Name: CLAUDIO FRANCESCHI

Adult Immunization Board

Country:
Italy

Affiliation:
Alma Mater Studiorum, University of Bologna, Italy

Function: Speaker

Main expertise:
Professor Emeritus of Immunology, Editor-in-Chief of Ageing Research Reviews (IF: 12.5)

UNIVERSITÀ DEGLI STUDI FIRENZE DSS DIPARTIMENTO DI SCIENZE DELLA SALUTE

University of Antwerp

BOLOGNA/UNIBO: The arcades of the oldest university in the world (founded in 1088)

Claudio Franceschi

Alma Mater Studiorum
Università di Bologna, Italy

Clarifying the older adults population for vaccination strategies: exploring age, comorbidities, immunosenescence, frailty.

Adult Immunization Board (AIB)

Technical meeting

Advancing vaccination strategies for the older adults: insights into epidemiology, immunity, and implementation

Warsaw, 7th and 8th of May 2025

Impact Factor: 12.5

Editor-in-Chief
Claudio Franceschi
University of Bologna, Italy

Managing Editor
Aurelia Santoro
University of Bologna, Italy

Associate Editors
Pravir Kumar, Alexey Moskalev, Benedetta Nacmias, Nicole Noren Hooten, Fabiola Olivieri, M. Cristina Polidori, P. Hemachandra Reddy, Yang Yang

Do we need a PERSONALIZED VACCINATION for the elderly ?

Should vaccines for the elderly
(with chronic diseases?)
include
adjuvants or monoclonal antibodies
that promote
anti-inflammatory immunity ?

A personal approach

- Everybody knows that old people have problems regarding vaccination…
- I decided to focus my talk on what I think are **the three major, general problems of aging in this regard** :

1. **Heterogeneity**
2. **Biological *versus* Chronological Age**
3. **Inflammaging**

H. sapiens ages
at different rates at
population, gender
and individual levels

Aging is not democratic

- **Each person get old following his/her own trajectory;**
- **The two extremes** of such peculiar combination of different genetic and environmental factors are :

  1. healthy aging/successfull longevity (centenarians)

  2. age-related diseases (ARD)

Aging is heterogeneous

and largely different in:

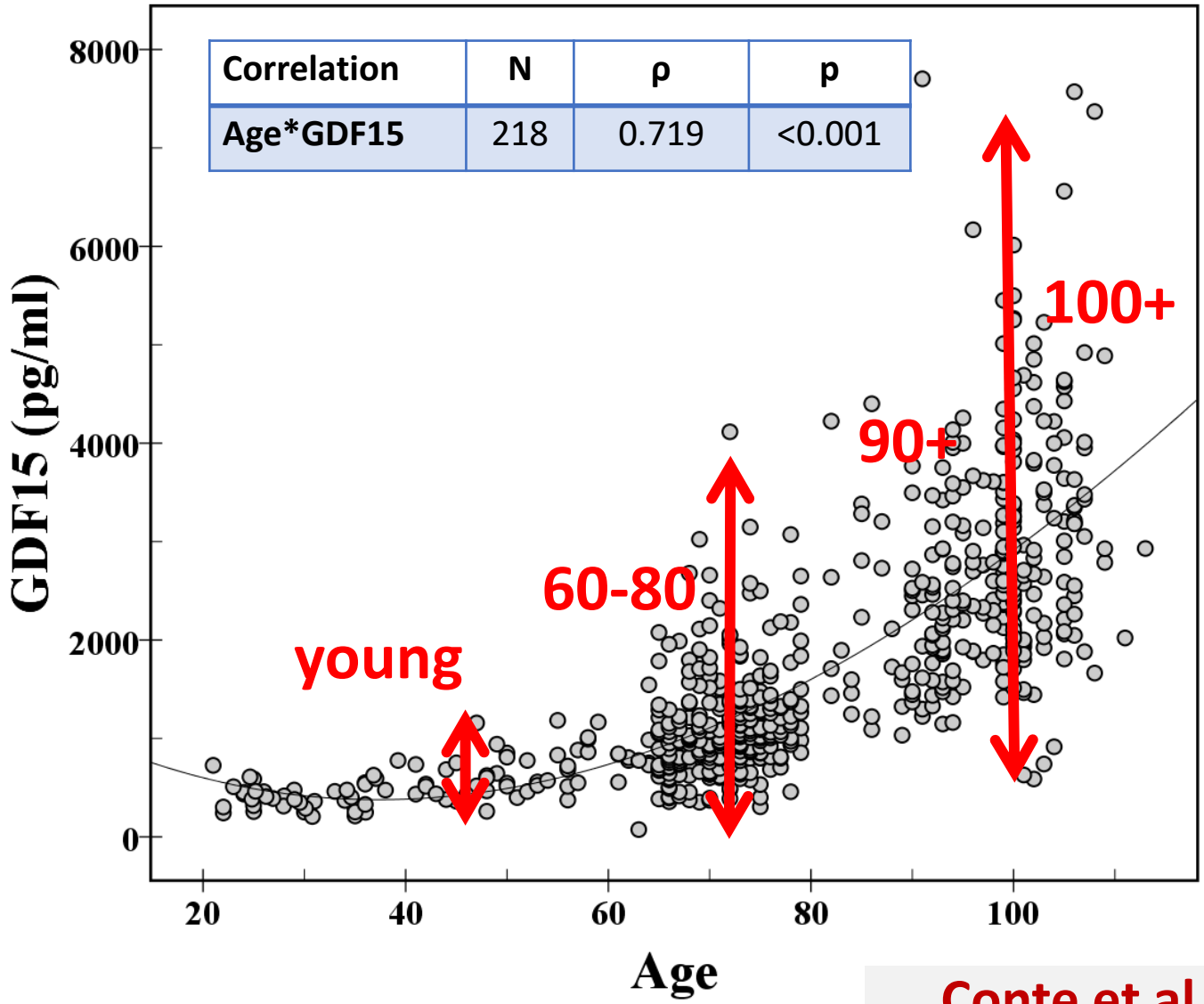
- each person/individual
- in different populations
- Historically/geographically

Major Characteristic of AGING:

Increased Heterogeneity
Individual Variability

Plasma level of GDF15 increases with age

in 693 healthy subjects of different age (21-113 years)

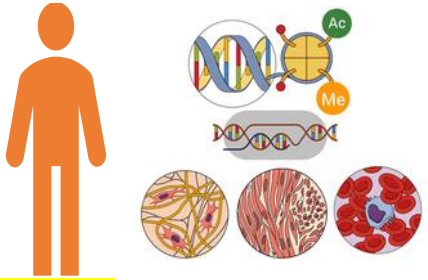


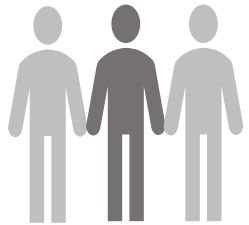
GDF15 is the protein which increases the most with aging

Conte et al., J. Gerontol 2019

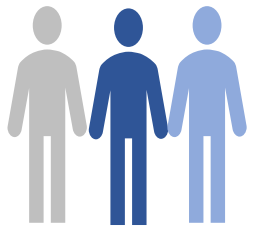
Different levels of Aging Heterogeneity

Intraindividual heterogeneity

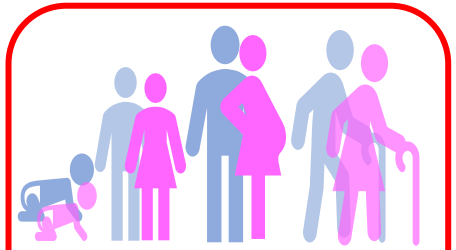




Stochastic variation
(stochastic gene regulation, epigenetic changes; de novo mutations)

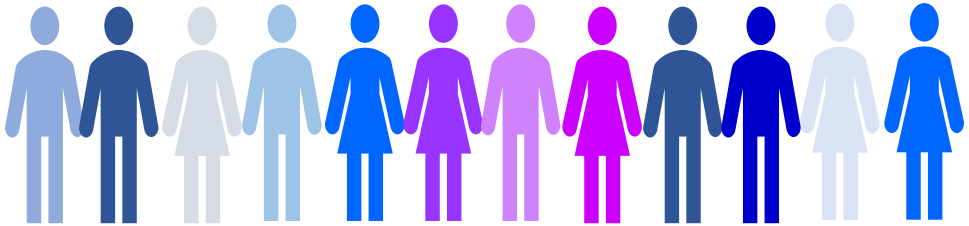


Environmental perturbation
(vaccination, infection, diet)



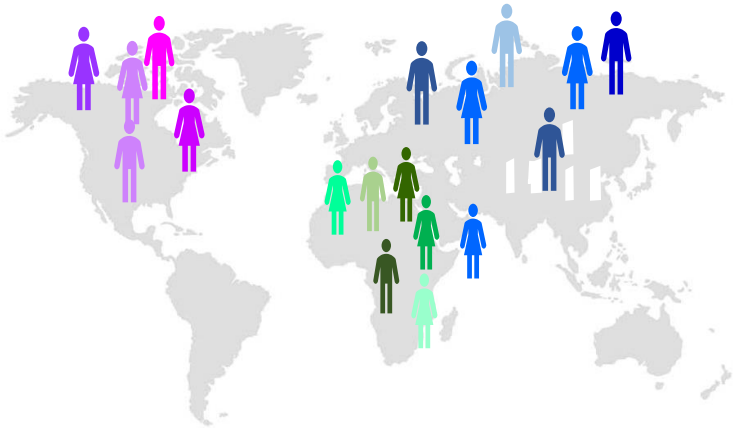
Developmental change
(maturation, puberty, pregnancy, aging)

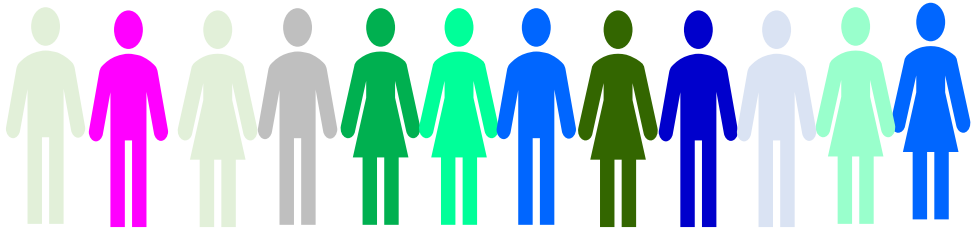
Interindividual variations



within the same population

Interpopulation variations





between different populations

Adapted from Pulendran M & Davis M Science 2020

Population aging is largely unexplored

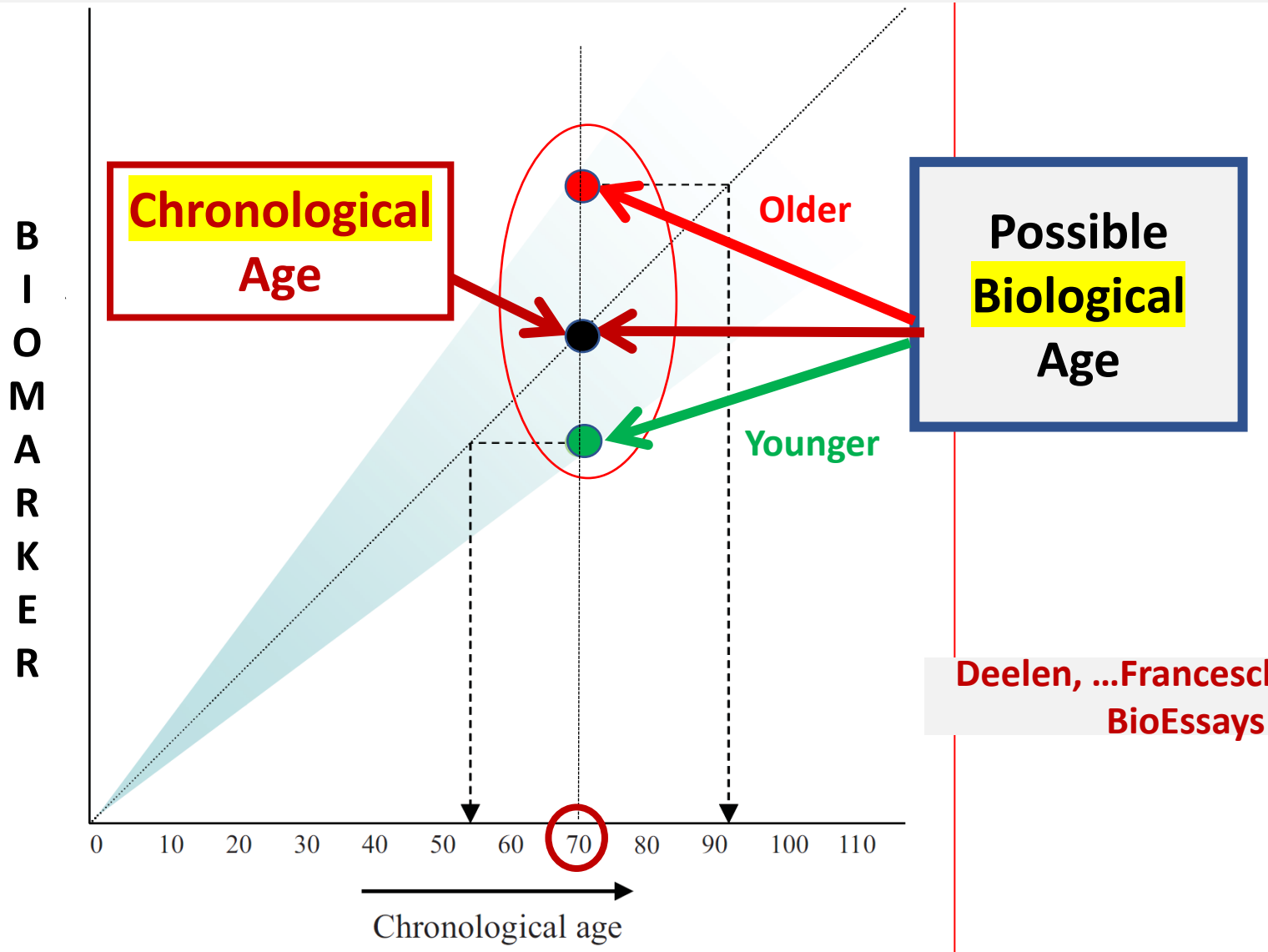
Major Characteristic of AGING:

Increased Heterogeneity
Individual Variability

The urgent need to go beyond chronological age

How to measure biological age in humans?

BIOMARKERS
of biological *vs* chronological age



Deelen, …Franceschi…Slaagboom
BioEssays 2013

THE FIRST EPIGENETIC CLOCK

Steve Horvath (UCLA) in 82 databases on **DNA methylation data**
obtained by Illumina 450 BeadChip platforms (**485,577 CpG/Genome**)
identified in the whole genome

353 CpGs

whose methylation level is a

MULTI-TISSUES PREDICTOR OF AGE

which allows to estimate

DNA METHYLATION AGE *vs* CHRONOLOGICAL AGE

Steve Horvath
DNA methylation age
of human tissues and cell types
***Genome Biology* 2013, 14:R115**

Correlation 0.97 between
DNAm age and chronol age
error = 2.9 years

105+ and their offspring are younger than their chronological age

www.impactaging.com AGING, December 2015, Vol 7 N 12

Research Paper

Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring

Steve Horvath[1,2*], Chiara Pirazzini[3,4*], Maria Giulia Bacalini[3,4,5], Davide Gentilini[6], Anna Maria Di Blasio[6], Massimo Delledonne[5,7], Daniela Mari[8,9], Beatrice Arosio[8,9], Daniela Monti[10], Giuseppe Passarino[11], Francesco De Rango[11], Patrizia D'Aquila[11], Cristina Giuliani[12], Elena Marasco[3,4], Sebastiano Collino[13], Patrick Descombes[14], Paolo Garagnani[3,4,15,§], and Claudio Franceschi[3,4,16,17,§]

Whole genome DNA methylation profile of 105+ & their offspring

Illumina *Infinium* HumanMethylation450 BeadChip (485,577 CpG/genome)

	Milano **	Bologna *	Calabria ***	TOTAL	Mean Age (± std)	Male (N)	Female (N)
105+	29	33	20	**82**	**105.5 ± 1.7**	18	64
Offspring	28	22	13	**63**	69.8 ± 7.2	22	25
Controls	17	16	14	**47**	71.6 ± 8.0	26	37
TOTAL	74	71	47	**192**			

* PI: Prof. Claudio Franceschi, DIMES, UNIBO

** PI: Prof. Daniela Mari, DIP. DI SCIENZE CLINICHE E DI COMUNITA', UNIVERSITÀ DI MILANO

***PI: Prof. Giuseppe Passarino, DIP. DI BIOLOGIA ED ECOLOGIA, UNIVERSITÀ DELLA CALABRIA

DNAmeth age *versus* Chronological age in 105+ and their offspring (OFF)

According to the Horvath's DNAmet clock:

- **semi-supercentenarians are 8.7 years biologically younger** than their chronological age;
- **105+ OFF are 5.2 years younger** than age-matched controls (p=0.00051)
- **In OFF' controls** DNAmethyl age and chronological age overlap

Horvath et al., AGING 2015

Accelerated epigenetic aging in Down syndrome

Steve Horvath,[1,2,*] Paolo Garagnani,[3,4,5,*] Maria Giulia Bacalini,[3,4,6] Chiara Pirazzini,[3,4] Stefano Salvioli,[3,4] Davide Gentilini,[7] Anna Maria Di Blasio,[7] Cristina Giuliani,[8] Spencer Tung,[9] Harry V. Vinters[9] and Claudio Franceschi[4,10]

Here, we utilize a quantitative molecular marker of aging (known as the epigenetic clock) to demonstrate that trisomy 21 significantly increases the age of blood and brain tissue (on average by 6.6 years, $P = 7.0 \times 10^{-14}$).

