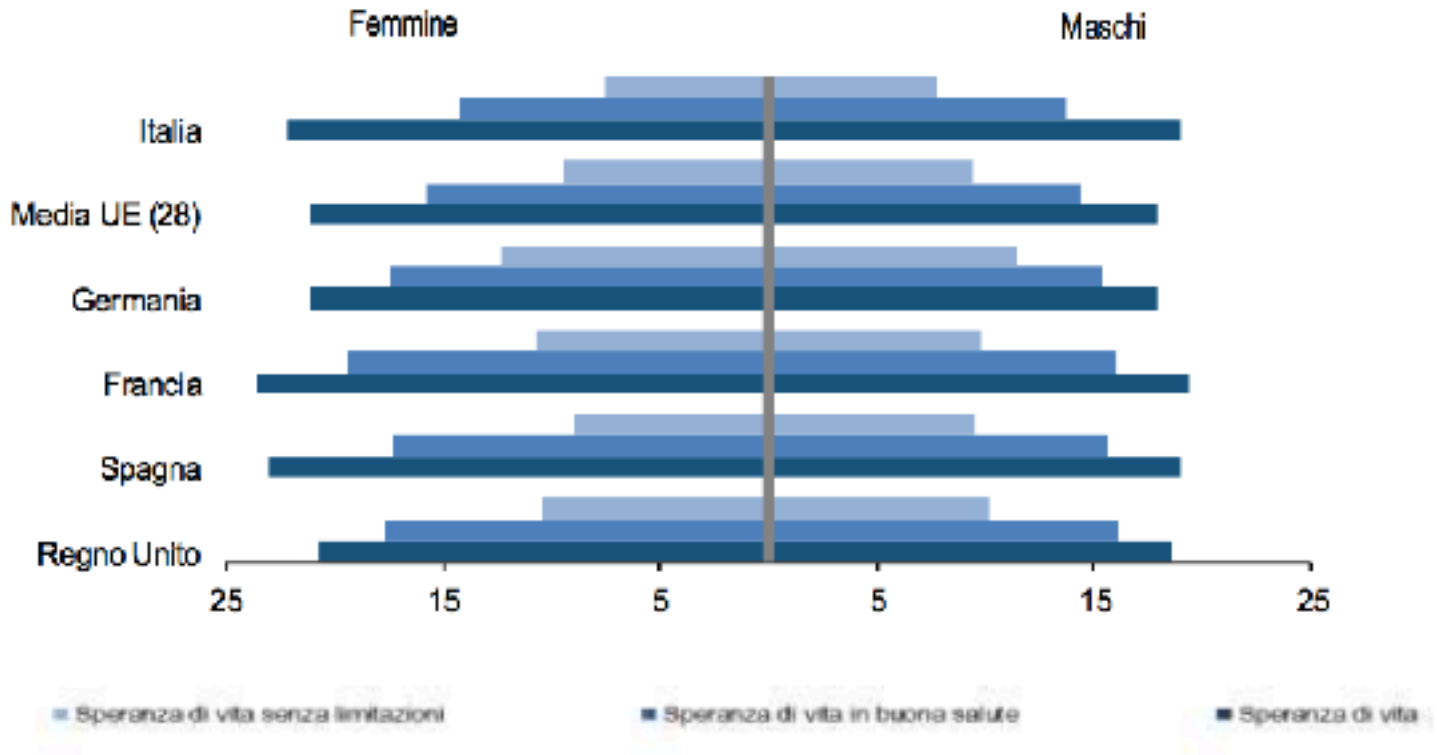
Gruppo di Ricerca Geriatrica

Brescia, 23 febbraio 2018

WELL AGING: ruolo della geriatria

Lina Falanga

FIGURA 1. SPERANZA DI VITA, SPERANZA DI VITA IN BUONA SALUTE, SPERANZA DI VITA SENZA LIMITAZIONI A 65 ANNI IN ALCUNI PAESI UE PER SESSO. Anno 2015, anni di vita media



Fonte: Eurostat, http://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tsdph100&plugin=1

Principali biomarker dell'aging

Misurabili senza arrecare danno alla persona

Indicatori età correlati sia nell'invecchiamento fisiologico che patologico

Consentono di individuare i diversi **fenotipi dell'invecchiamento**

Testati e validati negli animali di laboratorio e poi nell'uomo

Johnson, 2006; Butler et al., 2004; Federazione Americana per la Ricerca sull'Età (AFAR)

EBioMedicine 21 (2017) 29–36

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

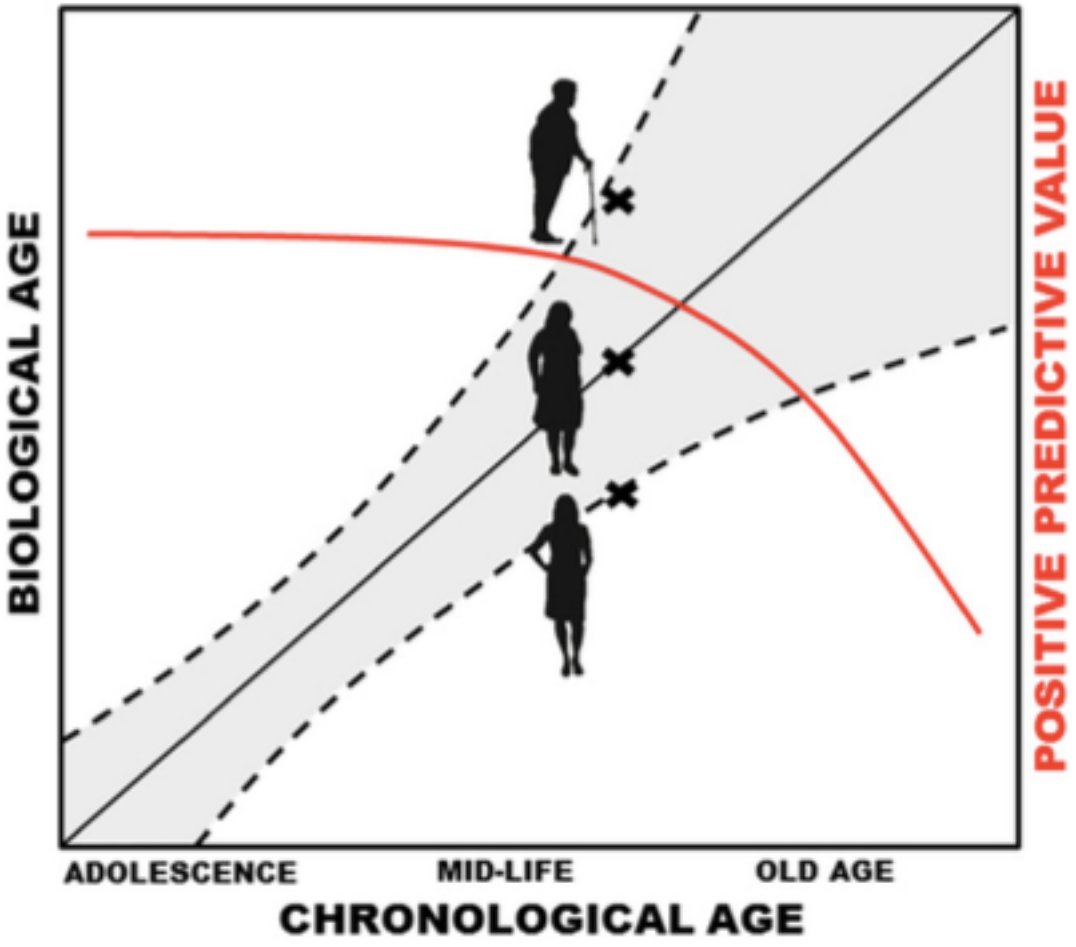
Review

Biological Age Predictors

Juulia Jylhävä, Nancy L. Pedersen, Sara Hägg *

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Biological Age Predictors



Ebiomedicine 2017

Principali biomarker dell'aging

Fenotipici:
misure standard di fragilità, insulinemia, adiponectina, IGF-1, lipidogramma, massa magra e massa grassa, indici infiammatori, cognitività, pressione arteriosa, FC max a riposo, fx diastolica, spessore intima-media della carotide, n°linfociti, Cl renale

Molecolari: DNA

Aging Cell (2015) Valter D.Longo, Adam Antebi, Andrzey Bartke, Nir Barzilai et all.

