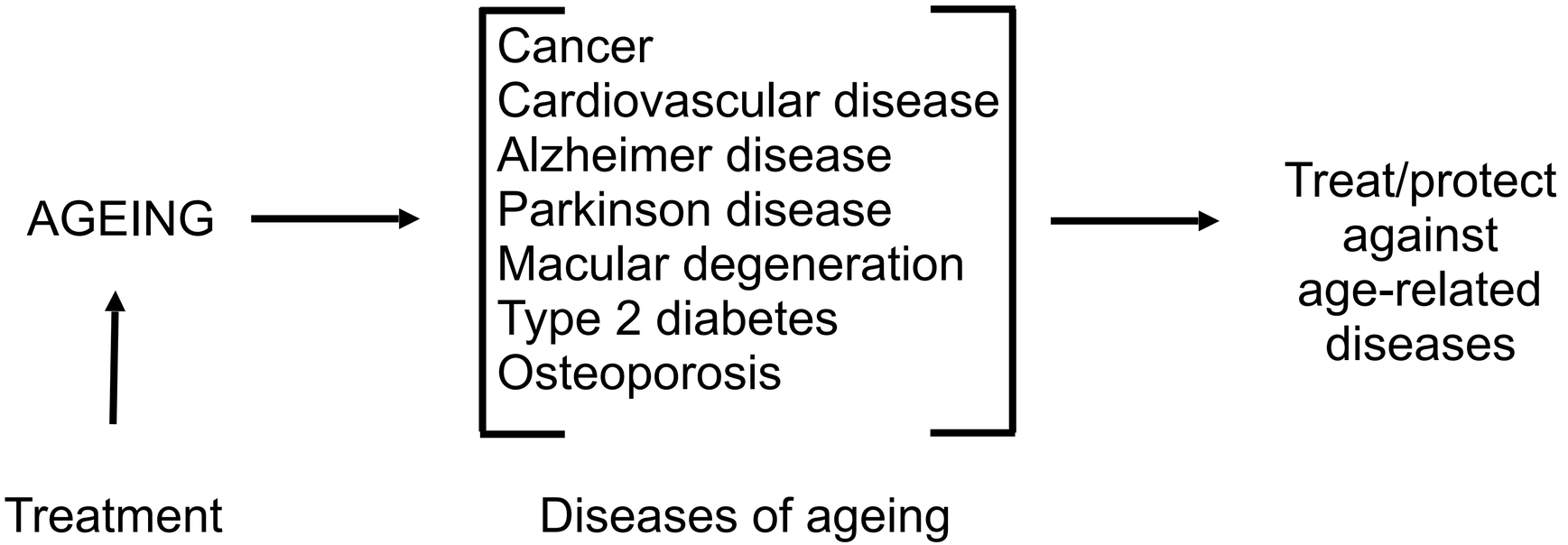


[Gesundheitsberichterstattung des Bundes, 2015]

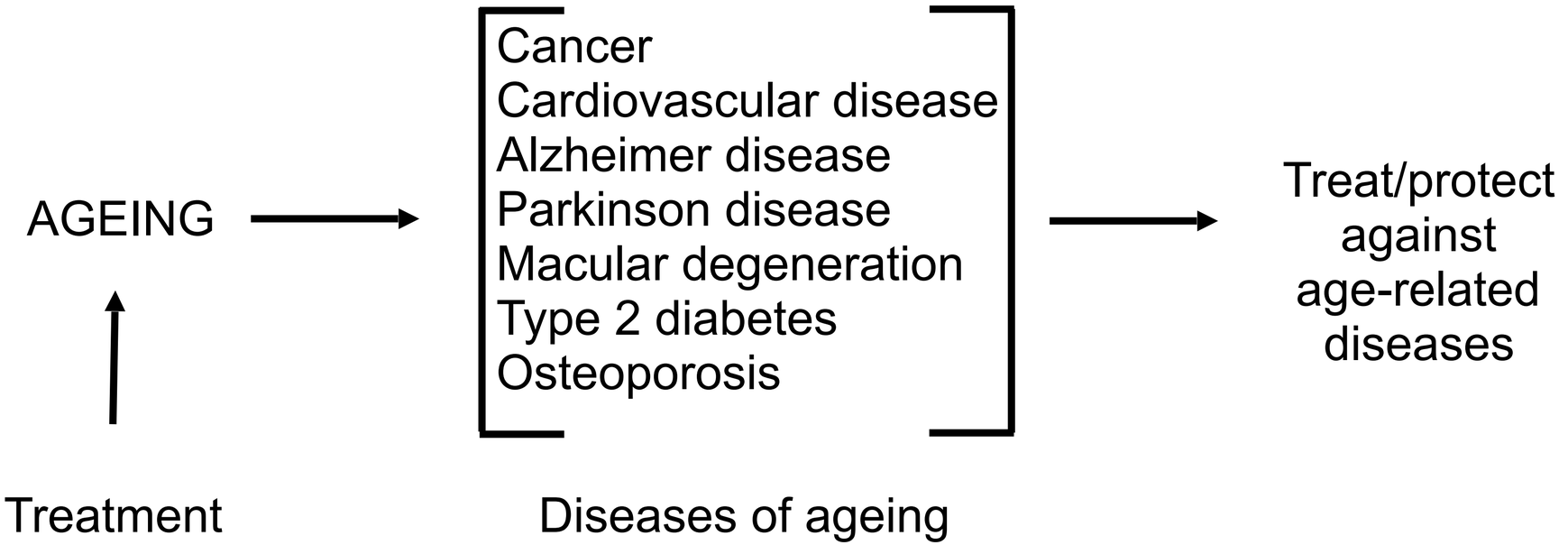
Ageing-associated disorders: the classic approach