Age acceleration for DS:

Leukocytes:	**3.9 years**
Brain:	**11.5 years**
Whole blood:	**4.6 years**
Buccal cells:	**2.8 years**

Aging Cell, 2015

WILEY

Aging Cell Best Paper Prize

Awarded for the most outstanding paper published in 2015

'Acceleated epigenetic aging in Down syndrome'

Horvath, S., Garagnani, P., Bacalini, M. G., Pirazzini, C., Salvioli, S., Gentilini, D., Di Blasio, A. M., Giuliani, C., Tung, S., Vinters, H. V. and Franceschi, C.

Aging Cell, Volume 14, Issue 3, June 2015, pages 491-495

Peter Adams
Editor-in-Chief

Adam Antebi
Editor-in-Chief

Ana Maria Cuervo
Editor-in-Chief

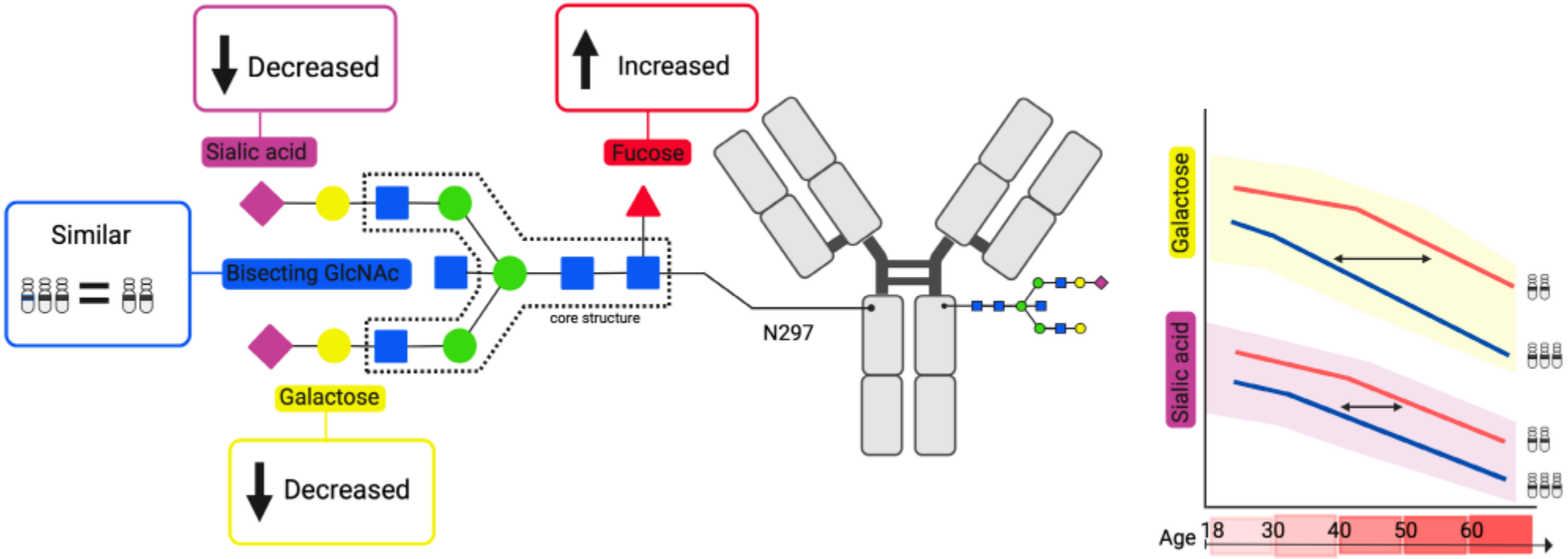
Brian Kennedy
Editor-in-Chief

John Sedivy
Editor-in-Chief

T. Clive Lee
President of the Anatomical Society

The N-glycan clock

Serum N-glycan profile shift during human ageing. **Vanhooren V**, Dewaele S, Libert C, Engelborghs S, De Deyn PP, Toussaint O, Debacq-Chainiaux F, Poulain M, Glupczynski Y, **Franceschi C**, Jaspers K, van der Pluijm I, Hoeijmakers J, et al. **Exp Gerontol. 2010**;45:738–743.



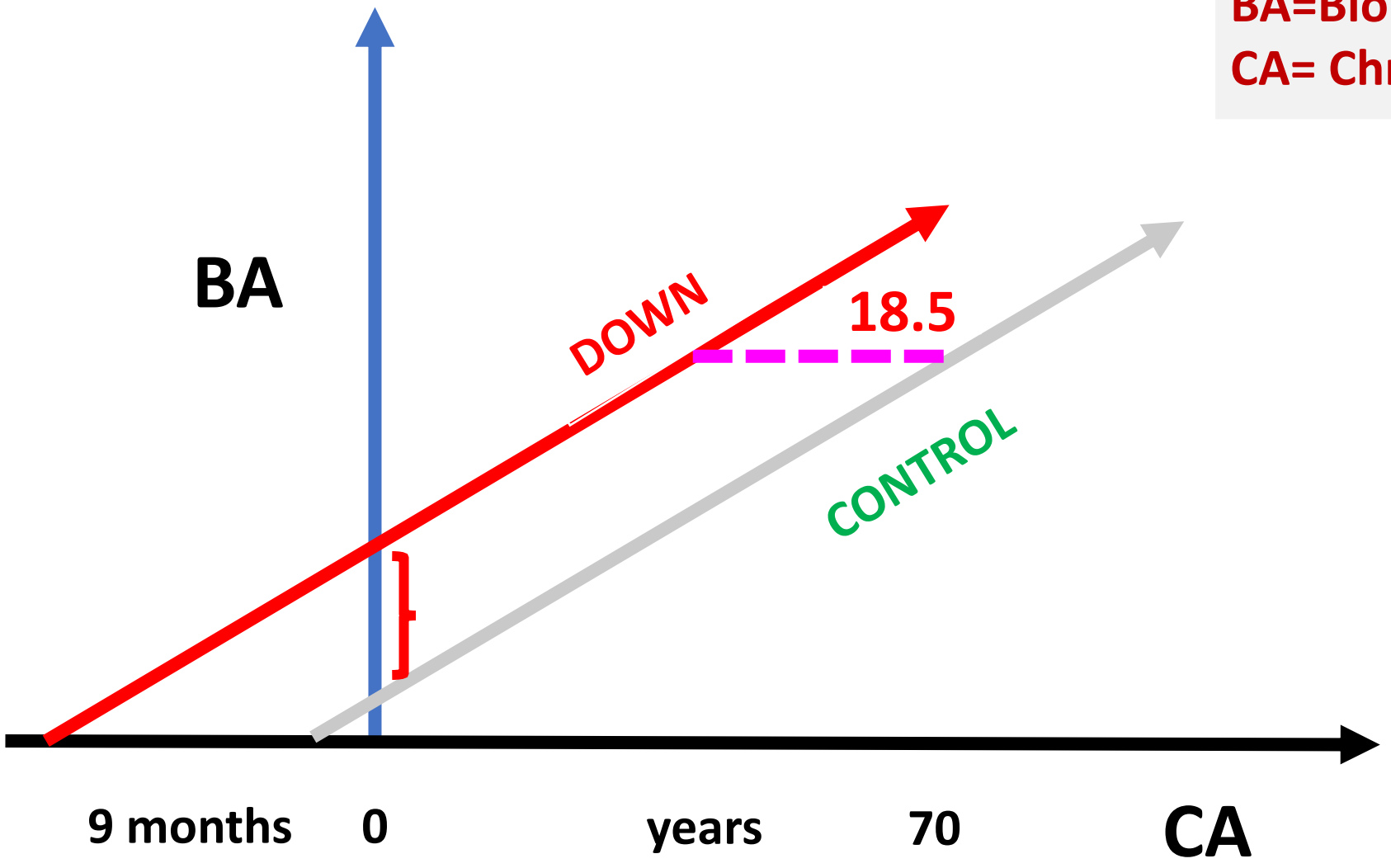
Plasma N-Glycome Signature of Down Syndrome. **Borelli V**, Vanhooren V, Lonardi E, Reiding KR, Capri M, Libert C, Garagnani P, Salvioli S, **Franceschi C**, Wuhrer M. **J Proteome Res. 2015** Oct 2;14(10):4232-45.

Dose imbalance of DYRK1A kinase causes systemic progeroid status in Down syndrome by increasing the un-repaired DNA damage and reducing LaminB1 levels.

Murray A, …, Borelli V, …Spector T,…, Franceschi C, Lauc G,…Nižetić D. **EBioMedicine. 2023** Aug;94:104692.

- **Plasma N-Glycome biological age** was estimated in **246 individuals with DS** **from three European populations** and compared to n= 256 age-, sex- and demography-matched healthy controls.
- On average, biological age in adults with **DS is 18.4-19.1 years older** than in chronological-age-matched controls and is **detectable from early childhood.**
- Using isogenic **hiPSC models** we show that chromosome-21 gene DYRK1A overdose is sufficient and necessary to cause excess unrepaired DNA damage that can be pharmacologically corrected in hiPSCs and derived cerebral organoids.

BA=Biological Age
CA= Chronological Age



A Targeted Epigenetic Clock for the Prediction of Biological Age.

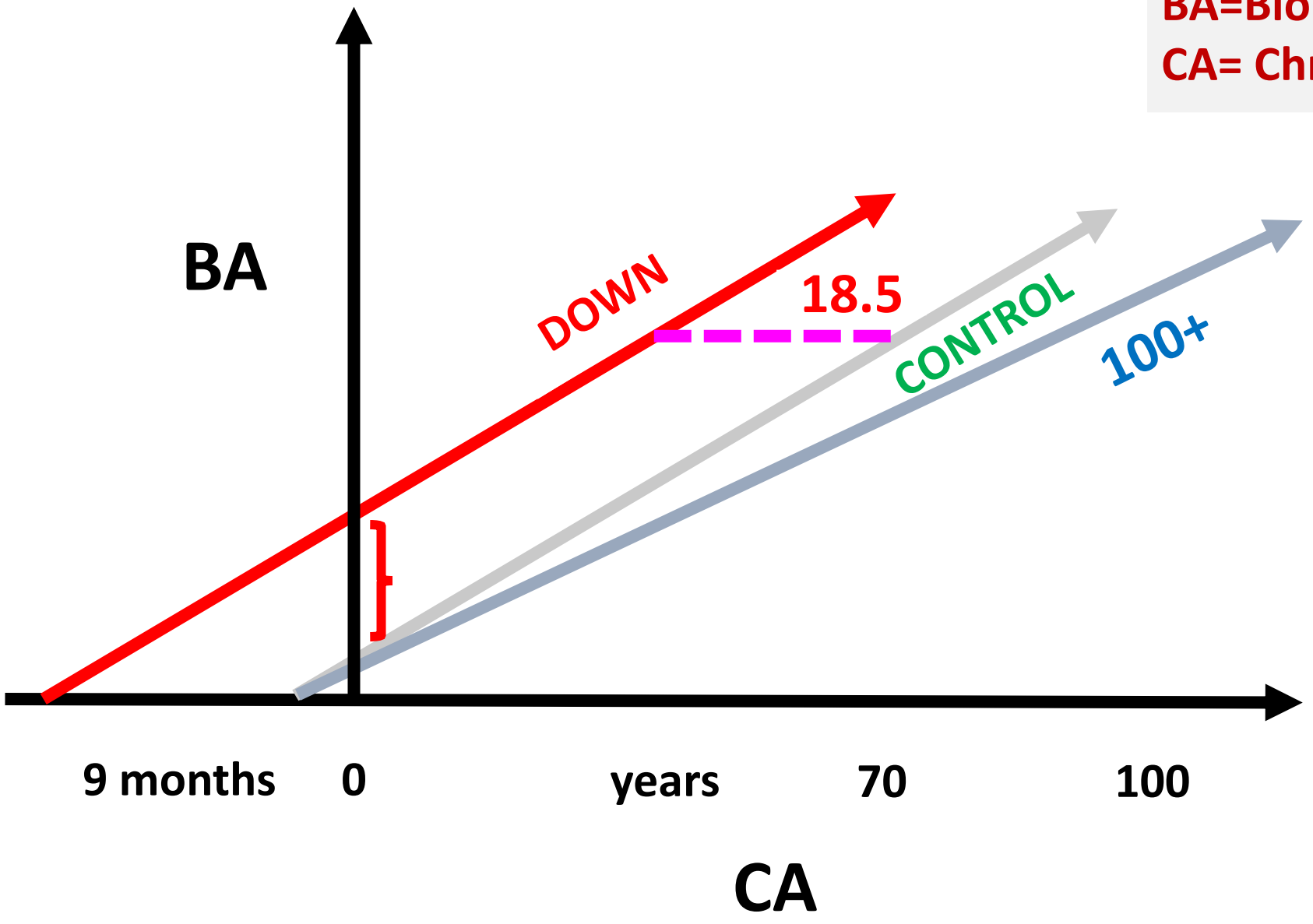
Gensous N, Sala C, Pirazzini C, Ravaioli F, Milazzo M, Kwiatkowska KM, Marasco E, De Fanti S, Giuliani C, Pellegrini C, Santoro A, Capri M, Salvioli S, Monti D, Castellani G, Franceschi C, Bacalini MG, Garagnani P.

Cells. 2022 Dec 14;11(24):4044

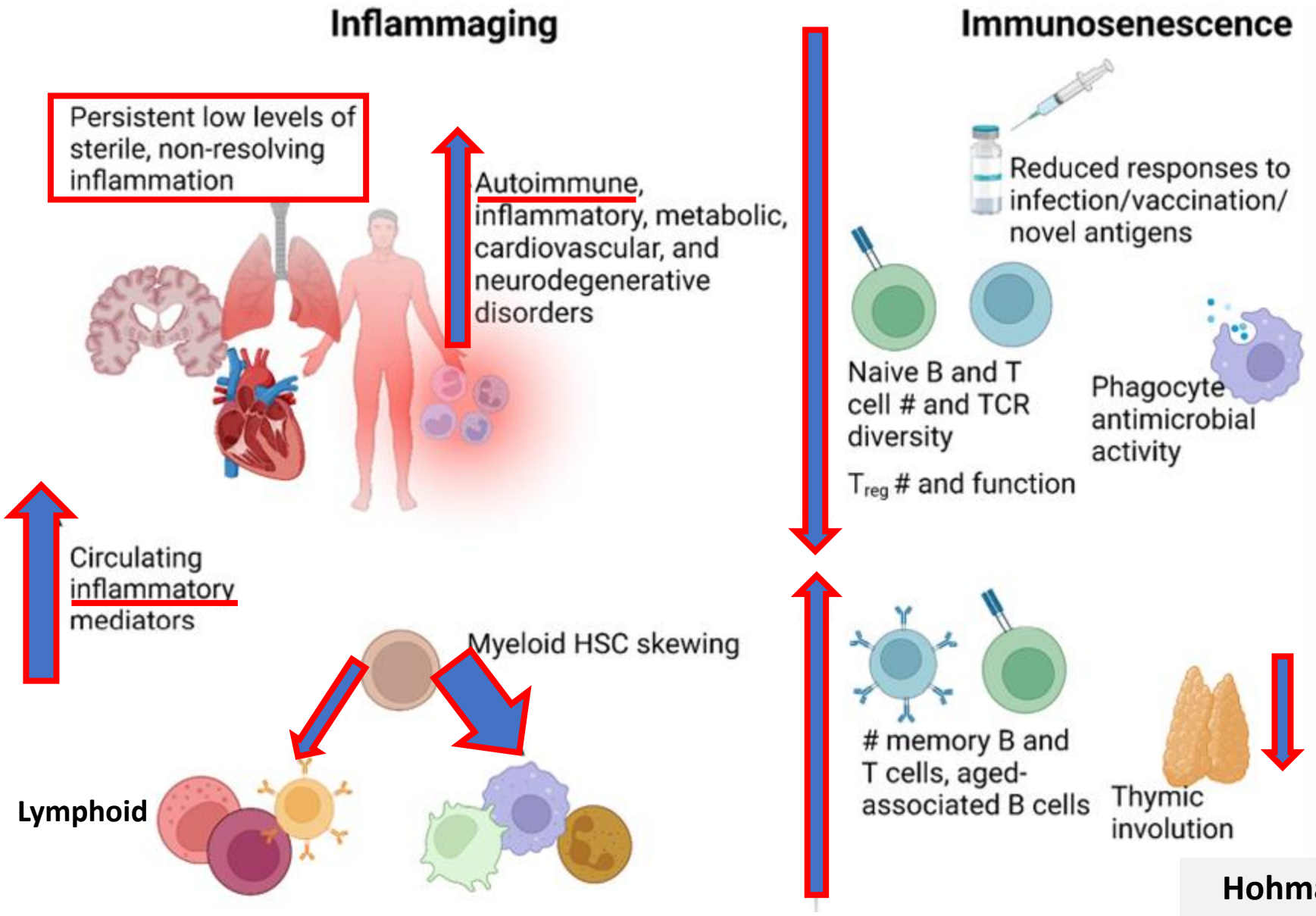
- This new clock includes six genomic regions mapping in ***ELOVL2, NHLRC1, AIM2, EDARADD, SIRT7*** **and** ***TFAP2E*** genes.
- This clock was:

- highly correlated with chronological age in 278 healthy subject;
- **significantly higher in 62 Down syndrome subjects**;
- **significantly lower** than expected in **106 centenarians and 143 centenarians' offspring**, **as expected**.

