

Recent Advances in Understanding Aging

Science Circle
November 26th 2022

Stephen Gasior, Ph.D.
a.k.a. Stephen Xootfly
Researcher

Company that has nothing to do with this talk
Former University Biology Instructor

Neurological impairment

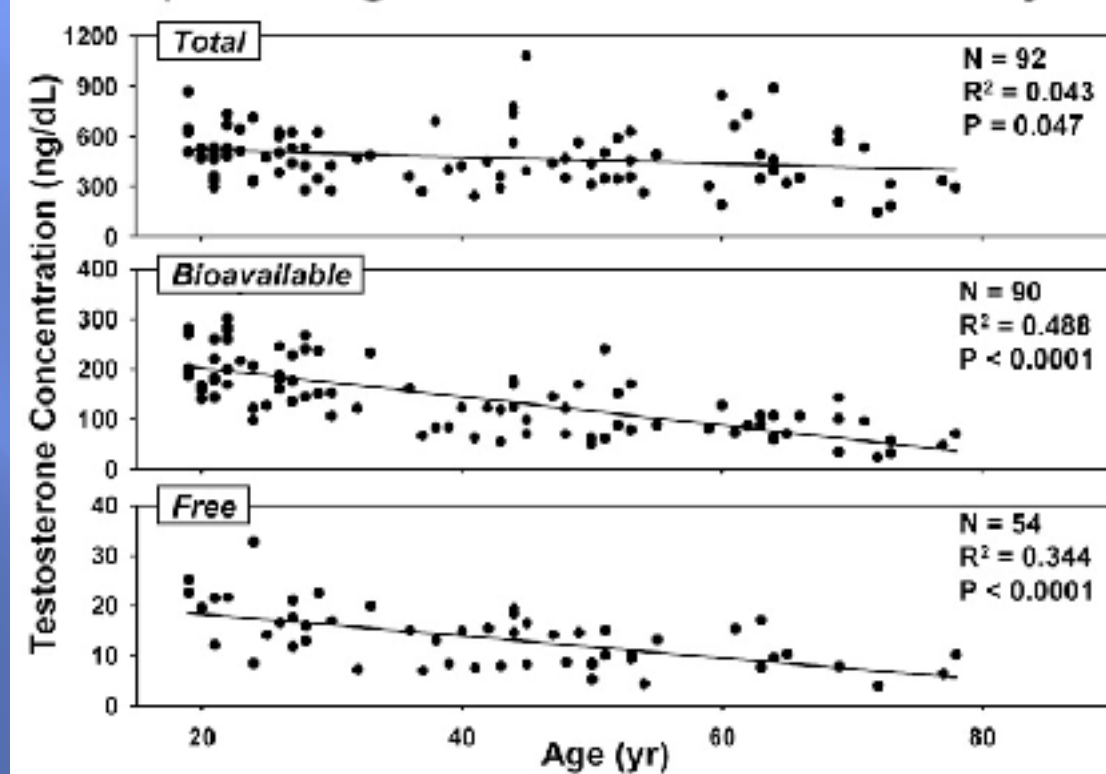


Grey hair

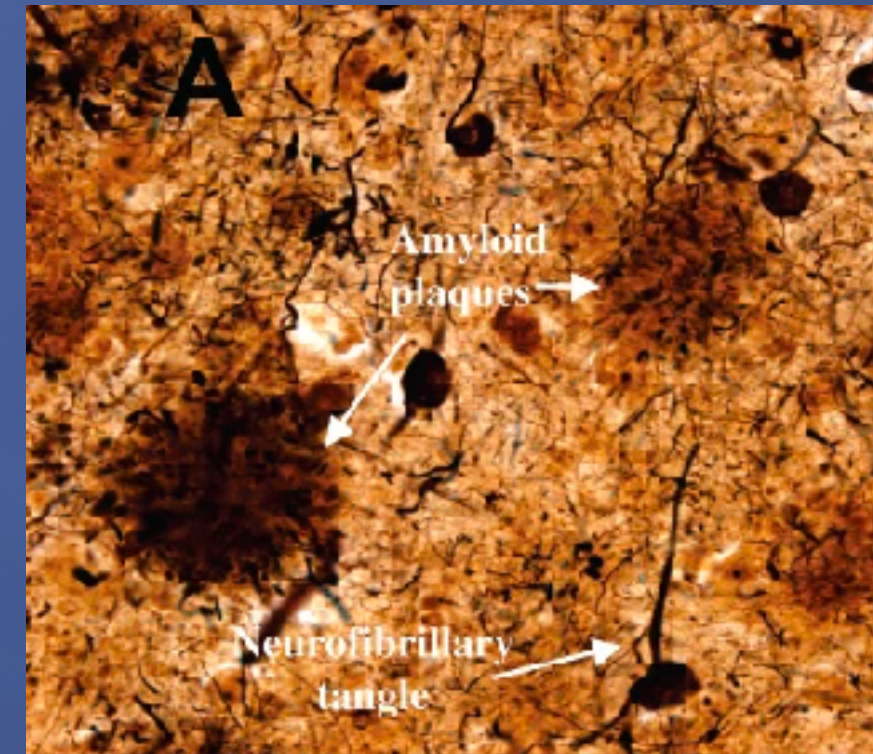
https://www.onhealth.com/content/1/gray_hair_facts_beauty

Hormone levels

Impact of Age on Testosterone Availability



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



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

Disease susceptibility

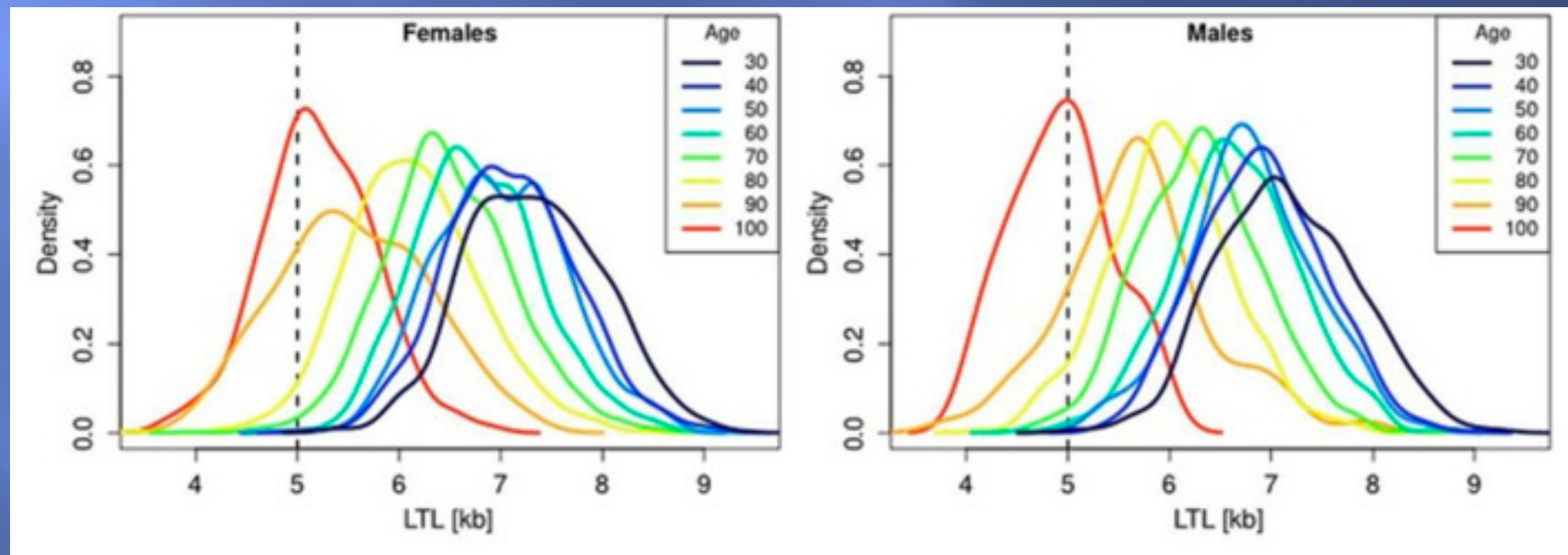
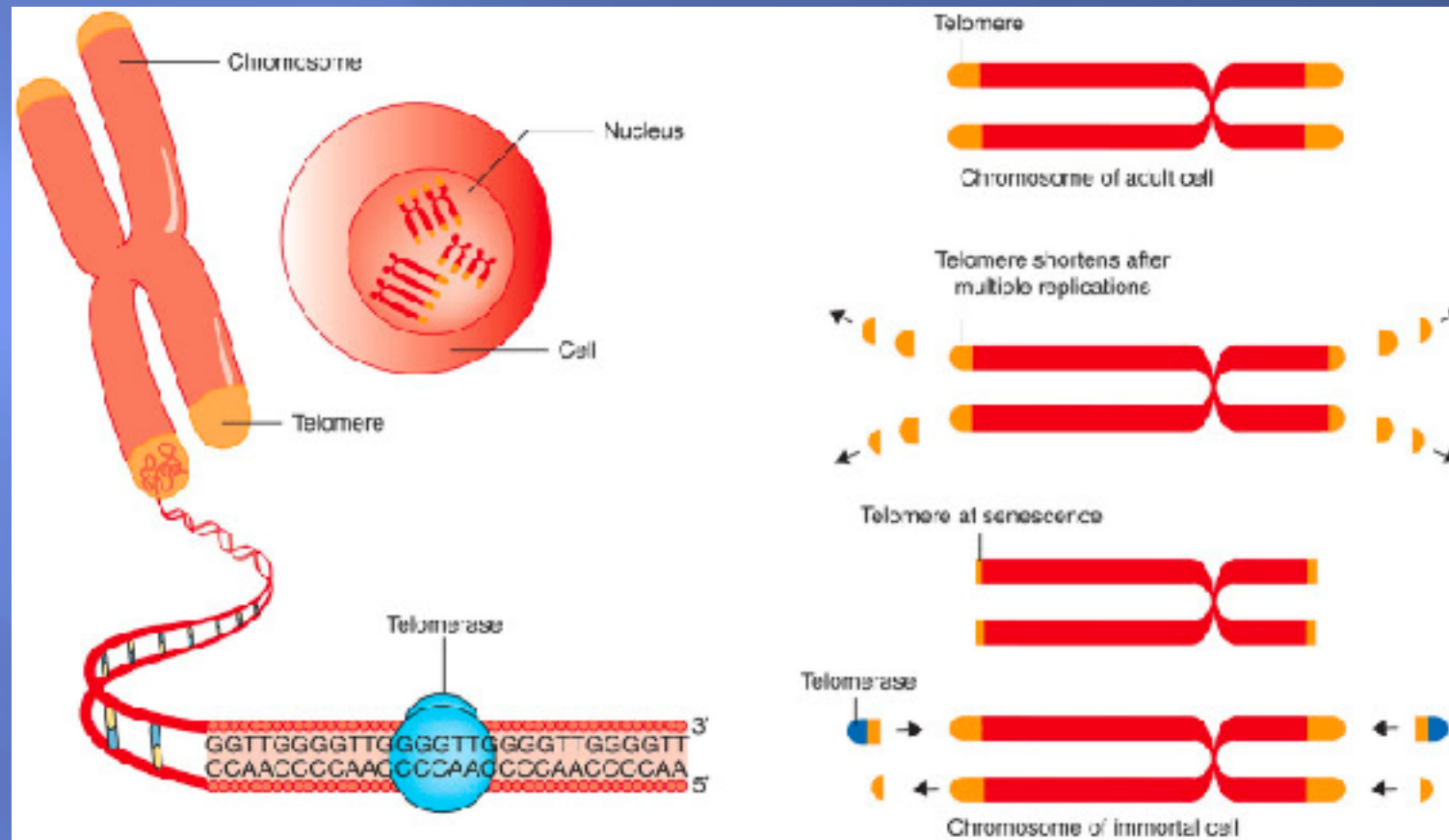
RATES OF HOSPITALIZATION FOR COVID-19 INCREASE WITH AGE

March 1-30, 2020



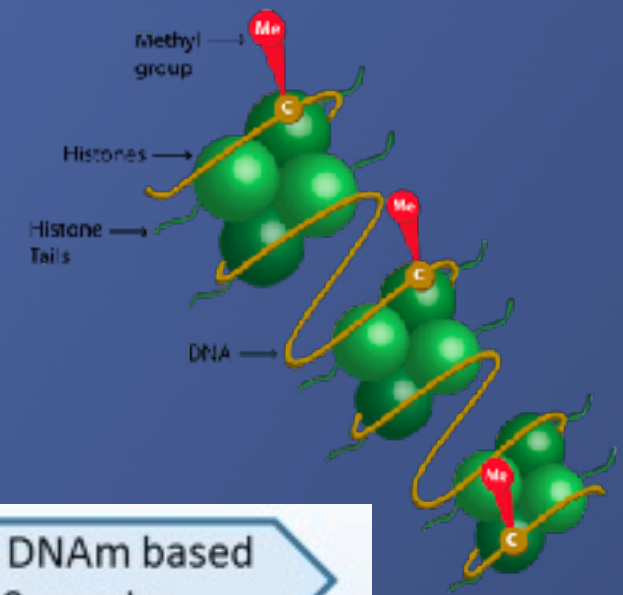
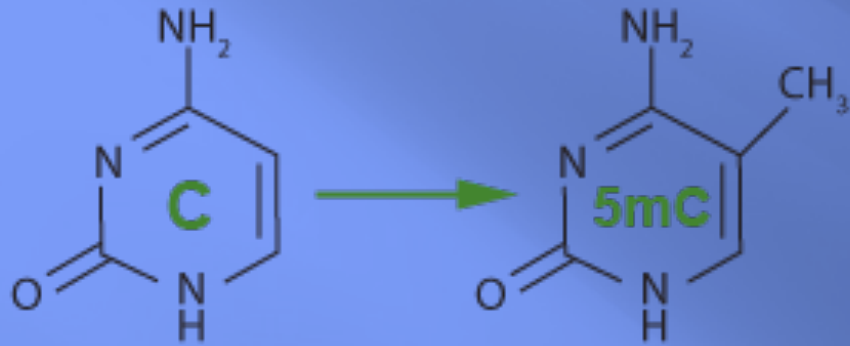
Everyone, especially older adults, should: ✓ stay home
✓ use face coverings in public settings ✓ wash hands frequently

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



Stage 1: Develop DNAm based surrogates for plasma proteins & smoking pack years

Stage 2: Regress time-to-death on DNAm based biomarkers (from step1), age & gender

1. Candidate biomarker

- Immunoassay measured 88 plasma proteins
- Smoking pack year

2. Conduct ElastNet regression to establish DNAm based surrogates

- Use the FHS training data.
- Regress each candidate biomarker (dependent variable) on 485k CpGs, chronological age and gender.

3. Test process

Validate the accuracy of the DNAm based surrogates in the FHS test data.

4. Results

A total of 12 DNAm based biomarkers correlate with their target biomarkers at $r > 0.35$ in both training and test datasets (e.g. DNAm ADM, DNAm B2M, DNAm GDF-15, etc.).

Resulting ElasticNet Cox model



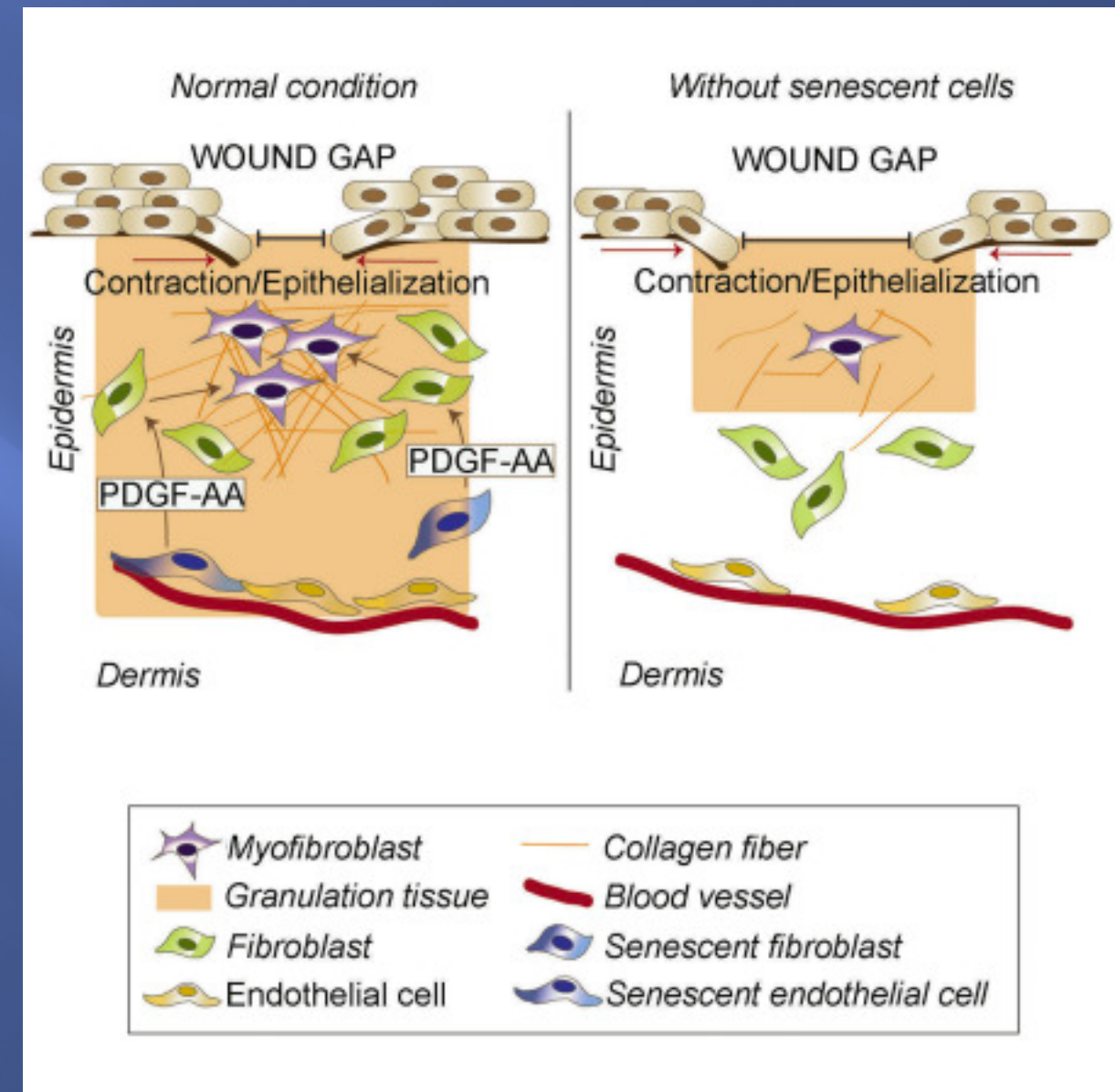
$$\text{DNAm GrimAge} = -50.28483 + 8.3268 * X^T \beta$$

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.