Ageing-associated disorders: the novel approach

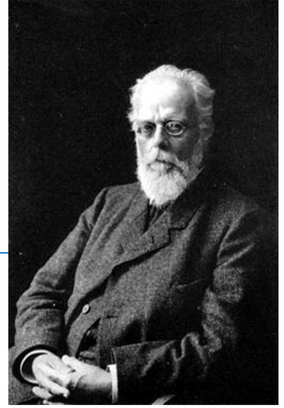


Ageing-associated disorders: the novel approach

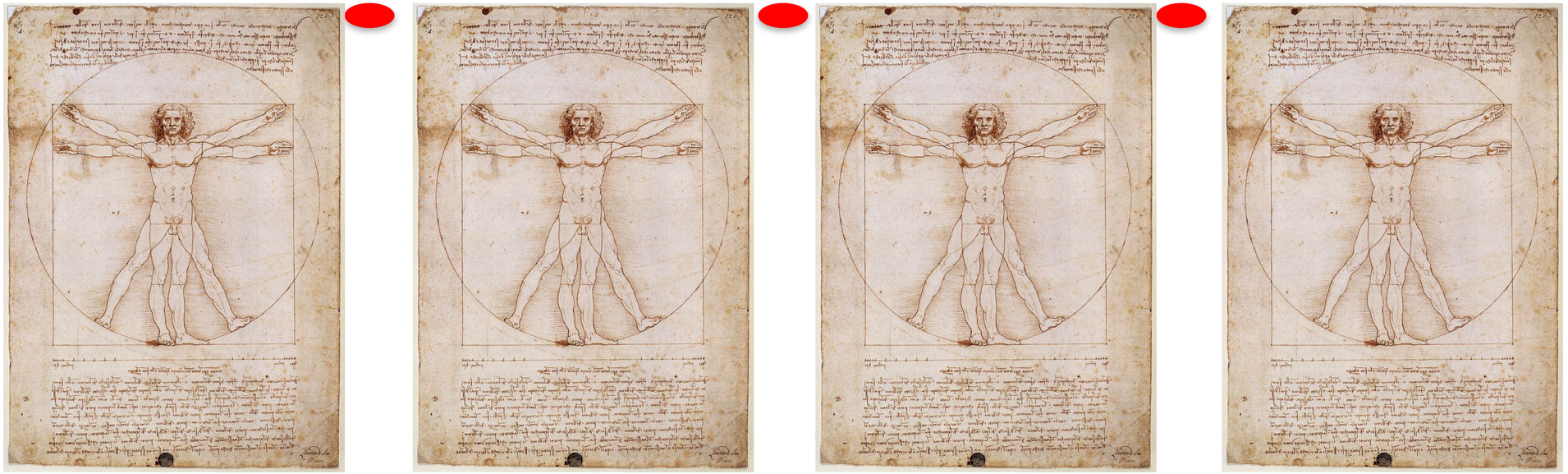


Requires the understanding of the mechanisms of ageing

August Weismann (1889): The mortal soma and the immortal germline



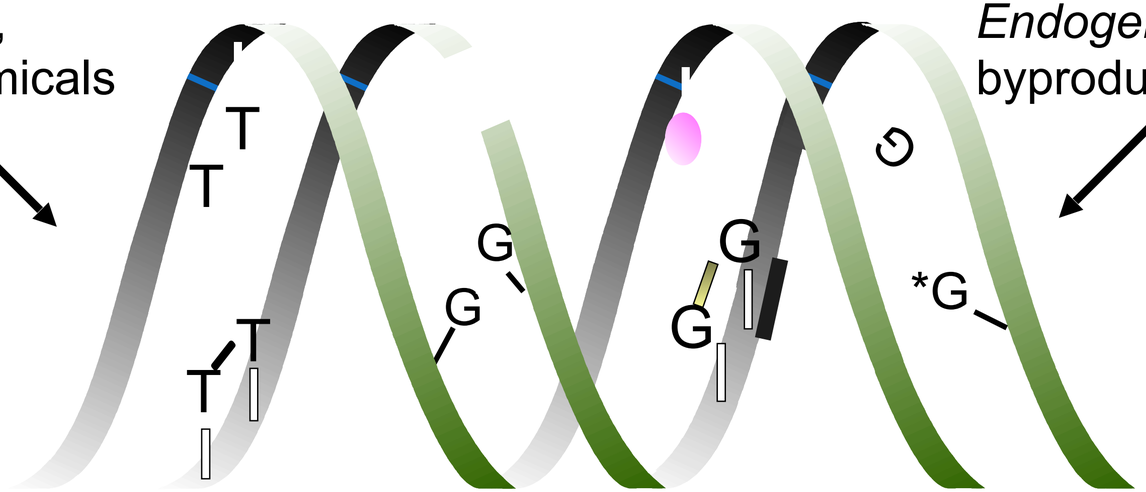
Germ cells Germ cells Germ cells



Which mechanisms maintain the body and thus determine the aging process?

