Recent Advances in Understanding Aging

Science Circle
November 26th 2022

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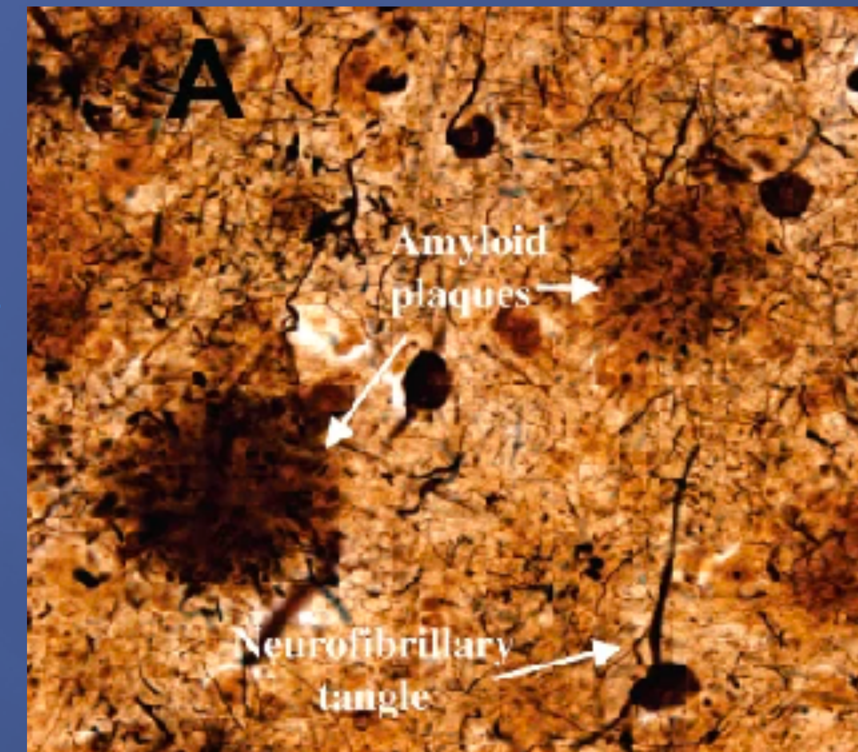
a.k.a. Stephen Xootfly
Researcher
Company that has nothing to do with this talk
Former University Biology Instructor

Neurological impairment

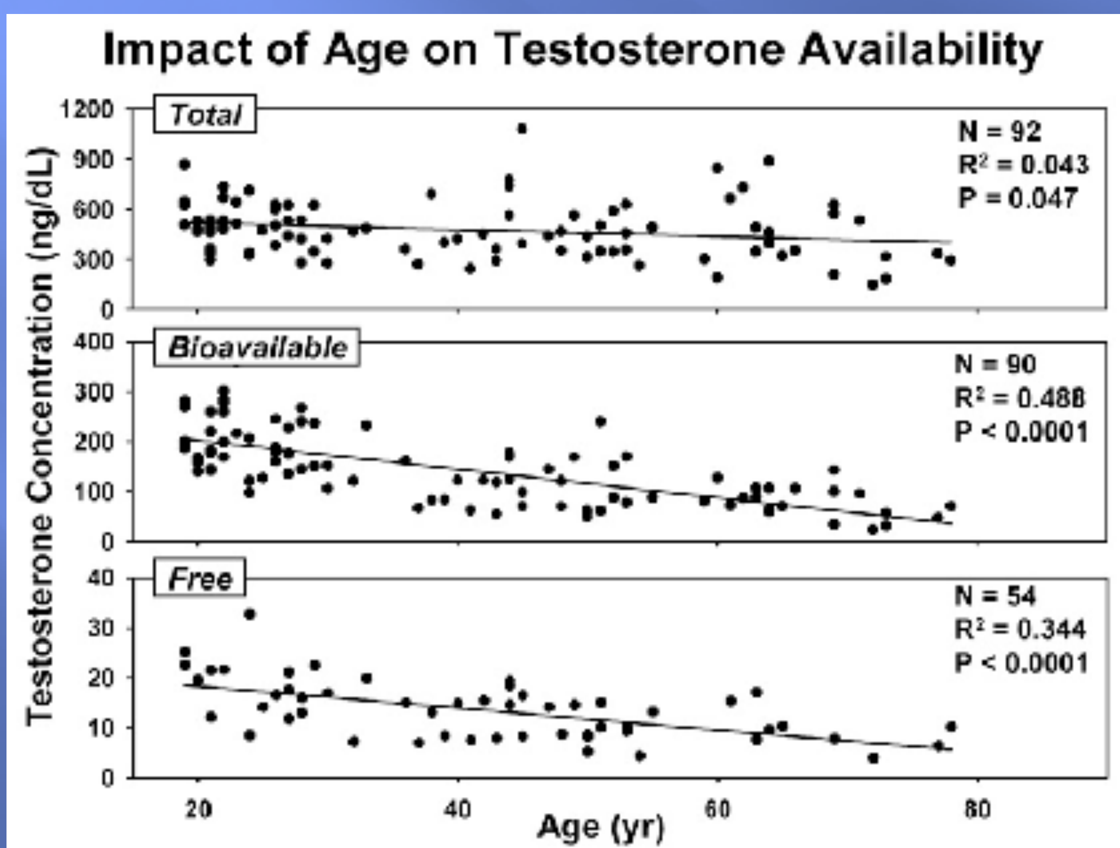
Grey hair

https://www.onhealth.com/content/1/gray_hair_facts_beauty



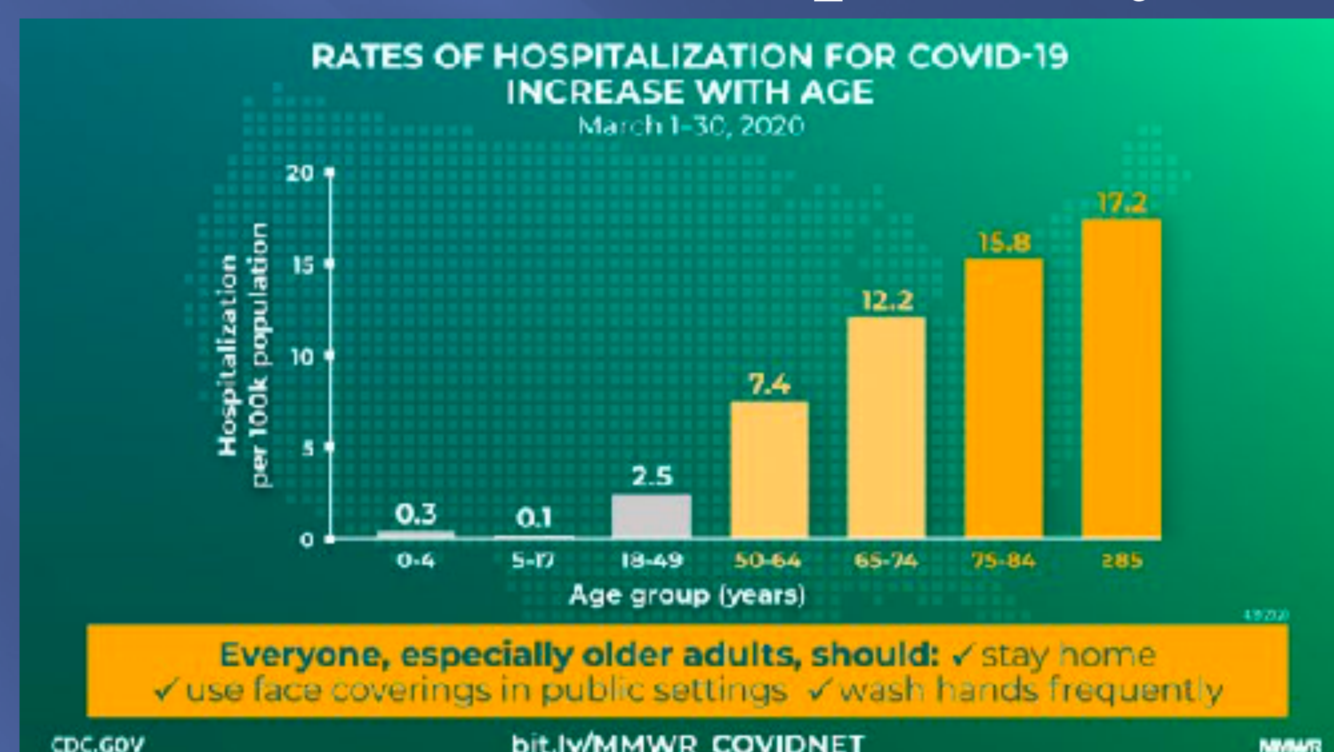
https://molmed.biomedcentral.com/articles/10.2119/2007-00100.Irvine/figures/1

Hormone levels

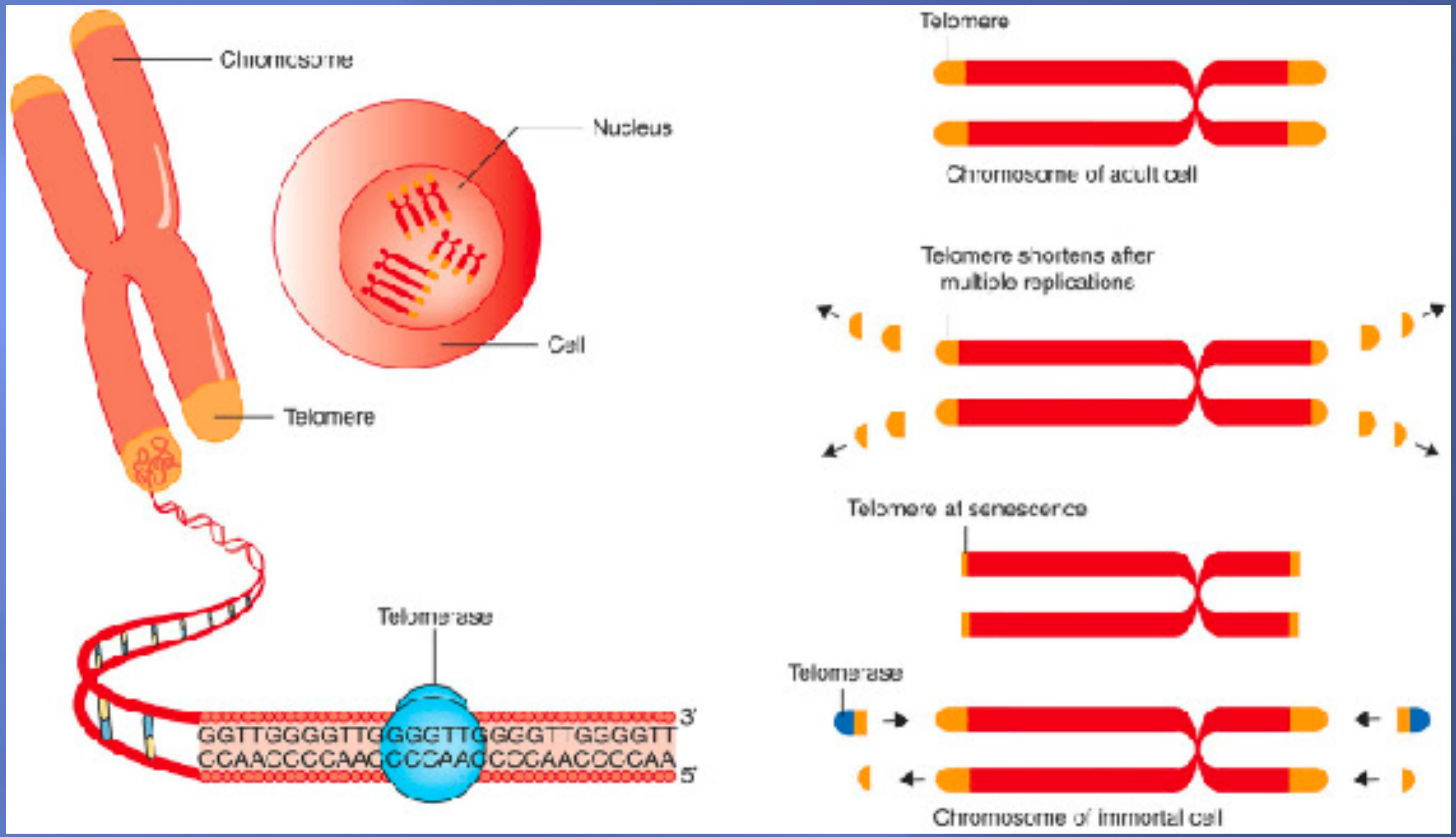


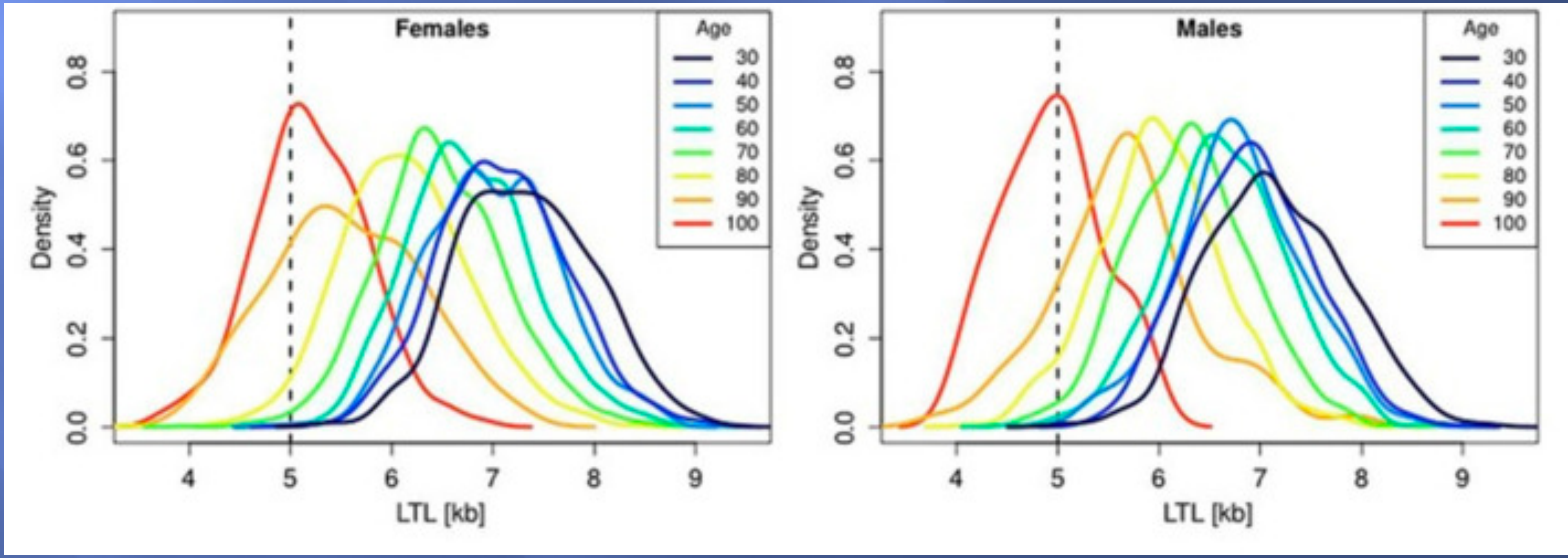
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2583117/

