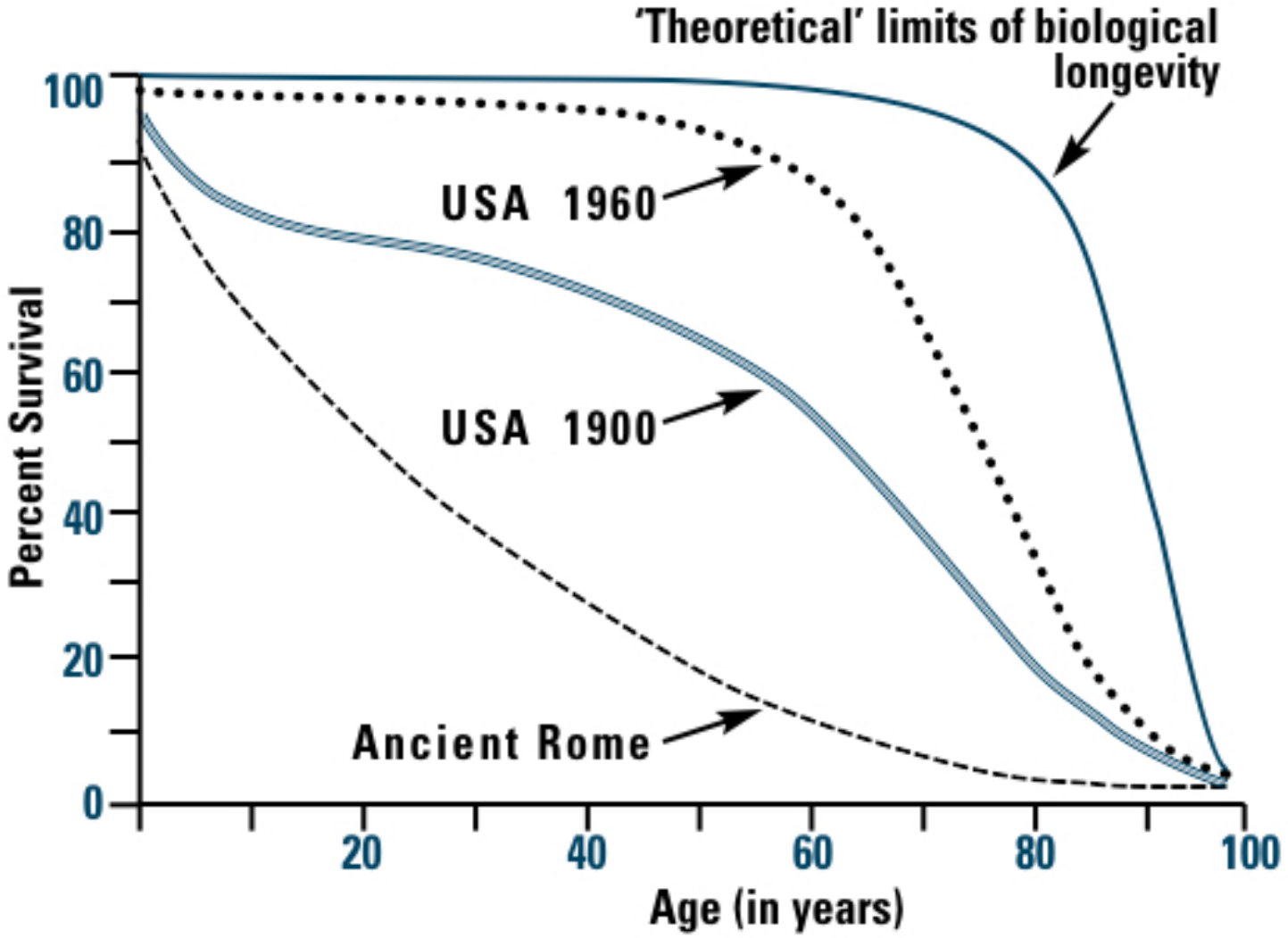
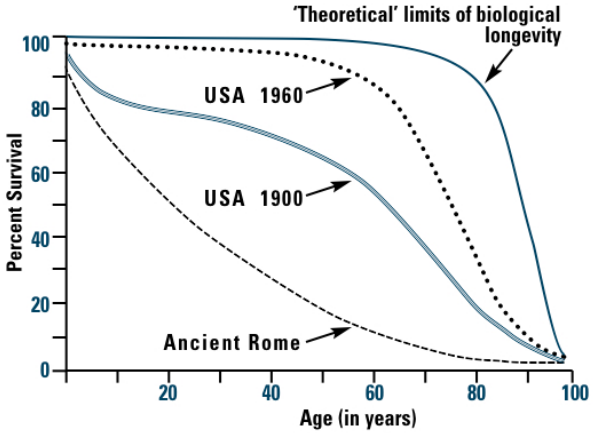
Molecular models of aging