Principali biomarker dell'aging

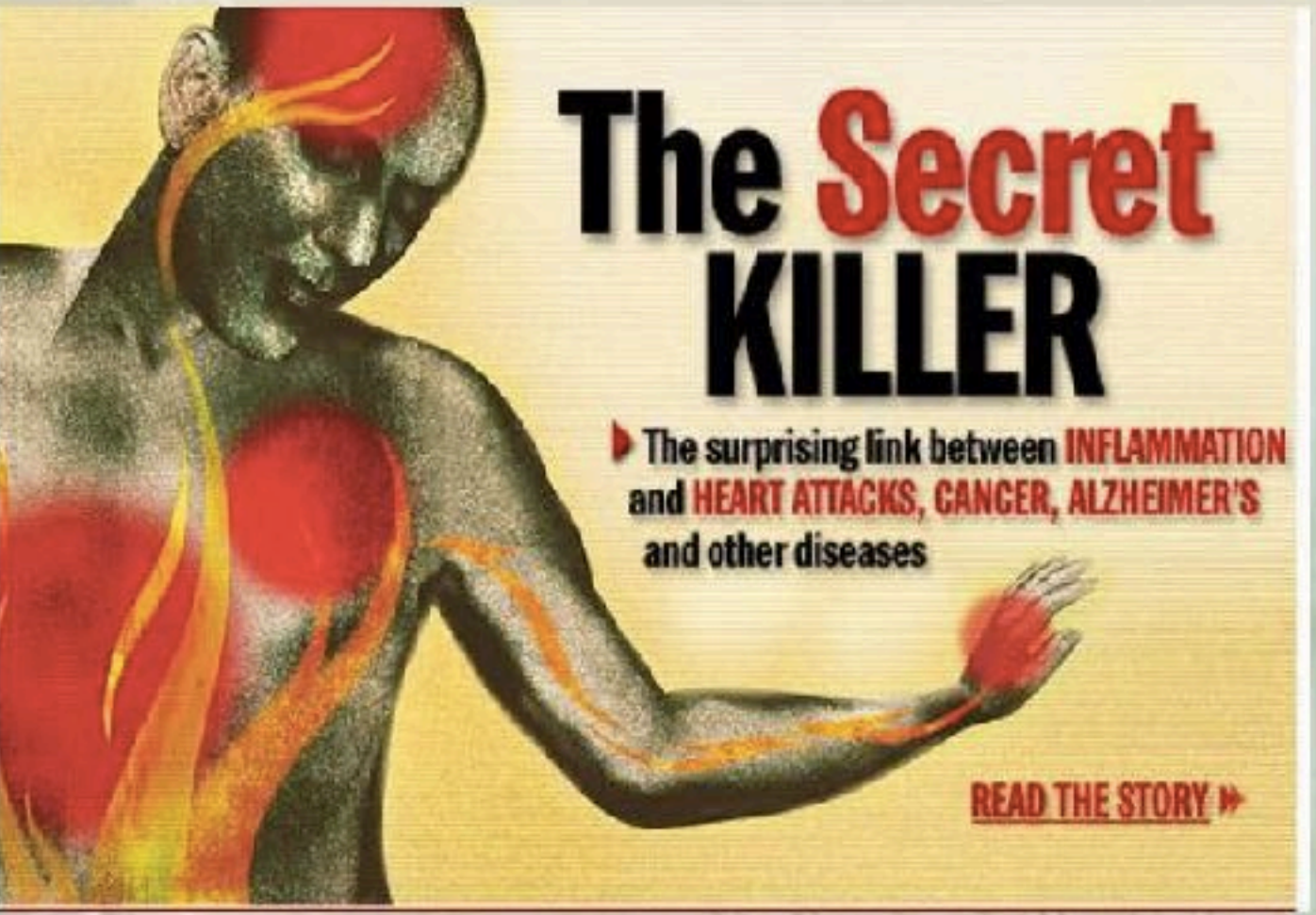
Inflamming

Glicazione

Metilazione

Stress ossidativo

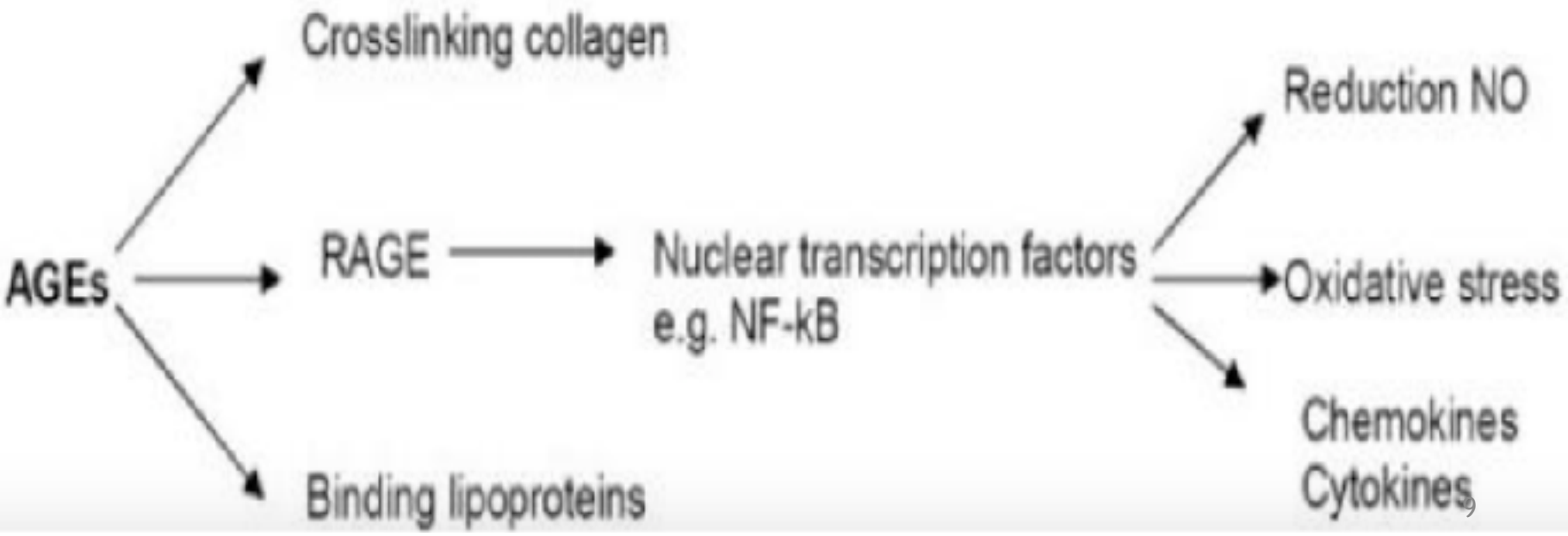
INFLAMMATION



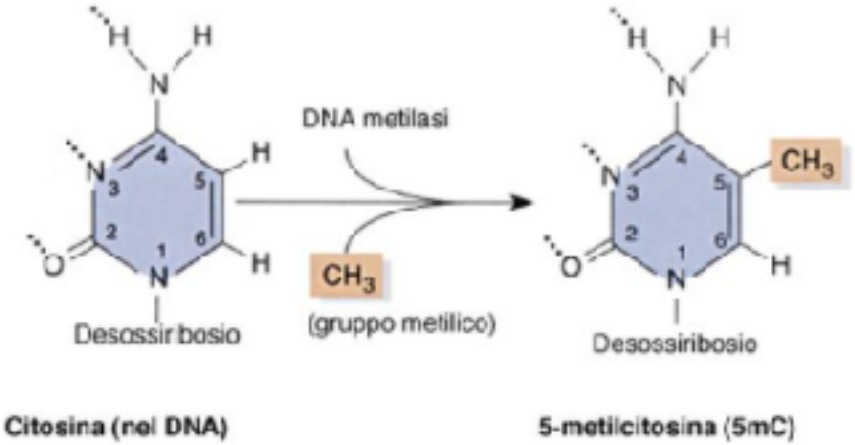
Glicazione: AGE (Advanced Glycation End products)

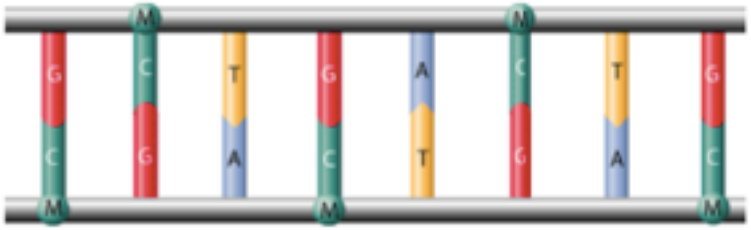
Sono riconosciuti da alcuni recettori espressi dalla componente mesenchimali e macrofagica dei tessuti

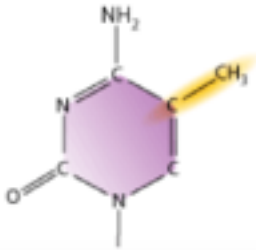
Il legame AGE-rAGE provoca un'attivazione cellulare che comporta la sintesi di citochine proinfiammatorie e fattori di crescita



Metilazione del DNA



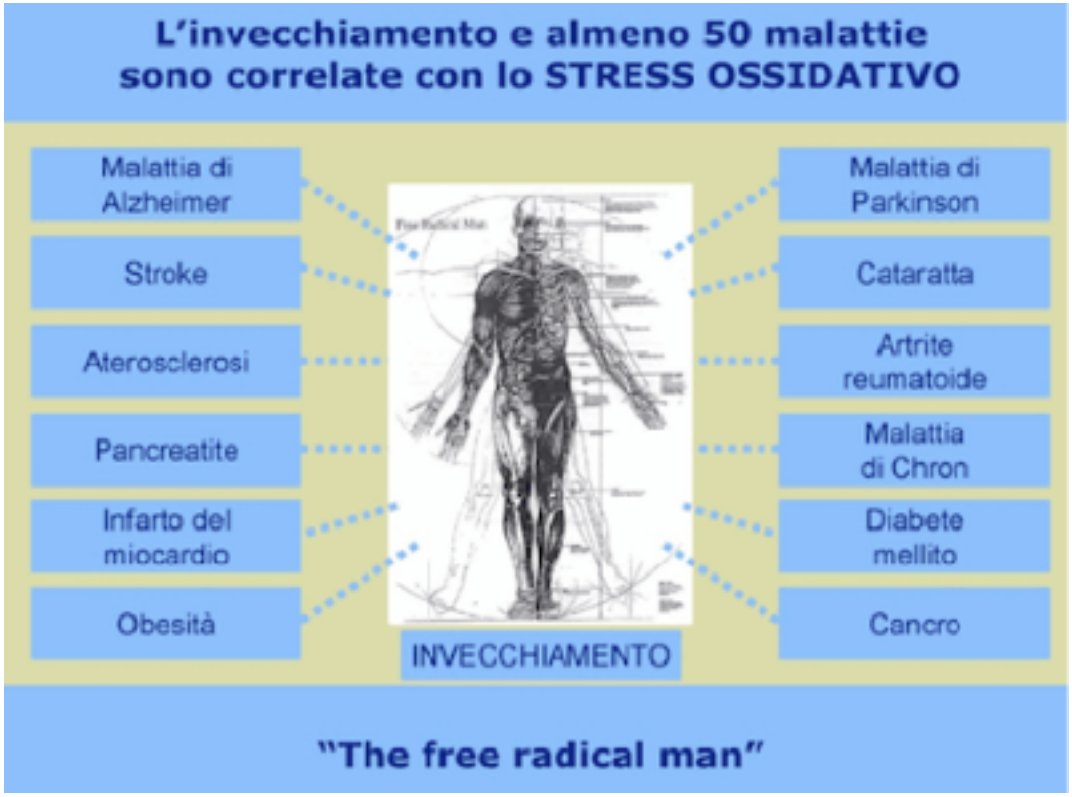




DNA methylation is the addition of a methyl group (M) to the DNA base cytosine (C).

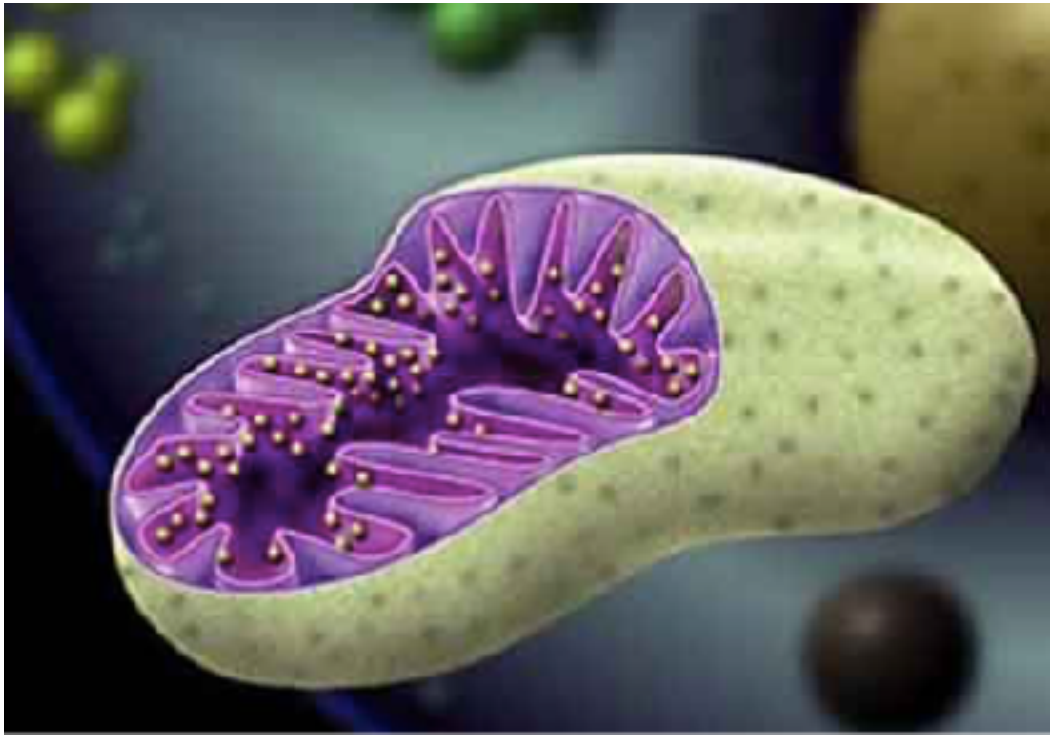
Stress ossidativo

Eccesso di specie chimiche generalmente centrate sull'ossigeno (Reactive Oxygen Species, ROS) secondario ad un'aumentata produzione delle stesse e/ o ad una ridotta efficienza dei sistemi fisiologici antiossidanti (Sies, 1991)