Disease susceptibility



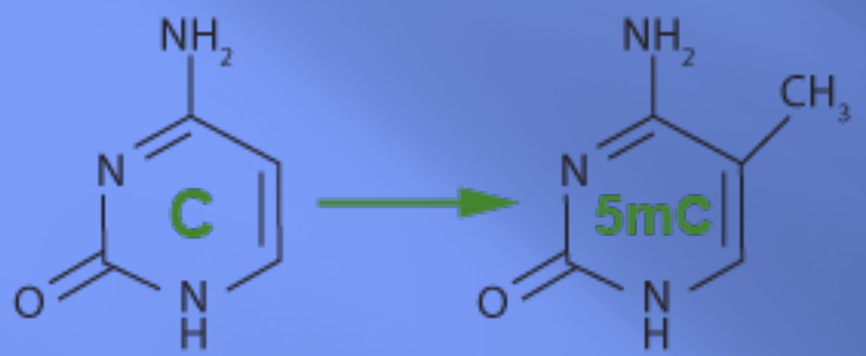
Telomeres

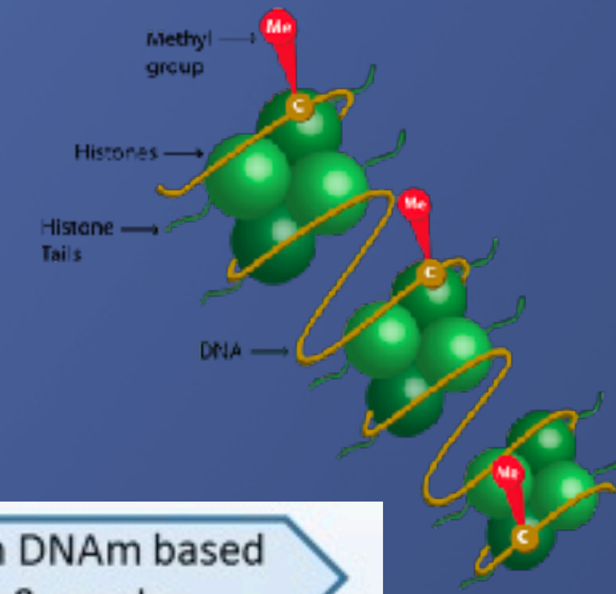


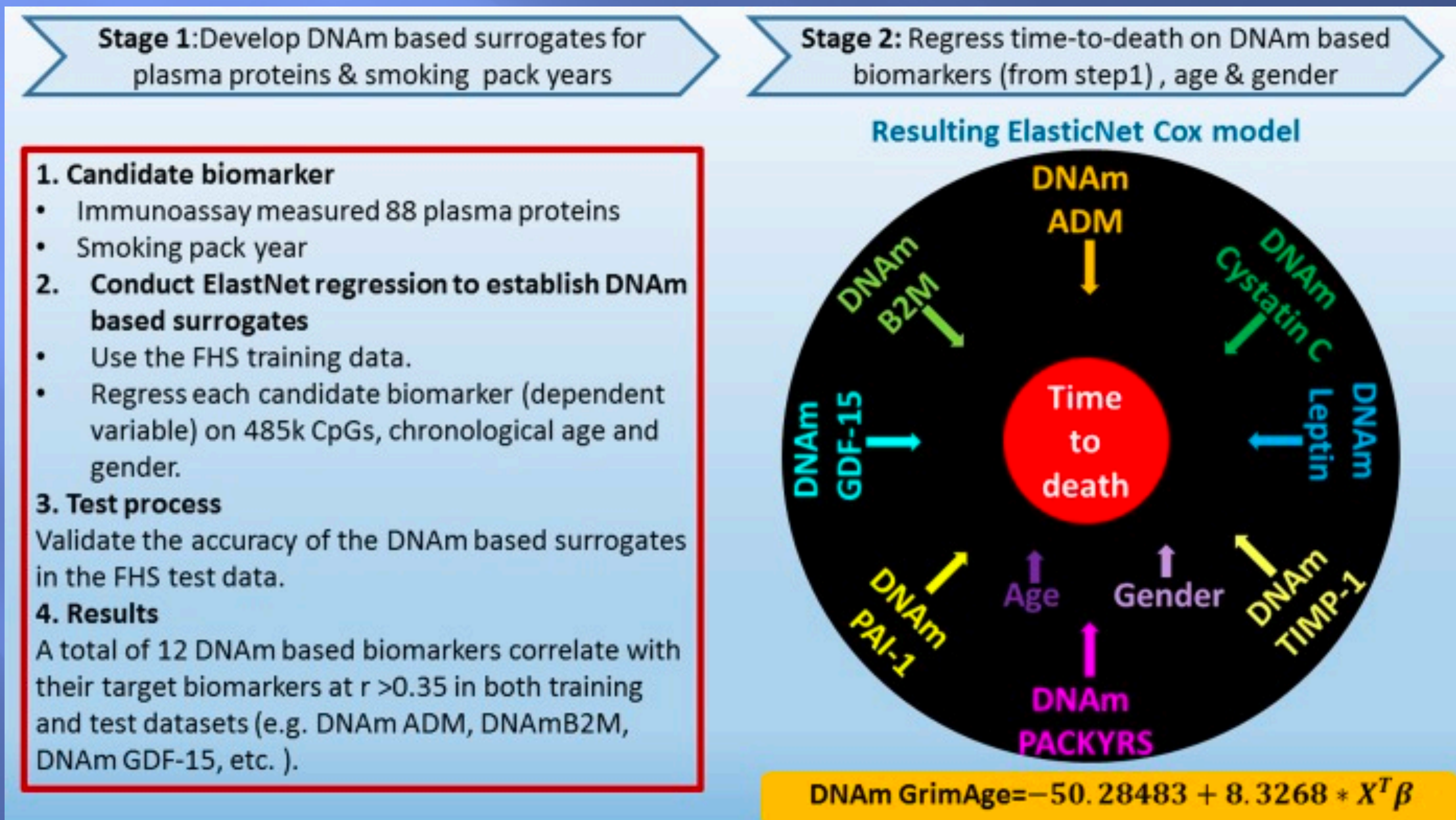


Vaiserman, A., & Krasnienkov, D. (2021). Telomere length as a marker of biological age: state-of-the-art, open issues, and future perspectives. *Frontiers in Genetics*, *11*, 630186.

Methylation



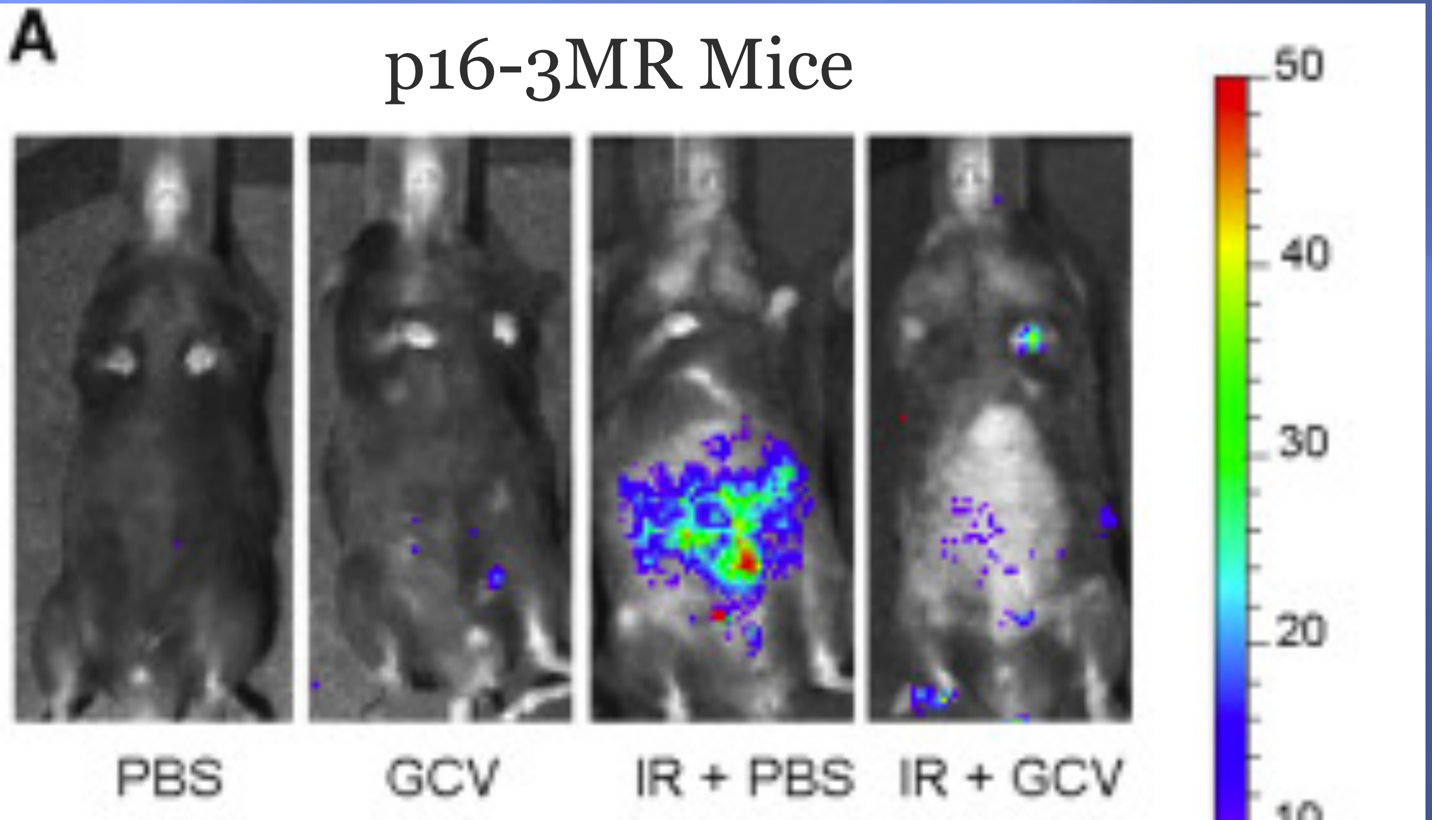




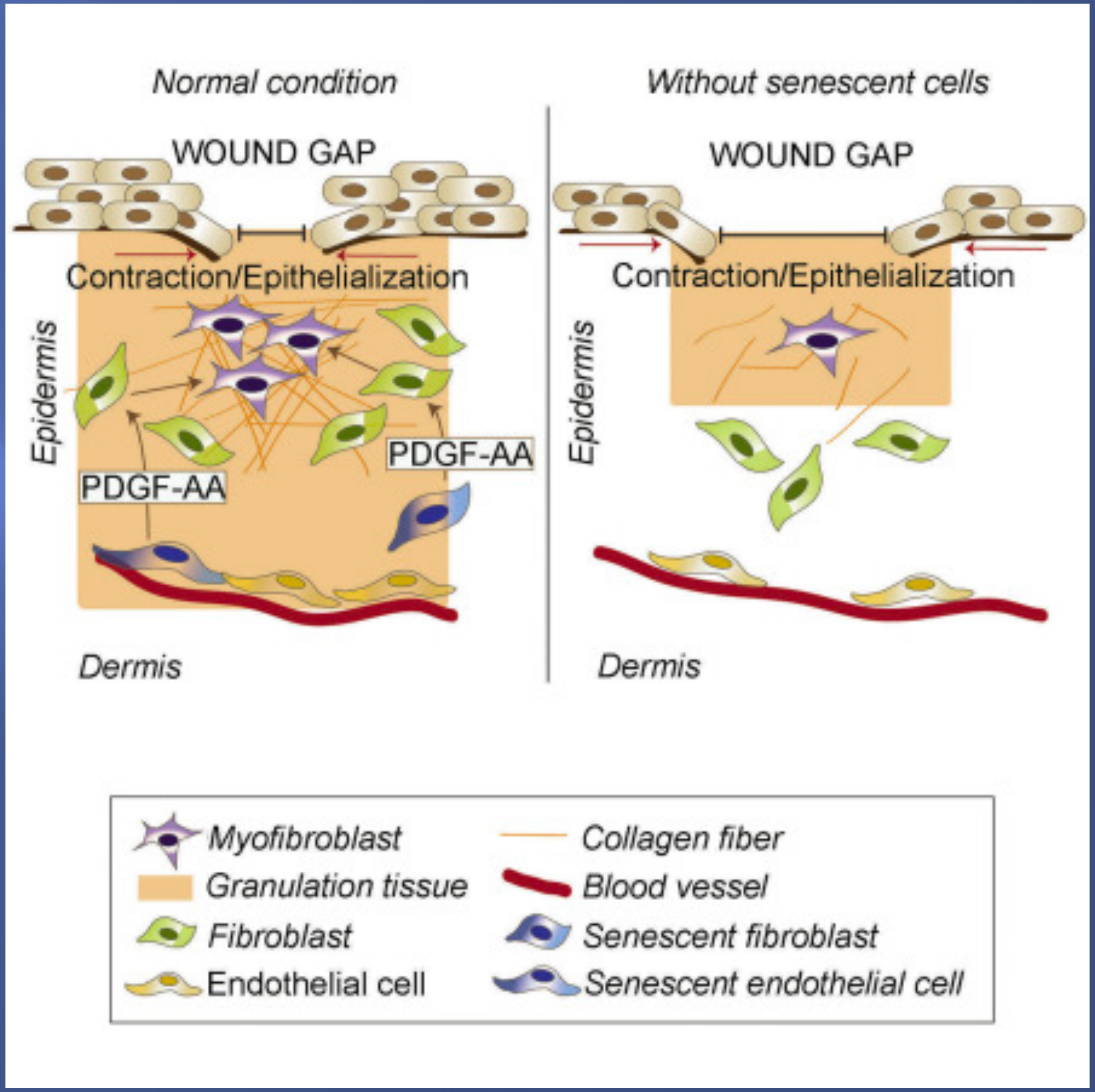
Lu, A. T., Quach, A., Wilson, J. G., Reiner, A. P., Aviv, A., Raj, K., ... & Horvath, S. (2019). DNA methylation GrimAge strongly predicts lifespan and **healthspan**. *Aging (Albany NY)*, *11*(2), 303.

Senescence

https://fineartamerica.com/featured/elderly-man-doses-on-his-porch-underwood-archives.html



color = senescent cells; IR = irradiation

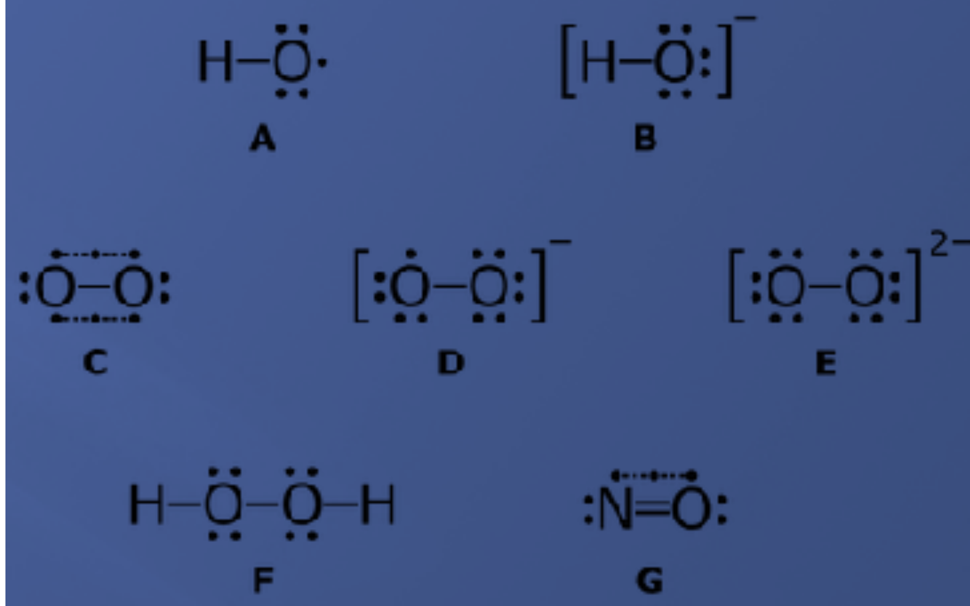


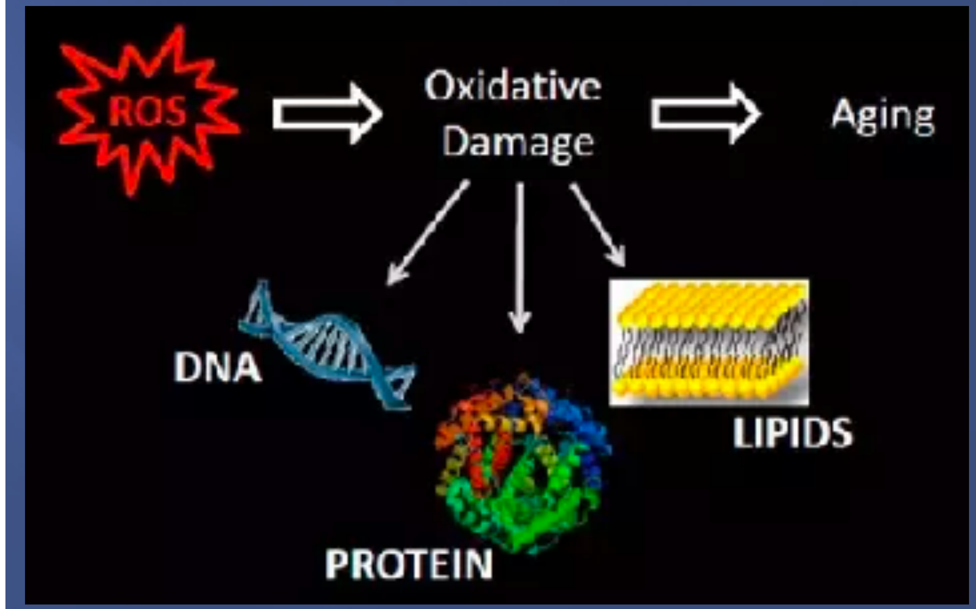
Demaria, M., Ohtani, N., Youssef, S. A., Rodier, F., Toussaint, W., Mitchell, J. R., ... & Campisi, J. (2014). An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. *Developmental cell*, 31(6), 722-733.

free radical theory of aging

"The free radical theory of aging was originally described by Denham Harman in the 1950s. It proposes that organisms age because they accumulate oxidative damage. This damage comes from reactive oxygen species (ROS), which are partially reduced metabolites of molecular oxygen generated as products of metabolic reactions or as by-products of various cellular processes, such as respiration."

"The free radical theory of aging is consistent with numerous studies, but many other reports clearly contradict this idea. Collectively, these studies argue against the universal role of oxidative damage in aging."