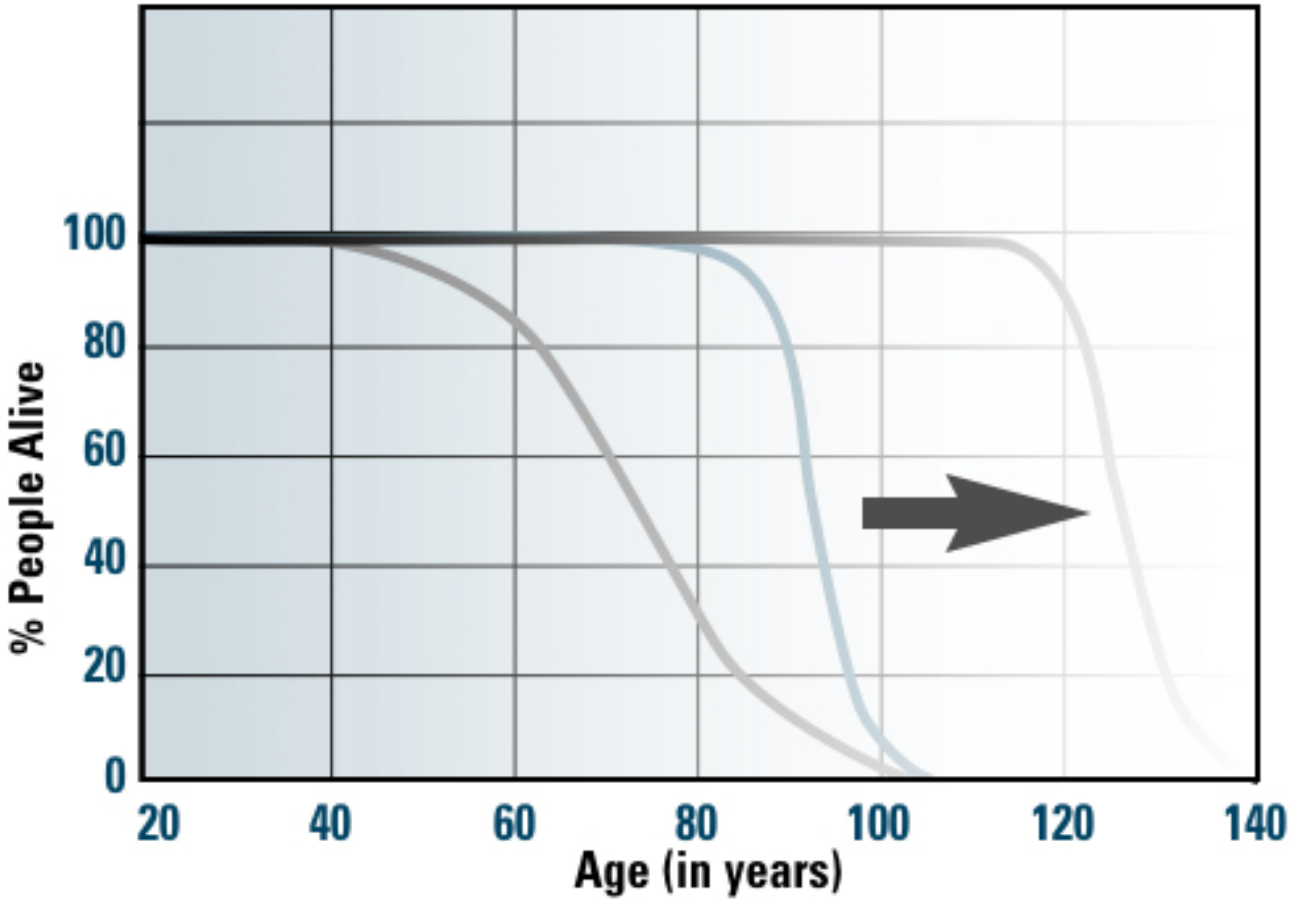
Claus Desler

Average lifespan vs. Healthspan



Average lifespan vs. Healthspan



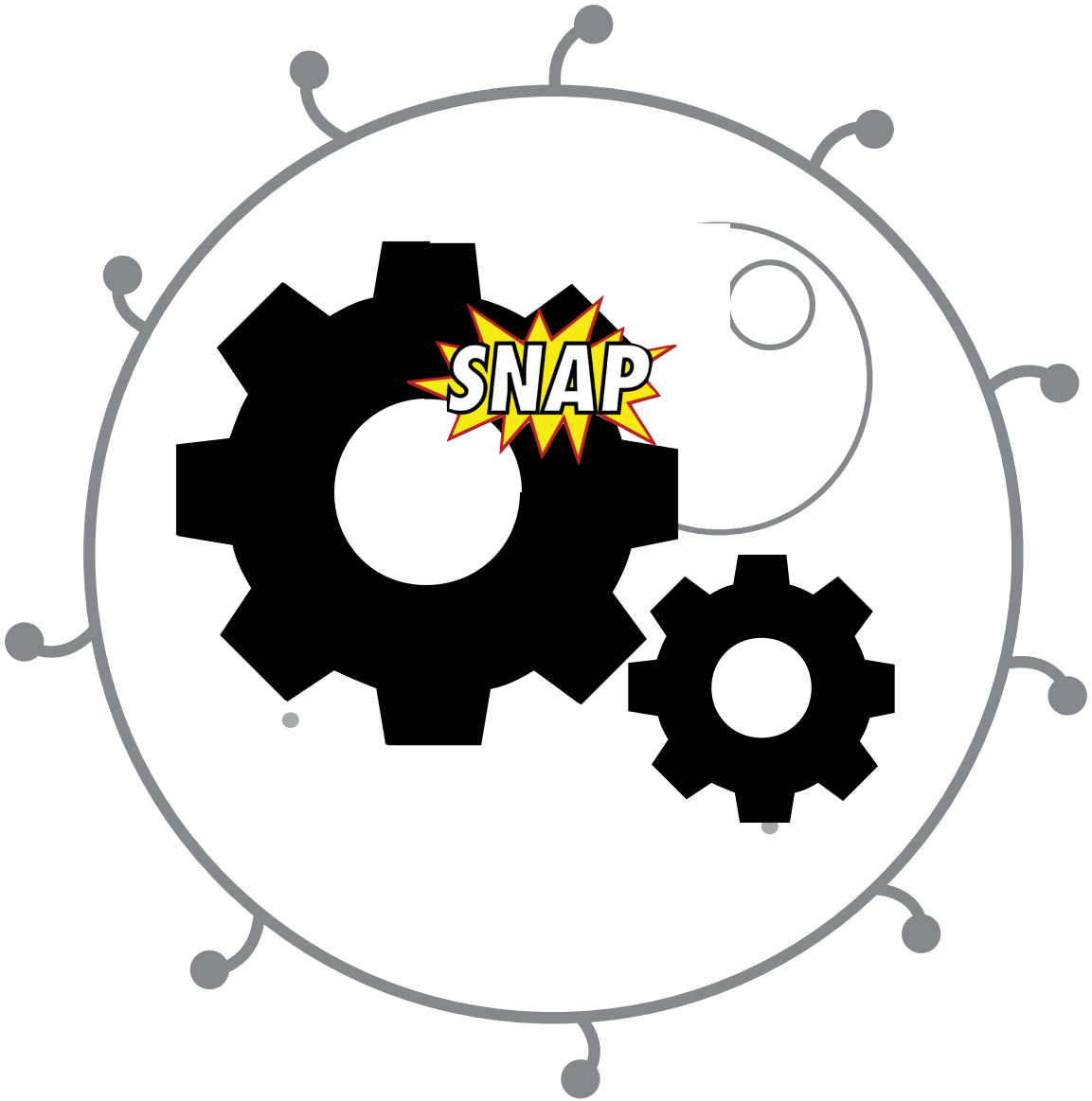


Top 5

- Stroke
- Lung disease
- Cardiovascular disease
- Dementia
- Cancer

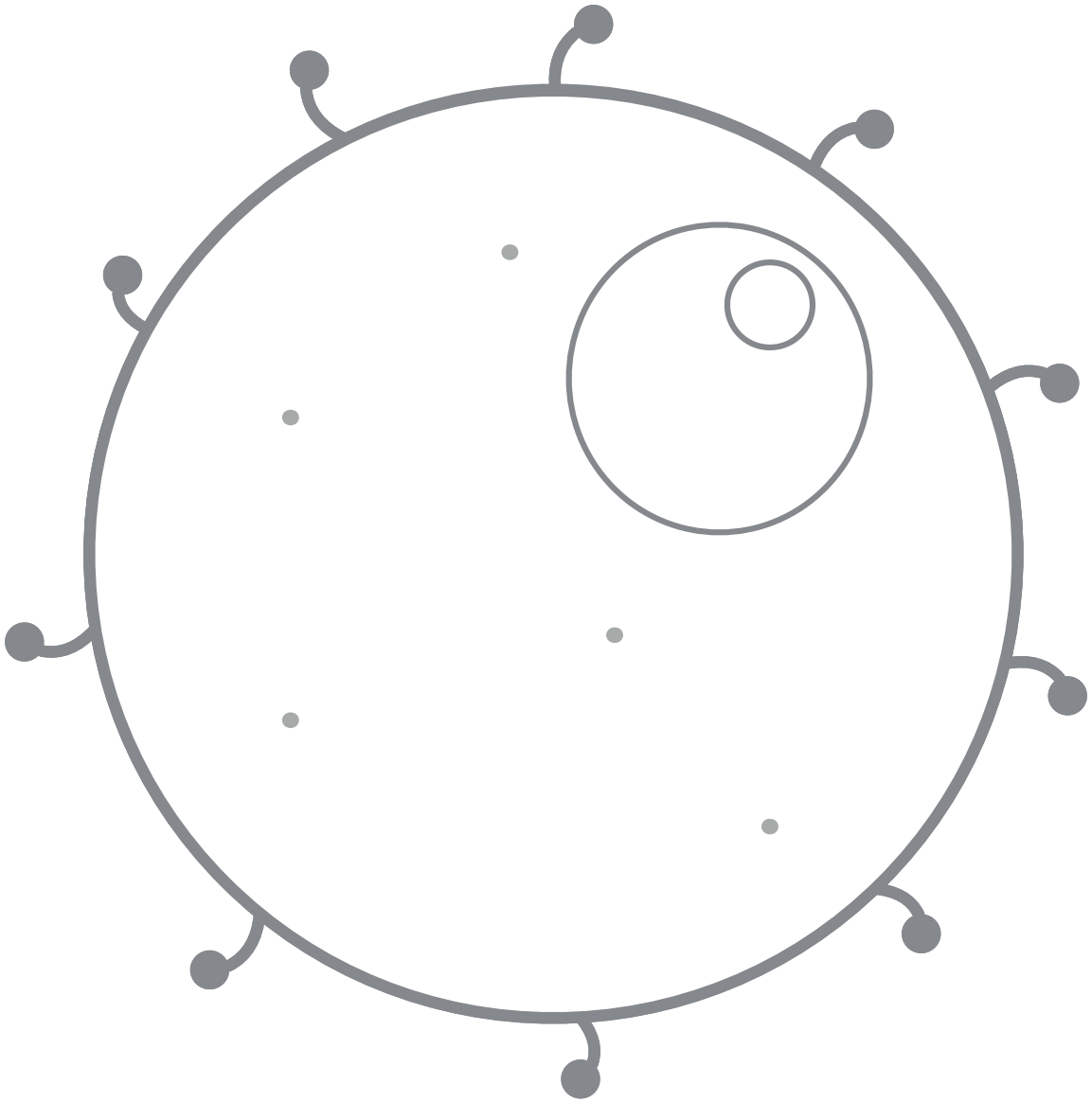
Age
Stroke
Lung disease
Cardiovascular disease
Dementia
Cancer

Cellular Senescence



Cell product (f.ex insulin)

Cell



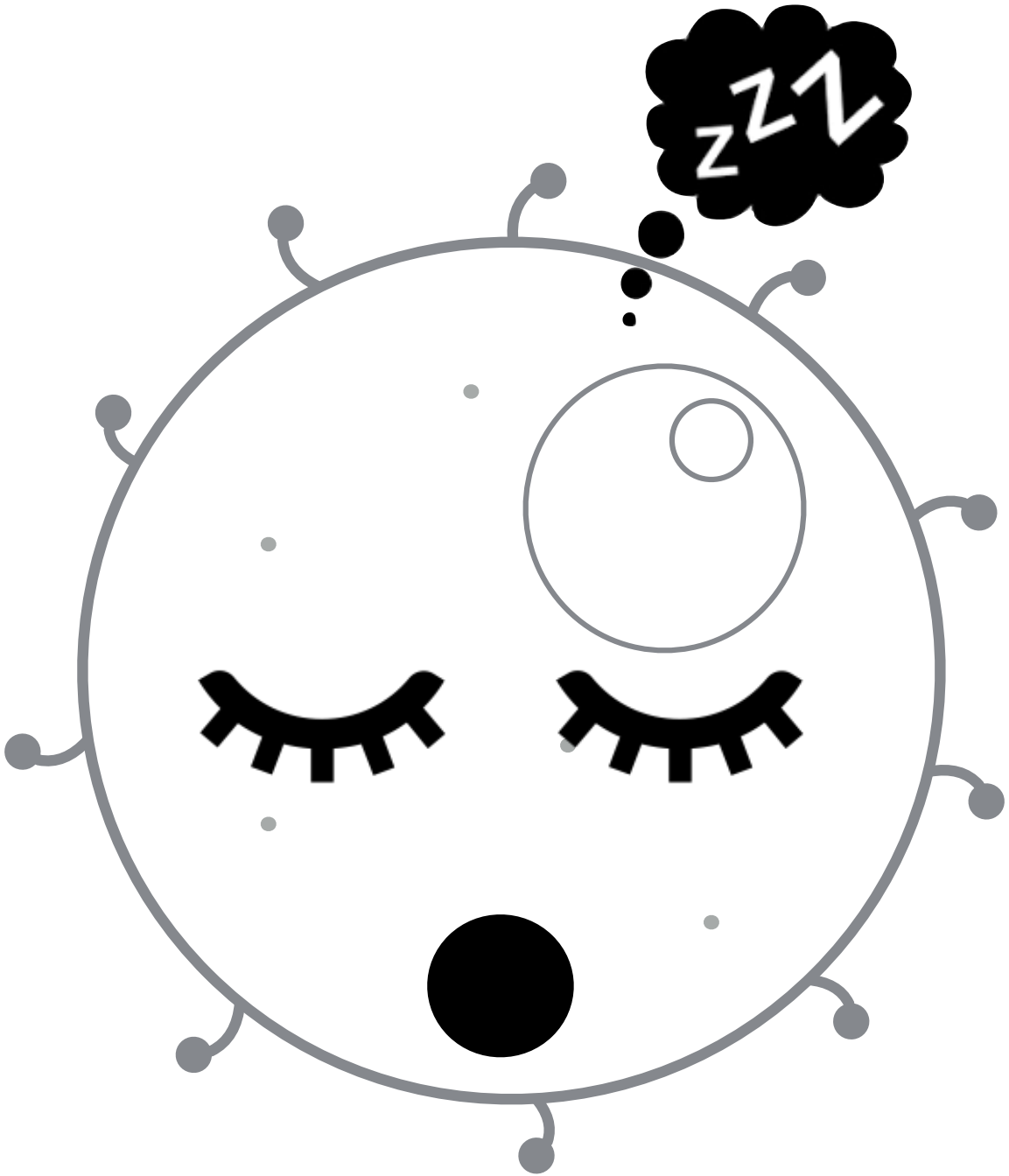
Apoptosis

(Programmed cell death)

Cell damage / redundant

Self destruction and cell fragmentation

Makes room for a new cell

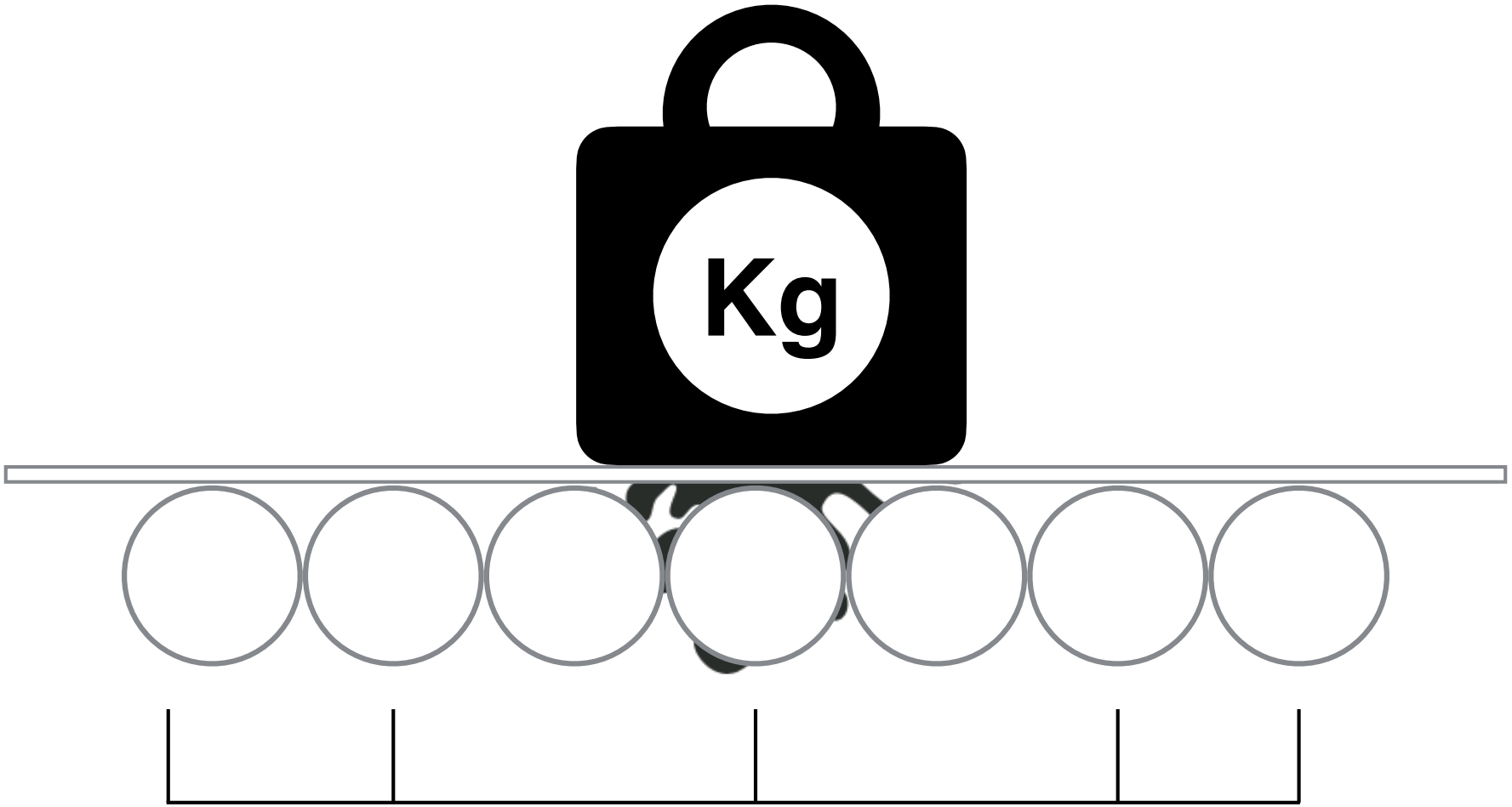


Cellular senescense

Cell damage

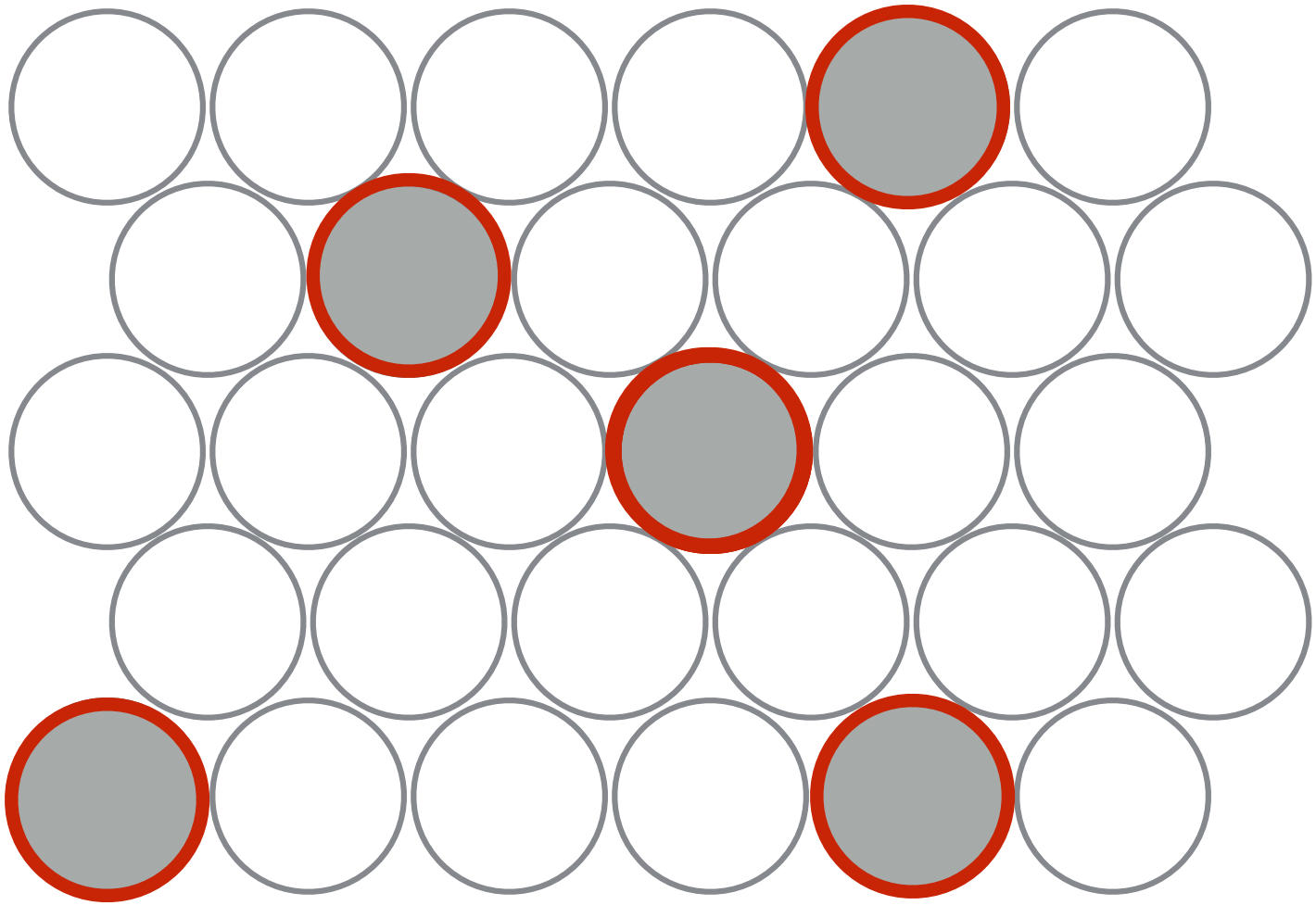
Division and activity are arrested

Does *not* leave space for a new cell


Kg
Senescent cells

SASP

Senescence-associated secreting phenotype



Tissue (liver, muscle, other)