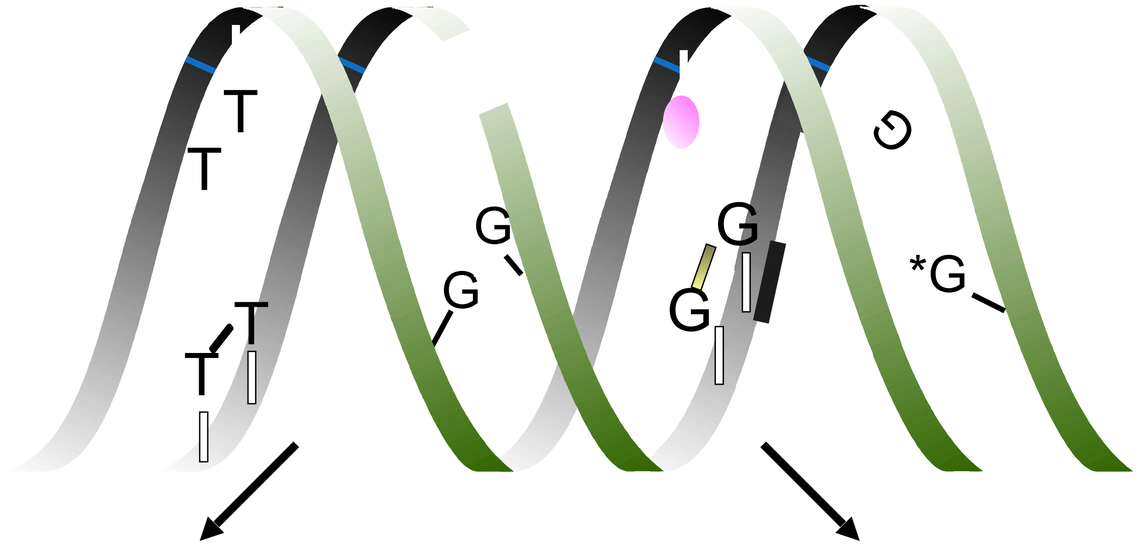
Consequences of Genome Damage

Exogenous: UV, irradiation, chemicals



Endogenous: Metabolic byproducts

Consequences of Genome Damage



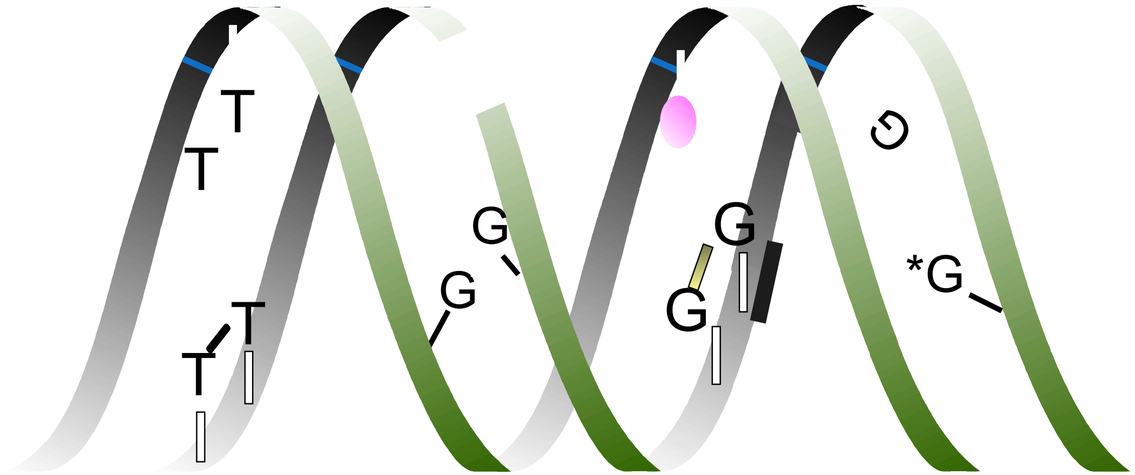
Changes in the Genome:
Mutations

CANCER

Persistent damage:
Functional loss, cell death

AGING

Consequences of Genome Damage



DNA Repair Systems

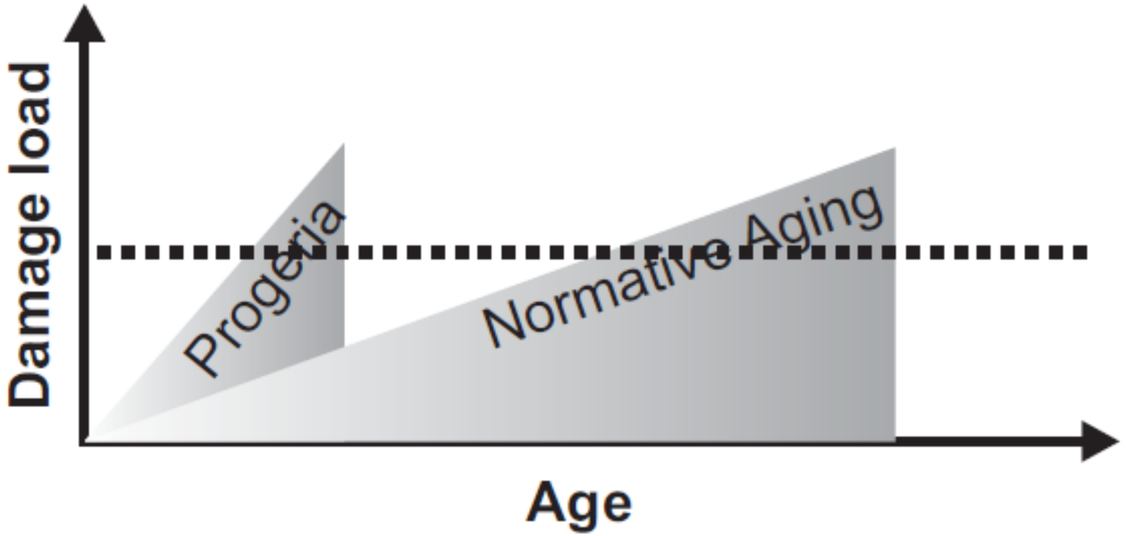
When the Genom cannot be repaired: High cancer risk and premature aging