BA=Biological Age
CA= Chronological Age



Hallmarks of the Immune System Aging



Hohman LS, Osborne LC. Aging Cell 2022

INFLAMMAGING
&
Inflammatory clocks

Inflamm-aging

An Evolutionary Perspective on Immunosenescence

CLAUDIO FRANCESCHI,[a,b,e] MASSIMILIANO BONAFÈ,[a] SILVANA VALENSIN,[a] FABIOLA OLIVIERI,[b] MARIA DE LUCA,[d] ENZO OTTAVIANI,[c] AND GIOVANNA DE BENEDICTIS[d]

[a]*Department of Experimental Pathology, University of Bologna, Bologna, Italy*

[b]*Department of Gerontological Research, Italian National Research Center on Aging (INRCA), Ancona, Italy*

[c]*Department of Animal Biology, University of Modena and Reggio Emilia, Modena, Italy*

[d]*Department of Cell Biology, University of Calabria, Calabria, Italy*

"chronic", "low grade", "sterile"

Inflammaging is based on studies on

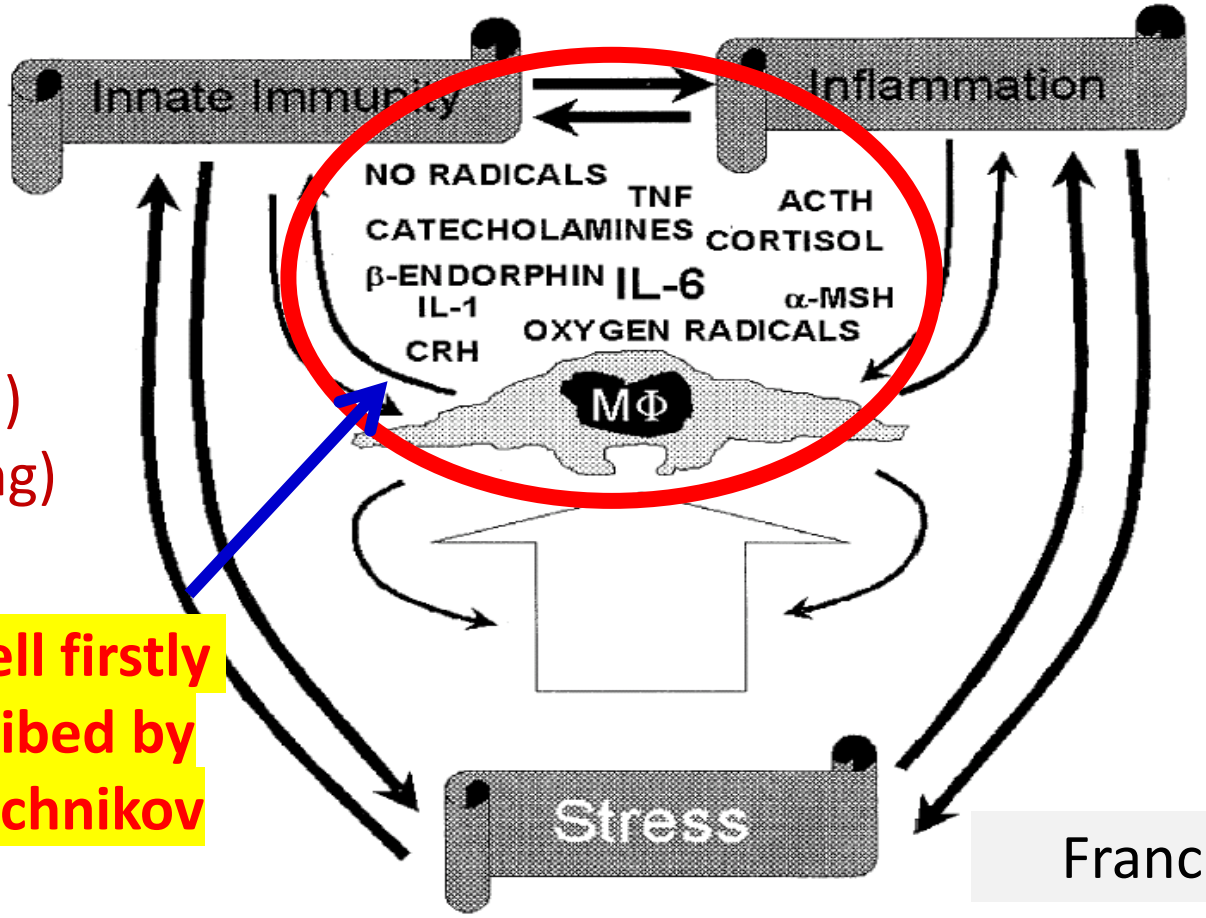
immunosenescence and the evolution of immune response and stress from invertebrates to mammals

Ann. N.Y. Acad. Sci., 908, 244-254, 2000

5842 citations (05/05/2025)

The “ancestral” macrophage as the central cell of inflammaging

Macrophages polarize into
M1 (inflammation)
M2 (wound healing)



The cell firstly described by E. Mechnikov

- Macrophages are able to modify their phenotype
- producing **pro- and anti-inflammatory** mediators
- orchestrating many vital functions, including aging.

Franceschi et al., 2000

Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans

Claudio Franceschi [a,b,c,e,*], Miriam Capri [a], Daniela Monti [d], Sergio Giunta [e], Fabiola Olivieri [e], Federica Sevini [b], Maria Panagiota Panourgia [b], Laura Invidia [a], Laura Celani [b], Maria Scurti [b], Elisa Cevenini [b], Gastone C. Castellani [b,f], Stefano Salvioli [a,b,c]

[a] *Department of Experimental Pathology, University of Bologna, via S. Giacomo 12, 40126 Bologna, Italy*
[b] *Centro Interdipartimentale "L. Galvani", University of Bologna, via S. Giacomo 12, 40126 Bologna, Italy*
[c] *ER-GenTech laboratory, via Saragat 1, 44100 Ferrara, Italy*
[d] *Department of Experimental Pathology and Oncology, University of Florence, Viale Morgagni 50, 50134 Florence, Italy*
[e] *I.N.R.C.A., Department of Gerontological Sciences, via Birarelli 8, 60121 Ancona, Italy*
[f] *DIMORFIPA, University of Bologna, Via Tolara di Sopra 50, 40064 Ozzano dell'Emilia, Italy*

Mechanisms of Ageing and Development 128 (2007) 92–105

Centenarians are inflamed but the data suggest that the increase of pro-inflammatory molecules is accompanied by a concomitant adaptive increase of anti-inflammatory molecules

2458 citations (05/05/2025)

INFLAMMAGING IS HIGHLY HETEROGENEOUS & DYNAMIC LIFELONG

Fulvia, 109 years

The study of centenarians suggested us the hypothesis that a reason of their longevity could be

AN OPTIMAL BALANCE

between

pro-inflammatory

(CRP, IL-6, TNFα...)

and

anti-inflammatory

TGFβ, Cortisol, IL-1RA, Adiponectin… molecules

Inflammaging in centenarians is of low grade and counter-balanced by **anti-inflammaging**

Aging is the single most important risk factor for all major ARDs

Leading Edge
Commentary

GEROSCIENCE SUMMIT
NIH, Bethesda Oct-Nov 2013

Cell

Geroscience: Linking Aging to Chronic Disease

ARDs= Age-Related Diseases
GSs= Geriatric Syndromes

Brian K. Kennedy,[1,*] Shelley L. Berger,[2,3] Anne Brunet,[4,5] Judith Campisi,[1,6] Ana Maria Cuervo,[7,8] Elissa S. Epel,[9] Claudio Franceschi,[10,11,12] Gordon J. Lithgow,[1] Richard I. Morimoto,[13] Jeffrey E. Pessin,[14] Thomas A. Rando,[5,15,16] Arlan Richardson,[17,18] Eric E. Schadt,[19] Tony Wyss-Coray,[15,16] and Felipe Sierra[20]

Cell *159*, November 6, 2014

We have to ARDs altogether and not one by one

2482 citations 05/05/2025

Aging (?) is the single most important risk factor for all major ARDs

Leading Edge
Commentary

GEROSCIENCE SUMMIT
NIH, Bethesda Oct-Nov 2013

Cell

Geroscience: Linking Aging to Chronic Disease

ARDs= Age-Related Diseases
GSs= Geriatric Syndromes

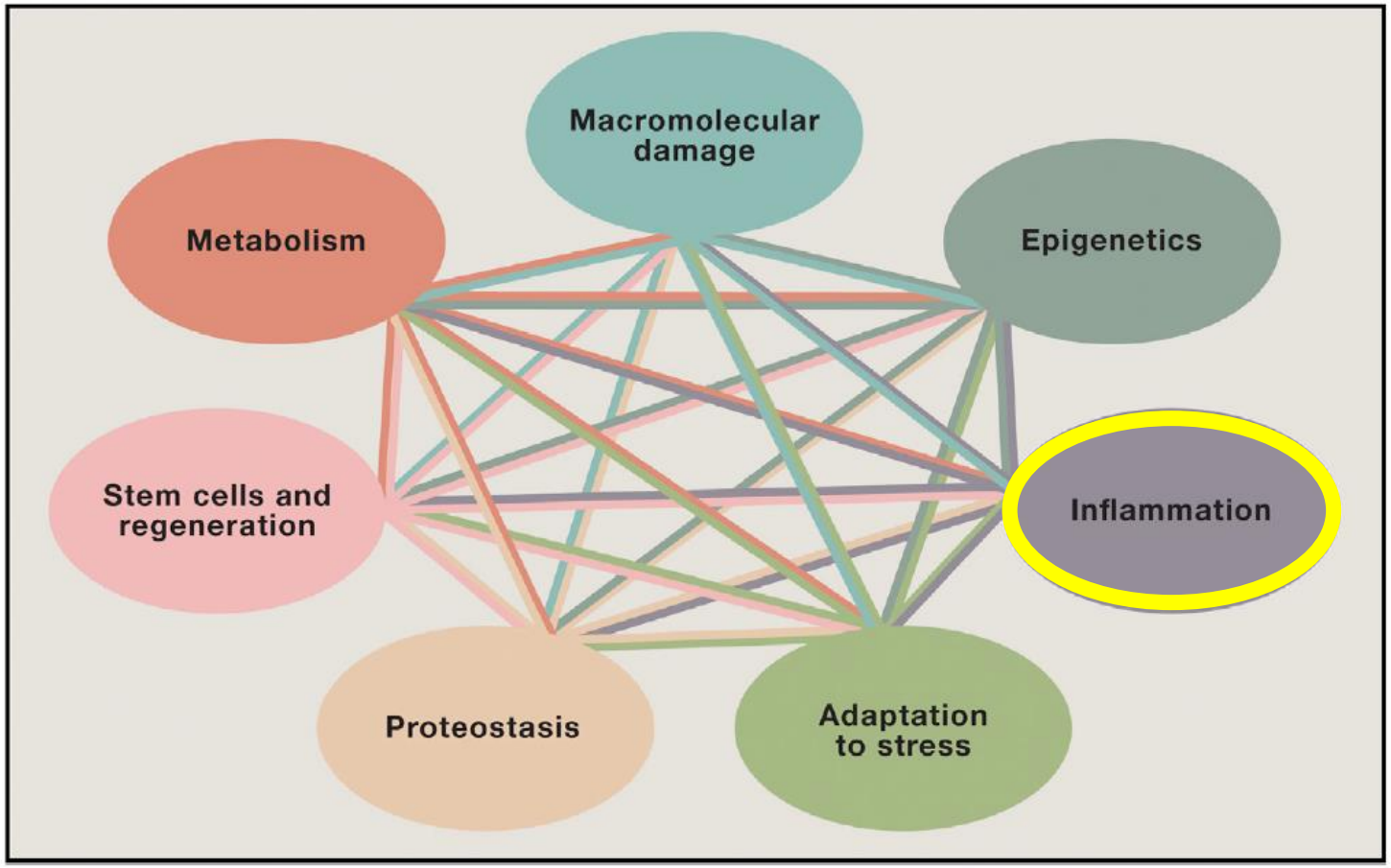
Brian K. Kennedy,[1,*] Shelley L. Berger,[2,3] Anne Brunet,[4,5] Judith Campisi,[1,6] Ana Maria Cuervo,[7,8] Elissa S. Epel,[9] Claudio Franceschi,[10,11,12] Gordon J. Lithgow,[1] Richard I. Morimoto,[13] Jeffrey E. Pessin,[14] Thomas A. Rando,[5,15,16] Arlan Richardson,[17,18] Eric E. Schadt,[19] Tony Wyss-Coray,[15,16] and Felipe Sierra[20]

Cell *159*, November 6, 2014

We have to ARDs altogether and not one by one

2482 citations 05/05/2025

GEROSCIENCE: Aging and Age-Related Diseases share few highly connected mechanistic pillars



Kennedy et al., Cell 2014

GEROSCIENCE:

the accompanying paper on the inflammaging pillar

Advances in Geroscience: Impact on Healthspan and Chronic Disease Perspective

Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases

Claudio Franceschi[1,2] and Judith Campisi[3,4]

[1]DIMES, Department of Experimental, Diagnostic and Specialty Medicine and CIG, Interdepartmental Center "Luigi Galvani", University of Bologna, Italy.
[2]IRCCS Institute of Neurological Sciences, and CNR-ISOF, Bologna, Italy.
[3]Buck Institute for Research on Aging, Novato, California.
[4]Life Sciences Division, Lawrence Berkeley National Laboratory, California.

Address correspondence to Claudio Franceschi, MD, DIMES, Department of Experimental, Diagnostic and Specialty Medicine and CIG, Interdepartmental Center "Luigi Galvani", University of Bologna, Via S. Giacomo 12, 40126 Bologna, Italy. Email: claudio.franceschi@unibo.it

J Gerontol A Biol Sci Med Sci 2014 June;69(S1):S4–S9

4117 citations 05/05/2025)

INFLAMMAGING:

- the fuel
- the mechanisms

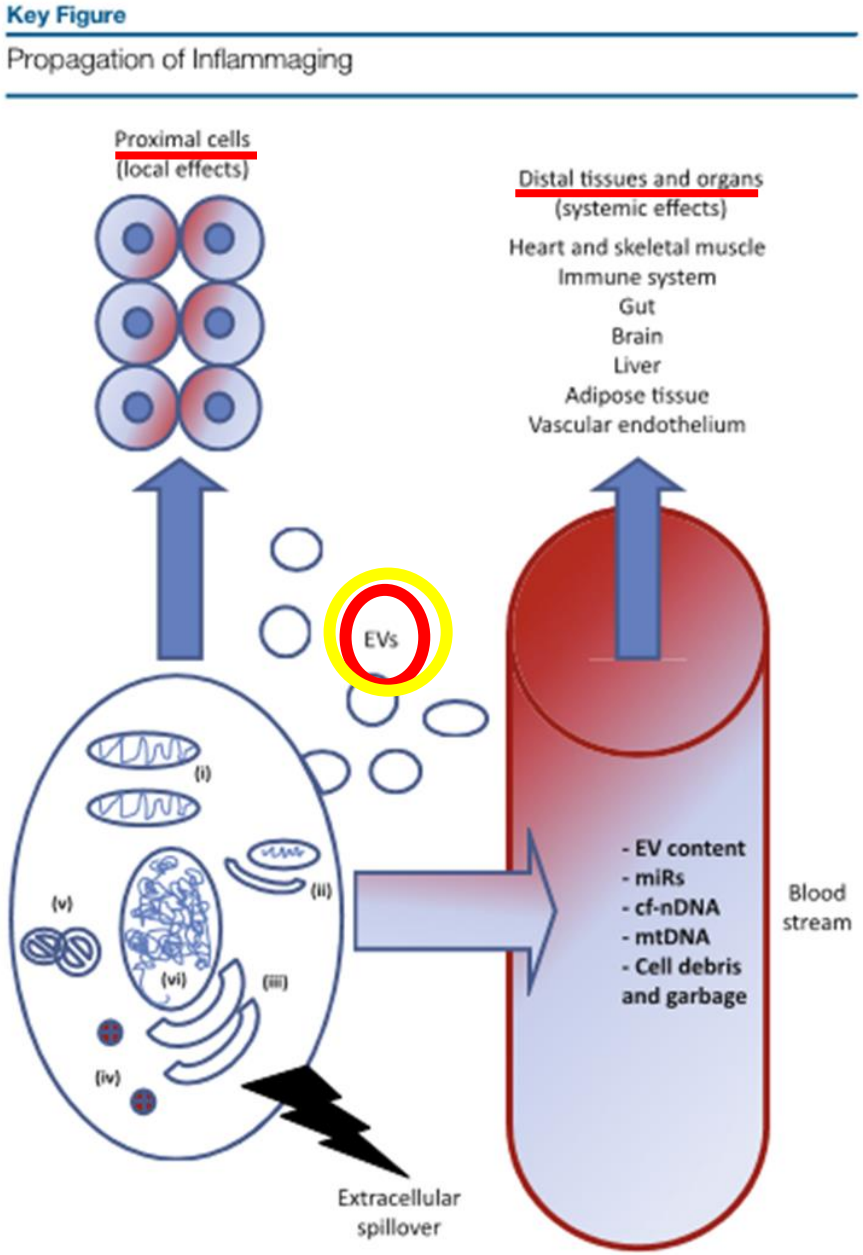
MECHANISMS UNDERPINNING THE PRODUCTION OF PRO-INFLAMMATORY MOLECULES

Inflammaging and 'Garb-aging'

Claudio Franceschi,[1] Paolo Garagnani,[2,3] Giovanni Vitale,[4,5] Miriam Capri,[2,3,‡,*] and Stefano Salvioli[2,3,‡]

Trends Endocrinol Metab. 2017 Mar;28(3):199-212.

