



67° CONGRESSO NAZIONALE SIGG

LA LONGEVITÀ DECLINATA AL FEMMINILE

Riccardo Calvani

IL LEGAME TRA RICERCA CLINICA E RICERCA BIOGERONTOLOGICA



SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Roma, 30 novembre - 3 dicembre 2022
UNIVERSITÀ CATTOLICA DEL SACRO CUORE



Outline

- **Translational medicine: «Death Valley», «Complexity», and «Mouse Traps»**
- **Geroscience: linking aging to chronic disease**
- **Geroprotectors: Hopes or Hypes?**



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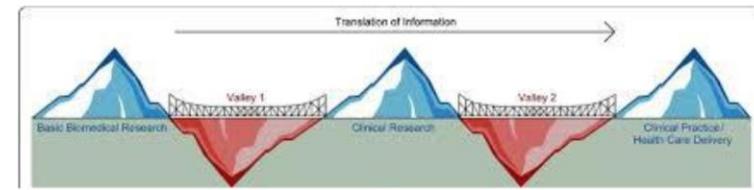
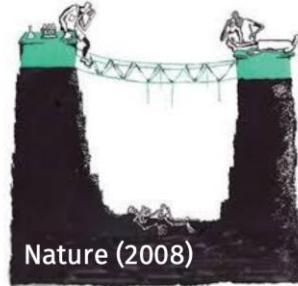


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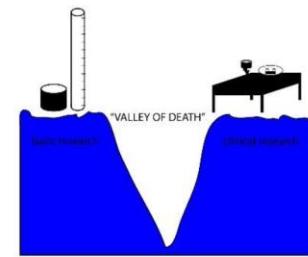
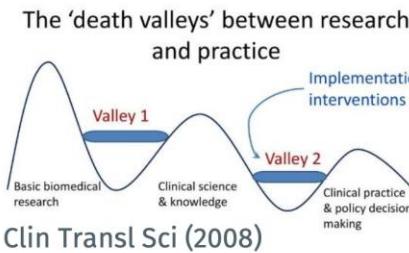
- **Translational medicine: «Death Valley», «Complexity», and «Mouse Traps»**
- **Geroscience: linking aging to chronic disease**
- **Geroprotectors: Hopes or Hypes?**



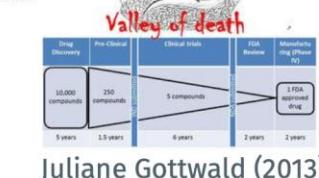
Death Valley



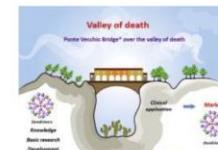
Canadian journal of kidney health and disease 2015



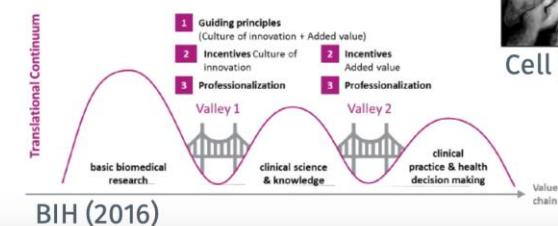
Genomic Enterprise
(2011)



Juliane Gottwald (2013)



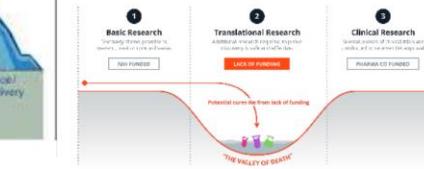
Advanced Drug Delivery
Reviews 2018



BIH (2016)



Gesundheitsindustrie-BW (2018)



HaloCures (2008)

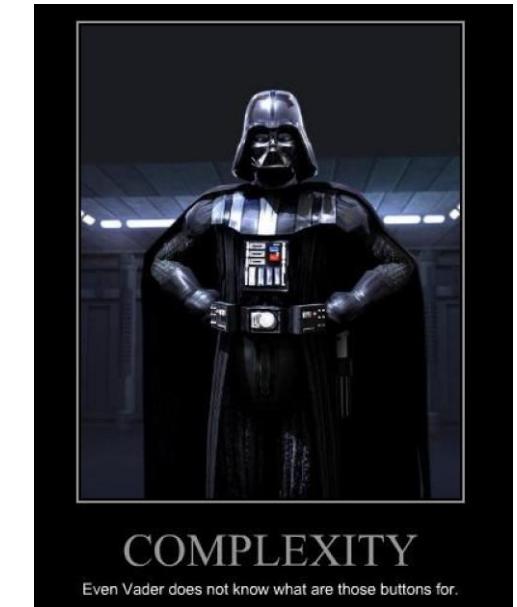
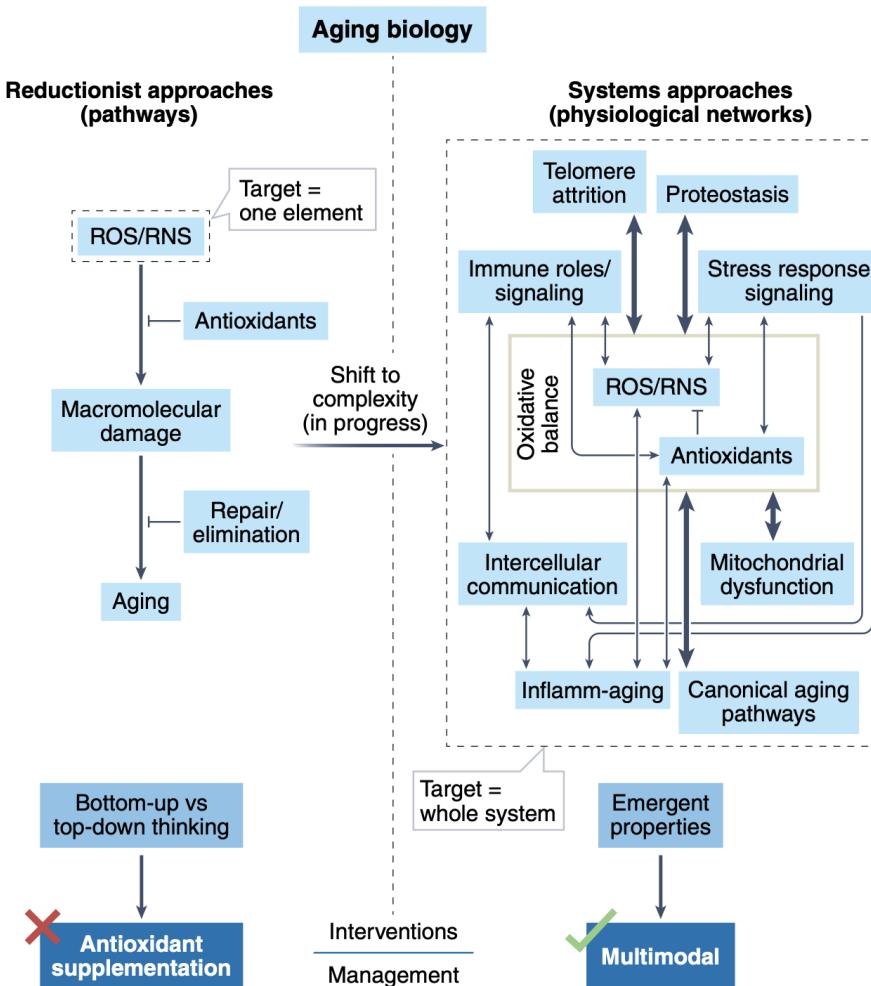