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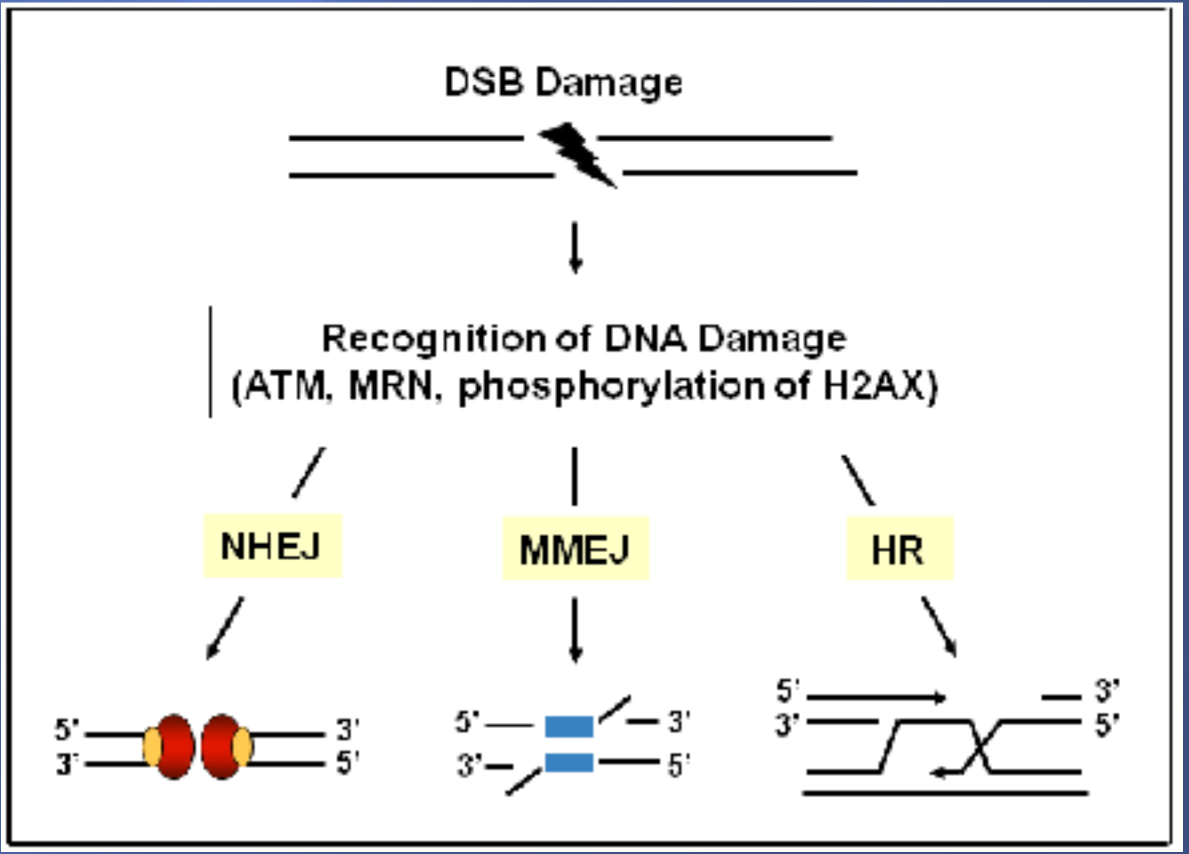
Progeria

Werner Syndrome
1904
RECQL2/SGS1

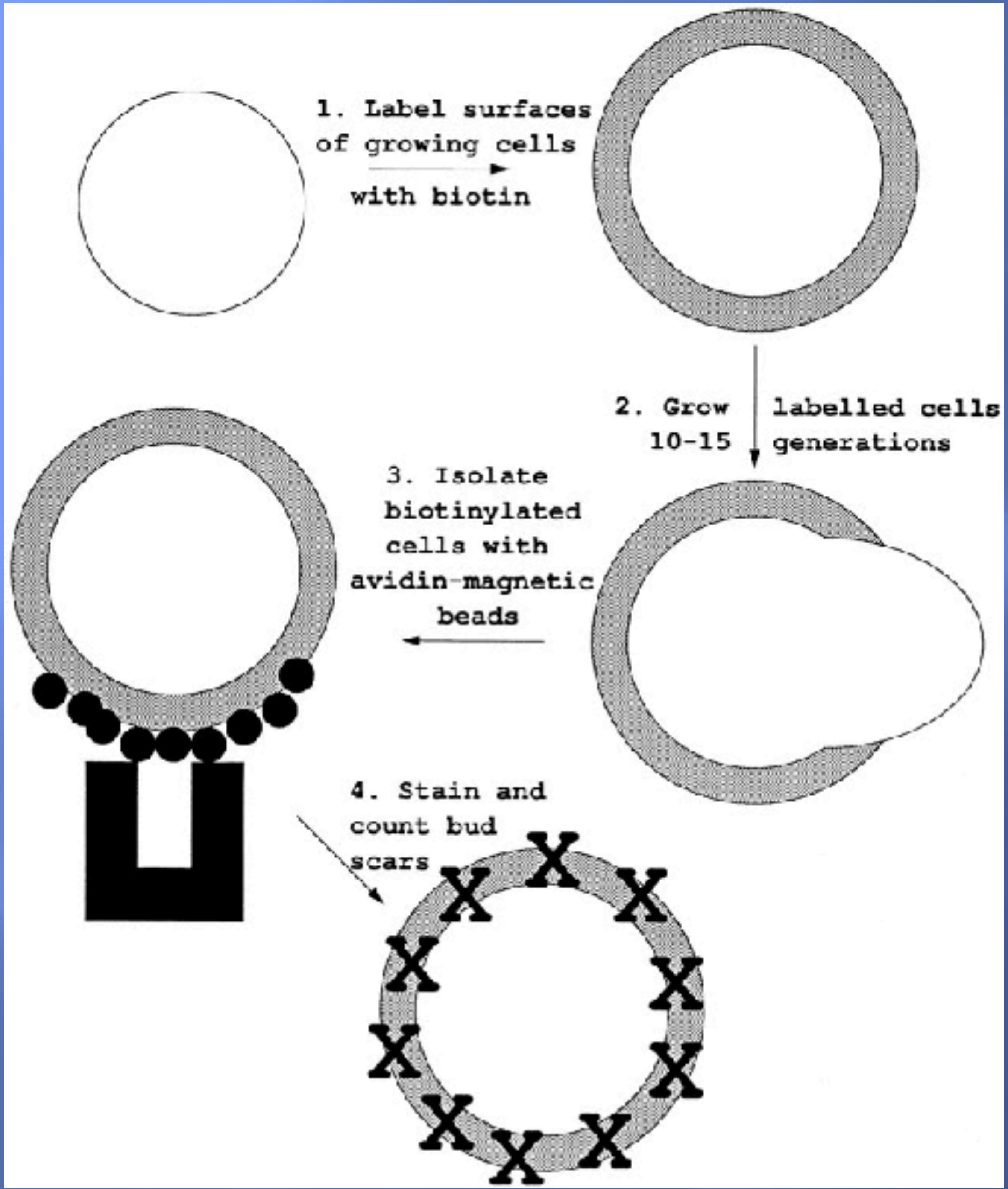
Bloom
Fanconi-Anemia
Cockayne
Rothmund–Thomson
Nijmegen breakage

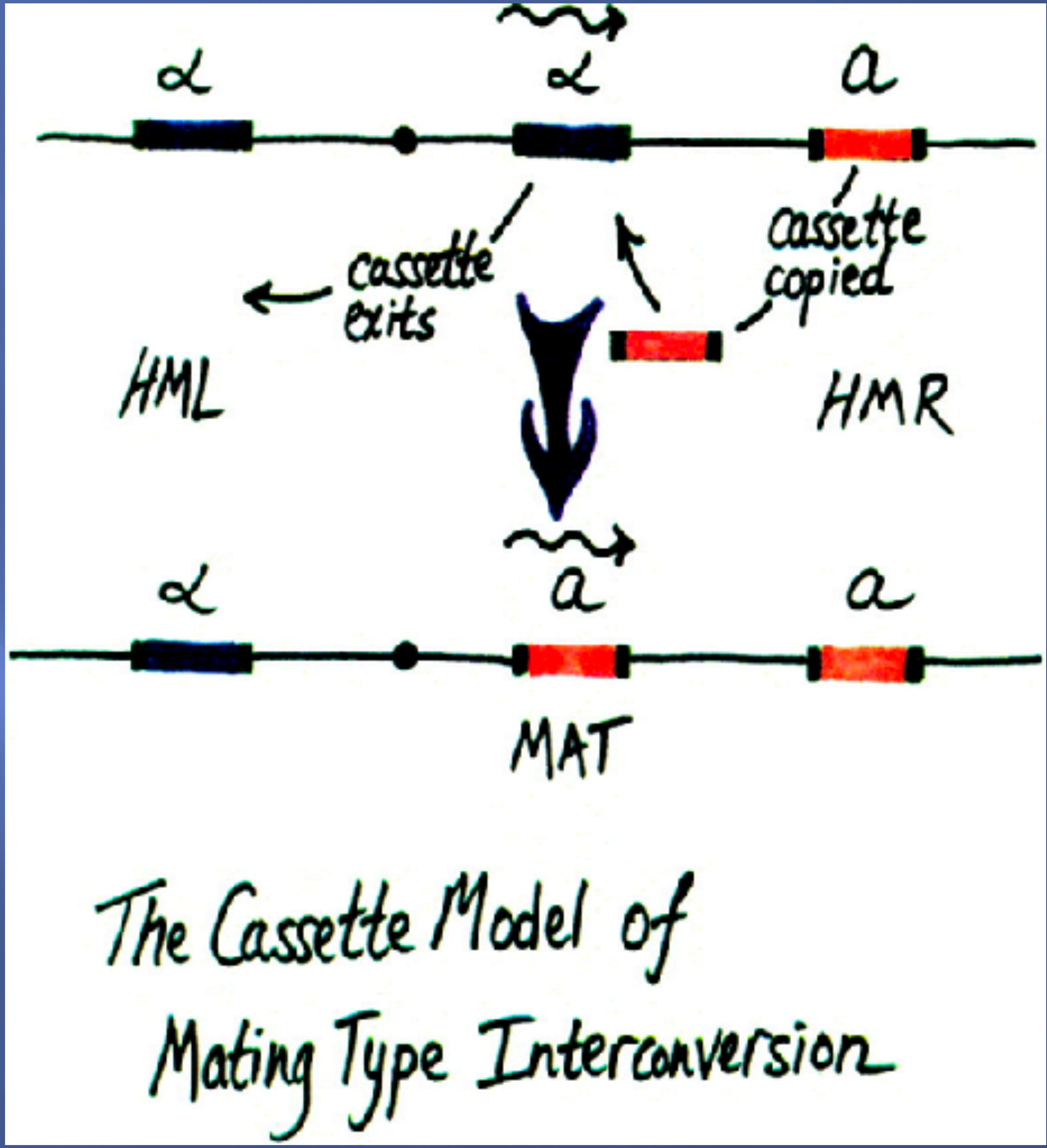
ataxia telangiectasia



https://www.intechopen.com/chapters/44483

yeast "aging"

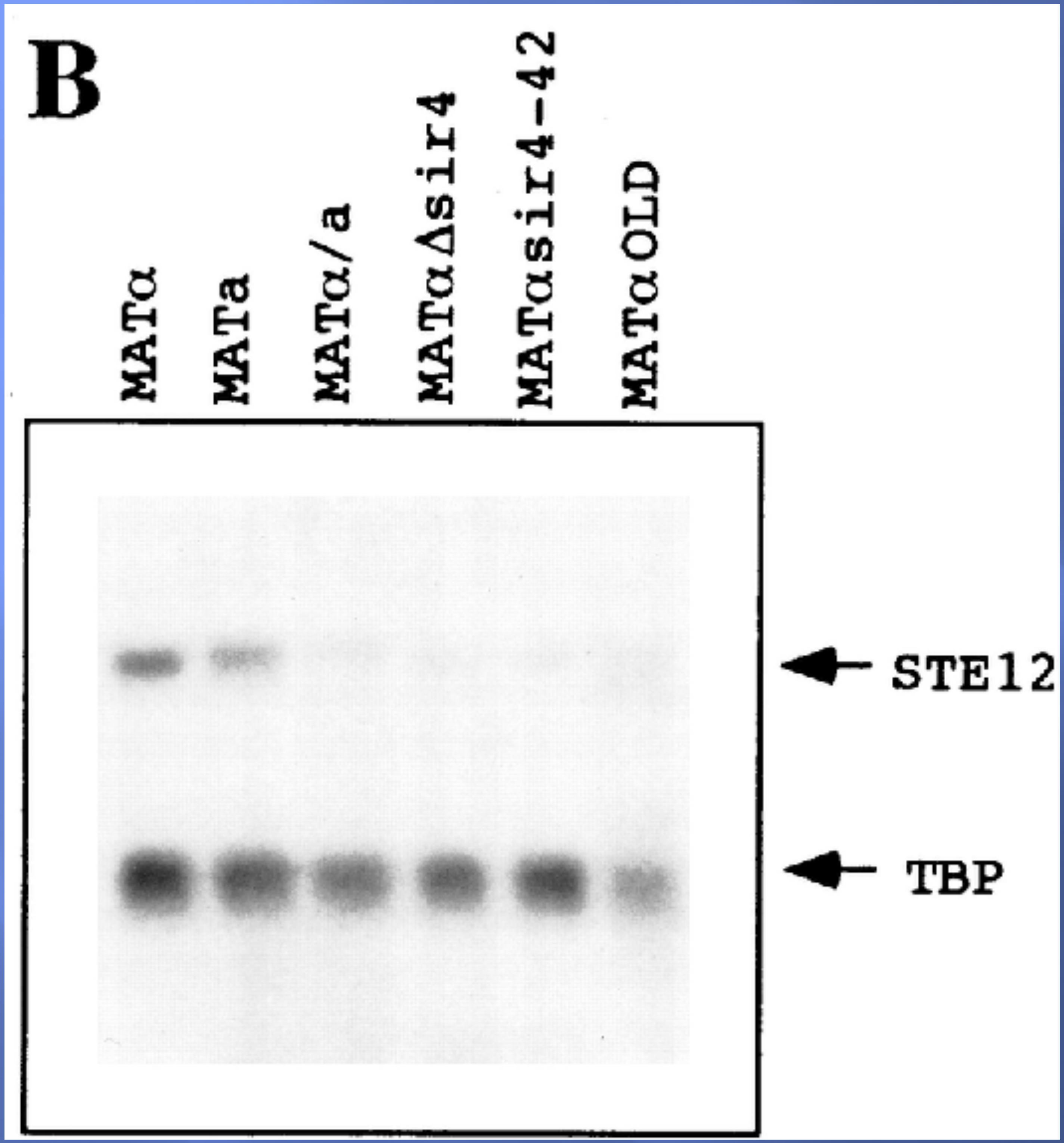




HML and HMR have to be silent, or else haploid cell becomes "gender confused"

Smeal, T., Claus, J., Kennedy, B., Cole, F., & Guarente, L. (1996). Loss of transcriptional silencing causes sterility in old mother cells of *S. cerevisiae*. *Cell*, *84*(4), 633-642.

yeast "aging"



STE12 is turned OFF in diploids by design

being OFF in haploid (MATalpha) when SIR4 is deleted (D) suggests the haploid has become more diploid

Smeal, T., Claus, J., Kennedy, B., Cole, F., & Guarente, L. (1996). Loss of transcriptional silencing causes sterility in old mother cells of *S. cerevisiae*. *Cell*, *84*(4), 633-642.

yeast "aging"

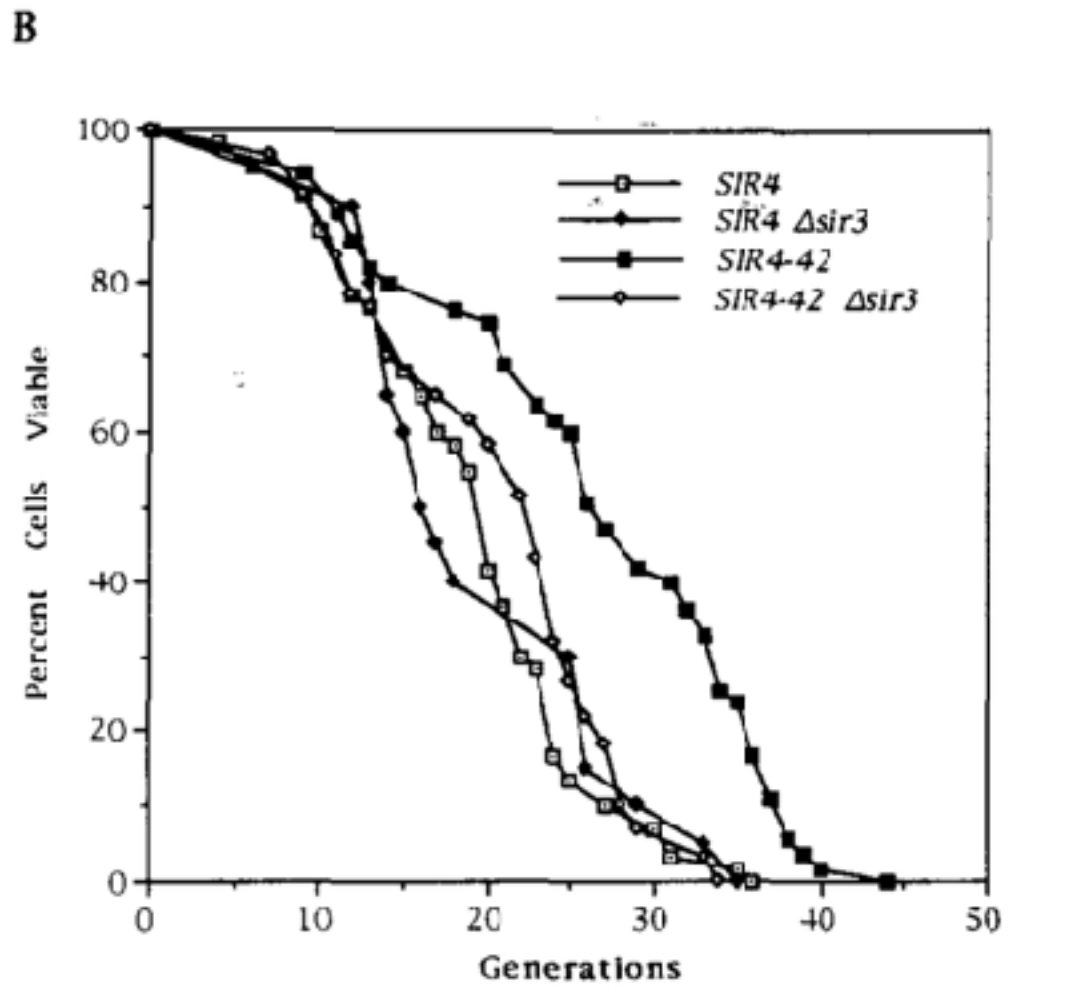


Figure 5. The Increased Longevity Conferred by *sir4-42* Requires *SIR3* but Not *SIR1*