975 citations (05/05/2025)



A change of paradigm:
the enemy from within

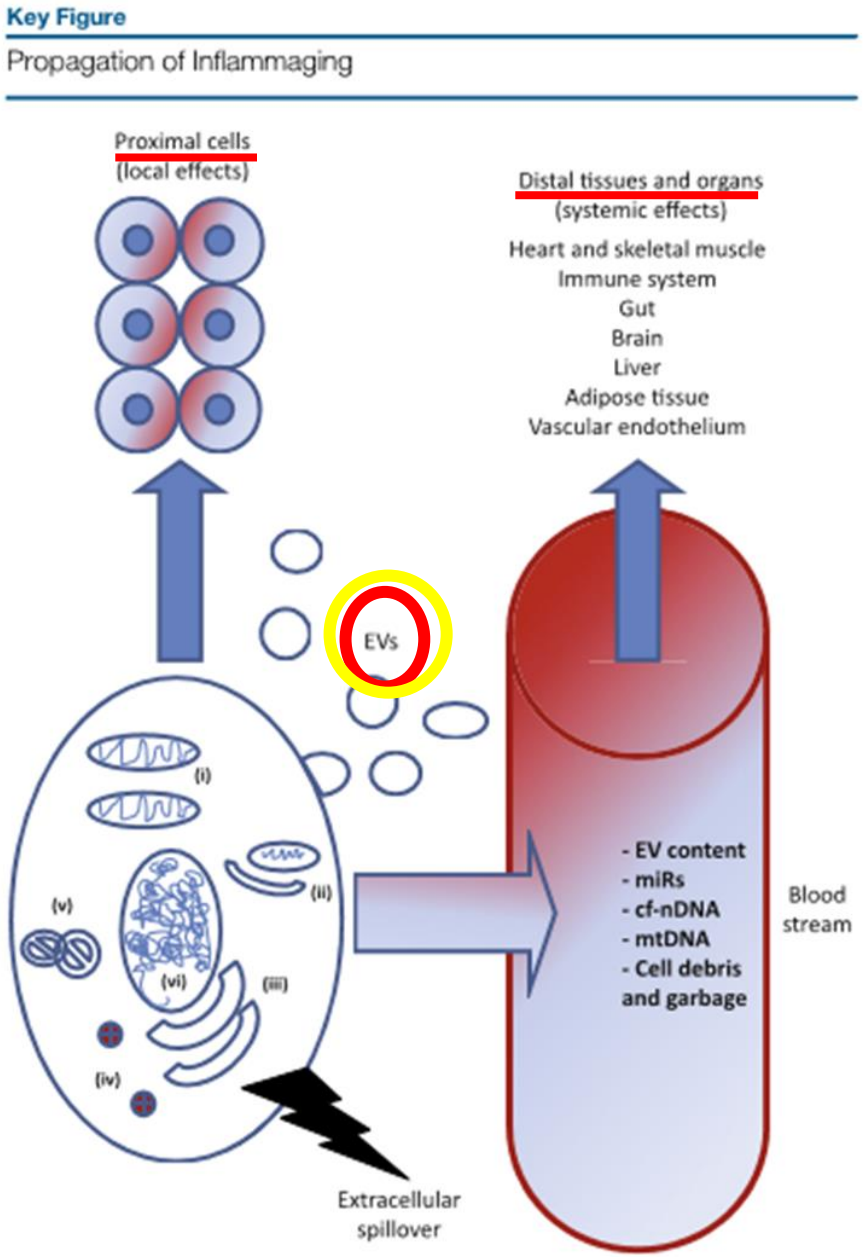
Inflammaging and 'Garb-aging'

Claudio Franceschi,[1] Paolo Garagnani,[2,3] Giovanni Vitale,[4,5]
Miriam Capri,[2,3,‡,*] and Stefano Salvioli[2,3,‡]

Trends Endocrinol Metab. 2017 Mar;28(3):199-212.

ENDOGENOUS GARBAGE DISPOSAL DECLINES WITH AGE
(proteasome, autophagy and mitophagy)
- **CELLULAR AND MOLECULAR GARBAGE INCREASES WITH AGE** (cell debris resulting from cell death, misplaced/ altered/oxidized molecules, Gut Microbiome products , internal exposome, among others)
and PROPAGATES VIA EXTRACELLULAR VESICLES

-



Endogenous/Self Garbage

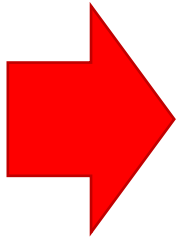
- In human body over **50-70 billion cells die each day**
- Forms of cell death like **NECROPTOSIS & PYROPTOSIS** increase with age and result in:
- **the release of DAMPs** (Damage-Associated Molecular Patterns)
- **misplacing of proteins and nucleic acids**.

The clearance of such molecular garbage is imperative!

Franceschi et al., TEM 2017

MECHANISMS UNDERPINNING THE PRODUCTION OF PRO-INFLAMMATORY MOLECULES

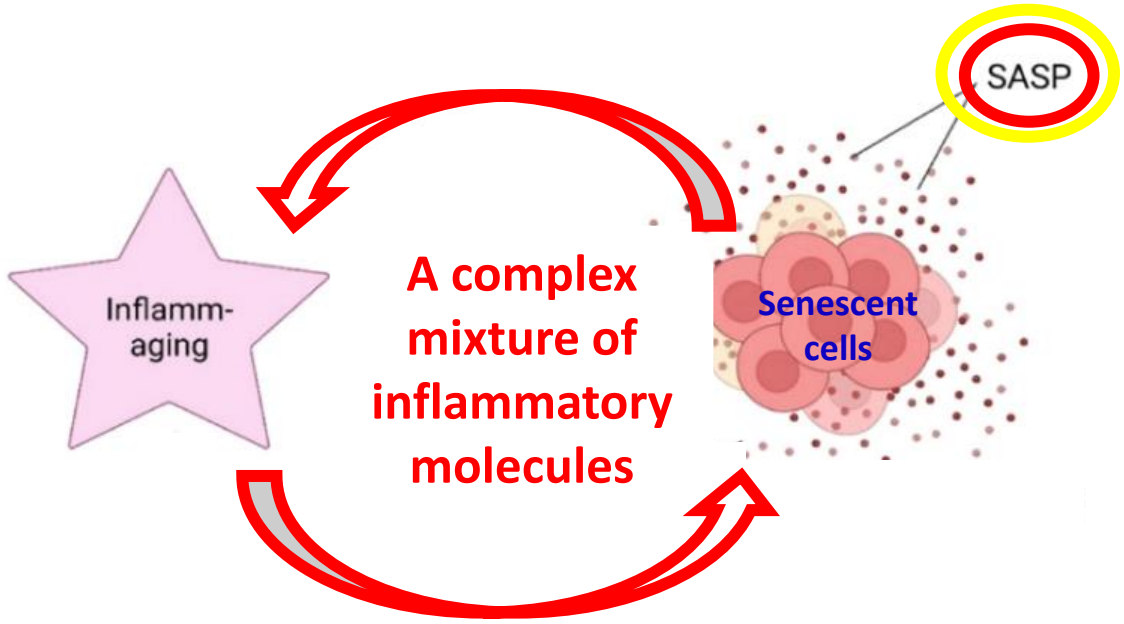
1. SENESCENT CELLS & THEIR SASP
2. SEVERELY DYSFUNCTIONAL MITOCHONDRIA
3. DEFECTIVE AUTOPHAGY
4. GUT MICROBIOTA PRODUCTS
5. ACTIVATION OF DNA DAMAGE RESPONSE
6. ACTIVATION OF INFLAMMASOME
7. DEFECTIVE UBIQUITIN/PROTEASOME SYSTEM
8. ENDOPLASMIC RETICULUM (ER) STRESS



INFLAMMAGING

Franceschi et al., Trends Endocr. Metab. 2017

SASP (Senescence-Associated Secretory Phenotype) is a phenotype associated with senescent cells capable of secreting high levels of inflammatory cytokines, immune modulators, growth factors, and proteases.



Senescent cells are highly heterogeneous
and are present at different levels in the different organs of the body

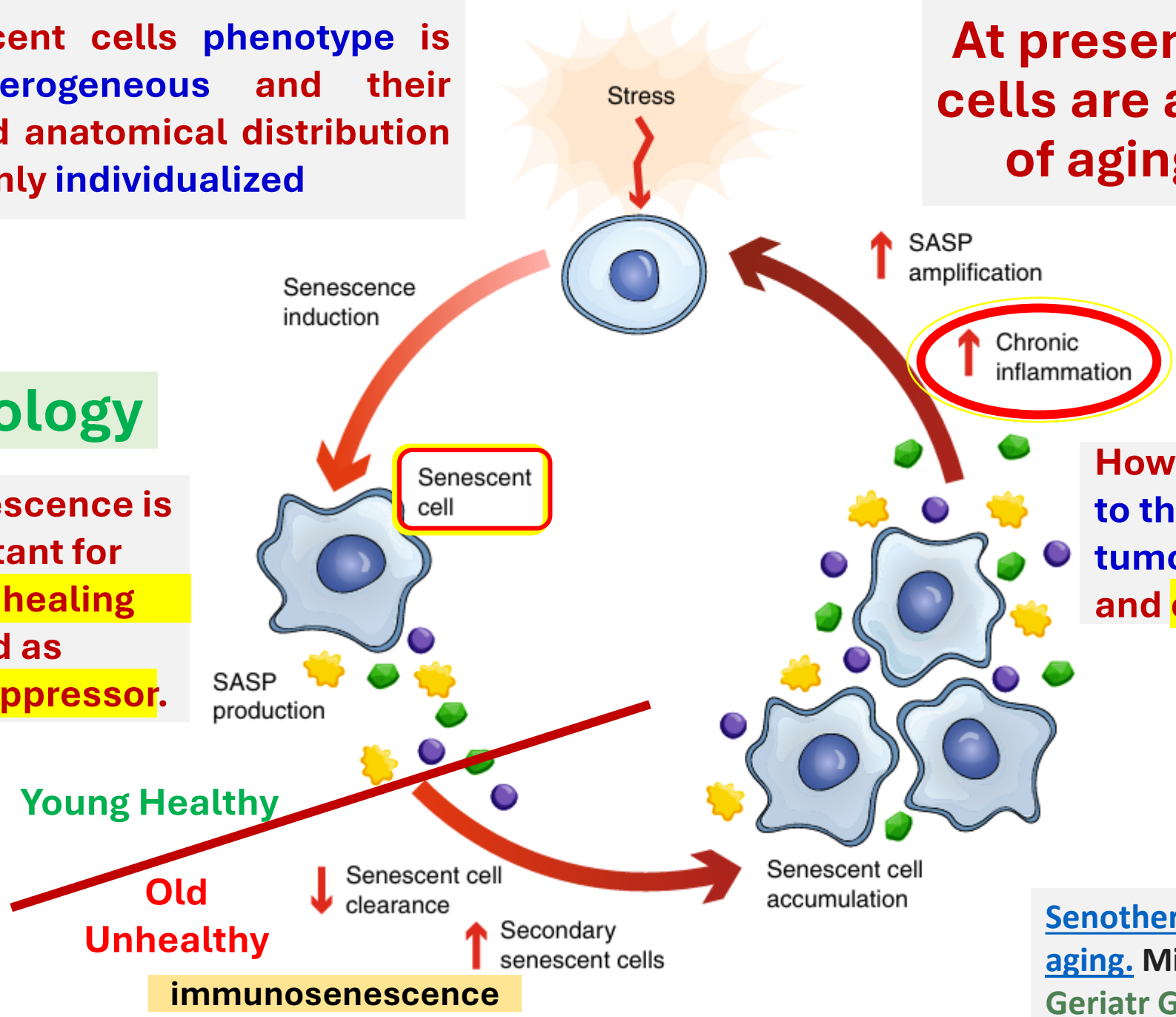
SASP molecules and their immune role

SASP Molecule	Role
IL-1	Pro-inflammatory
IL-6	Pro-inflammatory activity contributing to inflammation and DNA damage
IL-7	Promotes B lymphocyte growth and T lymphocyte activation
IL-11	Hematopoiesis and tissue cell proliferation
IL-15	Necessary for T cell regulation; high levels are pro-inflammatory
IL-8	Chemotaxis and enhancement of pro-inflammatory activity
CXCL1	Neutrophil activation
MCP2	Monocyte chemotaxis
TNFα	Induces apoptosis
VEGF	Blood vessel formation
IGF-1	Proliferation and apoptosis

Senotherapy preserves resilience in aging. Mikawa T, Yoshida K, Kondoh H.Geriatr Gerontol Int. 2024 Aug 4.

The senescent cells phenotype is highly heterogeneous and their number and anatomical distribution are also highly individualized

At present senescent cells are a major focus of aging research



Physiology

Cell senescence is important for wound healing and as tumor suppressor.

Pathology

However, SASP contributes to the highly inflammatory tumor microenvironment and cancer progression.

Modified from

Senotherapy preserves resilience in aging. Mikawa T, Yoshida K, Kondoh H. Geriatr Gerontol Int. 2024 Aug 4.

Senescent cells are highly heterogeneous regarding quality, quantity and localization

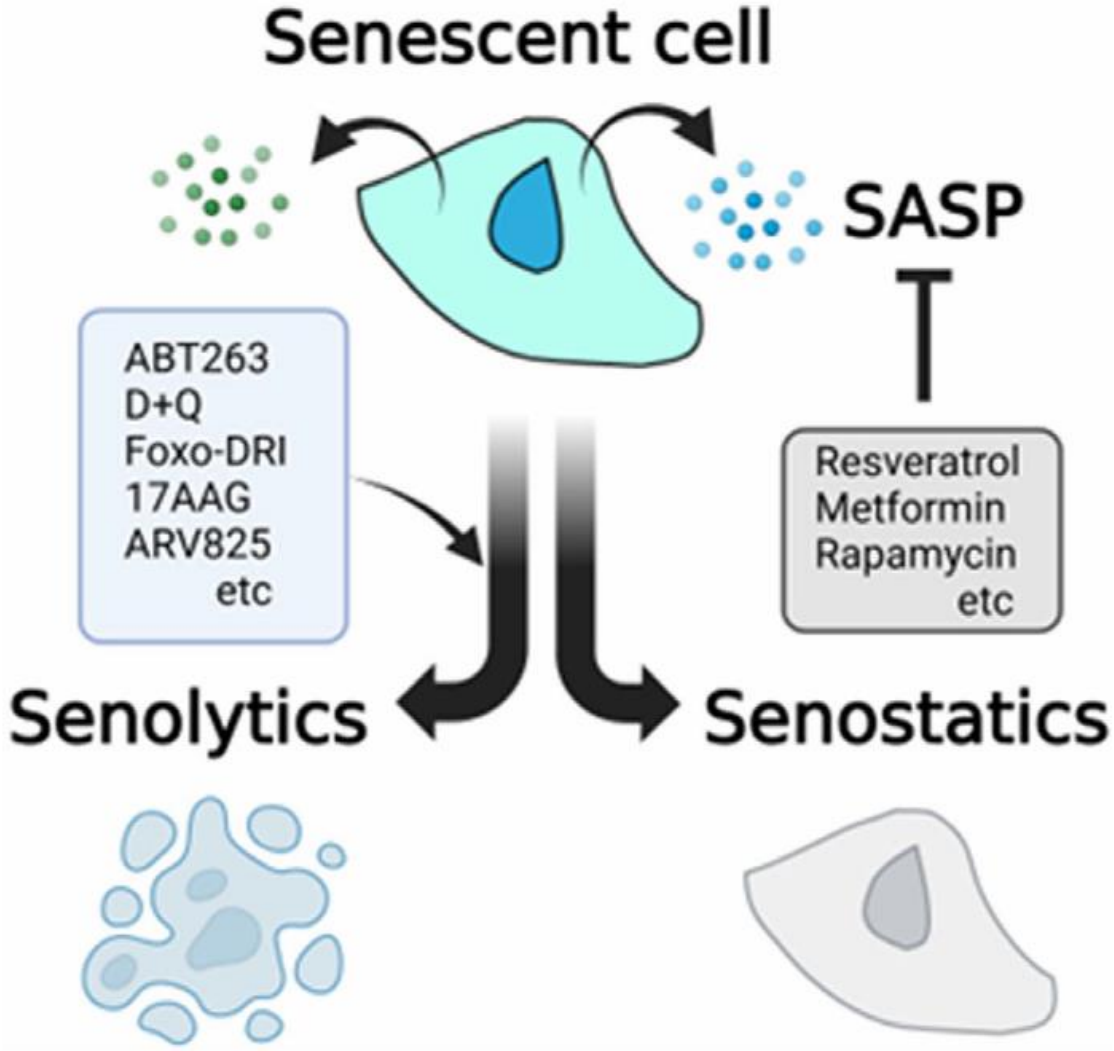
Heterogeneity of Cellular Senescence: Cell Type-Specific and Senescence Stimulus-Dependent Epigenetic Alterations. Kwiatkowska KM, Mavrogonatou E, Papadopoulou A, Sala C, Calzari L, Gentilini D, Bacalini MG, Dall'Olio D, Castellani G, Ravaioli F, **Franceschi C**, Garagnani P, Pirazzini C, Kletsas D.
Cells. 2023 Mar 17;12(6):927.