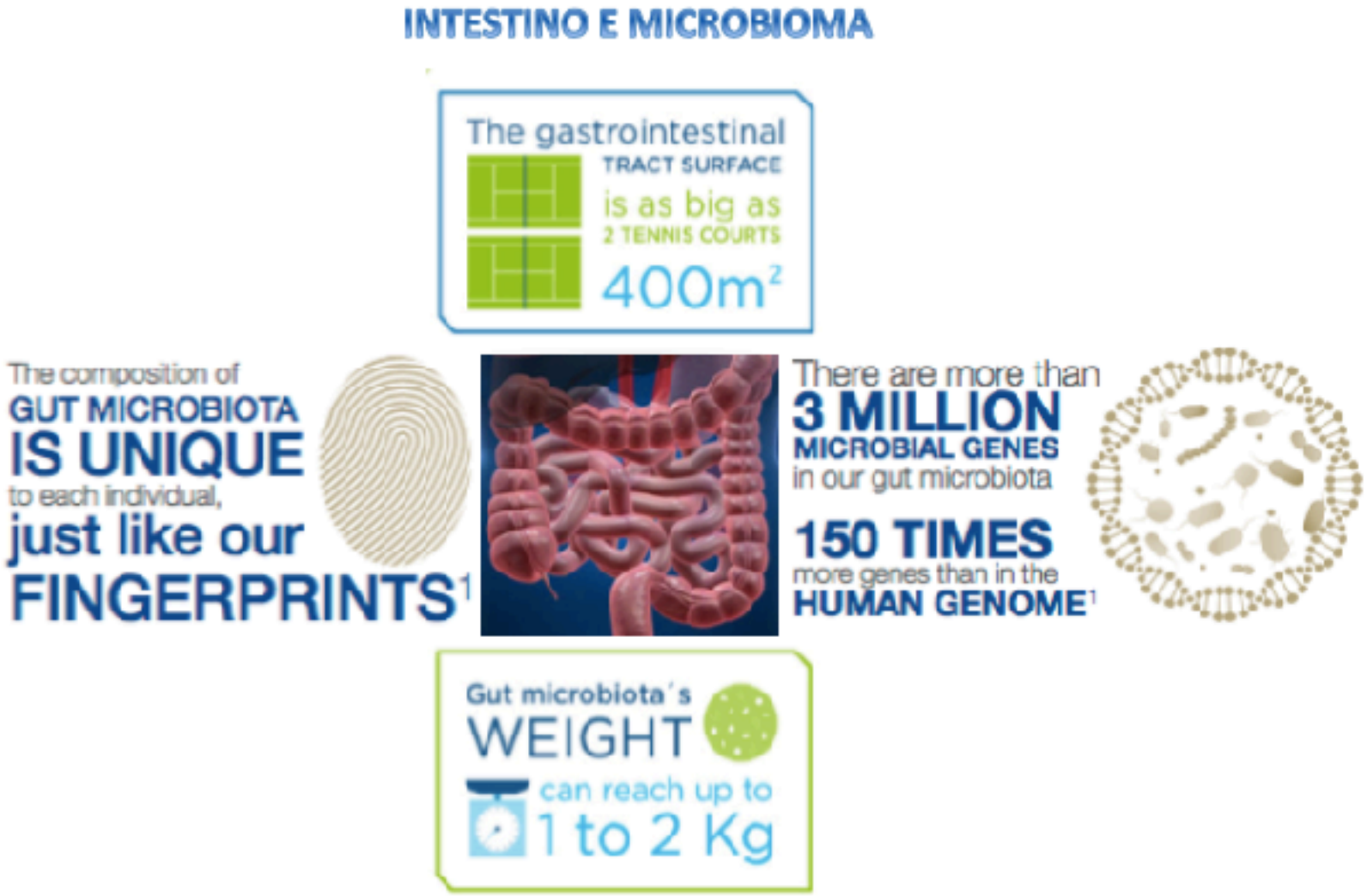


Stress ossidativo

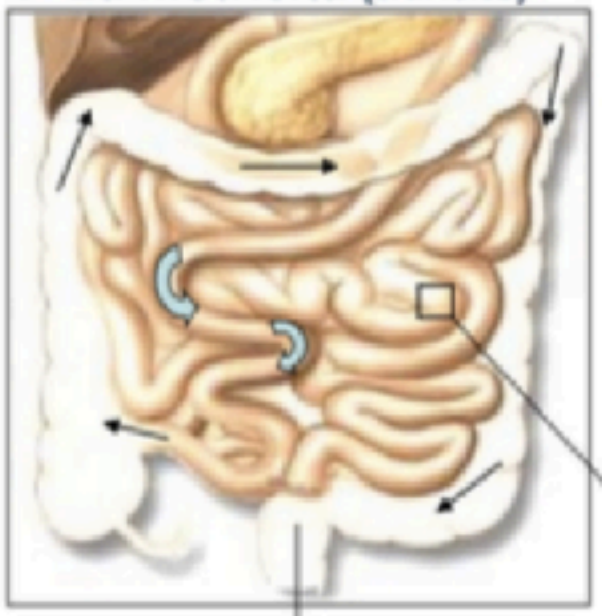
I mitocondri sono la fonte principale di ROS cellulari perché i radicali superossido sono generati costantemente durante la fosforilazione ossidativa e possono essere convertiti in H2O2 e altre specie reattive dell'ossigeno



Microbiota

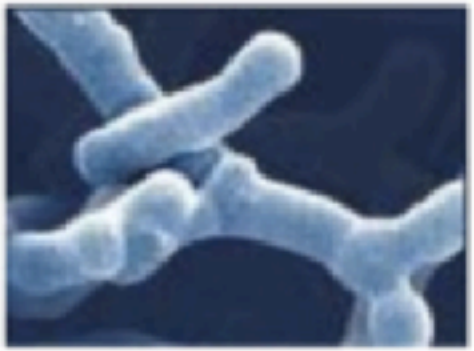

INTESTINO E MICROBIOMA
The gastrointestinal
TRACT SURFACE
is as big as
2 TENNIS COURTS
400m²
The composition of
GUT MICROBIOTA
IS UNIQUE
to each individual,
just like our
FINGERPRINTS[1]
There are more than
3 MILLION
MICROBIAL GENES
in our gut microbiota
150 TIMES
more genes than in the
HUMAN GENOME[1]
Gut microbiota´s
WEIGHT
can reach up to
1 to 2 Kg

1- La motricità (transito)



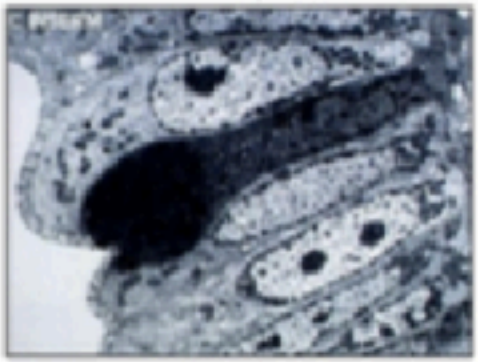
Evita l'adesione di batteri patogeni alle cellule epiteliali

2- La flora intestinale



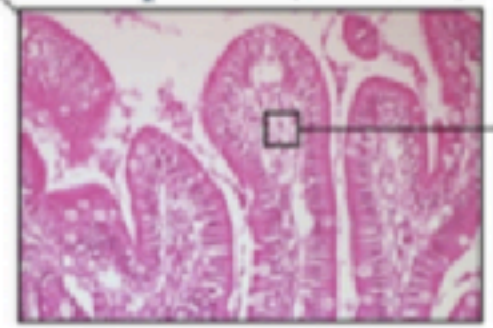
Si oppone alla colonizzazione da parte di batteri estranei

3- Il muco (cellule caliciformi)



Protezione dell'epitelio

4- L'epitelio (enterociti)



Transporto selettivo trans- e paracellulare

5- Le cellule immunitarie

Difesa rapida, aspecifica

Gut microbiota and diabetes: from pathogenesis to therapeutic perspective, Acta Diabetol (2011):48:257-273

CURRENT OPINION

Microbiota and neurodegenerative diseases

Moira Marizzoni[a], *Stefania Provasi*[b], *Annamaria Cattaneo*[b,c], *and Giovanni B. Frisoni*[a,d]

Purpose of review
Despite the extensive research carried out in the past decades, the current pathophysiological notions of neurodegenerative disease as well as effective treatments to reduce their progression are largely unknown. Alterations of the human microbiota, the plethora of different microscopic organisms that our body hosts, have been linked to neurodegenerative disease risk, onset and progression. This review summarizes the current knowledge on the possible role of microbiota in neurodegenerative disorders and briefly discusses strategies to restore microbiota homeostasis.

Recent findings
Preclinical evidences and human cross-sectional studies posit the gut microbiota as a key actor in the Parkinson's disease onset and progression, reporting the presence of a specific gut microbiota profile in association with the modulation of disease and symptoms. Gut microbiota alterations have been correlated with brain disease and peripheral inflammation also in Alzheimer's patients.

Summary
The interaction between the microbiota and the host is promising to answer clinical questions that have so far escaped clarification with the current pathophysiological notions of health and disease. However, human longitudinal studies starting in the earlier disease phases are needed to understand the causative relation between microbiota and the hallmarks of these neurodegenerative disorders and to develop innovative treatments aimed at preventing or slowing brain damages.

Keywords
Alzheimer's disease, gut microbiota, oral microbiota, Parkinson's disease

THE GERONTOLOGICAL SOCIETY OF AMERICA®

The Gerontologist
cite as: *Gerontologist*, 2015, Vol. 55, No. 6, 901–911
doi:10.1093/geront/gnv130
Advance Access publication November 10, 2015

OXFORD

Feature Article

Lifespan and Healthspan: Past, Present, and Promise

Eileen M. Crimmins*

Davis School of Gerontology, University of Southern California, Los Angeles.