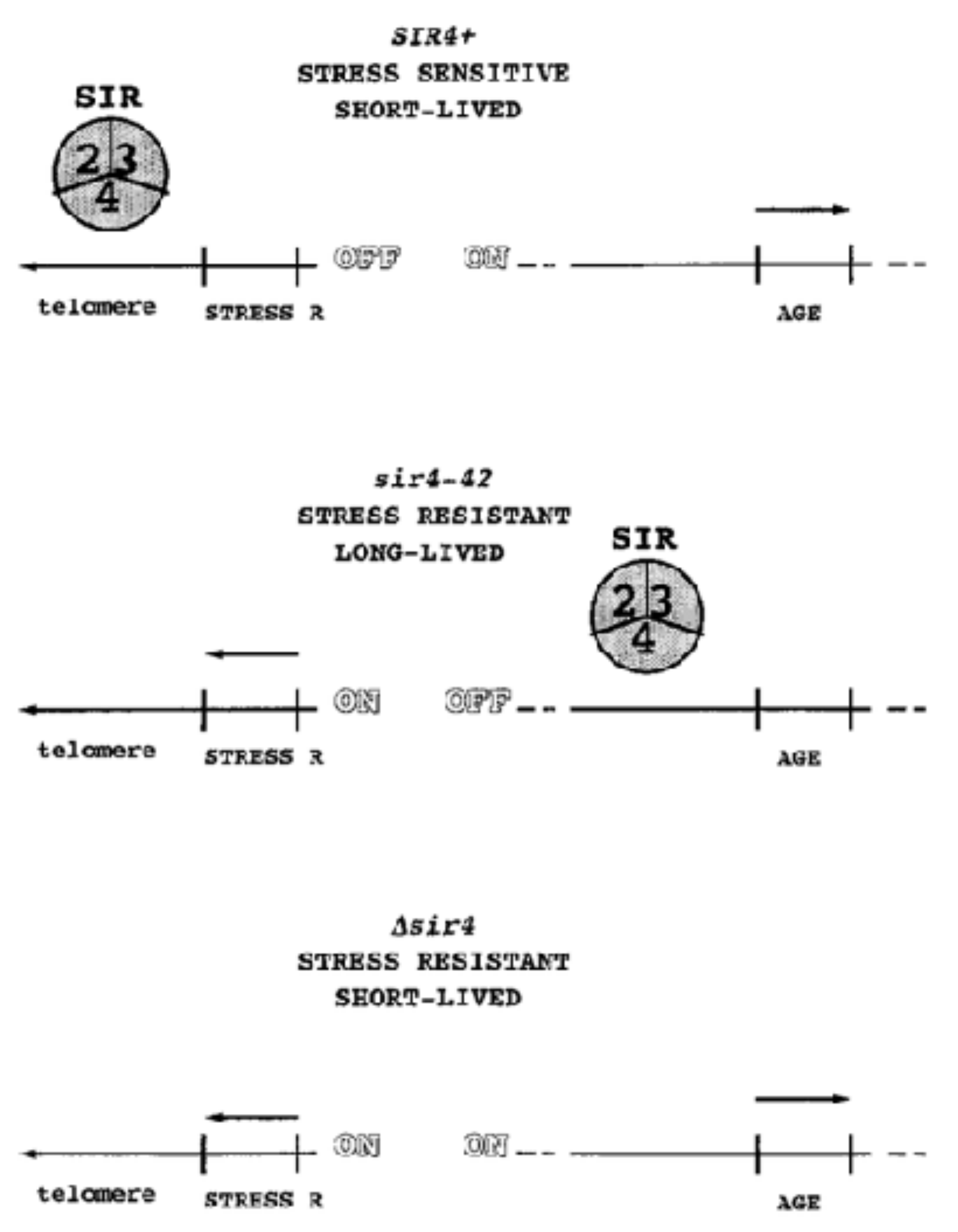


Figure 8. A Model for the Effects of Silencing on Yeast Life Span

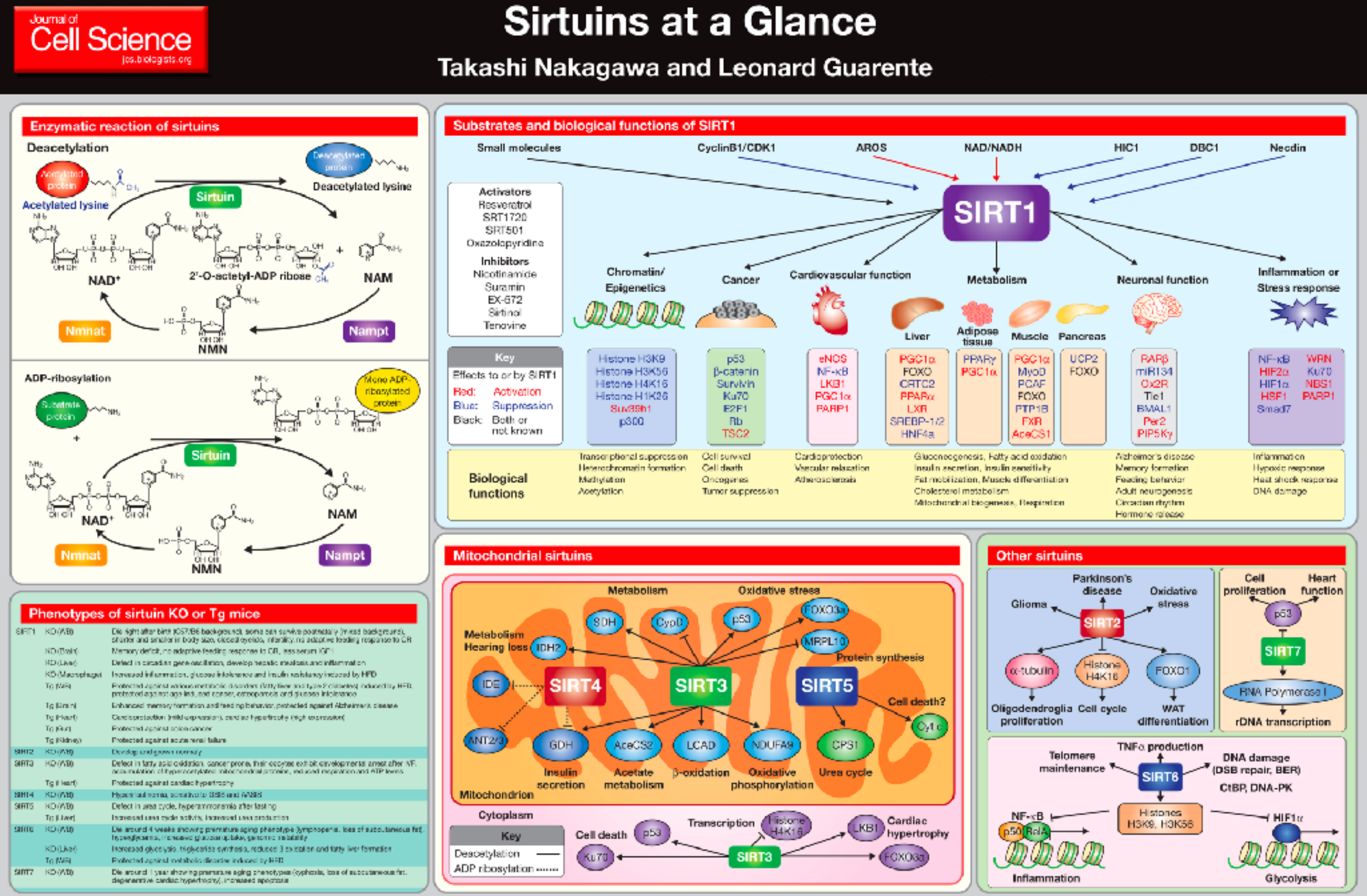
Specific Sir4 (Silent Information Regulator) mutant enhances yeast longevity

showed elsewhere the sir4-deletion does not

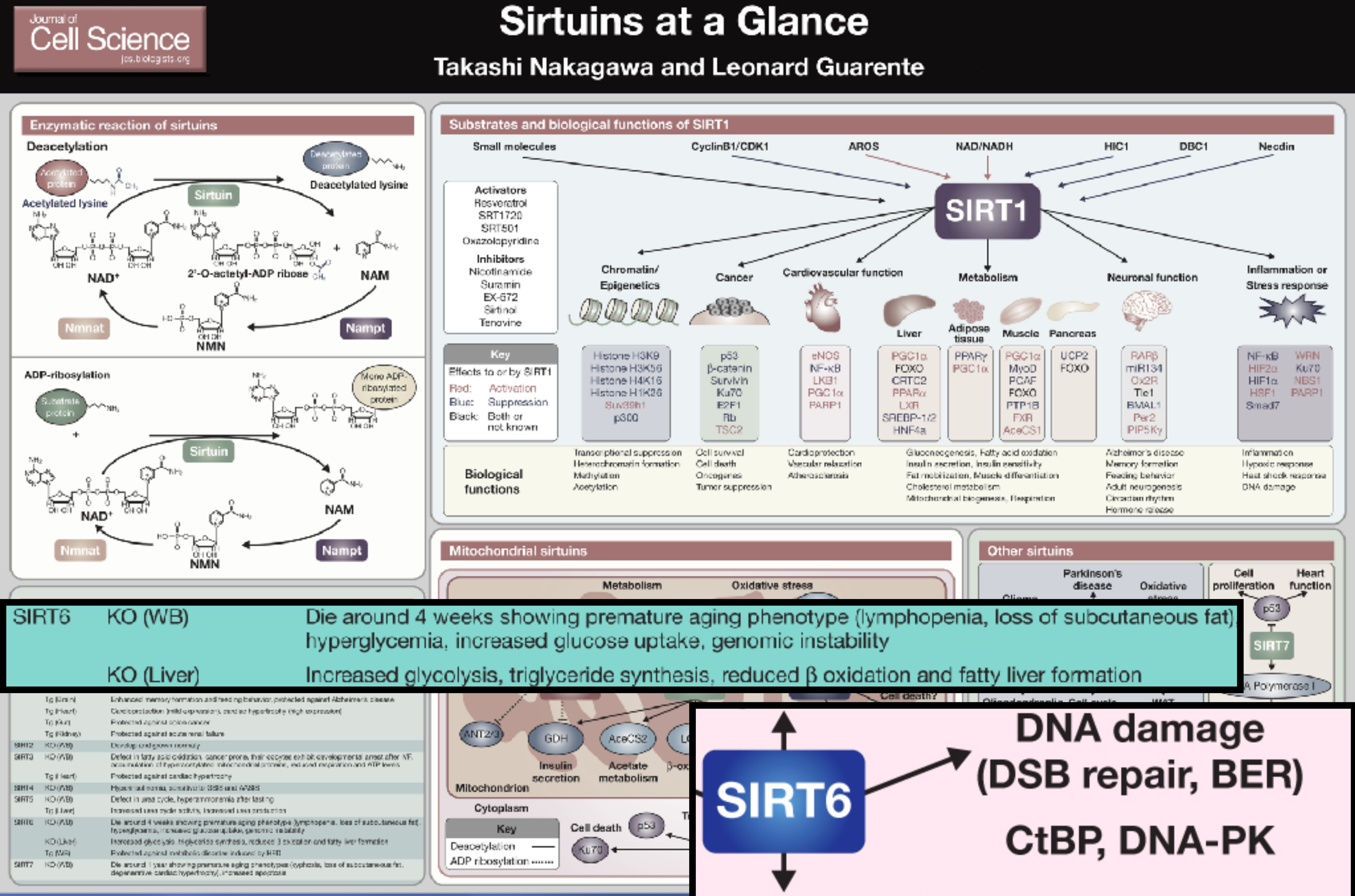
is part of the SIR2/3/4 complex

Sir4-mutant complex relocates and silences aging factor

Kennedy, B. K., Austriaco Jr, N. R., Zhang, J., & Guarente, L. (1995). Mutation in the silencing gene S/R4 can delay aging in *S. cerevisiae*. *Cell*, *80*(3), 485-496.

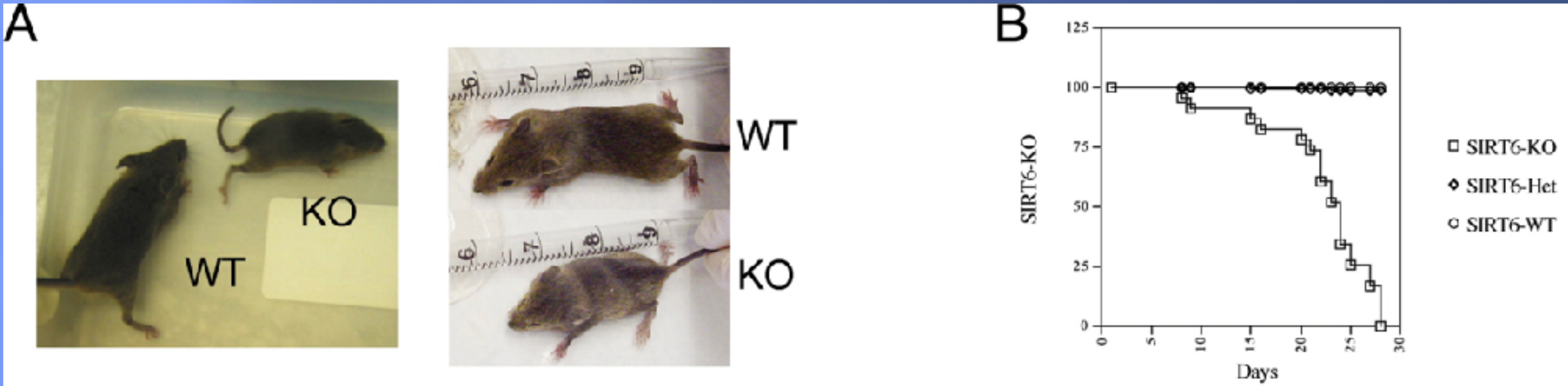


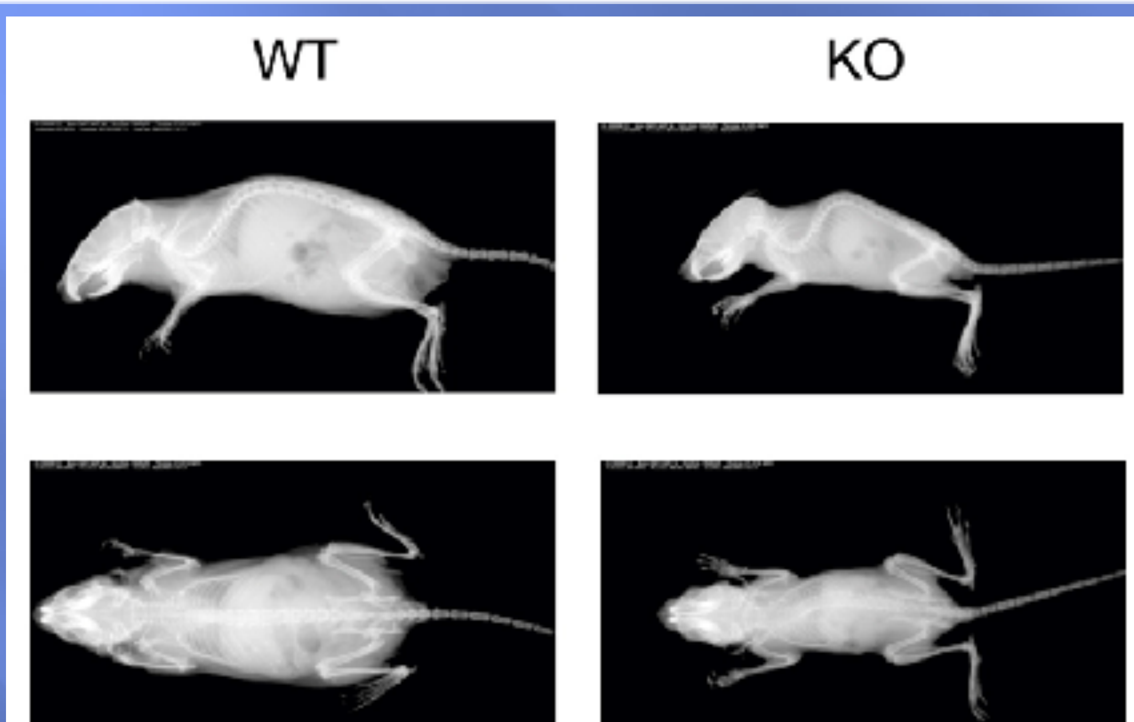
Nakagawa, T., & Guarente, L. (2011). Sirtuins at a glance. *Journal of cell science*, *124*(6), 833-838.