***X*eroderma *P*igmentosum**

Cockayne Syndrom

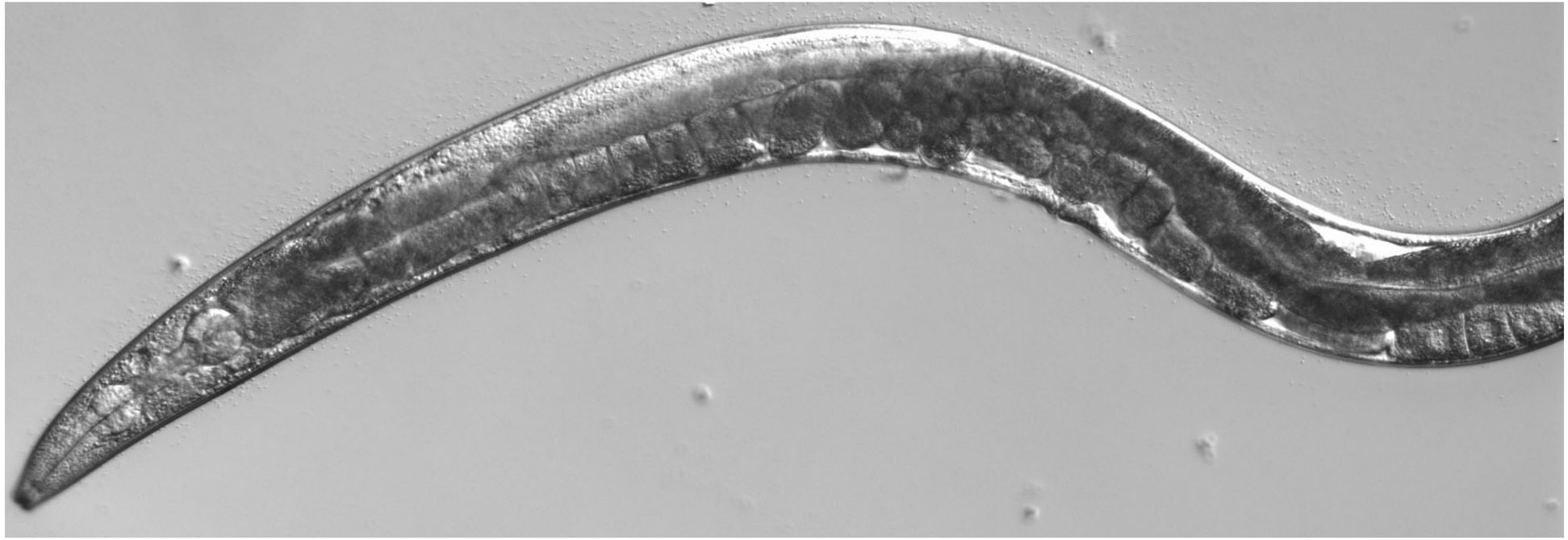
9 y

Rapid accumulation of DNA damage accelerates the aging process

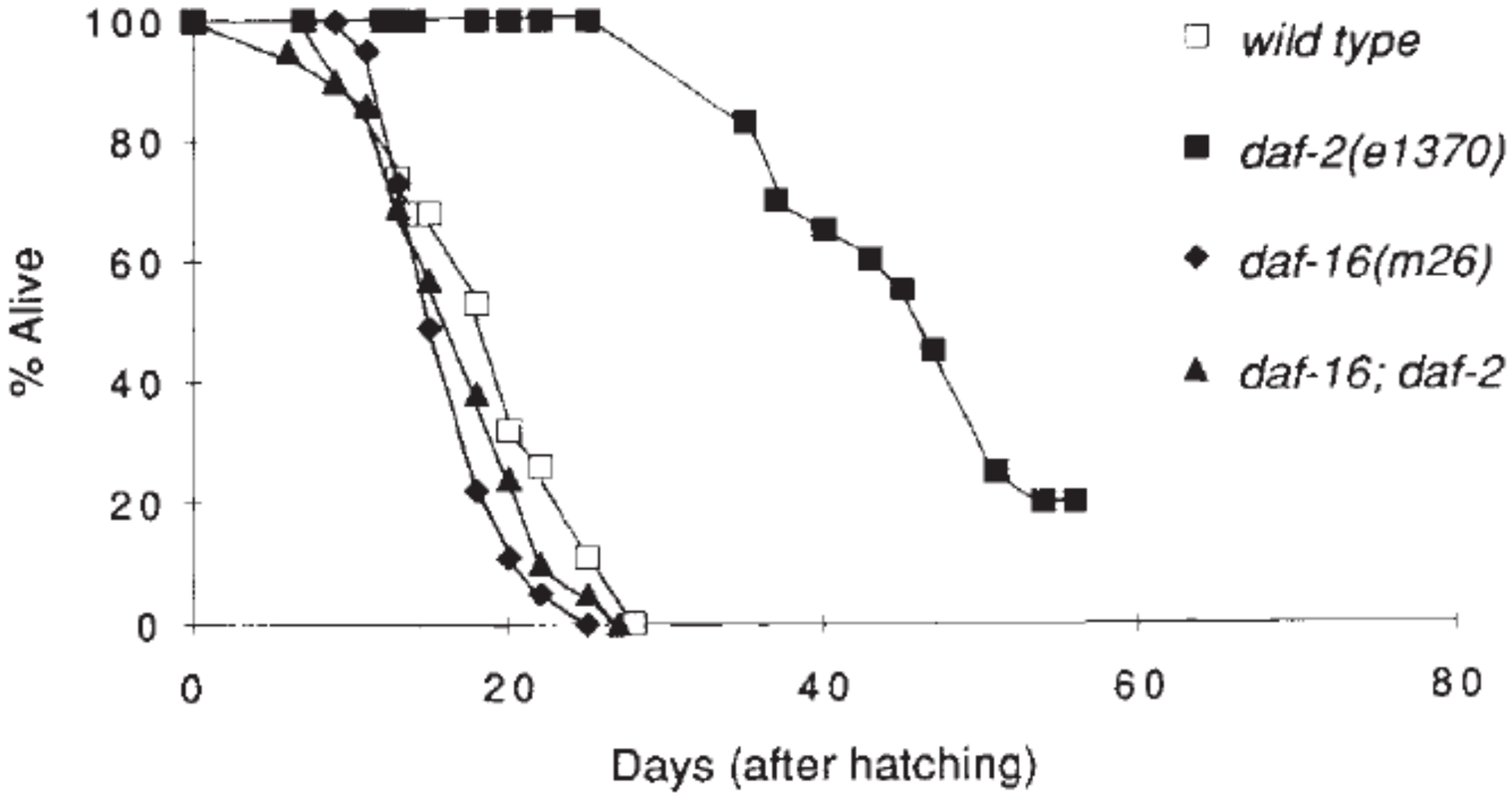


Threshold of tolerance

A nematode worm and the discovery of the genetics of aging



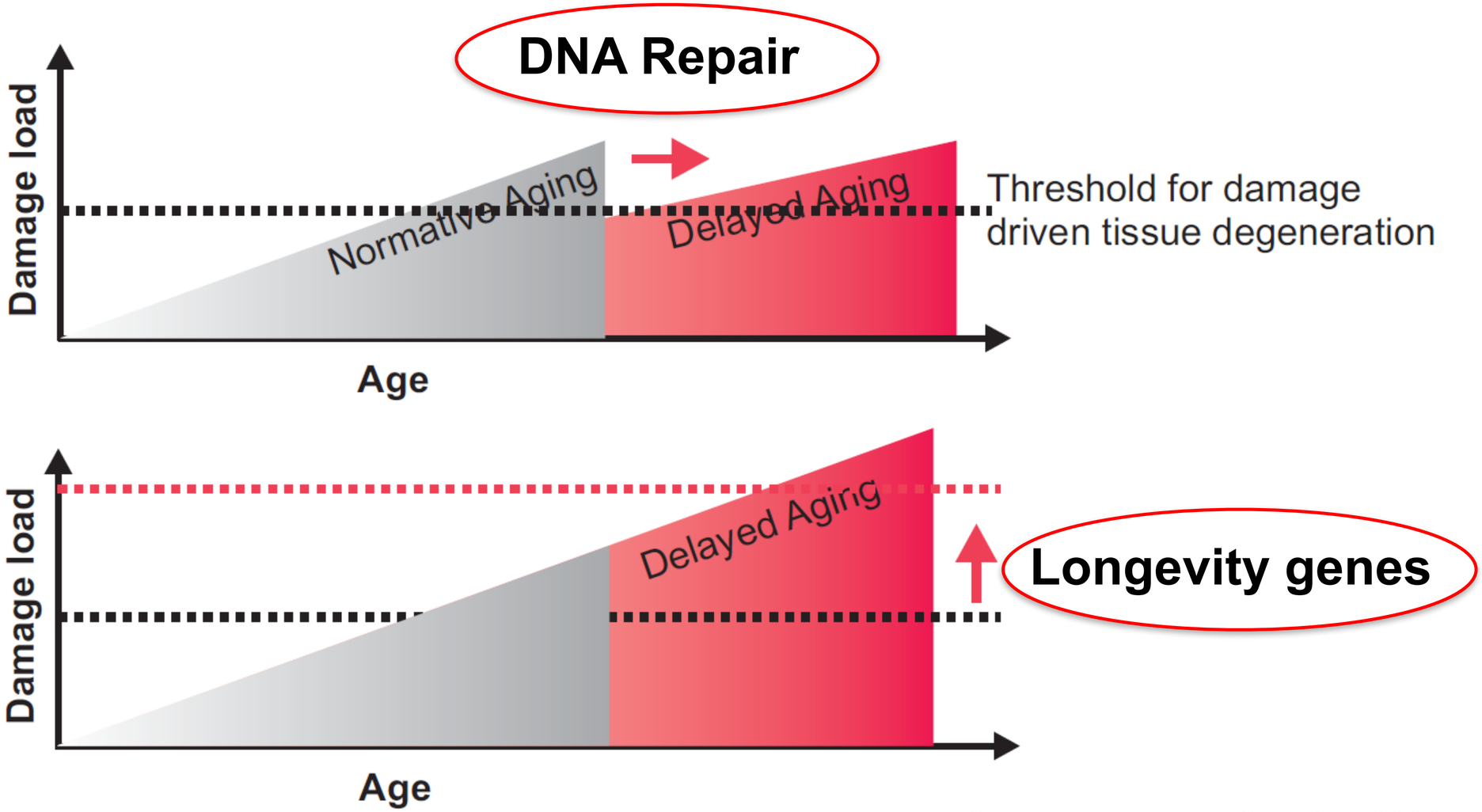
Cynthia Kenyon (1993): Mutations in a single gene could double the lifespan