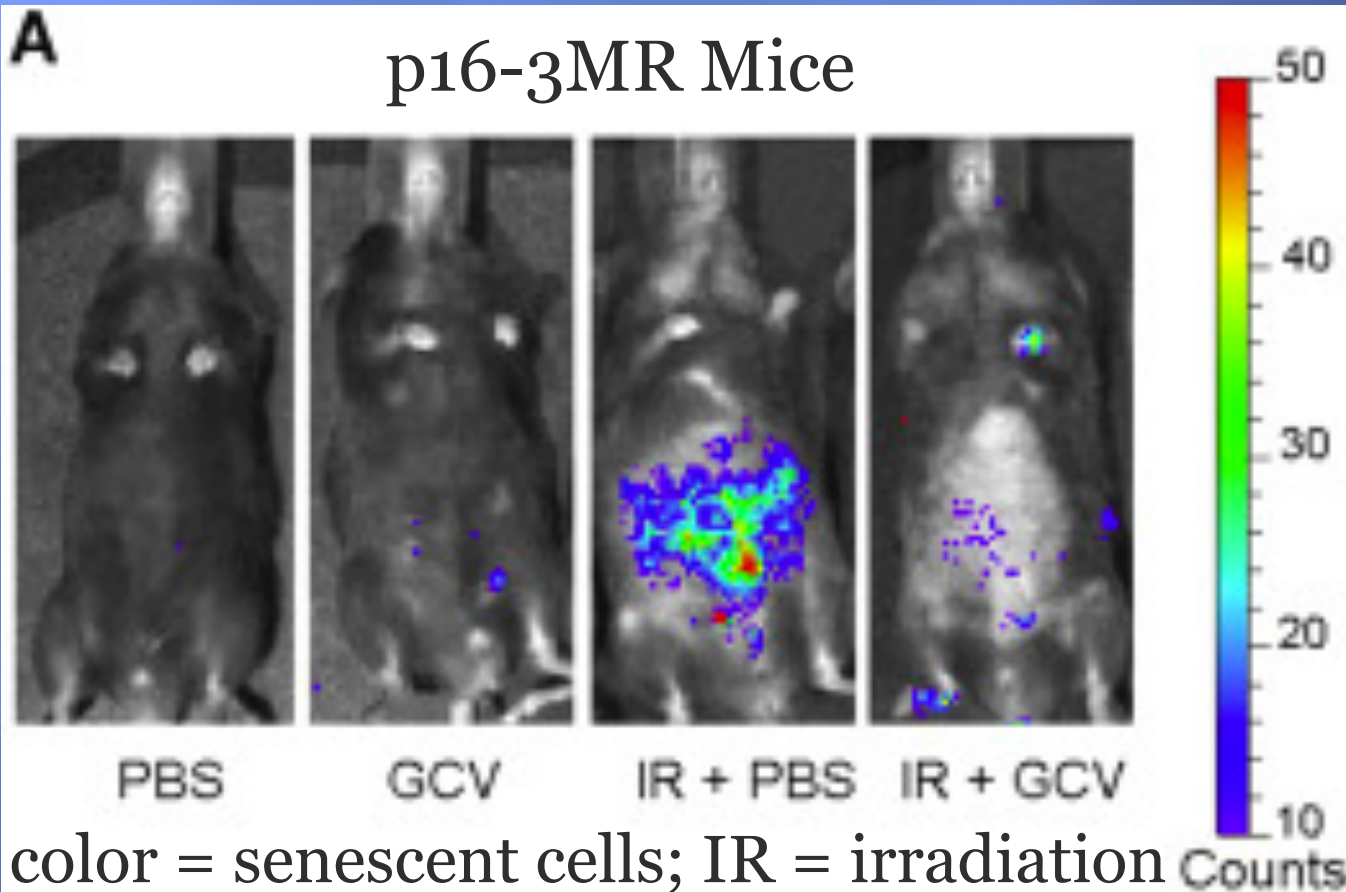


Senescence

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



p16-3MR Mice

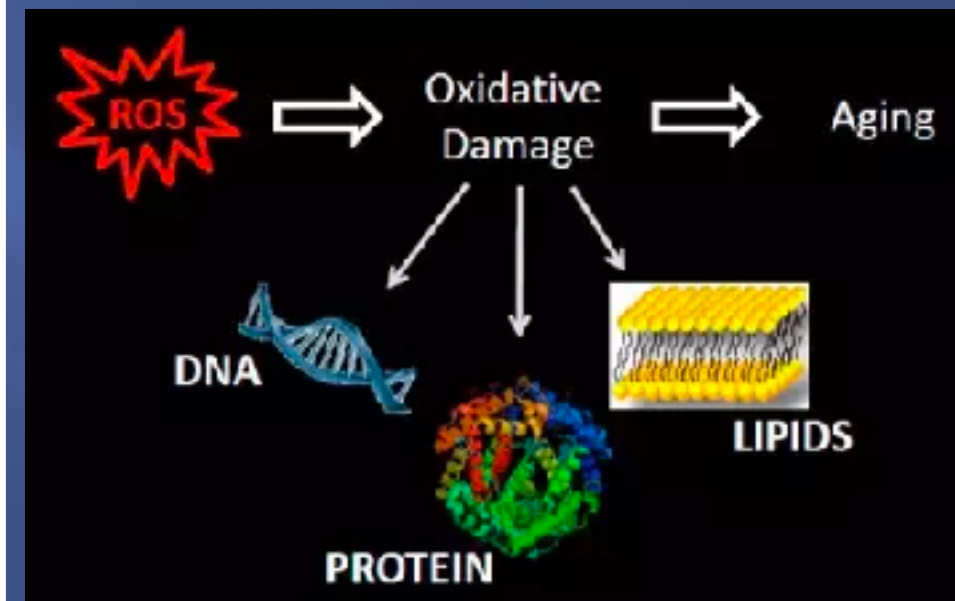
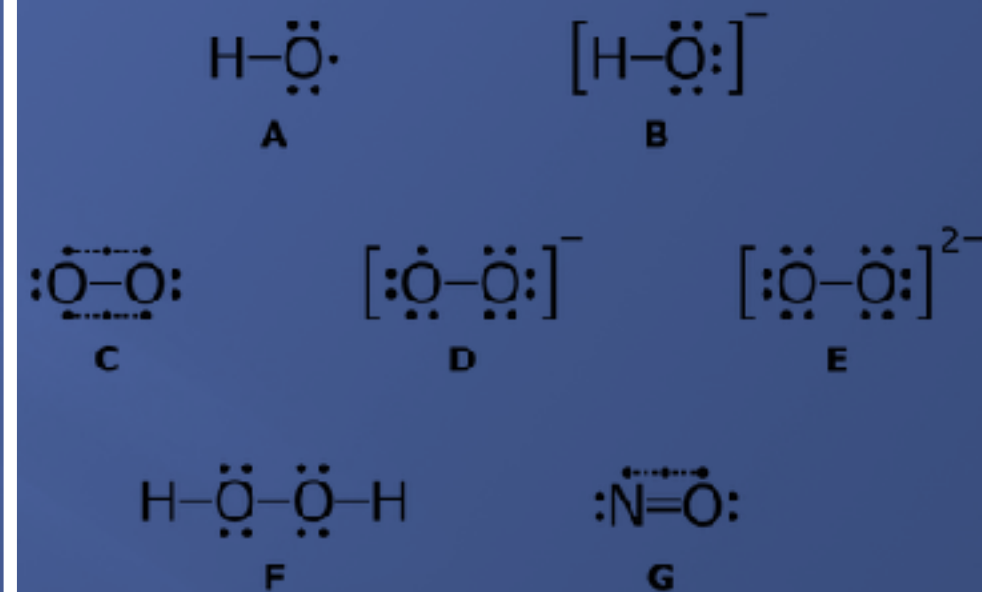


Demaria, M., Ohtani, N., Youssef, S. A., Rodier, F., Toussaint, W., Mitchell, J. R., ... & Campisi, J. (2014). An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. *Developmental cell*, 31(6), 722-733.

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.”



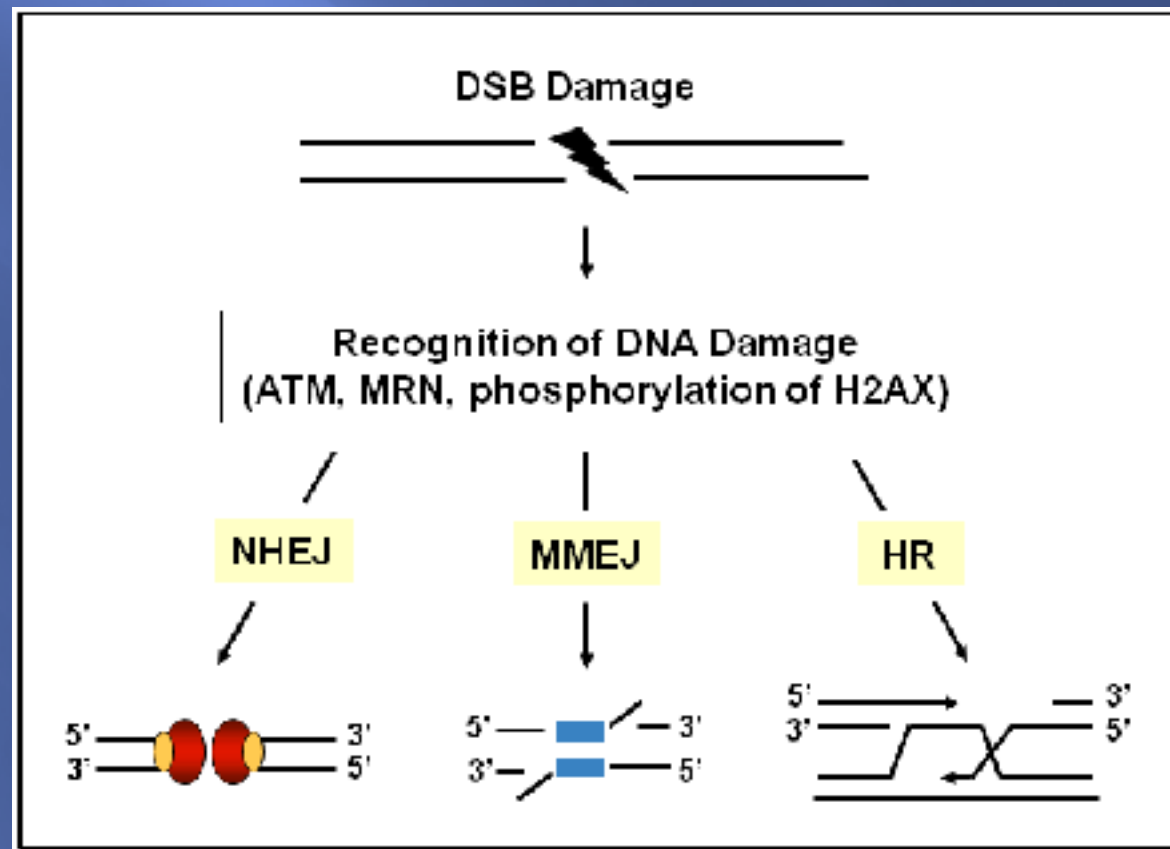
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Progeria

Werner Syndrome
1904
RECQL2/SGS1

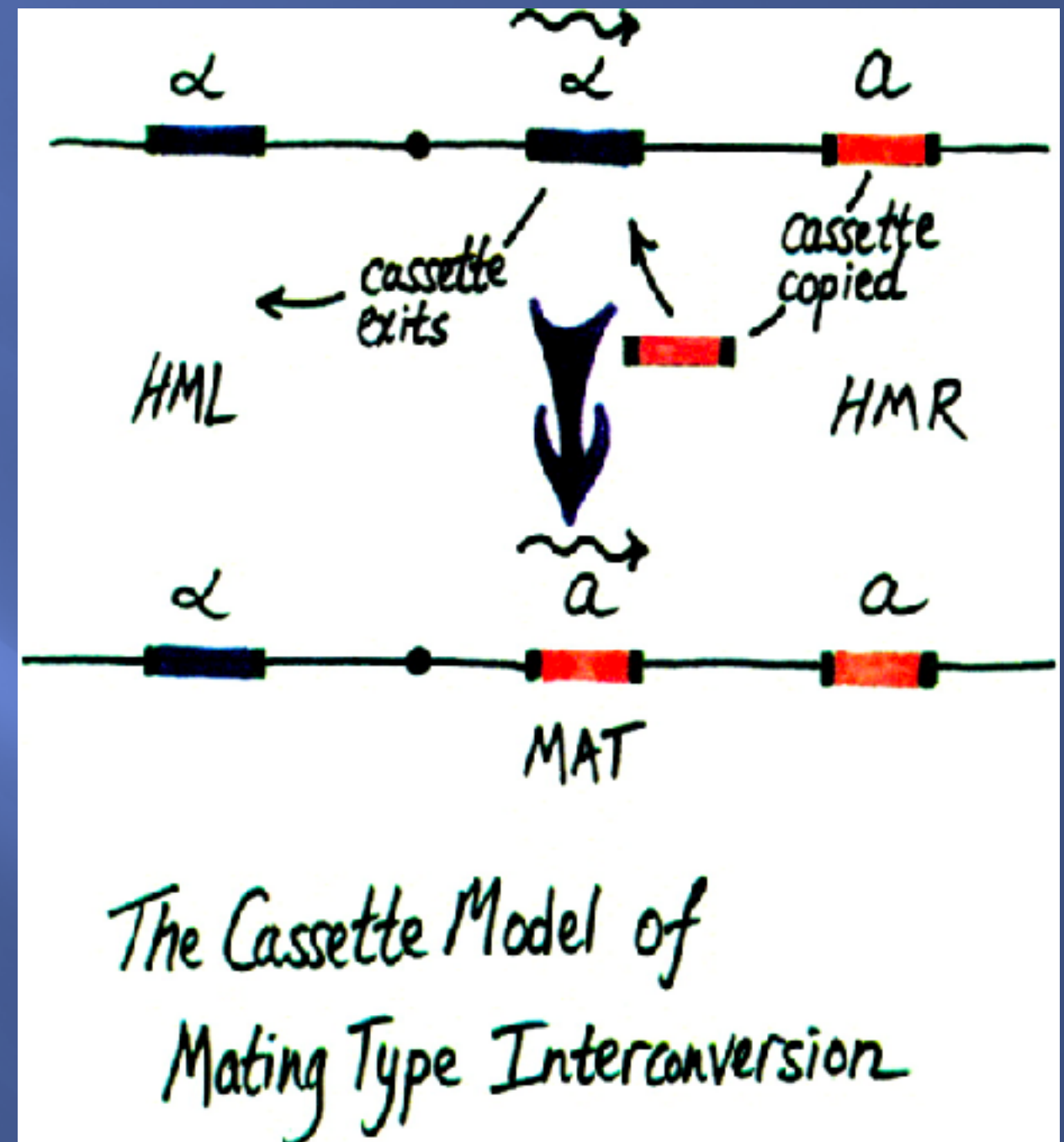
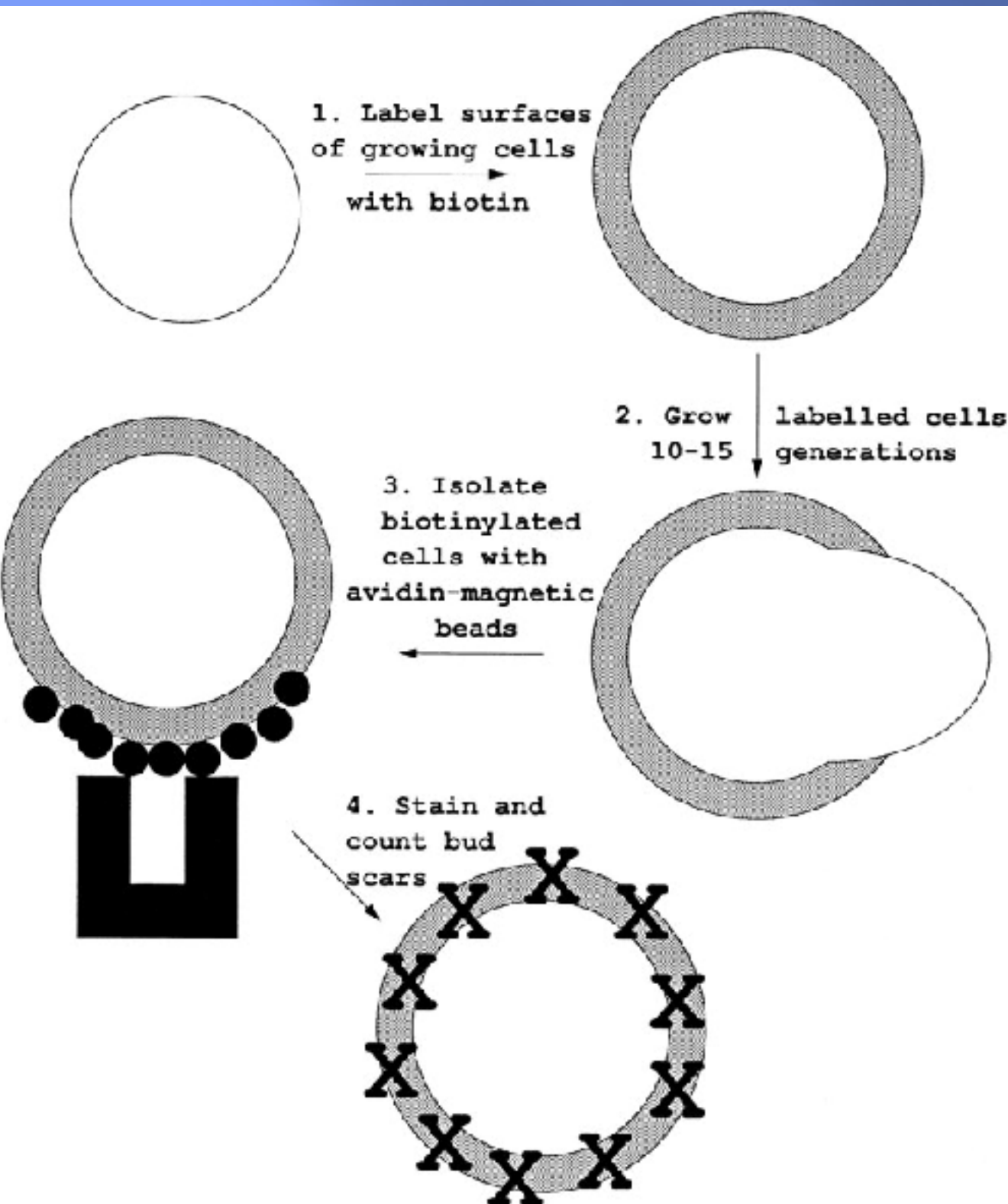