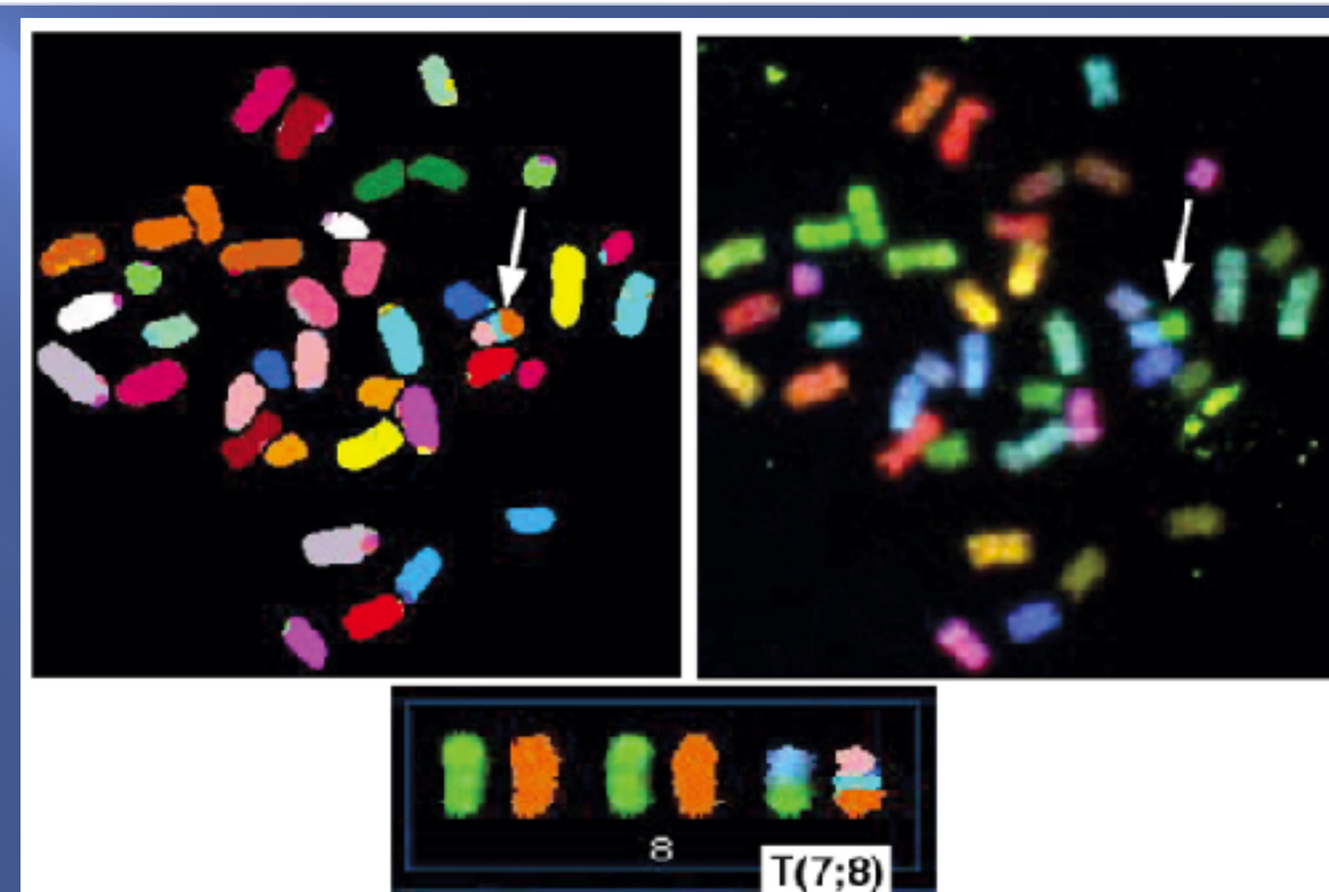


Nakagawa, T., & Guarente, L. (2011). Sirtuins at a glance. *Journal of cell science*, *124*(6), 833-838.

life without SIRT6





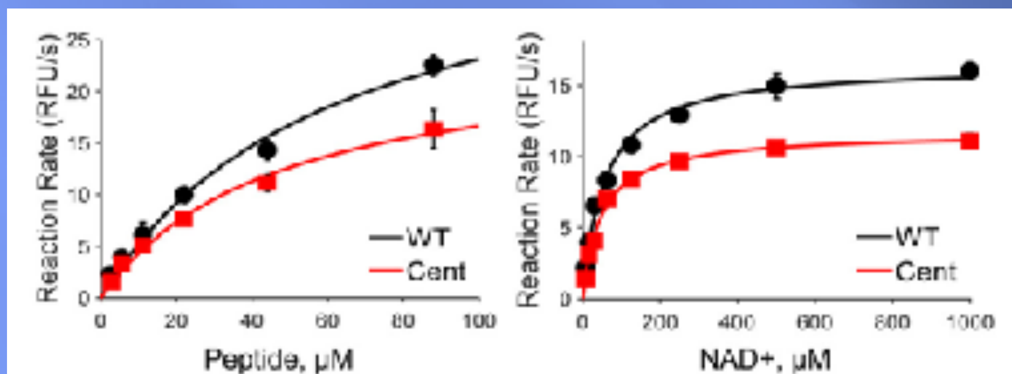


quick mention: SIRT6 overexpression mice live longer and healthier

Mostoslavsky, R., Chua, K. F., Lombard, D. B., Pang, W. W., Fischer, M. R., Gellon, L., ... & Alt, F. W. (2006). Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. *Cell*, *124*(2), 315-329.

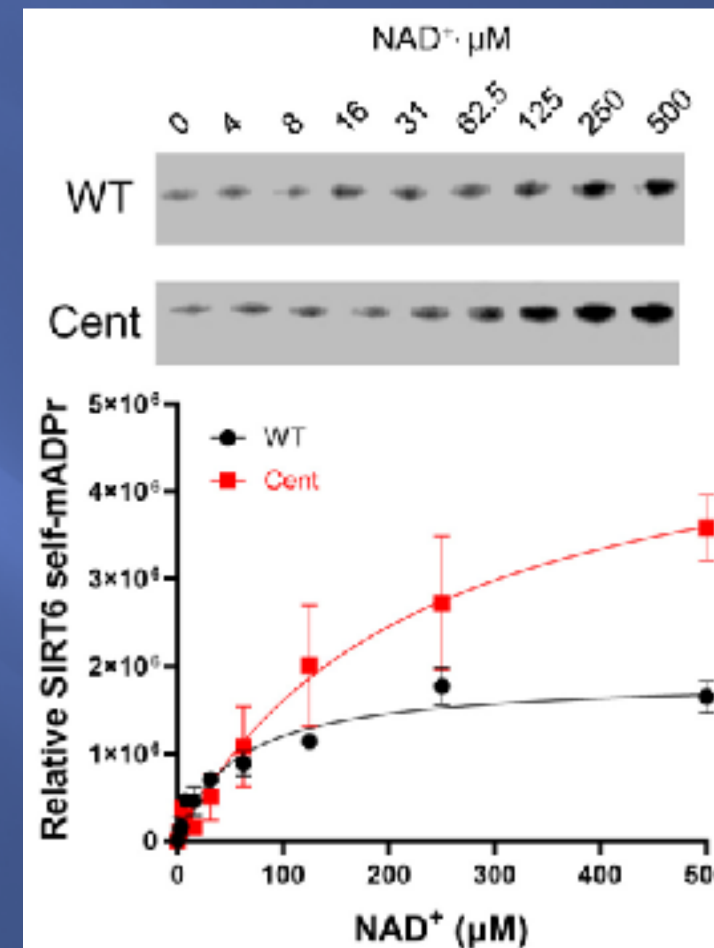
SIRT6 allele in long-lived cohort (humans)

"Compared with other alleles at similar MAF (0.1–1%), the centSIRT6 allele was in the top 5th percentile of 75+ enriched SNPs and in the 9th percentile of all missense mutations (Fig 1B and C)."



	Km_{NAD} (μM)	Km_{pep} (μM)	Vmax (RFU/s)	$Vmax/Km_{pep}$
WT	55.5 ± 5.4	61.1 ± 12.4	37.2 ± 4.1	0.61
Cent	48.4 ± 3.7	46 ± 11.3	24.3 ± 2.9*	0.53

reduced deacetylation activity

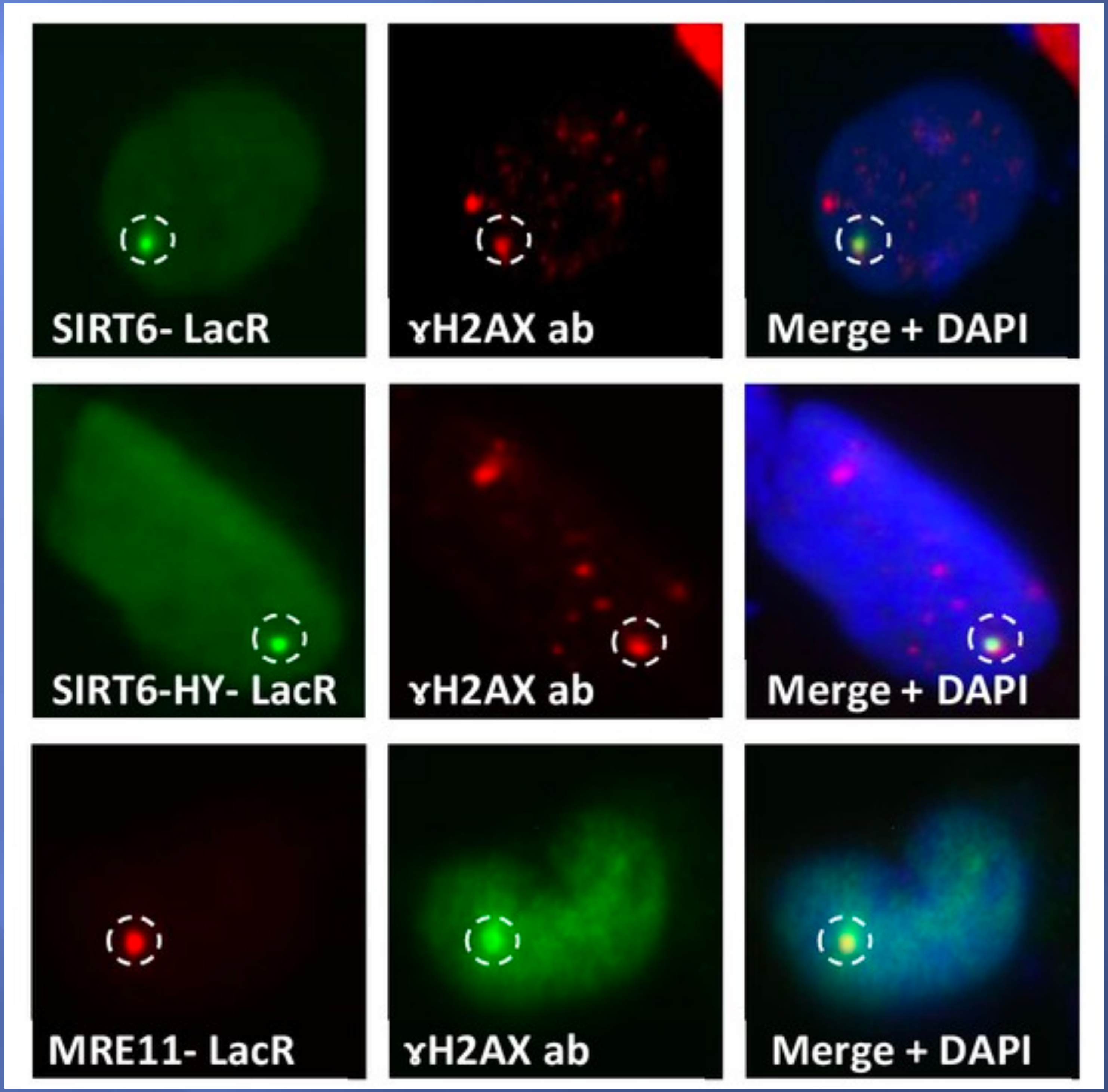


enhanced mono-ADP ribosylation (mADPr) activity

Simon, M., Yang, J., Gigas, J., Earley, E. J., Hillpot, E., Zhang, L., ... & Gorbunova, V. (2022). A rare human centenarian variant of SIRT6 enhances genome stability and interaction with Lamin A. *The EMBO Journal*, 41(21), e110393.

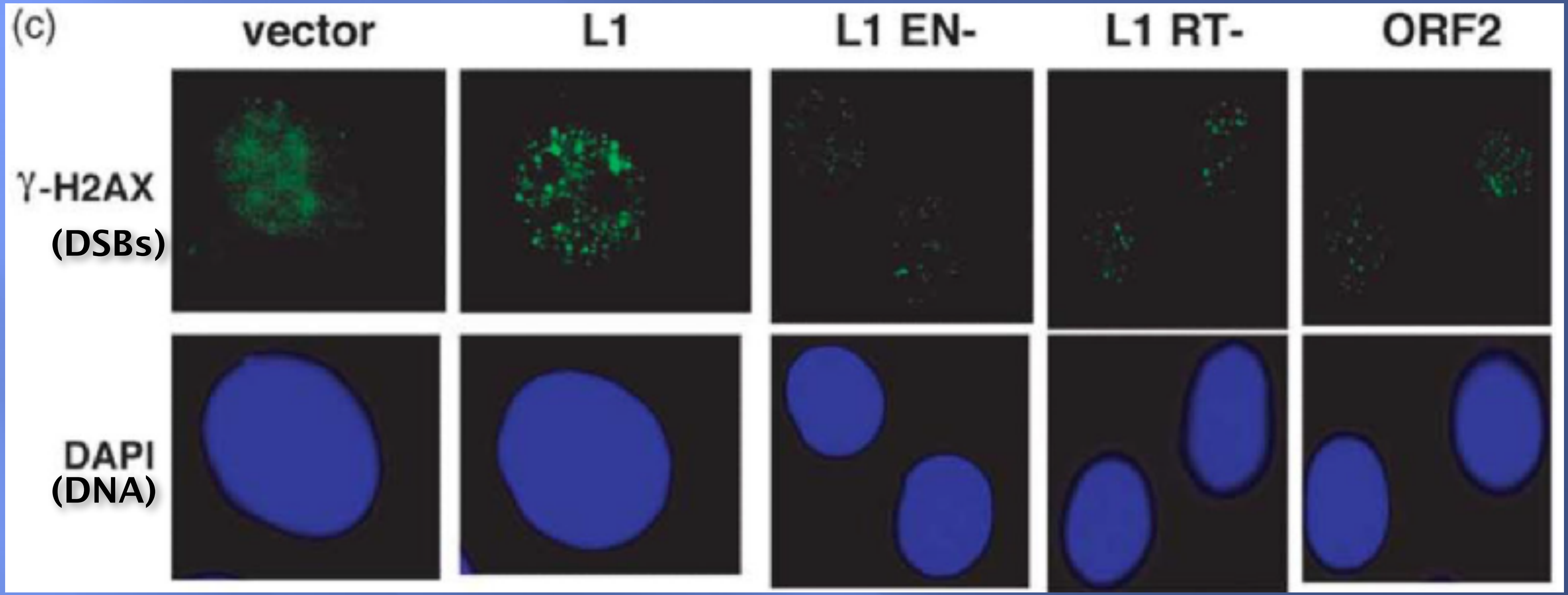
SIRT6 recognizes DSBs

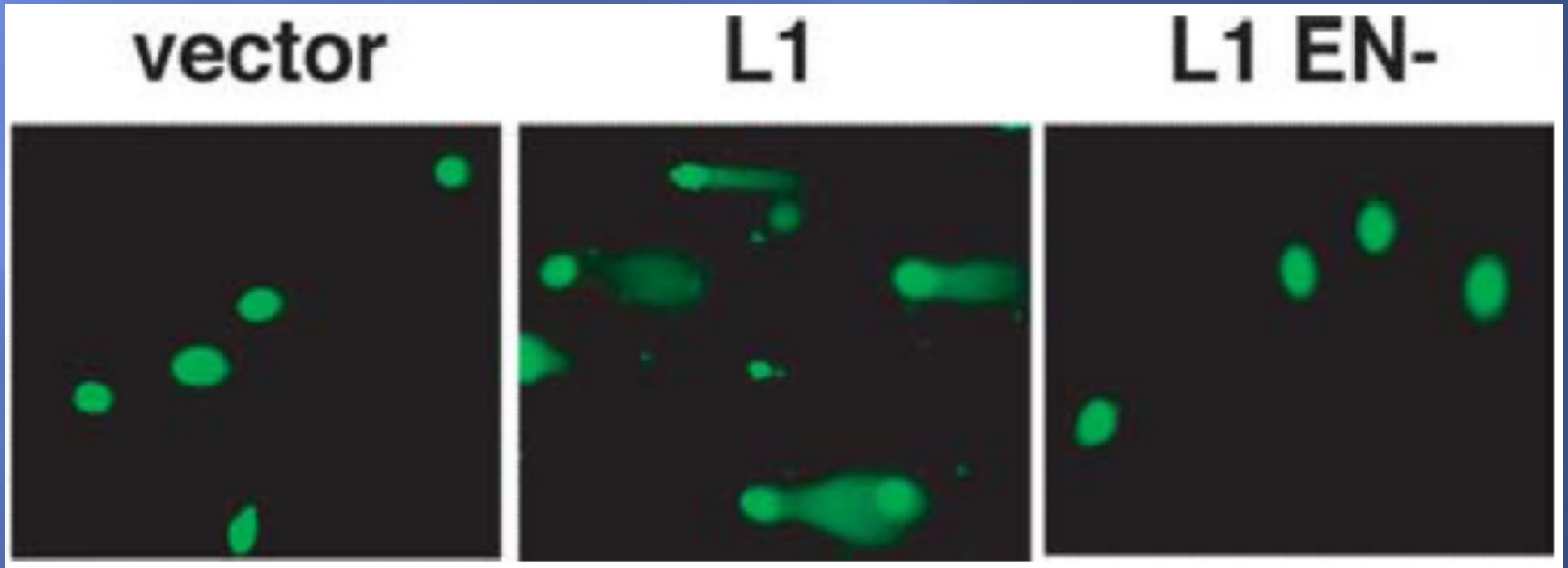
DSBs being made inside the dotted circle with a laser



Onn, L., Portillo, M., Ilic, S., Cleitman, G., Stein, D., Kaluski, S., ... & Toiber, D. (2020). SIRT6 is a DNA double-strand break sensor. *Elife*, *9*, e51636.

