Experimental approaches to promote healthy aging

Alejandro Martín-Montalvo

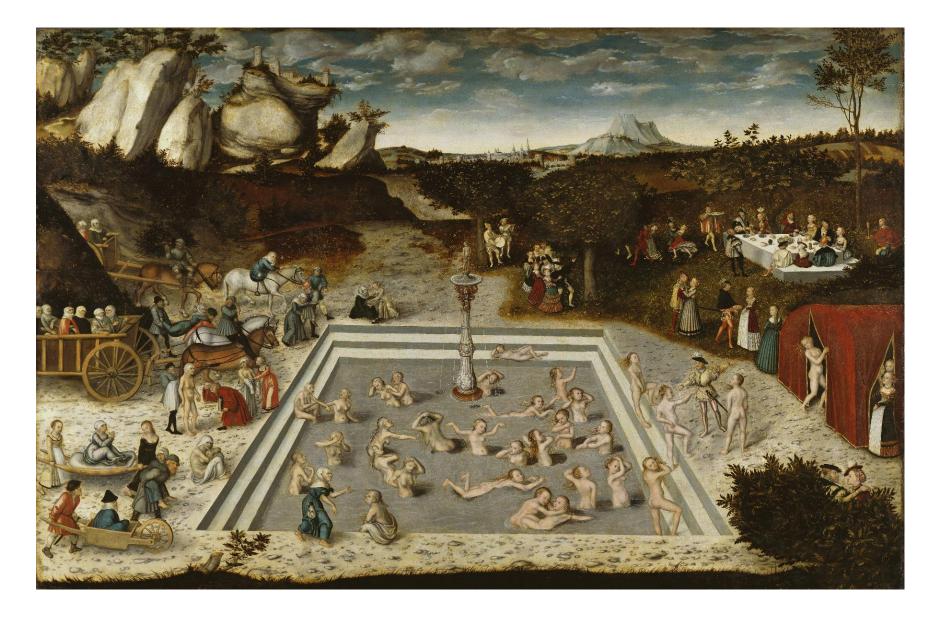




We are aging!



The hope of restoring youth, an old aspiration



A reality and a major achievement in human history

		Life exp	Life expectancy at birth (years)			Healthy life expectancy (HALE) at birth (years)		
		Both	Male	Female	Both	Male	Female	
		sexes			sexes			
Europe	2016	77.5	74.2	80.8	68.4	66.1	70.7	
	2015	77.2	73.8	80.5	68.1	65.7	70.5	
	2010	75.7	72.0	79.3	66.9	64.3	69.5	
	2005	73.5	69.5	77.6	65.1	62.2	68.2	
	2000	72.5	68.4	76.7	64.2	61.2	67.3	
(WHO)	2016	72.0	69.8	74.2	63.3	62.0	64.8	
Global	2015	71.7	69.5	73.9	63.0	61.7	64.5	
	2010	70.1	68.0	72.3	61.7	60.4	63.1	
	2005	68.2	66.1	70.3	60.0	58.7	61.3	
	2000	66.5	64.4	68.7	58.5	57.2	59.9	



New estrategies to improve the aging experience



		Life expectancy at birth (years)			Healthy life expectancy (HALE) at birth (years)		
		Both	Male	Female	Both	Male	Female
		sexes			sexes		
Europe	2016	77.5	74.2	80.8	68.4	66.1	70.7
	2015	77.2	73.8	80.5	68.1	65.7	70.5
	2010	75.7	72.0	79.3	66.9	64.3	69.5
	2005	73.5	69.5	77.6	65.1	62.2	68.2
	2000	72.5	68.4	76.7	64.2	61.2	67.3
(WHO)	2016	72.0	69.8	74.2	63.3	62.0	64.8
Global	2015	71.7	69.5	73.9	63.0	61.7	64.5
	2010	70.1	68.0	72.3	61.7	60.4	63.1
	2005	68.2	66.1	70.3	60.0	58.7	61.3
	2000	66.5	64.4	68.7	58.5	57.2	59.9



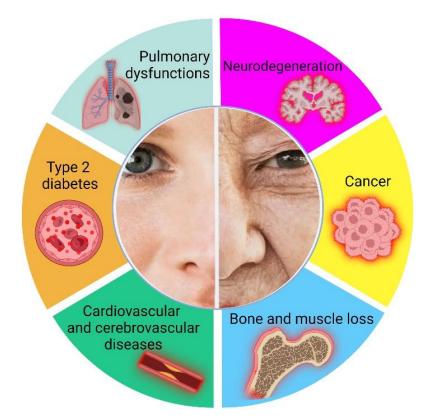
What is aging?

A continuous, universal, progressive, intrinsic, and deleterious process that decreases an organism's ability to maintain homeostasis in the face of environmental stressors and therefore increases the organism's likelihood of dying.



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The hallmarks of aging and cancer

Leading Edge Review

Cell

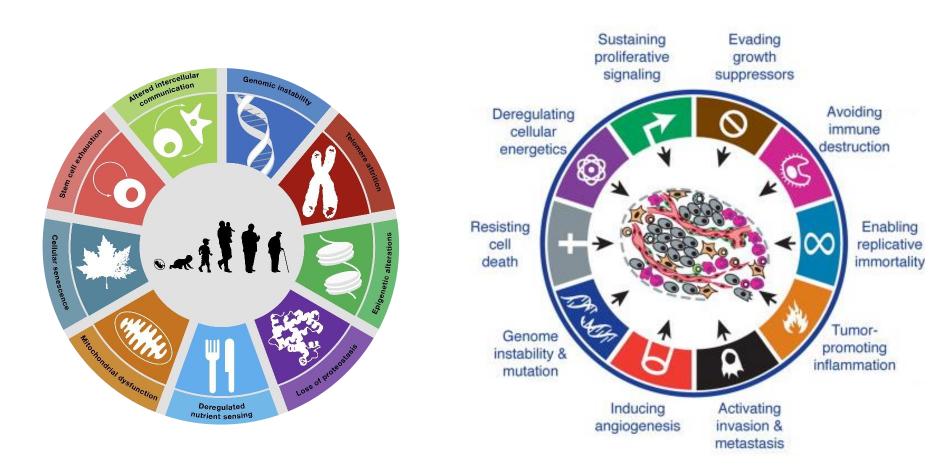
Leading Edge Review

The Hallmarks of Aging

Carlos López-Otín,¹ Maria A. Blasco,² Linda Partridge,^{3,4} Manuel Serrano,^{5,*} and Guido Kroemer^{6,7,8,9,10}

Hallmarks of Cancer: The Next Generation

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The hallmarks of aging and cancer

Leading Edge Review

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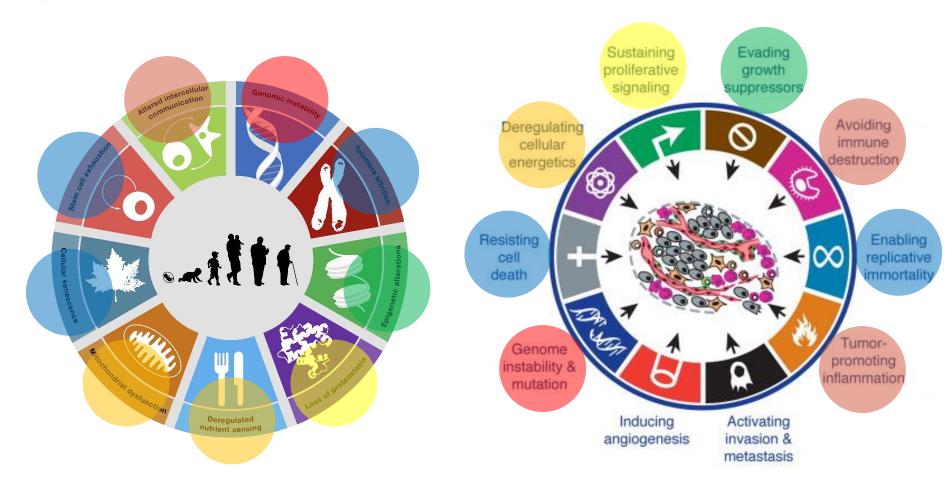


The Hallmarks of Aging

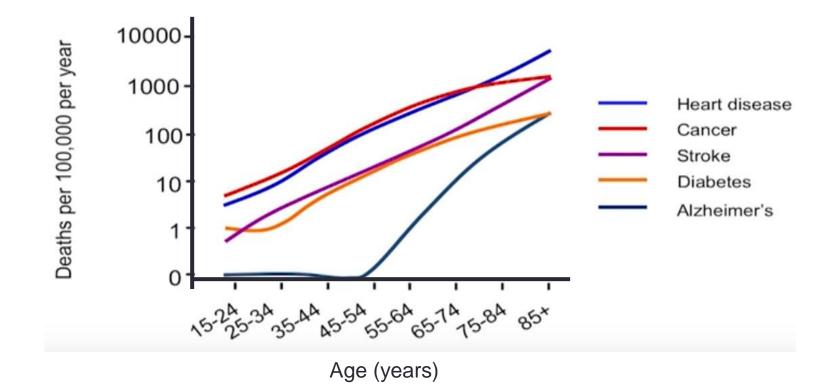
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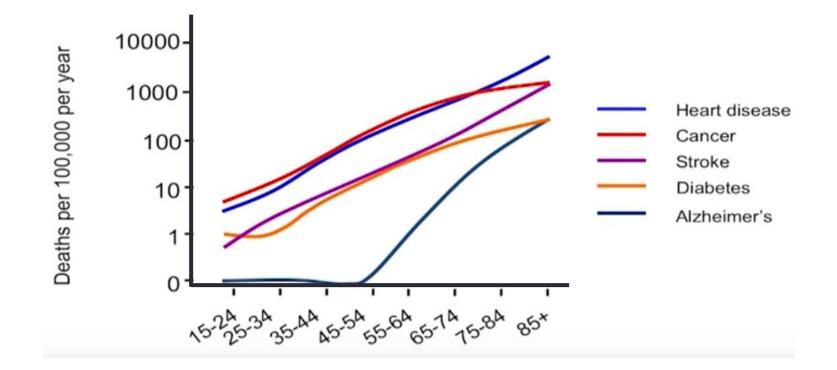
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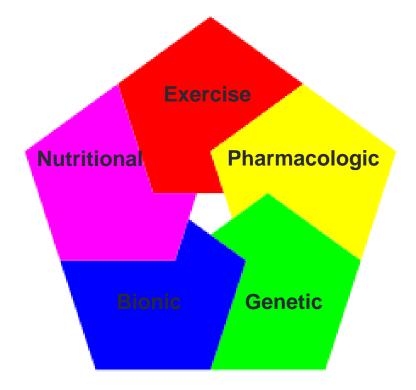
The causes of death by age



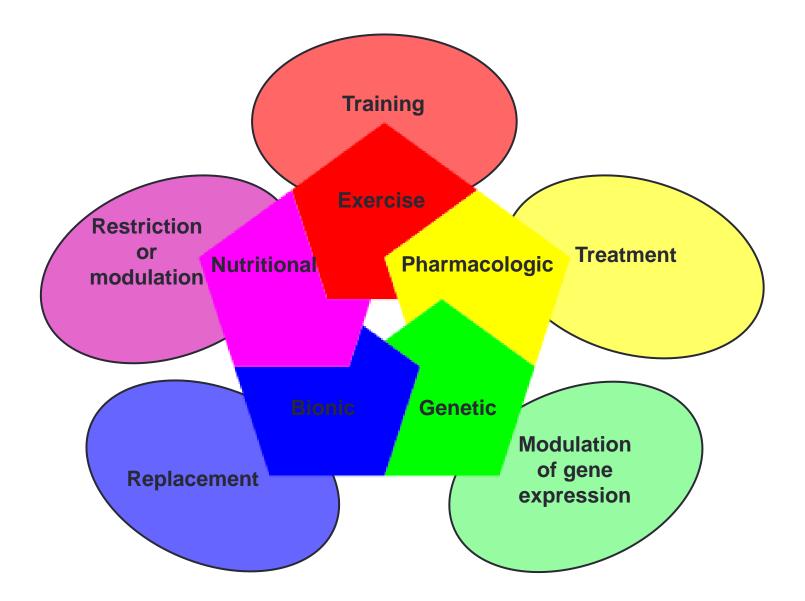
The causes of death by age; One strategy to rule them all



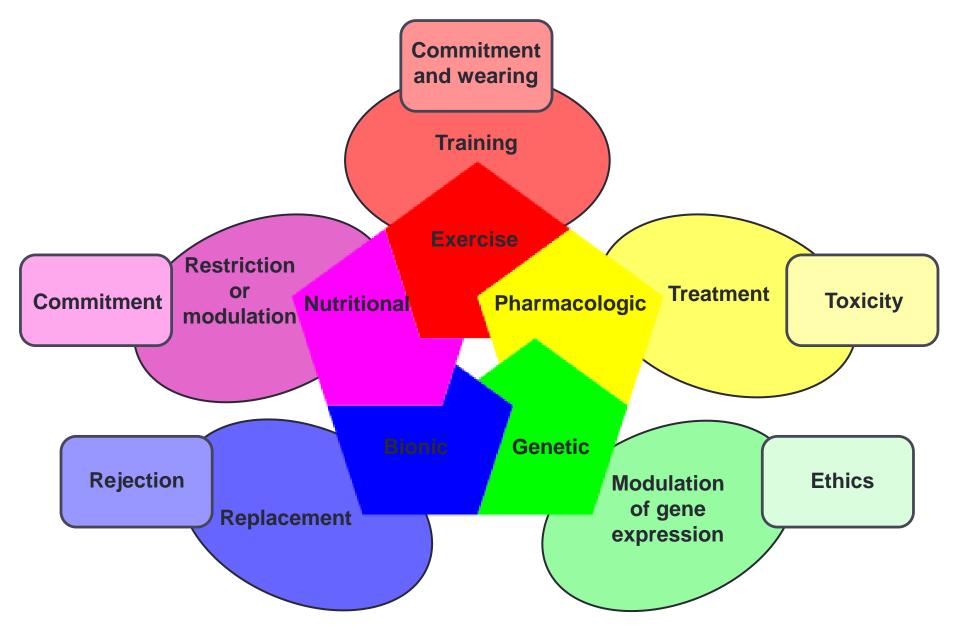
How do we approach to improve the aging experience?



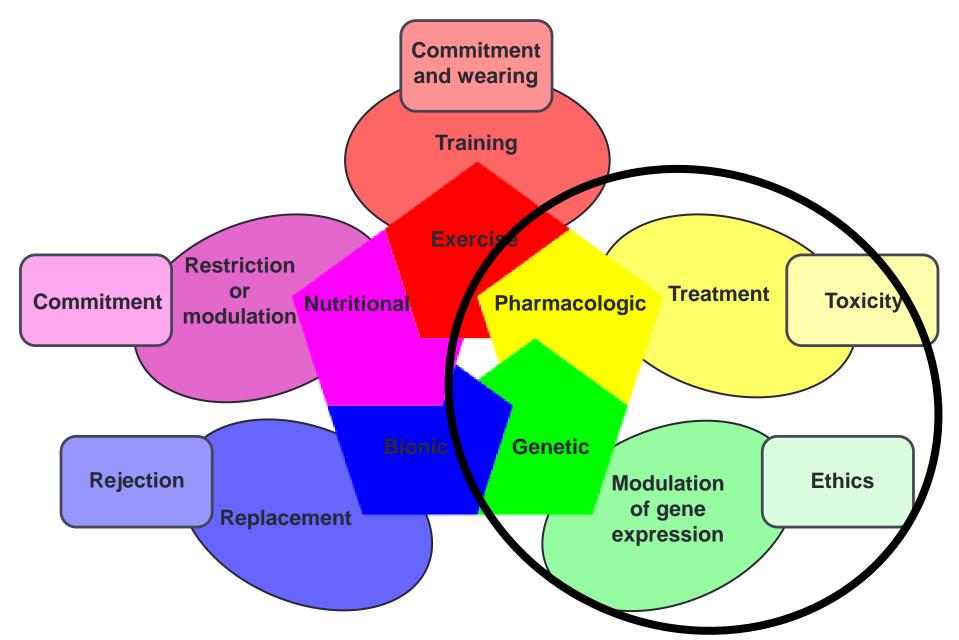
How do we approach to improve the aging experience?