USF Health News (2008)



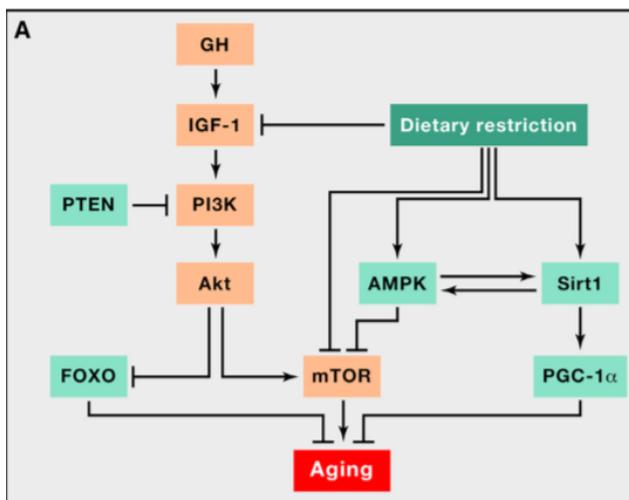
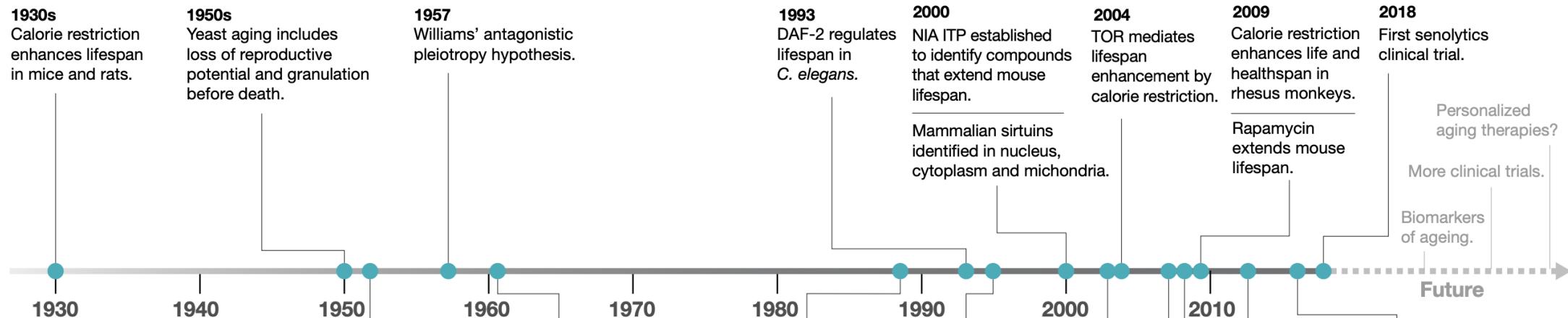


Complexity





Mouse traps



1952
Medawar's mutation accumulation theory.

1961
Hayflick limit proposed.

1988
AGE-1 enhances lifespan in *C. elegans*.

1995
Sir2 regulates aging in yeast.
Senescence observed in human aging.

2003
Sirtuin activators extend lifespan in yeast.

2016
Targeting senescence improves healthspan in mice.

TAME trial in humans.

2013
Metformin extends mouse life and healthspan.

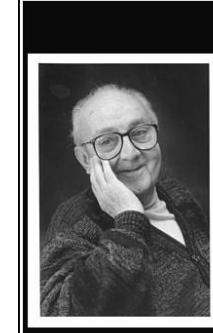


Table 1 | Conserved ageing phenotypes

Phenotype	<i>H. sapiens</i>	<i>M. musculus</i>	<i>D. melanogaster</i>	<i>C. elegans</i>
Decreased cardiac function	Yes	Yes	Yes	NA
Apoptosis, senescence (somatic cells)	Yes	Yes	Yes	?
Cancer, hyperplasia	Yes	Yes	No	No
Genome instability	Yes	Yes	Yes	Yes
Macromolecular aggregates	Yes	Yes	Yes	Yes
Reduced memory and learning	Yes	Yes	Yes	NA
Decline in GH, DHEA, testosterone, IGF	Yes	Yes	?	?
Increase in gonadotropins, insulin	Yes	Yes	?	?
Decreased thyroid function	Yes	Yes	NA	NA
Decrease in innate immunity	Yes	Yes	Yes	Yes
Increase in inflammation	Yes	Yes	No	No
Skin/cuticle morphology changes	Yes	Yes	?	Yes
Decreased mitochondrial function	Yes	Yes	Yes	Yes
Sarcopenia	Yes	Yes	Yes	Yes
Osteoporosis	Yes	Yes	NA	NA
Abnormal sleep/rest patterns	Yes	Yes	Yes	?
Decrease in vision	Yes	Yes	?	NA
Demyelination	Yes	Yes	?	No
Decreased fitness	Yes	Yes	Yes	Yes
Arteriosclerosis	Yes	No	NA	NA
Changes in fat*	Yes	Yes	?	?

* Although changes in fat content and distribution have been reported for long-lived invertebrate mutants, at present there are no data on fat-related changes during normal ageing in these organisms. GH, growth hormone; DHEA, dehydroandrosterone; NA, not applicable.

NATURE|Vol 454|28 August 2008



Essentially, all models are wrong, but some are useful.

(George E. P. Box)

izquotes.com

	Human	Rat ^a	Times faster in rat	One human year ≈ rat days	One human day ≈ rat hours	One human hour ≈ rat minutes
m/tRNA turnover (12, 14, 15)	0.8/day/kg	2/day/kg	2.5			
Protein turnover (12, 13)	1.25/day/kg	12/day/kg	9.6			
Metabolic rate (16)	1.25 W/kg	8 W/kg	6.4			
Heart rate (21)	60–80	260–400	4.7			
Respiratory rate (21)	12–18	75–115	6.3			
Gestation (21, 22)	280 days	21–23 days	12.7	28.7	1.9	4.7
Weaning (8, 23)	180 days	21 days	8.6	42.6	2.8	7
Reaching sexual maturity (8, 23, 24)	4,197 days (11.5 years)	50 days	84	4.3	0.3	0.8
Reaching adulthood (8, 23, 24)	7,300 days (20 years)	210 days	35	10.5	0.7	1.7
Reaching reproductive senescence ^b (21)	18,615 days (51 years)	532 days (1.6 years)	35	10.4	0.7	1.7
Post-senescence (8, 23)	10,585 days (29 years)	486 days	22	16.8	1.1	2.7
Life span (8, 23)	29,200 days (80 years)	1,095 days (3 years)	26.7	13.7	0.9	2.3

^a*Rattus norvegicus*.

^bFemales only.