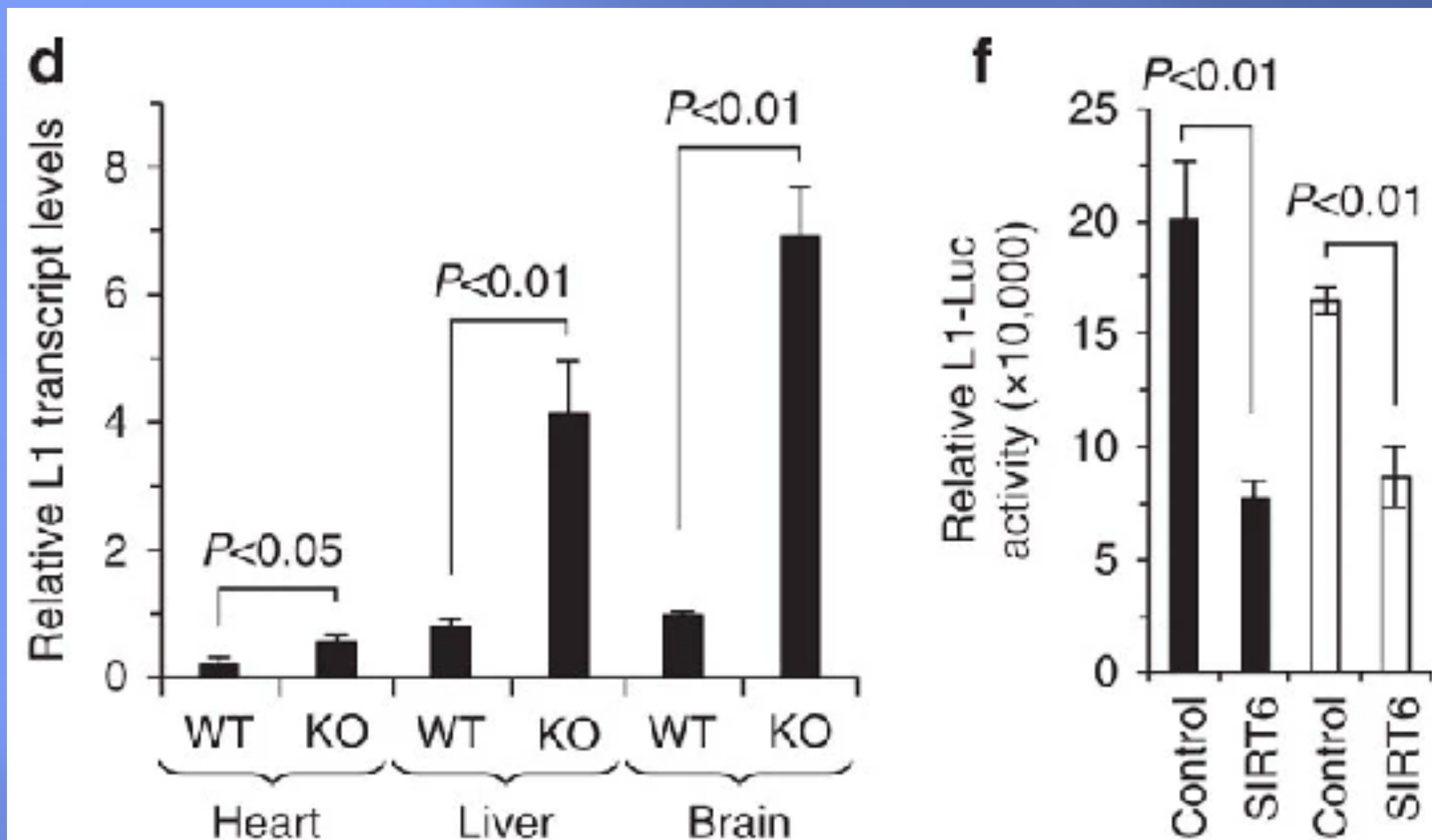
LINE-1 Creates DSBs

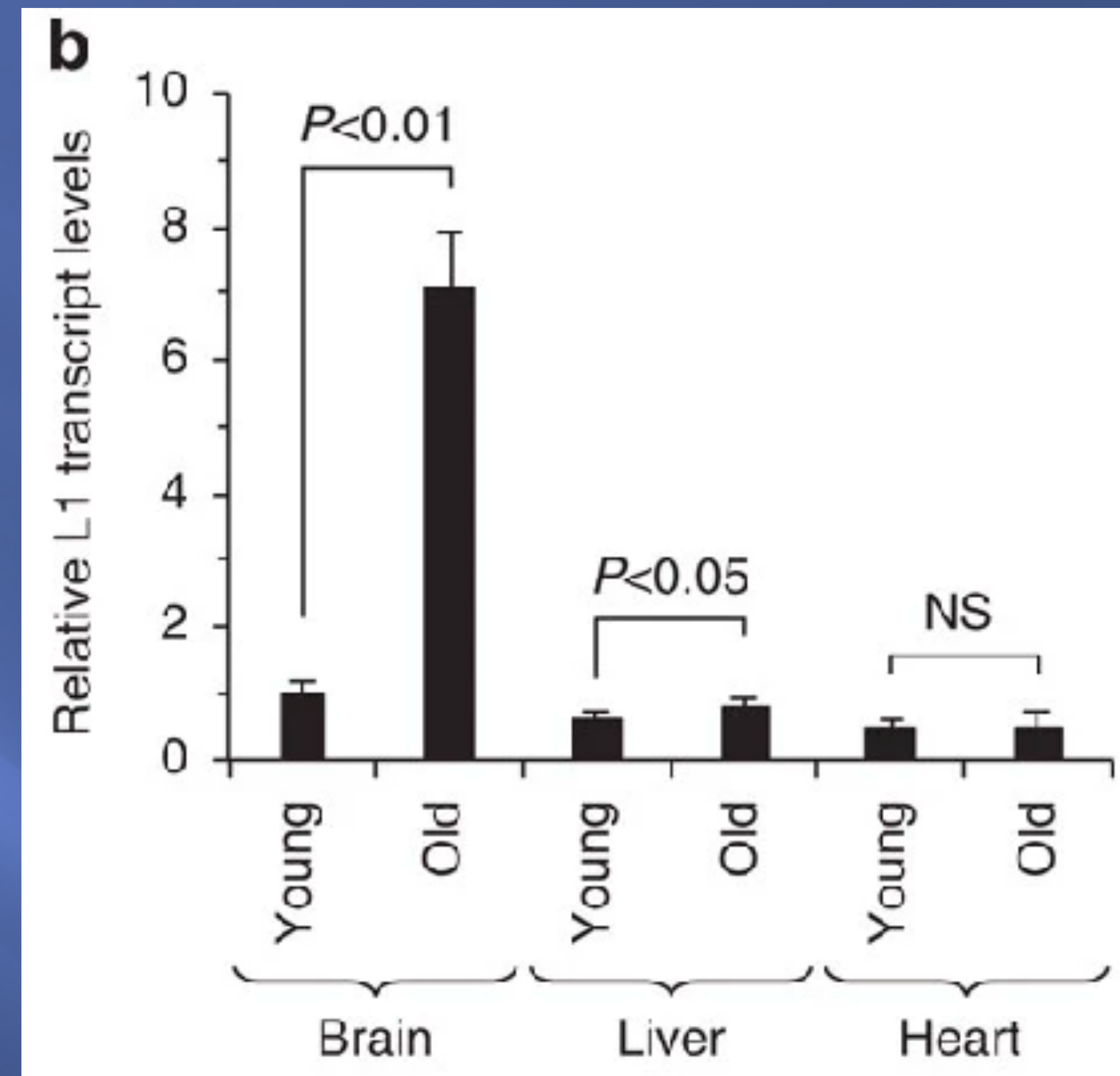




Gasior, S. L., Wakeman, T. P., Xu, B., & Deininger, P. L. (2006). The human LINE-1 retrotransposon creates DNA double-strand breaks. *Journal of molecular biology*, 357(5), 1383-1393.

life without SIRT6

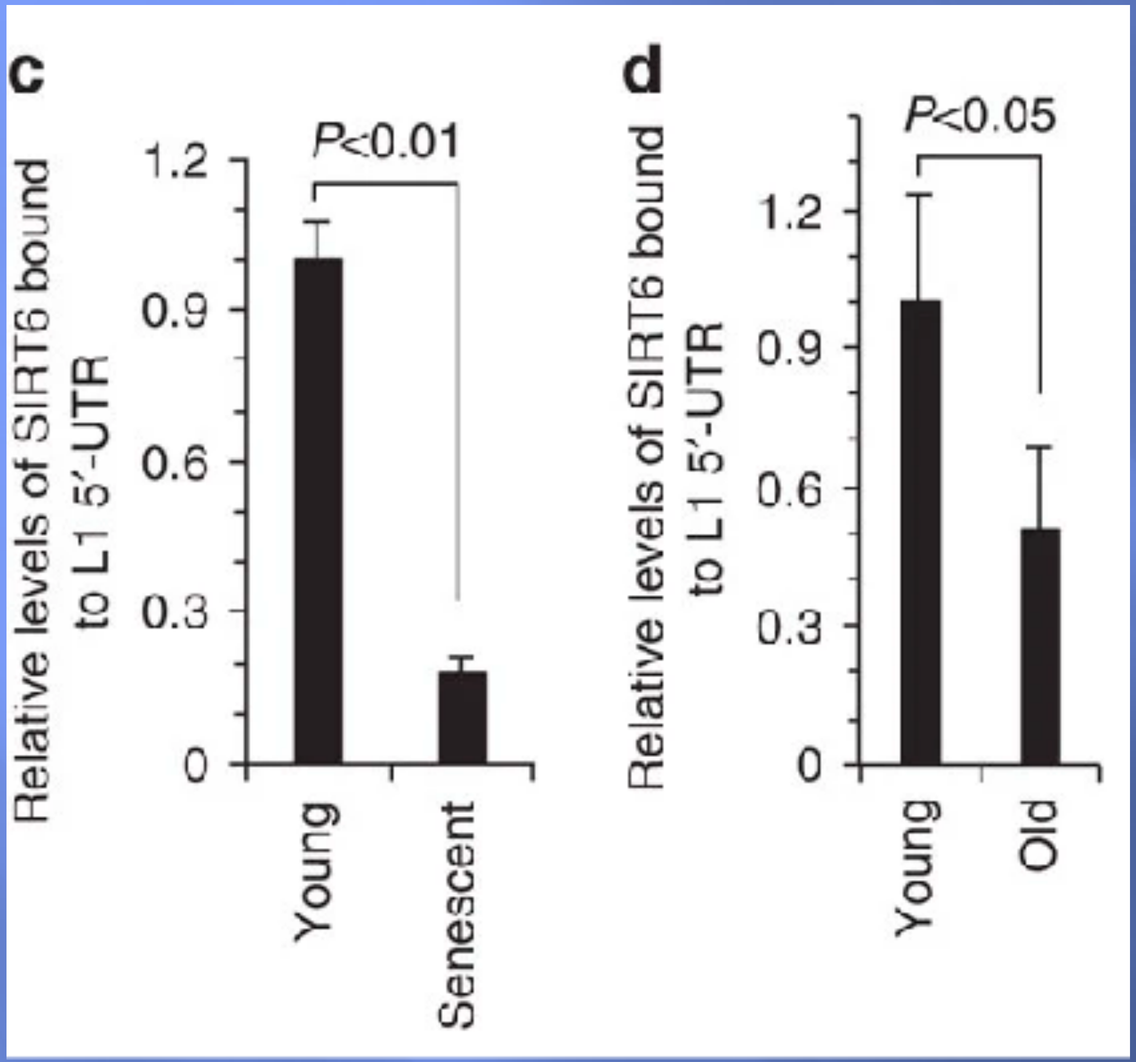


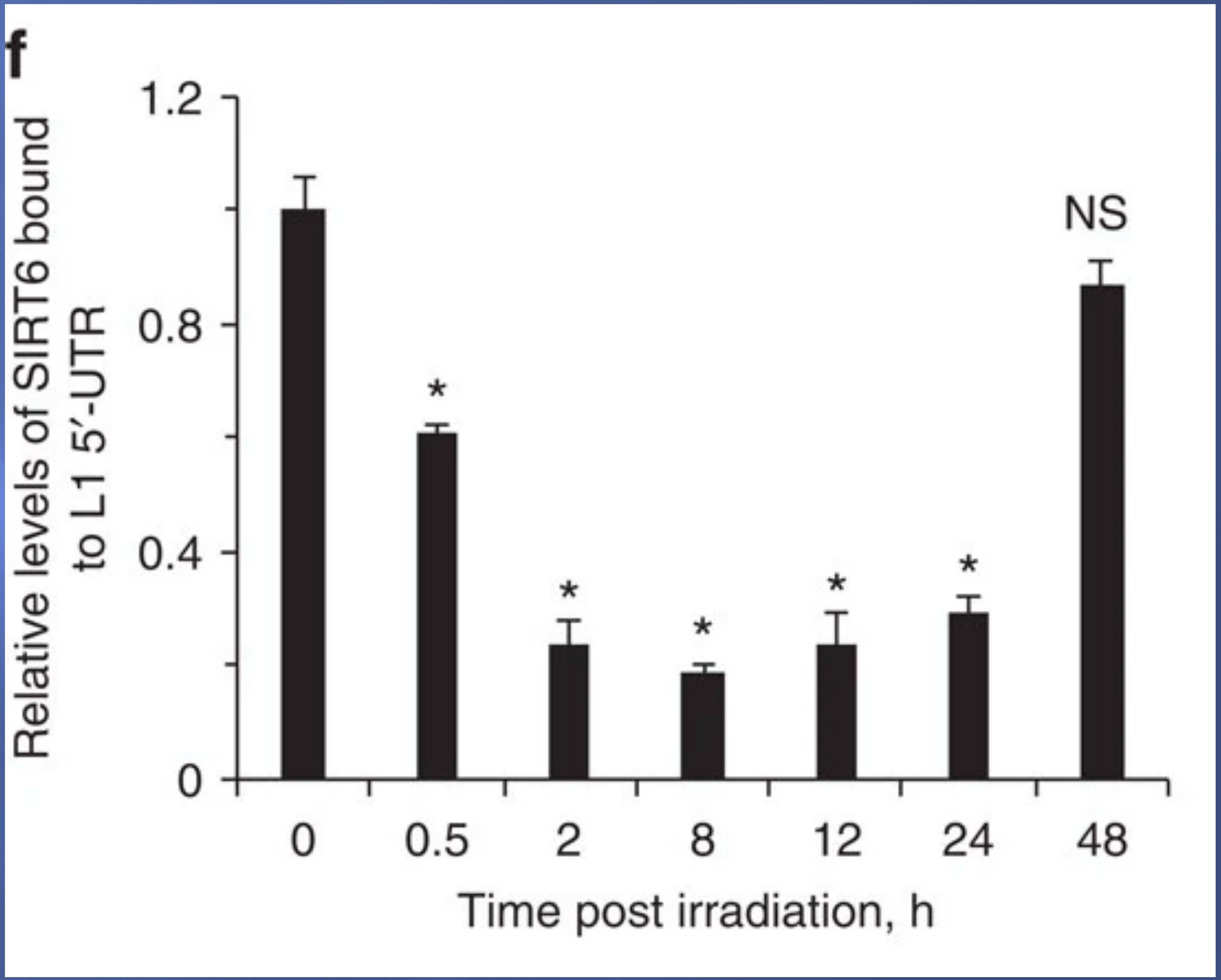


KO = SIRT6 knock-out mice

Van Meter, M., Kashyap, M., Rezazadeh, S., Geneva, A. J., Morello, T. D., Seluanov, A., & Gorbunova, V. (2014). SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. *Nature communications*, *5*(1), 1-10.

life without SIRT6





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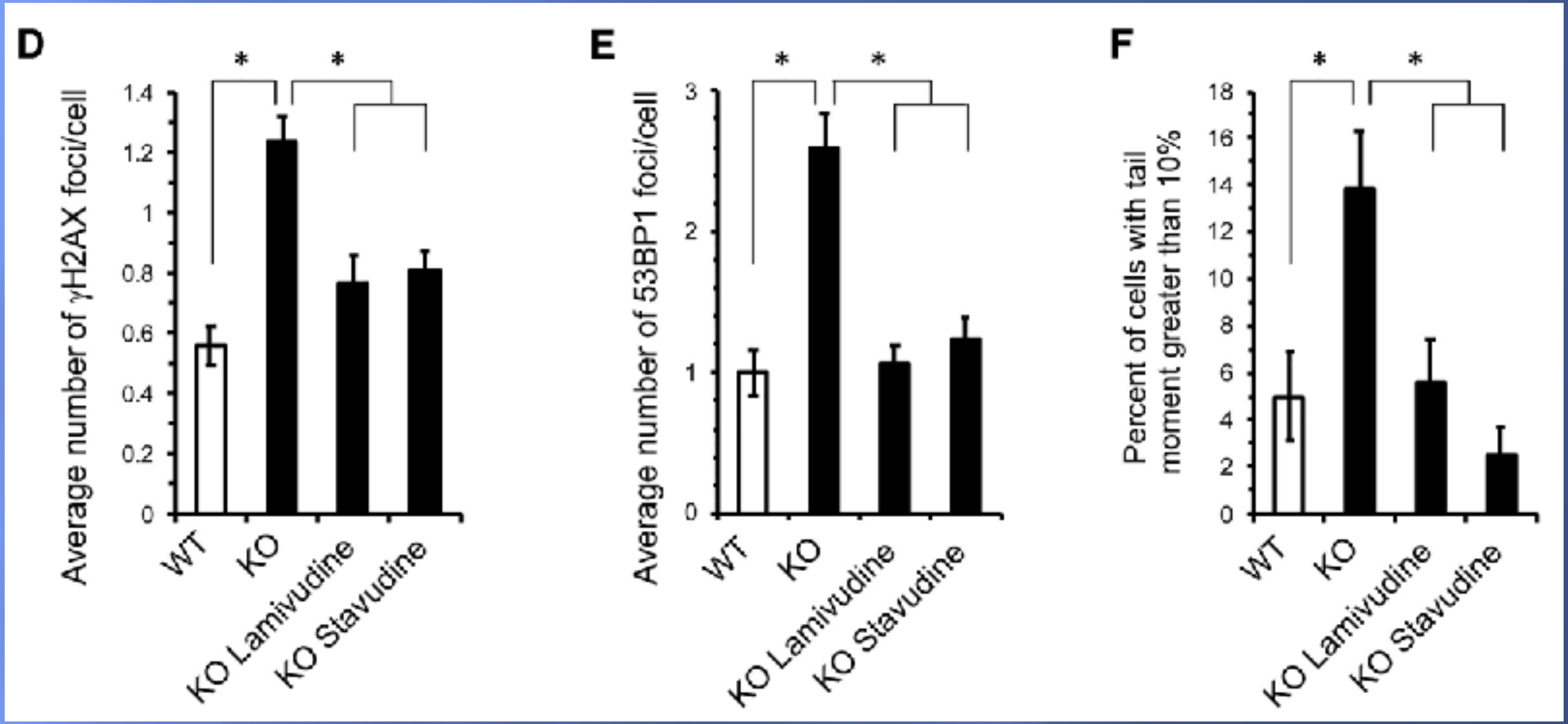
life without SIRT6