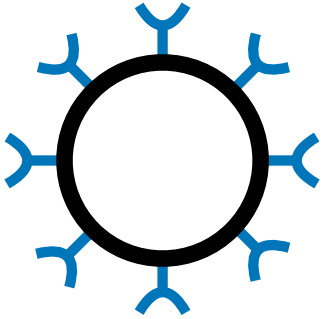
First senescent cell

Secretion of cytokines, growth factors & more

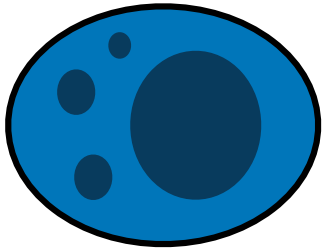
Stress of adjacent cells

Dysfunctional tissue / disease

Macrophages

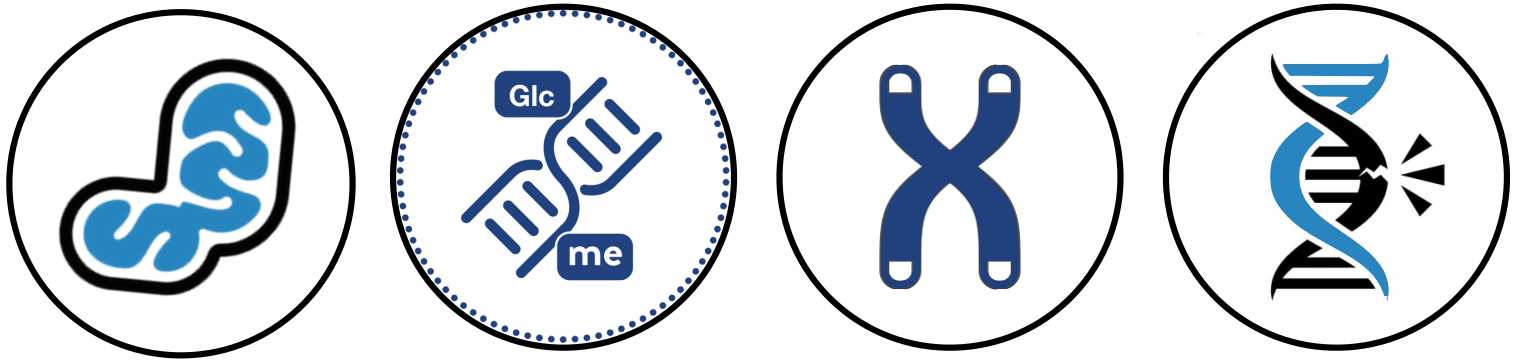


T cells



NK cells

Are attracted by SASP. Will induce destruction of senescent cells

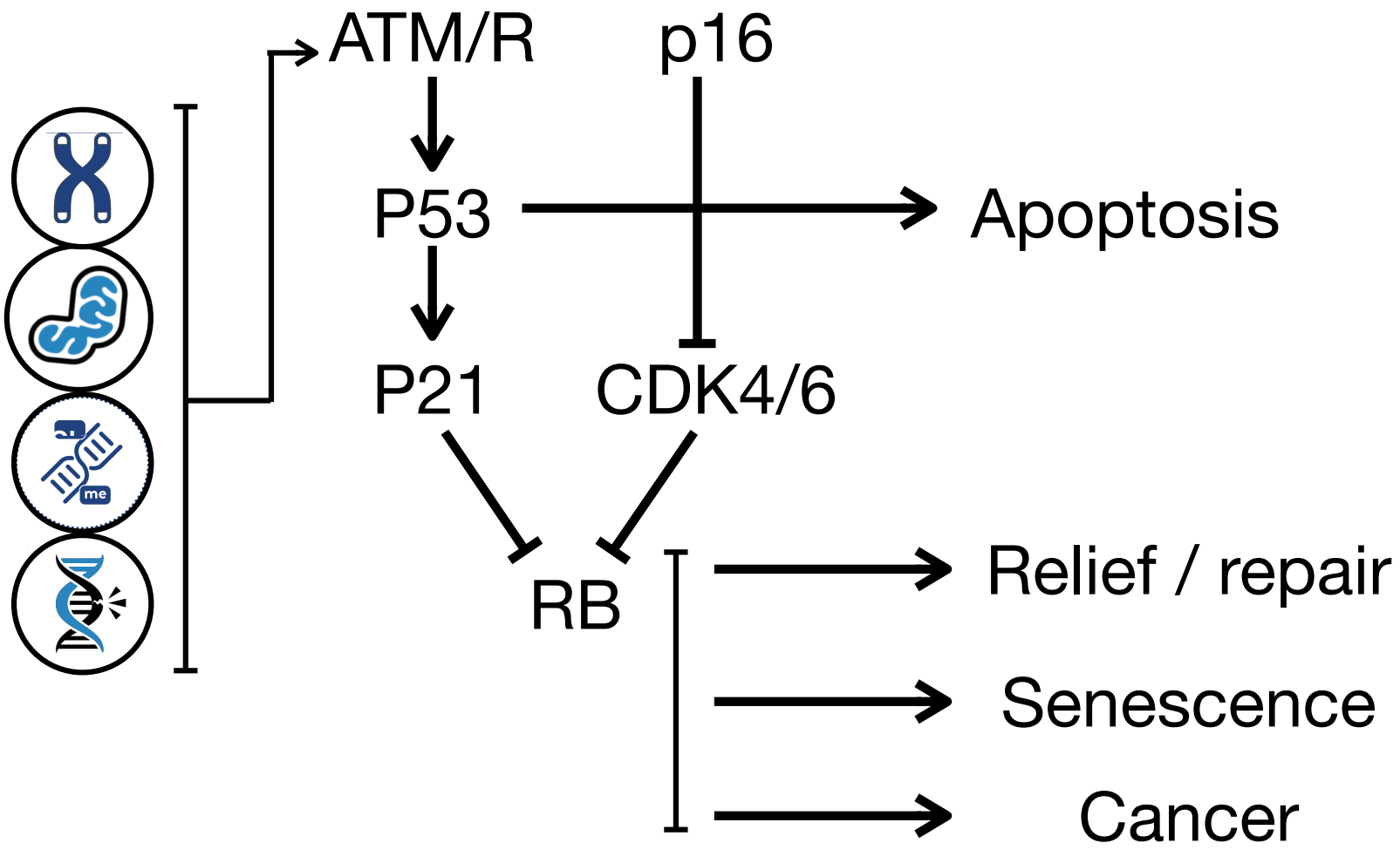


Mitochondria dysfunction

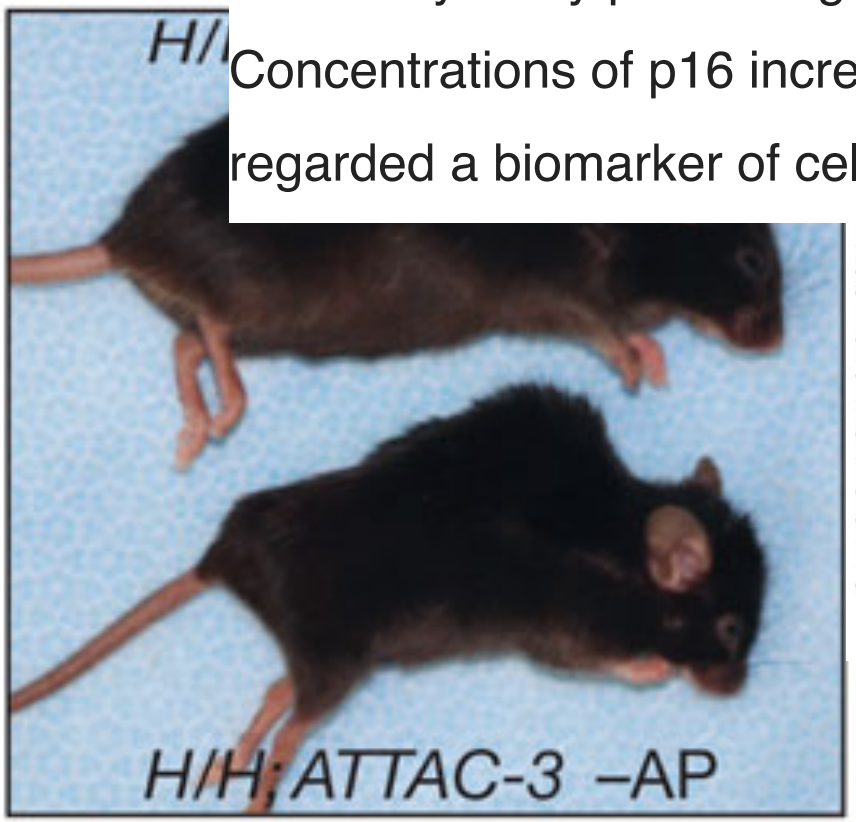
Epigenetic factors

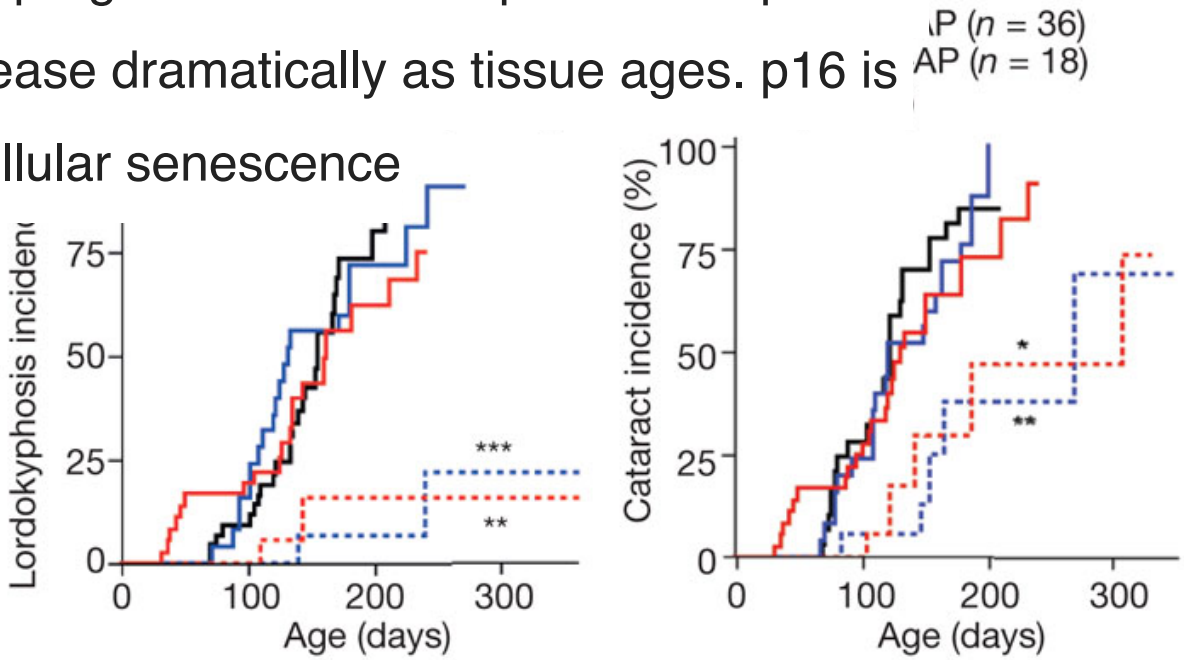
Telomere erosion

DNA damage


ATM/R
p16
P53
Apoptosis
P21
CDK4/6
RB
Relief / repair
Senescence
Cancer

p16 is a cyclin-dependent kinase (CDK) inhibitor that slows down the cell cycle by prohibiting progression from G1 phase to S phase. Concentrations of p16 increase dramatically as tissue ages. p16 is regarded a biomarker of cellular senescence





DJ Baker *et al*. *Nature* **000**, 1-5 (2011)
doi:10.1038/nature10600

Senolytic drugs

Baar *et al*. *Cell* **169**, p132 (2017)

Company (year founded)	Business focus/technology
1E Therapeutics (2020)	Antisense oligonucleotide–based senolytics
Atropos Therapeutics (2018)	Targeting transition between quiescence and senescence (senescence after growth arrest, or SAGA)
Cleara Biotech (2018)	Targeting FOXO4 to release proapoptotic p53
Deciduous Therapeutics (2018)	Activating immune cells to clear senescent cells
Dialectic Therapeutics (2018)	Systemic delivery of senolytic agents using proteolysis-targeting chimeras (PROTACs)
Dorian Therapeutics (2018)	Targeting USP16, a deubiquitination enzyme, to reverse senescence
Eternans (2017)	FOXO4-binding peptide
FoxBio (2018)	Targeting p53/FOXO4 prosurvival pathways in senescent cells
Genome Protection (2018)	Stimulating innate immunity to eradicate genome-compromised cells
Geras Bio (2020)	SASP inhibitors
Insilico Medicine/Taisho (2020)	AI target identification and generation/validation
NRTK Biosciences (2020)	Synthetic optimization of approved drugs and supplements
Numeric Biotech (2017)	Selective targeting of FOXO4-p53
Oisín Biotechnologies (2014)	Gene therapy with caspase-9 activated in p16-positive cells
Oncosence (2019)	Monoclonal antibodies targeting tumor cells after inducing them to senescence
OneSkin (2016)	Peptide that modulates senescence-related signaling pathways and enhances DNA repair
Recursion Pharma (2013)	AI drug discovery platform
Rejuversen (2020)	Antibody against PD-L2 that promotes immune-mediated clearance of senescent cancer cells
Rubedo Life Sciences (2018)	Small-molecule senolytics
Senisca (2020)	Antisense oligonucleotides against splicing factors
Senolytic Therapeutics (2017)	Senolytic and senomorphic drugs to treat fibrosis
SIWA Therapeutics (2006)	Antibody against glycation surface molecule
Unity Biotechnology (2011)	Targeting various senescence-related proteins (Bcl-xL)