We studied **3 type of senescence inducers** (replicative, ionizing irradiation and doxorubicin-induced) **in 3 different human cell types** (skin fibroblasts and bone marrow-derived and adipose tissue-derived mesenchymal stem cells.

THE HETEROGENEITY of senescent cells depends on:

- **TISSUE OF ORIGIN**
- **SENESCENCE INDUCER**.

Targeting senescent cells in age-related disease and cancer



Senotherapy preserves resilience in aging. Mikawa T, Yoshida K, Kondoh H.Geriatr Gerontol Int. 2024 Aug 4.

INFLAMMAGING and the Antagonistic Pleiotropy theory of aging

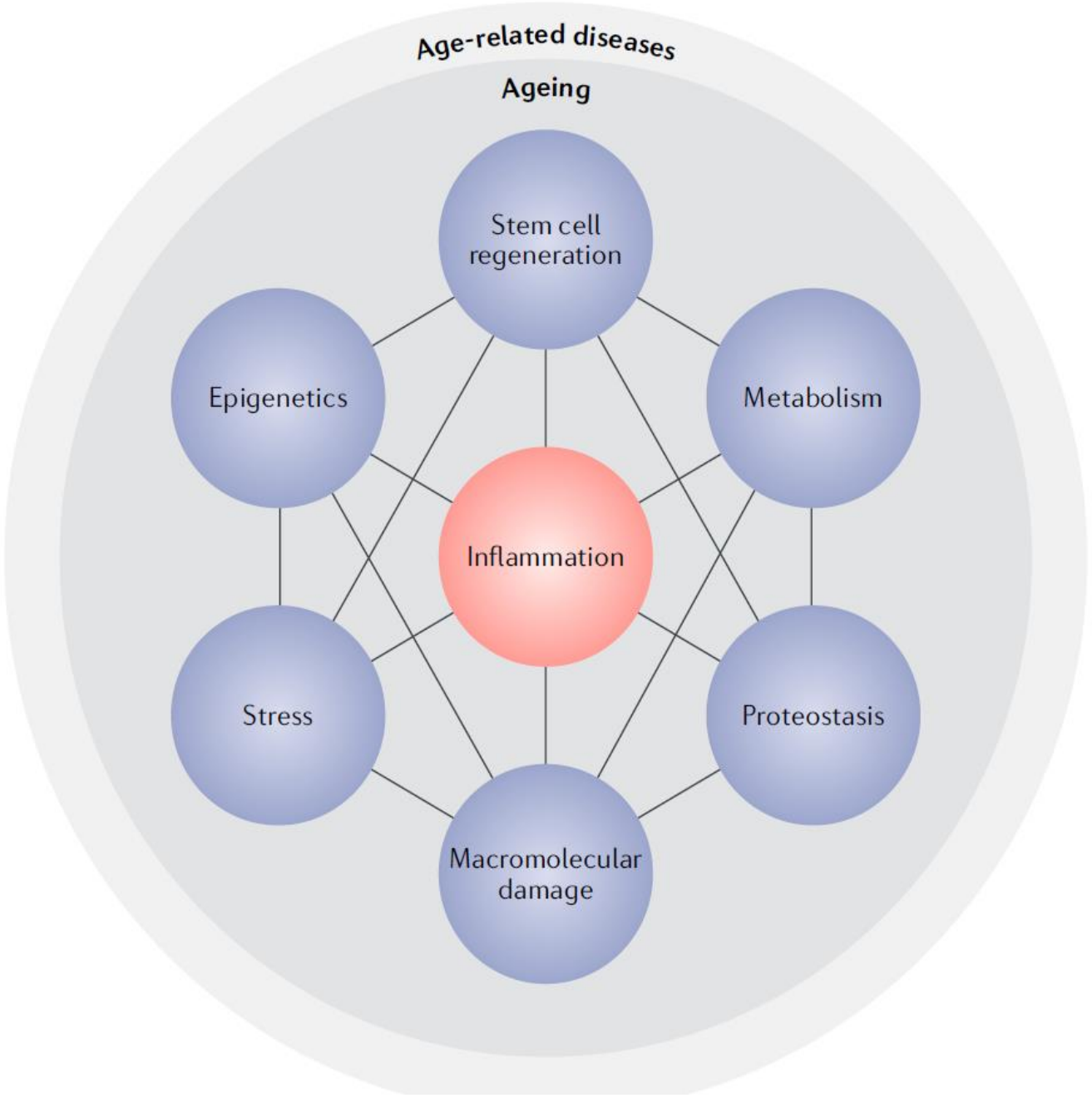
Inflammaging: a new immune–metabolic viewpoint for age-related diseases

Claudio Franceschi[1,8], Paolo Garagnani[2,3,4,5,8], Paolo Parini[3], Cristina Giuliani[6,7] and Aurelia Santoro[2,7]*

NATURE REVIEWS | ENDOCRINOLOGY
2018 July 25

A theoretical unitarian vision of inflammaging

2653 citations (05/05/2025)



The mechanistic pillars converge on Inflammation/ Inflammaging

Franceschi et al., Nat Rev Endocrinol, 2018

A unitarian perspective of ARDs

Chronic inflammation in the etiology of disease across the life span

David Furman[1,2,3,4*], Judith Campisi[1,5], Eric Verdin[1], Pedro Carrera-Bastos[6], Sasha Targ[4,7], Claudio Franceschi[8,9], Luigi Ferrucci[10], Derek W. Gilroy[11], Alessio Fasano[12], Gary W. Miller[13], Andrew H. Miller[14], Alberto Mantovani[15,16,17], Cornelia M. Weyand[18], Nir Barzilai[19], Jorg J. Goronzy[20], Thomas A. Rando[20,21,22], Rita B. Effros[23], Alejandro Lucia[24,25], Nicole Kleinstreuer[26,27] and George M. Slavich[28]

Although intermittent increases in inflammation are critical for survival during physical injury and infection, recent research has revealed that certain social, environmental and lifestyle factors can promote systemic chronic inflammation (SCI) that can, in turn, lead to several diseases that collectively represent the leading causes of disability and mortality worldwide, such as cardiovascular disease, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease and autoimmune and neurodegenerative disorders. In the present Perspective we describe the multi-level mechanisms underlying SCI and several risk factors that promote this health-damaging phenotype, including infections, physical inactivity, poor diet, environmental and industrial toxicants and psychological stress. Furthermore, we suggest potential strategies for advancing the early diagnosis, prevention and treatment of SCI.

NATURE MEDICINE | VOL 25 | DECEMBER 2019 | 1822–1832 |

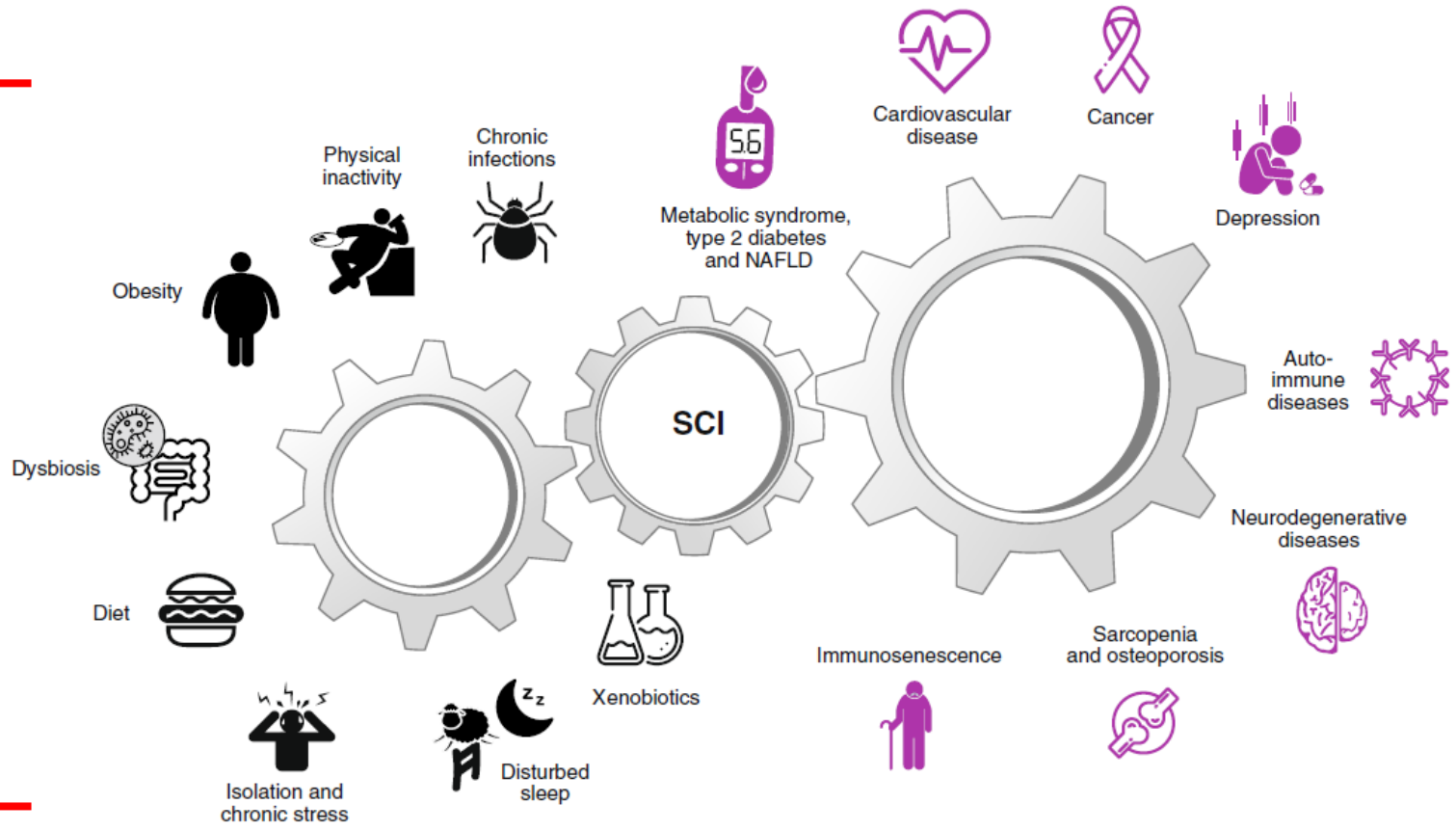
Systemic Chronic Inflammation = SCI

4226 citations (05/05/2025)

SCI/Inflammaging:
a unitarian perspective of ARDs

A variety of causes triggers a variety of outcomes (ARDs) through inflammaging

Isolated or in combination



Systemic Chronic Inflammation = SCI

Furman et al., Nature Medicine 2019

A LIFELONG PERSPECTIVE OF INFLAMMAGING

the emerging of INDIVIDUALITY of the Immune System

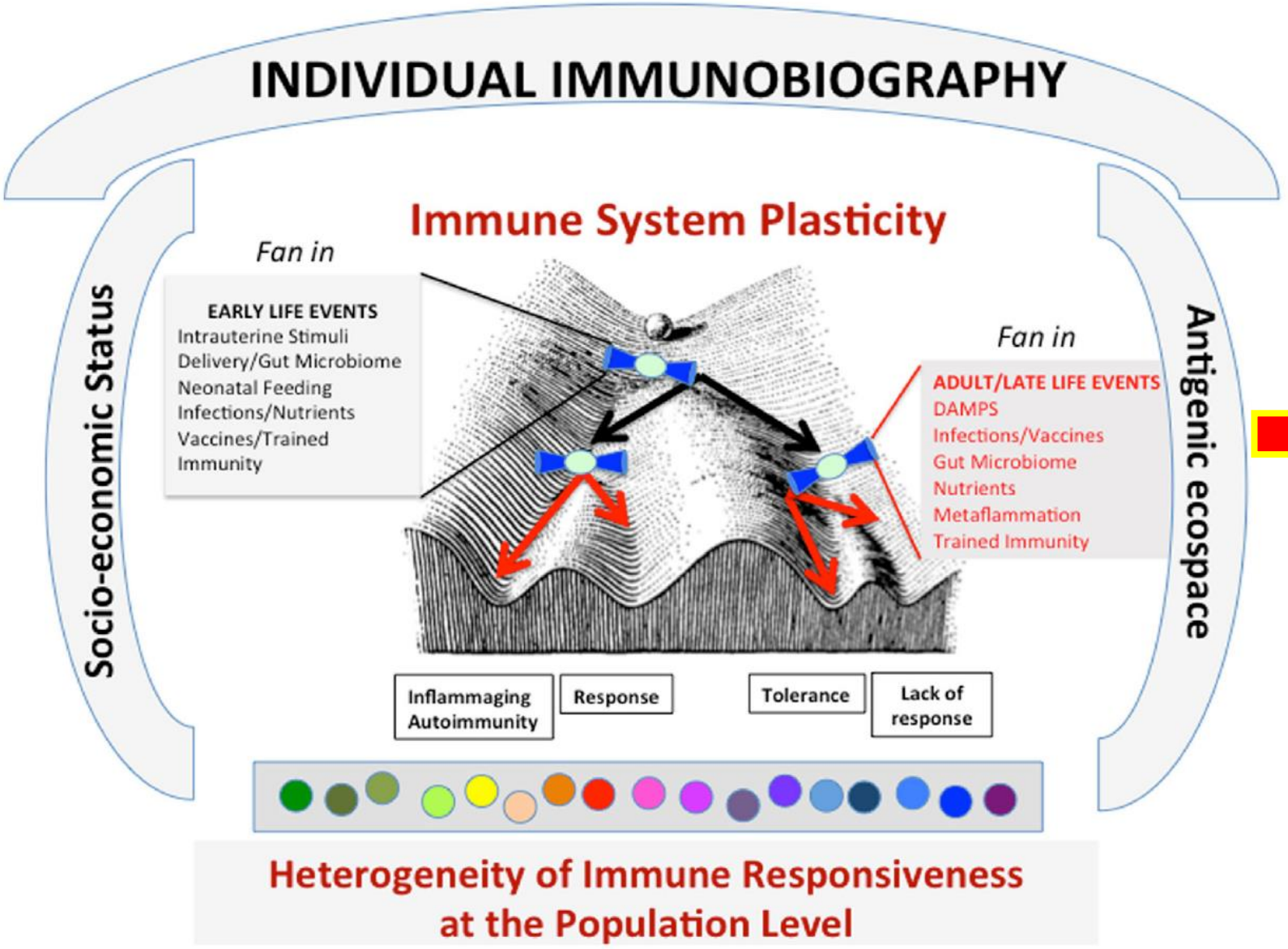
Front Immunol. 2017 Aug 15;8:982.2017

Aging/Inflammaging/Immunosenescence
beyond chronological age

Immunobiography and the Heterogeneity of Immune Responses in the Elderly: A Focus on Inflammaging and Trained Immunity

Claudio Franceschi[1†], Stefano Salvioli[2,3†], Paolo Garagnani[2,3], Magda de Eguileor[4], Daniela Monti[5‡] and Miriam Capri[2,3‡]*

[1] Institute of Neurological Sciences of Bologna IRCCS, Bologna, Italy, [2] Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy, [3] Interdepartmental Centre 'L. Galvani' (CIG), University of Bologna, Bologna, Italy, [4] Department of Biotechnology and Life Science, University of Insubria, Varese, Italy, [5] Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy



The fundamental HETEROGENEITY of the aging phenotype, becoming progressively more and more INDIVIDUALIZED

Franceschi et al.,
Front Immunol 2017

- The biomedical concept of **IMMUNOBIOGRAPHY** (Franceschi et al., 2017) is in accord with the more general philosophical and psychological concept of **PRINCIPIUM INDIVIDUATIONIS.**
- Accordingly, **the more we become old the more we become UNIQUE**, and highly different from all other human beings (Carl Gustav **Jung**, but also **Avicenna**, **Duns Scoto**, **Leibniz**, **Locke**, **Schopenhauer**, **Nietzsche** …among others)