Front. Neurol. 8:92.

doi: 10.3389/fneur.2017.00092



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- **Geroscience: linking aging to chronic disease**
- **Geroprotectors: Hopes or Hypes?**



The Hallmarks of Aging

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

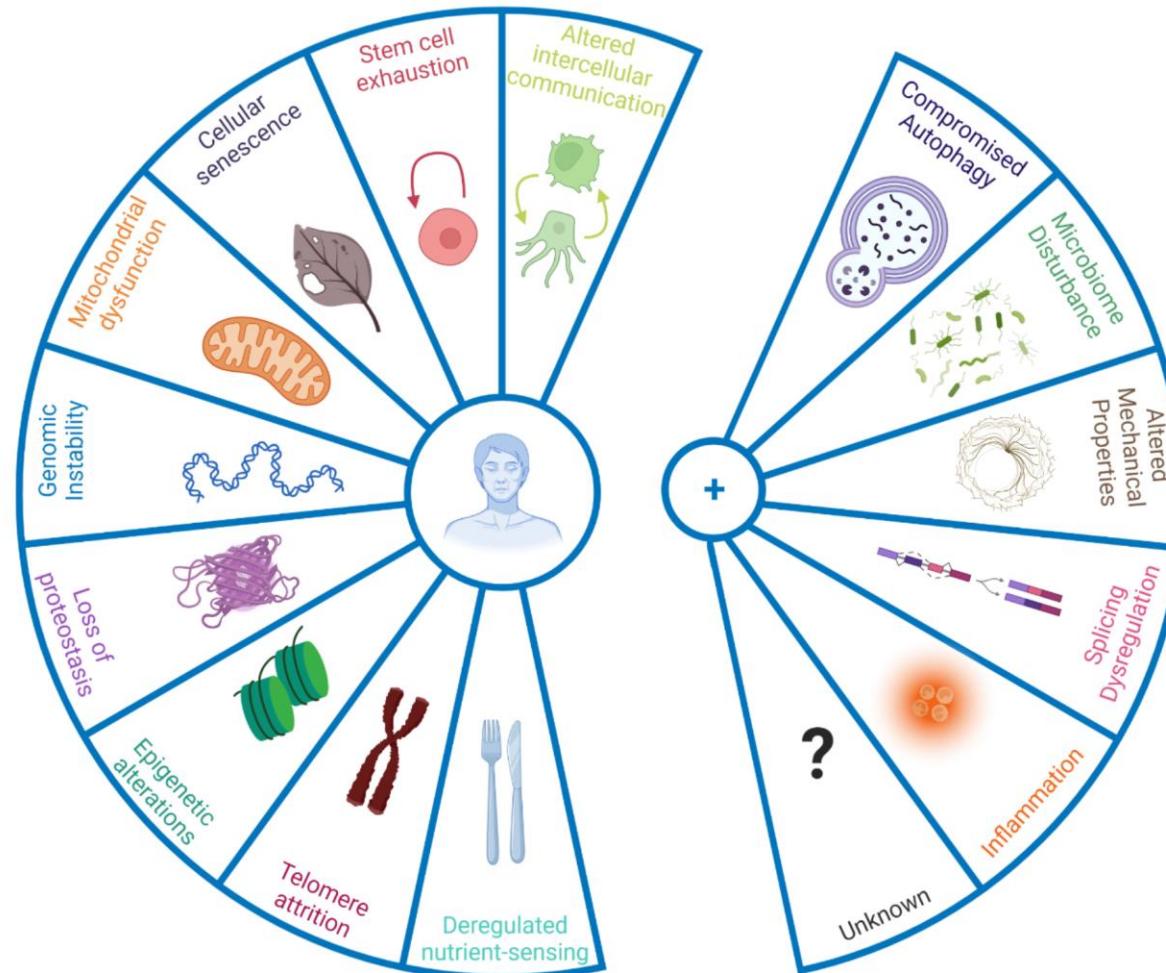
Cell





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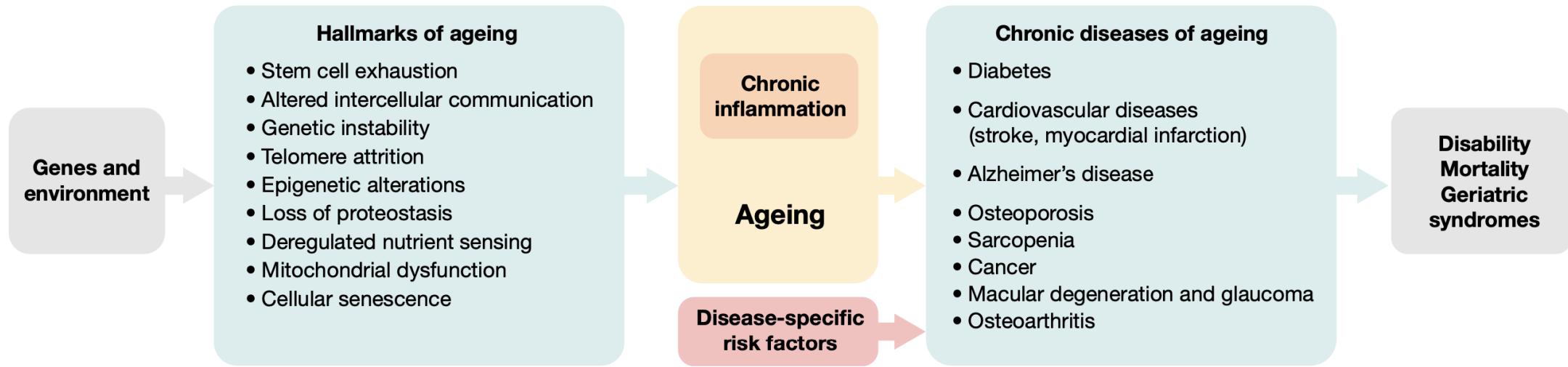
New hallmarks of ageing: a 2022 Copenhagen ageing meeting summary