Bloom
Fanconi-Anemia
Cockayne
Rothmund-Thomson
Nijmegen breakage
ataxia telangiectasia



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

yeast “aging”

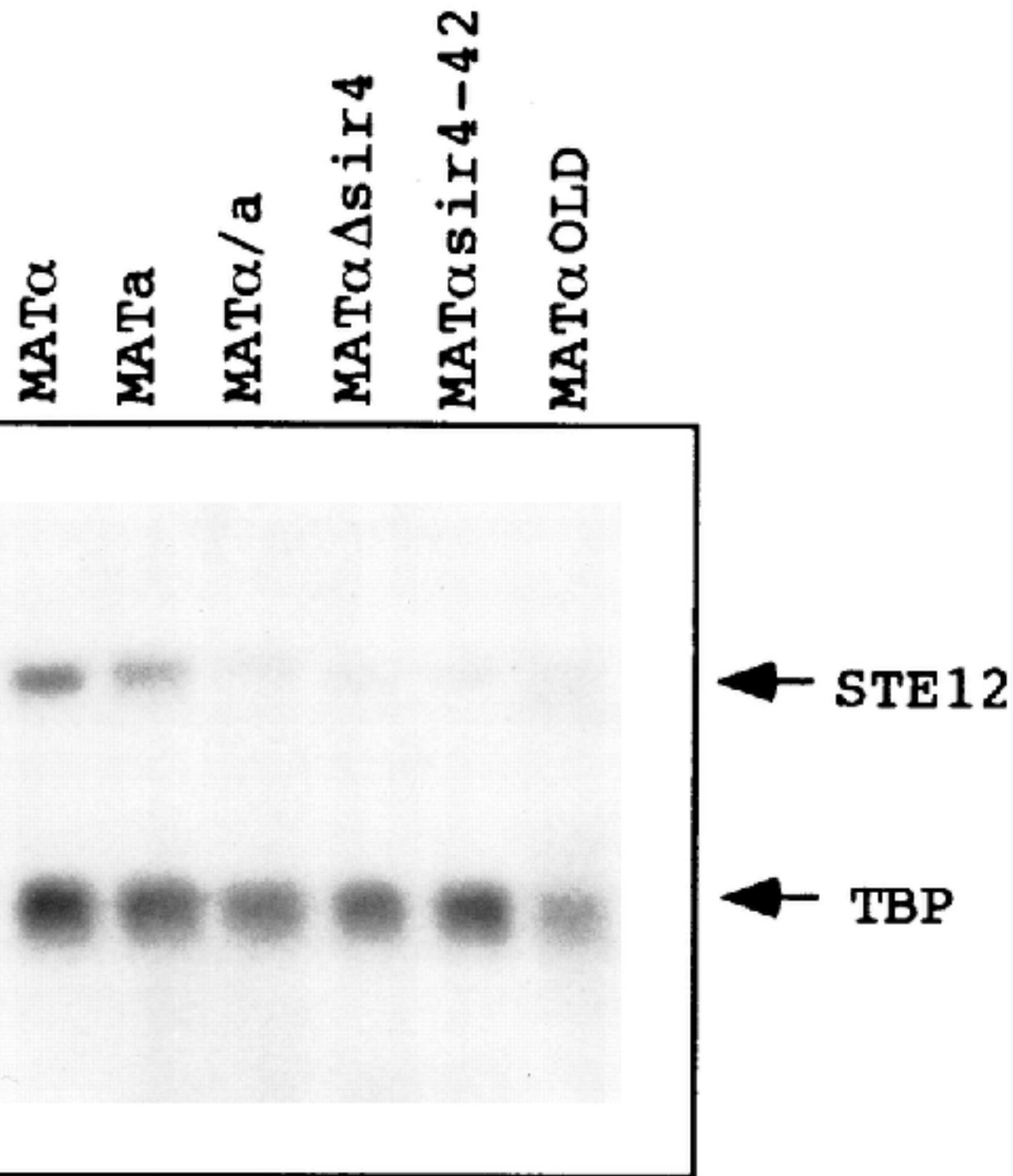


HML and HMR have to be silent, or else haploid cell becomes “gender confused”

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”

B



STE12 is turned OFF in diploids by design

being OFF in haploid (MAT α) 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”

B

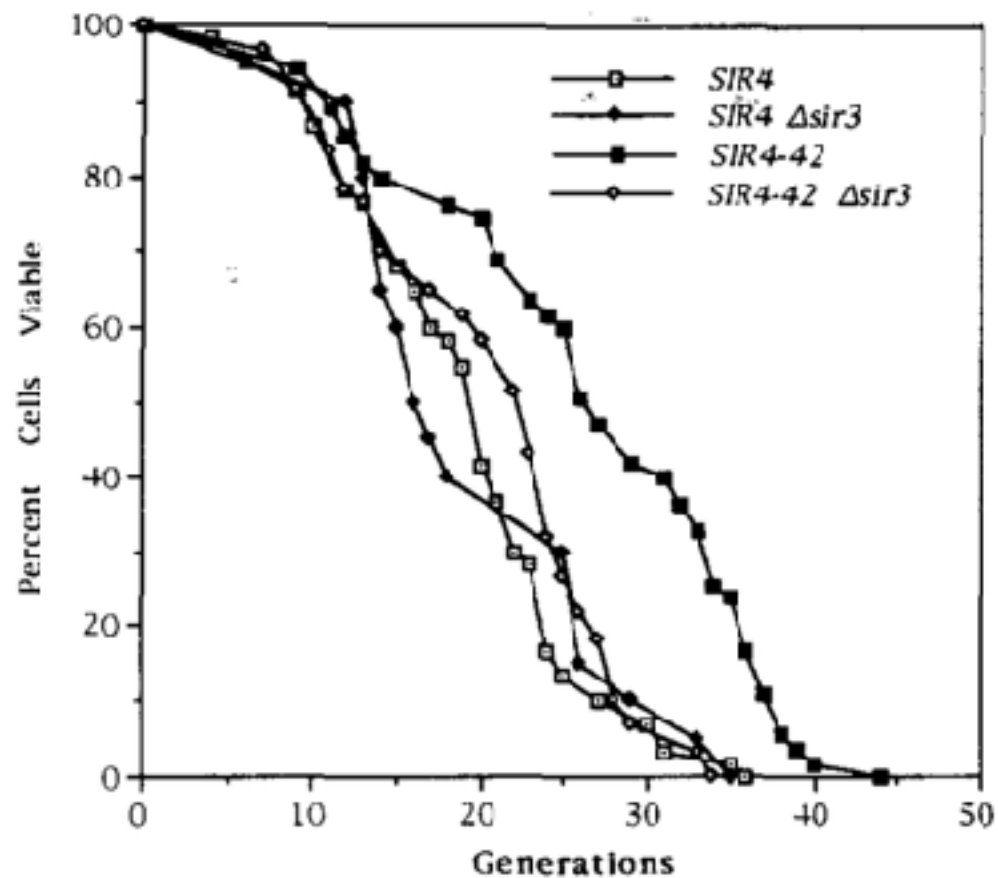


Figure 5. The Increased Longevity Conferred by *sir4-42* Requires *SIR3* but Not *SIR1*

Specific Sir4 (Silent Information Regulator) mutant enhances yeast longevity

showed elsewhere the *sir4*-deletion does not

is part of the SIR2/3/4 complex

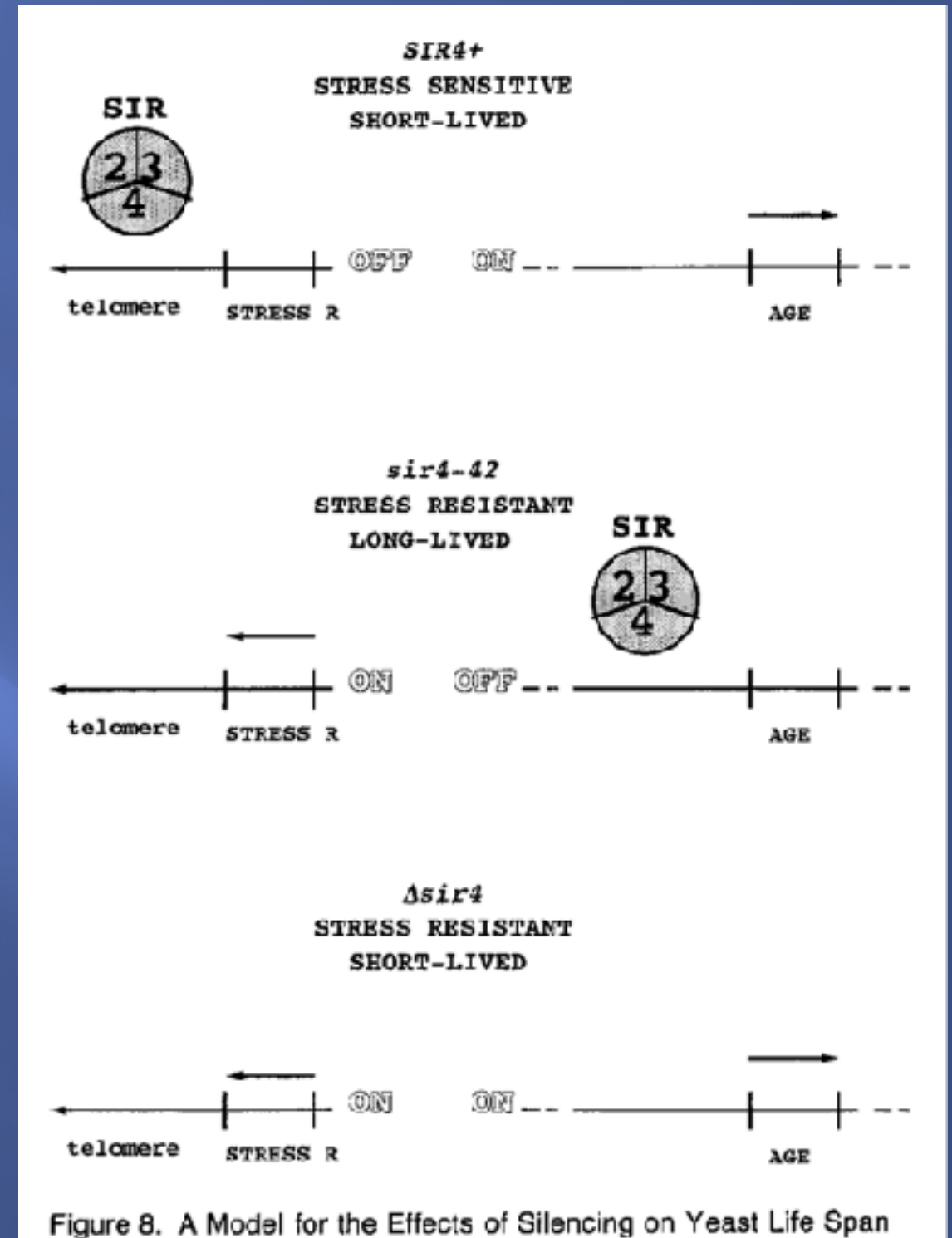


Figure 8. A Model for the Effects of Silencing on Yeast Life Span

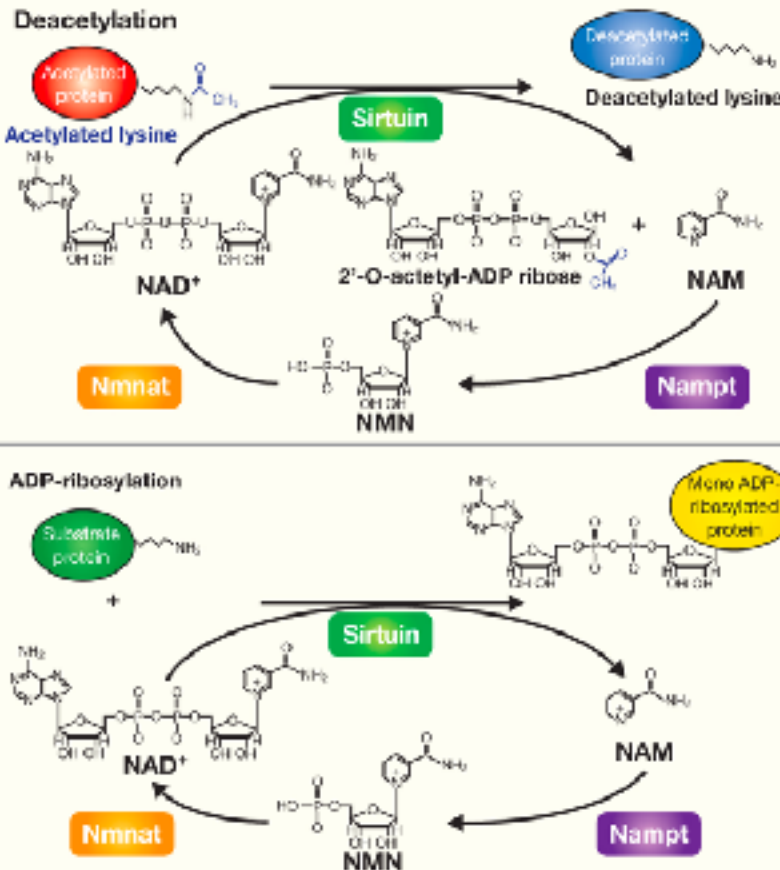
Sir4-mutant complex relocates and silences aging factor

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.