When I started adding the FOXO4-DRI in the past week I have noticed some definite changes. Weight loss, better sleep, more endurance and perhaps an improvement in lung function now well over 100% for the 3 measures, FVC, FEV and PEF, for a 63 yo. I know that the dose, a little less than 1 mg over 7 days, is a lot lower than the threshold dose indicated by the mouse model of .4 mg per kg of body weight for a human but I can't reconcile my results with

ptide

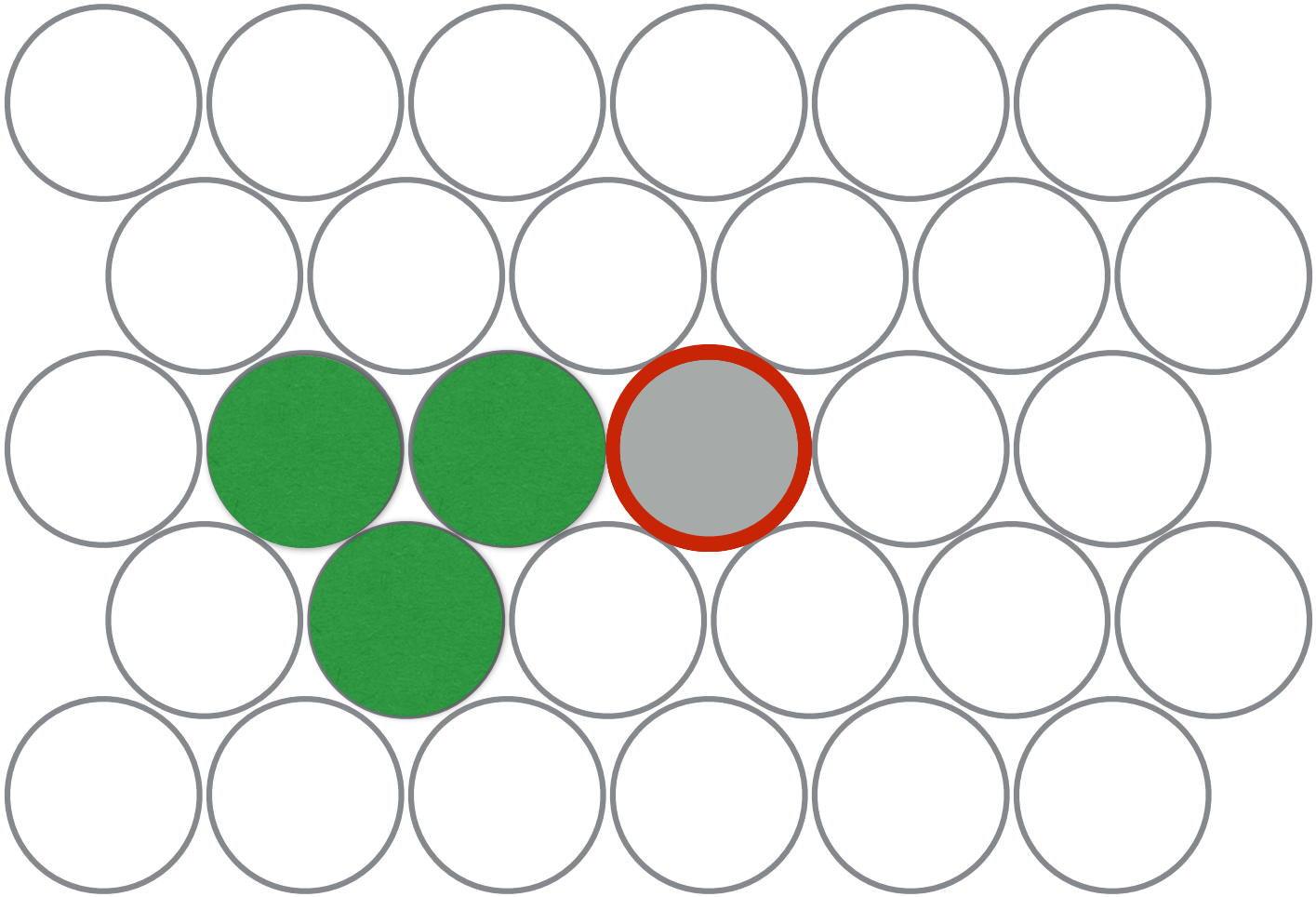
human

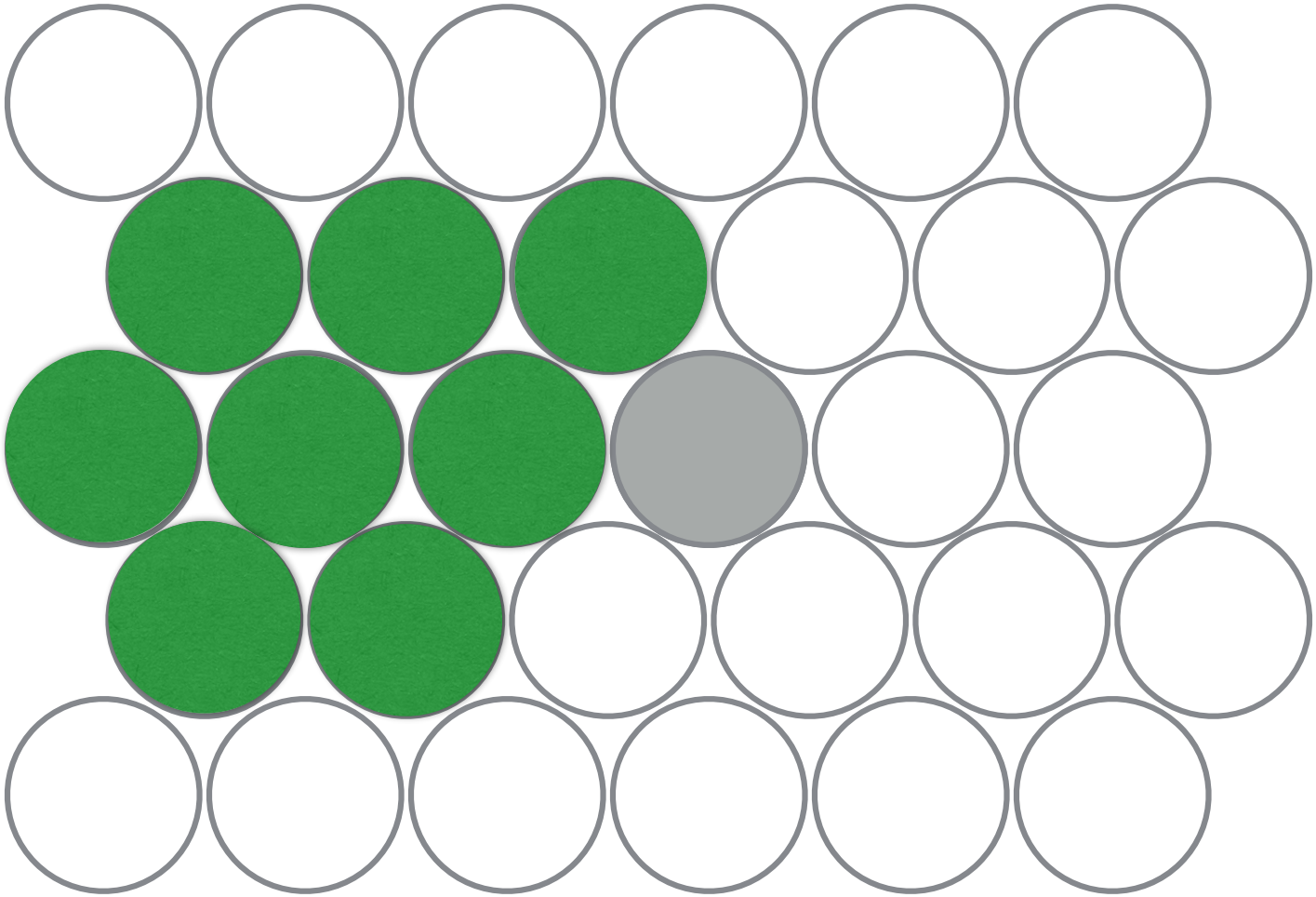
The bottom line is that Meatsauce (to my knowledge the only one so far to have taken it) has -- I think -- developed a mild case of **gout**, presumably from hyperuricemia caused by tumor lysis syndrome.

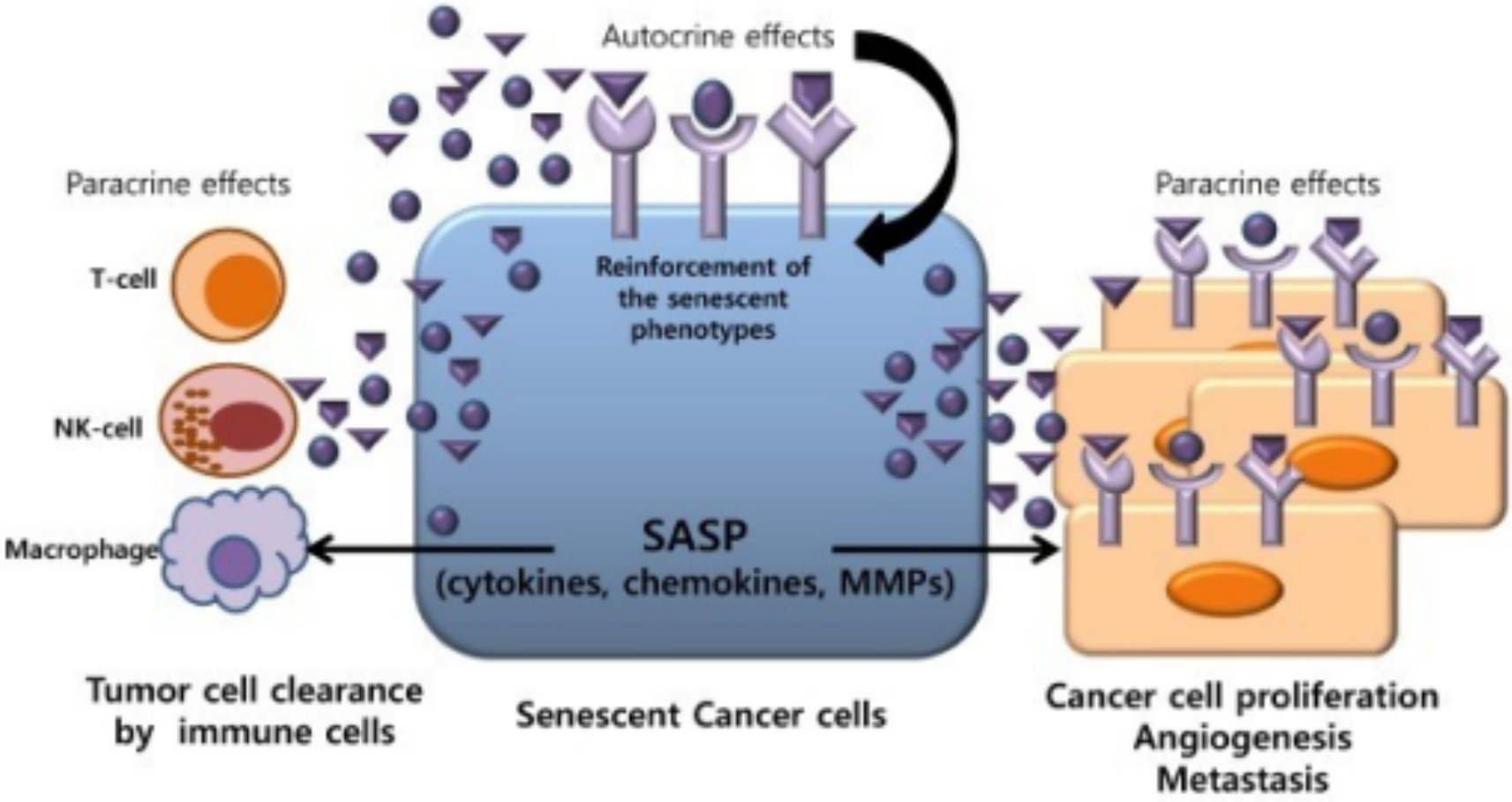
My Friend has brain cancer, his treatment stops, has anybody with cancer experience with foxo4-DRI?
In Holland the claim that mice with braintumer cells, have being cured.

*

comprehensive modifications available. Getting an automatic online quote here.