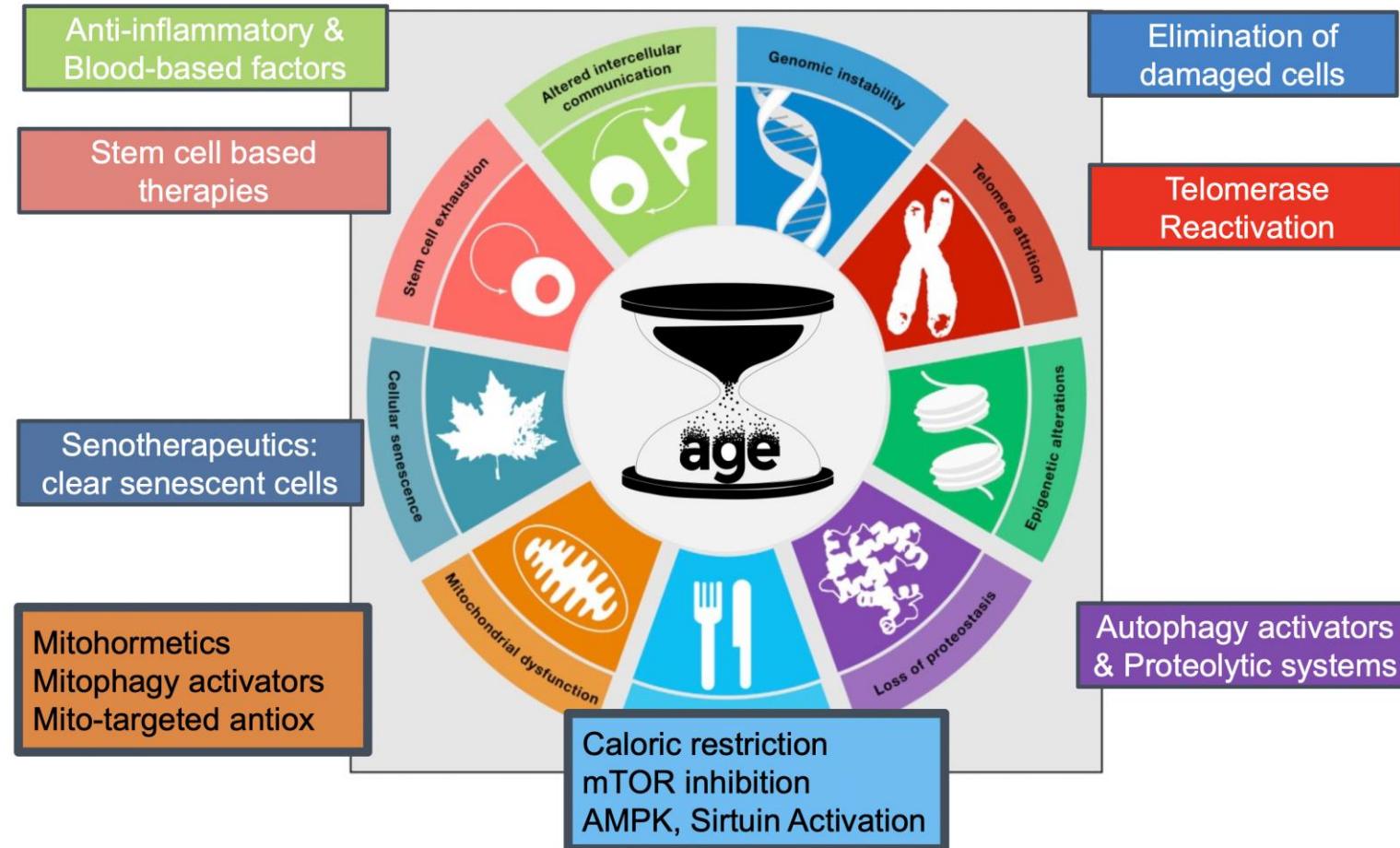
From discoveries in ageing research to therapeutics for healthy ageing

Judith Campisi¹, Pankaj Kapahi¹, Gordon J. Lithgow¹, Simon Melov¹, John C. Newman¹ & Eric Verdin^{1*}





Intervene on biological aging process to extend healthy lifespan





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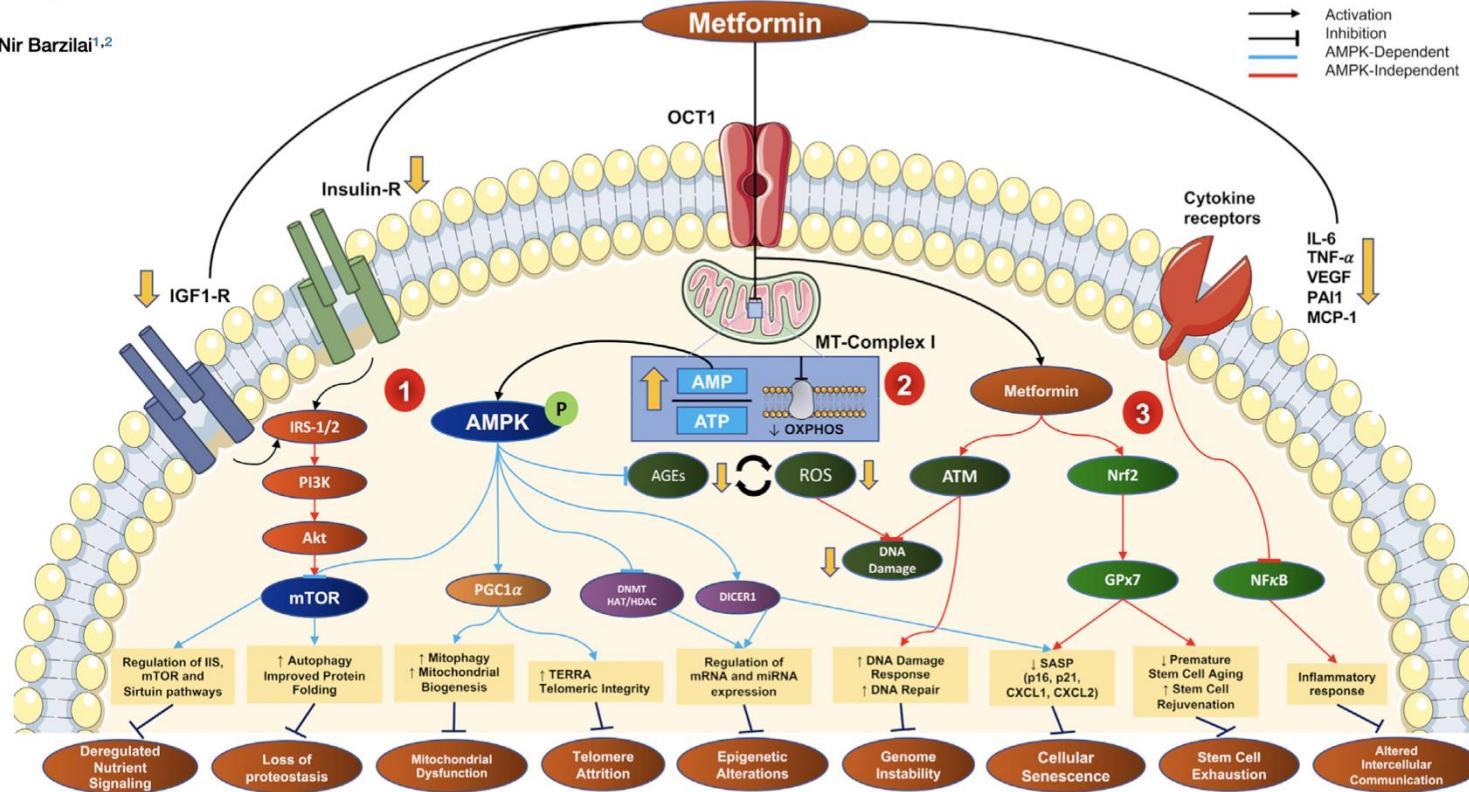
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Benefits of Metformin in Attenuating the Hallmarks of Aging

Ameya S. Kulkarni,^{1,2,*} Sriram Gubbi,³ and Nir Barzilai^{1,2}





Overview of Epidemiologic Evidence

What makes metformin attractive?