Longevity program responds to genome damage

Longevity genes maintain youthfulness

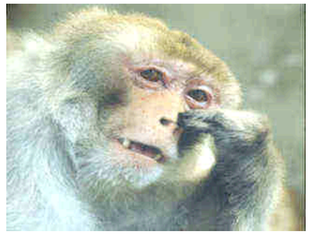
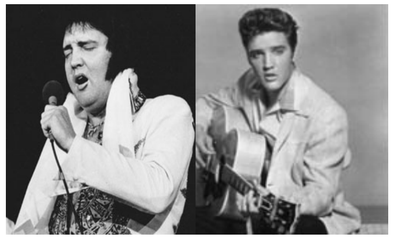
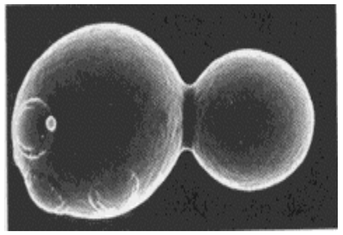
Longevity assurance pathways extend tissue functionality amid persistent DNA damage



Garinis *et al.*, Nat Cell Biol 2009
Mueller *et al.*, Nat Cell Biol 2014

Interventions for healthy ageing I

Calorie restriction extends lifespan












Humans???

Budding Yeast

Rhesus Monkey?

Rotifer

Labrador

Daphnia

Rat

C. elegans

Dietary restriction lengthens life span in diverse organisms

Mouse

D. melanogaster

Chicken

Medfly

Guppy

Waterstrider

Carabid Beetle

Bowl & Doily Spider

photo-Clyde Tamaru, U.of Hawaii Sea Grant

Ad libitum **Diet Restricted**

Decreased body mass
Decreased TAG
Decreased Risk Factors of
-Atherosclerosis
-Diabetes
Increased energy

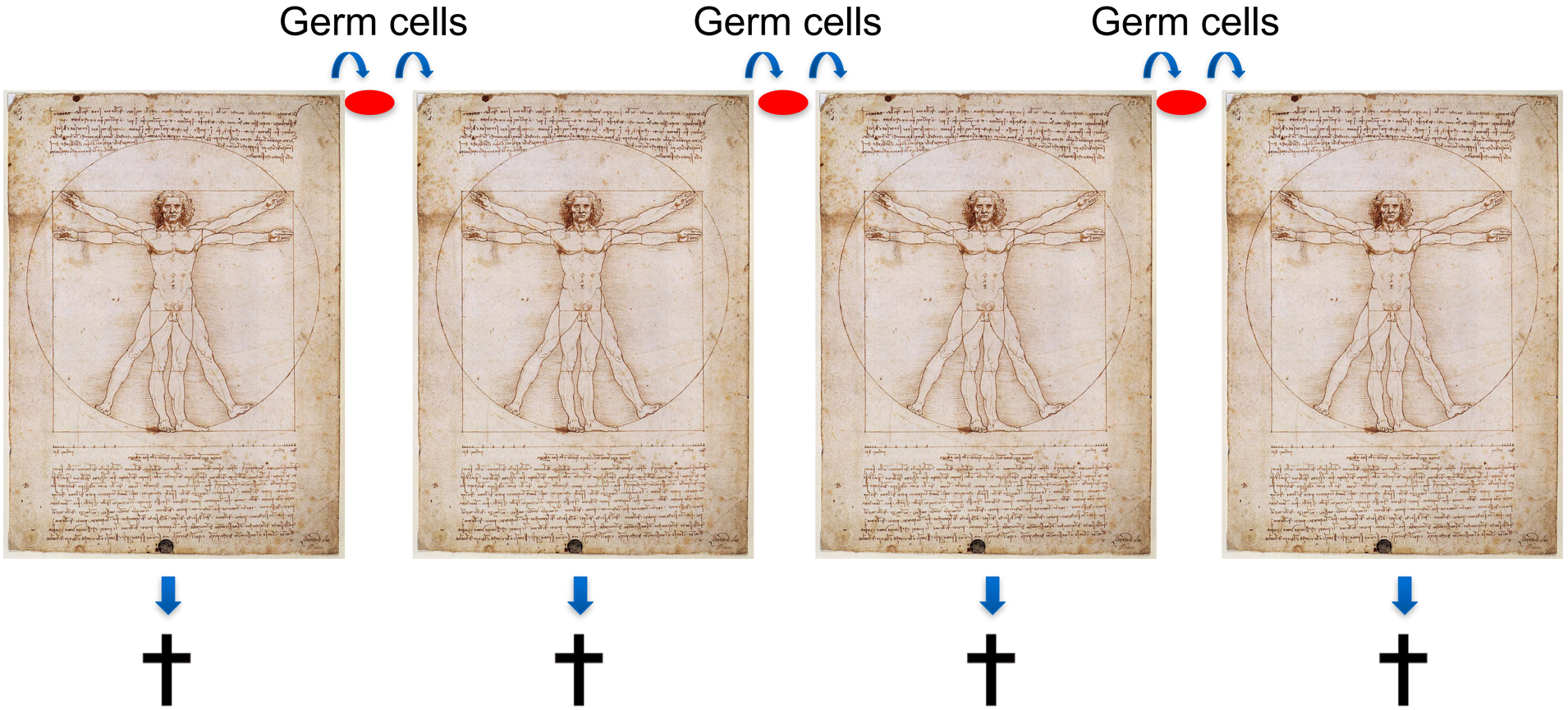
Colman *et. al.* 2009 Fontana *et. al.* 2010

Calorie restriction for humans?