For this reason it is important to quantify inflammaging

ARTICLES
https://doi.org/10.1038/s43587-021-00082-y

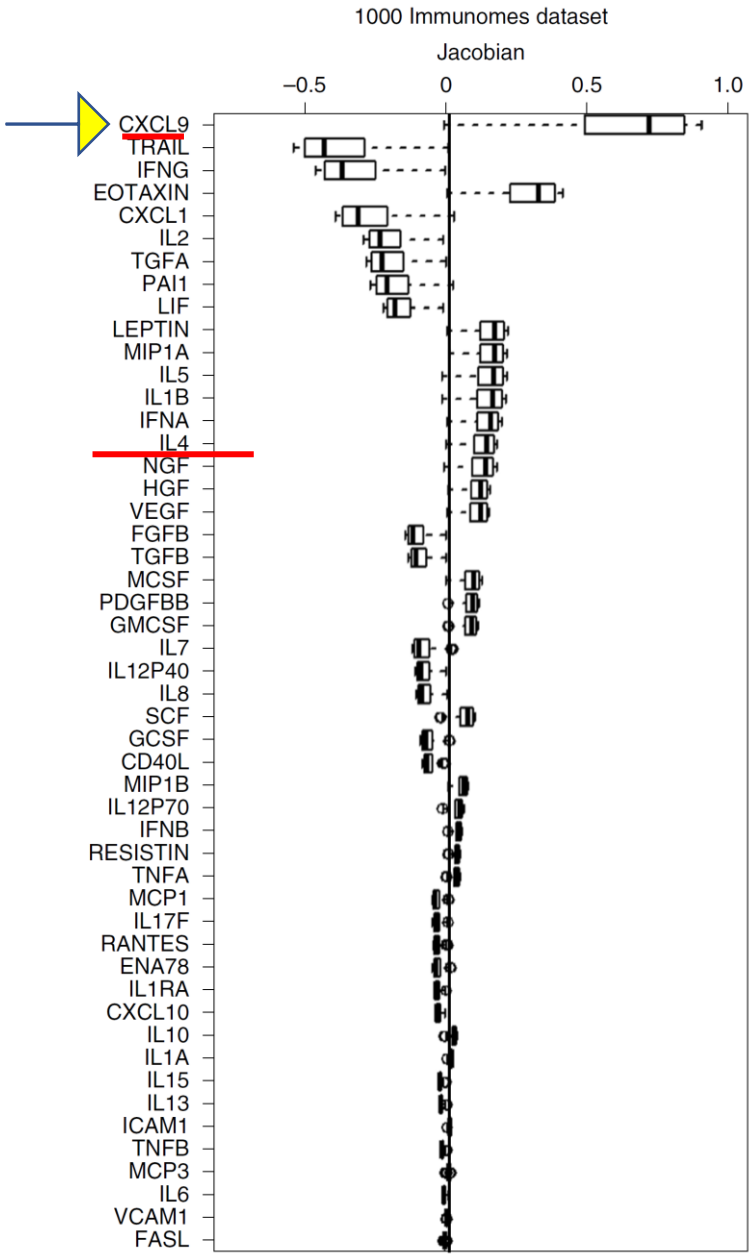
The first Inflammaging clock

nature aging

An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging

Nazish Sayed[1,2,3,24], Yingxiang Huang[4,24], Khiem Nguyen[4], Zuzana Krejciova-Rajaniemi[5], Anissa P. Grawe[4], Tianxiang Gao[6], Robert Tibshirani[7], Trevor Hastie[7], Ayelet Alpert[8], Lu Cui[9], Tatiana Kuznetsova[10], Yael Rosenberg-Hasson[11], Rita Ostan[12], Daniela Monti[13], Benoit Lehallier[14], Shai S. Shen-Orr[8], Holden T. Maecker[11], Cornelia L. Dekker[15,16], Tony Wyss-Coray[14,17], Claudio Franceschi[18], Vladimir Jojic[5,19], François Haddad[2], José G. Montoya[20], Joseph C. Wu[2,21], Mark M. Davis[1,16,22] and David Furman[1,4,5,23] ✉

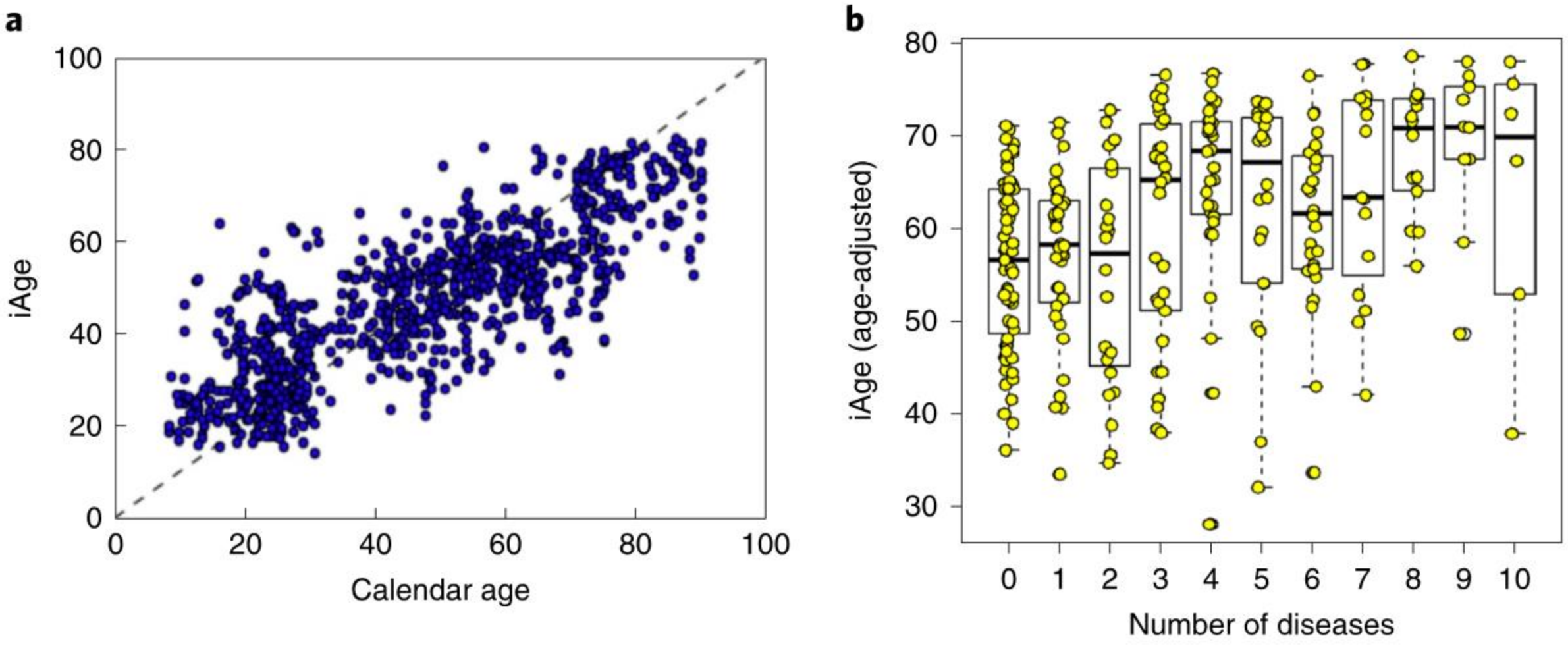
Nat Aging. 2021 Jul;1:598-615.



The top 15 variables contributing to the chronological age-independent **inflammatory index (iAGE)** are:

1. **positive** contributors: CXCL9, EOTAXIN, Mip-1α, LEPTIN, IL-1β, IL-5, IFN-α and IL-4;
2. **negative** contributors TRAIL, IFN-γ, CXCL1, IL-2, TGF-α, PAI-1 and LIF.

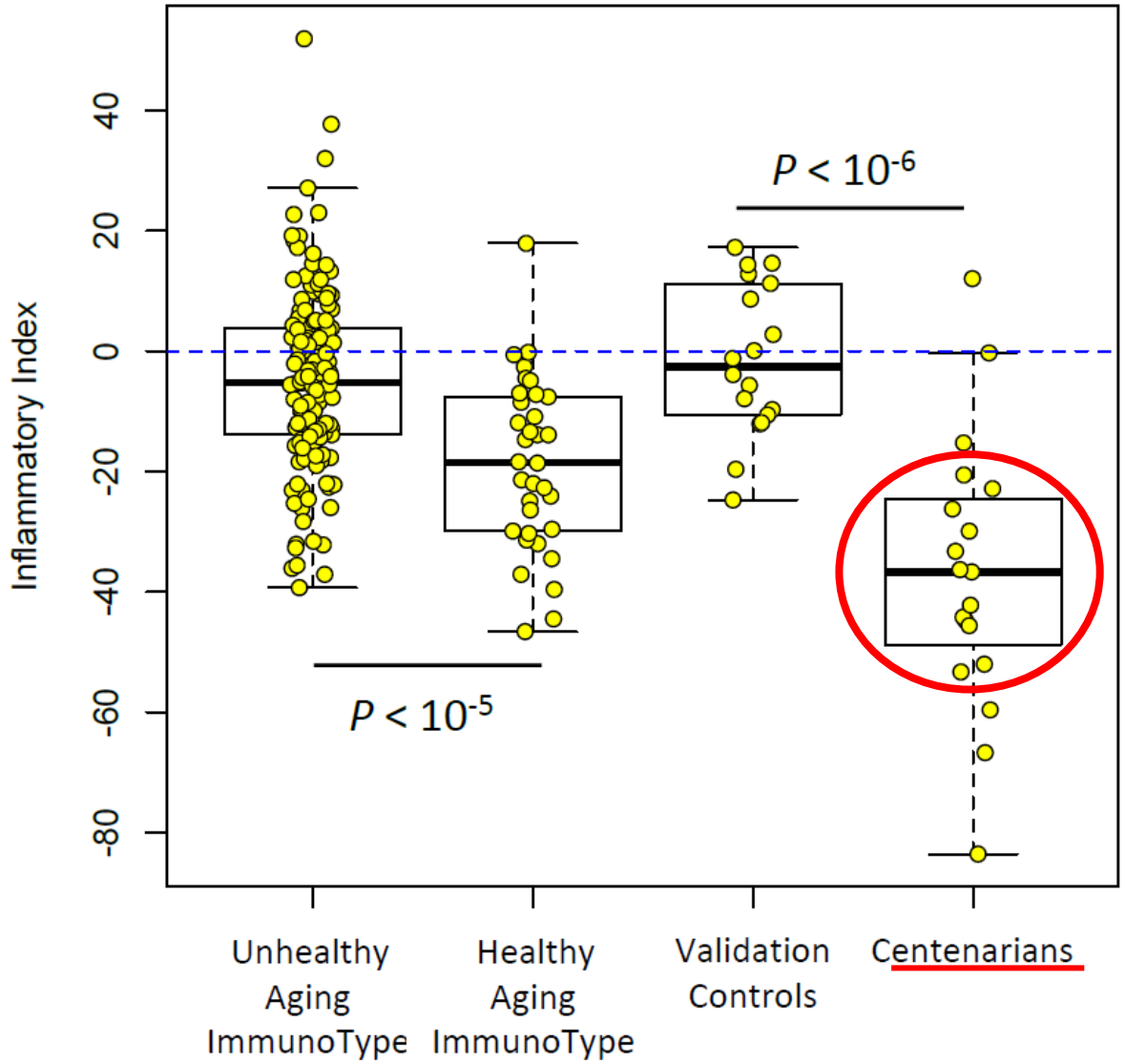
NATURE AGING | VOL 1 | JULY 2021 | 598–615 |



Furman et al., Nature Aging 2021

Inflammatory Index

(inflammatory age *minus* chronological age)



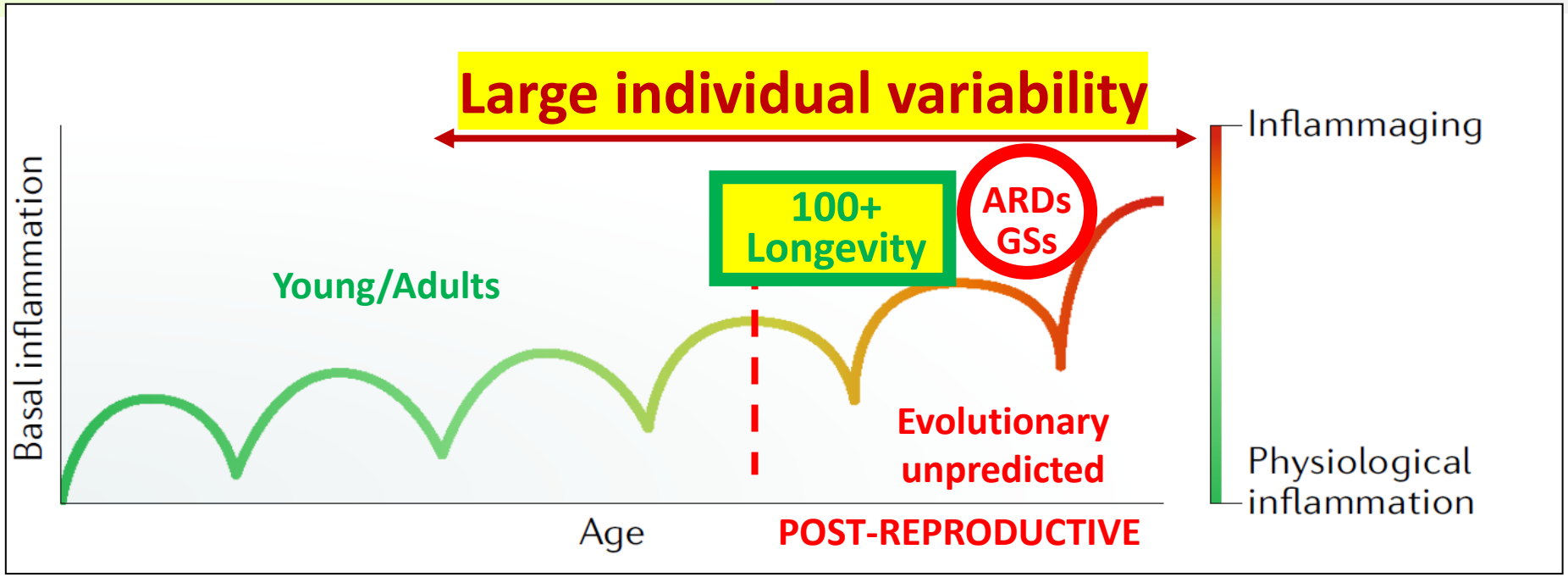
From an inflammaging point of view centenarians are much younger than their chronological age

Furman et al., 2021

Inflammaging fits the Antagonistic Pleiotropy theory of aging

Inflammation is the most important, BENEFICIAL, ADAPTIVE, EVOLUTIONARY-CONSERVED response to «damage stimuli», and is crucial for repair/survival

When overstimulated, particularly in the post-reproductive period of life, inflammation can become CHRONIC and DETRIMENTAL



Franceschi et al., Nat Rev Endocrinol, 2018

INFLAMMAGING

- beneficial/adaptive

or

- chronic/detrimental

according to the crucial role of

IMMUNOBIOGRAPHY

Thus, Inflammaging is basically

DICOTOMIC

but fundamentally ADAPTIVE

For this reason
it is particularly important
to quantify inflammaging
in single persons

frontiers | Frontiers in Immunology

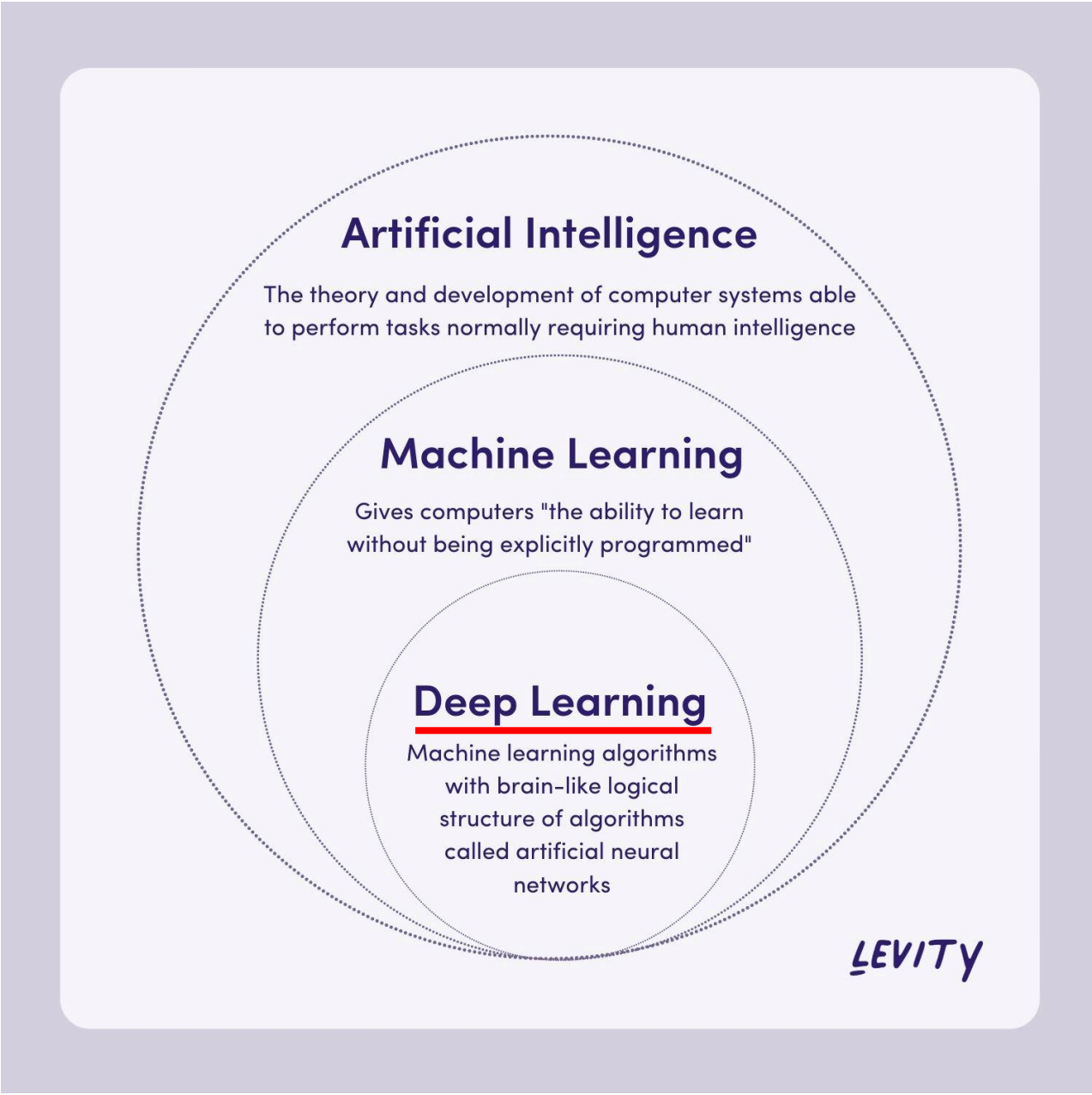
Small immunological clocks identified by deep learning and gradient boosting

Alena Kalyakulina[1,2,3*†], Igor Yusipov[1,2,3†], Elena Kondakova[3,4], Maria Giulia Bacalini[5], Claudio Franceschi[2,3], Maria Vedunova[3] and Mikhail Ivanchenko[2,3]

The second personalized Inflammaging clock

TYPE Original Research
PUBLISHED 25 August 2023
DOI 10.3389/fimmu.2023.1177611

- The study involved:
- 1. a group of **300 healthy volunteers (227 women and 113 men, 21-101 years old)** recruited in the Nizhny Novgorod region.
- **43 ESRD (End-Stage chronic Renal Disease) patients** in hemodialysis.