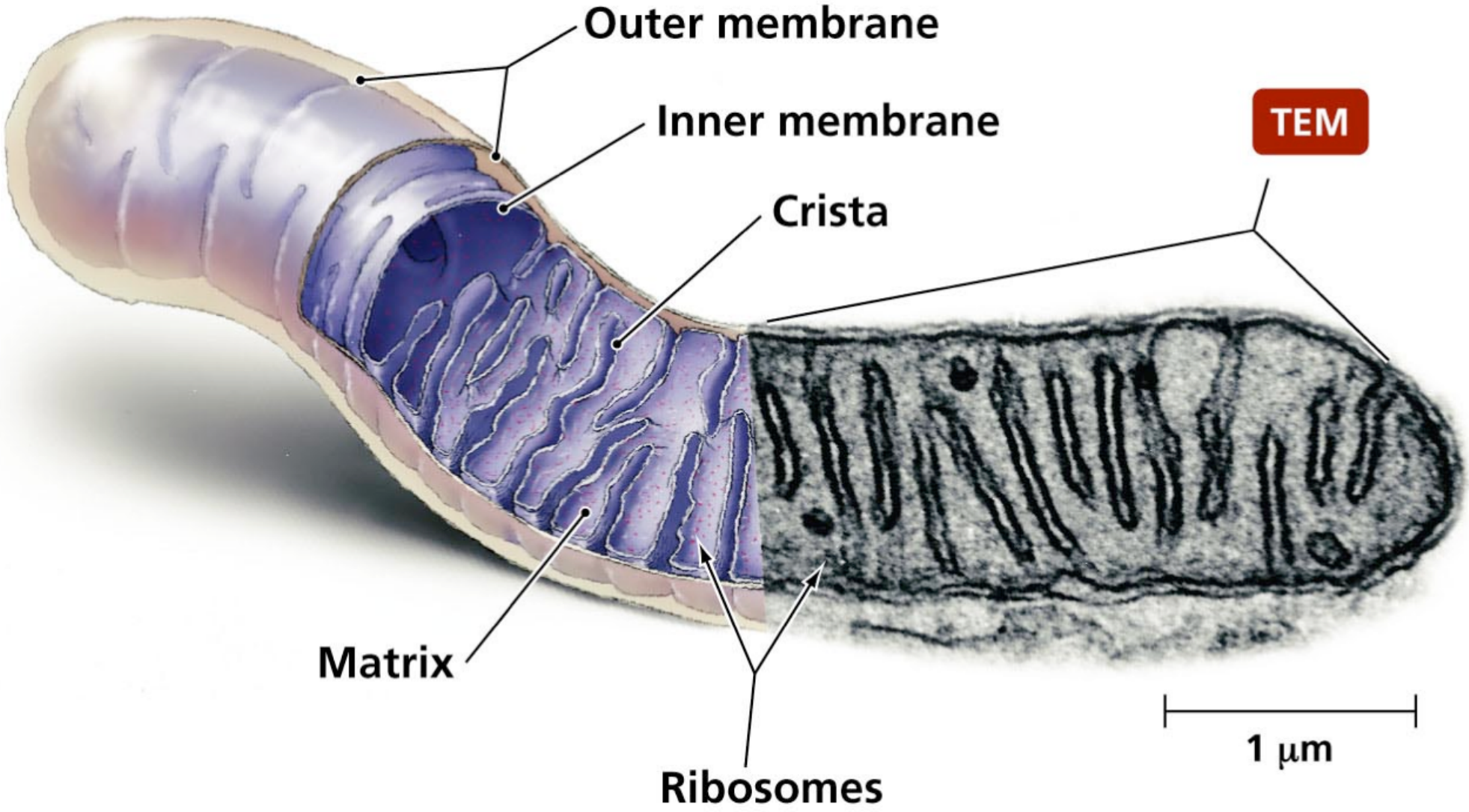


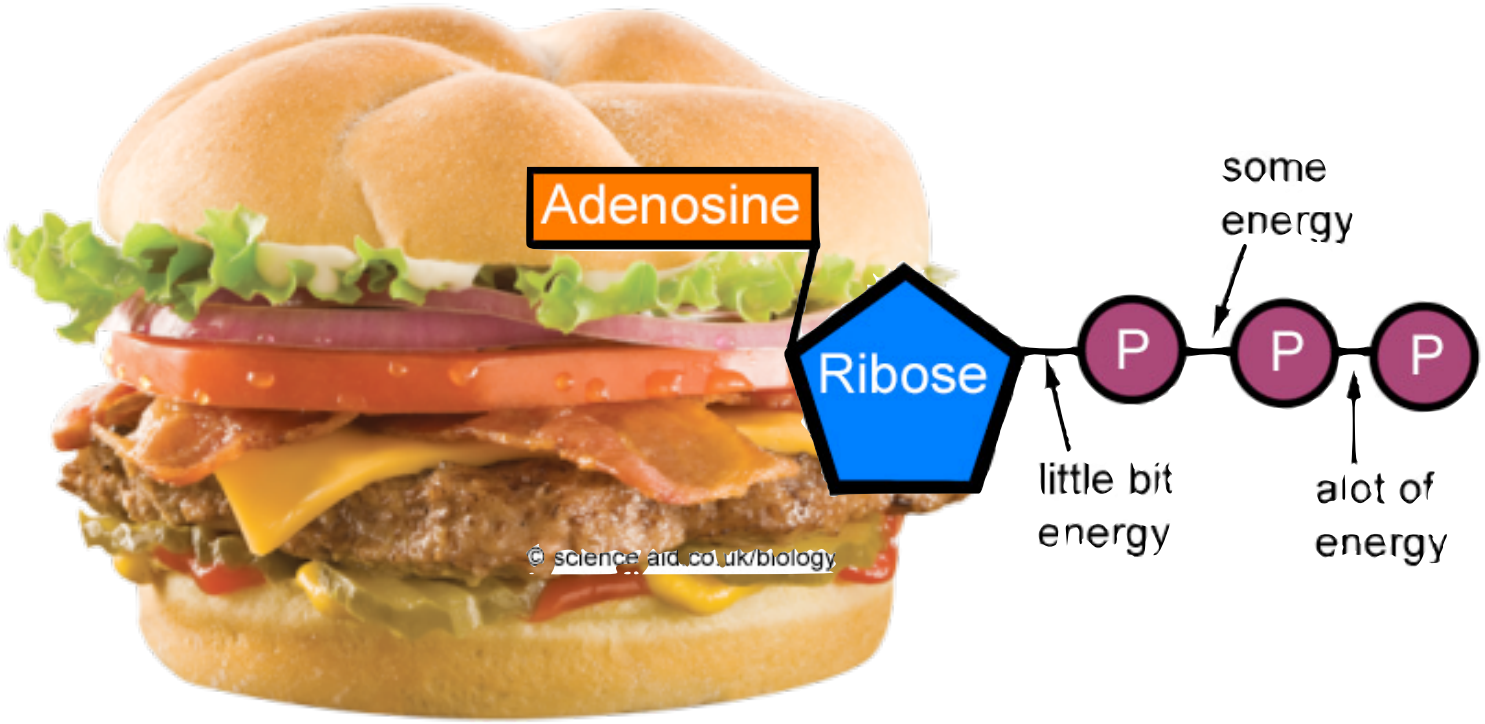


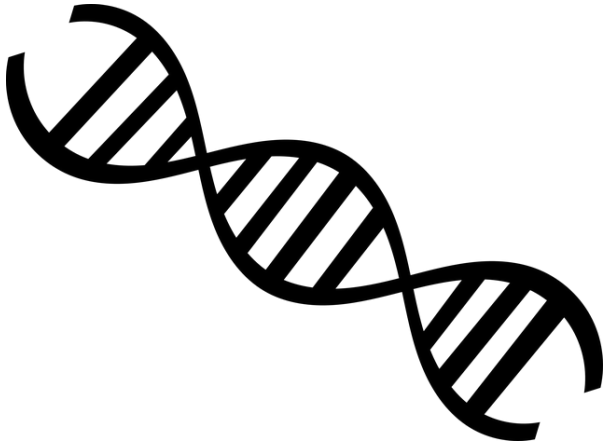

Autocrine effects
Paracrine effects
T-cell
NK-cell
Macrophage
Reinforcement of
the senescent
phenotypes
SASP
(cytokines, chemokines, MMPs)
Paracrine effects
Tumor cell clearance
by immune cells
Senescent Cancer cells
Cancer cell proliferation
Angiogenesis
Metastasis

Mitochondria and ageing

Mitochondria

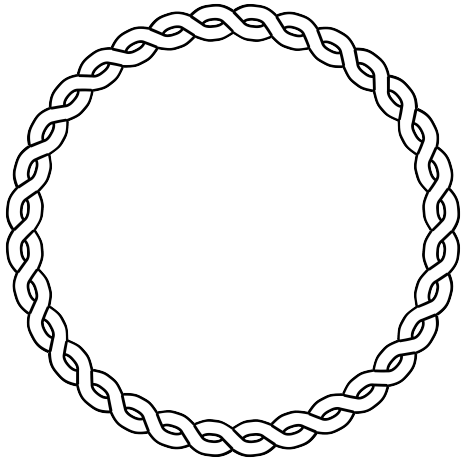



Adenosine
Ribose
P
P
P
some energy
little bit energy
alot of energy
© science aid.co.uk/biology