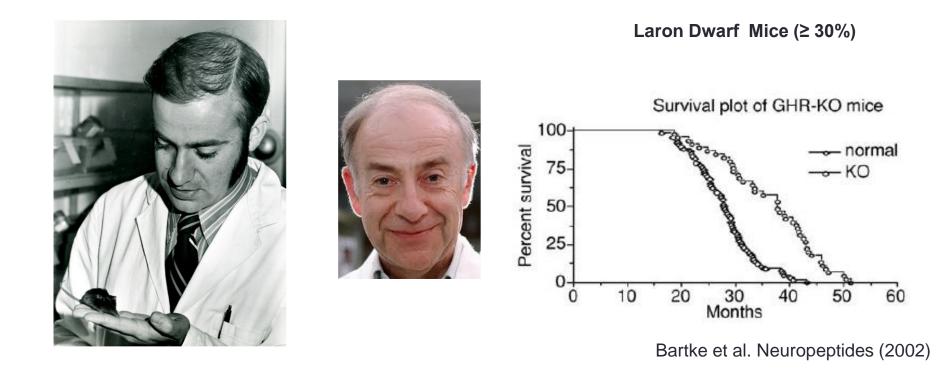
Important aspects to improve the aging experience



Experimental approaches to modulate aging; clinical trials

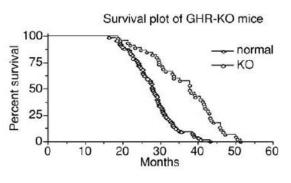


Methuselah prize of mouse longevity 1,819 days (~180 years in human)

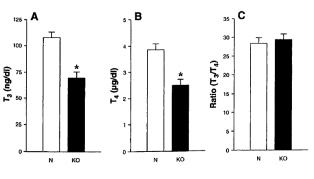


Thyroid hormones are low in the longest living mice

Laron Dwarf (GH Receptor KO)

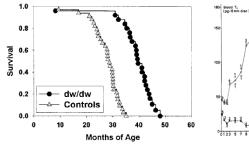


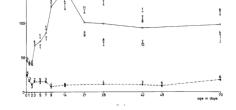
Bartke et al. Neuropeptides (2002)



Hauck SJ. Exp Biol Med (2001)

Snell dwarf mice (Pit1 mutated mice)

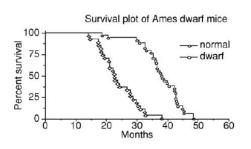


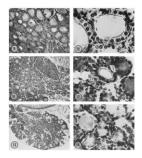


Flurkey et al. PNAS (2001)

van Buul-Offers S et al. Acta Endo. (1983)

Ames dwarf mice (Prop1 mutated mice)





Brown-Borg et al. Nature (1996)

Bartke The Anat. Record. (1964)

Thyroid hormones are reduced in calorie resticted humans



TABLE 1. Characteristics of the study subjects

	CR group	EX group	WD group		P value	
	(n = 28)	(n - 28)	(n - 28)	CR or. EX	CR cs. WD	EX DR. WD
Age (yr)	52.0 ± 12	52.1 ± 12	52.3 ± 10	ns	DS .	ns
Sax (M/F)	24/4	24/4	24/4			
Height (m)	1.73 ± 0.1	1.75 ± 0.1	1.77 ± 0.1	ns	ns	115
Weight (kg)	58.8 ± 5.9	68.2 ± 7.6	81.9 ± 14.6	0.003	0.0001	0.0001
BMI (kg/m ²)	19.7 ± 1.7	22.2 ± 1.9	26.0 ± 3.2	0.0001	0.0001	0.0001
TSH (mIU/liter)	1.27 ± 0.7	1.68 ± 1.0	1.24 ± 0.6	ns	ns	115
T ₂ (ng/dl)	73.6 ± 22	94.3 ± 17	91.0 ± 13	0.0001	0.001	ns
$T_4 (\mu g/dl)$	5.4 ± 1.5	5.1 ± 0.7	5.7 ± 0.9	ns	ns	DS .
FT4 (ng/dl)	0.96 ± 0.14	1.0 ± 0.09	0.97 ± 0.22	ns	ns	ns
hsCRP (mg/liter)	0.23 ± 0.27	0.65 ± 0.76	1.11 ± 1.17	0.001	ns	D.S
TNF-a (pg/ml)	0.74 ± 0.5	1.42 ± 1.3	1.54 ± 0.9	0.030	0.009	ns

Normal ranges: TSH, 0.47–5.0 mIU/liter; T₂, 70–165 ng/dl; T₄, 4.5–12 µg/dl; and FT4, 0.71–1.85 ng/dl. Values are means ± SD. M, Male; F, female; ns, not significant; hsCRP, high-sonsitivity CRP.

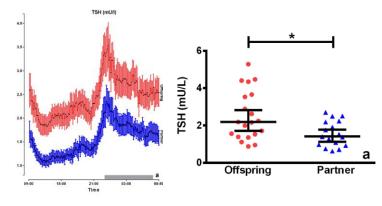
Centenarians and their offspring have lower T3/high TSH

	Offspring	Partners	p Value
All			
Thyrotropin (0.3-4.8 mU/L)	1.65 (1.59–1.71)	1.57 (1.49–1.66)	.11
Free thyroxine (10-24 pmol/L)	15.0 (14.9–15.2)	15.2 (15.0–15.4)	.045
Free triiodothyronine (2.5-5.5 pmol/L)	4.08 (4.04-4.12)	4.14 (4.09-4.20)	.024
Ratio triiodothyronine thyroxine	0.28 (0.27-0.28)	0.28 (0.27–0.28)	.84

Table 2. Serum Levels of Thyroid Hormone Axis Parameters for Offspring and Partners

Rozing et al. J Gerontol A Biol Sci Med Sci. (2010)

	Controls	Offspring	Centenarians
n (females/males)	163 (79/84)	366 (185/181)	232 (100/00)
Age (yr)			
All	70 (53-80)	69 (59-79)	97 (95-105)
Females	67 (52-80)	68 (59-79)	97 (95-103)
Males	74 (59-80)	69 (59-79)	97 (95-103)
TSH (mIU/liter)			
All	1.55 (0.63-3.93)	1.68 (0.65-4.79) ^a	1.97 (0.42-7.15) ^a
Females	1.60 (0.60-4.7)	1.72 (0.51-6.3)*	2.00 (0.53-7.34) ^a
Males	1.50 (0.55-4.50)	1.68 (0.65-5.9)?	1.93 (0.61-6.9)
FT4 (ng/dl)			
All	1.00 (0.69-1.7)	1.03 (0.67-2.0)	1.02 (0.62-2.02)
Females	0.99 (0.74-1.5)	1.04 (0.66-1.9) ^a	1.04 (0.65-2.02) ^a
Males	1.00 (0.57-1.7)	1.02 (0.67-2.0)	0.95 (0.48-2.06)*



Data are expressed as median (97.5% Cl).

^a P < 0.05 vs. controls.

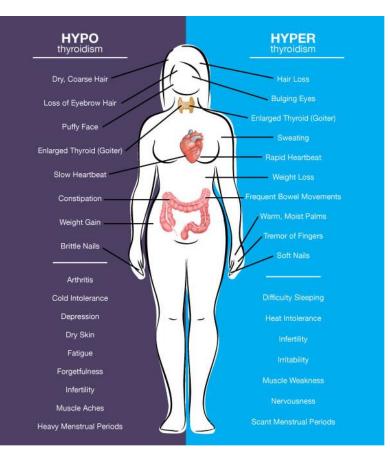
Atzmon et al. J Clin Endocrinol Metab. (2009)

Jansen et al. Sci Rep. (2015)

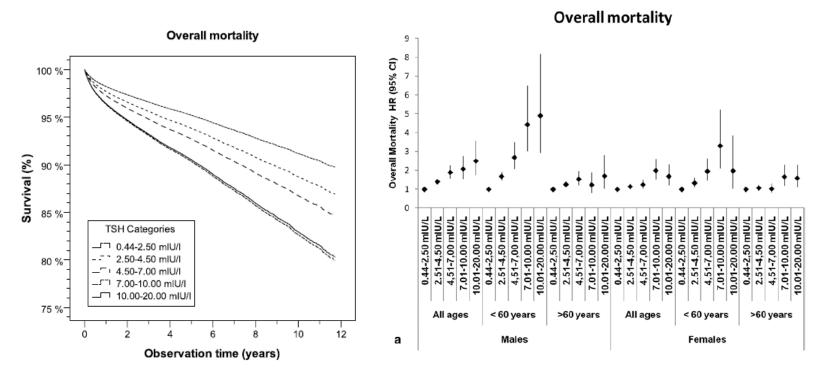
Alterations in thyroid Hormones lead to human diseases

	0.1 mIU	TSH concentratior J/L 4.5 n	nIU/L		
tration 57.9 nM	Secundary hyporthyroidi hypothalamus or p	Primary hypothyroidism			
l T4 concent	Subclinical hyperthyroidism	Euthyroidism	Subclinical hypothyroidism		
Tota 169.9 nM	Primary hyperthyroidism or thyroxine intoxication	ng adenoma ce to THs			



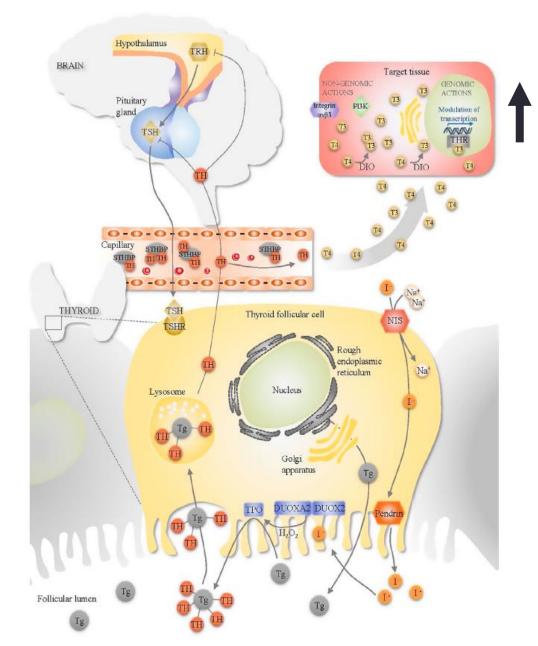


Hypothyroid humans have increased mortality



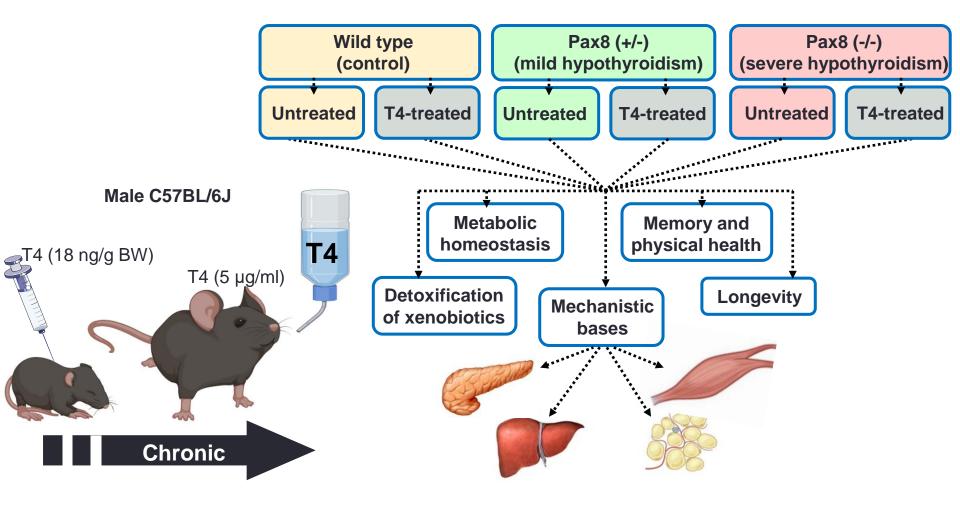
Kovar FM. Et al. Wien Klin Wochenschr. (2015)