AI applied to aging and longevity:
a terrific opportunity that cannot be missed

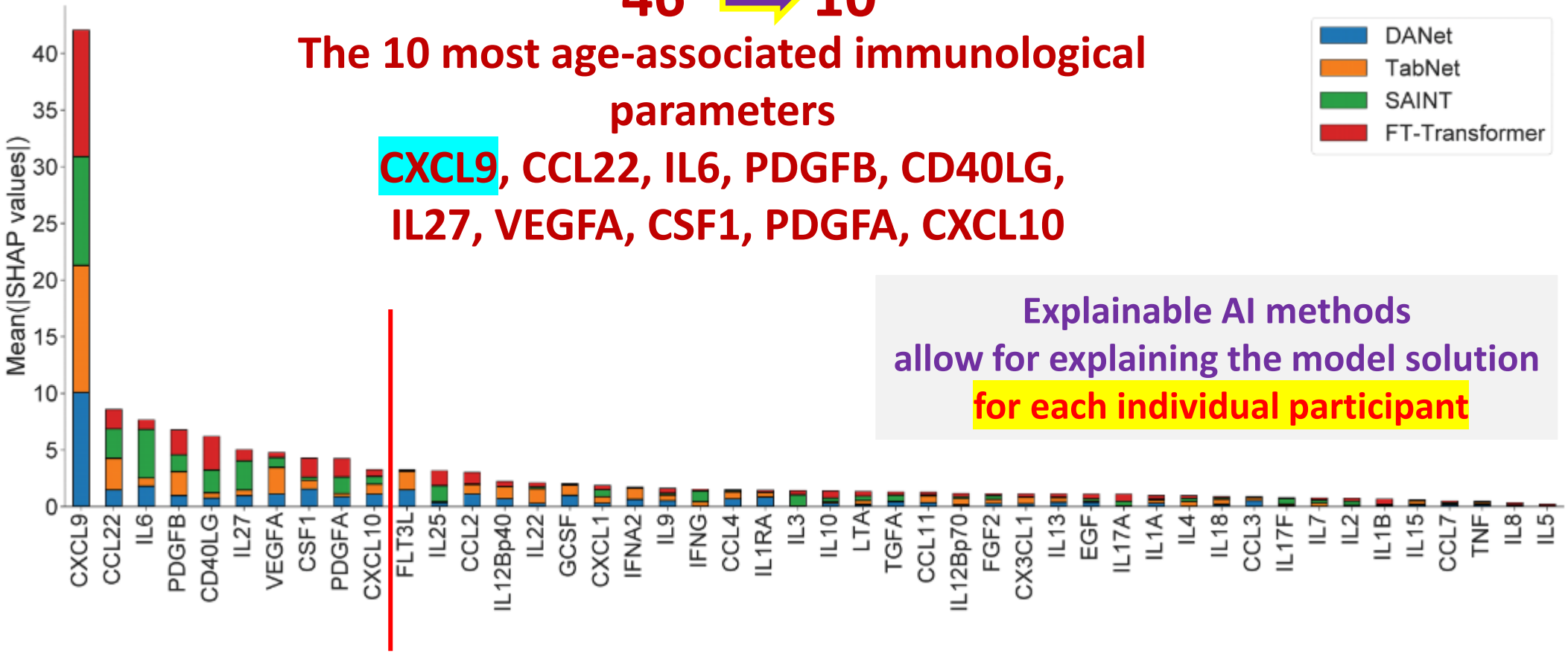
The 10 most important immunological features that were selected for the construction of the small immunological clocks

Ranking of the features according to their averaged absolute SHAP values in the best models:
DANet (blue), TabNet (orange), SAINT (green), FT-Transformer (red).
The 10 selected biomarkers with the highest importance values are taken for building small models.

46 ➡ 10

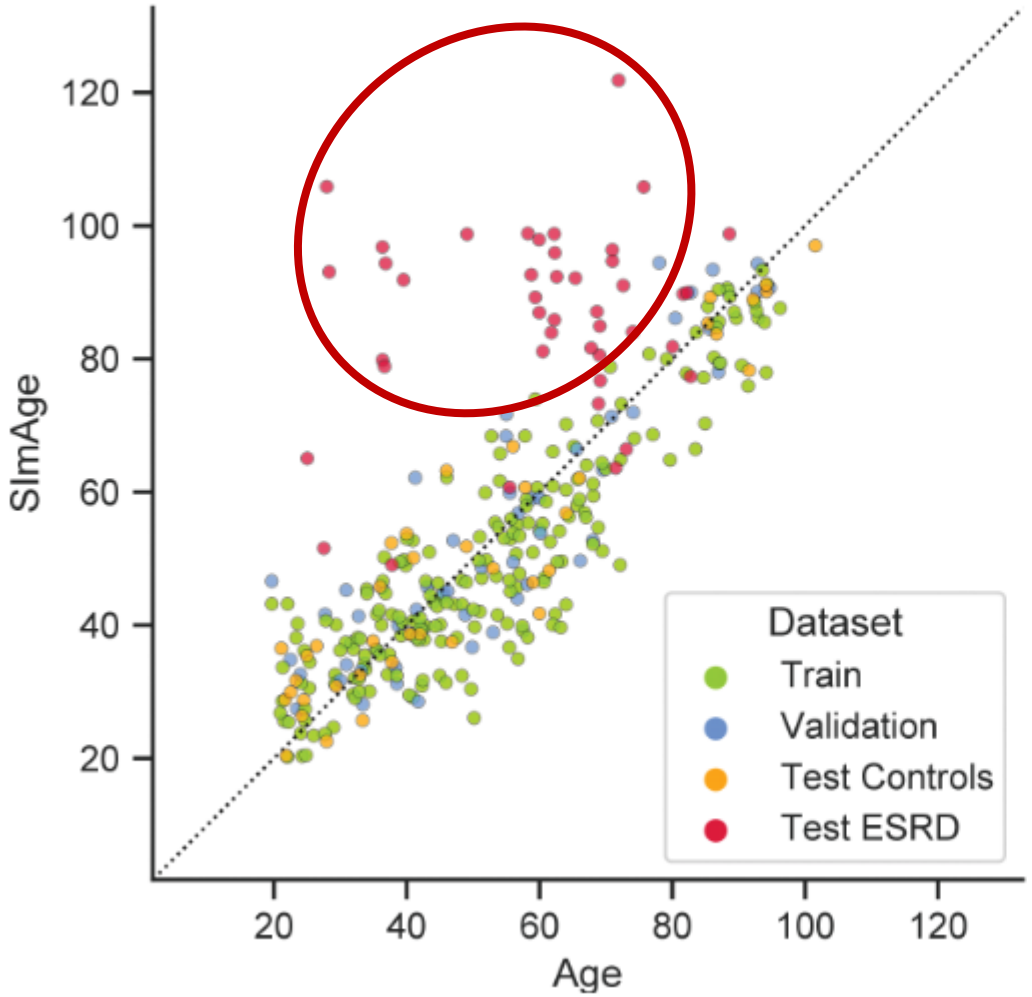
The 10 most age-associated immunological parameters

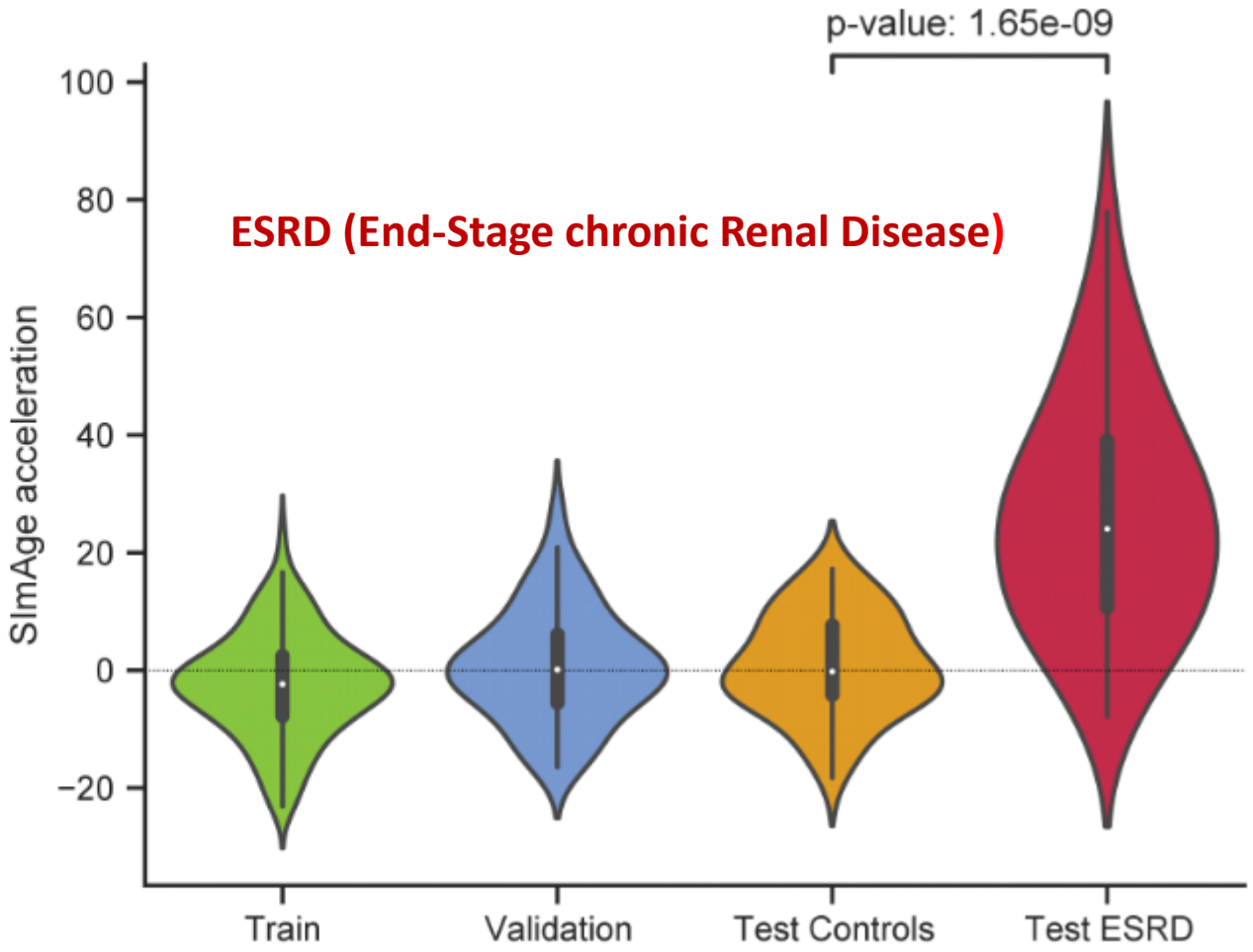
CXCL9, CCL22, IL6, PDGFB, CD40LG, IL27, VEGFA, CSF1, PDGFA, CXCL10



Explainable AI methods allow for explaining the model solution for each individual participant

Results for the best model predicting age on a small number of immunological biomarkers (SImAge).



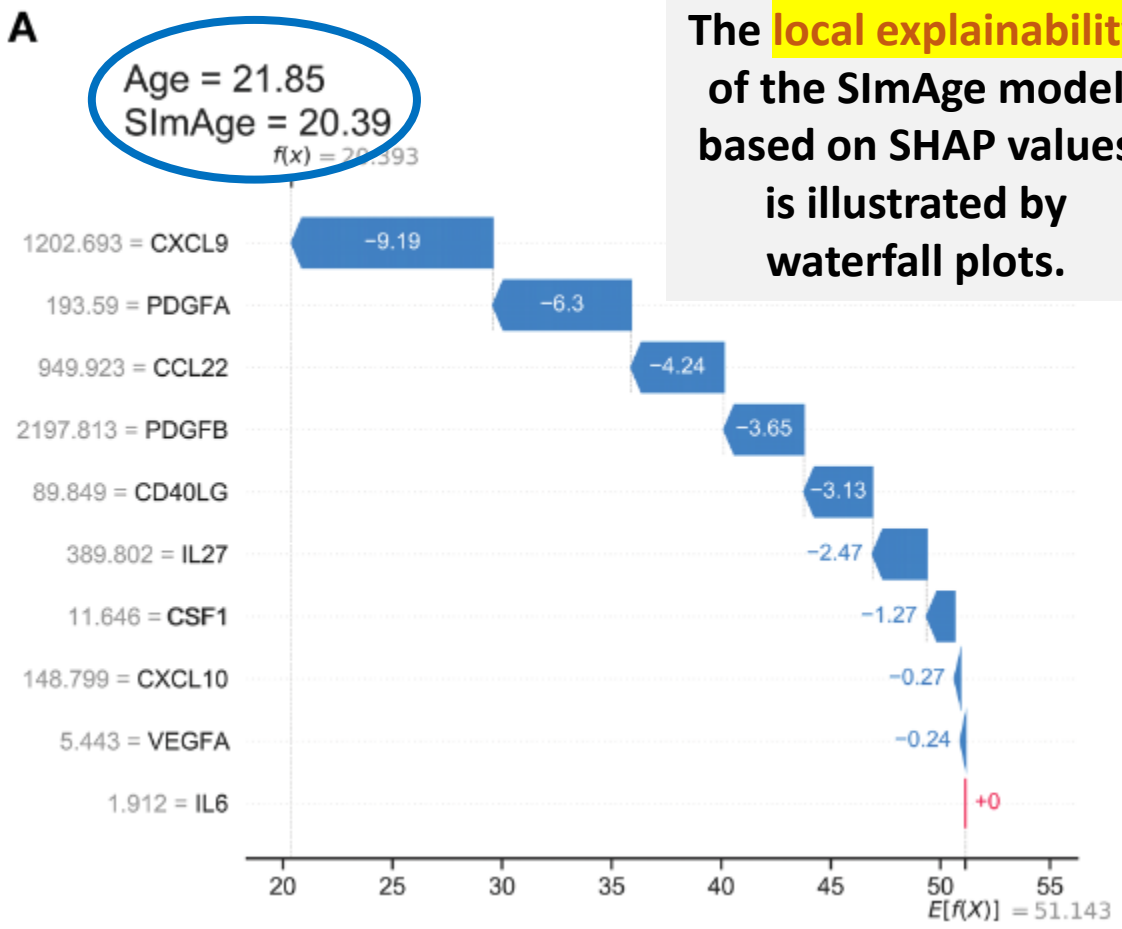


eXplainable Artificial Intelligence

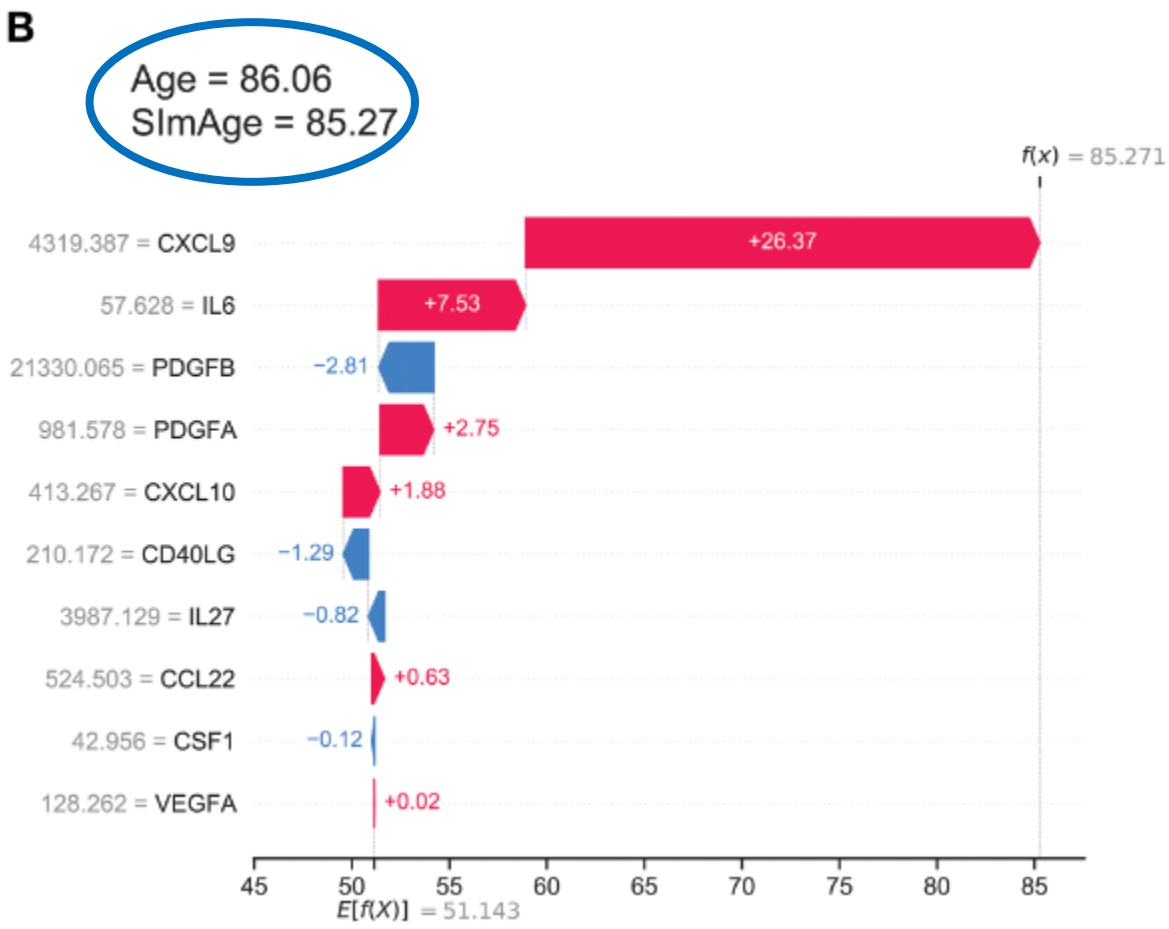
- SHAP VALUES (SHapley Additive exPlanations) measure how much each feature (such as each inflammatory marker) contributes to the model's prediction and have the greatest influence on the trait.
- LOCAL EXPLAINABILITY was illustrated by waterfall plots, where features pushing the prediction higher are shown in red, while those pushing the prediction lower are in blue.