Nuclear DNA

3.200.000.000 Basepairs
20.000-25.000 genes
1.000 - 1.500 mito genes



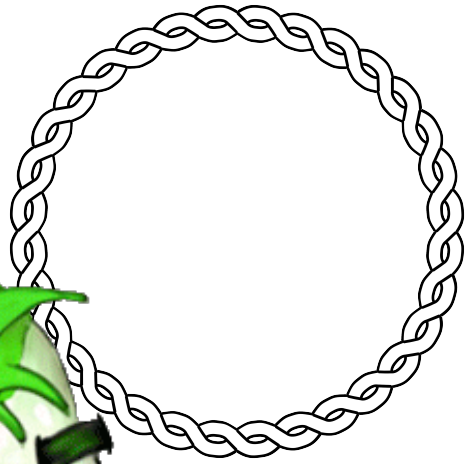
Mitochondrial DNA

16569 Basepair
37 genes

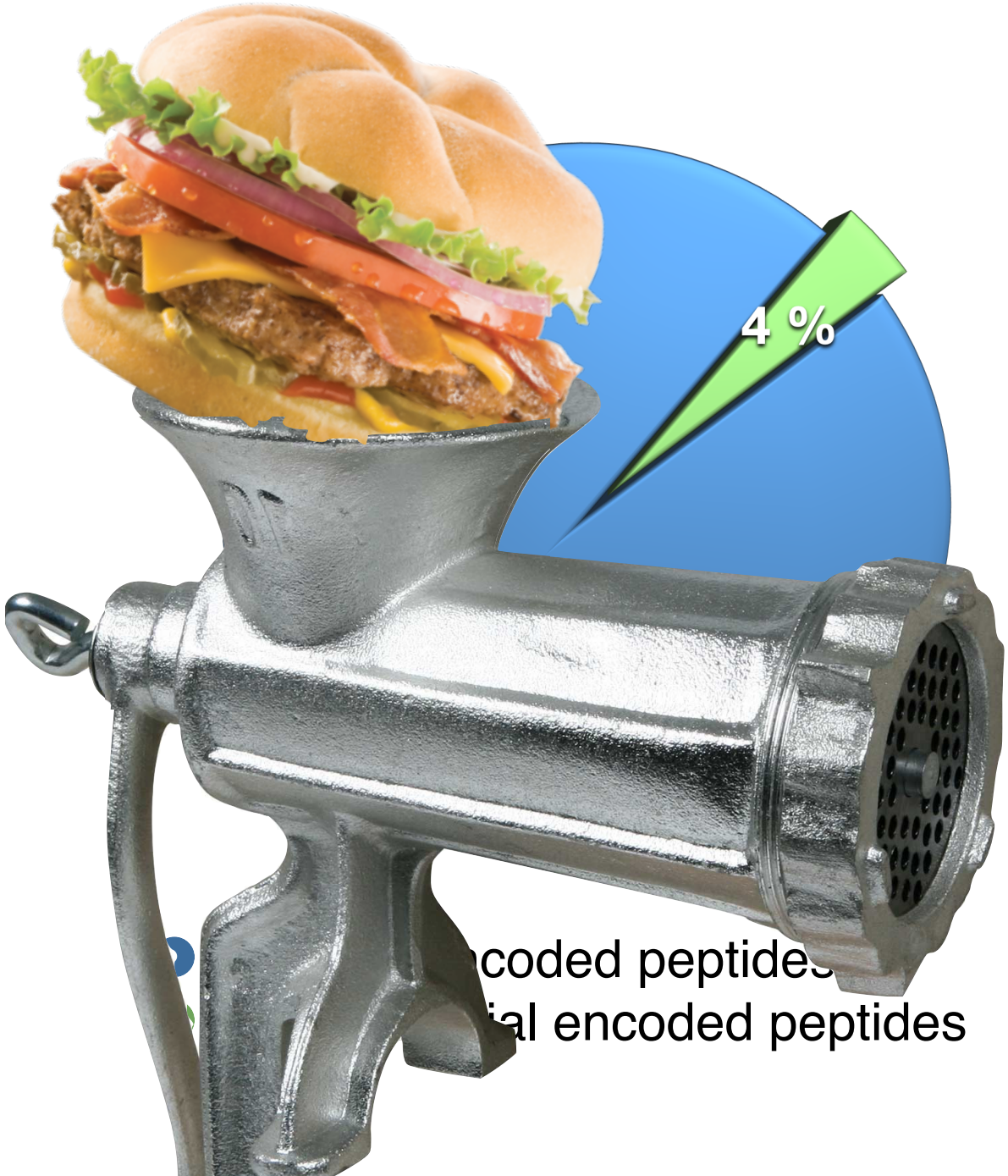
Nuclear DNA

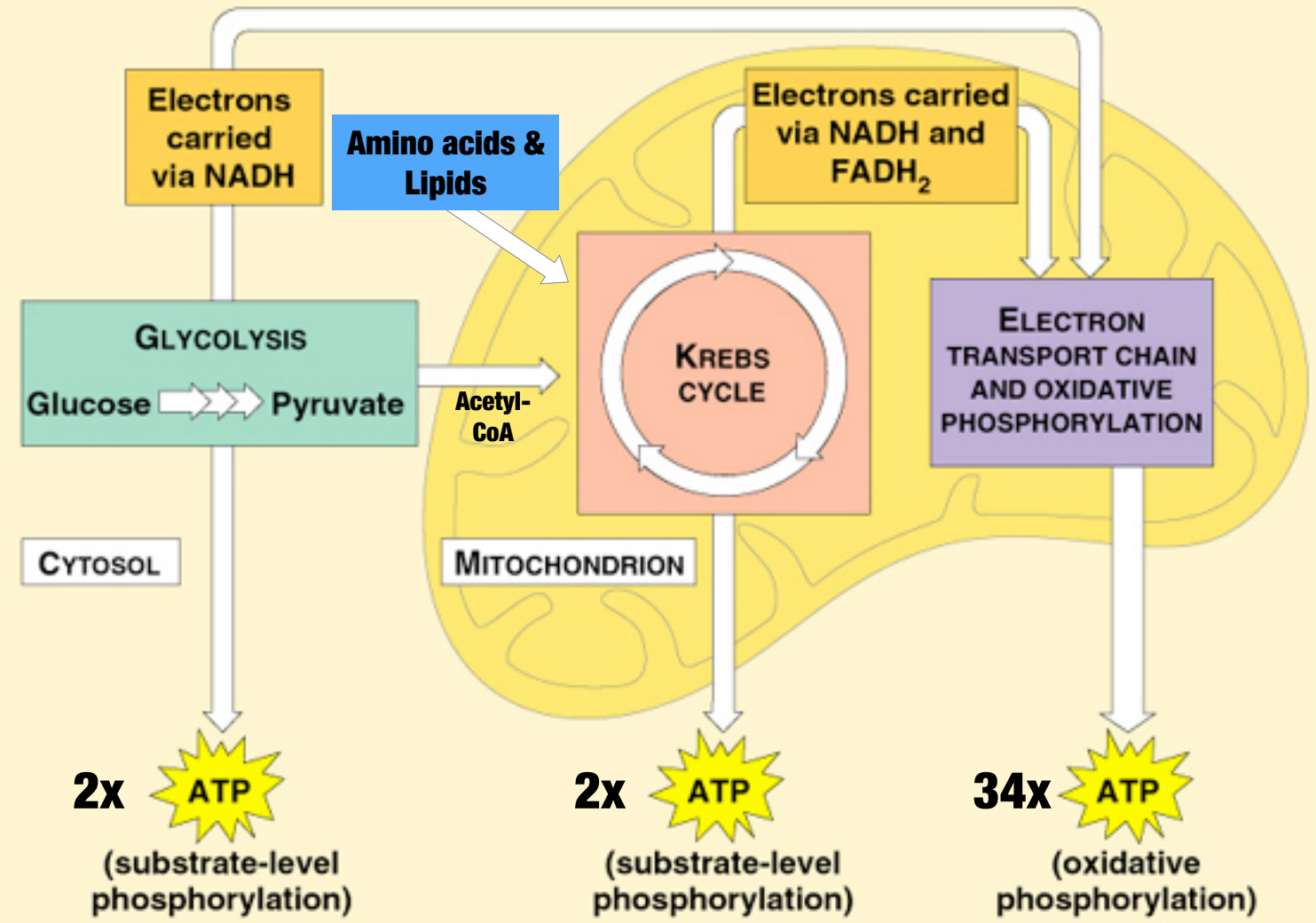
- Histones
- Introns
- Complex DNA repair respon

Mitochondrial DNA

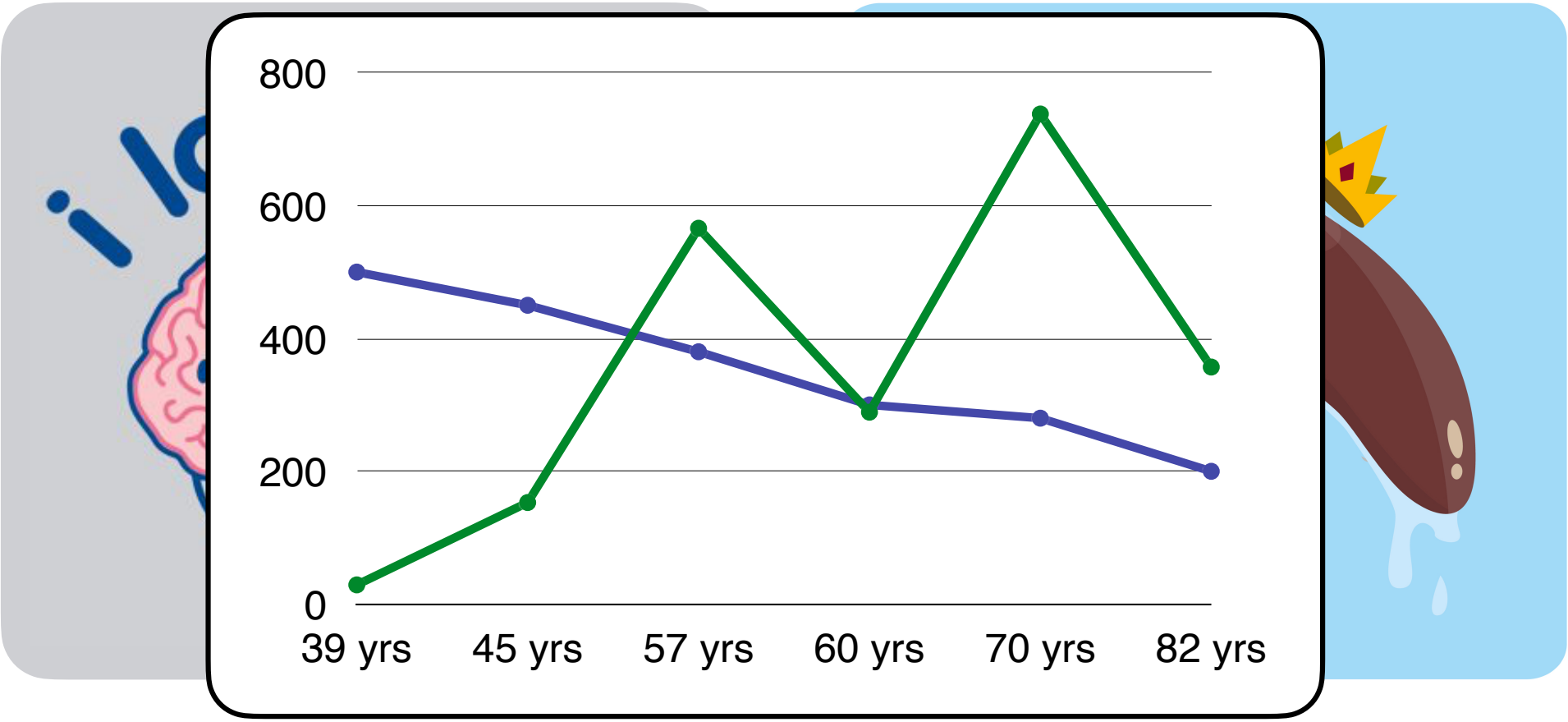


- istones
- No introns
- Rudimentary DNA repair response

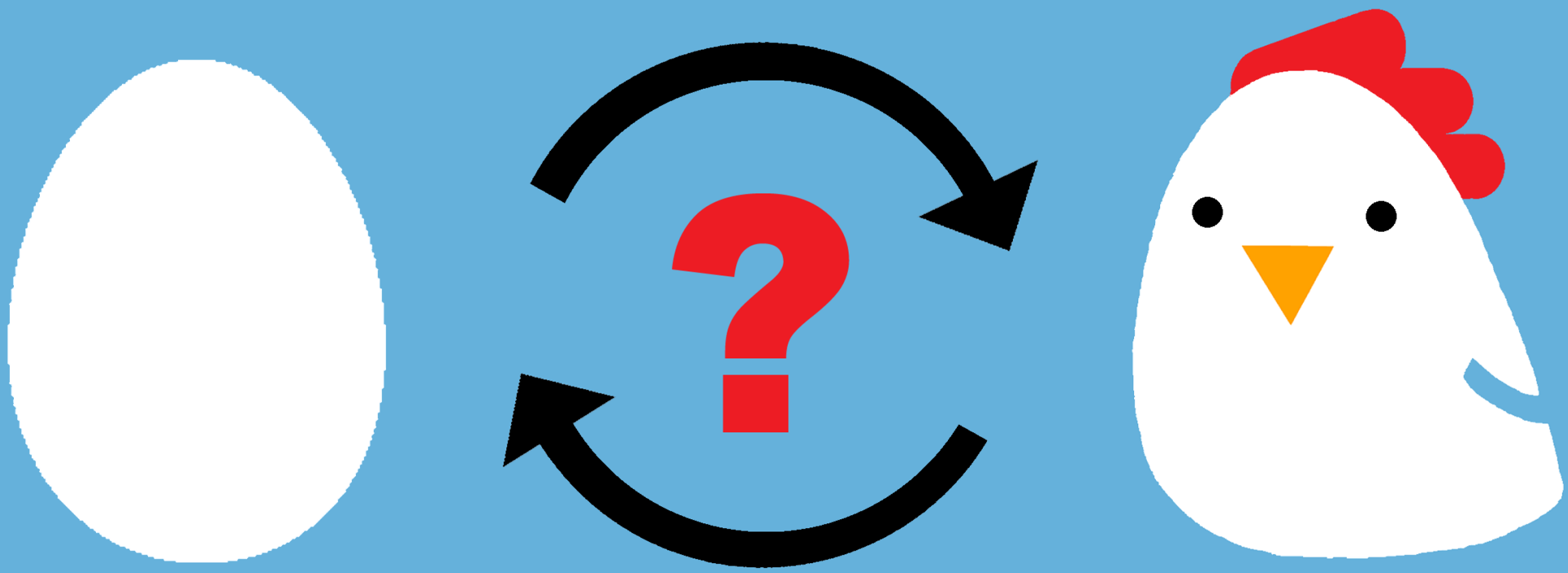

4 %
ncoded peptides
ial encoded peptides


Electrons carried via NADH
Amino acids & Lipids
Electrons carried via NADH and $FADH_2$
GLYCOLYSIS
Glucose
Pyruvate
Acetyl-CoA
KREBS CYCLE
ELECTRON TRANSPORT CHAIN AND OXIDATIVE PHOSPHORYLATION
CYTOSOL
MITOCHONDRION
2x ATP
(substrate-level phosphorylation)
2x ATP
(substrate-level phosphorylation)
34x ATP
(oxidative phosphorylation)

Mitochondrial / MtDNA content decreases with age

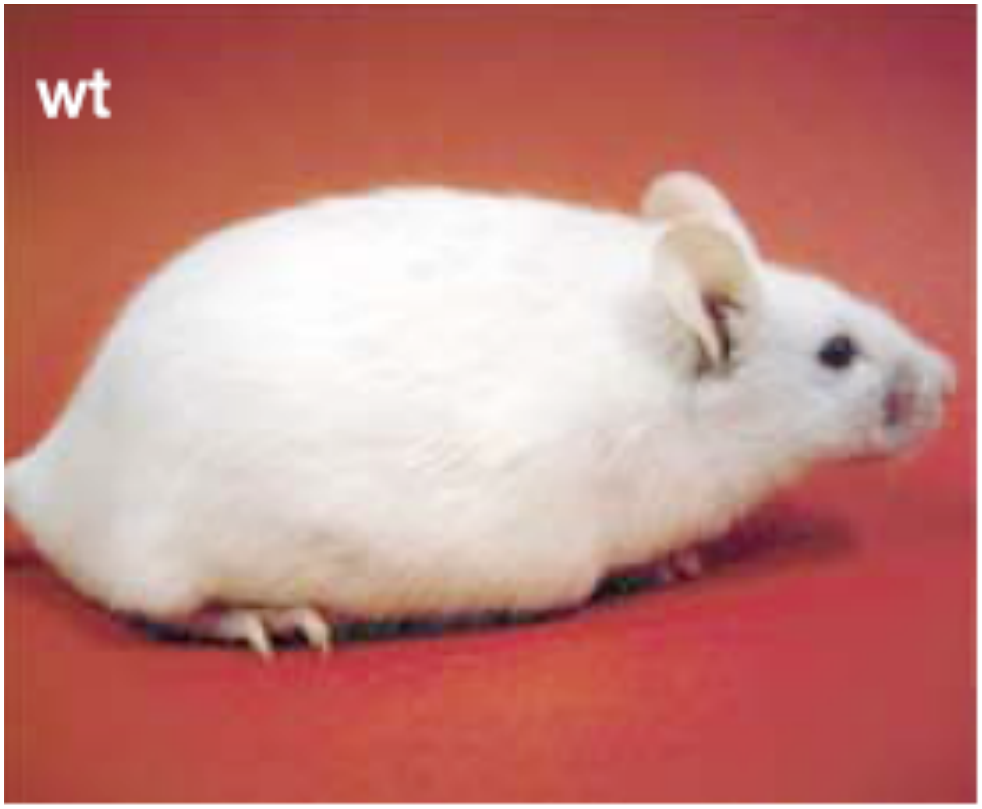


- Nr of mitochondria per cell decline with age
- Nr of mtDNA mutations increases with age