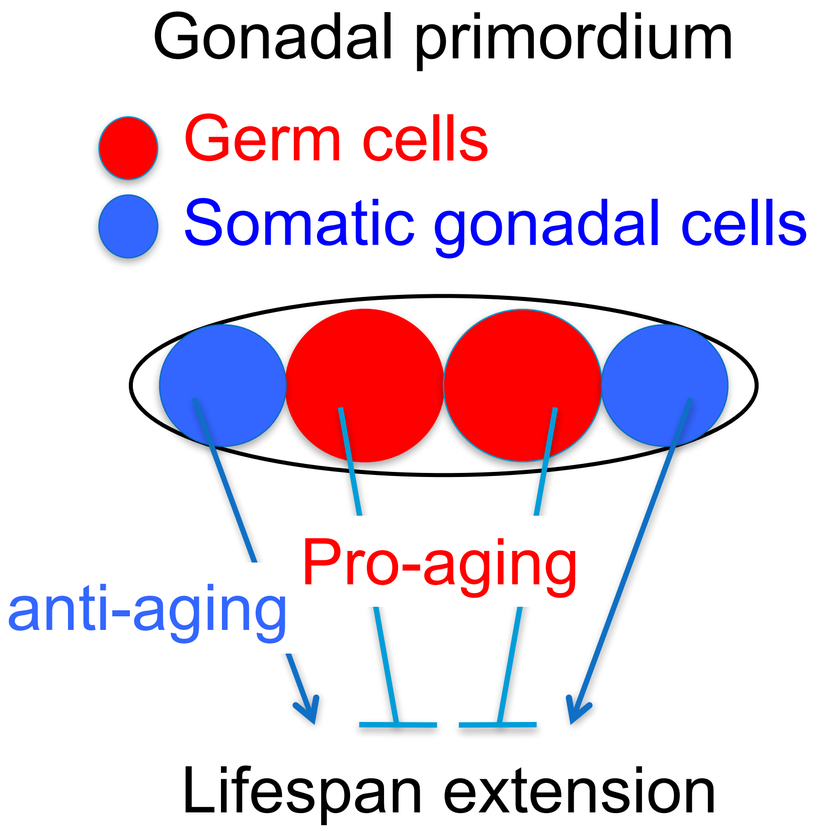
- Reduced calorie intake can be healthy, obesity is disease risk factor
- Calorie restriction requires optimum, malnutrition is dangerous
- This optimum can be individually very different
- Healthy diet is important but regular workout is also required
- Pharmacological interventions can target the signaling pathways of calorie restriction (metformin, rapamycin)

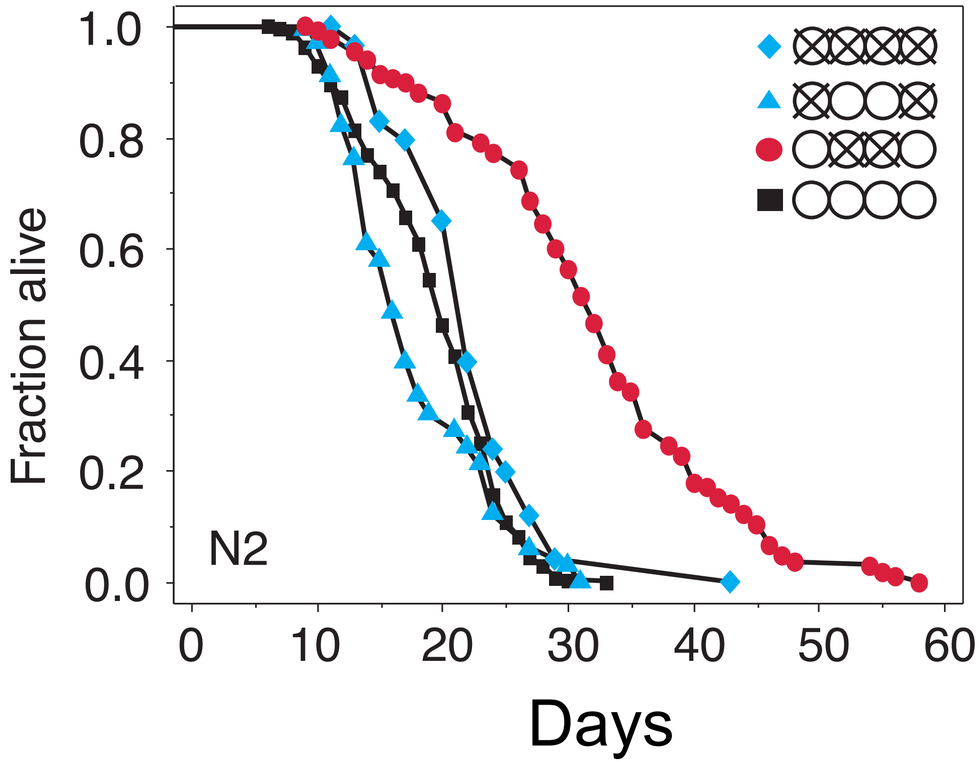
Interventions for healthy ageing II

The germline influences the ageing of the soma



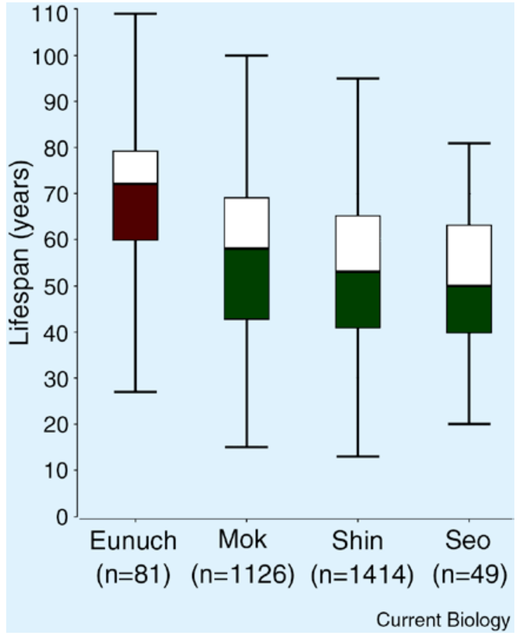
Removal of germ cells extends life span in *C. elegans*





Hsin 1999, Nature

Translational implications?



The lifespan of Korean eunuchs

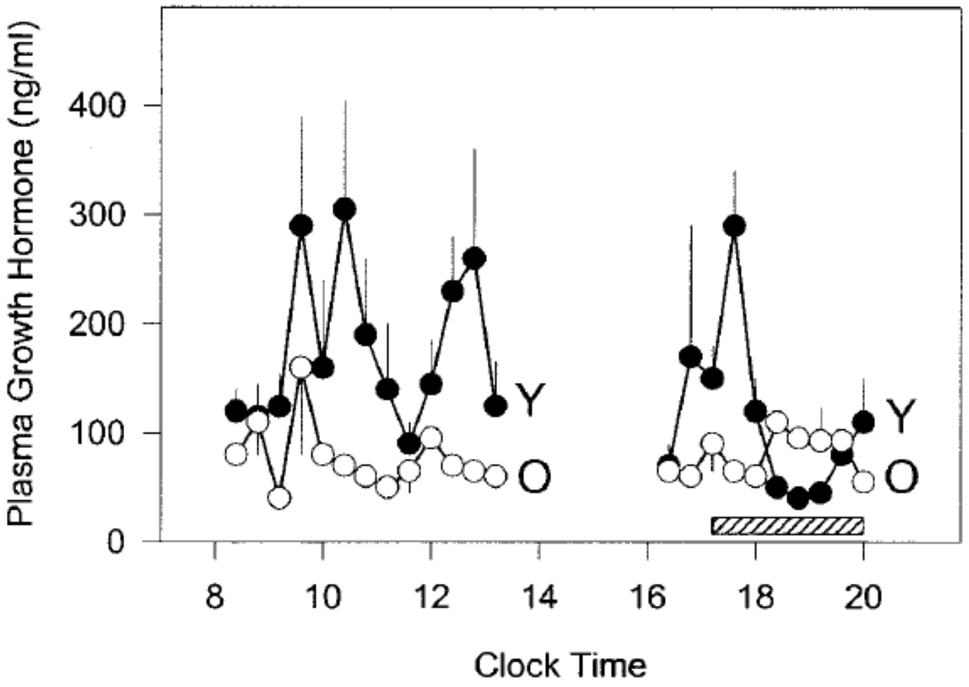
Kyung-Jin Min[1,*], Cheol-Koo Lee[2,*], and Han-Nam Park[3]