The hypothalamic-pituitary-thyroid axis

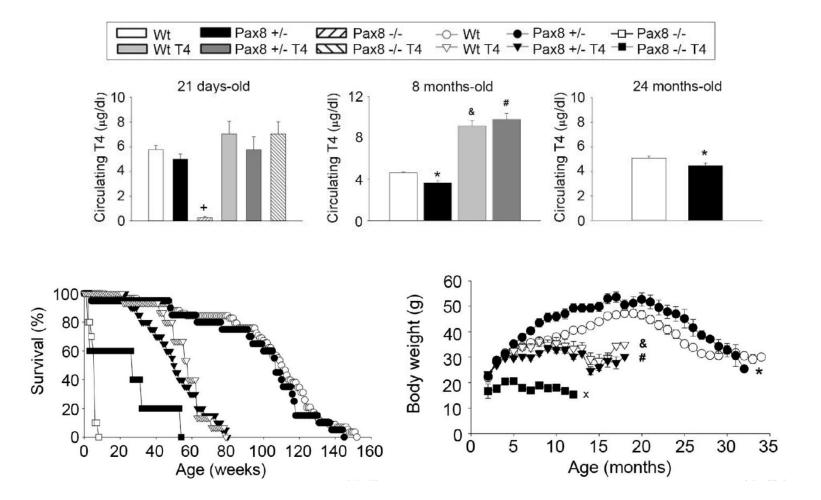


Metabolic rate

The thyroid axis in metabolic health, cancer, and life expetancy

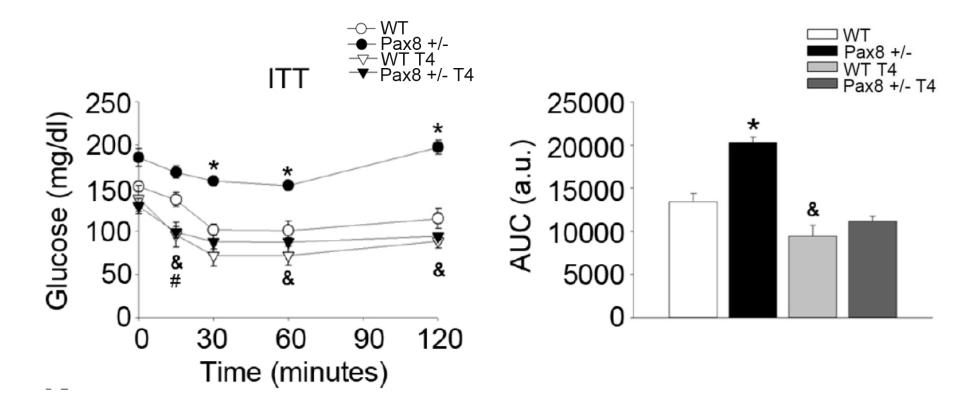


The effects of the modulation of the thyroid axis in longevity

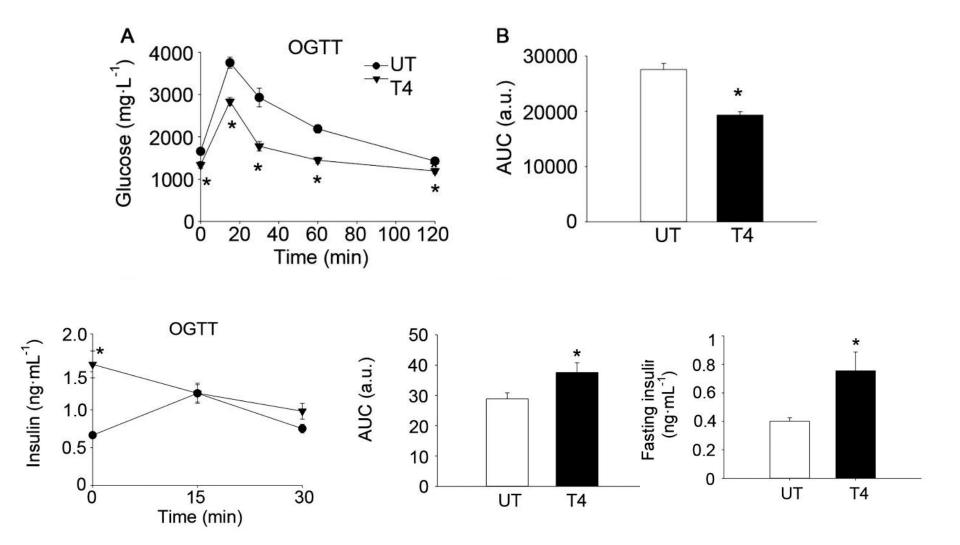


López-Noriega L. et al. Aging 2019

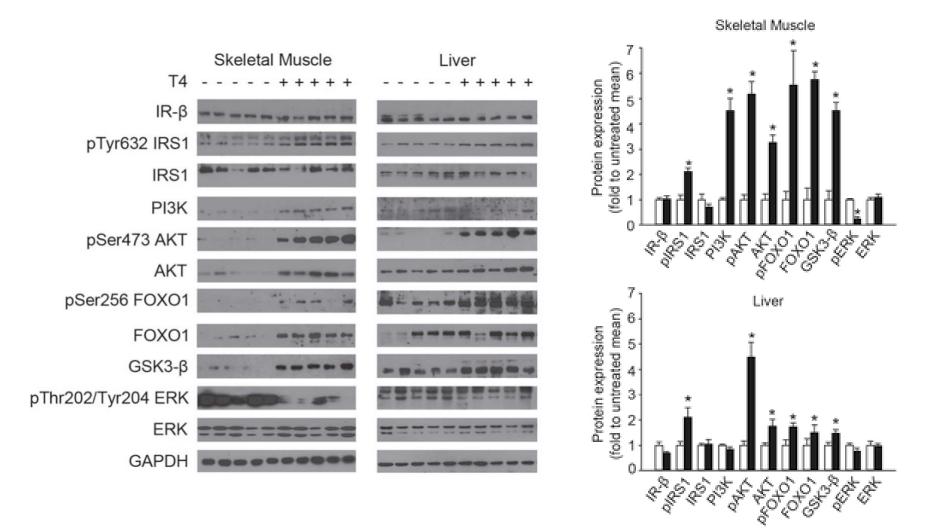
The modulation of thyroid hormones alters glucose metabolism



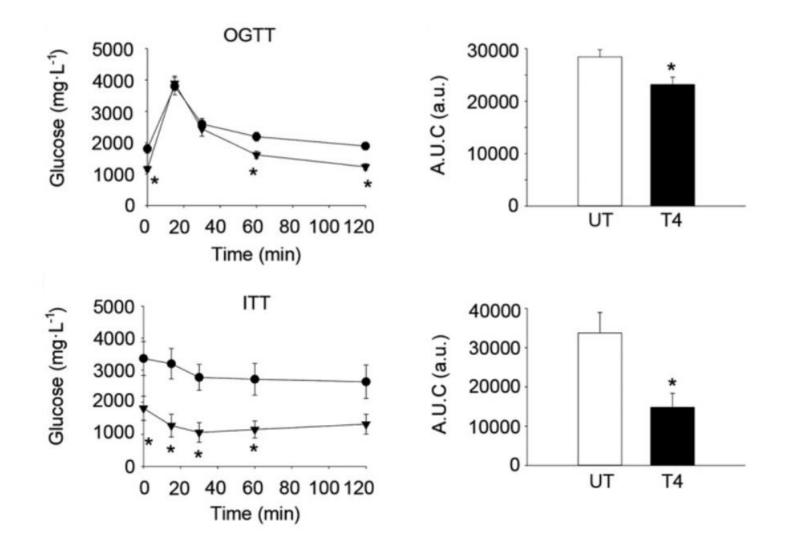
Thyroid hormones in female C57 increase insulin levels



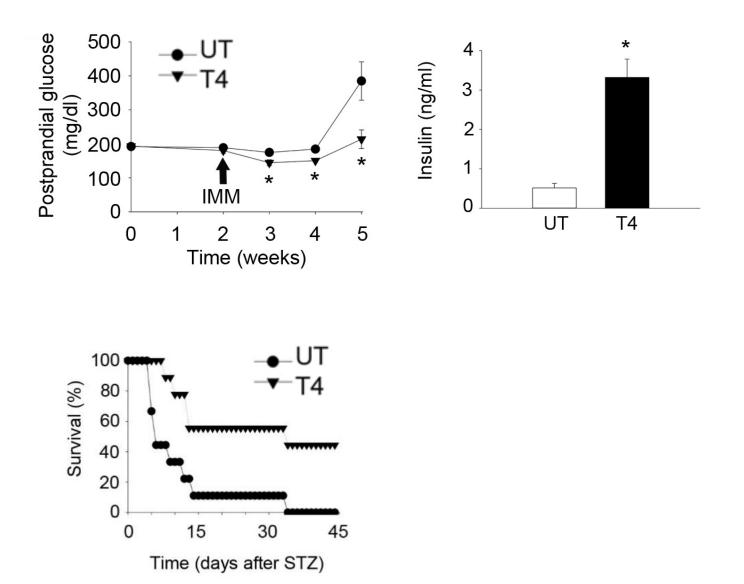
Increased insulin signaling in hyperthyroidism



Thyroid hormones improve glucose metabolism in RIP.B7.1 mice

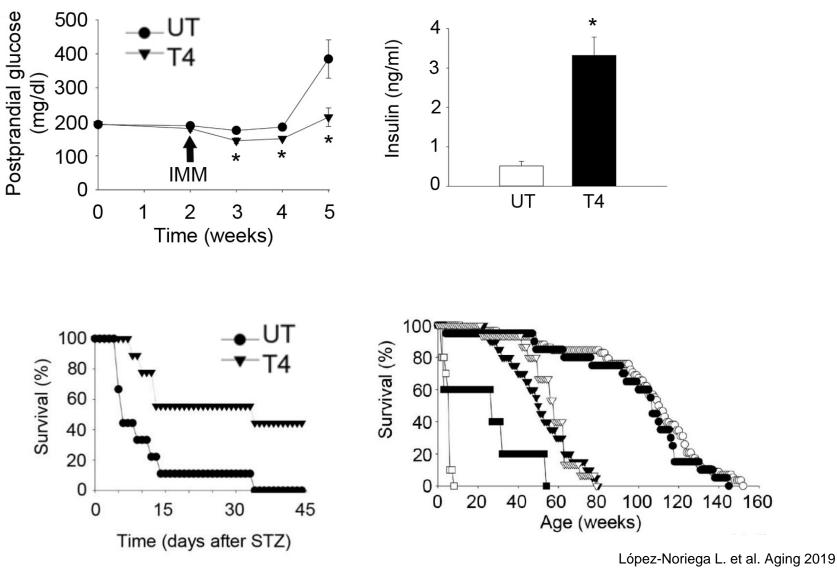


Thyroid hormones increase insulin levels and survival in ET1DM



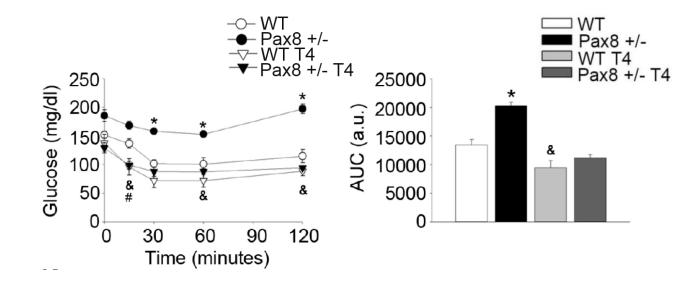
López-Noriega L. et al. B. J. Pharmacology 2017

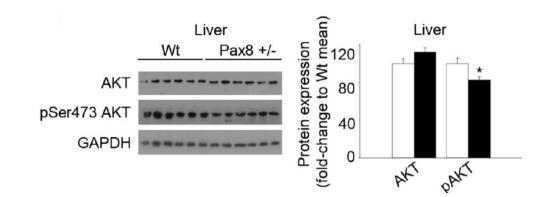
Thyroid hormones produce toxicity in healthy mice



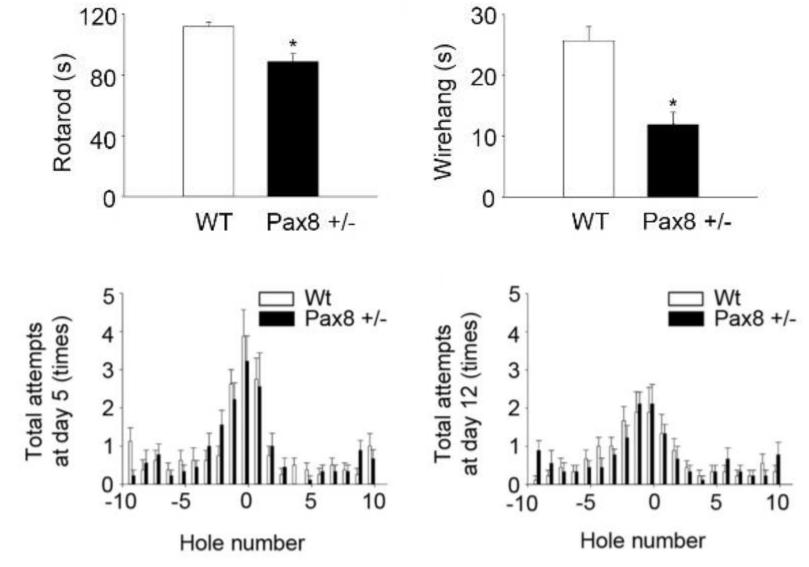
López-Noriega L. et al. B. J. Pharmacology 2017

The modulation of thyroid hormones alters glucose metabolism



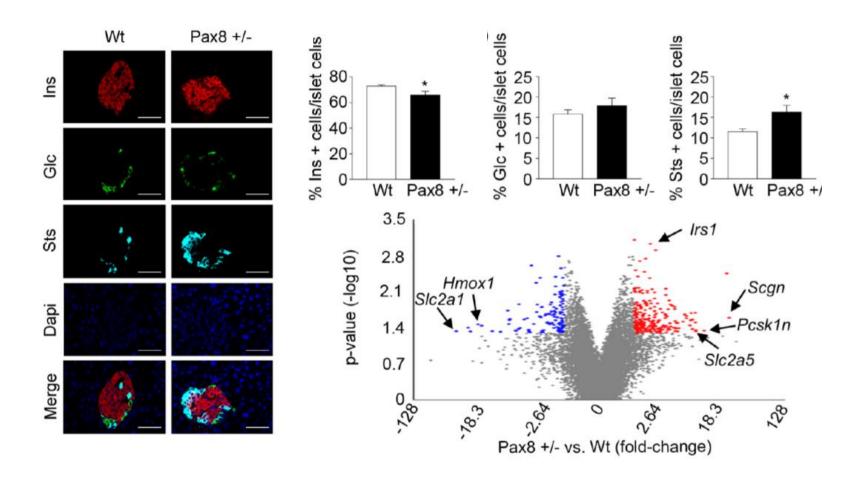


Mild hypothyroid mice have poor locomotor function



López-Noriega L. et al. Aging 2019

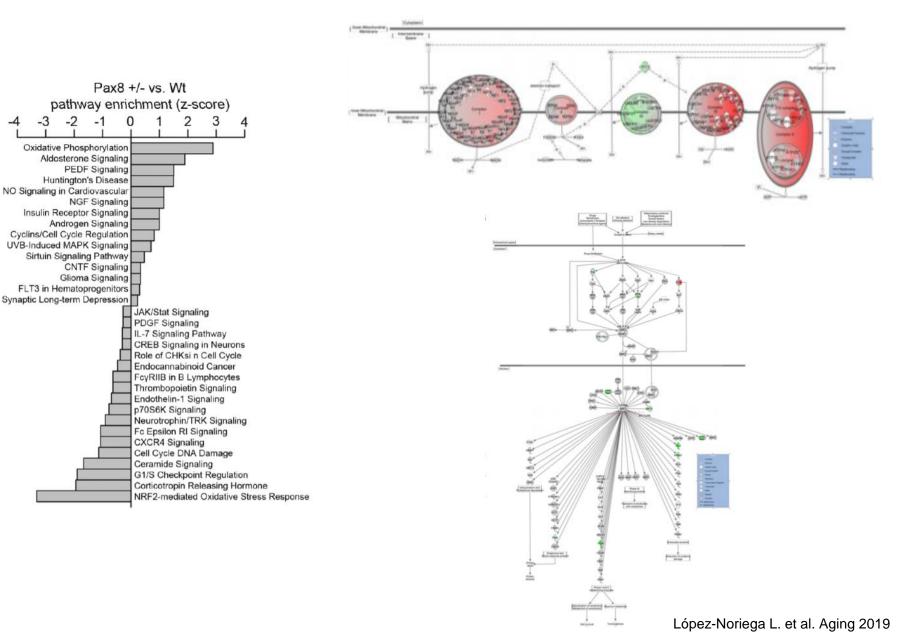
Mild hypothyroid mice have a distinct transcriptional profile



López-Noriega L. et al. Aging 2019

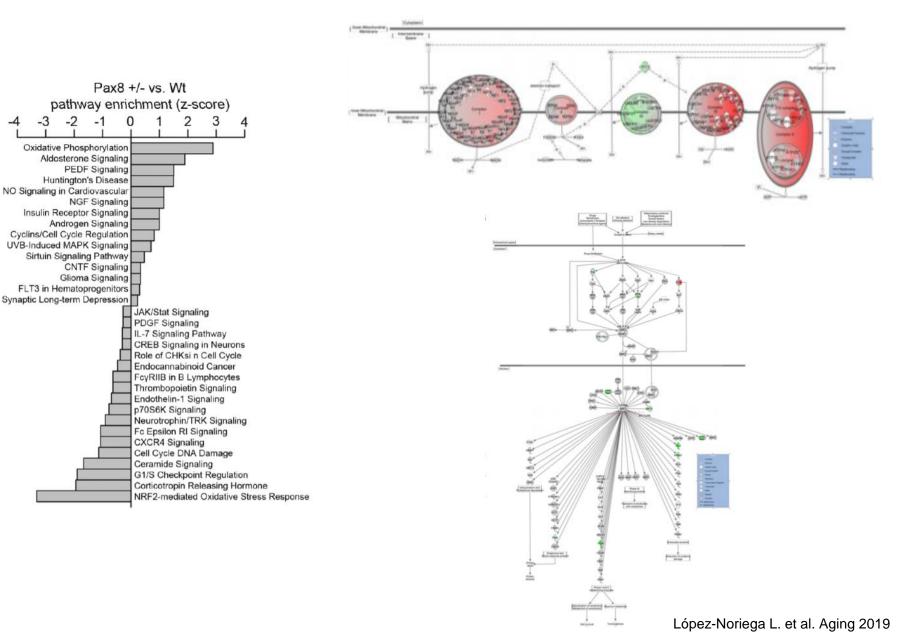
Mild hypothyroid mice have a distinct transcriptional profile