Sirtuins at a Glance

Takashi Nakagawa and Leonard Guarente

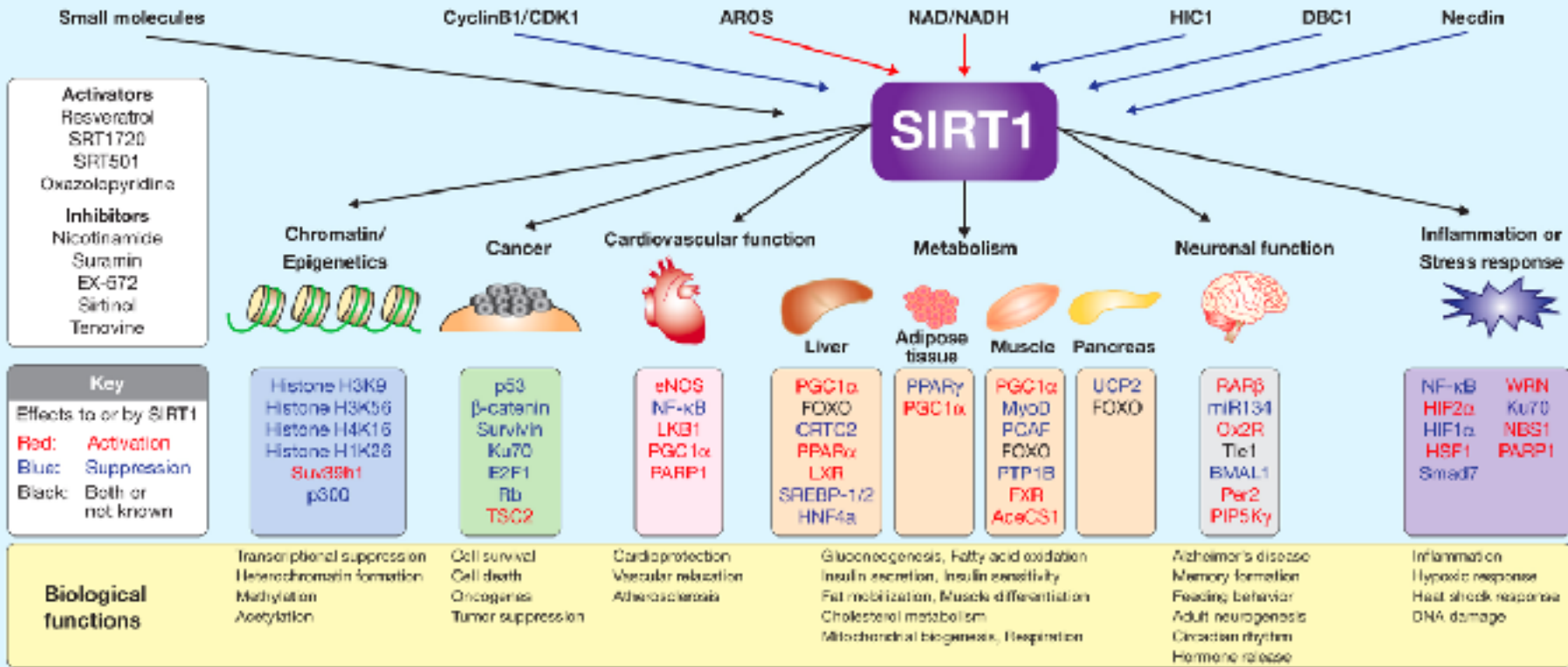
Enzymatic reaction of sirtuins



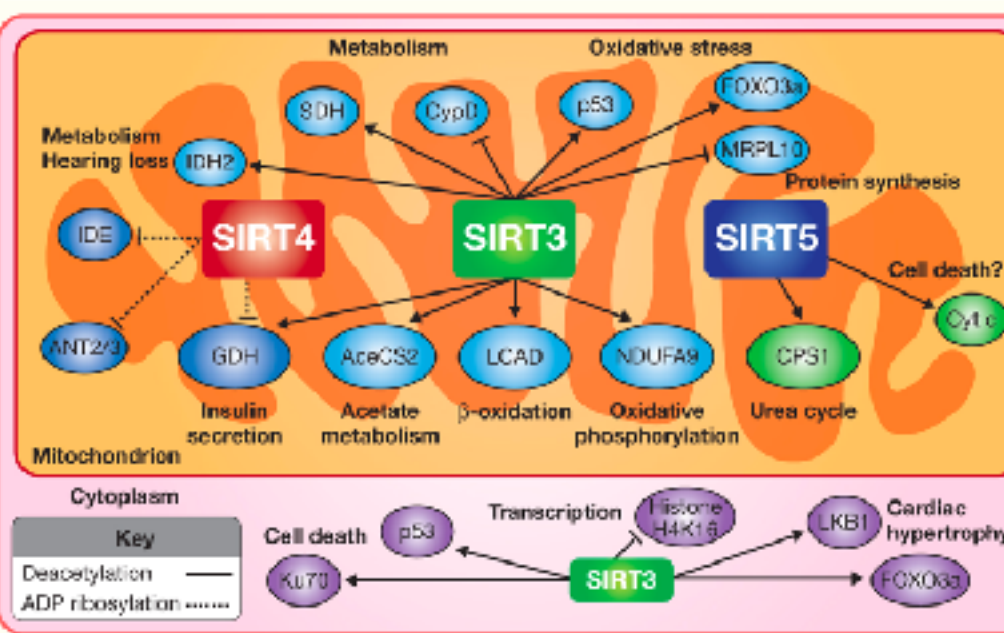
Phenotypes of sirtuin KO or Tg mice

SIRT1	KO (A/B)	Die right after birth (C57BL/6 background), some can survive postnatally (mixed background), shorter and similar in body size, closed eyelids, infertility, no adaptive feeding response to CR
	KO (Tad)	Memory deficit, no adaptive feeding response to CR, less serum IGF1
	KO (Lys)	Defect in circadian gene oscillation, develop hepatic steatosis and inflammation
	Tg (M/R)	Increased inflammation, glucose intolerance and insulin resistance induced by HFD
	Tg (M/R)	Protected against various metabolic disorders (fatty liver and type 2 diabetes) induced by HFD
	Tg (M/R)	Protected against age-related cancer, osteoporosis and glucose intolerance
	Tg (M/R)	Enhanced memory formation and feeding behavior, protected against Alzheimer's disease
	Tg (M/R)	Cardioprotection (myocardial hypertrophy), cardiac hypertrophy (high expression)
	Tg (M/R)	Protected against skin cancer
	Tg (M/R)	Protected against acute renal failure
SIRT2	KO (A/B)	Develop undigested normally
SIRT3	KO (A/B)	Defect in fatty acid oxidation, cancer prone, theirocytes exhibit developmental arrest after NF, accumulation of hyperacetylated mitochondrial proteins, reduced respiration and ATP levels
	Tg (M/R)	Protected against cardiac hypertrophy
SIRT4	KO (A/B)	Hypertrophic heart, sensitive to SGLS and AROS
SIRT5	KO (A/B)	Defect in urea cycle, hyperammonemia after fasting
	Tg (M/R)	Increased urea cycle activity, increased urea production
SIRT6	KO (A/B)	Die around 4 weeks showing premature aging phenotype (osteoporosis, loss of subcutaneous fat, hyperglycemia, increased glucose uptake, genomic instability)
	KO (Lys)	Increased glycolysis, triglyceride synthesis, reduced β -oxidation and fatty liver formation
	Tg (M/R)	Protected against metabolic disorder induced by HFD
SIRT7	KO (A/B)	Die around 1 year showing premature aging phenotype (osteoporosis, loss of subcutaneous fat, degenerative cardiac hypertrophy), increased apoptosis

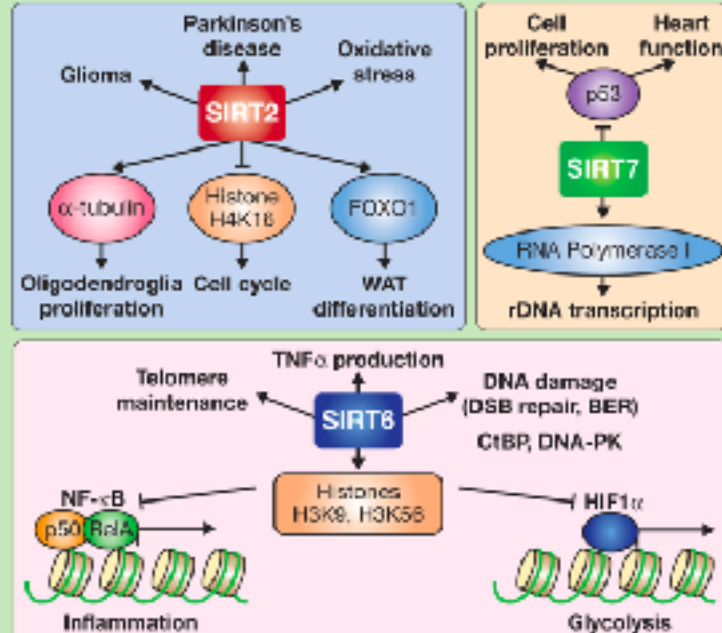
Substrates and biological functions of SIRT1



Mitochondrial sirtuins



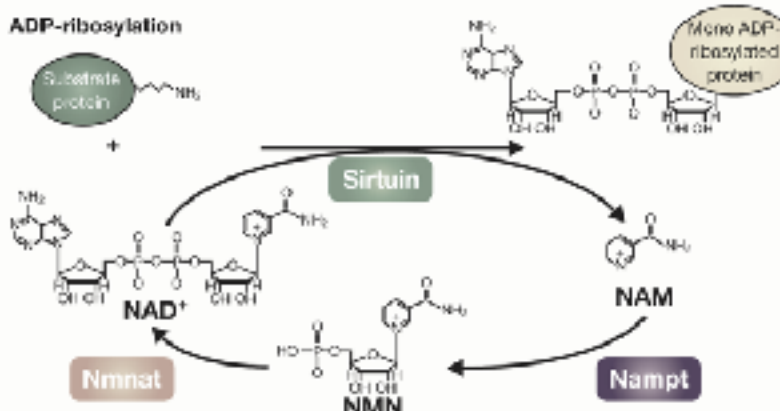
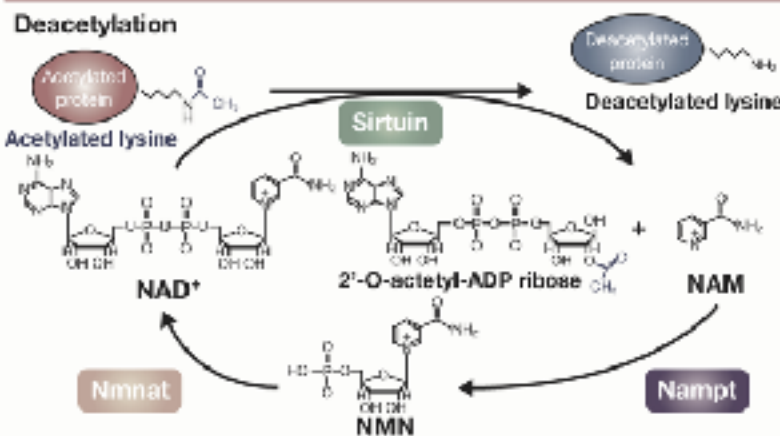
Other sirtuins



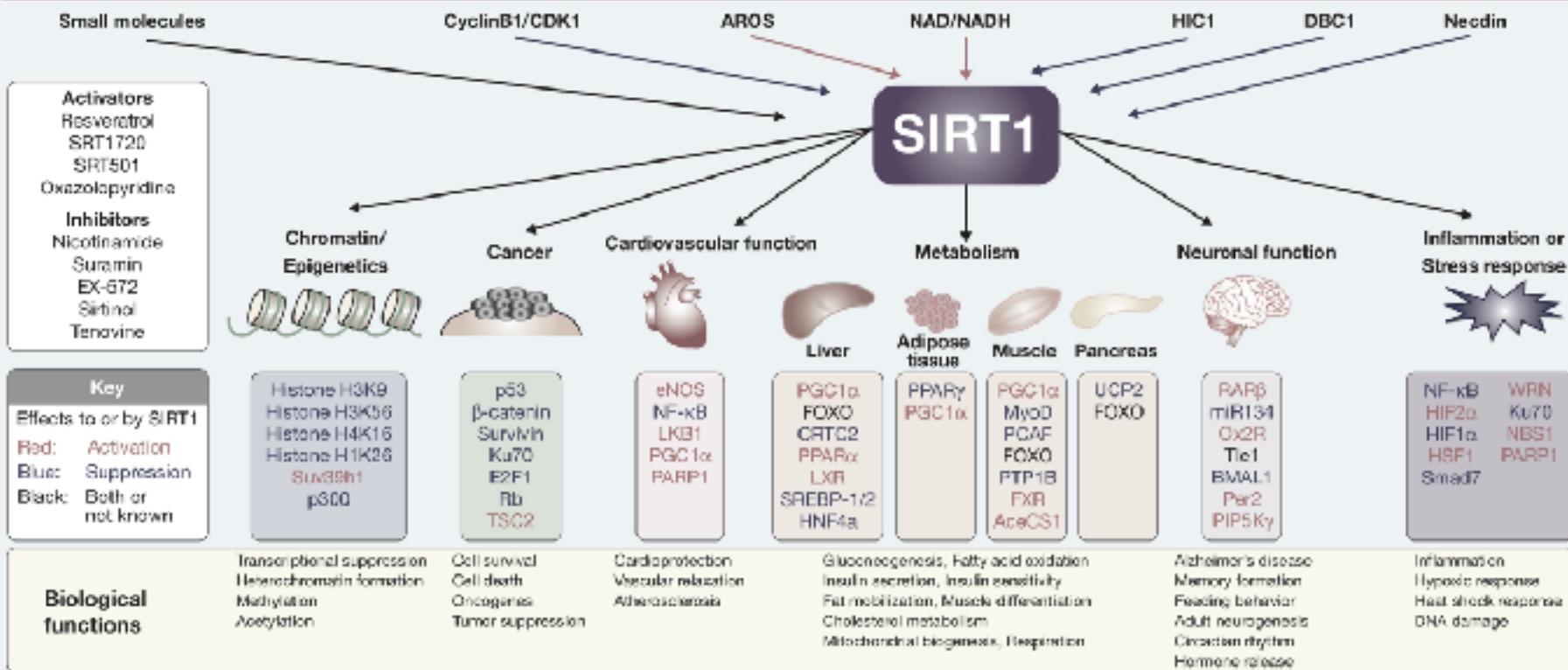
Sirtuins at a Glance

Takashi Nakagawa and Leonard Guarente

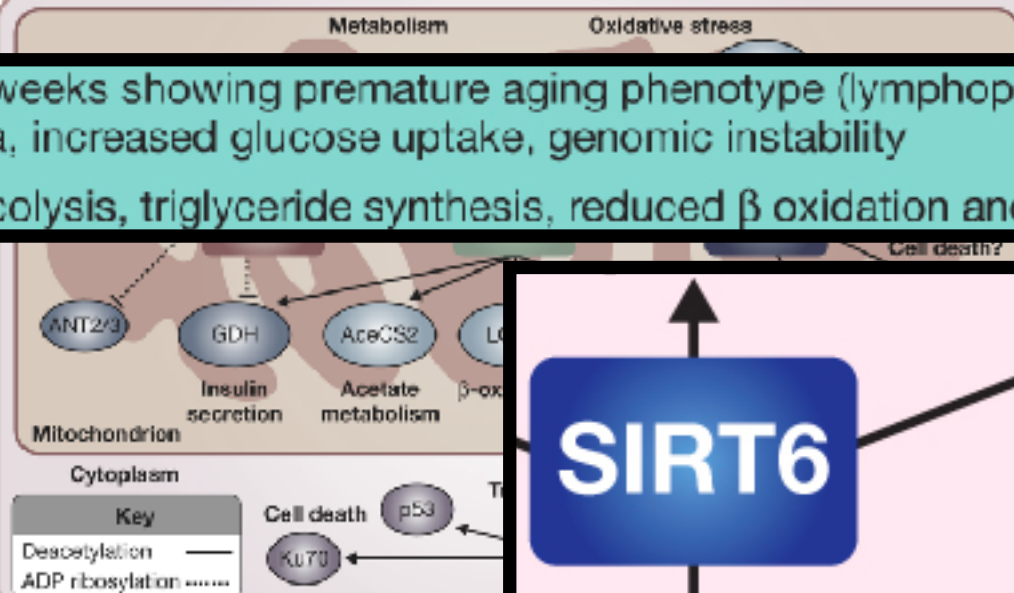
Enzymatic reaction of sirtuins



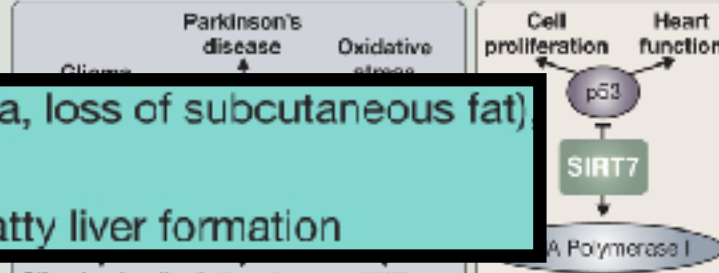
Substrates and biological functions of SIRT1



Mitochondrial sirtuins



Other sirtuins



SIRT6 KO (WB) Die around 4 weeks showing premature aging phenotype (lymphopenia, loss of subcutaneous fat), hyperglycemia, increased glucose uptake, genomic instability

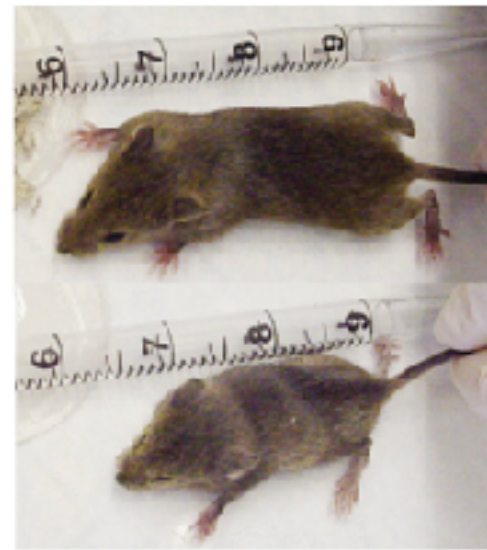
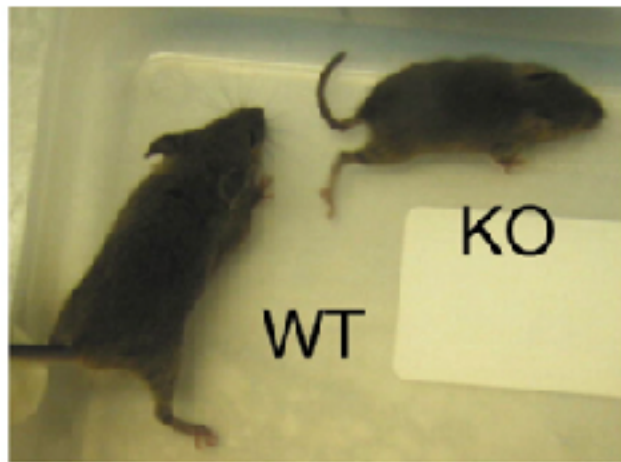
SIRT6 KO (Liver) Increased glycolysis, triglyceride synthesis, reduced β oxidation and fatty liver formation