*Address correspondence to Eileen M. Crimmins, PhD, Davis School of Gerontology, University of Southern California, 3715 McClintock Avenue, Los Angeles, CA 90089-0191. E-mail: crimmin@usc.edu

Received April 21, 2015; Accepted July 15, 2015

Decision Editor: Rachel Pruchno, PhD

J Physiol 594.8 (2016) pp 2001–2024

TOPICAL REVIEW

Physiological geroscience: targeting function to increase healthspan and achieve optimal longevity

Douglas R. Seals, Jamie N. Justice and Thomas J. LaRocca

Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO 80309, USA

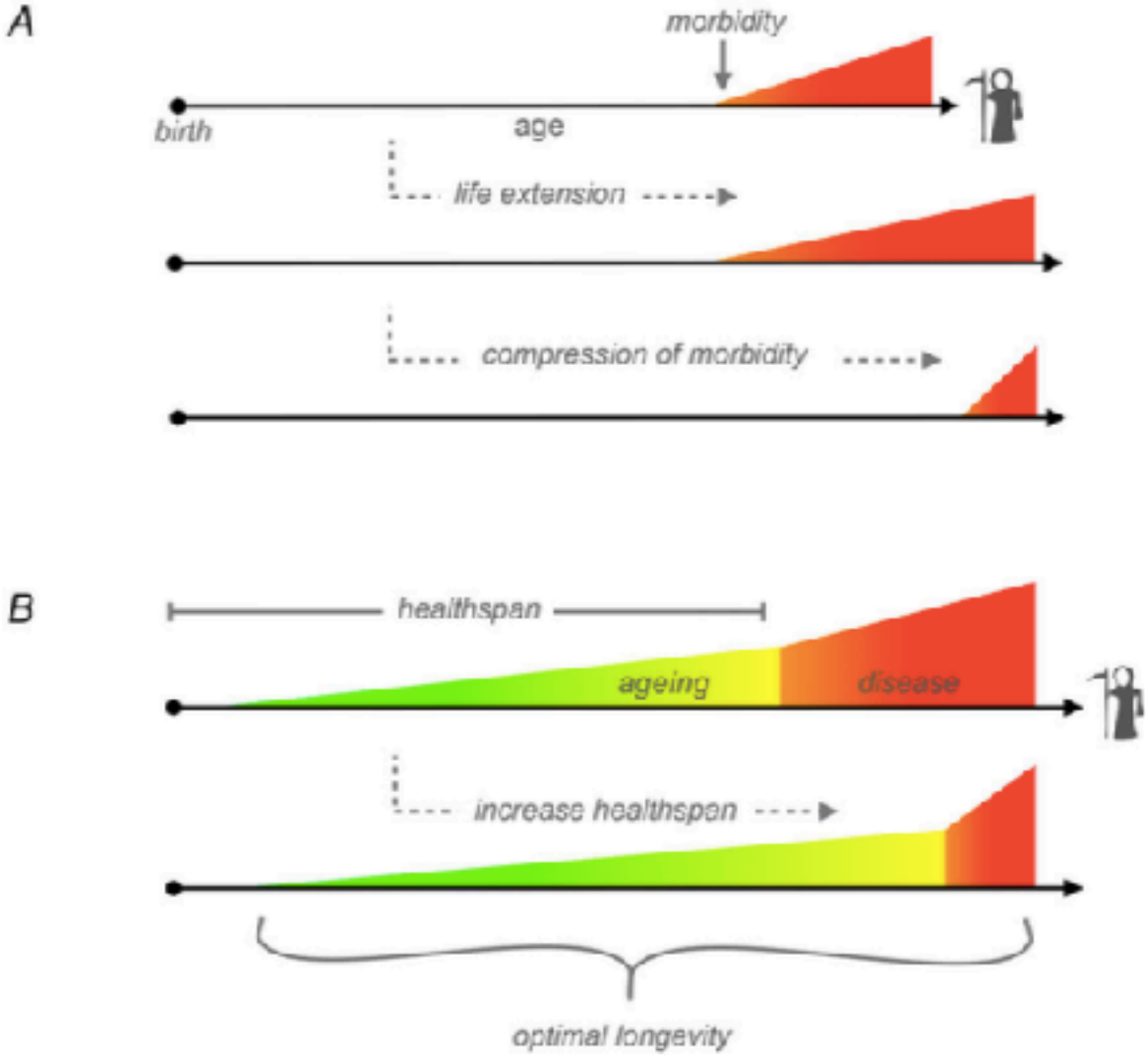


Figure 1. Compression of morbidity, healthspan and optimal longevity
A, delaying the age of onset of chronic diseases and disability (morbidity) longer than any associated increase in lifespan results in 'compression' of the overall morbidity incurred in a lifetime. *B*, healthspan is a period of healthy ageing with a modestly increasing ('subclinical') chronic disease burden, followed by a period of age-related clinical disease. To achieve optimal longevity (living long, but primarily in wellness) in the future, healthspan must be significantly extended. Modified from Blagosklonny (2012).

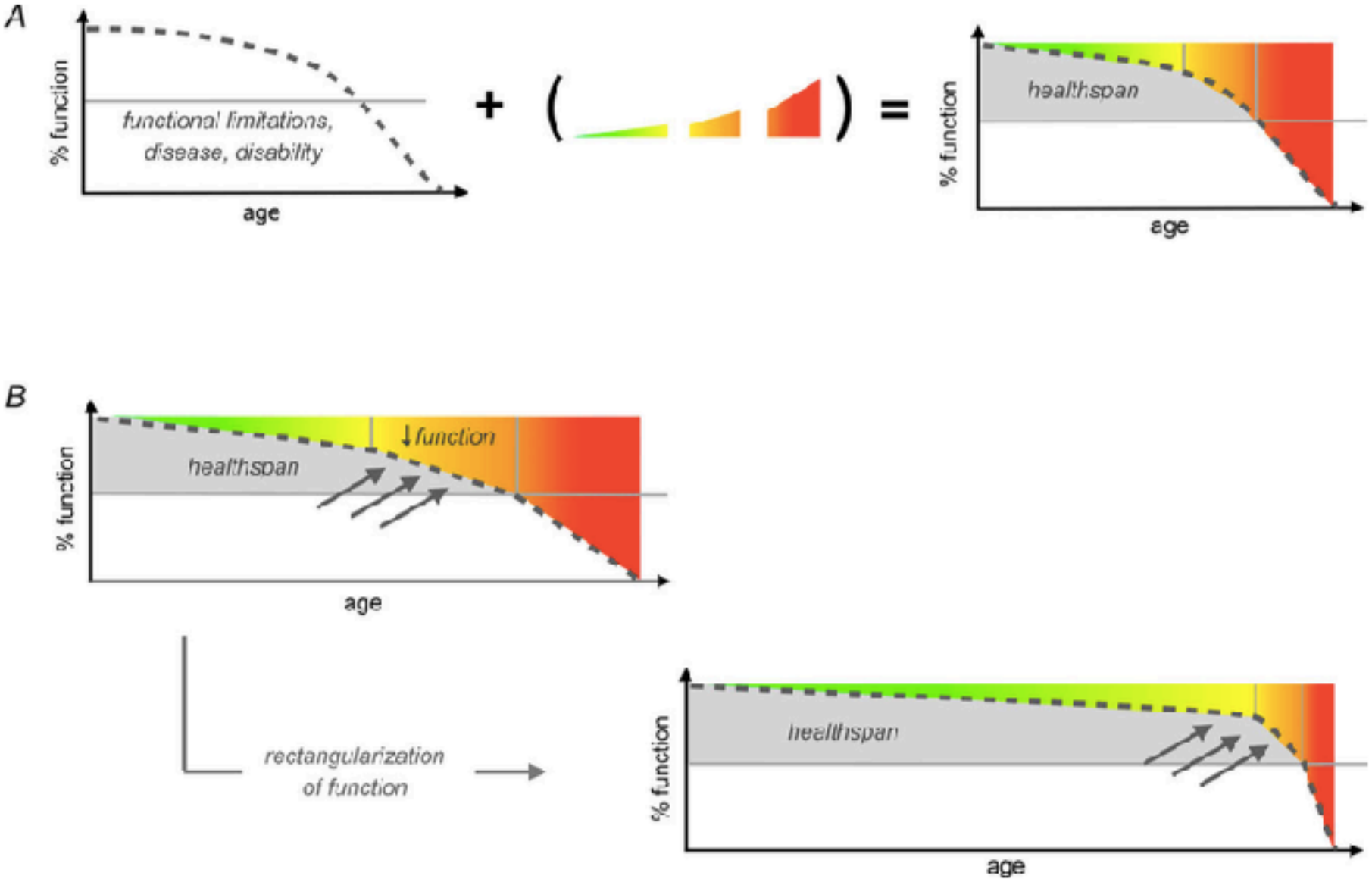


Figure 4. Optimization of function with ageing is required for increased healthspan
A, physiological function declines with ageing, and the portion of life during which function remains above the disease/morbidity threshold represents healthspan. *B*, to increase healthspan, it is necessary to compress severe dysfunction to a period later in life, effectively 'rectangularizing' function as much as possible throughout the lifespan.

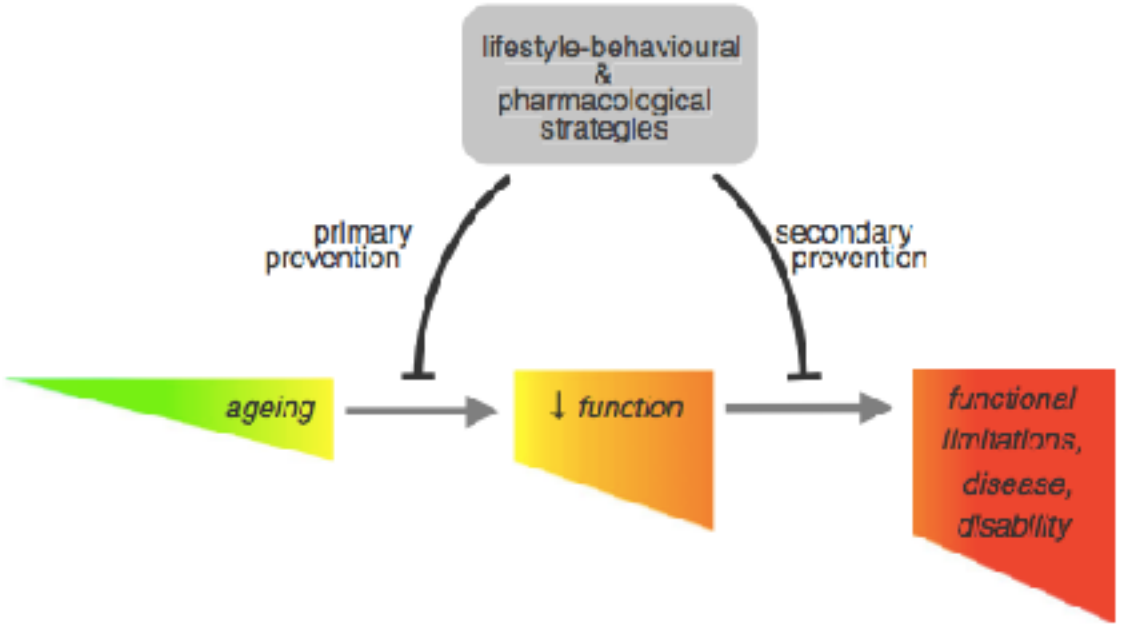
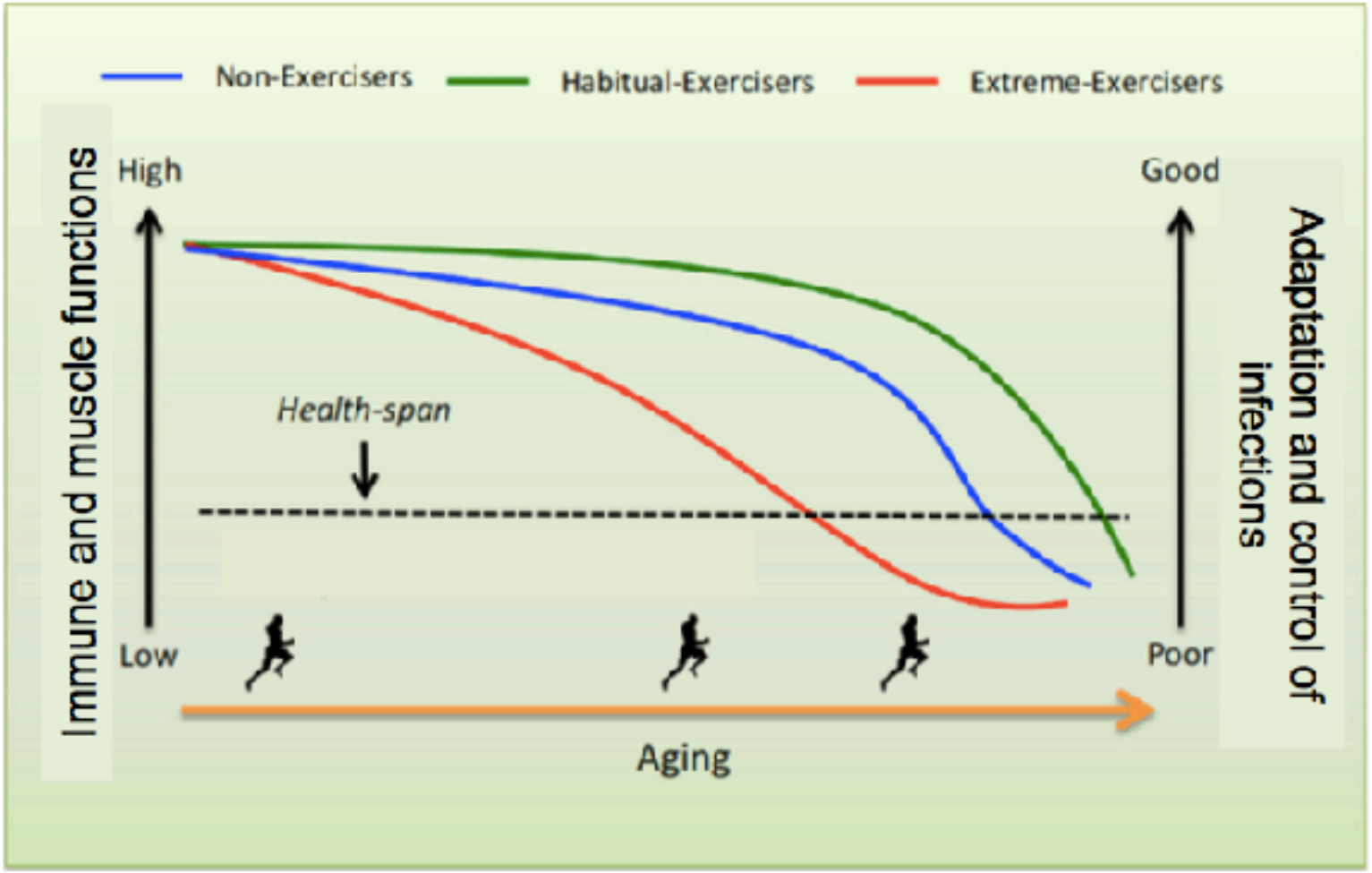