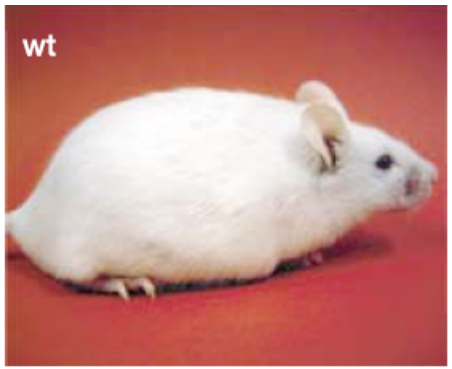


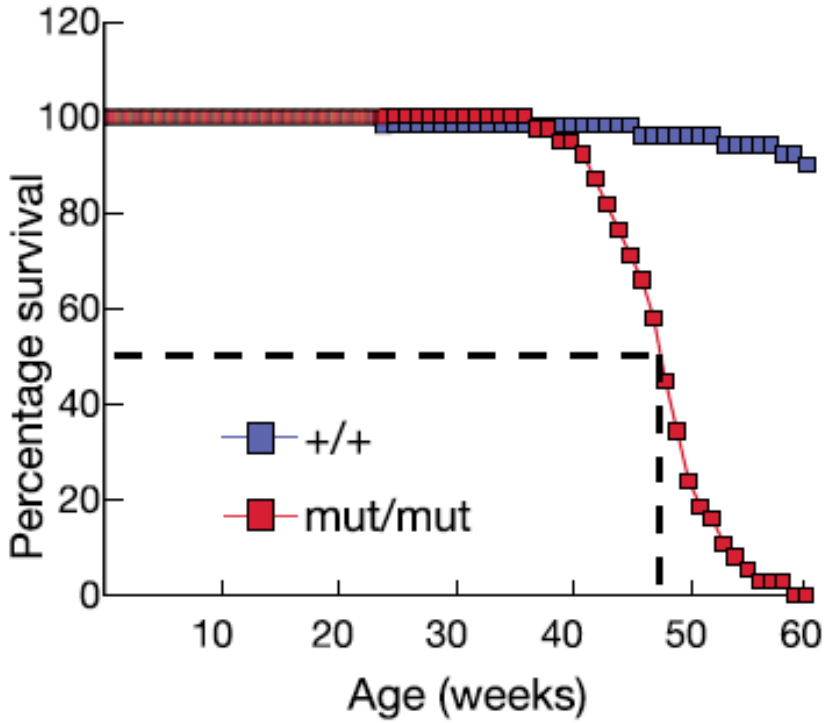
Cause / effect ?

Mutated Polymerase gamma



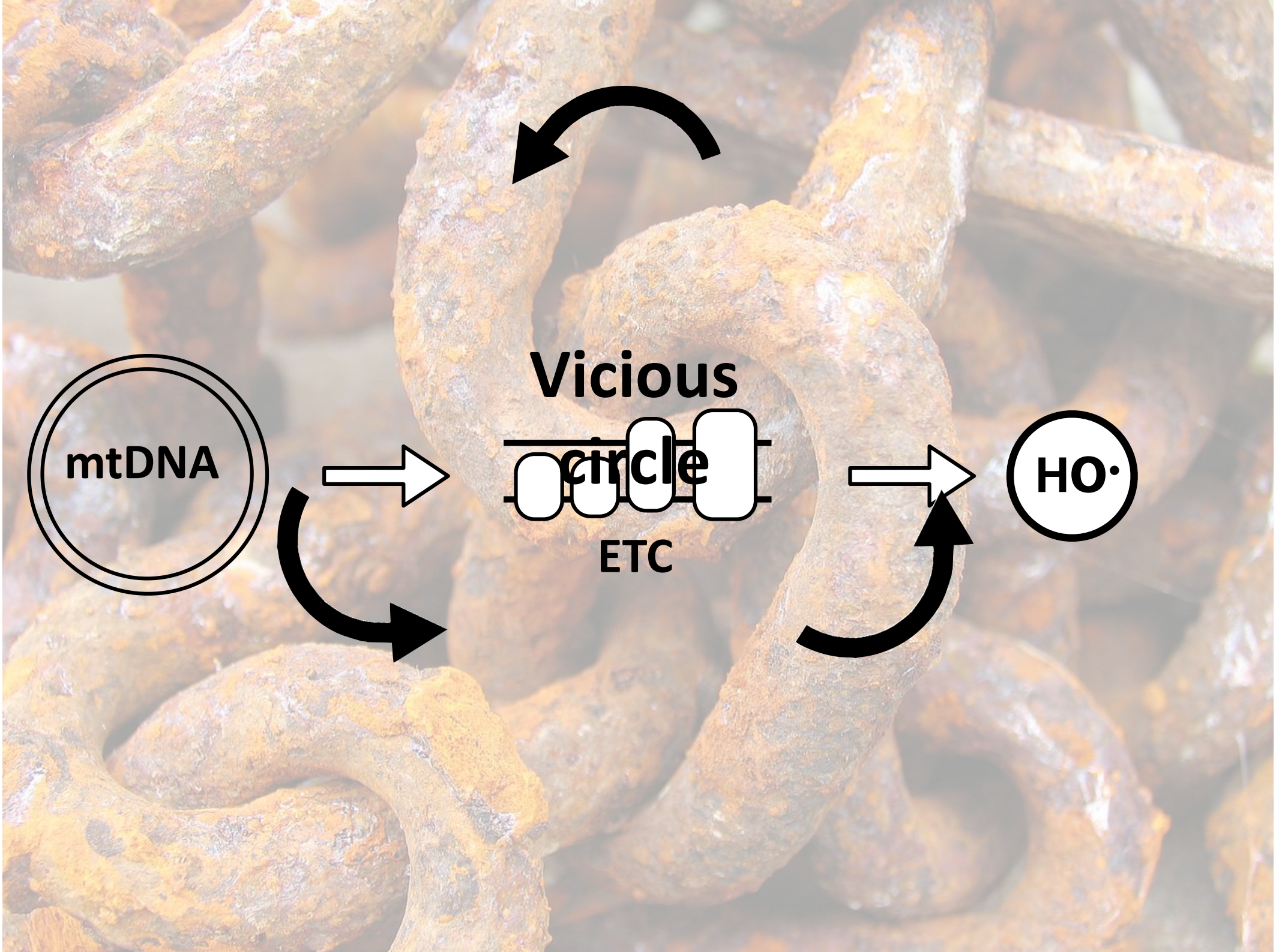
Mutated Polymerase gamma

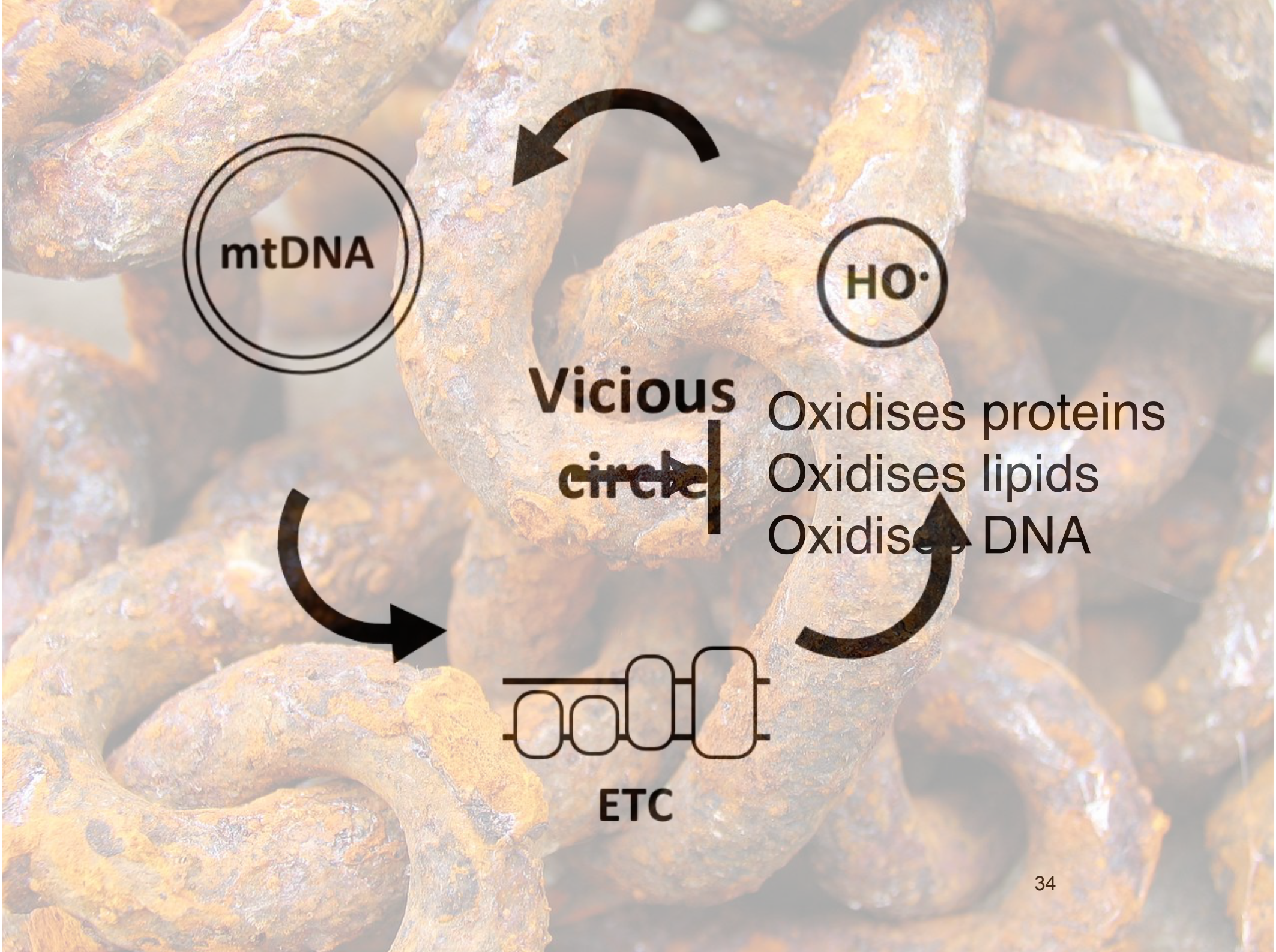




Weight loss, alopecia, osteoporosis, kyphosis, cardiomyopathy, anemia, gonadal atrophy, and sarcopaenia

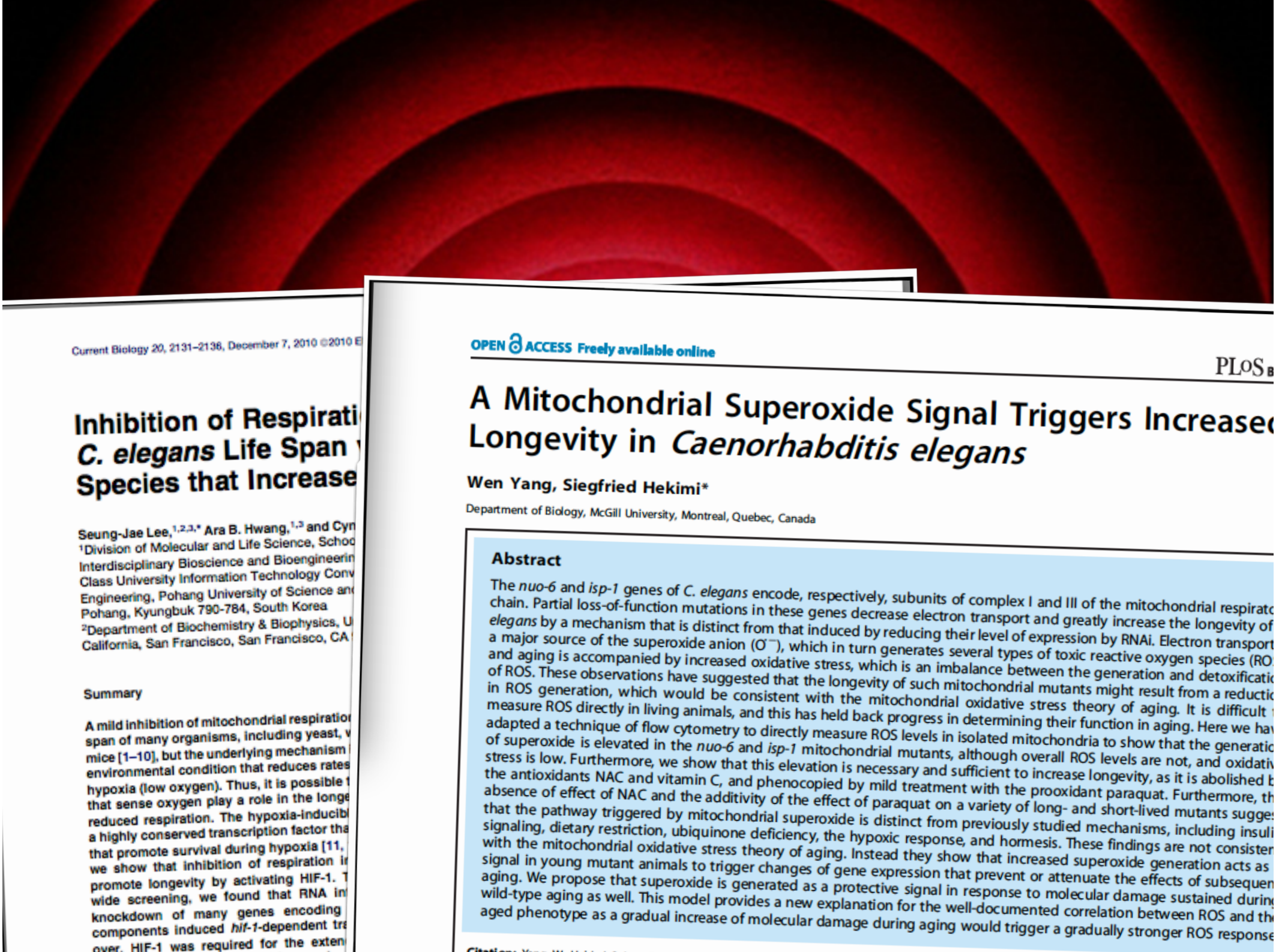
Trifunovic *et al.* 2007


Vicious
circle
mtDNA
ETC
HO·


mtDNA
HO·
Vicious
circle
Oxidises proteins
Oxidises lipids
Oxidises DNA
ETC

ROS productio… …d lifes…

…aster…
…ncou…
…dian…
…2005…



Current Biology 20, 2131–2136, December 7, 2010 ©2010 E

Inhibition of Respirati
C. elegans Life Span
Species that Increase

Seung-Jae Lee,[1,2,3,*] Ara B. Hwang,[1,3] and Cyn
[1]Division of Molecular and Life Science, Schoo
Interdisciplinary Bioscience and Bioengineerin
Class University Information Technology Conv
Engineering, Pohang University of Science an
Pohang, Kyungbuk 790-784, South Korea
[2]Department of Biochemistry & Biophysics, U
California, San Francisco, San Francisco, CA