Tg (Sirt1)	Enhanced memory formation and feeding behavior, protected against Alzheimer's disease
Tg (Sirt6)	Cardiovascular (high expression), cardiac hypertrophy (high expression)
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SIRT3 KO (WB)	Defect in fatty acid oxidation, cancer prone, thalycemia, embryonic lethality after NF, accumulation of hyperacetylated mitochondrial proteins, reduced respiration and ATP levels
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SIRT4 KO (WB)	Hypertension, sensitive to Sirt6 and AROS
SIRT5 KO (WB)	Defect in urea cycle, hyperammonemia after fasting
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Tg (Sirt6)	Protected against metabolic disorder induced by HFD
SIRT7 KO (WB)	Die around 1 year showing premature aging phenotype (lymphopenia, loss of subcutaneous fat, degenerative cardiac hypertrophy, increased apoptosis)



life without SIRT6

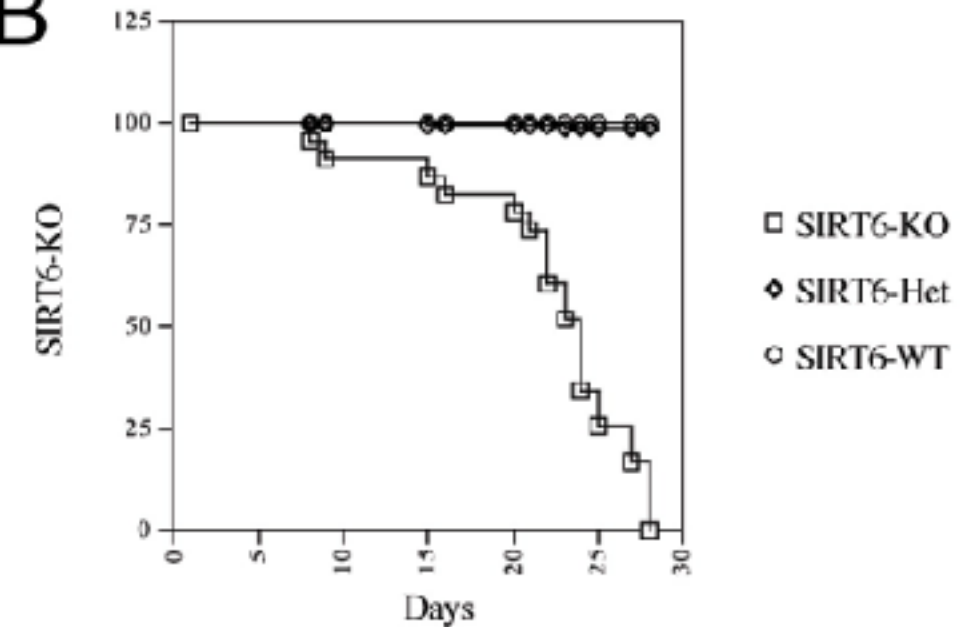
A



WT

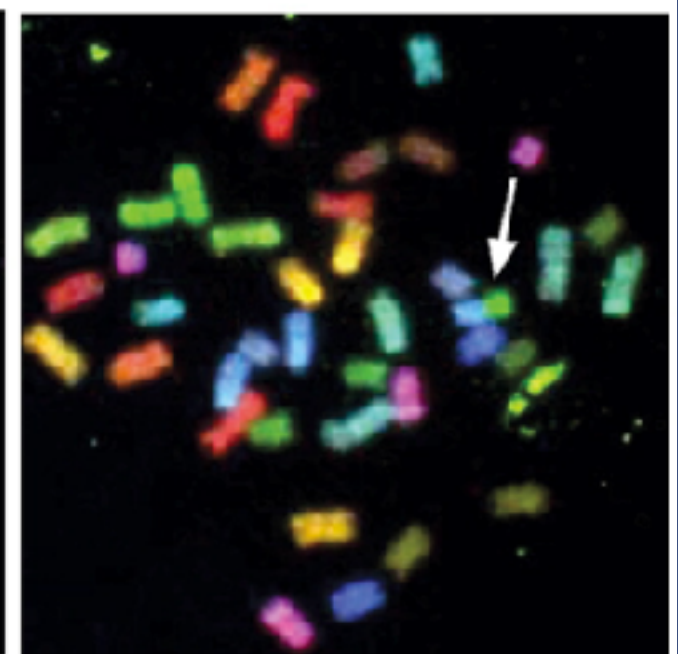
KO

B



WT

KO

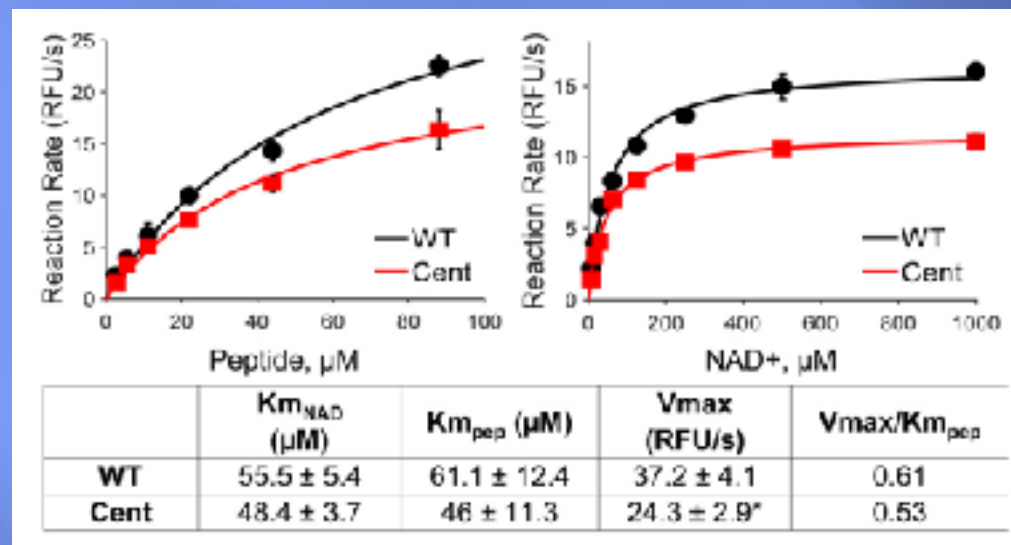


quick mention: SIRT6 overexpression mice live longer and healthier

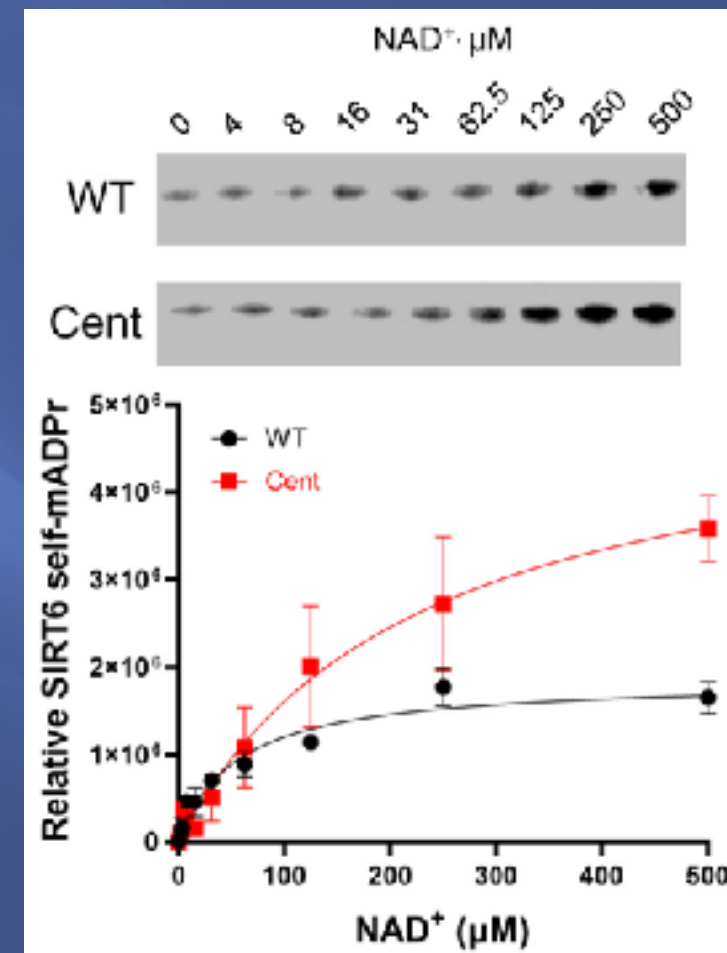
Mostoslavsky, R., Chua, K. F., Lombard, D. B., Pang, W. W., Fischer, M. R., Gellon, L., ... & Alt, F. W. (2006). Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. *Cell*, 124(2), 315-329.

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).”



reduced deacetylation activity

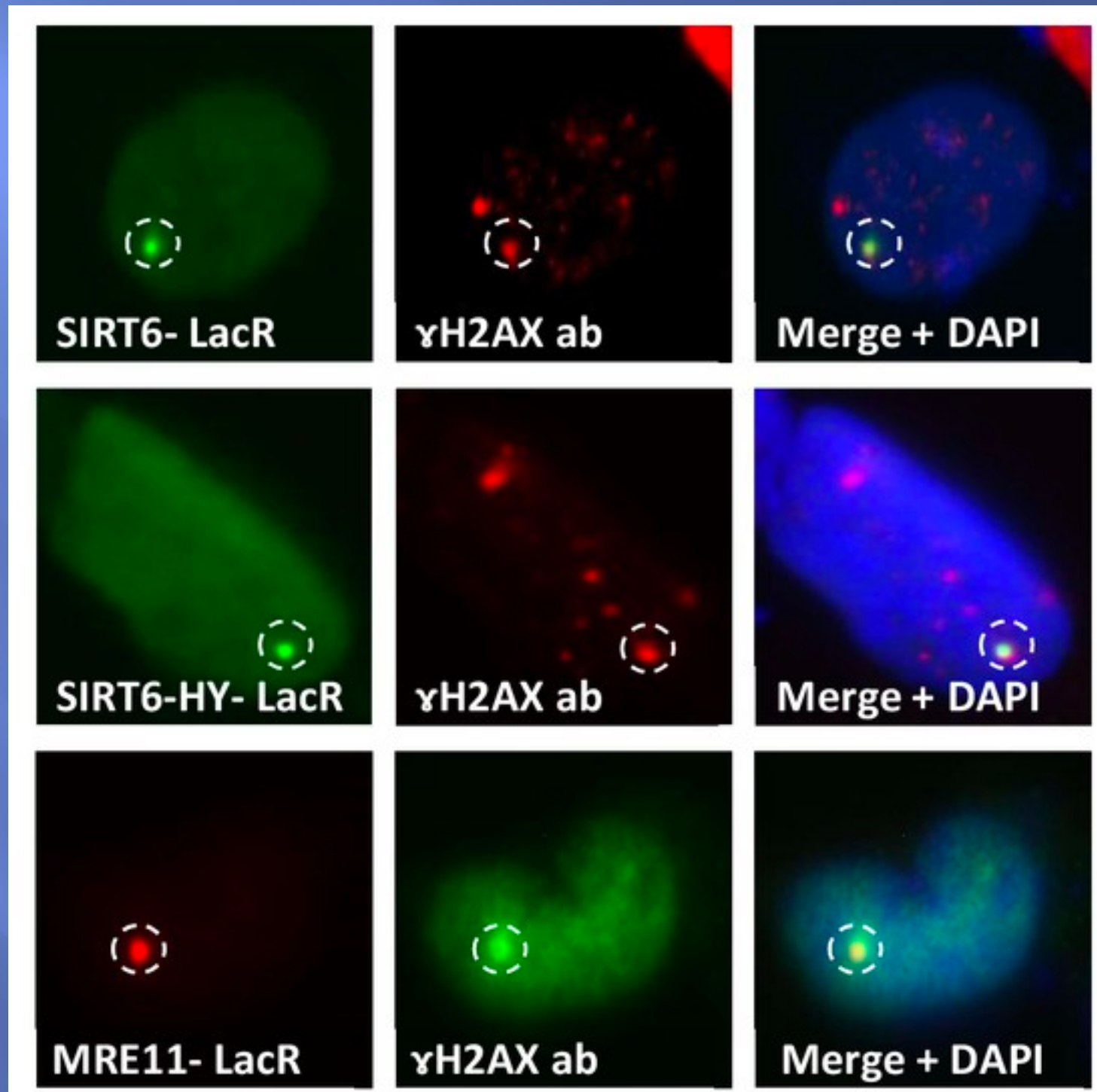


enhanced mono-ADP ribosylation (mADPr) activity

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.

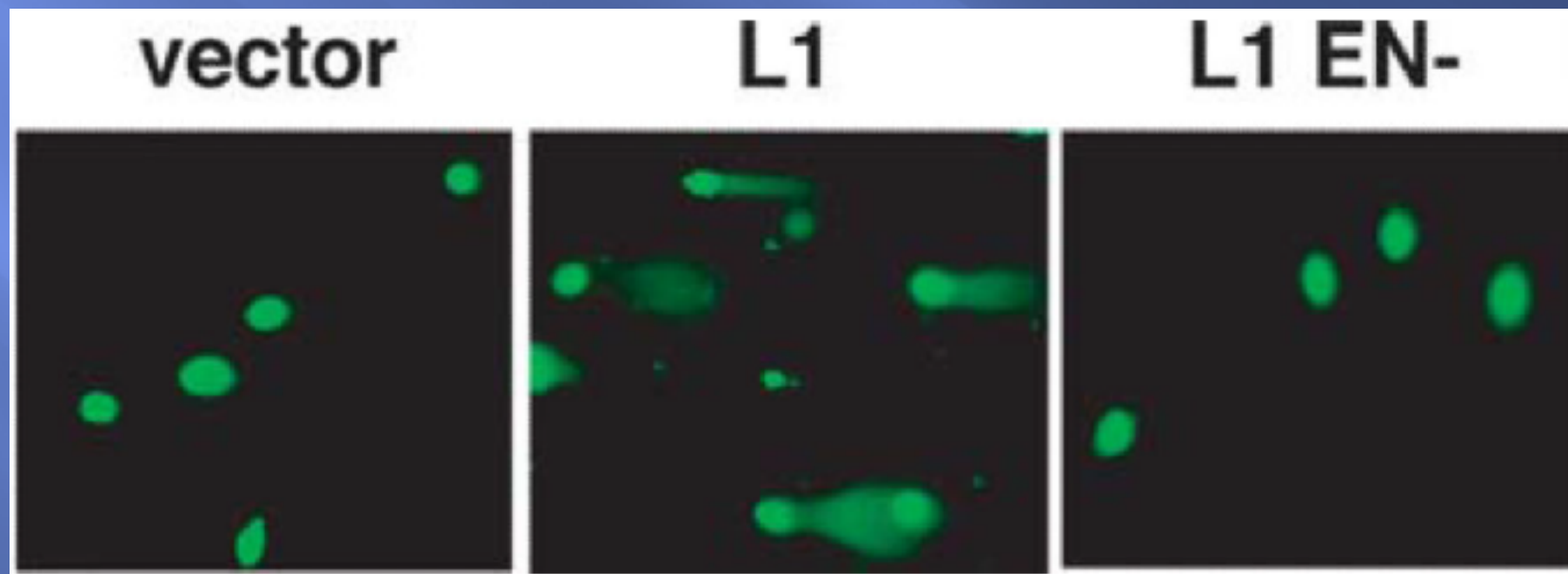
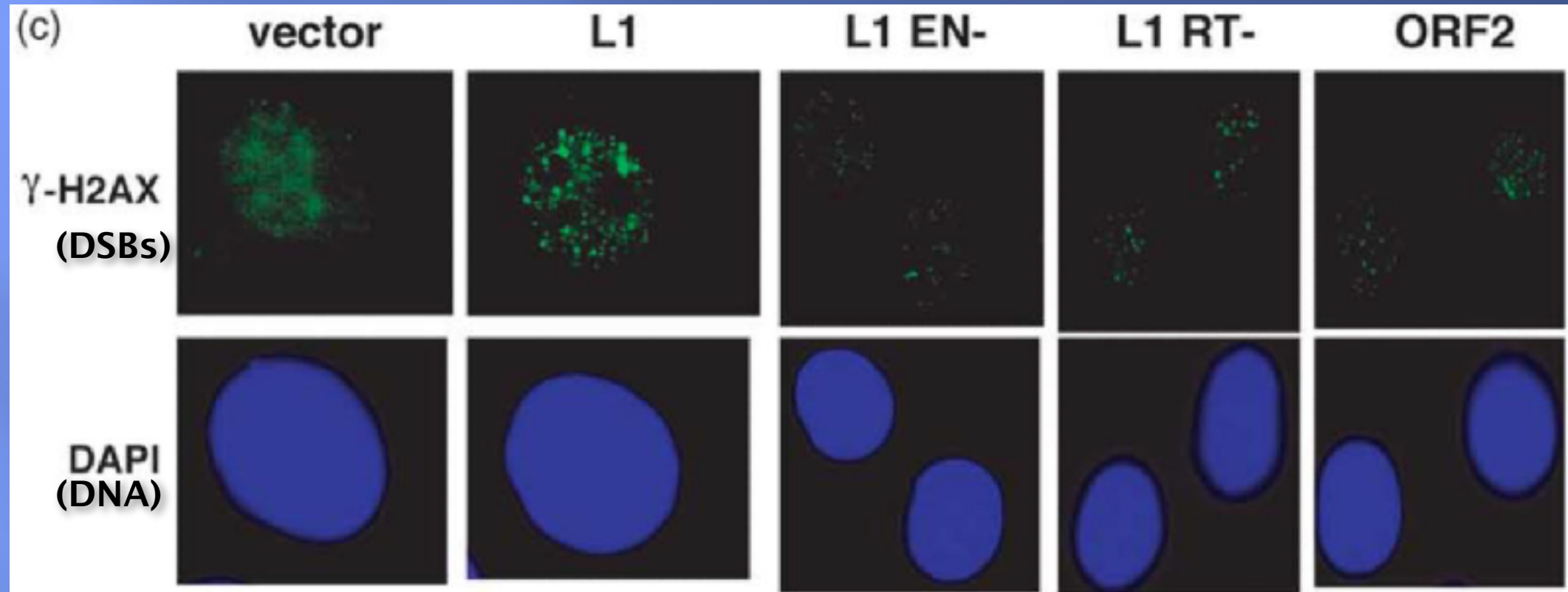
SIRT6 recognizes DSBs