-2

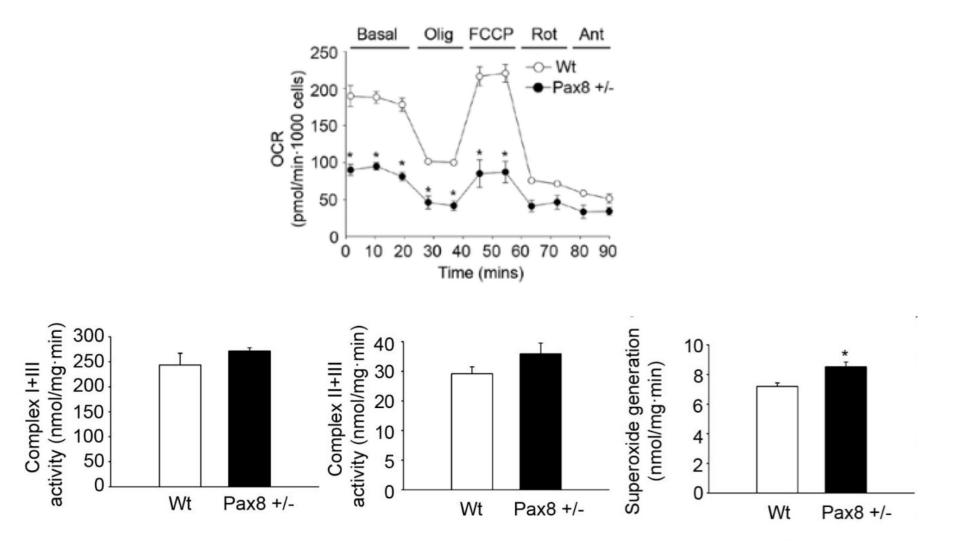


Mild hypothyroid mice have a distinct transcriptional profile

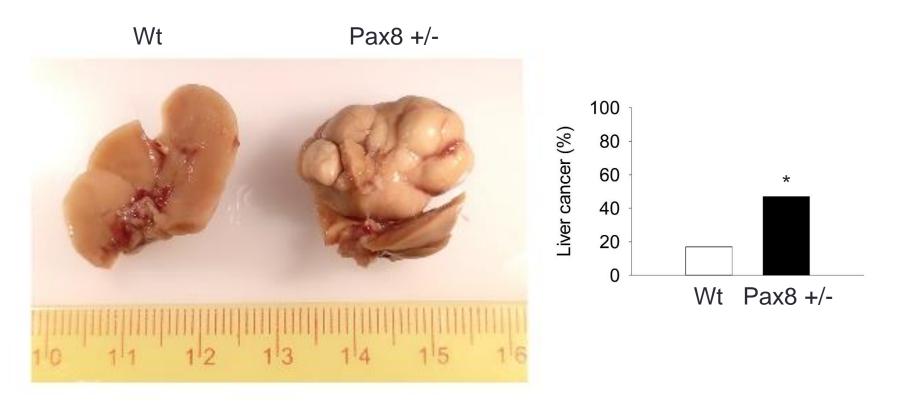
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Mild hypothyroidism is associated to increased ROS generation



Hypothyroidism increases spontaneous liver carcinogenesis



López-Noriega L. et al. Aging 2019

The thyroid axis alter mechanisms of aging and cancer

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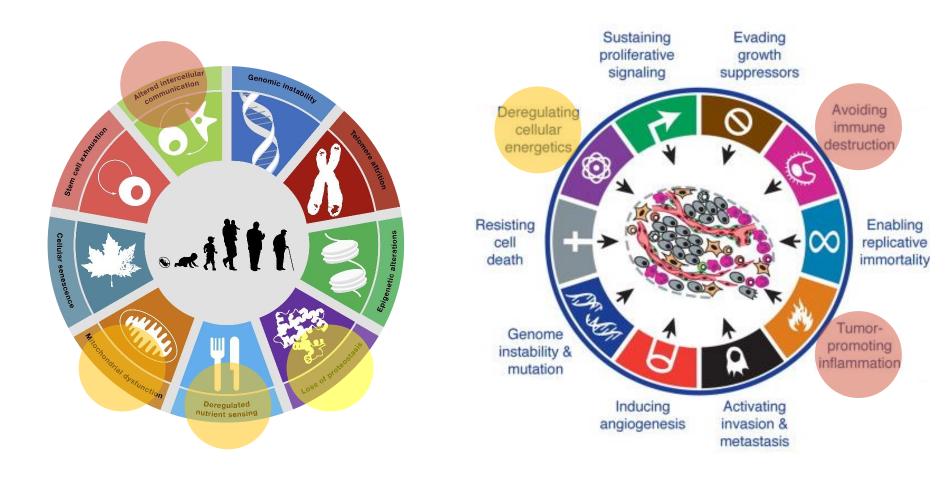


The Hallmarks of Aging

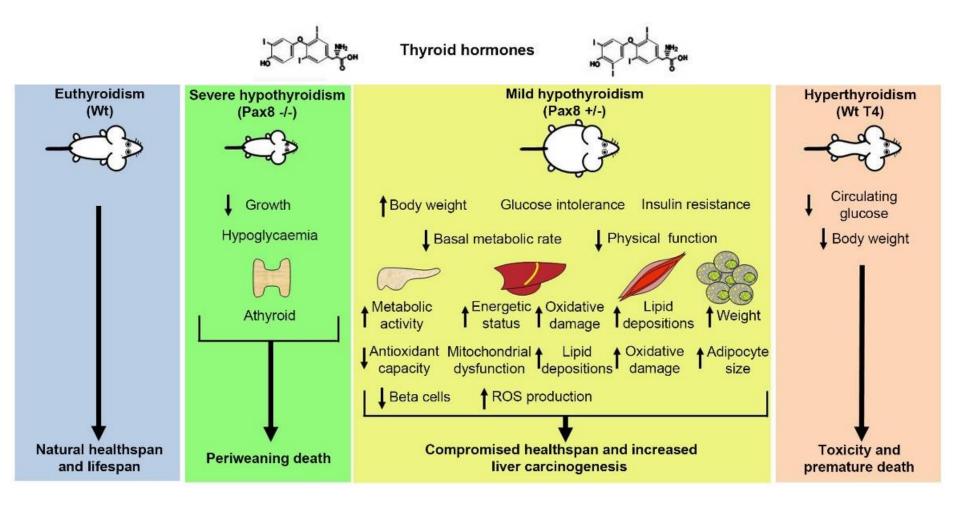
Carlos López-Otín,¹ Maria A. Blasco,² Linda Partridge,^{3,4} Manuel Serrano,^{5,*} and Guido Kroemer^{6,7,8,9,10}

Hallmarks of Cancer: The Next Generation

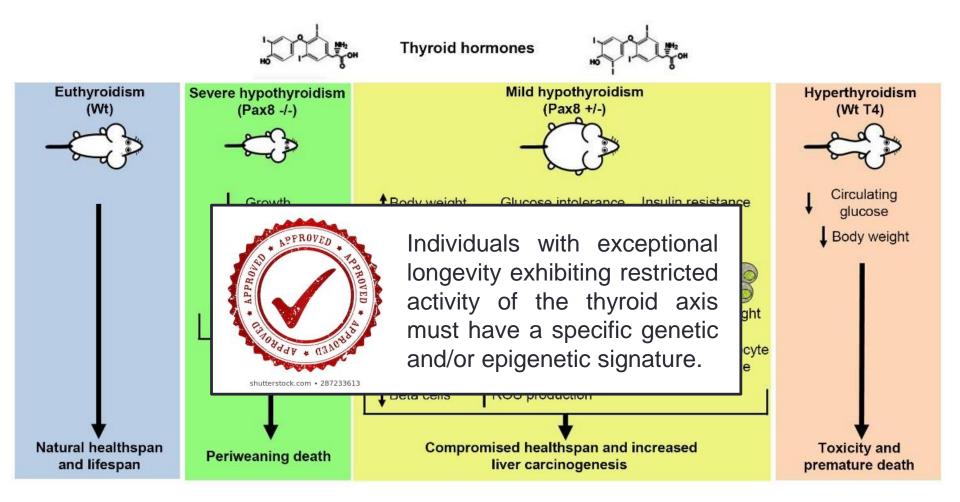
Douglas Hanahan^{1,2,*} and Robert A. Weinberg^{3,*}



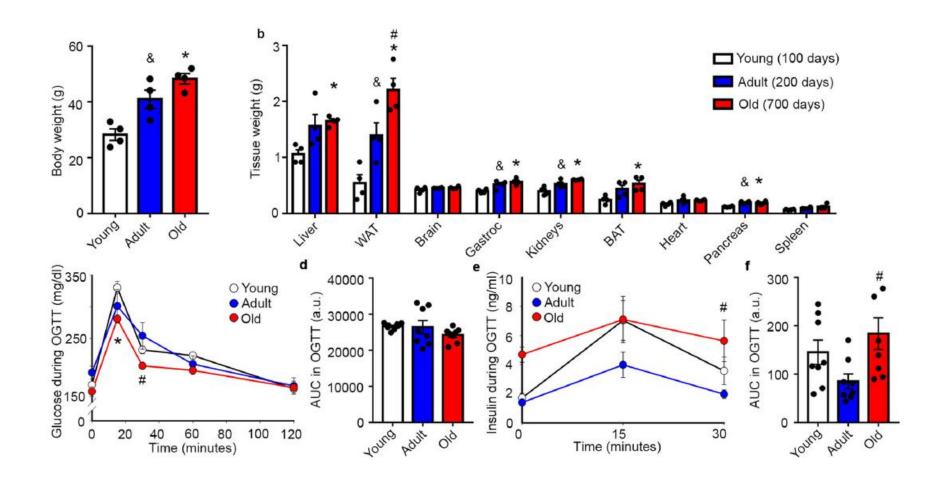
A delicate balance of thyroid function in health and survival



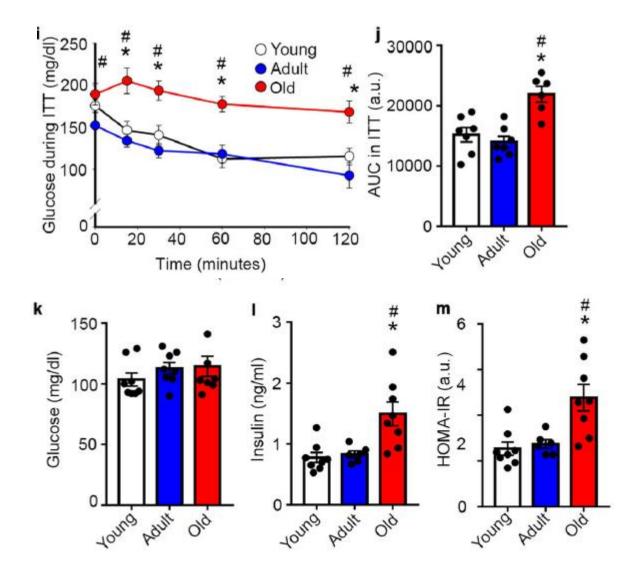
A delicate balance of thyroid function in health and survival



Another approach, what is wrong with aging?



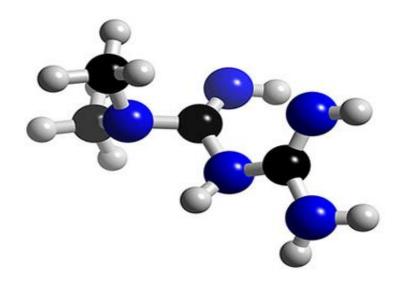
Another approach, what is wrong with aging?



Metformin extends lifespan

Metformin is the most widely prescribed antidiabetic drug.

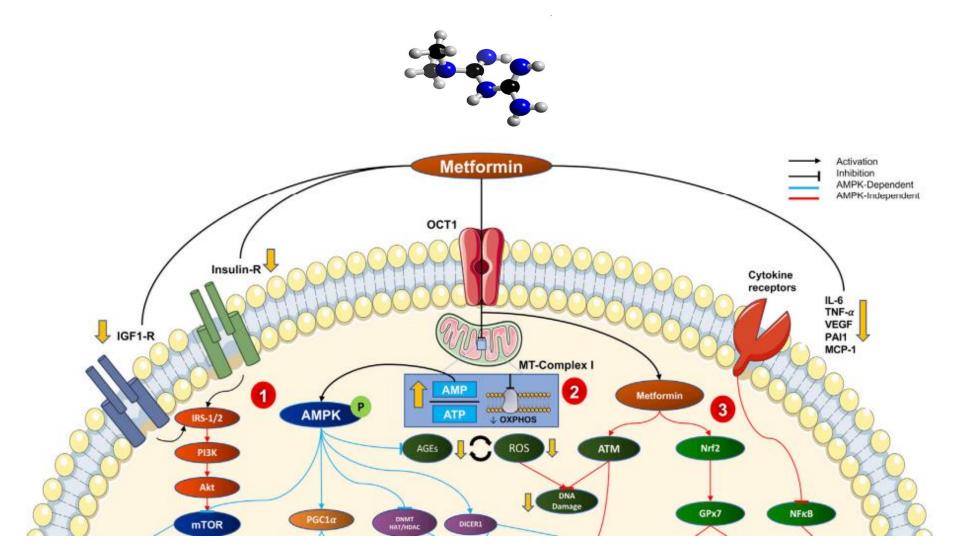




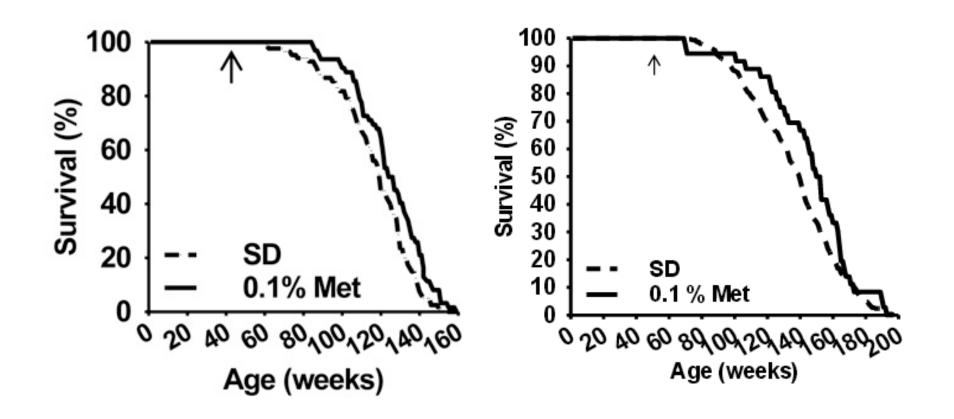
 $\begin{array}{c} \text{Metformin} \\ \text{C}_4\text{H}_{11}\text{N}_5 \end{array}$