Figure 5. Strategies for preserving physiological function with ageing: primary and secondary prevention
Lifestyle–behavioural and pharmacological strategies have the potential to delay, reduce or prevent age-related dysfunction (primary prevention) and/or to improve function in older adults with existing dysfunction to prevent disease and disability (secondary prevention).

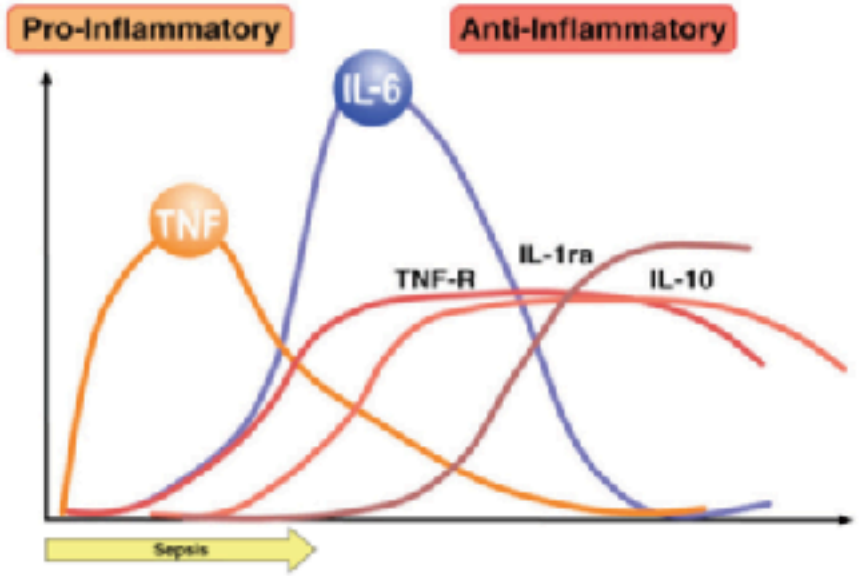
Table 1. Strategies for optimizing physiological function with ageing: outstanding issues

Strategy	Outstanding Issue
 **Exercise and Physical Activity**	most effective type, intensity, and volume for maintaining specific physiological functions (motor, cognitive, vascular, etc.)
 **Energy Intake**	effective, safe and feasible approaches in middle-aged and older adults, including intermittent fasting paradigms
 **Diet Composition**	effect of overall healthy "dietary patterns" (e.g. DASH, Mediterranean) vs. intake of specific diet components
 **Repurposed Pharmaceuticals**	use of prescription agents currently approved for clinical disease to prevent or treat physiological dysfunction with aging
 **New Pharmaceuticals and Nutraceuticals**	the role of other pharmacological agents, including nutraceuticals and new pharmaceutical drugs, as function-enhancing compounds with aging
 **Psycho-Social-Emotional Influences**	understanding the modulatory influence of cognitive and social stimulation, psycho-emotional state, and socio-economic status and stress on multiple domains of function with aging
 **Relative Efficacy**	determining the relative efficacy (comparative effectiveness studies), biological redundancy, and potential negative interactions among specific lifestyle and pharmacological strategies
 **Sex, Race and Genetics**	influence of sex/sex hormone status, race/ethnicity and genomics on physiological declines with aging and responsiveness to interventions

Aging modulates exercise-induced cytokines production and in general the efficacy of immune system.

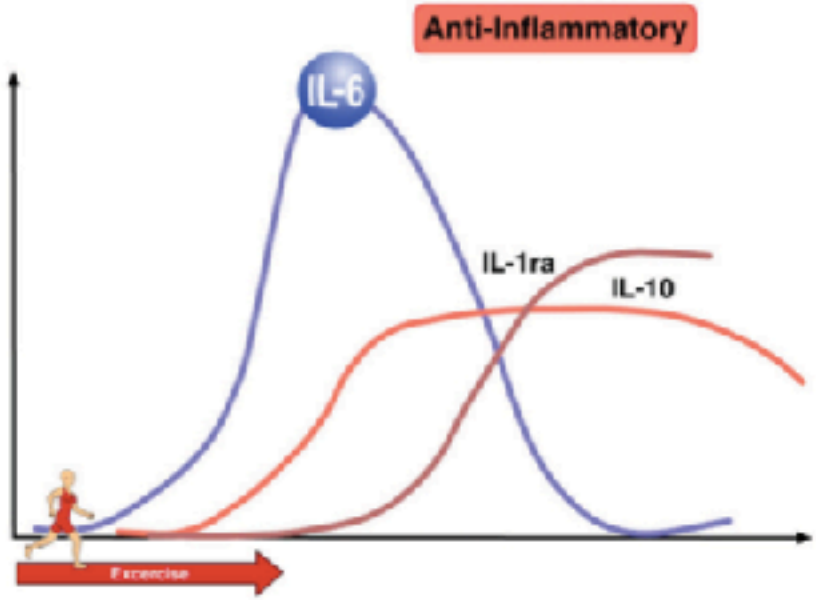


Modified from Simpson RJ, Bosch JA. Brain Behav Immun. 2014; 39:1-7



Model of "low grade inflammation":

In resting subjects, low dose of E. coli endotoxin induced a 2 to 3 fold increase in circulating levels of TNF-α.

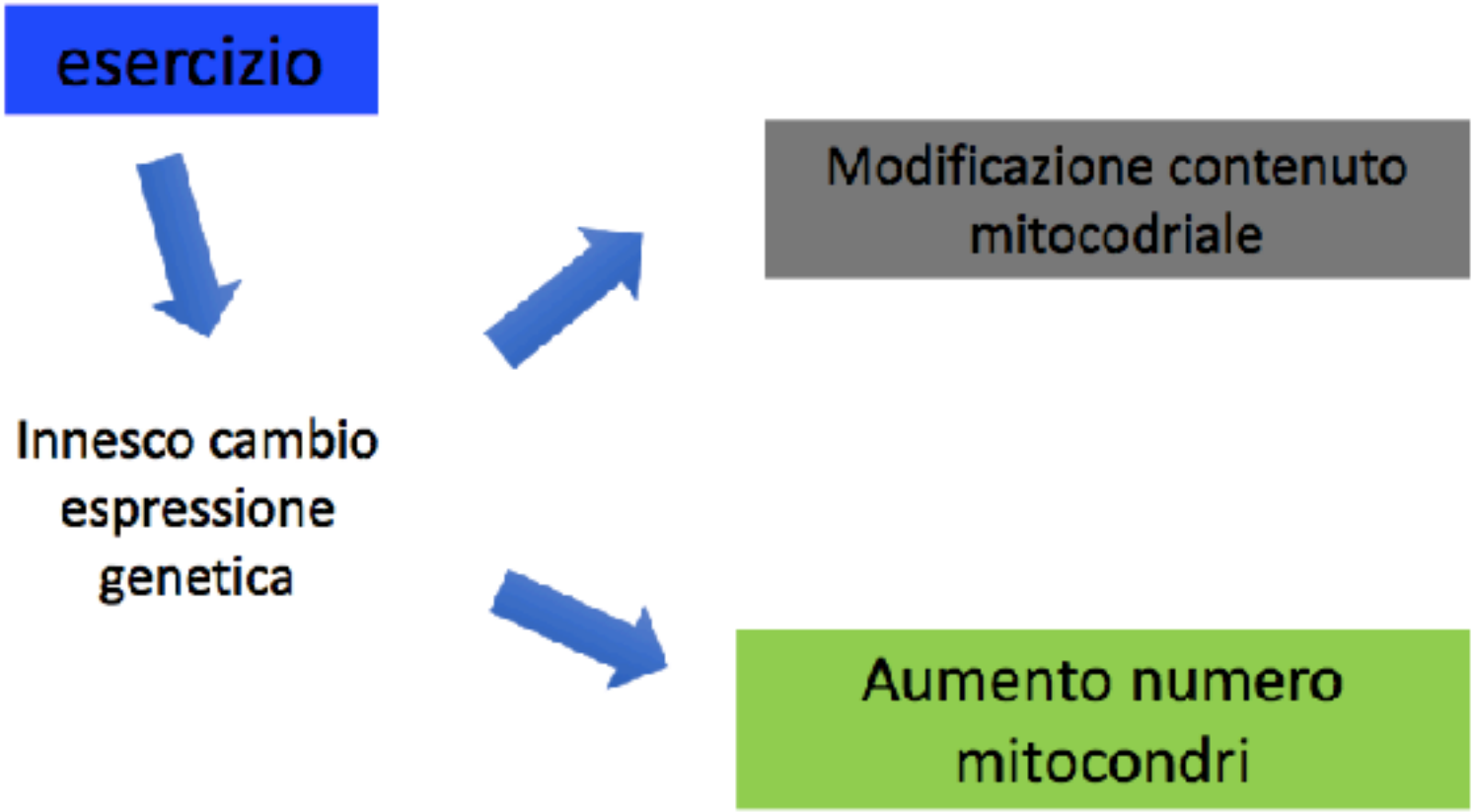


In contrast, when the subjects performed 3 h of ergometer cycling and received the endotoxin bolus at 2.5 h, the TNF-α response was totally blunted

This study provides some evidence that acute exercise may inhibit TNF-α production.

Starkie et al. FASEB J 17: 884-886, 2003.