DSBs being made
inside the dotted
circle with a laser



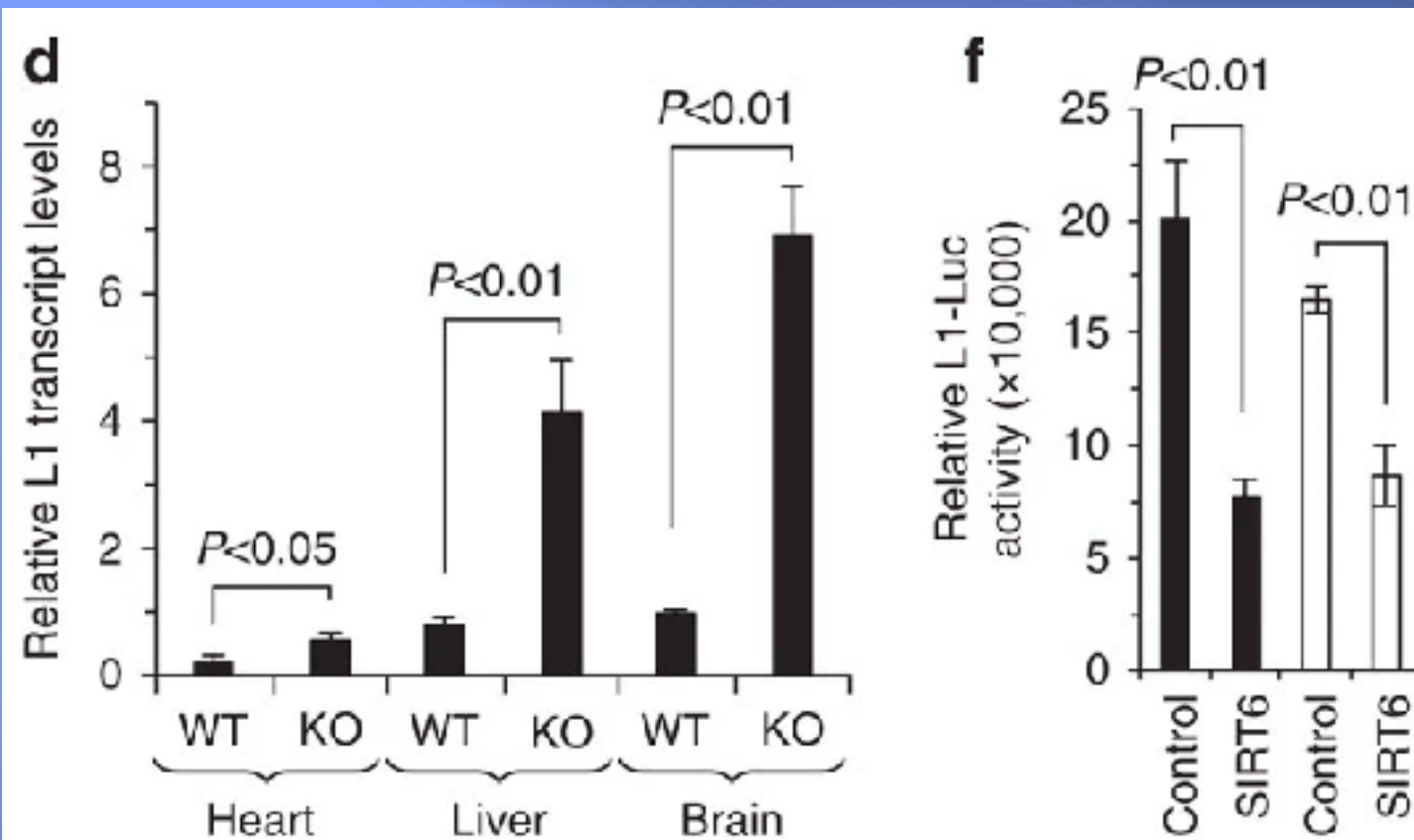
Onn, L., Portillo, M., Ilic, S., Cleitman, G., Stein, D., Kaluski, S., ... & Toiber, D. (2020). SIRT6 is a DNA double-strand break sensor. *Elife*, 9, e51636.

LINE-1 Creates DSBs

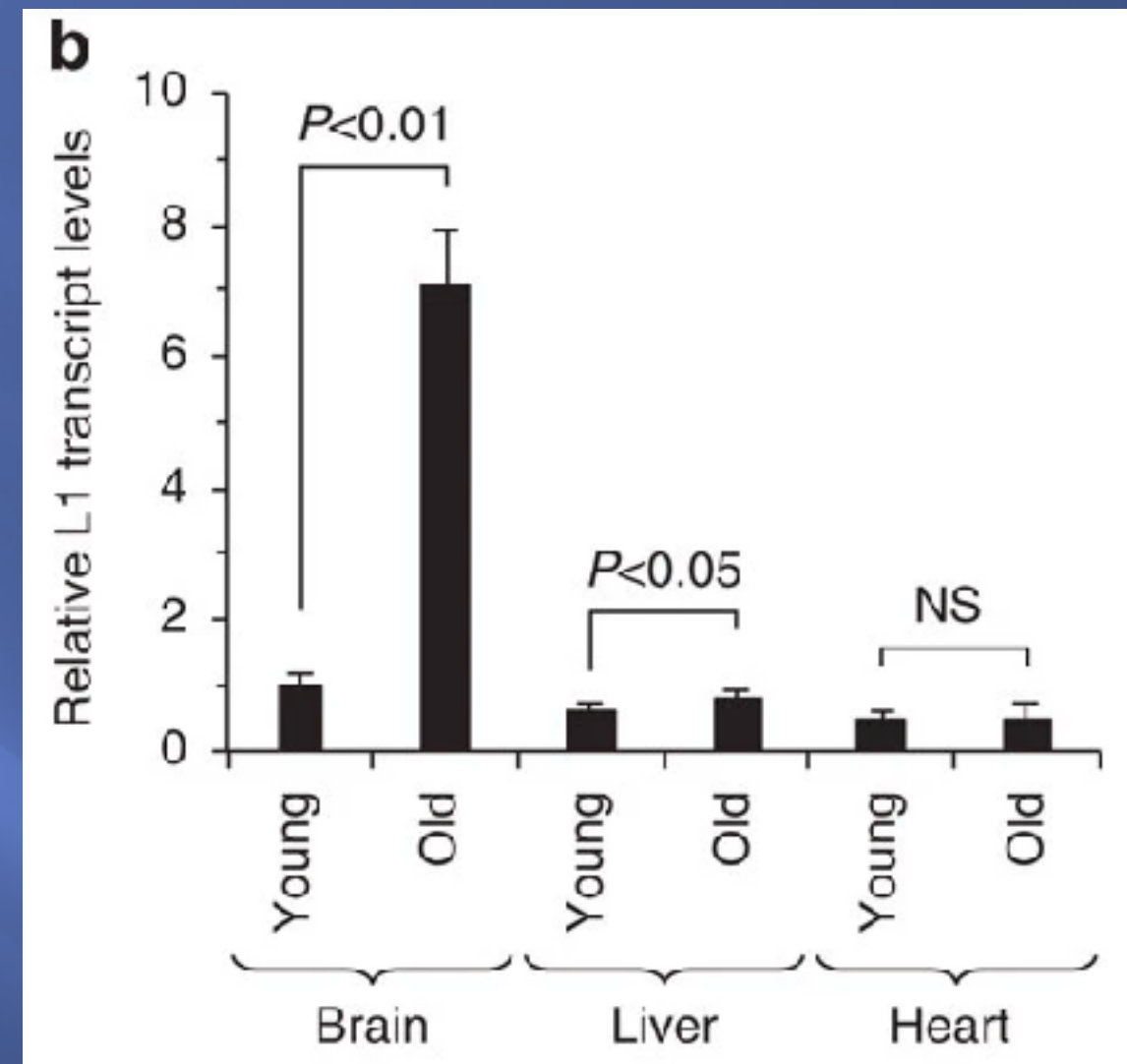


Gasior, S. L., Wakeman, T. P., Xu, B., & Deininger, P. L. (2006). The human LINE-1 retrotransposon creates DNA double-strand breaks. *Journal of molecular biology*, 357(5), 1383-1393.

life without SIRT6

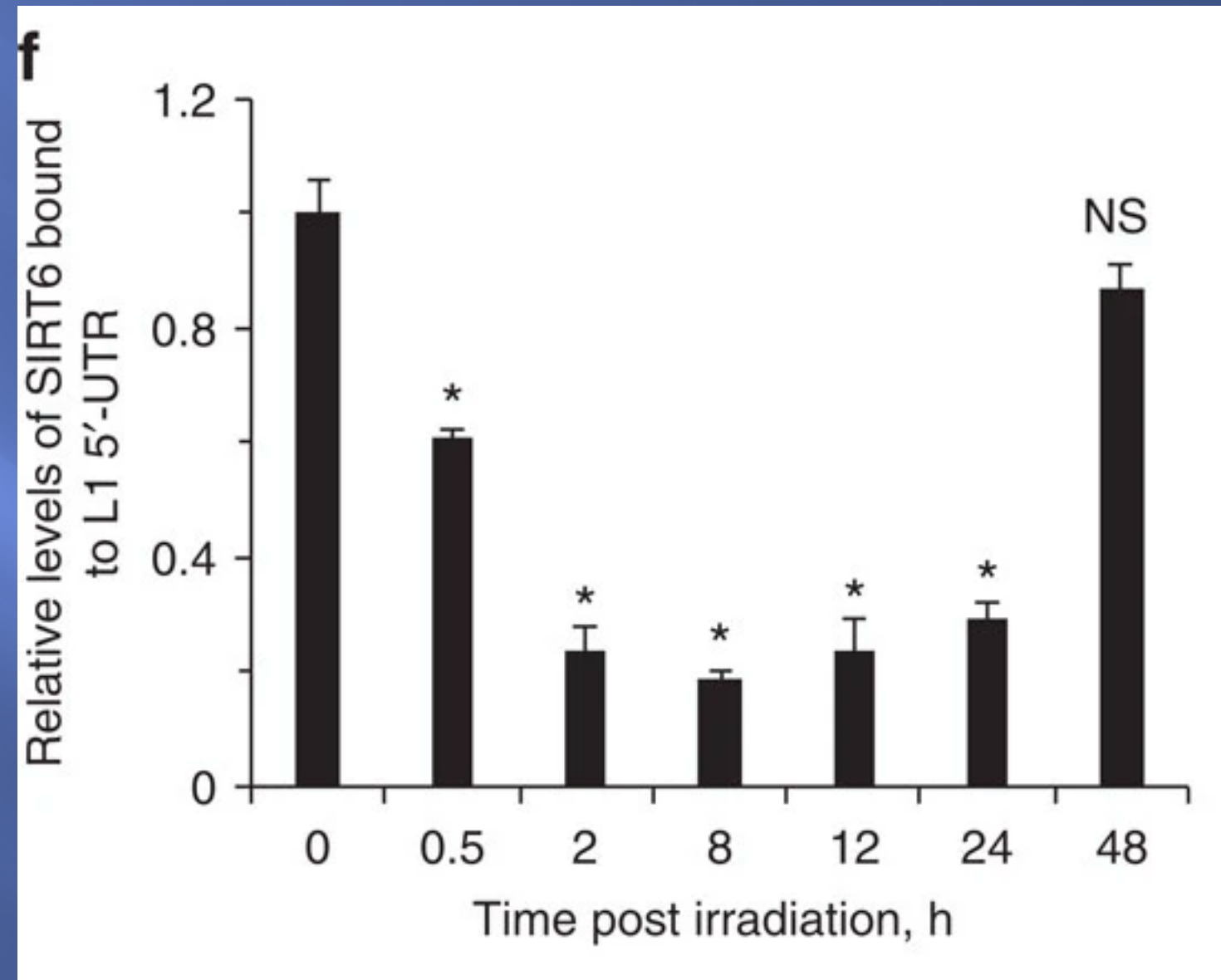
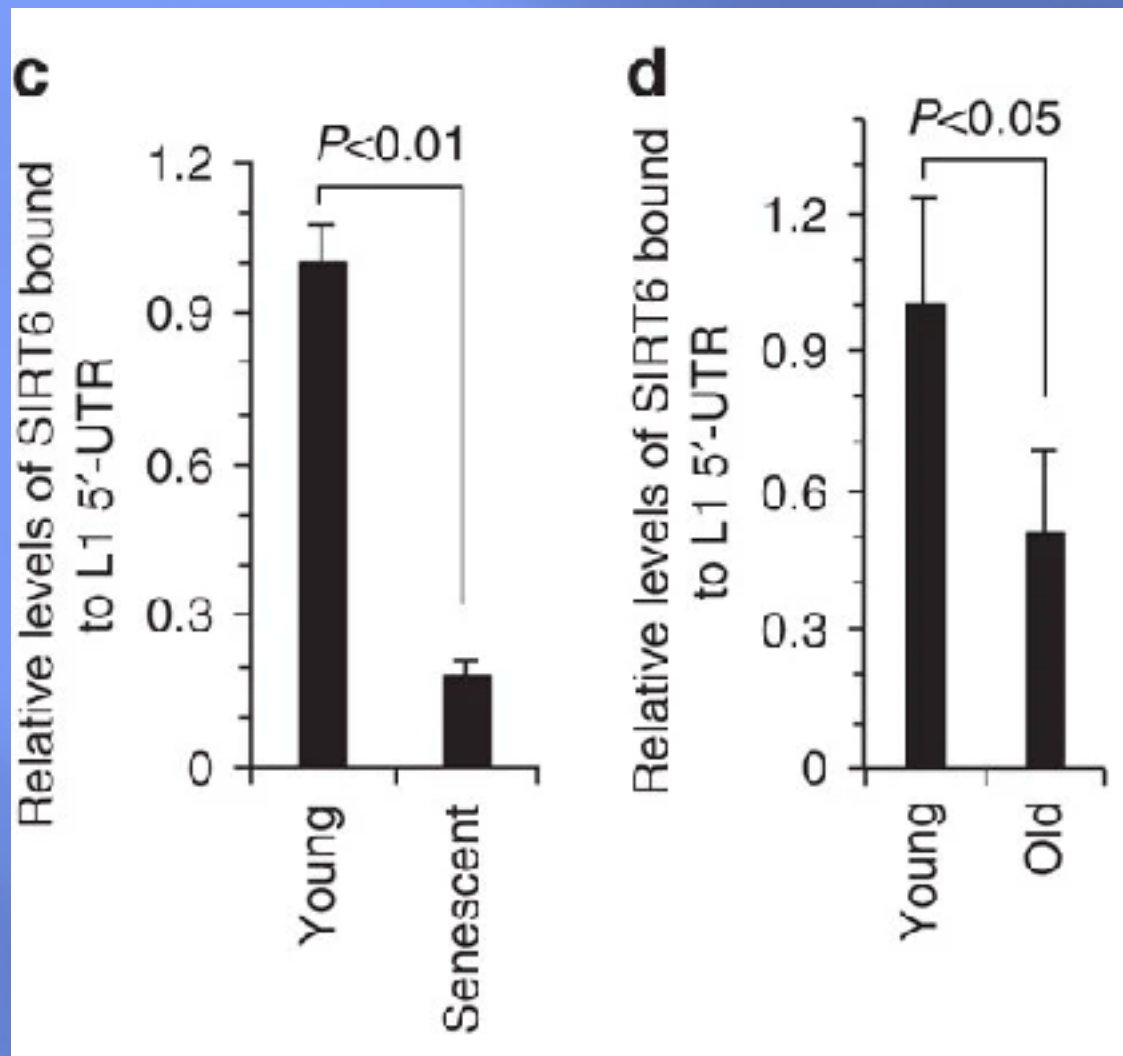