Galega officinalis

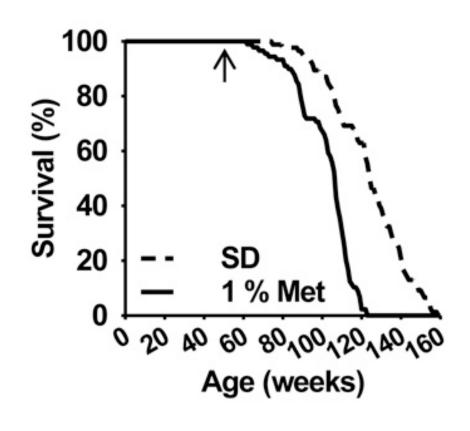
The mechanism of action of metformin: "cellular hunger"

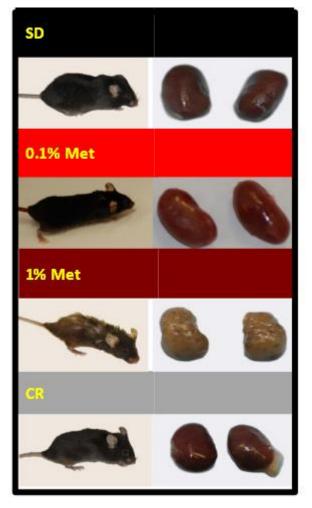


Metformin extends lifespan in mice

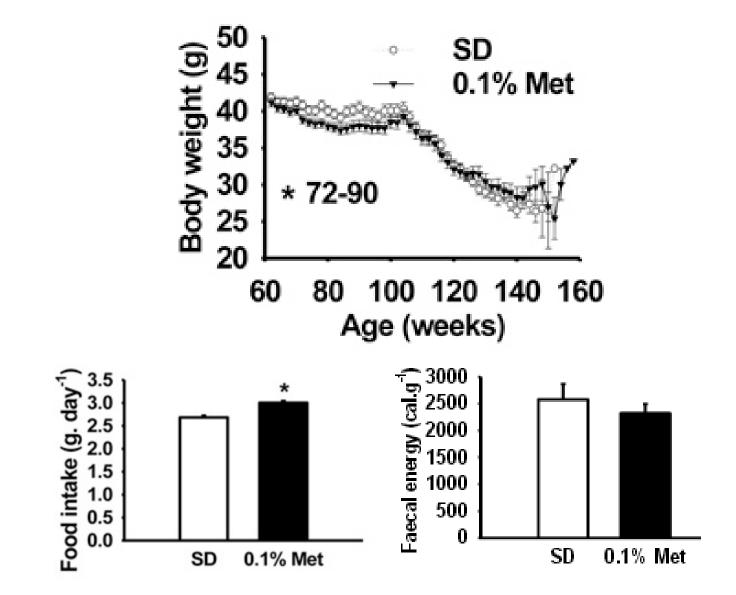


Less is more!

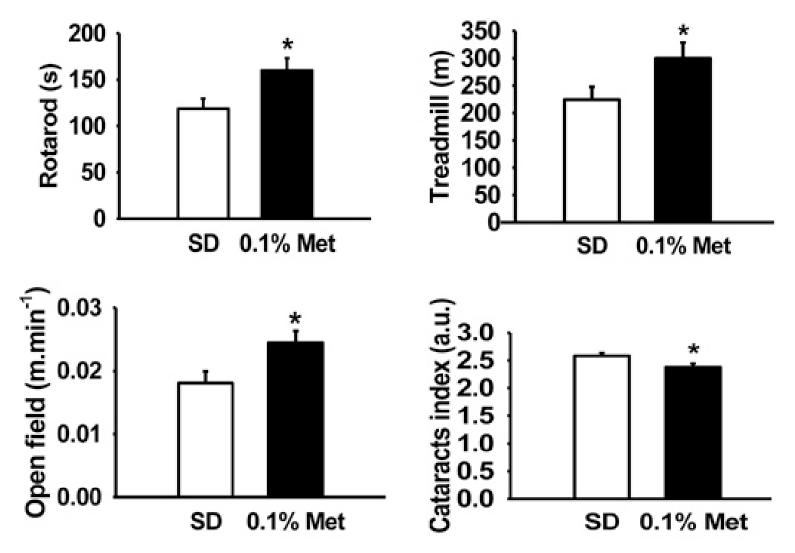




Metformin reduces body weight



Metformin improves healthspan

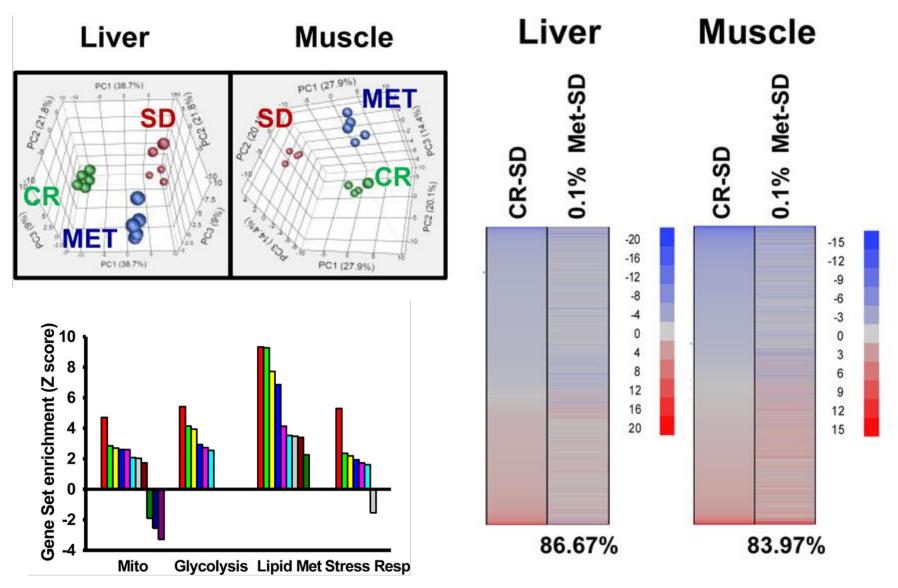


Martin-Montalvo A. et al. Nature Communications 2013

Metformin improves serum biomarkers

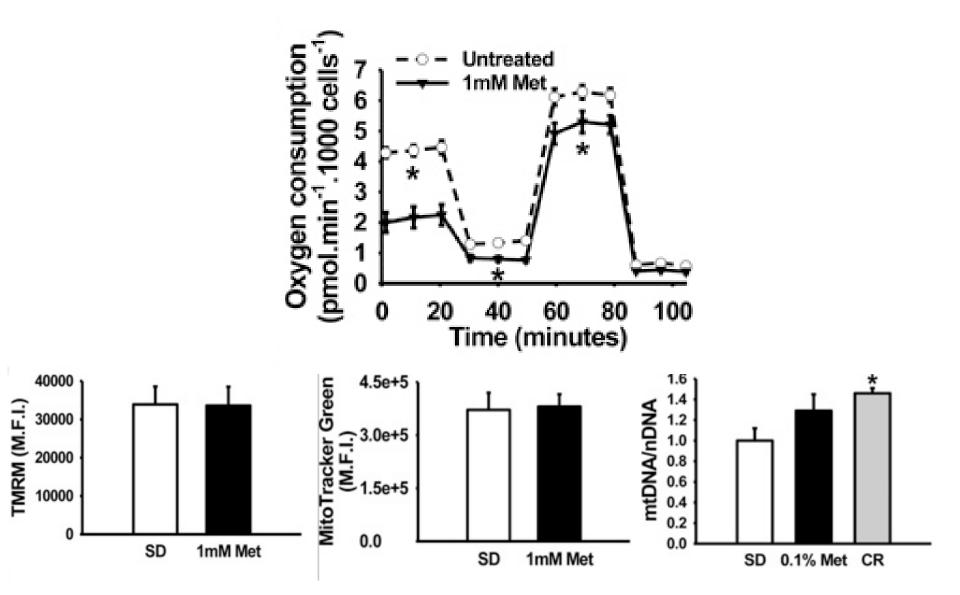
Parameter	Standard Diet (SD)	0.1% Metformin	CR
Ala aminotransferase (U/L)	90 ± 58	64 ± 29	50 ± 15
Cholesterol (mg/dl)	221 ± 30	143 ± 33 [*]	101 ± 8 [*]
Creatinine (mg/dl)	0.11 ± 0.01	0.13 ± 0.01 [*]	0.27 ± 0.25
Lactate	573 ± 82	623 ± 165	443 ± 109
Dehydrogenase (u/L)			
Low Density	40 ± 10	17 ± 10 [±]	16 ± 5 [±]
Lipoprotein (mg/dl)			
Triglycerides (mg/dl)	106 ± 28	129 ± 50	45 ± 7 [*]
Total protein (g/dl)	6.00 ± 0.39	6.04 ± 0.32	5.28 ± 0.04 [*]
Glucose-fed (mM)	10.94 ± 0.35	11.33 ± 0.76	ND
Glucose–fasted (mM)	8.23 ± 0.65	8.80 ± 0.43	4.10 ± 0.42 [*]
Insulin (pM)	428.08 ± 34.26	297.64 ± 29.72 [*]	46.75 ± 16.76
%HbA1c	6.33±0.47	5.81 ± 0.57 [*]	ND
HOMA-IR index	8.01 ± 0.57	5.87 ± 0.47 [*]	0.84 ± 0.30 [*]

Metformin mimics calorie restriction

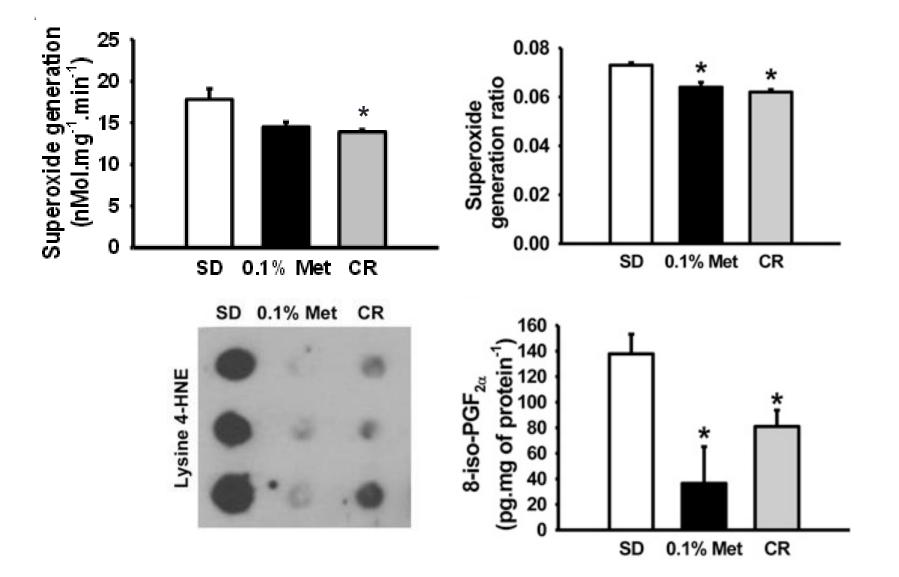


Martin-Montalvo A. et al. Nature Communications 2013

Metformin targets mitocondrial metabolism



Metformin reduces oxidative damage



Effects of metformin on the hallmarks of cancer and aging

Leading Edge Review

Cell

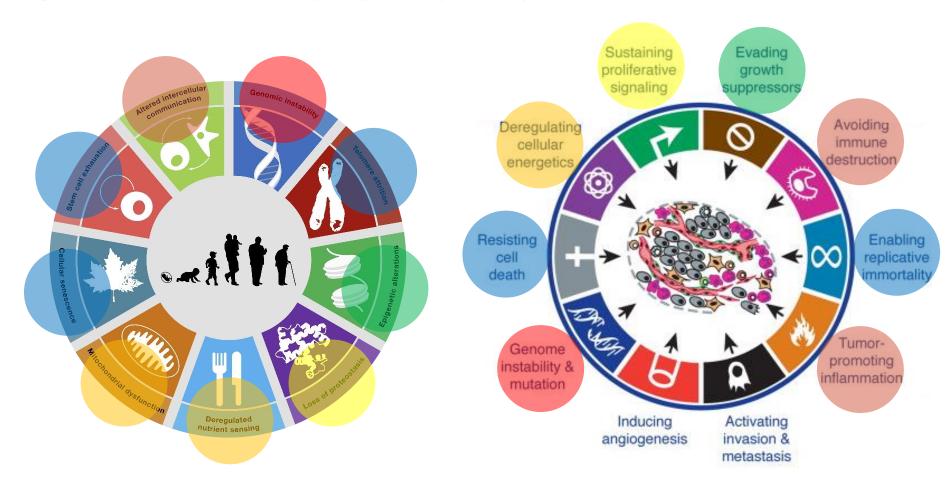
Leading Edge Review

The Hallmarks of Aging

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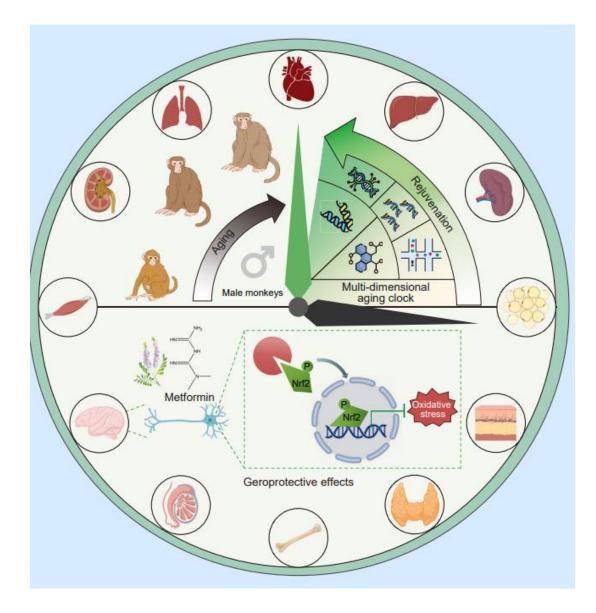
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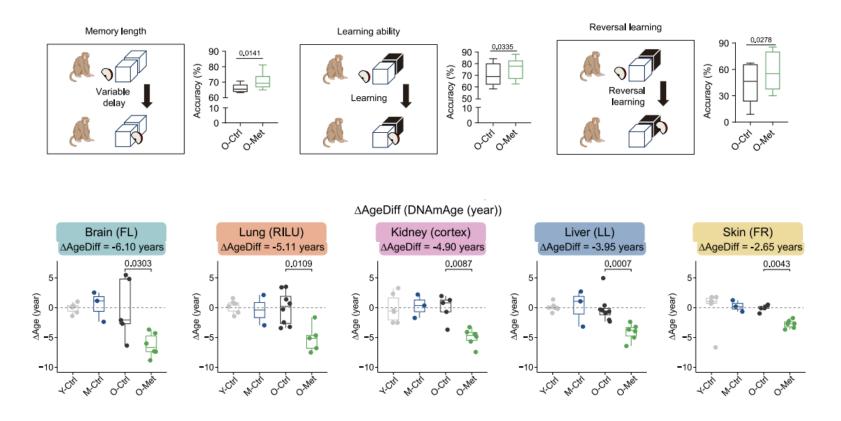