Interventions for healthy ageing III

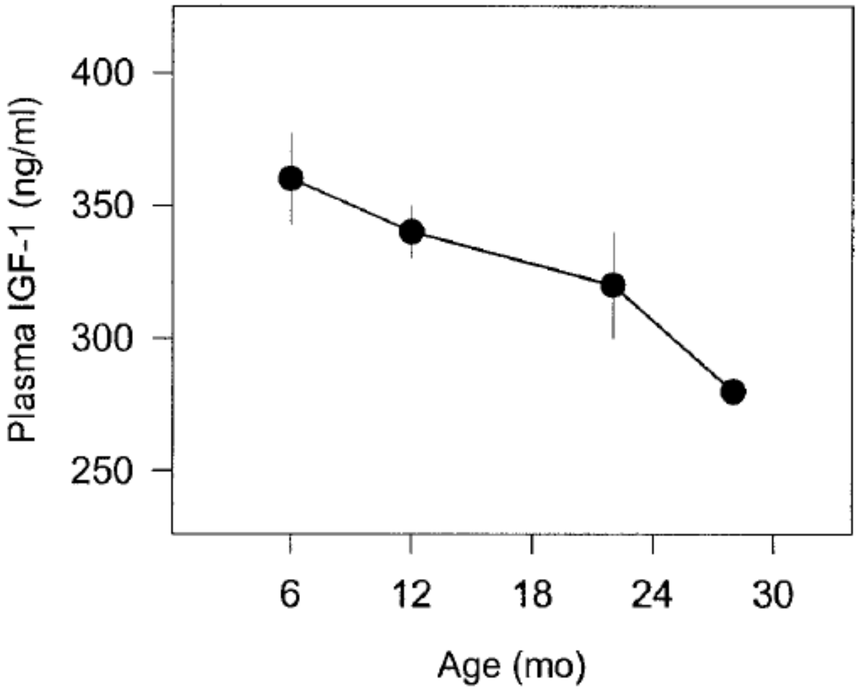
Systemic ageing: Are there endocrine factors (e.g. hormones, growth factors) that determine the ageing of tissues?