KO = SIRT6 knock-out mice



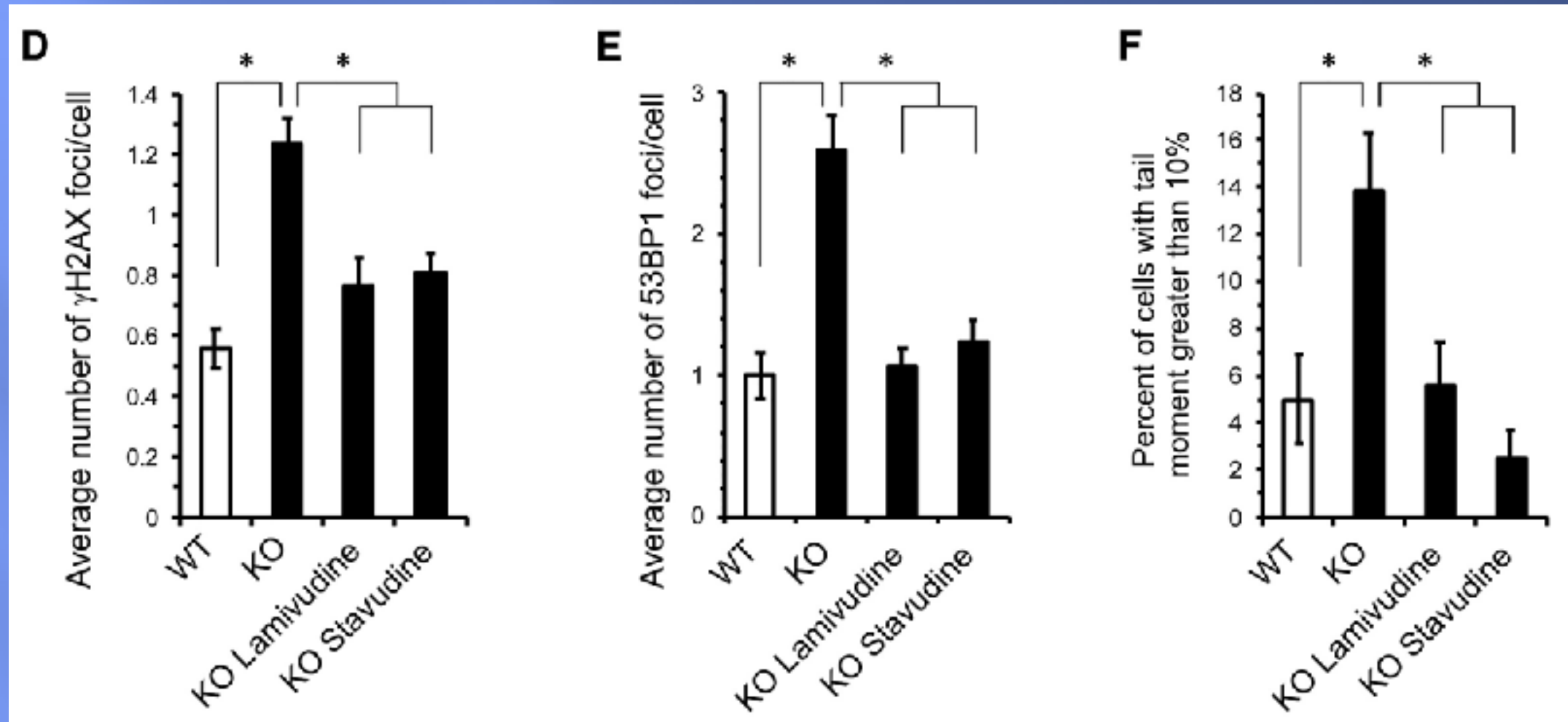
Van Meter, M., Kashyap, M., Rezazadeh, S., Geneva, A. J., Morello, T. D., Seluanov, A., & Gorbunova, V. (2014). SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. *Nature communications*, 5(1), 1-10.

life without SIRT6



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life without SIRT6

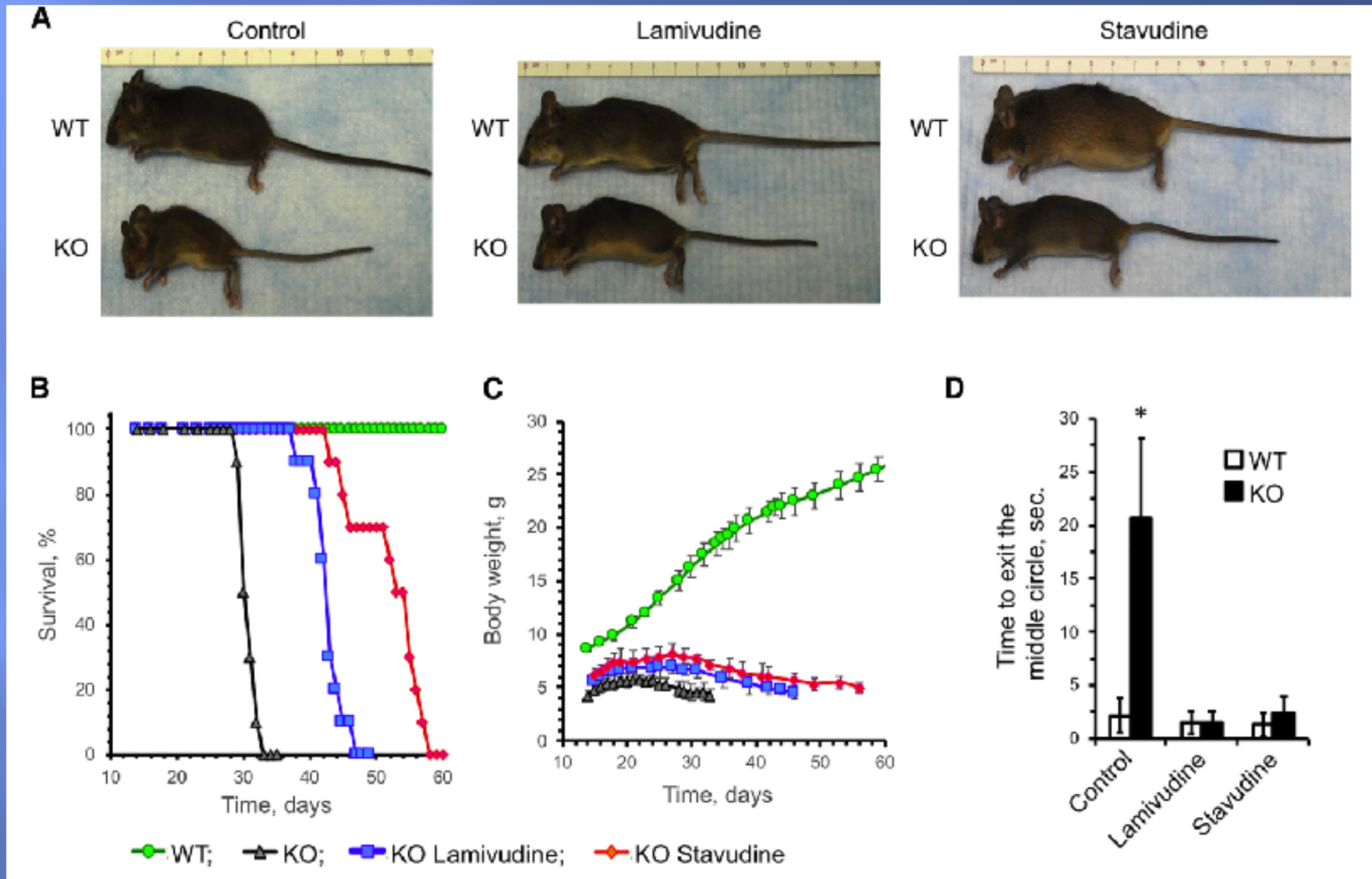


KO = SIRT6 knock-out mice

Lamivudine and Stavudine
are reverse transcriptase
inhibitors

Simon, M., Van Meter, M., Abulaeva, 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

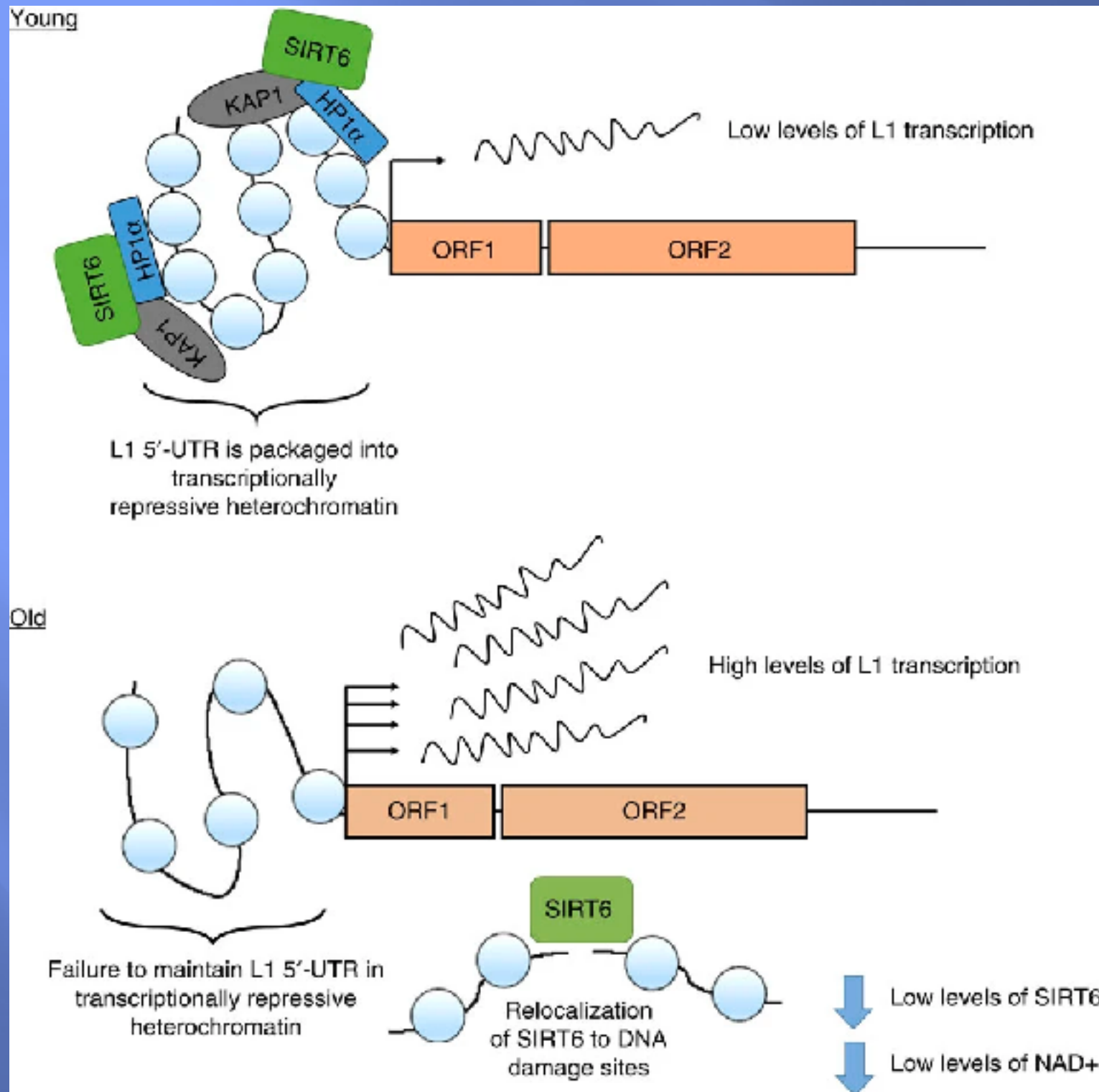


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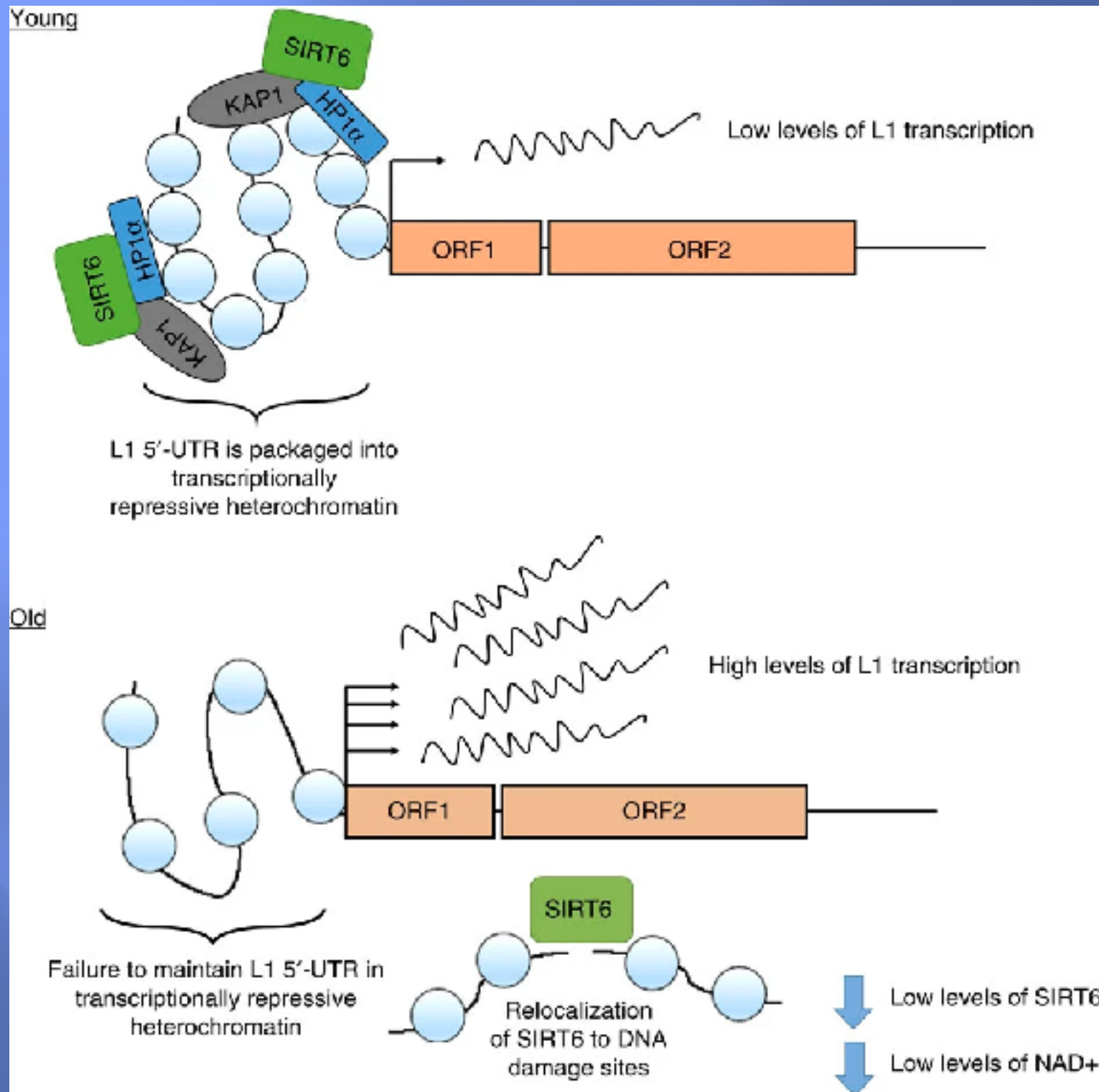
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The Model