Cell

Metformin, a cheap molecule extensively used in humans



Metformin resets the aging clock in monkeys



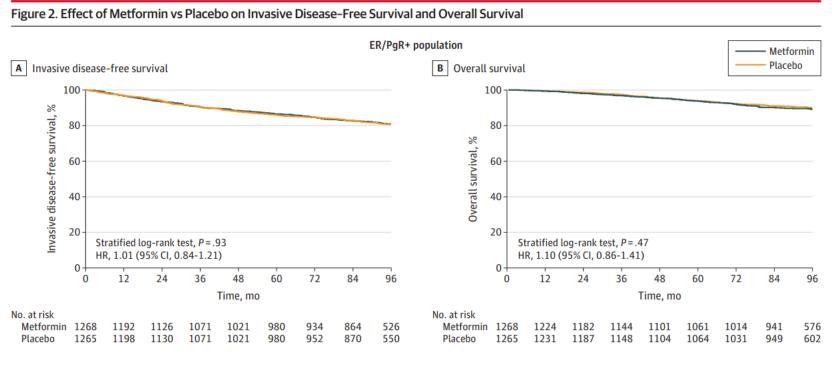
Yang et al. Cell 2024

Metformin reduces risk of cancer in diabetic patients

Metformin use in patients with type 2 diabetes and controls in Tayside, Scotland, 1993-2001

	No (%)			
	Cases (n=983)	Controls (n=1846)	Unadjusted odds ratios (95% CI)	Adjusted odds ratios (95% CI)
Exposure during year before index date:				
No	587 (63.6)	1114 (60.4)	1.00	1.00
Yes	336 (36.4)	732 (39.7)	0.86 (0.73 to 1.02)	0.85 (0.71 to 1.01)
Any exposure to metformin since January	/ 1993:			
No	547 (59.3)	996 (54.0)	1.00	1.00
Yes	376 (40.7)	850 (46.0)	0.79 (0.67 to 0.93)	0.77 (0.64 to 0.92)
Duration (days):				
0	547 (59.3)	996 (54.0)	1.00	1.00
1-634	127 (13.8)	282 (15.3)	0.81 (0.64 to 1.02)	0.80 (0.62 to 1.02)
635-1806	143 (15.5)	273 (14.8)	0.93 (0.74 to 1.17)	0.92 (0.72 to 1.17)
>1806	106 (11.5)	295 (16.0)	0.62 (0.47 to 0.80)	0.56 (0.43 to 0.74)
Total prescriptions dispensed:				
0	547 (59.3)	996 (54.0)	1.00	1.00
1-11	127 (13.8)	282 (15.3)	0.82 (0.65 to 1.04)	0.82 (0.64 to 1.04)
12-31	122 (13.2)	281 (15.2)	0.77 (0.61 to 0.99)	0.75 (0.58 to 0.97)
>31	127 (13.8)	291 (15.8)	0.76 (0.60 to 0.98)	0.73 (0.56 to 0.94)
Total amount of metformin dispensed (m	g):			
0	547 (59.3)	996 (54.0)	1.00	1.00
14 000-672 000	130 (14.1)	279 (15.1)	0.84 (0.67 to 1.06)	0.83 (0.65 to 1.06)
673 000-964 000	138 (15.0)	279 (15.1)	0.88 (0.69 to 1.10)	0.86 (0.68 to 1.10)
>964 000	108 (11.7)	292 (15.8)	0.63 (0.49 to 0.82)	0.57 (0.43 to 0.75)

Metformin does not affect survival in patients with breast cancer

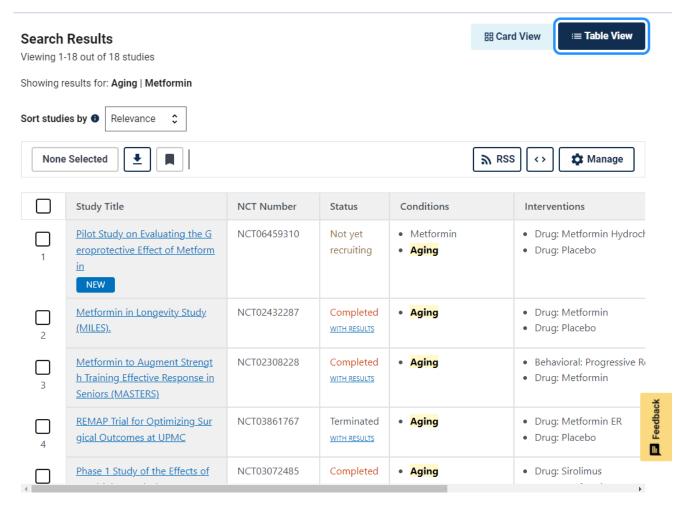


ER/pgR- population

Goodwin PJ etr al. JAMA 2022

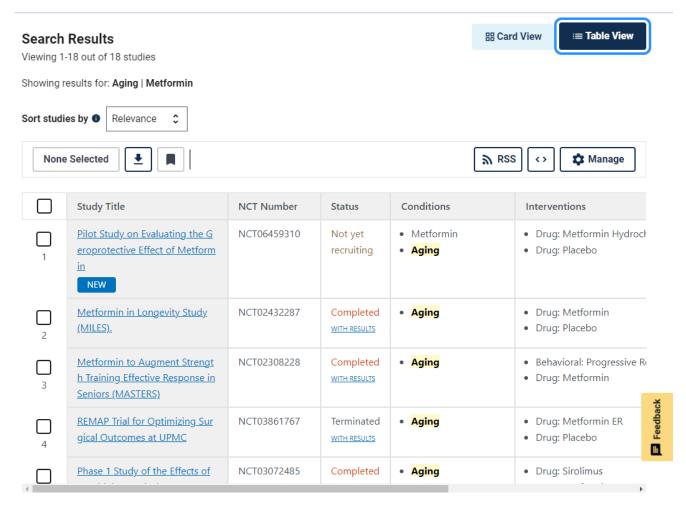
The need to do more research:

performing clinical trials targeting aging with Metformin



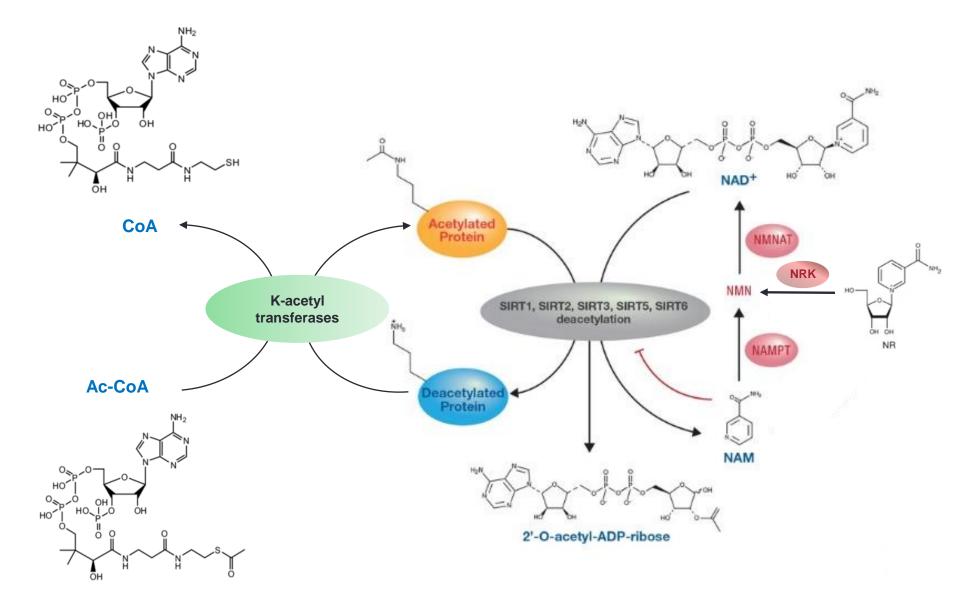
The need to do more research:

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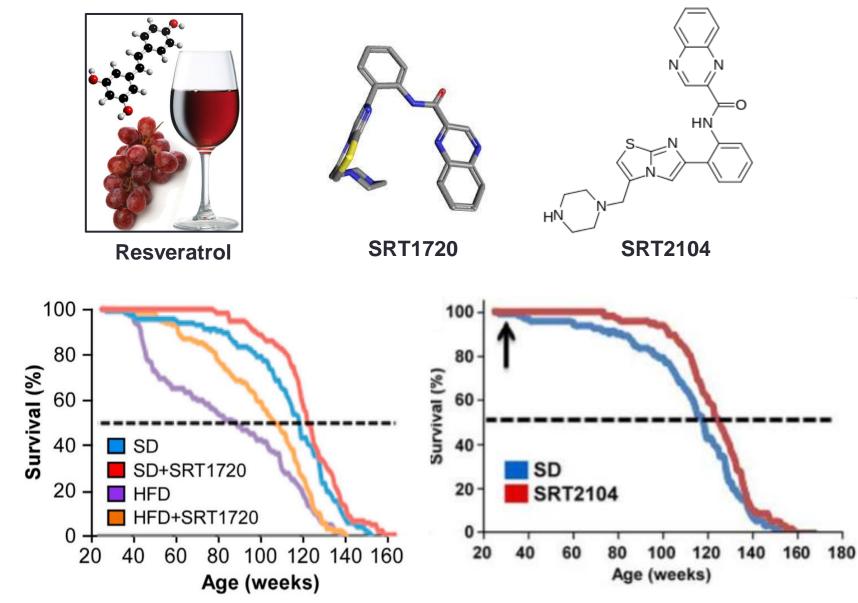


Metformin should not be taken without medical prescription

Another approach, the activation of sirtuins

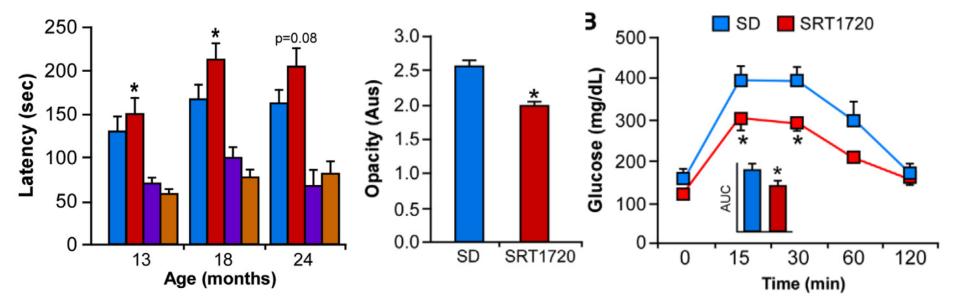


Sirtuin activation extends lifespan

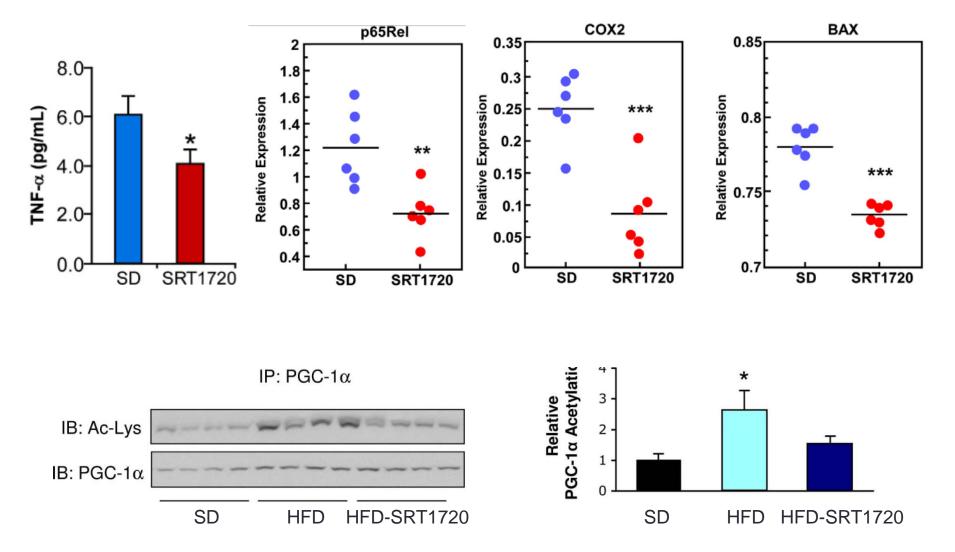


Mercken EM et al. Aging Cell 2014 Mitchell SJ*, Martín-Montalvo A* et al Cell Reports 2014

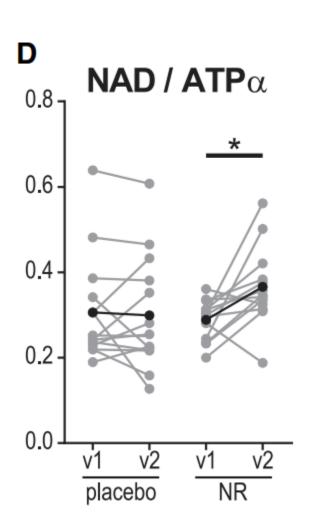
Sirtuin activation improves lifespan

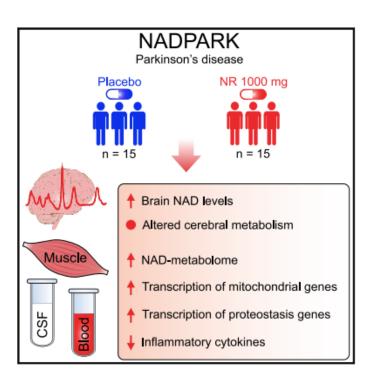


Sirtuin activation reduces inflammation



Nicotinamide riboside produces clinical improvements in Parkinson's disease

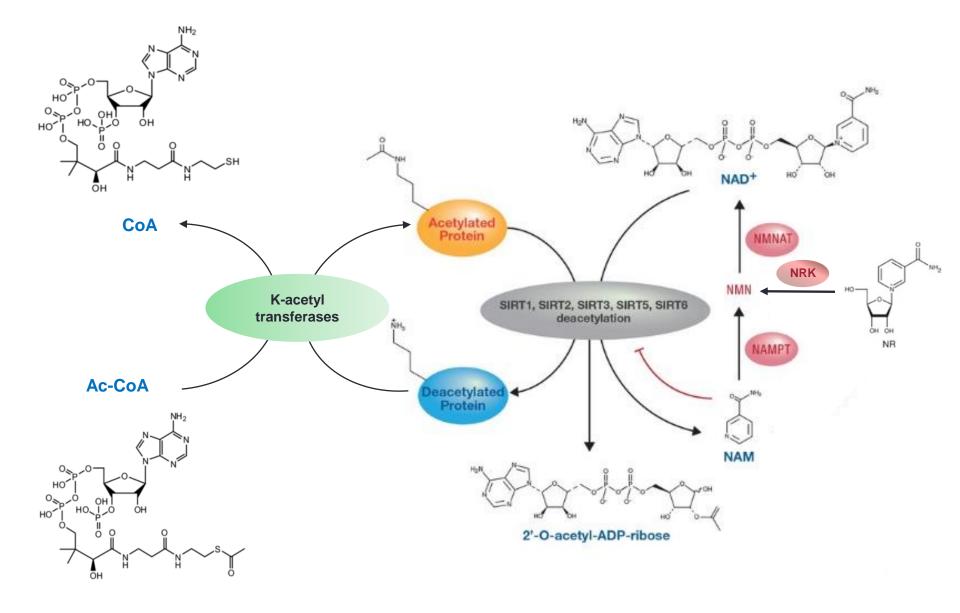




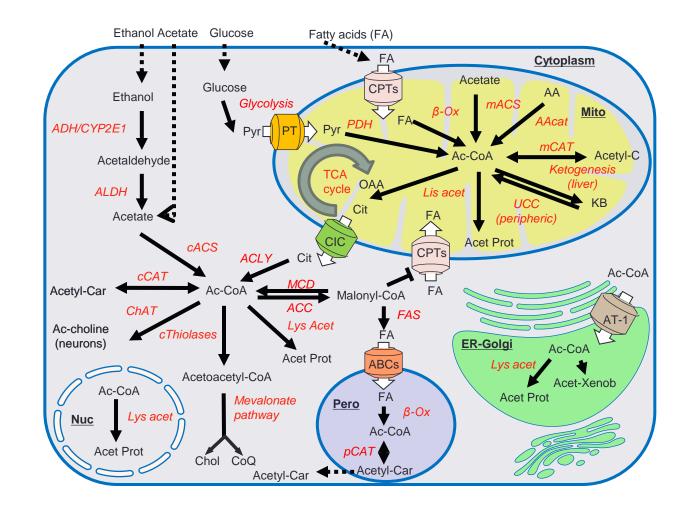
Highlights

- Oral NR increases brain NAD levels in individuals with Parkinson's disease
- NR intake alters cerebral metabolism in Parkinson's disease
- Cerebral NAD increase is associated with clinical improvement in Parkinson's disease
- NR induces transcription of mitochondrial, lysosomal, and proteasomal pathways