Adattamento mitocondriale all'esercizio



Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise

Garber et al. Medicine & Science in Sports & Exercise: 2011; 43 (7): 1334-1359

	Evidence-Based Recommendation
Cardiorespiratory ("aerobic") exercise	
Frequency	≥5 d·wk^{-1} of moderate exercise, or ≥3 d·wk^{-1} of vigorous exercise, or a combination of moderate and vigorous exercise on ≥3–5 d·wk^{-1} is recommended.
Intensity	Moderate and/or vigorous intensity is recommended for most adults. Light- to moderate-intensity exercise may be beneficial in deconditioned persons.
Time	30–60 min·d^{-1} (150 min·wk^{-1}) of purposeful moderate exercise, or 20–60 min·d^{-1} (75 min·wk^{-1}) of vigorous exercise, or a combination of moderate and vigorous exercise per day is recommended for most adults. <20 min·d^{-1} (<150 min·wk^{-1}) of exercise can be beneficial, especially in previously sedentary persons.
Type	Regular, purposeful exercise that involves major muscle groups and is continuous and rhythmic in nature is recommended.
Volume	**A target of volume of 500-1000 Kcal/wk is recommended** Increasing pedometer step counts by ≥2000 steps per day to reach a daily step count ≥7000 steps per day is beneficial. Exercising below these volumes may still be beneficial for persons unable or unwilling to reach this amount of exercise.
Pattern	Exercise may be performed in one (continuous) session per day or in multiple sessions of ≥10 min to accumulate the desired duration and volume of exercise per day. Exercise bouts of <10 min may yield favorable adaptations in very deconditioned individuals. Interval training can be effective in adults.
Progression	A gradual progression of exercise volume by adjusting exercise duration, frequency, and/or intensity is reasonable until the desired exercise goal (maintenance) is attained. This approach may enhance adherence and reduce risks of musculoskeletal injury and adverse CHD events.

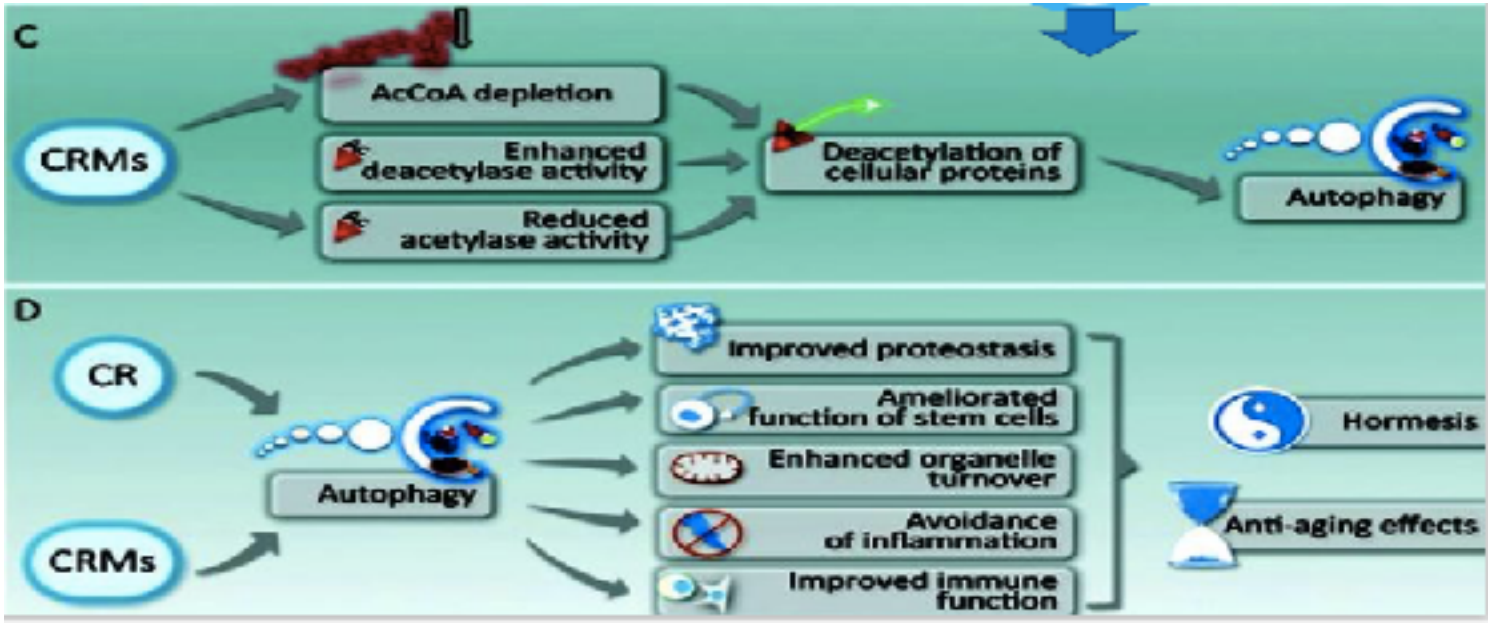
Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise

Garber et al. Medicine & Science in Sports & Exercise: 2011; 43 (7): 1334-1359

Resistance exercise	
Frequency	Each major muscle group should be trained on 2–3 d·wk^{-1}.
Intensity	60%–70% of the 1RM (moderate to hard intensity) for novice to intermediate exercisers to improve strength.
	≥80% of the 1RM (hard to very hard intensity) for experienced strength trainers to improve strength.
	40%–50% of the 1RM (very light to light intensity) for older persons beginning exercise to improve strength.
	40%–50% of the 1RM (very light to light intensity) may be beneficial for improving strength in sedentary persons beginning a resistance training program.
	<50% of the 1RM (light to moderate intensity) to improve muscular endurance.
	20%–50% of the 1RM in older adults to improve power.
Time	No specific duration of training has been identified for effectiveness.
Type	Resistance exercises involving each major muscle group are recommended.
	A variety of exercise equipment and/or body weight can be used to perform these exercises.
Repetitions	8–12 repetitions is recommended to improve strength and power in most adults.
	10–15 repetitions is effective in improving strength in middle aged and older persons starting exercise
	15–20 repetitions are recommended to improve muscular endurance
Sets	Two to four sets are the recommended for most adults to improve strength and power.
	A single set of resistance exercise can be effective especially among older and novice exercisers.
	≤2 sets are effective in improving muscular endurance.
Pattern	Rest intervals of 2–3 min between each set of repetitions are effective.
	A rest of ≥48 h between sessions for any single muscle group is recommended.
Progression	A gradual progression of greater resistance, and/or more repetitions per set, and/or increasing frequency is recommended.

Alimentazione: Caloric Restriction Mimetic e longevità

…"given that long-term CR can create heavy challenges to compliance in human diets, the concept of a calorie restriction mimetic (CRMs) has emerged as an active research area within gerontology"… *Ageing Resv. Rev.2015 Mar;20:46-62*



Dieta mediterranea frugale: CRM

Diversi studi mostrano il potenziale anti-aging della dieta mediterranea..

Tognon G. Does the Mediterranean diet predict longevity in the elderly? A Swedish perspective. Age (Dordr). 2011 Sep;33(3):439-50

Trichopoulou A et al. Traditional Mediterranean diet and longevity in the elderly: a review. Public Health Nutr. 2004 Oct;7(7):943-7

ma..

i nostri centenari usufruivano del metodo MedDiet?

Le zone blu italiane (Cilento, Nicotera, Orzulei, Monti Sicani..)

Sono caratterizzate da un consumo specifico di diverse categorie alimentari e mostrano modesta aderenza al modello ideale MedDiet:

alto intake di frutta, legumi, ortaggi

meno calorie rispetto ai LARN

prodotti e gastronomia locali

distribuzione circadiana dei pasti

Per essere longevi, occorre rispettare, negli anni, il nostro ritmo biologico

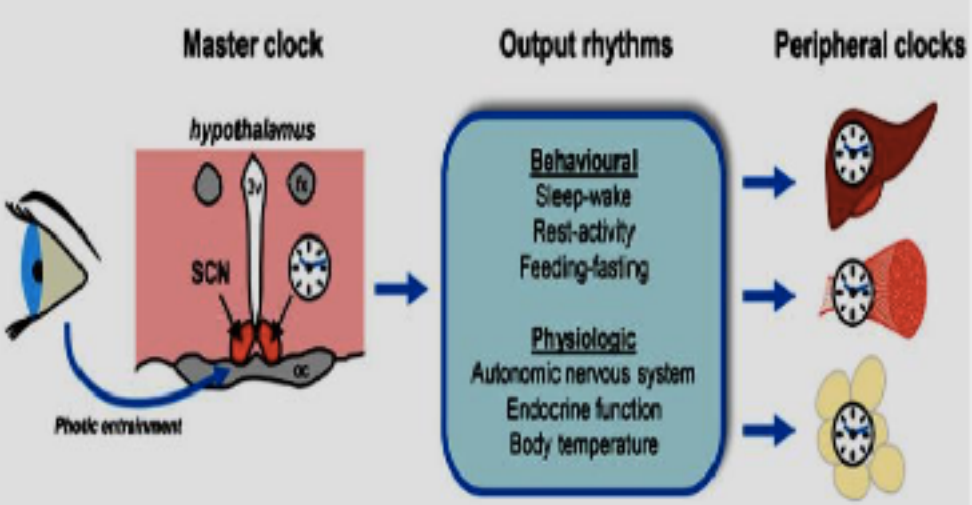
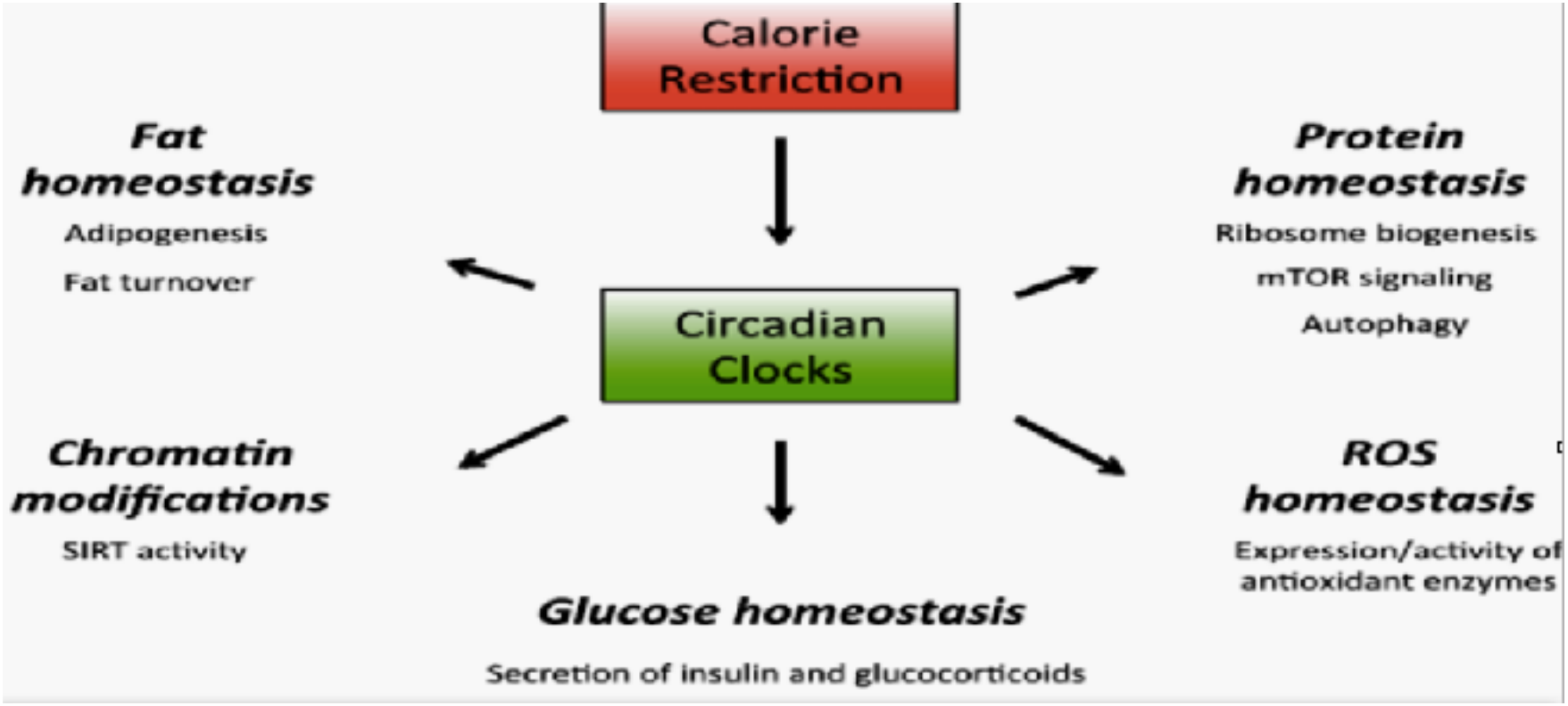