Summary

A mild inhibition of mitochondrial respiratio
span of many organisms, including yeast, w
mice [1–10], but the underlying mechanism
environmental condition that reduces rates
hypoxia (low oxygen). Thus, it is possible t
that sense oxygen play a role in the longe
reduced respiration. The hypoxia-inducibl
a highly conserved transcription factor tha
that promote survival during hypoxia [11,
we show that inhibition of respiration i
promote longevity by activating HIF-1. T
wide screening, we found that RNA in
knockdown of many genes encoding
components induced *hif-1*-dependent tra
over, HIF-1 was required for the exten

OPEN ACCESS Freely available online

PLoS B

A Mitochondrial Superoxide Signal Triggers Increased Longevity in *Caenorhabditis elegans*

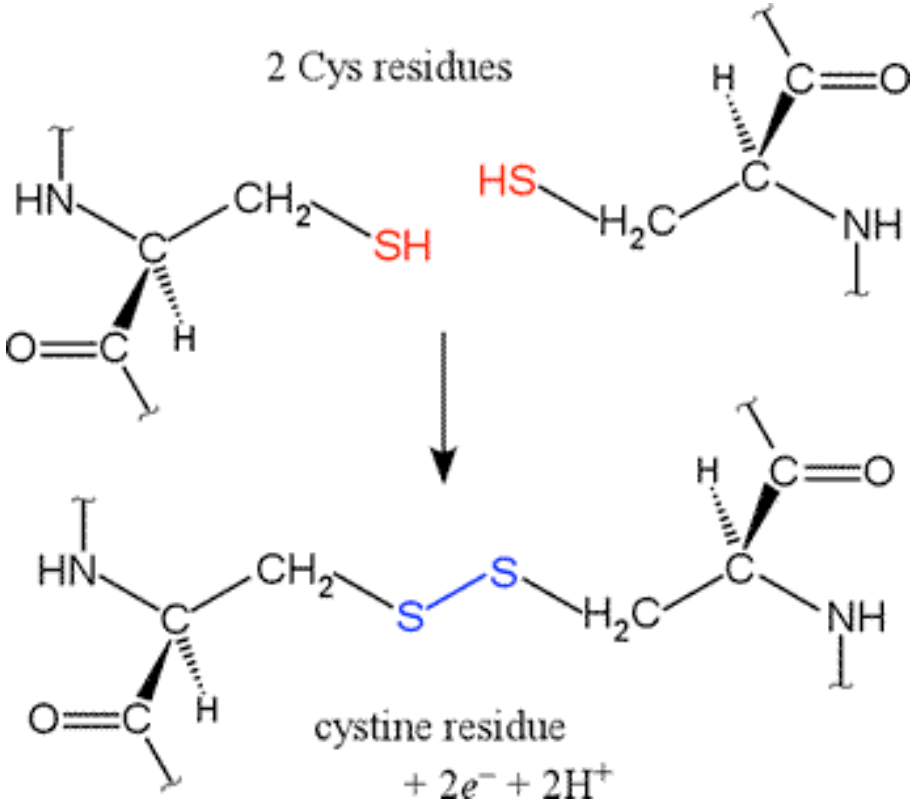
Wen Yang, Siegfried Hekimi*

Department of Biology, McGill University, Montreal, Quebec, Canada

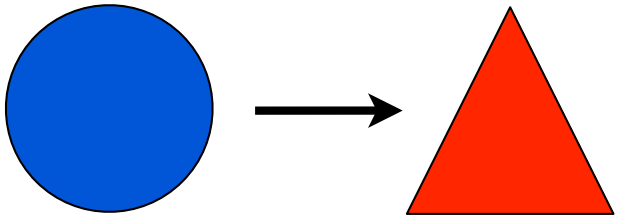
Abstract

The *nuo-6* and *isp-1* genes of *C. elegans* encode, respectively, subunits of complex I and III of the mitochondrial respirato
chain. Partial loss-of-function mutations in these genes decrease electron transport and greatly increase the longevity of
elegans by a mechanism that is distinct from that induced by reducing their level of expression by RNAi. Electron transport
a major source of the superoxide anion ($O^{\cdot-}$), which in turn generates several types of toxic reactive oxygen species (RO
and aging is accompanied by increased oxidative stress, which is an imbalance between the generation and detoxificatio
of ROS. These observations have suggested that the longevity of such mitochondrial mutants might result from a reductio
in ROS generation, which would be consistent with the mitochondrial oxidative stress theory of aging. It is difficult
measure ROS directly in living animals, and this has held back progress in determining their function in aging. Here we hav
adapted a technique of flow cytometry to directly measure ROS levels in isolated mitochondria to show that the generatio
of superoxide is elevated in the *nuo-6* and *isp-1* mitochondrial mutants, although overall ROS levels are not, and oxidativ
stress is low. Furthermore, we show that this elevation is necessary and sufficient to increase longevity, as it is abolished b
the antioxidants NAC and vitamin C, and phenocopied by mild treatment with the prooxidant paraquat. Furthermore, th
absence of effect of NAC and the additivity of the effect of paraquat on a variety of long- and short-lived mutants sugges
that the pathway triggered by mitochondrial superoxide is distinct from previously studied mechanisms, including insuli
signaling, dietary restriction, ubiquinone deficiency, the hypoxic response, and hormesis. These findings are not consisten
with the mitochondrial oxidative stress theory of aging. Instead they show that increased superoxide generation acts as
signal in young mutant animals to trigger changes of gene expression that prevent or attenuate the effects of subsequen
aging. We propose that superoxide is generated as a protective signal in response to molecular damage sustained during
wild-type aging as well. This model provides a new explanation for the well-documented correlation between ROS and the
aged phenotype as a gradual increase of molecular damage during aging would trigger a gradually stronger ROS response

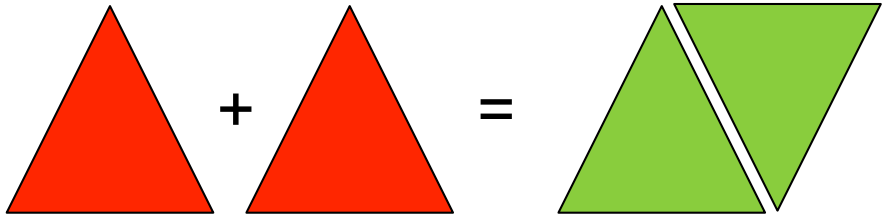
ROS as a signaling molecule



Cysteine rich proteins



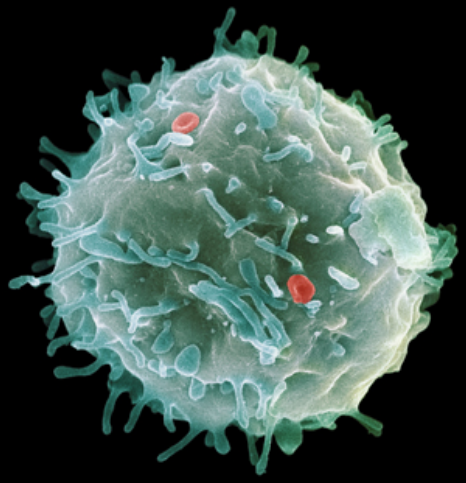
Conformational change



Dimerization

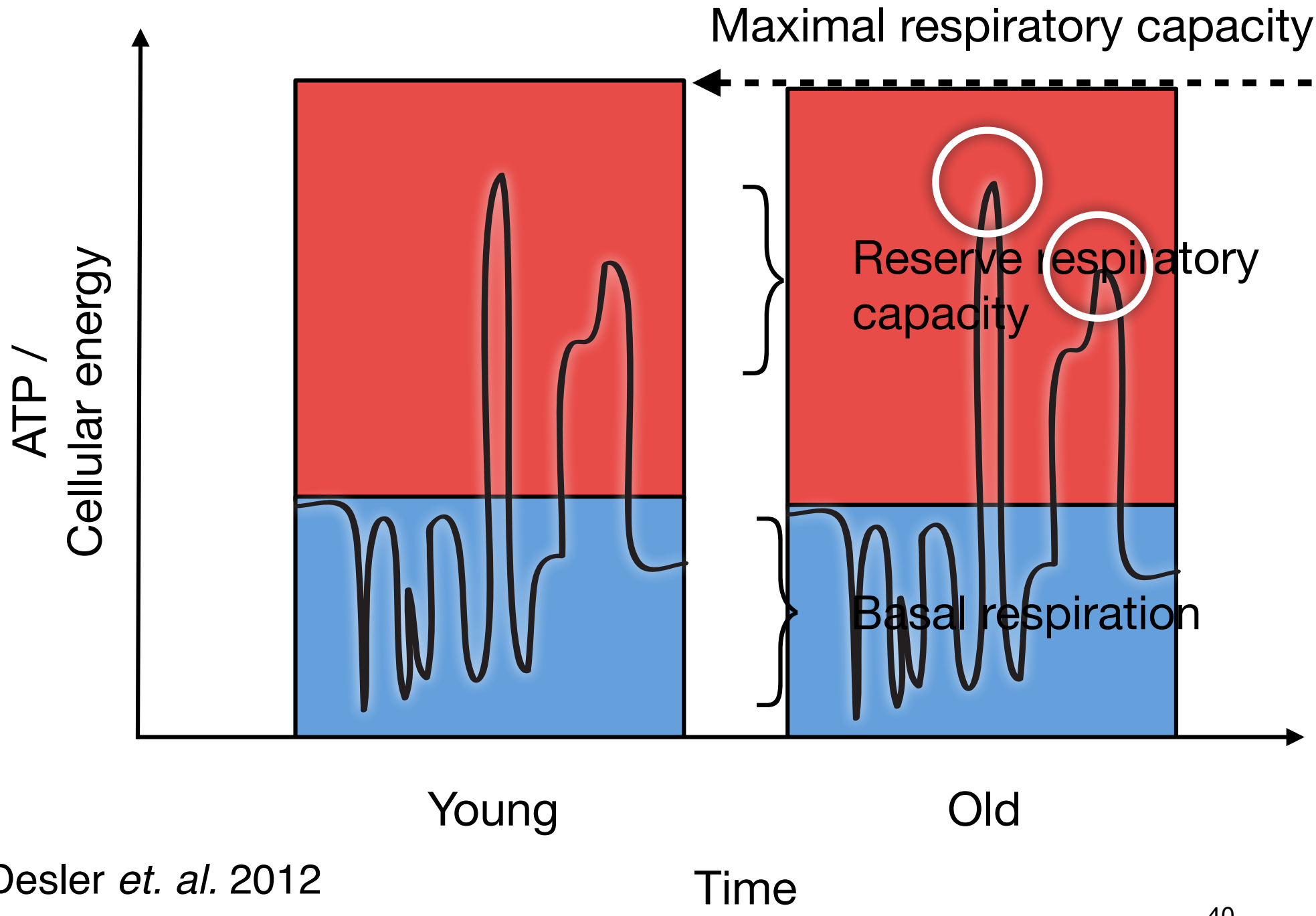
Mutated twinkle helicase

- Low levels of large-scale mtDNA deletions in postmitotic tissue
- Suffers late onset mitochondrial myopathy
- Do not display progeroid phenotype. Normal lifespan



- Polg-Mutator mice has neural and hematopeitic progenitor dysfunction already from embryogenesis
- Decrease of self-reneval *in vitro*
- Decreased abundance of stem cells *in vivo*

Ahlqvist *et al.* 2011



Desler *et. al.* 2012

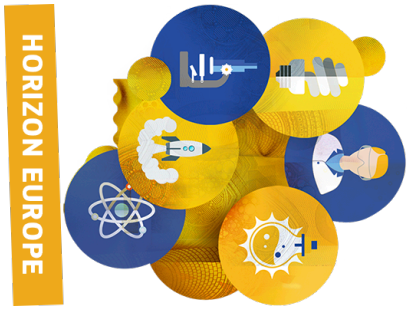
What are the applications today?

Top 5

- Stroke
- Lung disease
- Cardiovascular disease
- Dementia
- Cancer

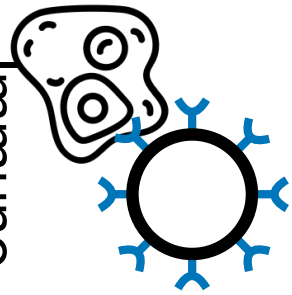

PREDICTION
PREVENTION
TREATMENT

Desler group - Projects



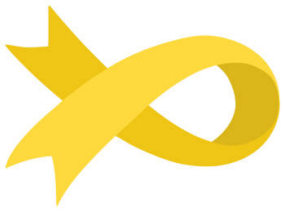
POINT - Post acute phase of COVID-19 and non-communicable diseases

Immuno senescence



Immunosenescence, energy metabolism and effect of exercise

Childhood cancer



Premature aging in childhood cancer survivors

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Build 22.5

Thank you for your attention

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