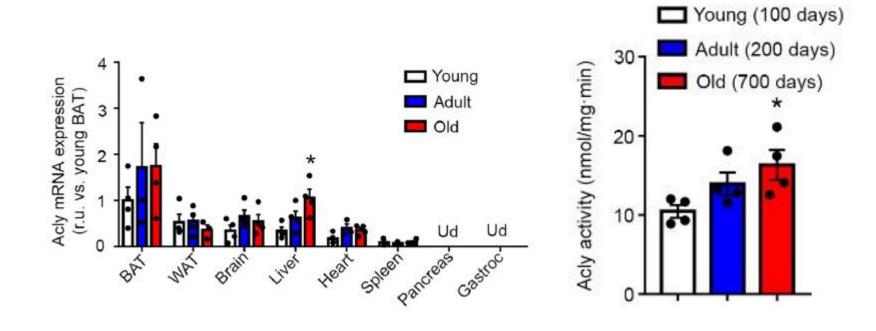
An alternative, could we mimic the activation of all sirtuins?



The main players in Ac-CoA metabolism

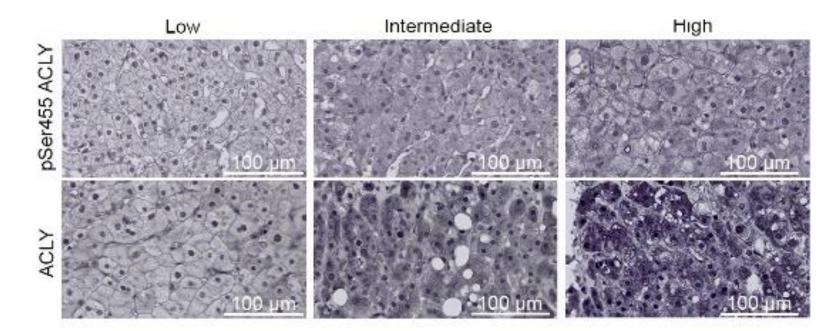


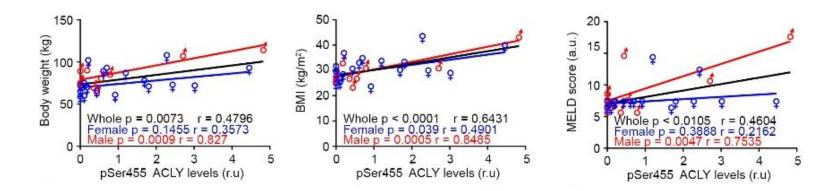
ATP-citrate lyase expression increases in liver with age



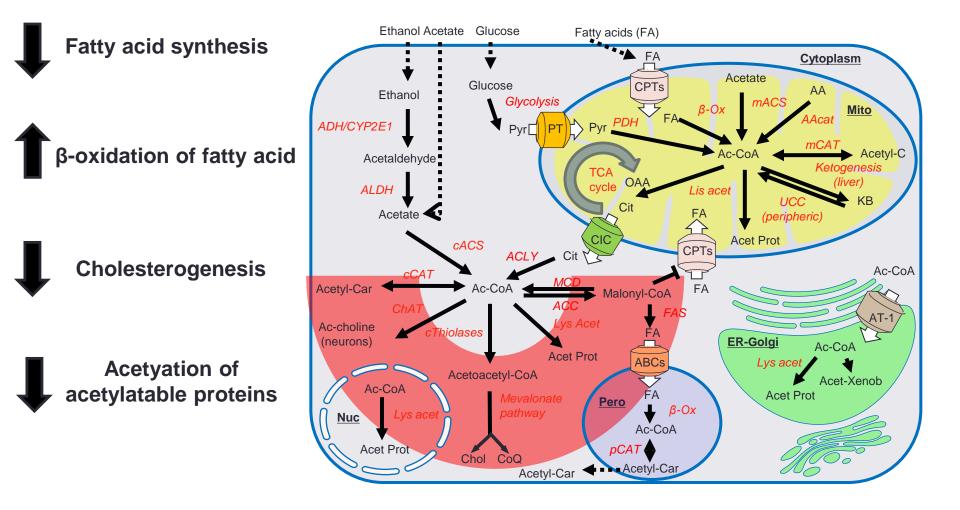
Sola-García et al. Comm. Biol 2023

pSer455 ACLY levels correlate with BMI and MELD in humans

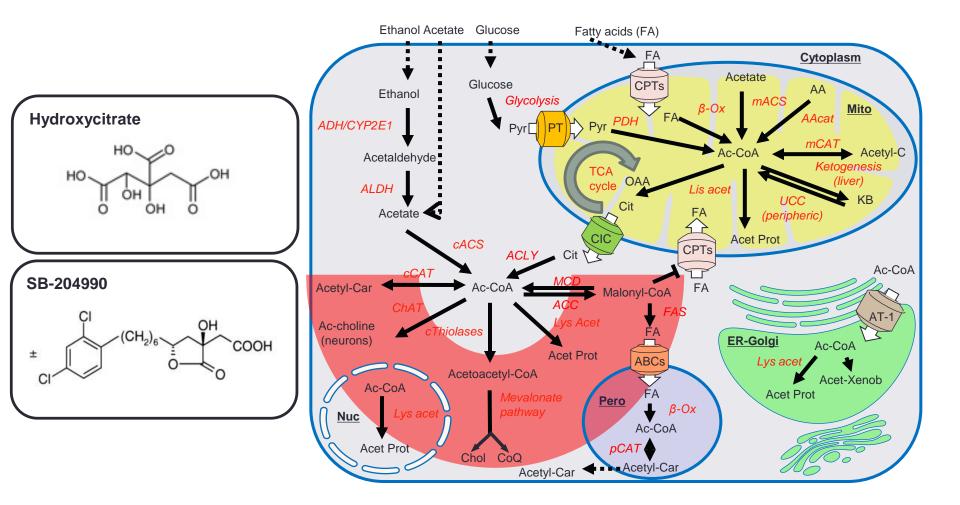




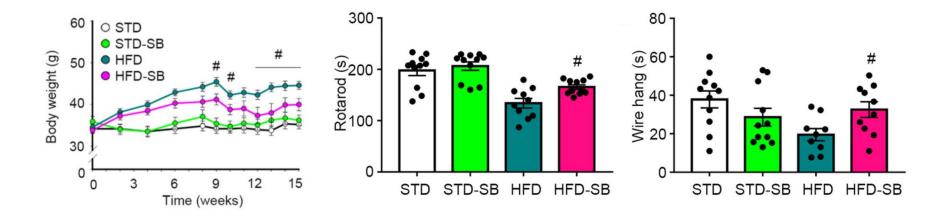
The relevance of Ac-CoA and ACLY inhibitors