Fig. 2. Organisation of the circadian system. Exposure to the light–dark cycle synchronises the master circadian clock in the suprachiasmatic nucleus (SCN) in the hypothalamus. The SCN clock can synchronise peripheral clocks through its effects on behavioural rhythms (e.g. rest-activity and feeding–fasting cycles), as well as neural and endocrine pathways. 3v, third ventricle; fx, fornix; oc, optic chiasm.

Il ritmo biologico

Il SNC regola il ritmo biologico e costituisce un meccanismo molecolare autonomo



Amo Chaudari et all. Clocks, diets and aging nutrition and healthy aging 4, 2017, 101-112

Cell Metabolism
Essay

Metformin as a Tool to Target Aging

Nir Barzilai,[1,*] Jill P. Crandall,[1] Stephen B. Kritchevsky,[2] and Mark A. Espeland[2]
[1]Institute for Aging Research, Albert Einstein College of Medicine, Bronx, NY 10461, USA
[2]Wake Forest Older Americans Independence Center and the Sticht Center on Aging, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA
*Correspondence: nir.barzilai@einstein.yu.edu
http://dx.doi.org/10.1016/j.cmet.2016.05.011

Aging has been targeted by genetic and dietary manipulation and by drugs in order to increase lifespan and health span in numerous models. Metformin, which has demonstrated protective effects against several age-related diseases in humans, will be tested in the TAME (Targeting Aging with Metformin) trial, as the initial step in the development of increasingly effective next-generation drugs.

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Biological Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 71, No. 11, 1395–1406
doi:10.1093/gerona/glw106
Advance Access publication August 16, 2016

OXFORD

Special Issue: Moving Geroscience Into Uncharted Waters: Perspective

Evaluating Health Span in Preclinical Models of Aging and Disease: Guidelines, Challenges, and Opportunities for Geroscience

Derek M. Huffman,[1] Jamie N. Justice,[2] Michael B. Stout,[3] James L. Kirkland,[3] Nir Barzilai,[1] and Steven N. Austad[4]

[1]Institute for Aging Research, Albert Einstein College of Medicine, Bronx, New York. [2]Department of Integrative Physiology, University of Colorado Boulder. [3]Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, Minnesota. [4]Department of Biology, University of Alabama at Birmingham.

Aging Cell (2015) 14, pp497–510 Doi: 10.1111/acel.12338

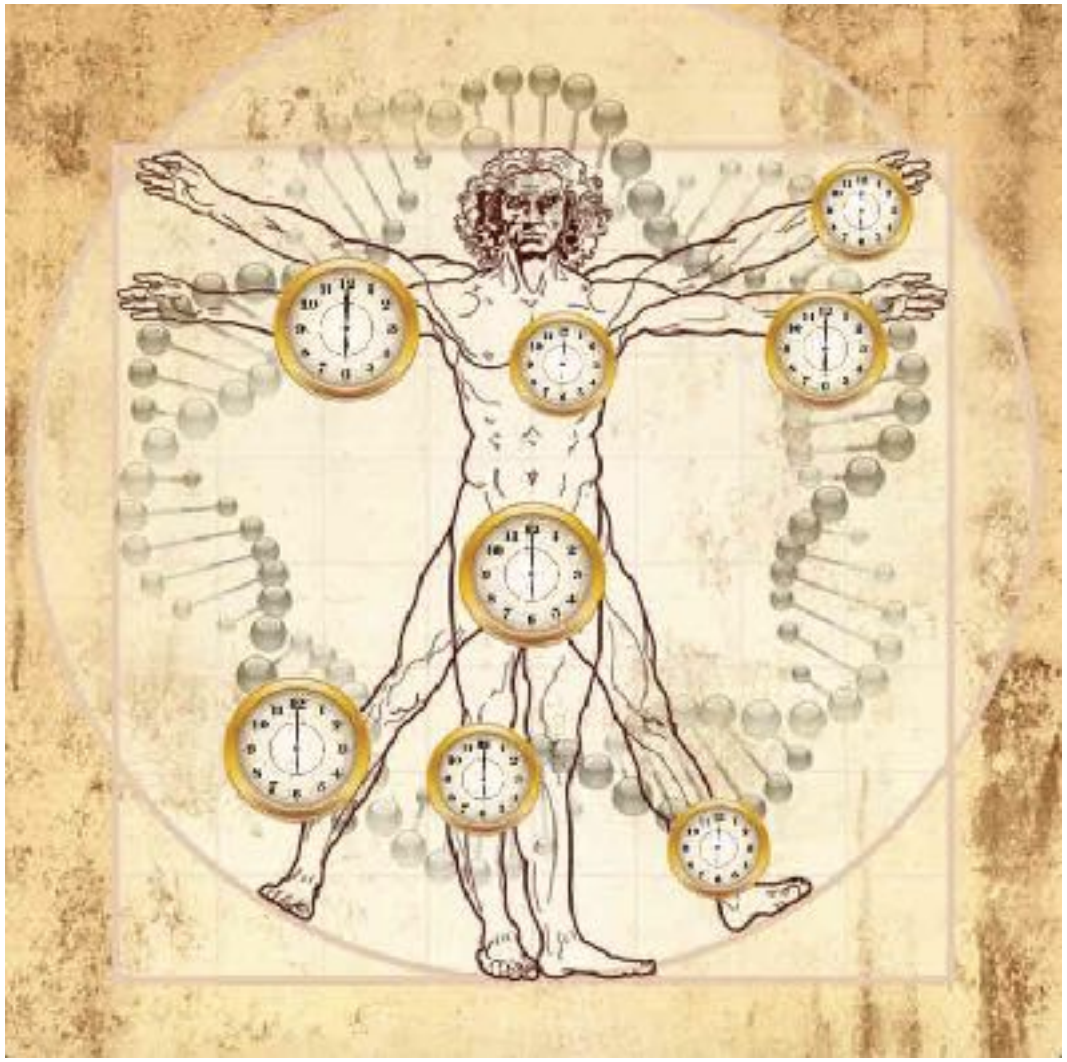
REVIEW

Interventions to Slow Aging in Humans: Are We Ready?

Valter D.Longo, Adam Antebi, Andrzey Bartke, Nir Barzilai et all.

DNA methylation age of human tissues and cell types

Steve Horvath[1,2,3]

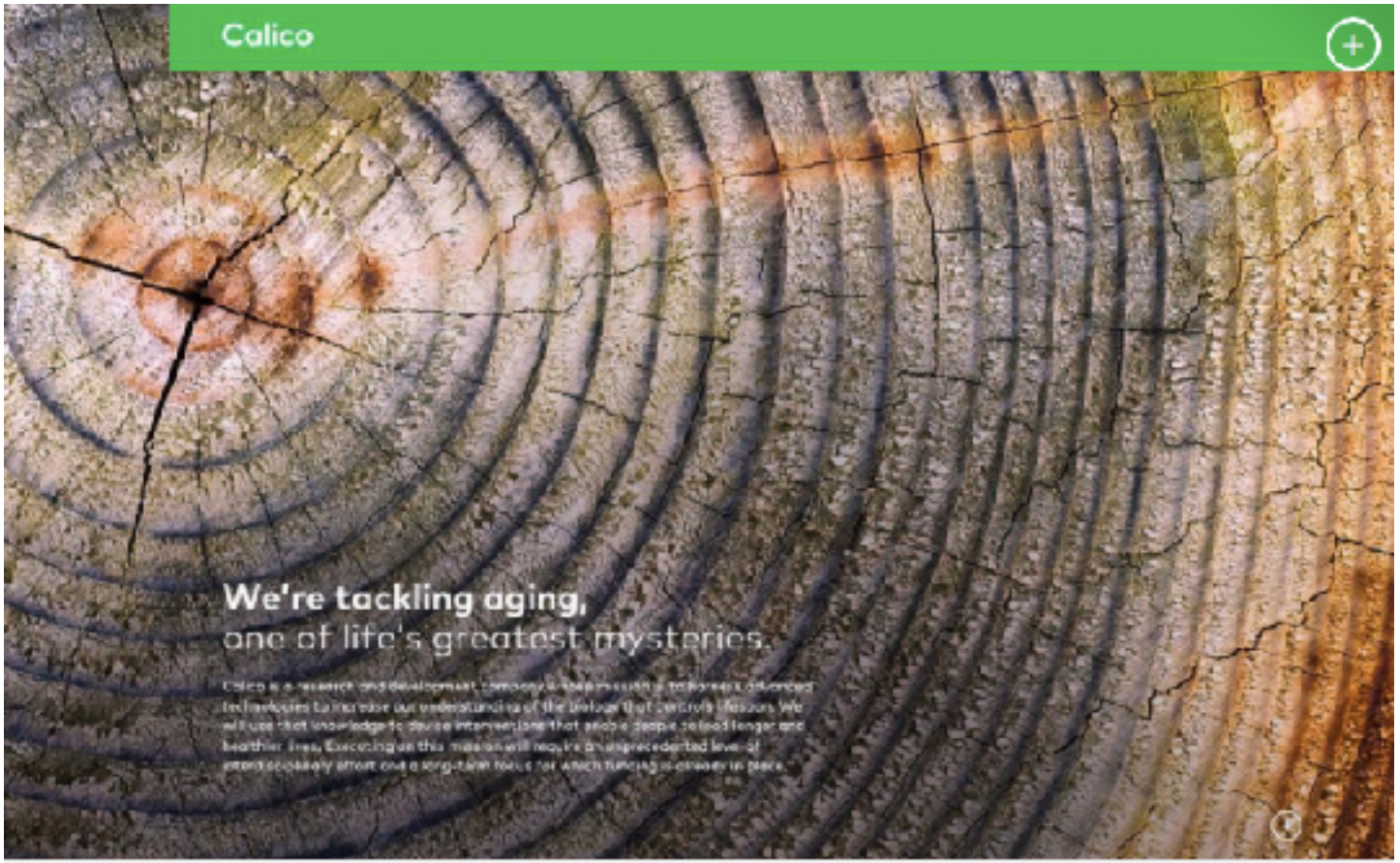


Genome Biology

Investitors in Silicon Valley:
Sergey Brin and Larry Page

Investitors in Silicon Valley:

Sergey Brin, Larry Page and Arthur D. Levinson



Google has launced Calico, a research and development company that studies aging. (GOOGLE)

250 milioni di dollari
University of Texas Southwestern Medical Center (2014)
Broad Institute of MIT and Harvard (2015)
Buck Institute for Research on Aging (2015)


TIME
CAN
Google
SOLVE
DEATH?
The search giant is launching a venture to extend the human life span.
That would be crazy—if it weren't Google
By Harry McCracken and Lev Grossman

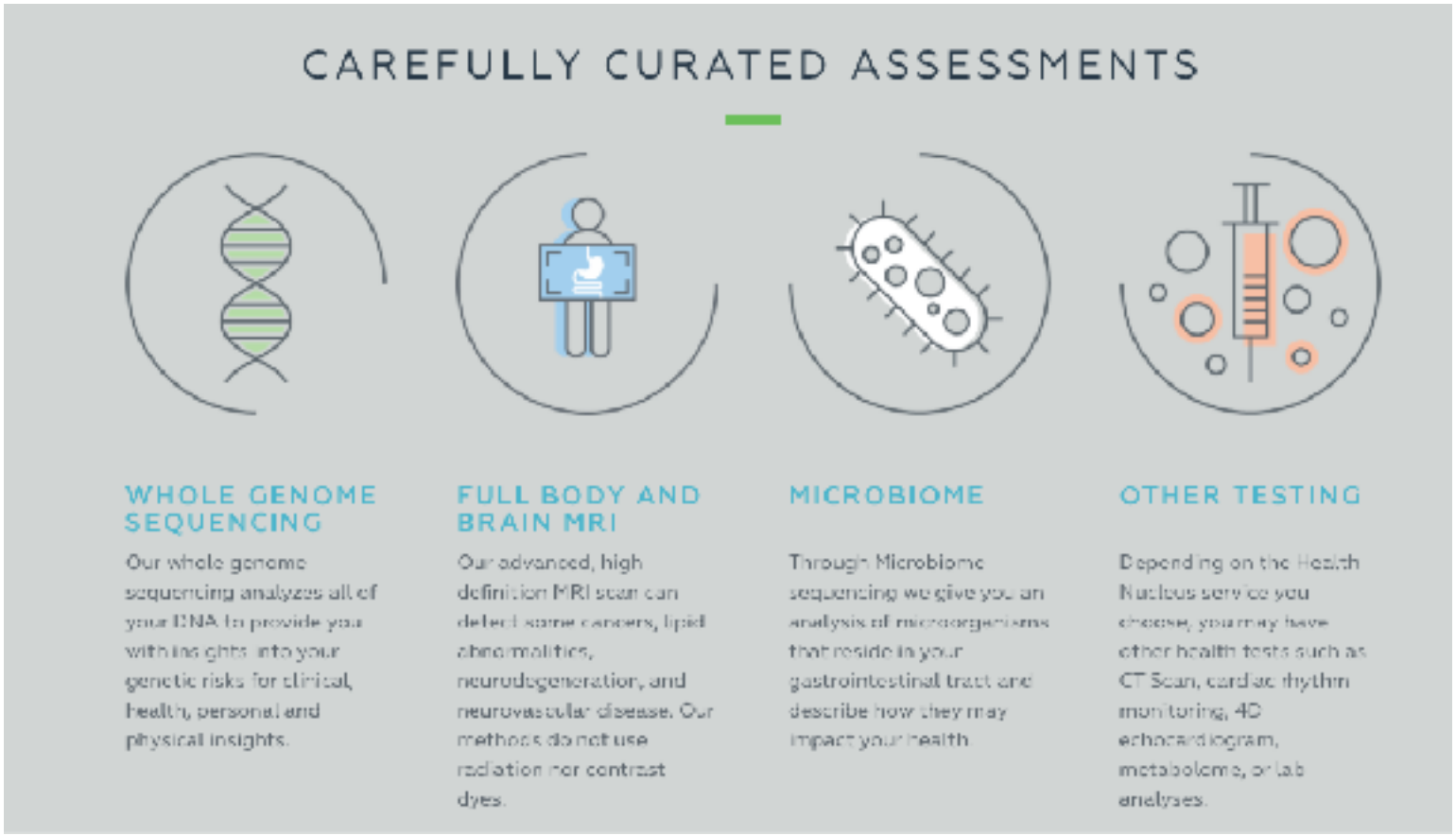
Investitors in Silicon Valley:

David H. Murdock

Investitors in Silicon Valley:
David H. Murdock

California Health and Longevity Institute

California Health and Longevity Institute



Investitors in Silicon Valley:

Larry Ellison

The longevity genes project, Nir Barzilai

EINSTEIN
Albert Einstein College of Medicine

The impact of cellular aging (senescence) on age-related dysfunction and chronic diseases, James Kirkland

MAYO CLINIC

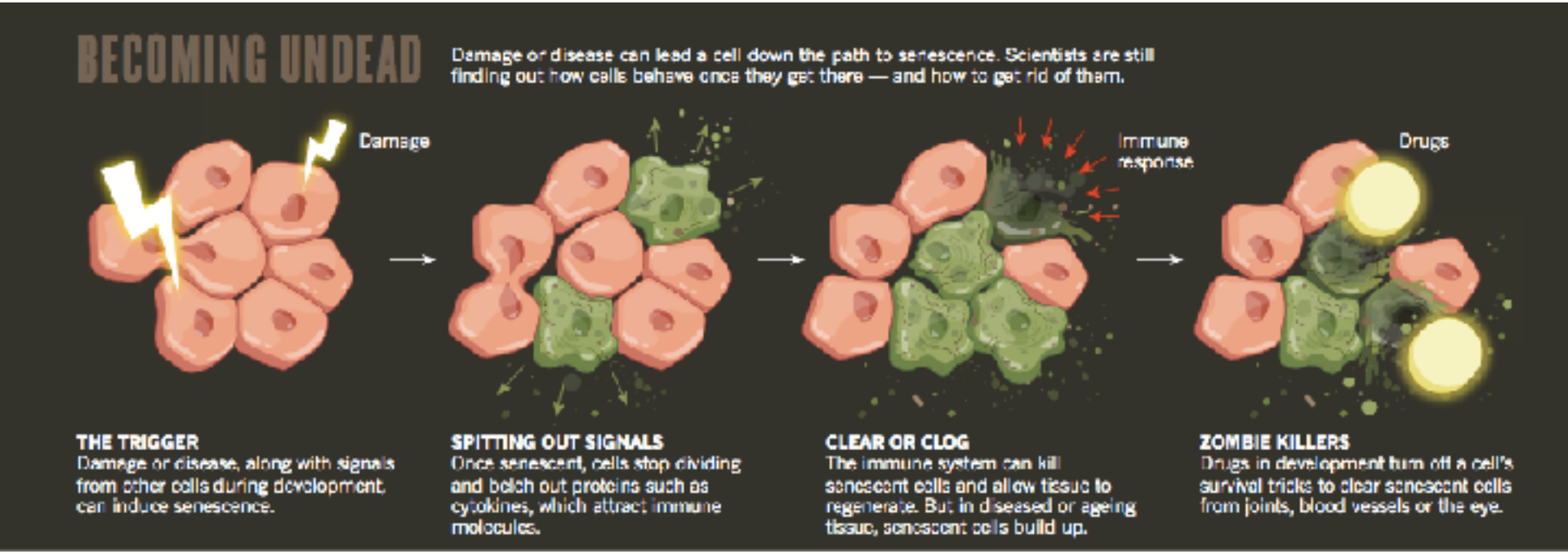
nature research

To stay young, kill zombies

Killing off cells that refuse to die on their own has proved a powerful anti-ageing strategy in mice. Now it's about to be tested in humans.

BY MEGAN SCUDELLARI

nature research



Il potenziale clinico dei farmaci senolitici

CLINICAL MANAGEMENT OF THE OLDER ADULT

The Clinical Potential of Senolytic Drugs

James L. Kirkland, MD, PhD, Tamara Tchkonia, PhD,* Yi Zhu, PhD,* Laura J. Niedernhofer, MD, PhD,† and Paul D. Robbins, PhD†*

Il potenziale clinico dei farmaci senolitici

..i farmaci senolitici potrebbero trasformare la medicina geriatrica da una disciplina concentrata sulla prevenzione terziaria o quaternaria a una disciplina con importanti opzioni preventive primarie centrate su solide basi scientifiche..

..vi è una grave carenza di geriatri con sufficiente conoscenza della biologia di base e della scienza trascrizionale per condurre studi clinici precostituiti di prova di concetto per determinare se questi interventi emergenti avranno utilità clinica..

James L.Kirkland et all.

Il potenziale clinico dei farmaci senolitici

…a quasi sessant'anni dalla sua scoperta iniziale, oggi Hayflick è convinto che l'invecchiamento sia un processo biofisico inesorabile che non può essere alterato eliminando le cellule senescenti**. "Il tentativi di interferire con il processo di invecchiamento sono in corso da quando esiste documentazione della storia umana",** dice Hayflick. **"E non conosciamo nulla, proprio nulla, che abbia dimostrato di interferire con il processo di invecchiamento…"**

Prima e dopo il trattamento per l'eliminazione delle cellule senescenti. Le due microfotografie a destra mostrano il differente stato di uno stesso tessuto. (Cortesia Baker et al., 2016, "Nature")

James L.Kirkland

Dal laboratorio alla clinica…

d-ROM test (<300 CARR U)

Test degli Omega 3 (1:4)

Test metagenomico (microbiota)

Così, poi, l'Aurora dai fiori d'oro rapì Titone,
della vostra stirpe, simile agl'immortali;
e **si avviò per chiedere a Zeus dalle nere nubi**

Inno Omerico ad Afrodite, 218-245

ch'egli fosse immortale, **e vivesse in eterno**:
a lei Zeus assentì con un cenno, ed esaudì il suo desiderio
Stolta, e non pensò nella sua mente, l'Aurora veneranda,
a chiedere la giovinezza, e a tener lontana la vecchiaia rovinosa.
E in verità, fin quando egli era nella molto amabile giovinezza,

godendo l'amore dell'Aurora dai fiori d'oro, che sorge di buon mattino,

dimorava presso le correnti dell'Oceano, ai confini della terra:
ma quando le prime ciocche bianche scesero
giù dal bel capo e dal nobile mento, dal suo letto si astenne l'Aurora veneranda;

tuttavia, tenendolo nelle sue stanze, lo nutriva
di cibo terreno e di ambrosia, e gli donava belle vesti.
Ma quando con tutto il suo peso gravò su di lui l'odiosa vecchiaia
ed egli non riusciva più a muovere né a sollevare le membra,
questa nel suo animo le sembrò la decisione migliore: lo relegò nell'interno della casa, e serrò su di lui le porte risplendenti.
La sua voce mormora senza fine, ma il vigore
non è più quello che un tempo risiedeva nelle agili membra.
Io certo non vorrei che tu, in tale stato, fra gl'immortali
fossi immortale, e vivessi in eterno. **Certo se tu continuassi a vivere così come sei ora**
nella figura e nell'aspetto, e fossi chiamato mio sposo,
il dolore non avvolgerebbe, in seguito, il mio saldo animo.
Ora invece ti avvolgerà la vecchiaia crudele, inesorabile, che poi non lascia più gli uomini, devastatrice, estenuante, che gli stessi dei hanno in odio.

Eos e Titone (XVIII sec.), Francesco De Mura