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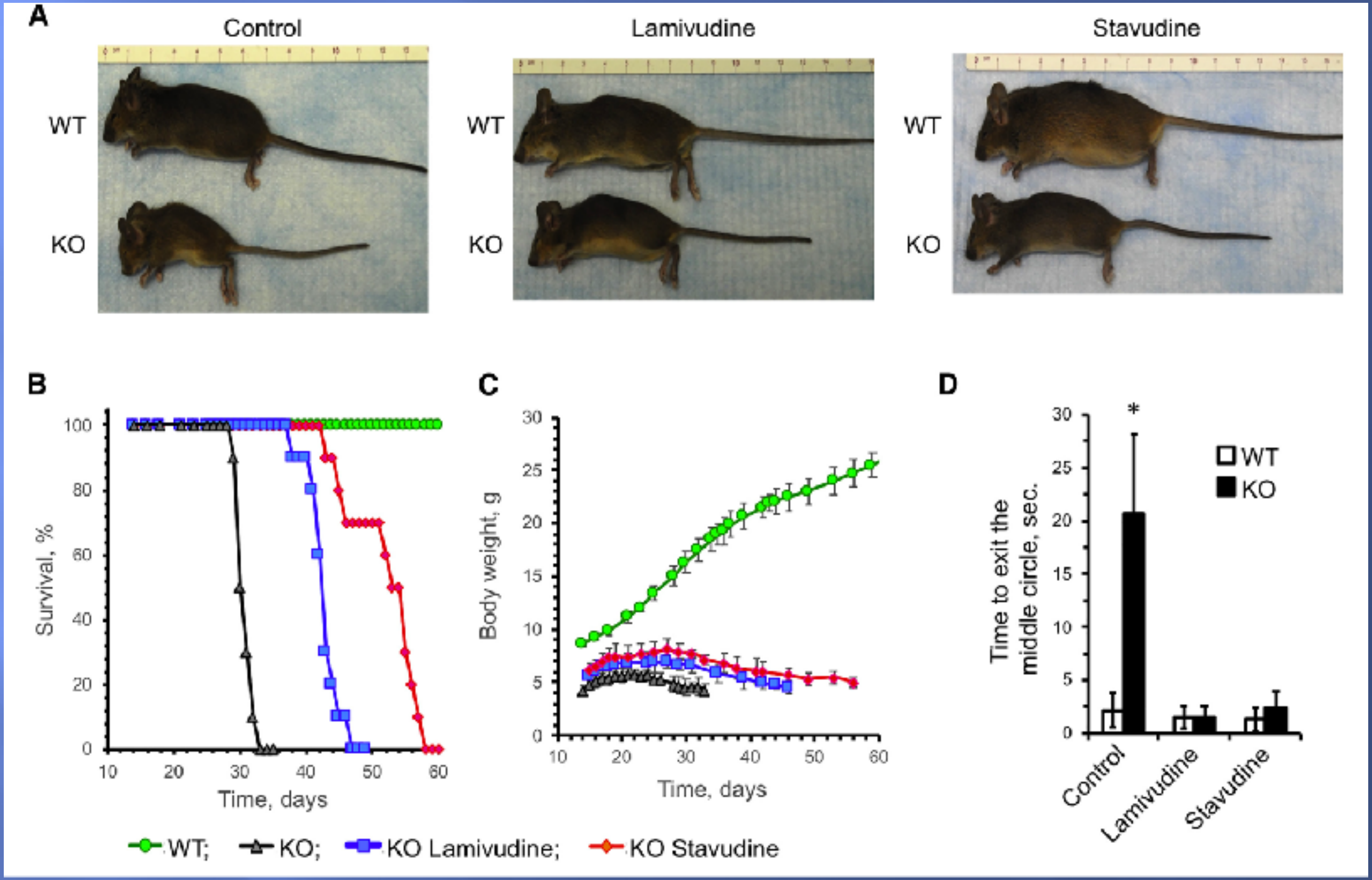
Lamivudine and Stavudine are reverse transcriptase inhibitors

Simon, M., Van Meter, M., Ablaeva, J., Ke, Z., Gonzalez, R. S., Taguchi, T., ... & Gorbunova, V. (2019). LINE1 derepression in aged wild-type and SIRT6-deficient mice drives inflammation. *Cell metabolism*, *29*(4), 871-885.

life without SIRT6



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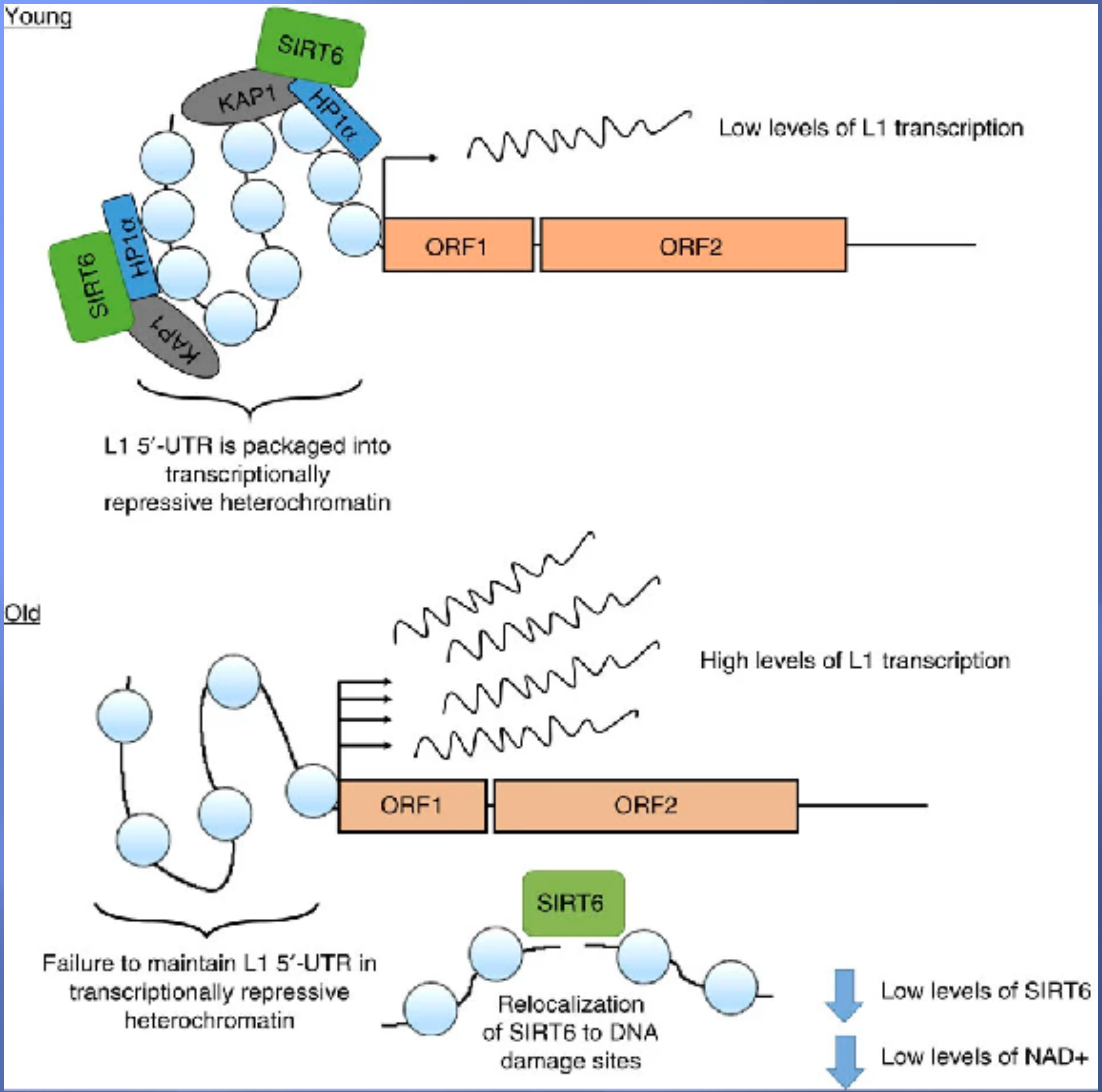
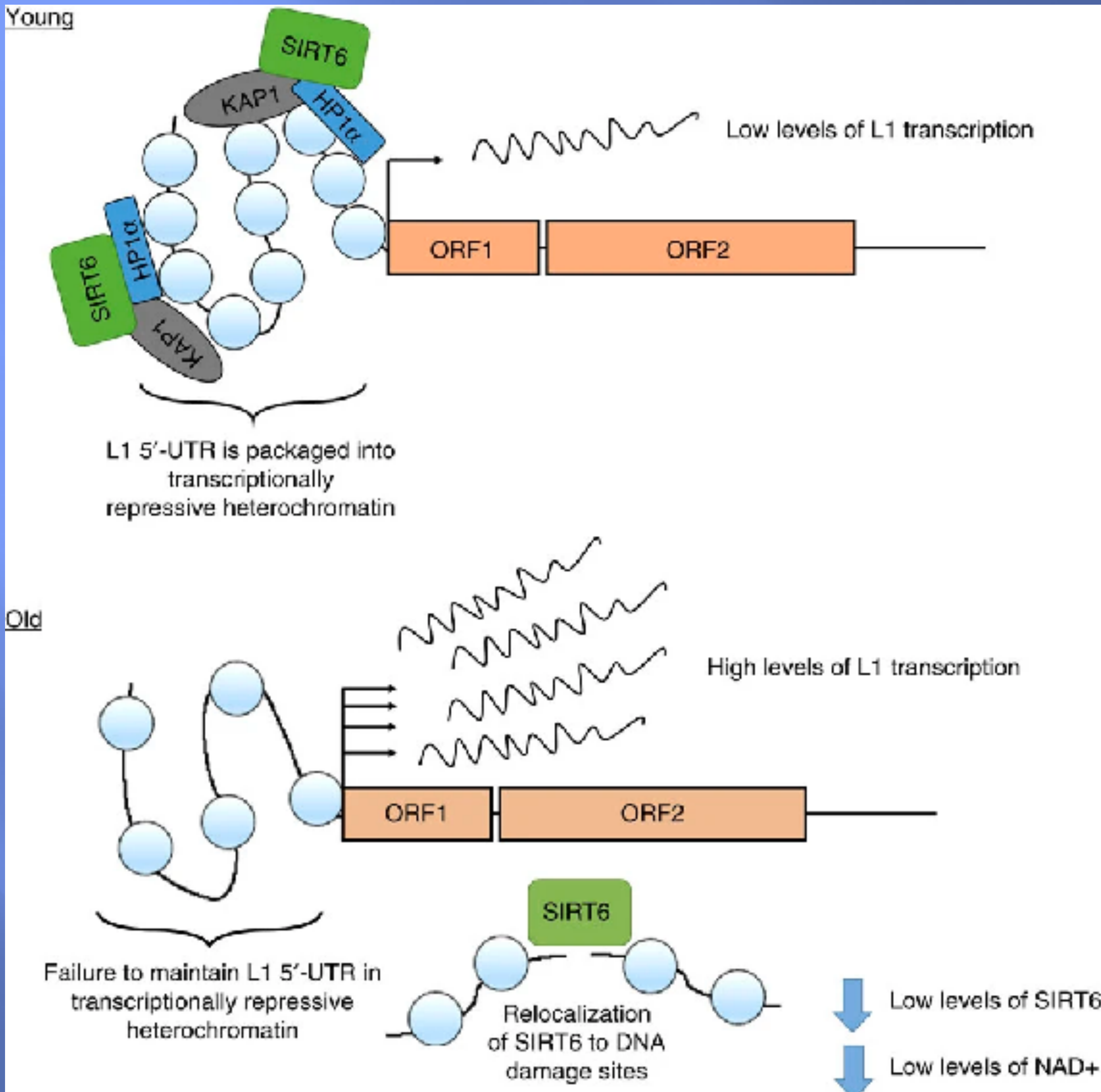
The Model



Van Meter, M., Kashyap, M., Rezazadeh, S., Geneva, A. J., Morello, T. D., Seluanov, A., & Gorbunova, V. (2014). SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. *Nature communications*, *5*(1), 1-10.