ACLY inhibitors to intervene in glucose metabolism and aging



SB-204990 improves locomotor function in high fat diet

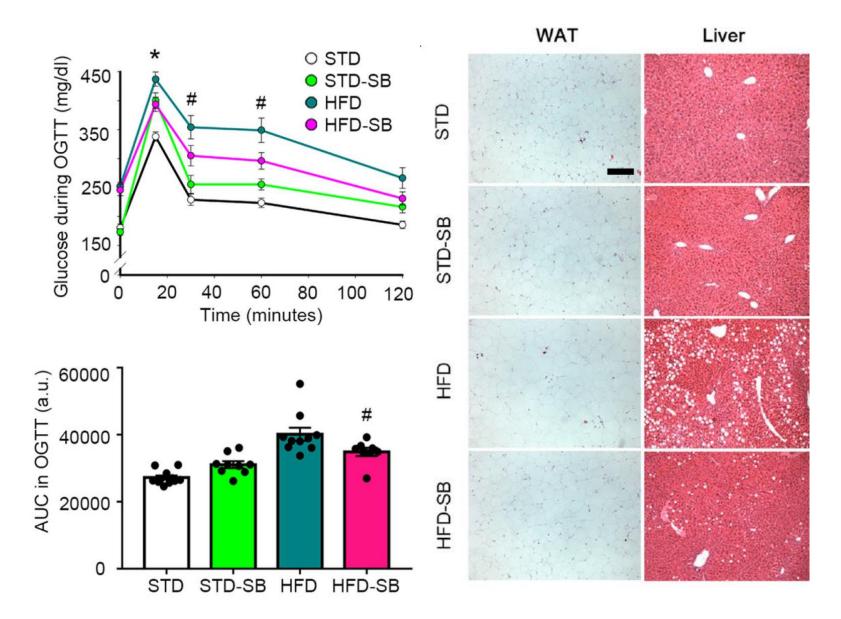




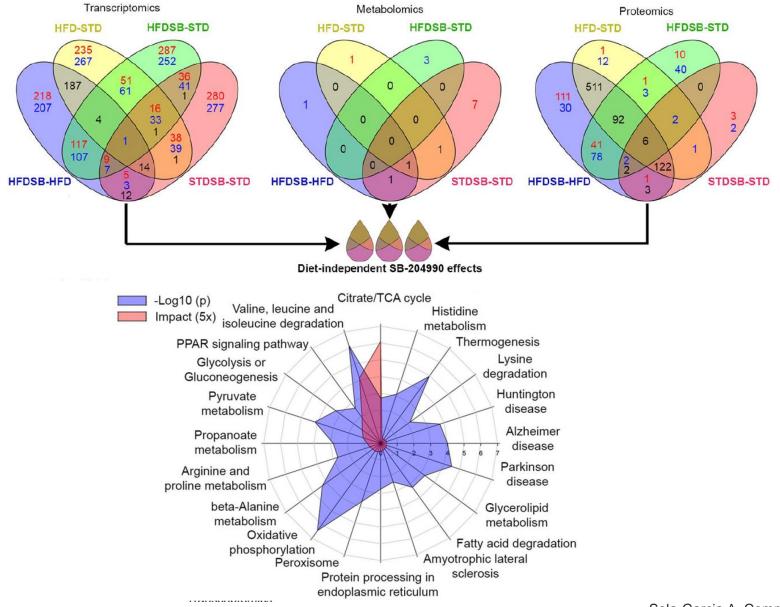


Sola-Garcia A. Comm. Biology 2023

SB-204990 reduces lipid inflantration in high fat diet



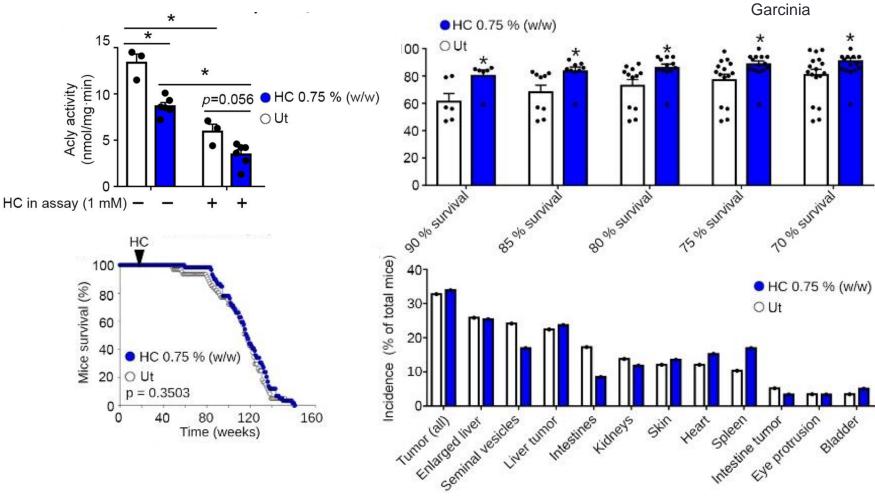
SB-204990 modulates mechanisms of aging



Sola-Garcia A. Comm. Biology 2023

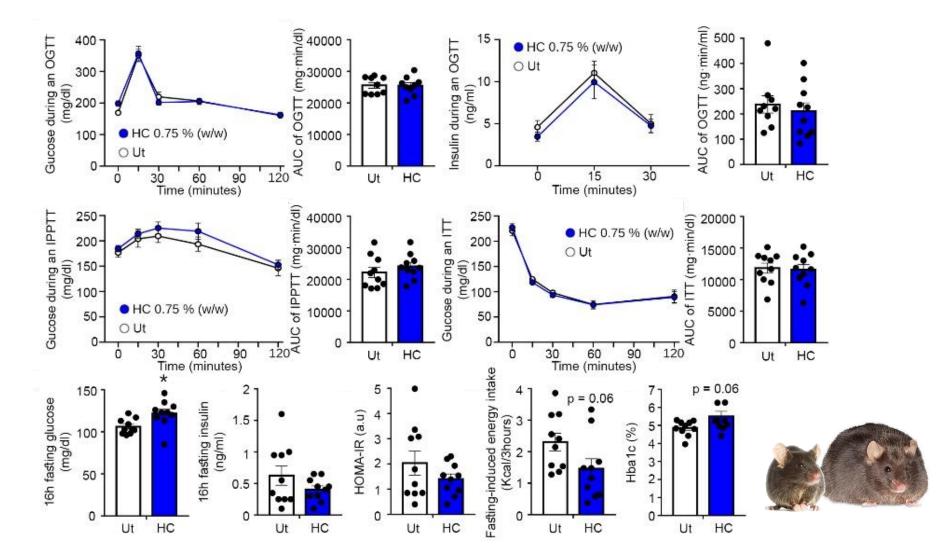
Hydroxycitrate delays early mortality



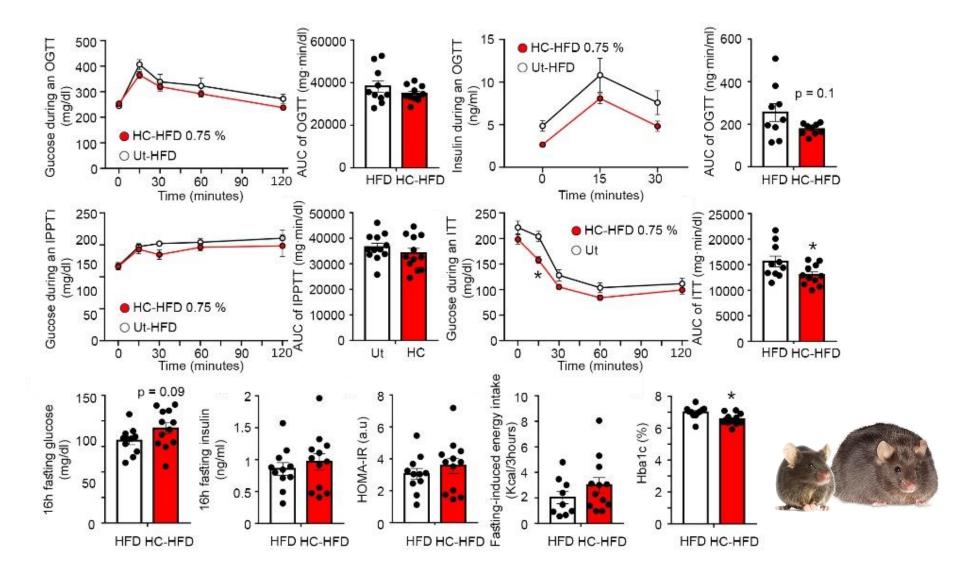


Espadas I. Aging Cell 2024

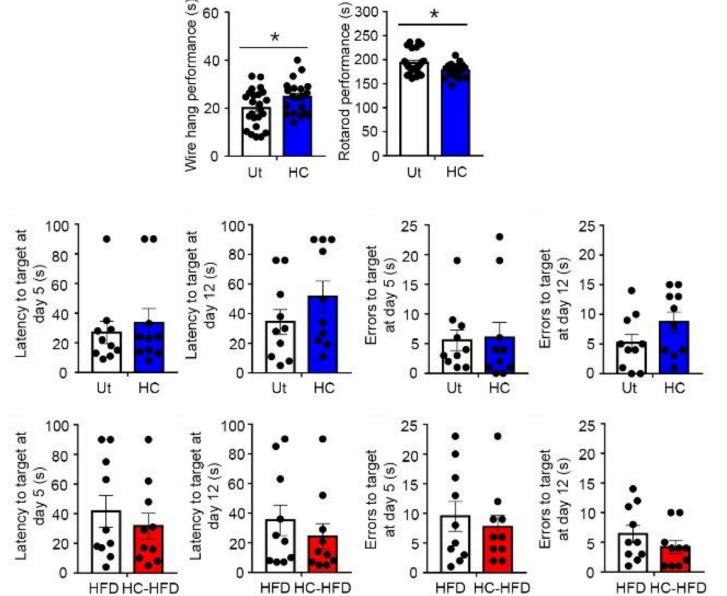
Hydroxycitrate has minor glucoregulatory in healthy-fed mice



Hydroxycitrate confers improvements in glucoregulation in HFD

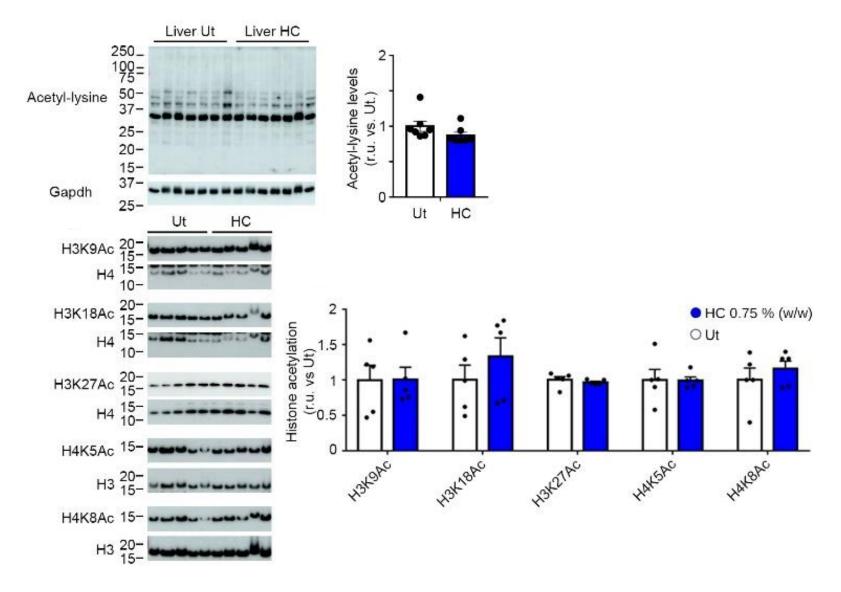


Hydroxycitrate does not alter neurocognitive function, and alters locomotor function

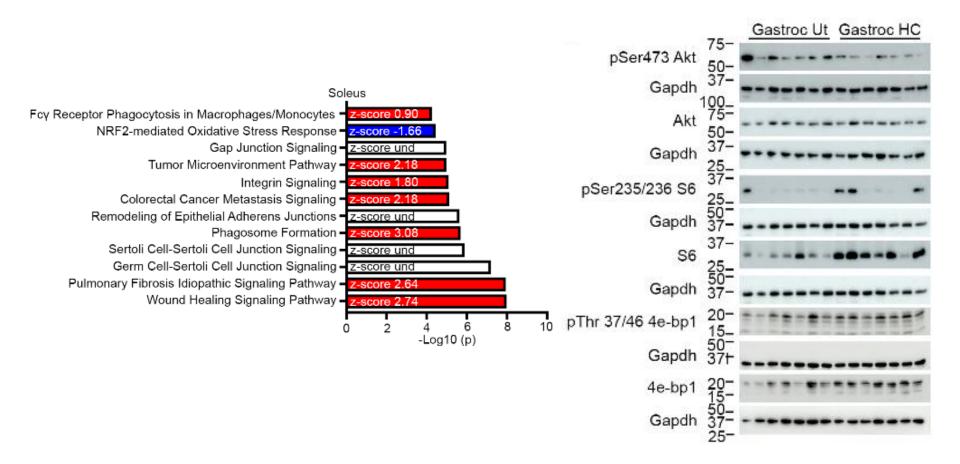


Espadas I. Aging Cell 2024

Hydroxycitrate does not alter protein acetylation levels

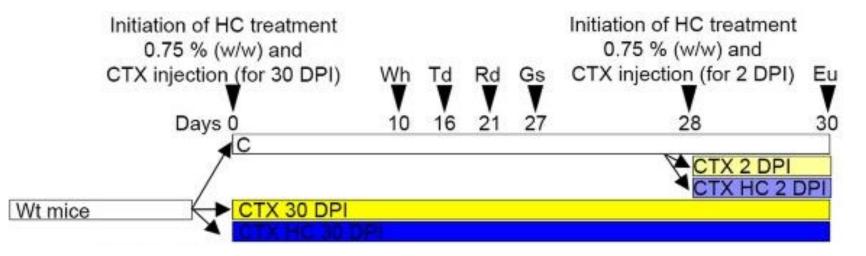


Hydroxycitrate enhances pathways related to muscle regeneration

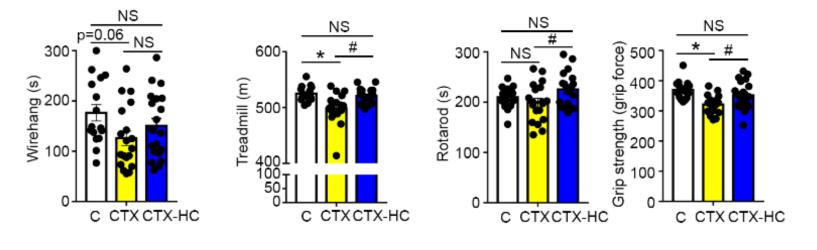


Hydroxycitrate in muscle de- and re-generation using CTX





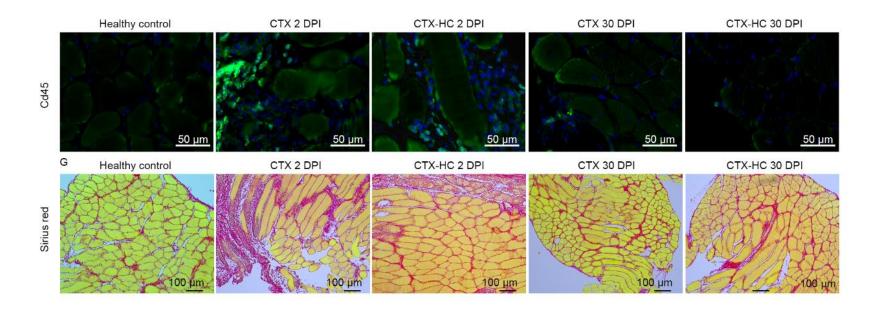
Hydroxycitrate improves physical function in CTX- treated mice

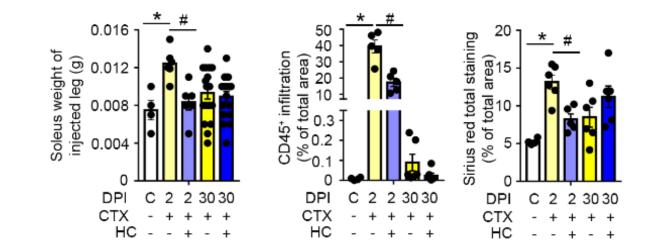




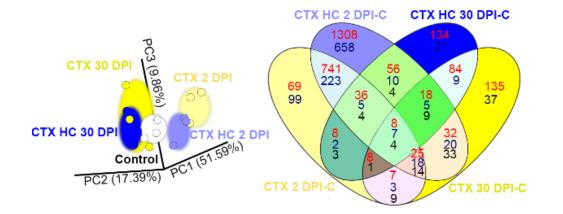


Hydroxycitrate reduces muscle swelling in mice treated with CTX





Hydroxycitrate enhances mechanisms of muscle regeneration





ACLY inhibition did not alter epigenetic alterations



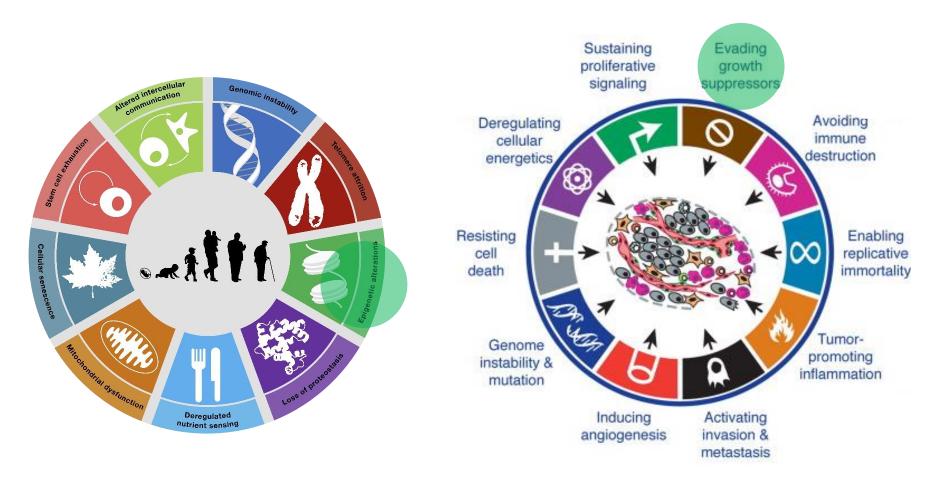
Leading Edge Review

The Hallmarks of Aging

Carlos López-Otín,¹ Maria A. Blasco,² Linda Partridge,^{3,4} Manuel Serrano,^{5,*} and Guido Kroemer^{6,7,8,9,10}

Hallmarks of Cancer: The Next Generation

Douglas Hanahan^{1,2,*} and Robert A. Weinberg^{3,*}



ACLY inhibition altered other hallmarks of aging

Leading Edge Cell Review

Leading Edge Review

The Hallmarks of Aging

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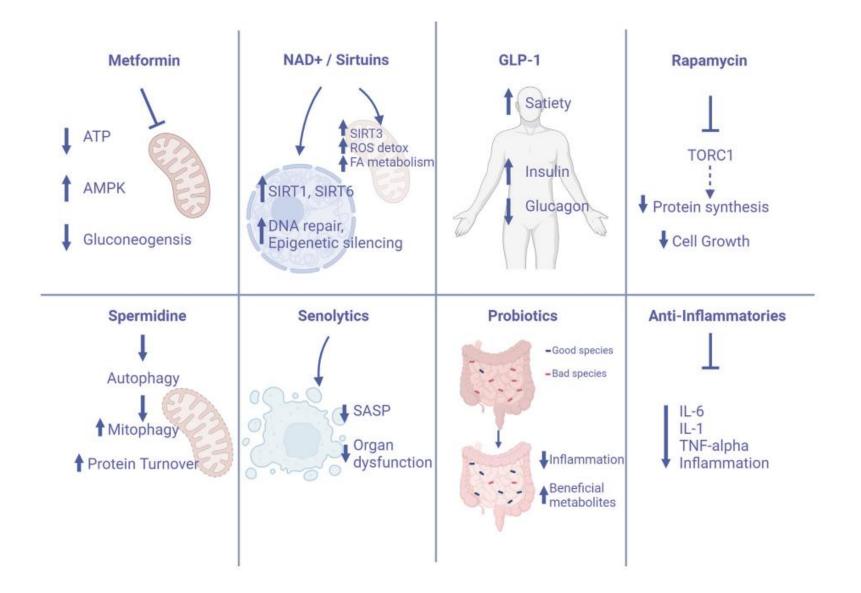
Hallmarks of Cancer: The Next Generation

Douglas Hanahan^{1,2,*} and Robert A. Weinberg^{3,*} Evading Sustaining proliferative growth Genomic instability signaling suppressors intercellular Avoiding Deregulating immune cellular destruction energetics Resisting Enabling Epigenetic alterations replicative cell immortality death Tumor-Genome promoting instability & inflammation Tal dysfunction mutation Inducing Activating Deregulated nutrient sensing invasion & angiogenesis metastasis

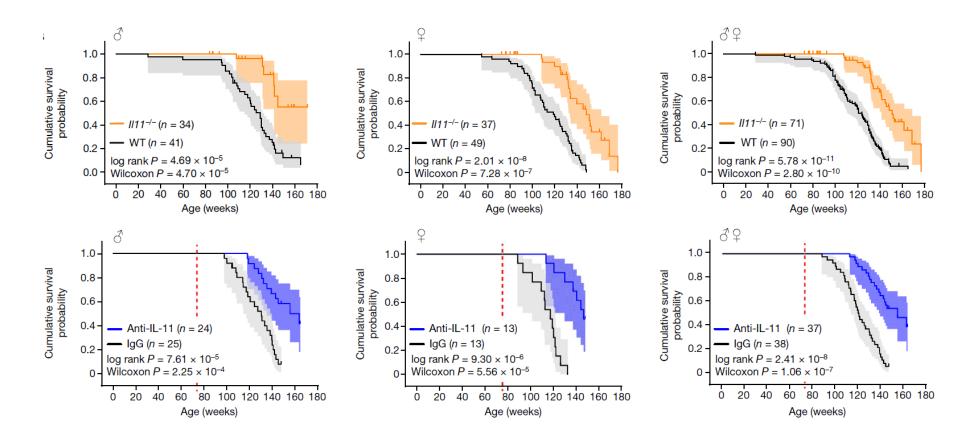
Stem Cell ett

Cellular senescenci

Other clinical trials targeting the aging process



Aging research is young but grows fast: IL-11 inhibition on lifespan



There is hope to age well!!!

Physical activity, mental activity, stress management and healthy diet



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Junta de Andalucía Consejería de Transformación Económica, Industria, Conocimiento y Universidades

Capimer

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AND REGENERATIVE MEDICINE

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