Gerotherapeutics	Effects on model organism lifespan	Effects on healthspan and age-related diseases in preclinical models	Hallmarks of Aging			
			Macromolecular Damage / Adaptation to Stress	Epigenetic effects / Stem Cell renewal and regeneration	Proteostasis / Inflammation / Senescence	Metabolism
Metformin (pre-2020 studies summarized previously (Kulkarni et al., 2020))	5.83% ↑ in mean lifespan of 84-weeks-old males (Martin-Montalvo et al., 2013)	<ul style="list-style-type: none"> ↑ cognitive function, ↓ microglial activation in 18-month old male mice (Kodali et al., 2021) ↑ motor symptoms in mouse model of Parkinson's disease via regulation of astrocytes transcriptome (Ryu et al., 2020) ↓ cartilage degeneration and chondrocyte aging in mouse model of osteoarthritis (X. Feng et al., 2020) 	<ul style="list-style-type: none"> ↑ mitochondrial function and ↓ endoplasmic reticular stress in aged mouse hearts (Q. Chen et al., 2021) ↓ ROS and RNS via ↑ FOXO3 in human immune cells (Hartwig et al., 2021) ↓ CKD-induced DNA damage (Kim et al., 2021) 	<ul style="list-style-type: none"> ↑ recruitment of neural stem cells, neurogenic potential, brain vascularization and cerebral angiogenesis in aged mouse brain (X. Zhu et al., 2020) ↓ senescence in mesenchymal stem cells (Kim et al., 2021) ↓ senescence in dental pulp stem cells via ↓ miR-34a-3p and ↑ CAB39 (S. Zhang et al., 2021) 	<ul style="list-style-type: none"> ↑ autophagy in hippocampus and ↓ pro-inflammatory cytokines in 18-mo-old male mice (Kodali et al., 2021) ↓ leaky gut and inflammation via ↑ goblet cell mass and mucin production and modulating the gut microbiome (Ahmadi et al., 2020) ↓ hydrogen peroxide induced senescence in retinal pigment endothelium cells with ↑ autophagy; and human lens epithelial B3 cells (C. Zhang et al., 2020; Zhao et al., 2020) 	Regulation of UPR via AMPK/ERK1/2 pathway to attenuate age-related hearing loss, cell apoptosis and neurodegeneration in old rats (Cai et al., 2020)



Overview of Epidemiologic Evidence

What makes metformin attractive?

Gerotherapeutics	Observational Healthspan	Interventional Healthspan
Metformin	<ul style="list-style-type: none"> • Meta-analysis: ↓CV mortality (OR 0.44 [0.34–0.57]) + CV events (OR 0.73 [0.59–0.90]) (K. Zhang et al., 2020) • ↓ incident HTN (HR = 0.991 [0.989–0.994] per month of therapy) (C. Tseng, 2018) • Meta-analysis: ↓ abdominal aortic aneurysm progression (weighted mean difference: -0.83 [-1.38, -0.28] mm/year) (Yu et al., 2019) • ↓ incident dementia (HR = 0.19 [0.04–0.85]) (Samaras et al., 2020) • No Δ in cognition (Luchsinger et al., 2017) • ↓ cognitive performance (OR = 2.23 [1.05, 4.75]) (Luchsinger et al., 2017) • Meta-analysis: ↓ overall cancer incidence (SRR = 0.69 [0.52–0.90]) (Gandini et al., 2014) 	<ul style="list-style-type: none"> • ↓ T2D by 31% vs. plc in people with pre-diabetes (Knowler et al., 2002) • ↓ MI (RR = 0.61 [0.41–0.89]) and any macrovascular event (RR = 0.70 [0.52–0.95]) vs. conventional therapy ("Effect of Intensive Blood-Glucose Control with Metformin on Complications in Overweight Patients with Type 2 Diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group," 1998) • ↓ CV events (HR = 0.54 [0.30–0.90]) vs. glipizide (Hong et al., 2013) • Meta-analysis: ↓cIMT (weighted mean difference = -0.049 [-0.095, -0.004] mm) (Y. Chen et al., 2020) • ↑ memory in people with MCI in a pilot study (total recall in Selective Reminding Test 9.7 ± 8.5 vs. 5.3 ± 8.5, $p = 0.02$) (Luchsinger et al., 2016) • Meta-analysis: No Δ in cancer incidence (Stevens et al., 2012)



TAME Aging Outcomes Trial

Age 65-80 years AND
Slow gait speed OR Age-related disease

Metformin (1500 mg 1x/day)
vs. Placebo (0 mg 1x/day)



n = 3000, 6-year, 14 Clinical Sites;
double-blind randomized placebo
controlled trial

Inclusion
Criteria

(Clinical) Time to incidence of any age-related disease:
MI, stroke, CHF, cancer*, MCI/dementia, or death.

Primary
Outcome

(Functional) Decline in mobility or cognitive function.

Secondary
Outcome

AFAR Funded Aging Outcomes Trial

Pending: NIA, Div Aging Biology: U19 Biorepository & Biomarkers

(Biological) Change in biomarkers of aging.



Resource
&
Biomarkers
Outcomes

* Excluding non-melanoma skin cancer and prostate cancer



A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup

GeroScience (2018) 40:419–436

<https://doi.org/10.1007/s11357-018-0042-y>

Blood-based biomarkers for geroscience-guided trials

Biomarker	Underlying Biologic Process & Role
IL-6, CRP TNFRII	 Inflammation & Intercellular Signaling Interleukin 6 (IL-6) is a proinflammatory cytokine and Tumor Necrosis Factor- α RII is a TNF- α receptor involved in acute-phase response. C-Reactive Protein (CRP) is an acute phase protein produced in response to inflammation. Cytokine dysregulation is a driver of pathophysiologic processes leading to disease, functional decline, frailty, and death.
GDF15	 Stress Response & Mitochondria Growth Differentiating Factor 15 (GDF15) is a member of the TGF- β superfamily robustly associated with mortality, cardiovascular events, cognitive decline and dementia. GDF15 is increasingly recognized in mitochondrial dysfunction, and as a biomarker of aging.
IGF-1 Insulin	 Nutrient Signaling Disruption of the insulin/ insulin-like growth factor (IGF-1) signaling pathway is implicated in longevity in animal models. In humans, IGF-1 and fasting insulin are responsive to caloric restriction, and low IGF-1 in growth hormone receptor deficiency conveys disease protection.
Cystatin-C	 Kidney Aging Cystatin C, an extracellular inhibitor of cysteine proteases, is a marker of renal disease and aging. It is an independent risk factor for all cause and CVD-related mortality, and multi-morbidity, and higher levels are consistently associated with poor physical function and cognition.
NT-proBNP	 Cardiovascular Health B-type natriuretic peptides (BNP, NT-proBNP) are secreted in response to cardiomyocyte stretching to decrease vascular resistance. NT-proBNP has a greater-half life and accuracy compared with BNP and is used to diagnose and establish prognosis for heart failure.
HGBA1c	 Metabolic Aging Glycated hemoglobin (hemoglobin A1c, HGBA1c) is formed in a non-enzymatic glycation pathway and is a marker for 3-mo average plasma glucose. High HGBA1c reflects poor glucose control, and in older nondiabetics is strongly associated with death, chronic disease, and functional decline.
Molecular Signature	 Epigenetic, Interdependent, Multi-Omic Data intensive molecular platforms can explore global changes in epigenetic, transcriptomic, proteomic and proteostasis, and small metabolite signatures. These approaches may better capture complex and multifactorial processes underlying aging.