The Model



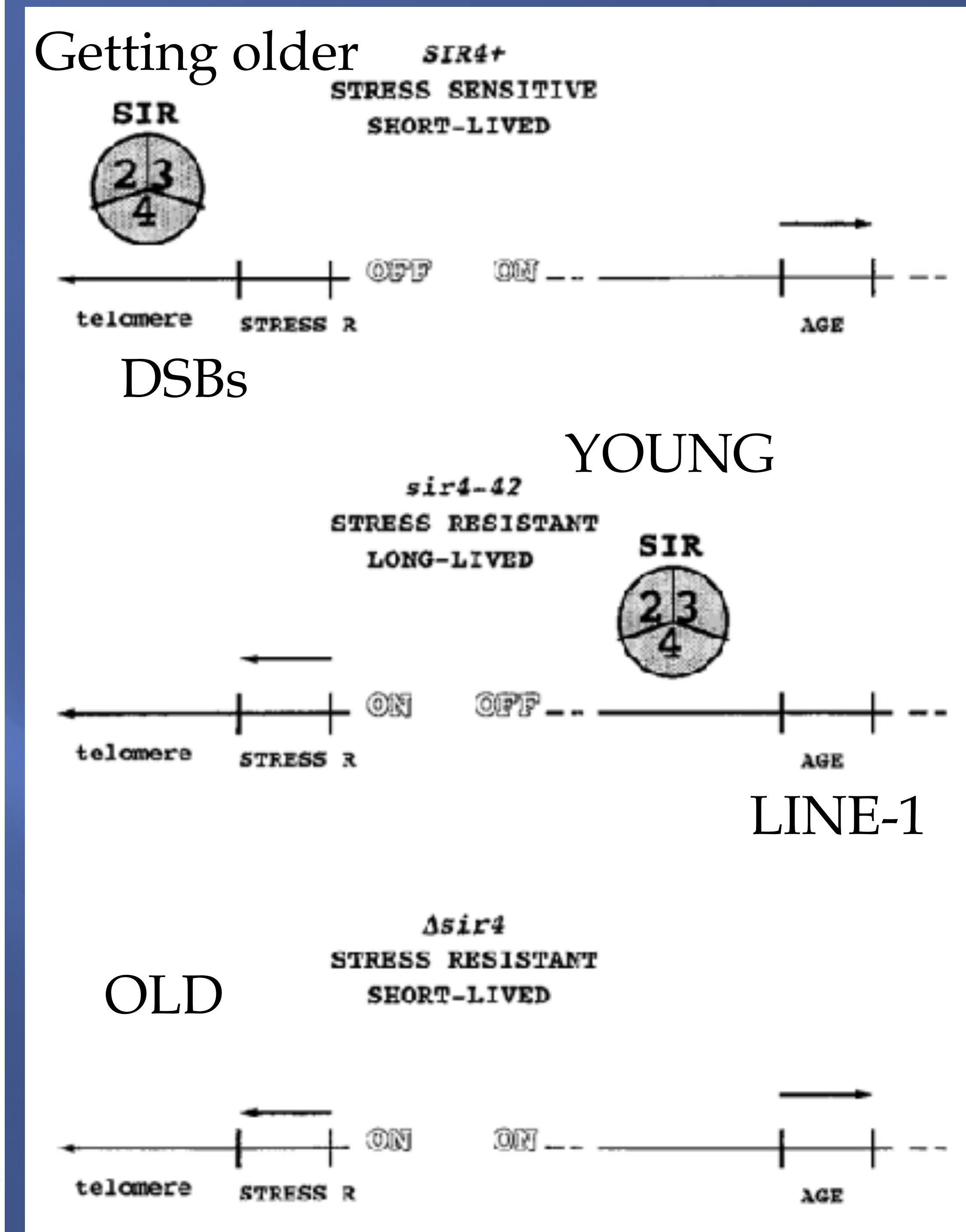


Figure 8. A Model for the Effects of Silencing on Yeast Life Span

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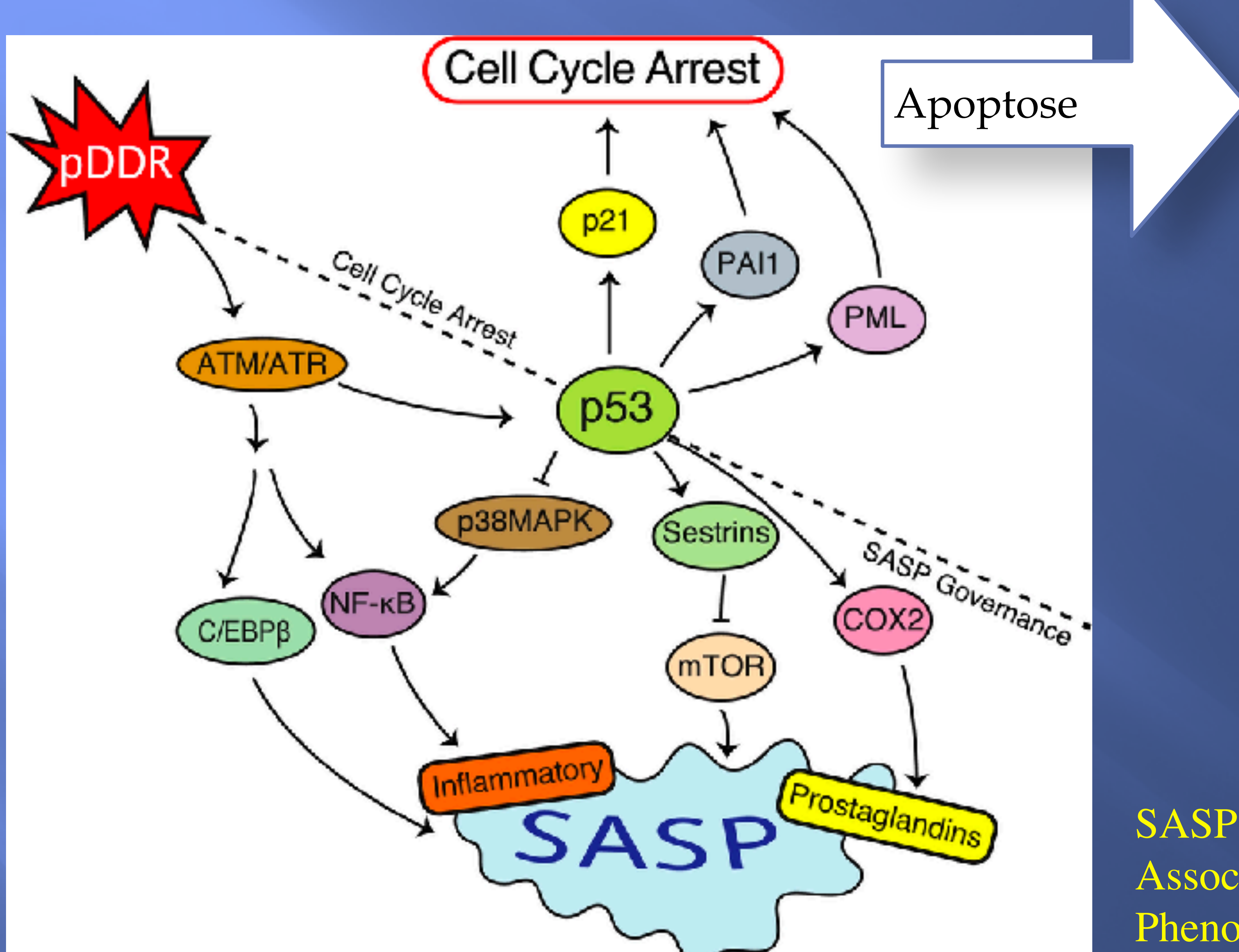
But is that aging?

Cells with DSBs should die…. however

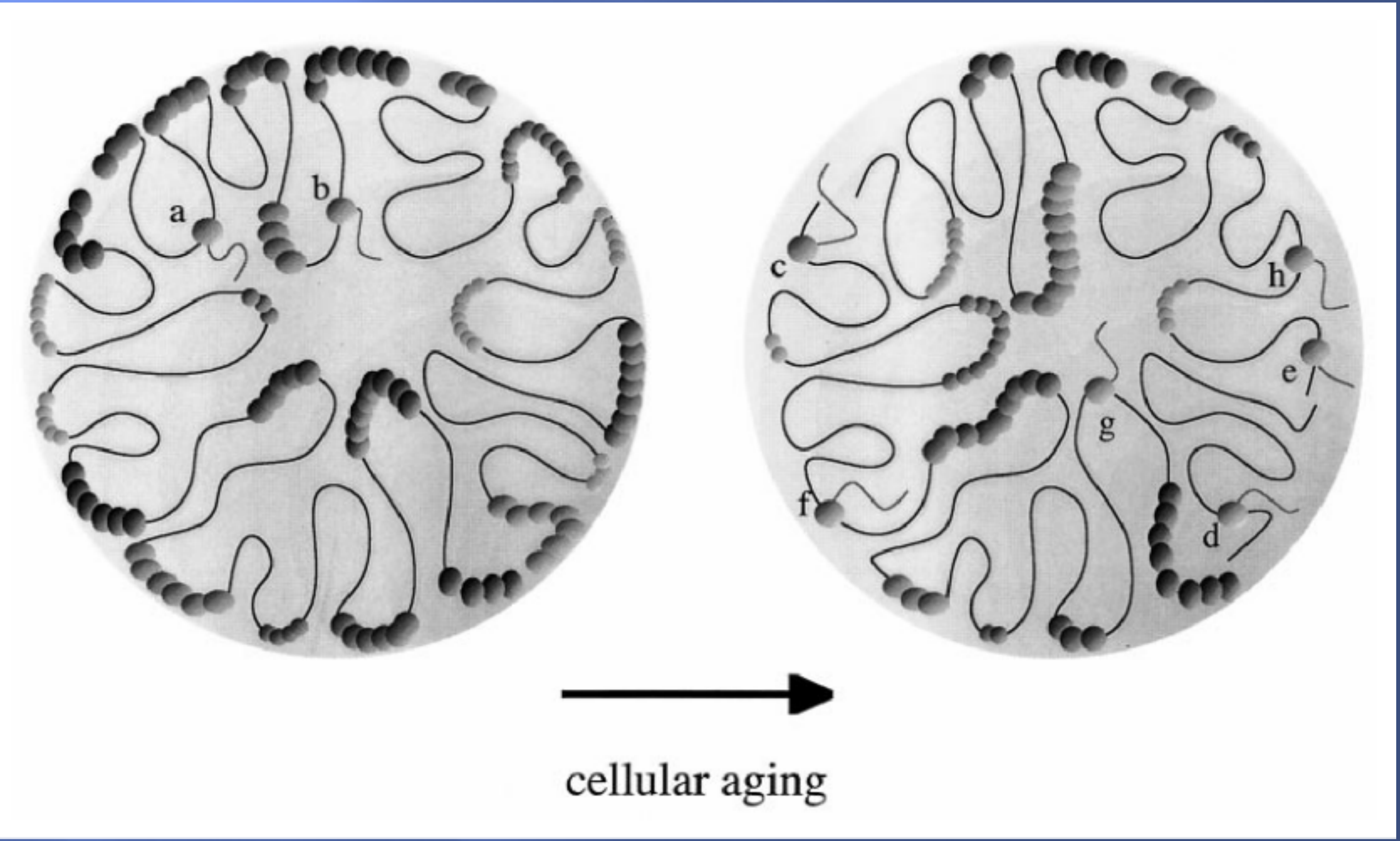


SASP - Senescence Associated Secretory Phenotype

Pawge, G., & Khatik, G. L. (2021). p53 regulated senescence mechanism and role of its modulators in age-related disorders. *Biochemical Pharmacology*, *190*, 114651.

But is that aging?

DSBs and relocalized SIRTs lead to disorganized heterochromatin state/expression



Imai, S., & Kitano, H. (1998). Heterochromatin islands and their dynamic reorganization: a hypothesis for three distinctive features of cellular aging. *Experimental gerontology*, *33*, 555-570.

Oldest hypothesis

Transposable Elements as a Factor in the Aging of *Drosophila melanogaster*

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STEPHEN W. McKECHNIE[b]

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Clayton, Victoria 3168, Australia

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Monash University
Clayton, Victoria 3168, Australia

1992

INTRODUCTION

A model of aging based on the possibility that somatic DNA may accumulate mutations has been discussed for several decades. The model has significant explanatory power, but many authors have pointed out substantial problems,[1,2] and hence various modifications to the model have been discussed.[1,2] Since the elucidation of the nature of transposable elements, it has become apparent that most spontaneous mutations in the germ line occur as a result of transposable element action.[3] It thus seems reasonable to consider a role for transposable elements in somatic mutation and aging. This possibility has been raised by other

Andrenacci, D., Cavaliere, V., & Lattanzi, G. (2020). The role of transposable elements activity in aging and their possible involvement in laminopathic diseases. *Ageing research reviews*, *57*, 100995.

Can we slow down or reverse aging?

Strategies:

inhibit LINE-1 (RT inhibitors)

maintain heterochromatin (SIRTs, *works in transgenic mice, "Resveratrol blocks retrotransposition of LINE-1 through PPAR α and sirtuin-6"*)

remove senescent cells

reverse aspects or the "signaling" of aging

maintain heterochromatin (SIRTs)

NR = nicotinamide riboside

NMN = nicotinamide mononucleotide

P7C3 = nicotinamide phosphoribosyltransferase (NAMPT) activator

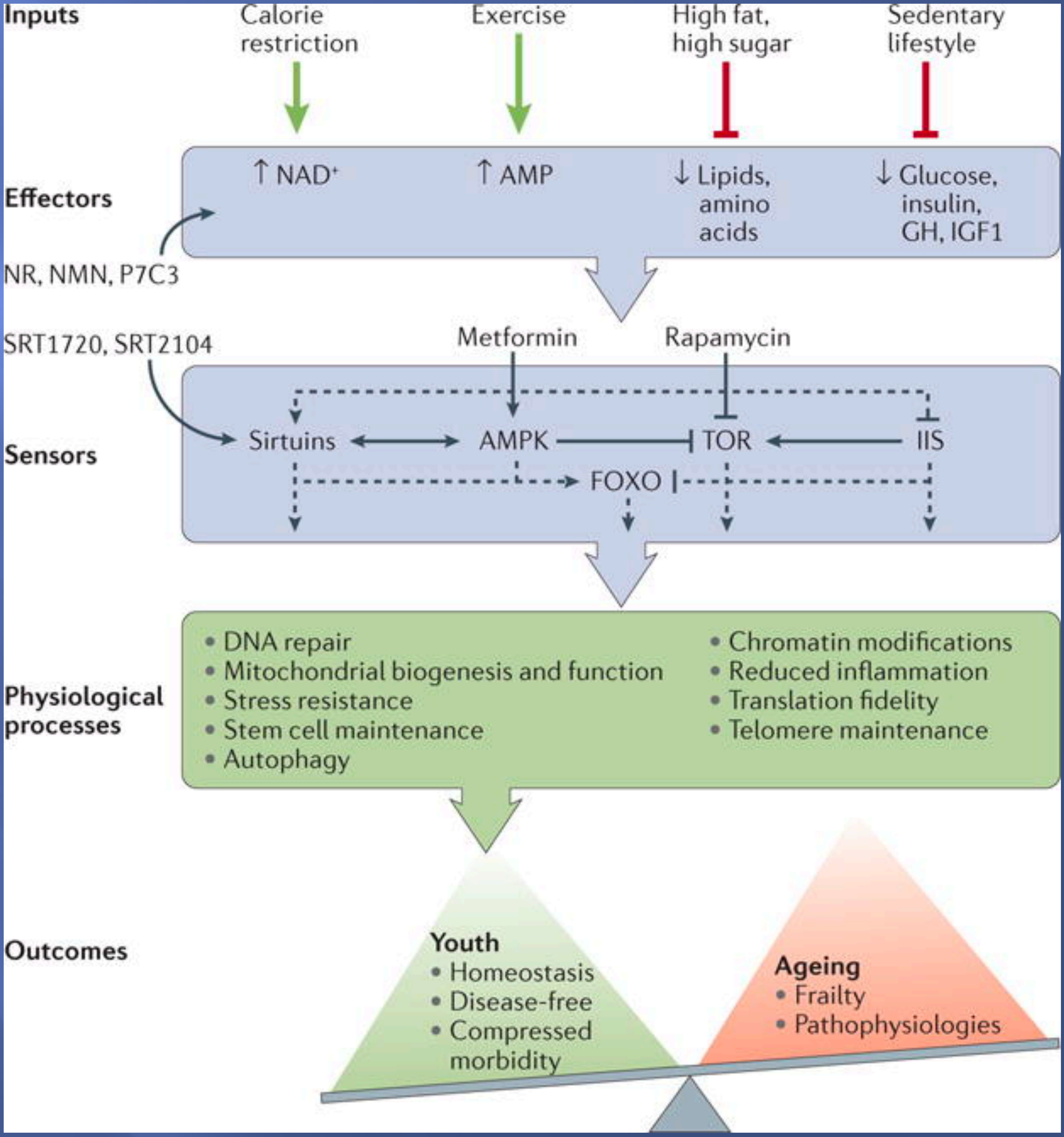
SRTs = proprietary candidates

not displayed:

resveratrol

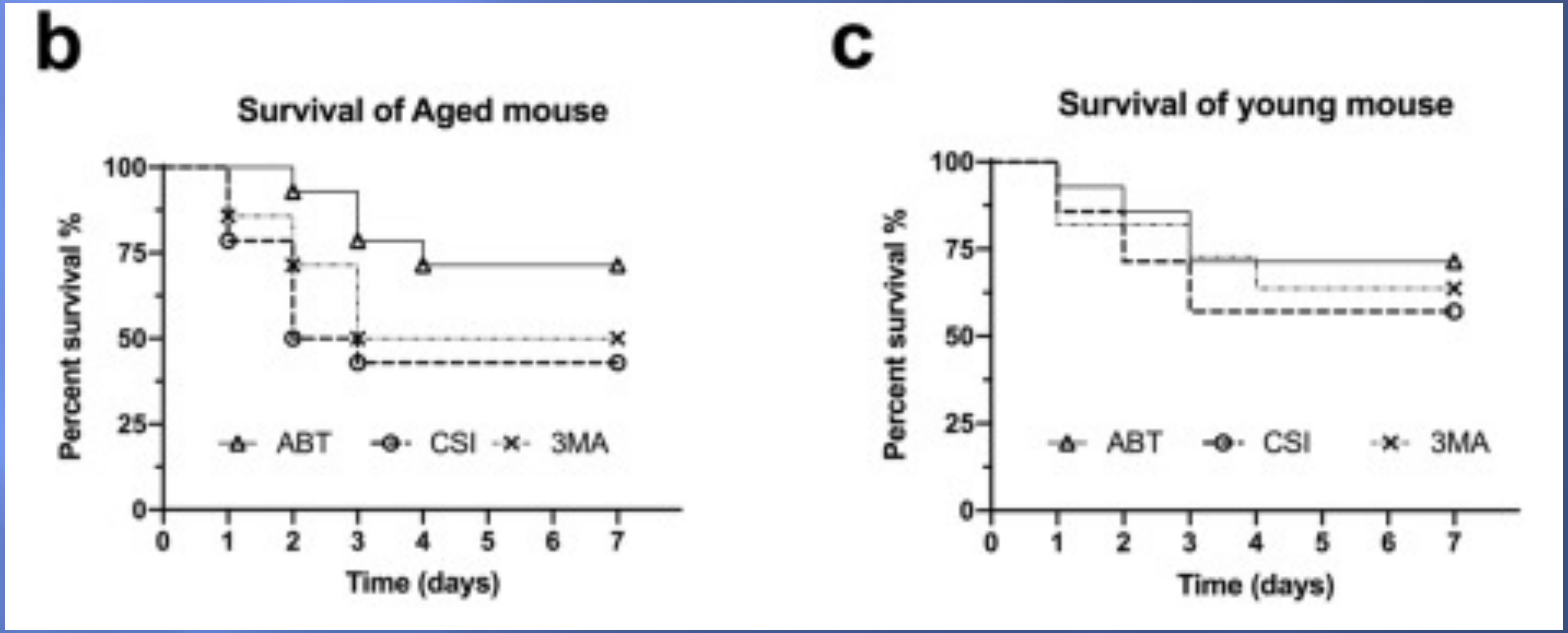
oleic acid

Bonkowski, M. S., & Sinclair, D. A. (2016). Slowing ageing by design: the rise of NAD+ and sirtuin-activating compounds. *Nature reviews Molecular cell biology*, *17*(11), 679-690.



remove senescent cells

"The results showed ABT-263 (helps kill senescent cells) treatment improved the survival rate of sepsis in the aged mouse which related to autophagy, while blocking the autophagy can eliminate this effect."



Zhang, Y., Tang, L., Lu, J., Xu, L., Cheng, B., & Xiong, J. (2020). Senolytic compound ABT-263 improved senescent macrophages function by inducing autophagy and protected the aged mouse from sepsis.

reverse aspects or the "signaling" of aging

Astaxanthin

Curcumin

Morphine

Nordihydroguaiaretic acid (NDGA)

Rapamycin

Resveratrol

Sappanone A

Spermidine

Tambulin

Urolithins

Ursolic acid

Coenzyme Q10

vitamins A and E

quercetin

caffeic acid

rosmarinic acid

genistein

EGCG

Protandim

chicoric acid

tyrosol

fisetin

TA-65

procyanidins

Alpha-ketoglutarate and Oxaloacetic acid

Dehydroepiandrosterone (DHEA) and 17α-estradiol

S-Linolenoyl glutathione

Melatonin …..

Liu, J. K. (2022). Antiaging agents: safe interventions to slow aging and healthy life span extension. *Natural Products and Bioprospecting*, *12*(1), 1-36.

Summary

Yeast model of aging and key genes

Human aging: healthspan vs lifespan

Maintaining chromatin structure and defending from genomic instability are the keys to health span

Learning lots more about the genes involved (Sirloins)

Potential key source of genetic instability is LINE-1

Lots of potential pharmaceuticals/supplements to aid

<u>Your humble presenter</u>

kindergarten 4 years ago current