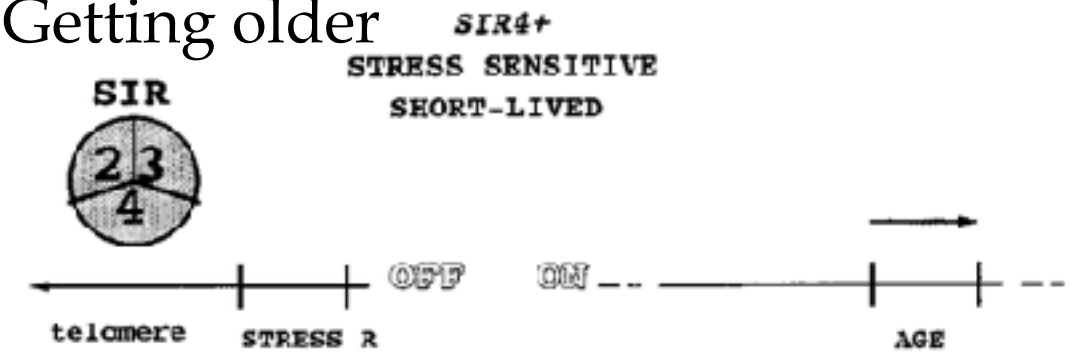


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The Model

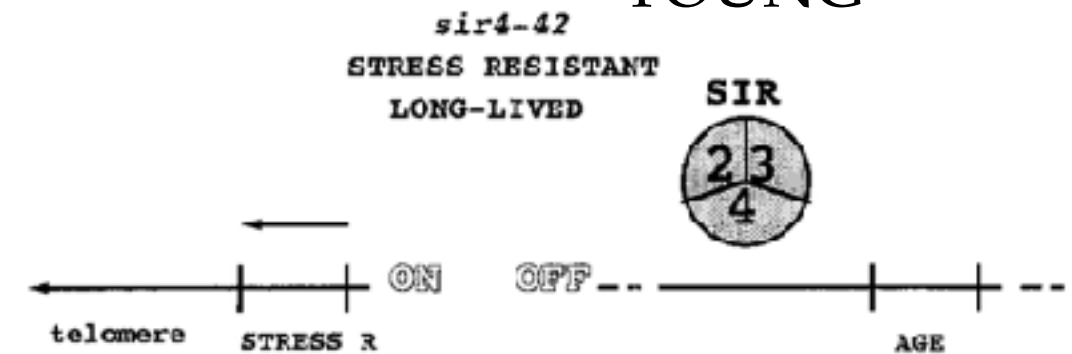


Getting older



DSBs

YOUNG



LINE-1

OLD

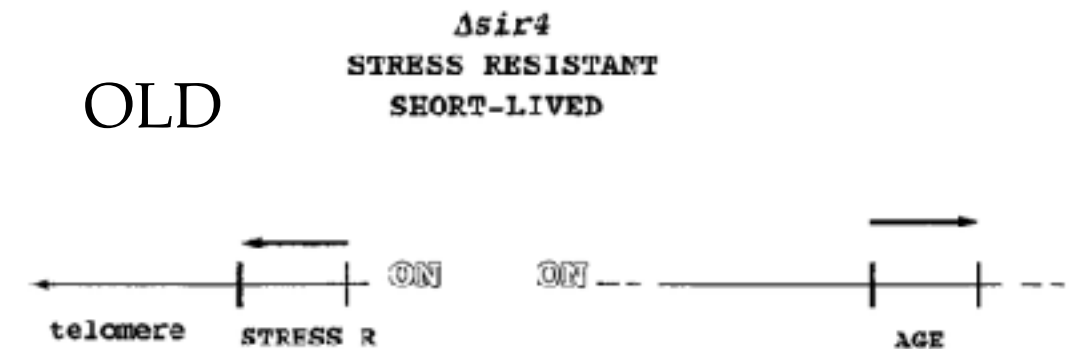
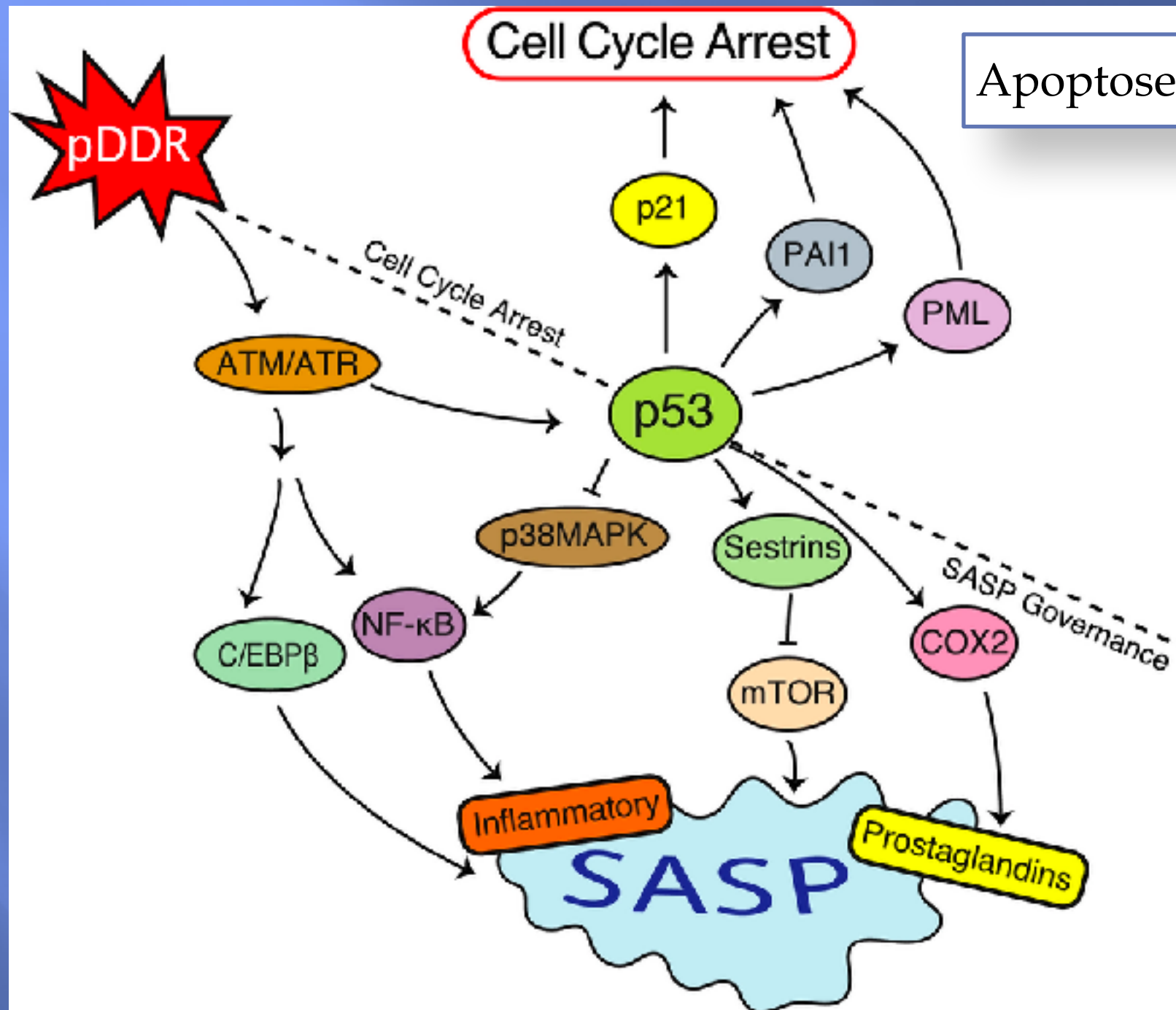


Figure 8. A Model for the Effects of Silencing on Yeast Life Span

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.

But is that aging?

Cells with DSBs should die.... however

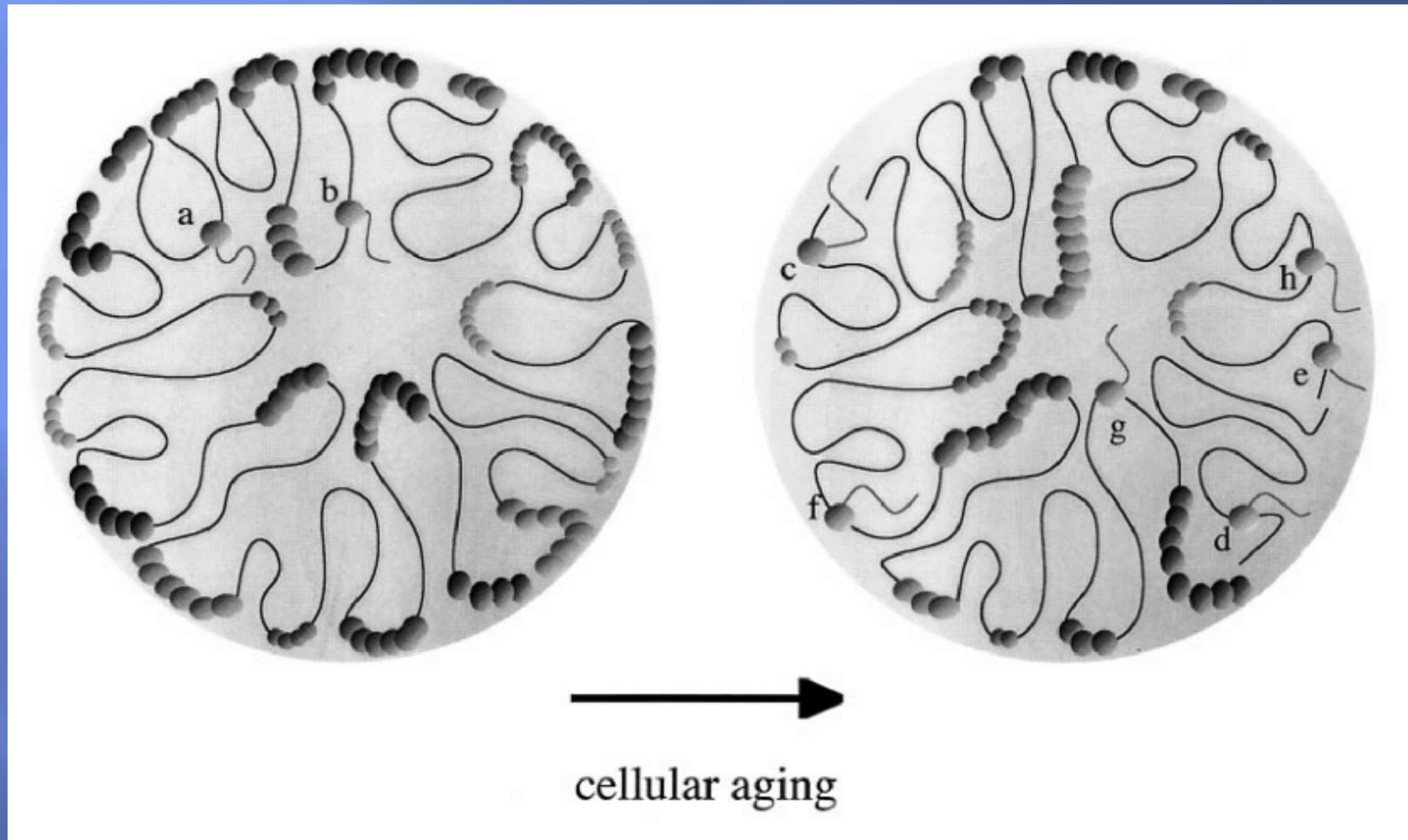


SASP - Senescence
Associated Secretory
Phenotype

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 SIRT6 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*

CHRISTOPHER J. I. DRIVER^a AND
STEPHEN W. McKECHNIE^b

^a*Department of Science
Deakin University–Rusden
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 (SIRT6, *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 (SIRT6)

NR = nicotinamide riboside

NMN = nicotinamide mononucleotide

P7C3 = nicotinamide phosphoribosyltransferase (NAMPT) activator

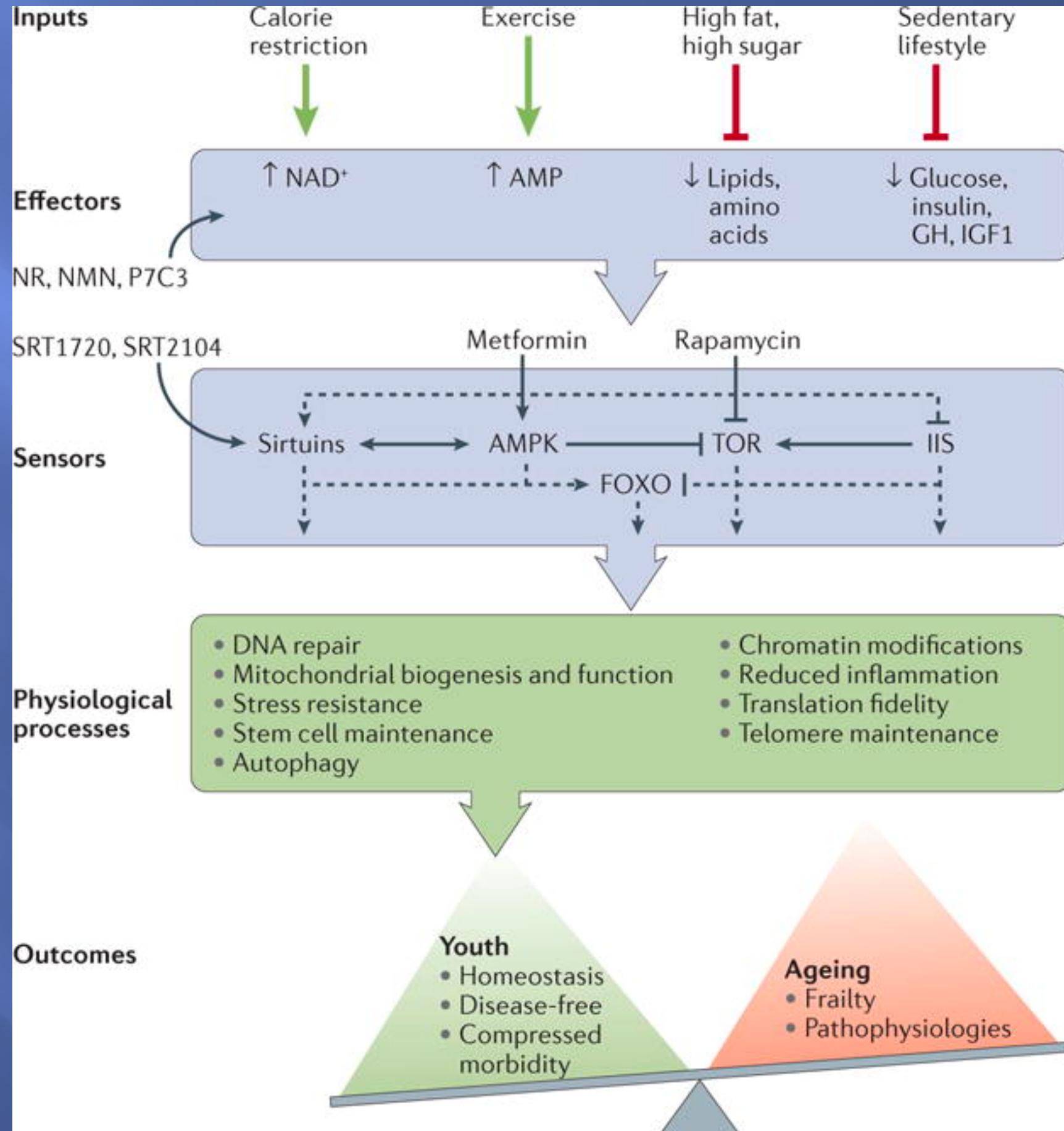
SRTs = proprietary candidates

not displayed:

resveratrol

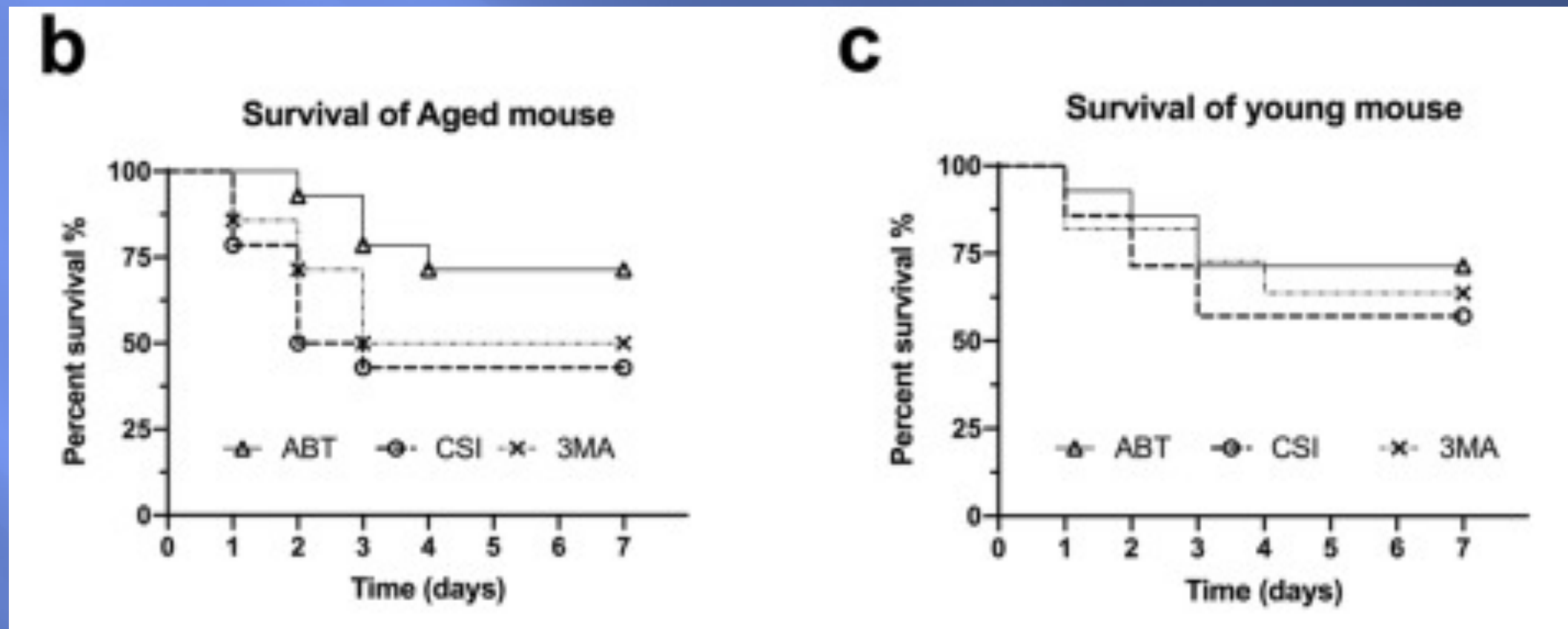
oleic acid

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	Ursolic acid	tyrosol
Curcumin	Coenzyme Q10	fisetin
Morphine	vitamins A and E	TA-65
Nordihydroguaiaretic acid (NDGA)	quercetin	procyanidins
Rapamycin	caffeic acid	Alpha-ketoglutarate and Oxaloacetic acid
Resveratrol	rosmarinic acid	Dehydroepiandrosterone (DHEA) and
Sappanone A	genistein	17 α -estradiol
Spermidine	EGCG	S-Linolenoyl
Tambulin	Protandim	glutathione
Urolithins	chicoric acid	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

Your humble presenter



kindergarten



4 years ago



current