Geroscience-guided repurposing of FDA-approved drugs to target aging: A proposed process and prioritization

Ameya S. Kulkarni¹ | Sandra Aleksić² | David M. Berger³ | Felipe Sierra⁴ |
George A. Kuchel⁵ | Nir Barzilai¹

TABLE 1 Ranking of FDA-approved drugs as potential gerotherapeutics based on scoring (out of 12) for preclinical and clinical evidence

Gerotherapeutics	Hallmarks of aging	Preclinical healthspan	Preclinical lifespan	Human healthspan	Human mortality	Score (out of 12)
SGLT-2 inhibitors	2	2	2	3	3	12
Metformin	2	2	1	3	3	11
Acarbose	2	2	2	3	0 (Not assessed)	9
Rapamycin/rapalogs	2	2	2	3*	0 (Not assessed)	9
Methylene blue	2	2	2	3*	0 (Not assessed)	9
ACEi/ARB	2	2	1	3	0	8
Dasatinib + (quercetin)	2	2	1	1	0 (Not assessed)	6
Aspirin	2	2	2	0 (Not assessed)	0 (Not assessed)	6
N-acetyl cysteine	1	2	2	0 (Not assessed)	0 (Not assessed)	5



REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Gliflozins in the Management of Cardiovascular Disease

Table 2. Cardiovascular Outcome Trials Involving Patients with Heart Failure.*

Variable	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	SOLOIST-WHF
Drug	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
No. of patients	4744	3730	5988	1222
Type 2 diabetes — % of patients	41.7	49.8	49.1	100
LVEF — %	31.1	27.4	54.3	35
Median NT-proBNP — pg/ml	1437	1907	970	1864
Mean eGFR — mL/min/1.73 m ²	65.7	62.0	60.5	49.0
Outcomes — hazard ratio (95% CI)				
Cardiovascular death or hospitalization for heart failure	0.74 (0.65–0.85)	0.75 (0.68–0.86)	0.79 (0.69–0.90)	0.67 (0.52–0.85)
Hospitalization for heart failure	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.64 (0.49–0.83)

* Data sources for the trials are as follows: DAPA-HF, McMurray et al.²⁴; EMPEROR-Reduced, Packer et al.²⁵; EMPEROR-Preserved, Anker et al.²⁶; SOLOIST-WHF, Bhatt et al.²⁷. The abbreviation eGFR denotes estimated glomerular filtration rate; LVEF left ventricular ejection fraction; and NT-proBNP N-terminal pro-B-type natriuretic peptide.

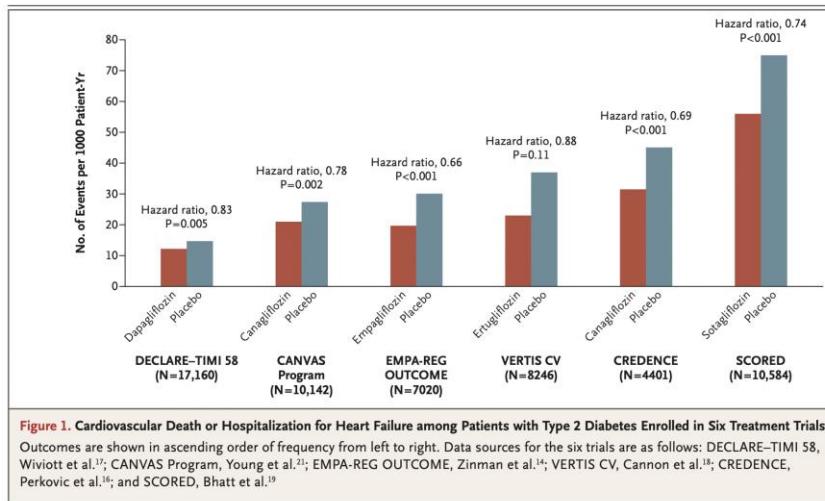
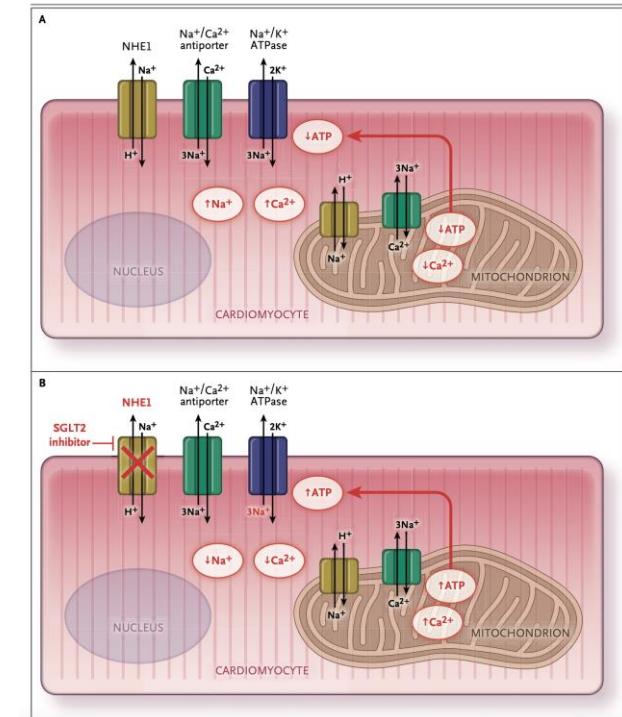
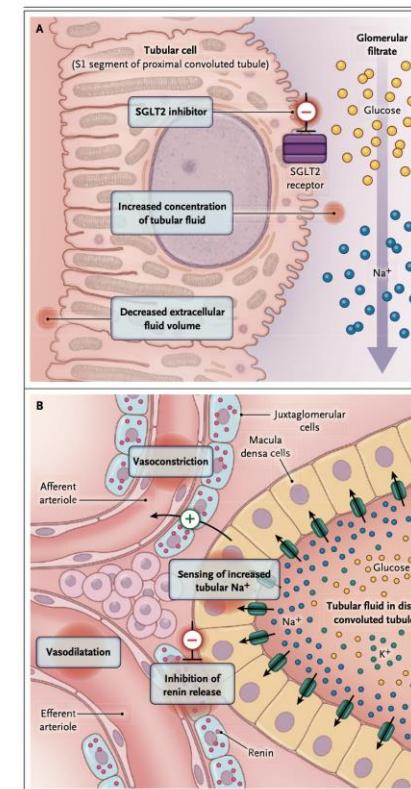


Figure 1. Cardiovascular Death or Hospitalization for Heart Failure among Patients with Type 2 Diabetes Enrolled in Six Treatment Trials. Outcomes are shown in ascending order of frequency from left to right. Data sources for the six trials are as follows: DECLARE-TIMI 58, Wiviott et al.¹⁷; CANVAS Program, Young et al.²¹; EMPA-REG OUTCOME, Zinman et al.¹⁴; VERTIS CV, Cannon et al.¹⁵; CREDENCE, Perkovic et al.¹⁶; and SCORED, Bhatt et al.¹⁹