Reduced growth hormones in ageing

Growth hormone

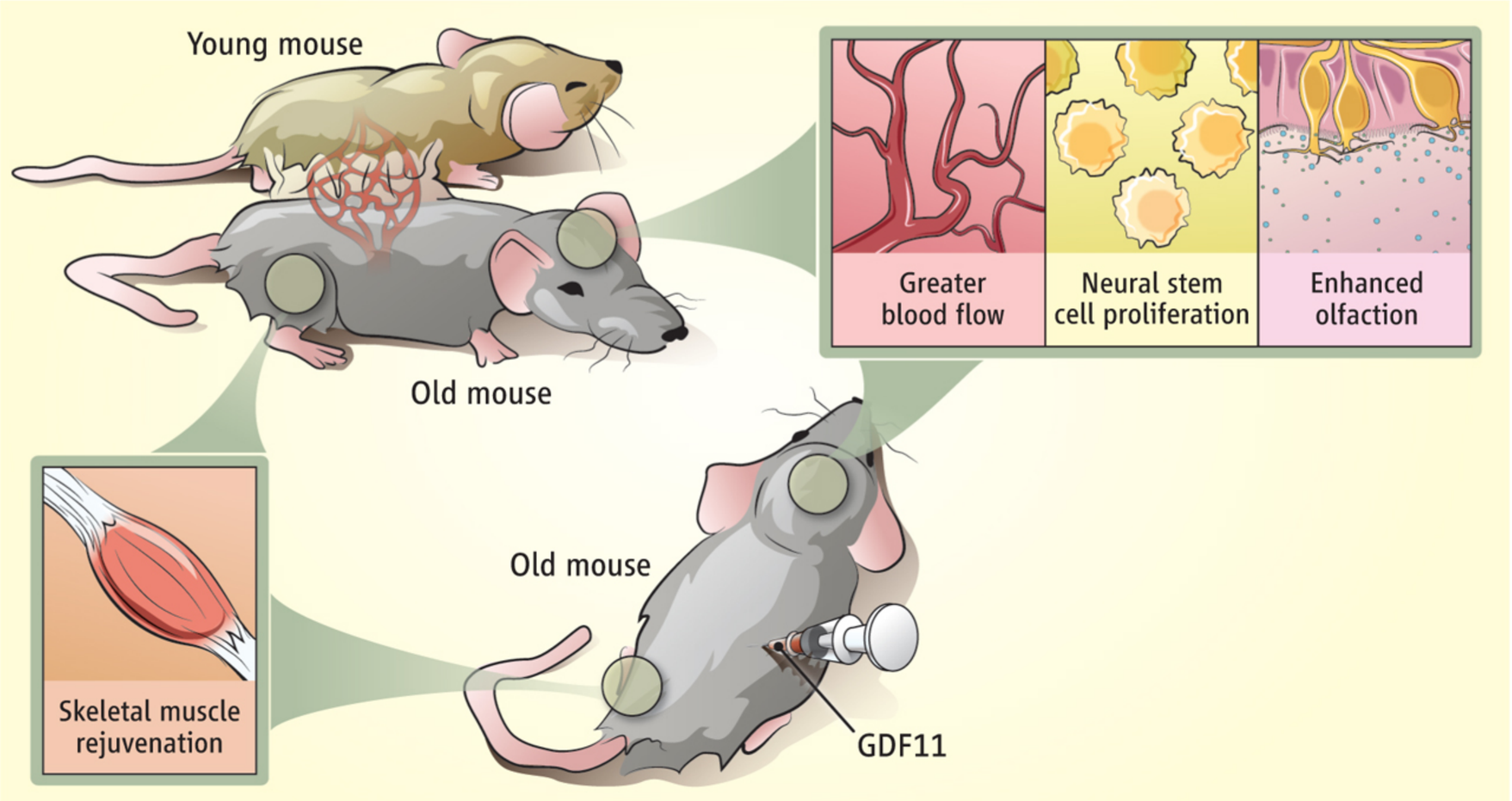


IGF-1



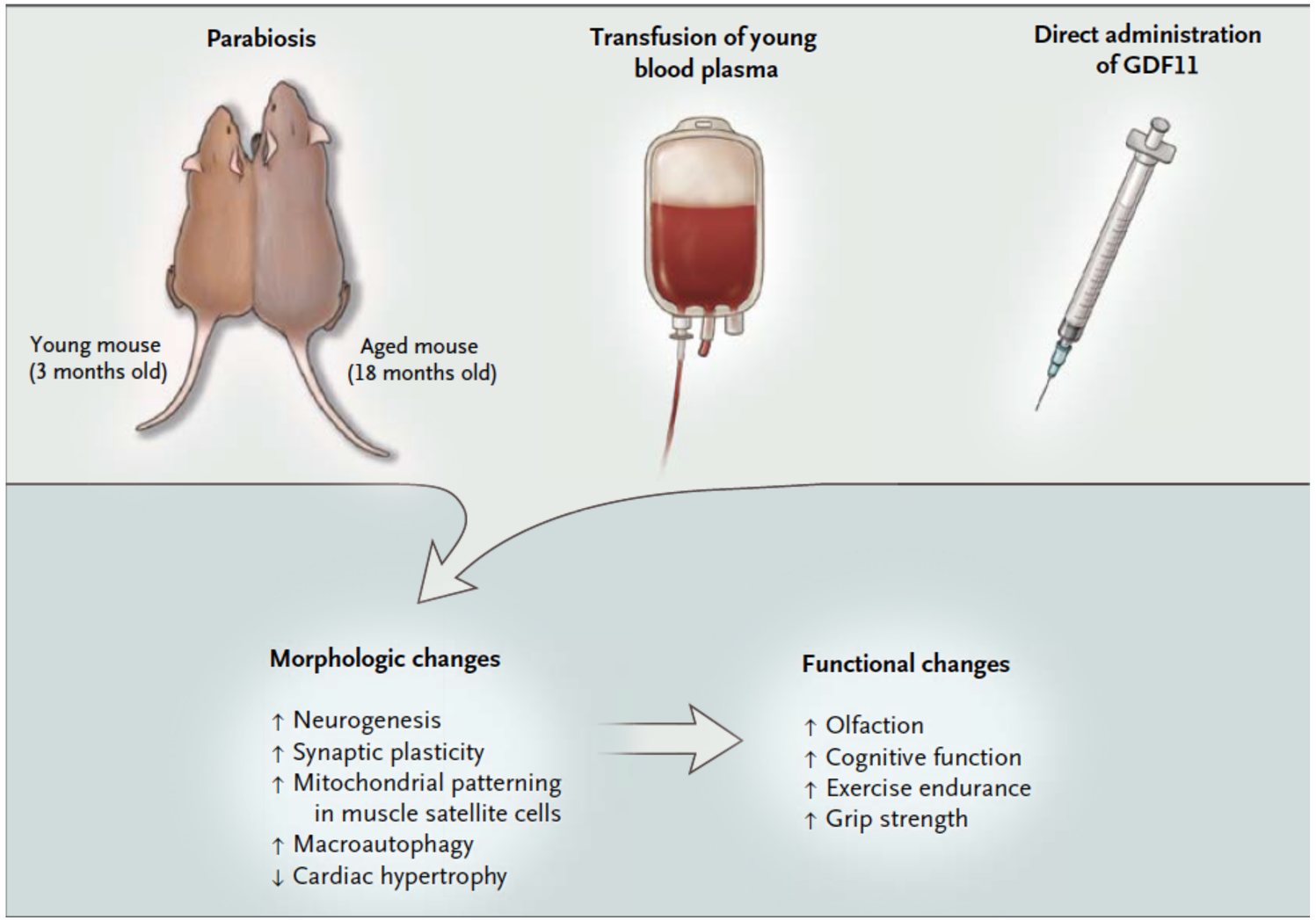
Carter *et al.*, 2002

Parabiosis:
Can circulating factors from young donor blood rejuvenate old animals?



Kaiser, Science 2014

From Parabiose and blood transfusions to application of specific factors

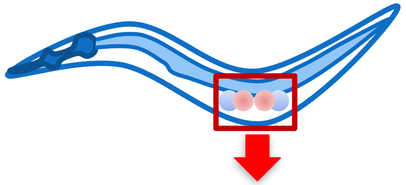


Laviano NEJM 2014

Interventions for healthy aging

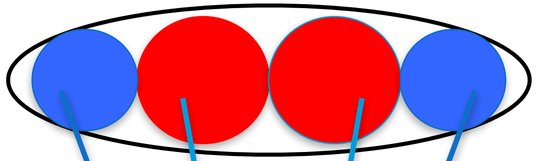
Calorie restriction

Influence of the germline



Germ cells

Somatic gonad

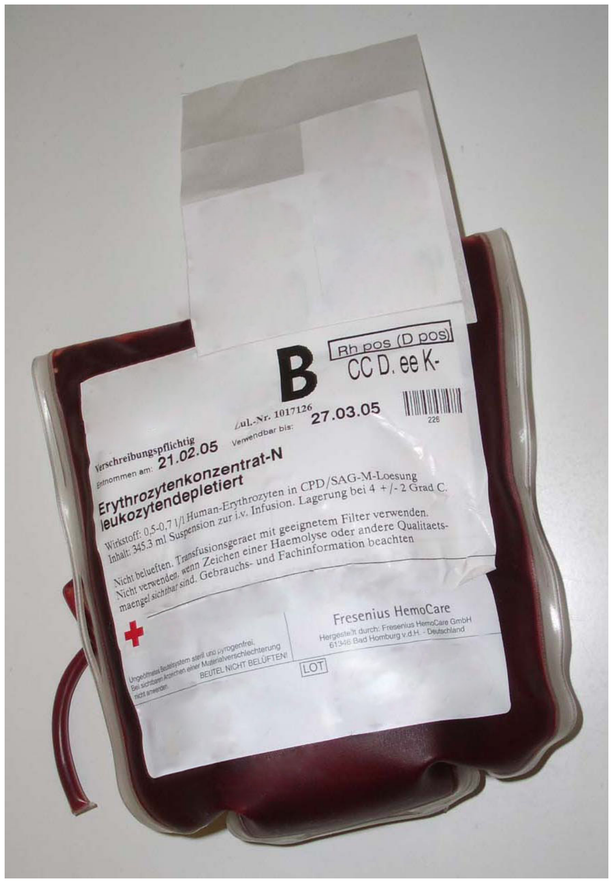


Pro-aging

anti-aging

Aging

Growth factors and hormones



Conclusions

1. The soma ages, the germline can be immortal
2. Our gene pool has not been selected for extreme longevity
3. Accumulation of damage with aging impairs functioning of cells and tissues
4. Genetic pathways regulate longevity
5. Diet and lifestyle can impact aging and aging-associated diseases
6. Interventions will influence cell renewal and maintenance depending on cell types
7. *Paradigm shift* in medicine: Instead of treating disease, maintenance of health will be therapy target