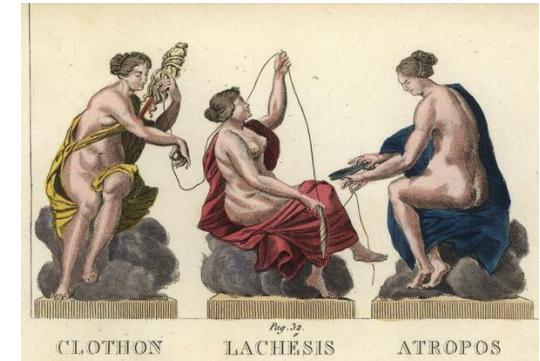
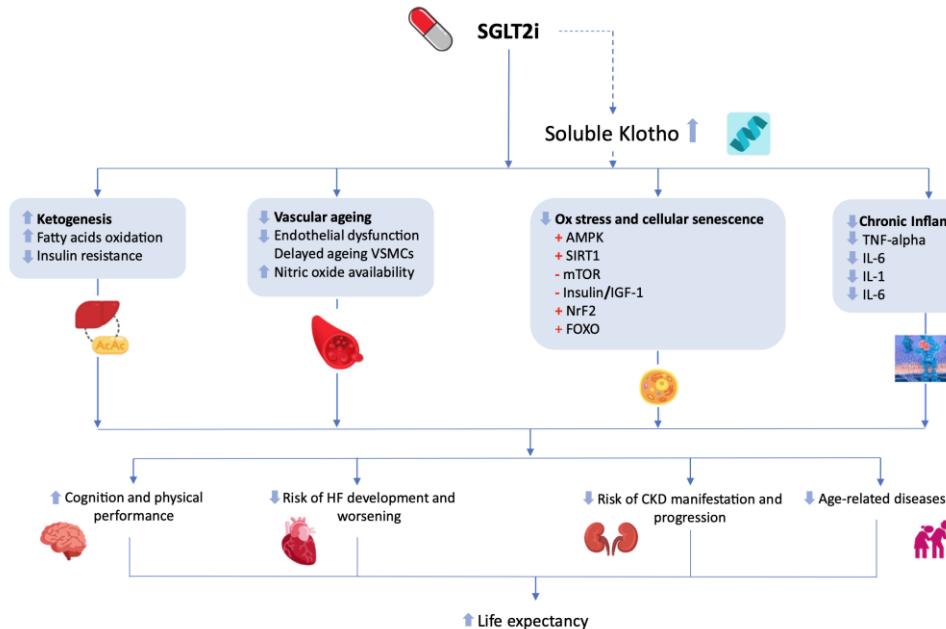
Gerotherapeutics	Effects on model organism lifespan	Effects on healthspan and age-related diseases in preclinical models	Hallmarks of Aging			
			Macromolecular Damage / Adaptation to Stress	Epigenetic effects / Stem Cell renewal and regeneration	Proteostasis / Inflammation / Senescence	Metabolism
SGLT2 inhibitors	ITP: Canagliflozin ↑ median lifespan by 14% in males (Miller et al., 2020)	Dapagliflozin ↓ atherosclerosis with macrophage infiltration in diabetic ApoE -/- mice (Leng et al., 2016)	Dapagliflozin restores Calcium uptake and prevents age-associated Calcium build up in the mitochondria of cardiomyocytes (Olgar et al., 2020)	No applicable studies	Empagliflozin reactivates glomerular autophagy in db/db mice (Korbut et al., 2020)	<ul style="list-style-type: none"> • Dapagliflozin ↑ cardiac function and glucose tolerance in IR rats with metabolic syndrome via ↑ mitochondrial function and oxidative stress (Durak et al., 2018) • Empagliflozin ↑ AMP/ATP ratio, AMPK and ↓ mitochondrial fission (Zhou et al., 2018) • Empagliflozin ↓ mTORC1 in diabetic mouse kidneys (Tomita et al., 2020)

Aging Cell. 2022;21:e13596.
<https://doi.org/10.1111/acel.13596>

Trends in Endocrinology & Metabolism

Can sodium-glucose cotransporter 2 inhibitors 'spin the thread of life'?

Giuseppe Maltese,^{1,2,*,@}
Theocharis Koufakis,³
Kalliopi Kotsa,³ and
Janaka Karalliedde¹





Effect of empagliflozin on circulating proteomics in heart failure: mechanistic insights into the EMPEROR programme

Structured Graphical Abstract

Key question

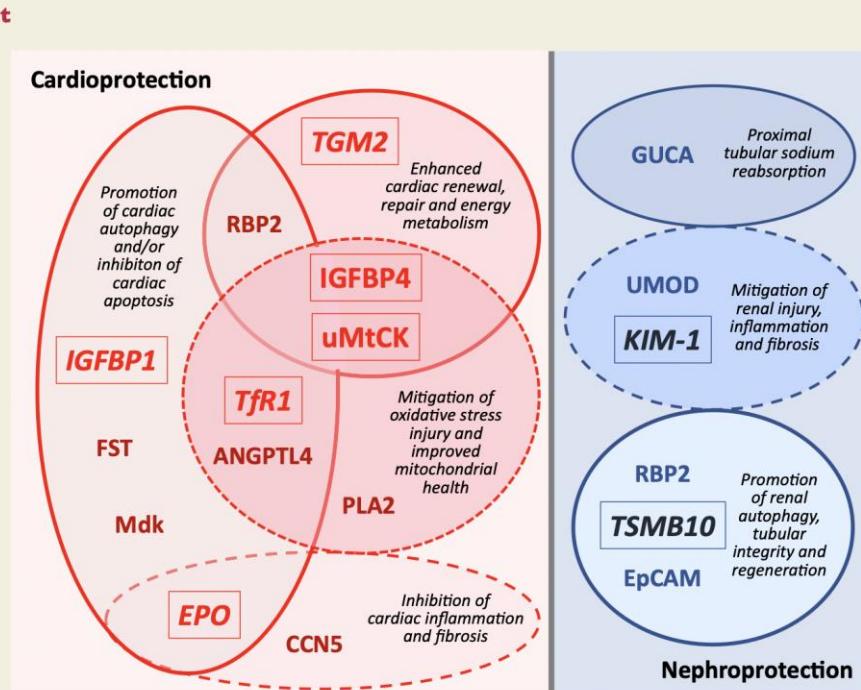
Mechanisms of clinical benefits of SGLT2 inhibitors in patients with heart failure are not fully understood. We evaluated the effect of empagliflozin using large-scale proteomics in participants in the EMPEROR Trials.

Key findings

We identified differential expression of a small group of circulating intracellular proteins, which promote autophagic flux, mitigate oxidative stress and inflammation, and promote repair and renewal in the heart and kidneys.

Take home message

The findings of experimental studies that have linked the benefits of SGLT2 inhibitors on the heart and kidney to their actions on autophagy, cellular stress and viability are likely relevant to the clinical setting.



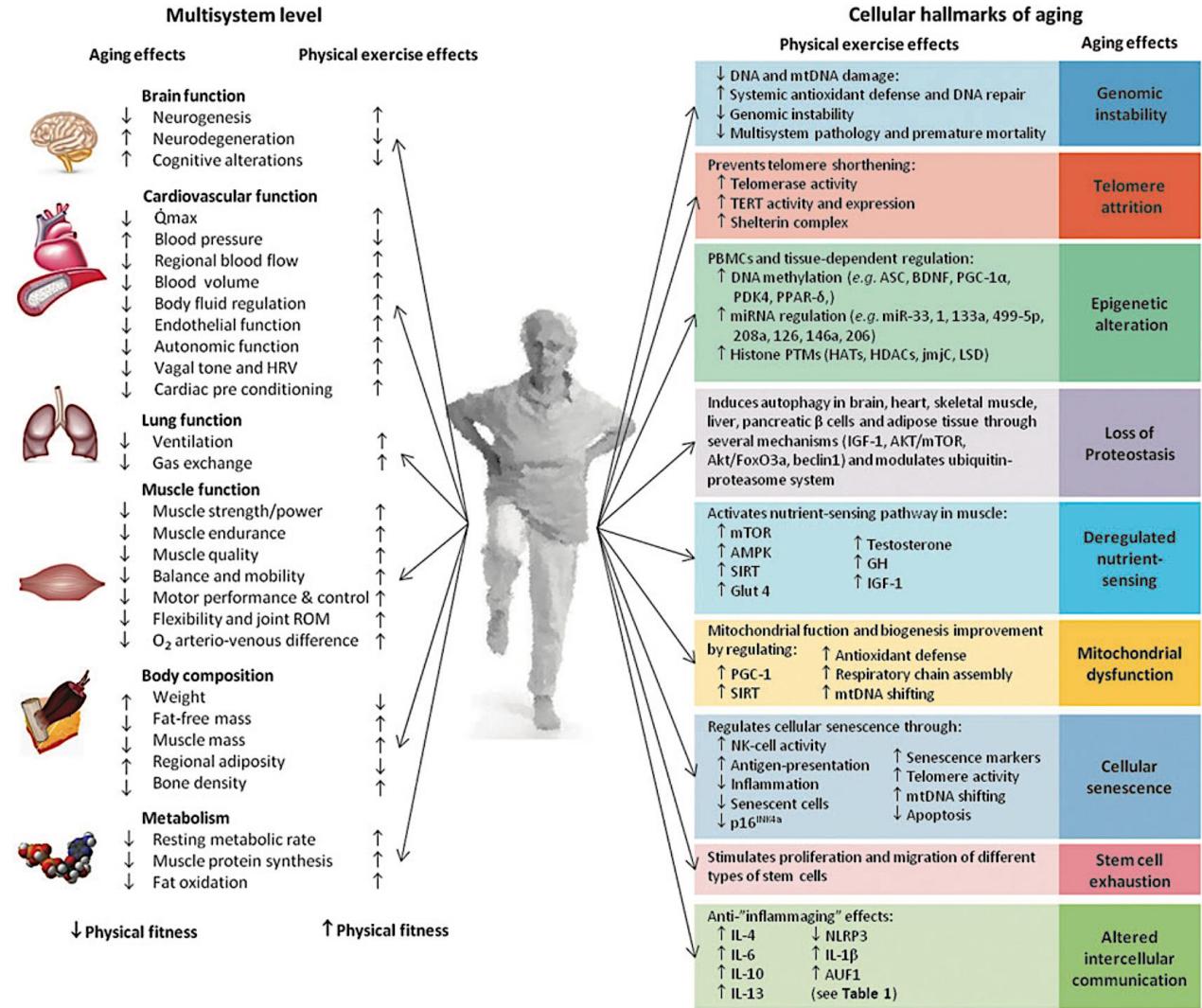
Favourable biological and cellular actions of differentially expressed proteins in the heart and kidney. IGFBP1, insulin-like growth factor-binding protein 1; Tfr1, transferrin receptor protein 1; EPO, erythropoietin; TGM2, protein-glutamine gamma-glutamyltransferase 2; TMSB10, thymosin beta-10; uMtCK, mitochondrial creatine kinase U-type; IGFBP4, insulin-like growth factor-binding protein 4; EpCAM, epithelial cell adhesion molecule; PLA2, phospholipase A2; ANGPTL4, angiopoietin-related protein 4; RBP2, retinol-binding protein 2; CCN5, CCN family member 5; FST, follistatin; Mdk, midkine; GUCA, guanylin.



Exercise Attenuates the Major Hallmarks of Aging

Nuria Garatachea,^{1,3,*} Helios Pareja-Galeano,^{2,4,*} Fabian Sanchis-Gomar,² Alejandro Santos-Lozano,² Carmen Fiuza-Luces,^{2,4} María Morán,^{2,5} Enzo Emanuele,⁶ Michael J. Joyner,^{7,†} and Alejandro Lucia^{2,4,†}

REJUVENATION RESEARCH
Volume 18, Number 1, 2015
© Mary Ann Liebert, Inc.
DOI: 10.1089/rej.2014.1623



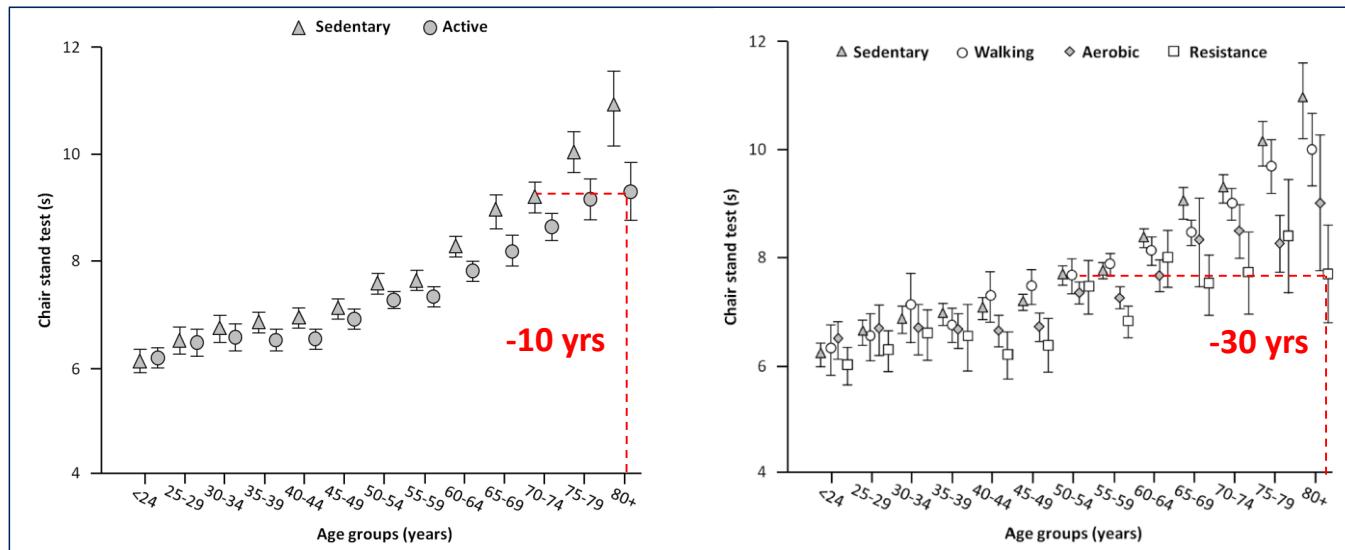


PLOS ONE

RESEARCH ARTICLE

Impact of habitual physical activity and type of exercise on physical performance across ages in community-living people

Francesco Landi, Riccardo Calvani*, Anna Picca, Matteo Tosato, Anna Maria Martone, Emanuela D'Angelo, Elisabetta Serafini, Roberto Bernabei, Emanuele Marzetti



n=6,242

Age: 54.4 ± 15.2 yrs (range: 18-98 yrs)

Women: 3,552 (57%)



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THMs

- **Geroscience approaches – Translational gap**
- **Geroprotectors – Healthspan/Lifespan gap**
- **New biomarkers – Chronological/biological age gap**



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Grazie per l'attenzione!!!



riccardo.calvani@policlinicogemelli.it