The local explainability of the SImAge model based on SHAP values is illustrated by waterfall plots.

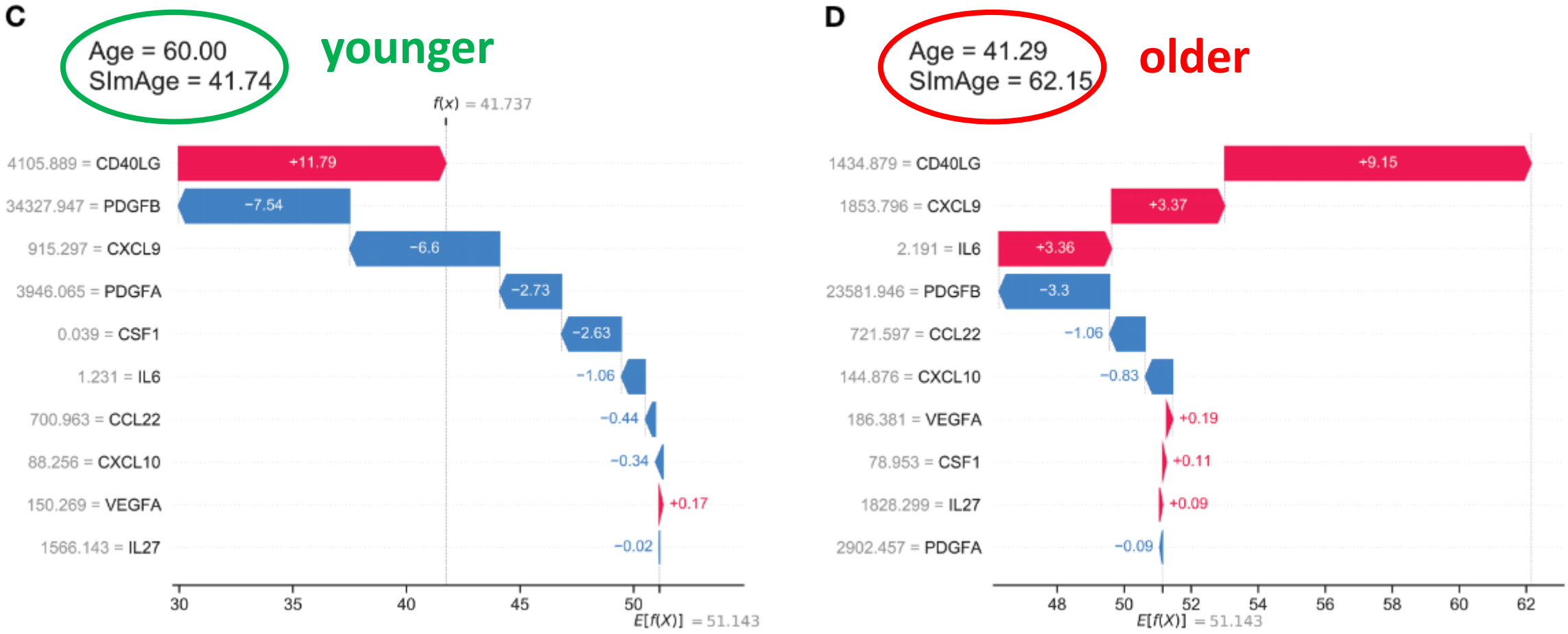
The bottom part of each WATERFALL PLOT starts with the expected value of the model output $E[f(X)]$.
Each row shows by how much in the positive (red) or negative (blue) direction each feature shifts the prediction relative to the expected value to the final model prediction for that sample $f(X)$.



The local explainability of the SImAge model based on SHAP values is illustrated by waterfall plots.



The local explainability of the SImAge model based on SHAP values is illustrated by waterfall plots.



Ageing Research Reviews 93 (2024) 102144

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

eXplainable Artificial Intelligence (XAI) in aging clock models

Alena Kalyakulina [a,b,c,*], Igor Yusipov [a,b,c], Alexey Moskalev [a], Claudio Franceschi [a], Mikhail Ivanchenko [a,c]

[a] *Institute of Biogerontology, Lobachevsky State University, Nizhny Novgorod 603022, Russia*
[b] *Research Center for Trusted Artificial Intelligence, The Ivannikov Institute for System Programming of the Russian Academy of Sciences, Moscow 109004, Russia*
[c] *Department of Applied Mathematics, Institute of Information Technologies, Mathematics and Mechanics, Lobachevsky State University, Nizhny Novgorod 603022, Russia*

Kalyakulina et al., Ageing Research Reviews, 2024

The Future

Current Biology

GM is an important source of NUTRIENTS and INFLAMMATORY STIMULI

Gut Microbiota and Extreme Longevity

Elena Biagi,[1,*] Claudio Franceschi,[2,3,4] Simone Rampelli,[1] Marco Severgnini,[5] Rita Ostan,[2,3] Silvia Turroni,[1] Clarissa Consolandi,[5] Sara Quercia,[1] Maria Scurti,[2,3] Daniela Monti,[6] Miriam Capri,[2,3] Patrizia Brigidi,[1] and Marco Candela[1,*]

[1]Department of Pharmacy and Biotechnology, Alma Mater Studiorum, University of Bologna, Bologna 40126, Italy
[2]DIMES-Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum, University of Bologna, Bologna 40126, Italy
[3]CIG-Interdepartmental Centre "L. Galvani," Alma Mater Studiorum, University of Bologna, Bologna 40126, Italy
[4]IRCCS, Institute of Neurological Sciences of Bologna, Bologna 40139, Italy
[5]Institute of Biomedical Technologies, National Research Council (ITB-CNR), Segrate, Milan 20090, Italy
[6]Department of Clinical, Experimental and Biomedical Sciences, University of Florence, Florence 50134, Italy

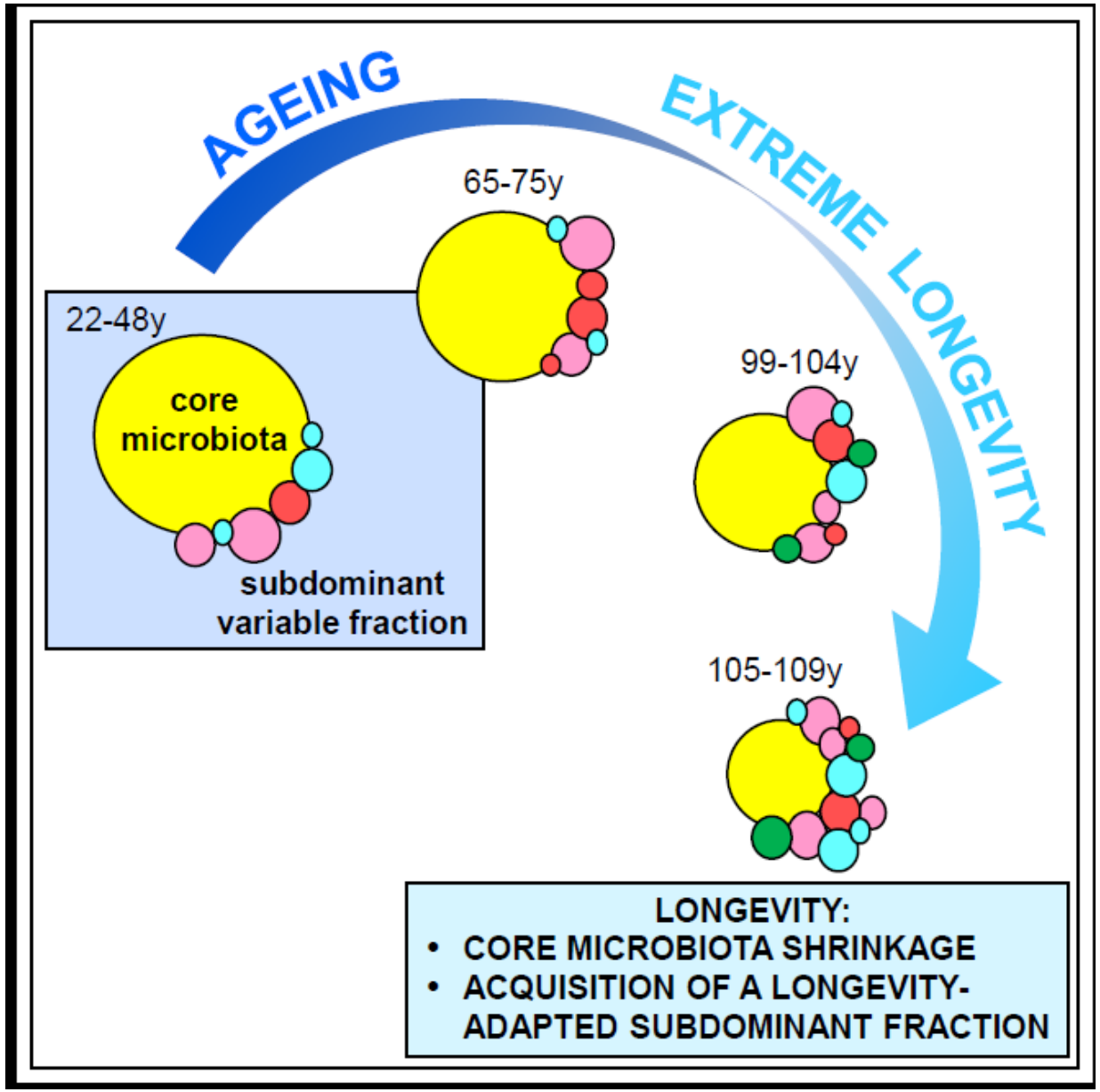
Curr Biol. 2016 Jun 6;26(11):1480-5

1001 citations at 05/05/2025

- **GM undergoes a continuous remodeling with age**
- **We reconstructed the longest available trajectory of GM in people from 20 to 109 years old**
- **NUTRITION HAS A MAJOR IMPACT ON GM**
- **There is a GM signature of aging and longevity**

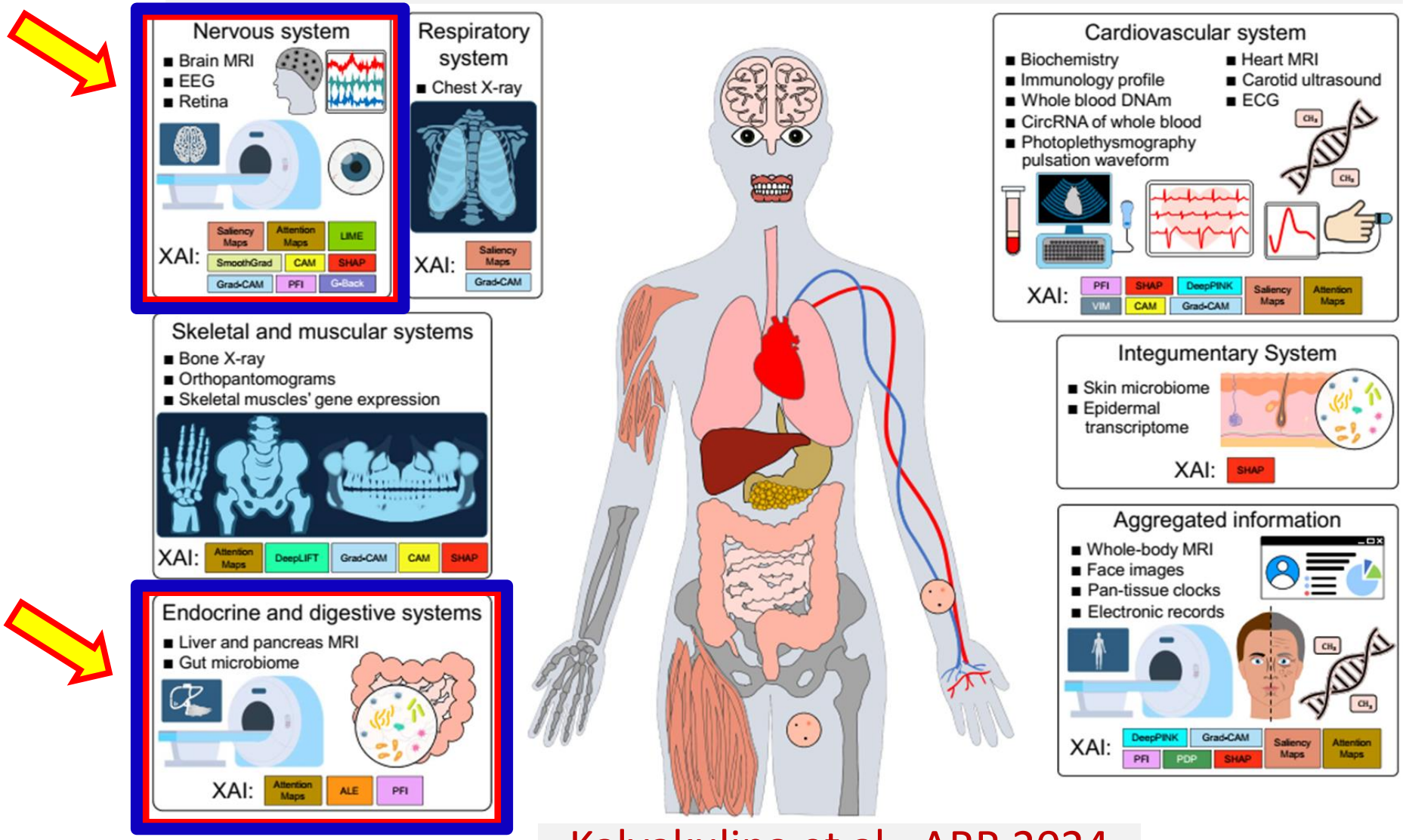
a new clock

Adaptive
pro- & anti-inflammatory clock of the Gut Microbiome from 22 to 109 years



Biagi et al., *Curr Biol* 2016

MULTIPLE ORGAN CLOCKS



Kalyakulina et al., ARR 2024

MULTI-OMICS & MULTIPLE CLOCKS TO STUDY AGING IN YOUNG PEOPLE

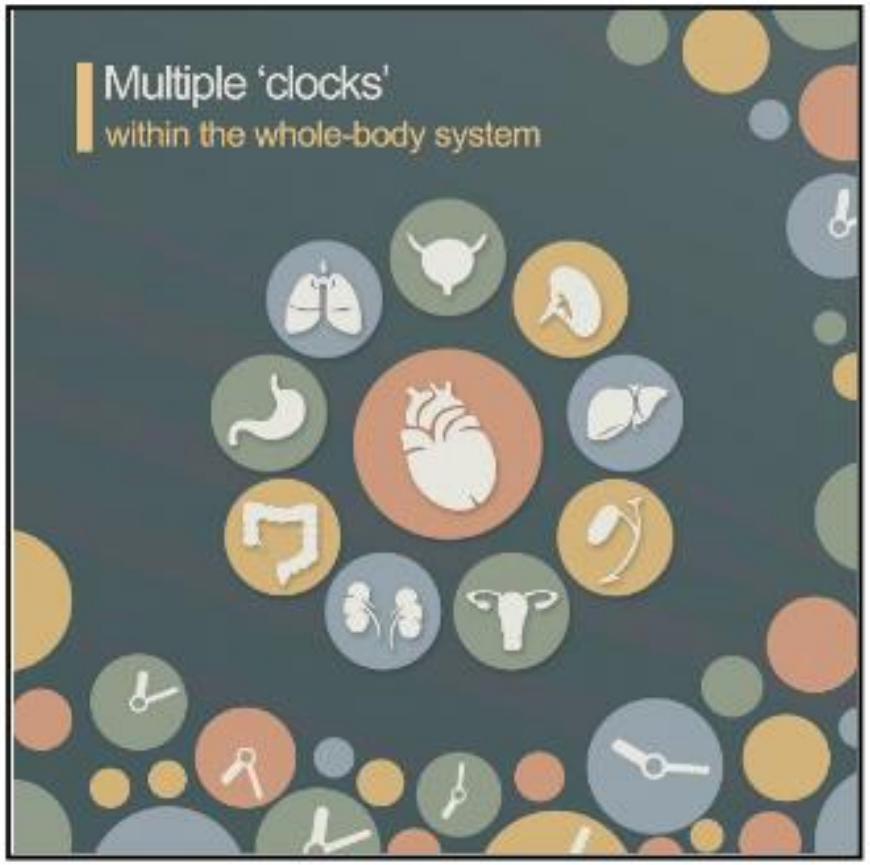
Cell Reports

Cell Rep. 2022 Mar 8;38(10):110459

Distinct biological ages of organs and systems identified from a multi-omics study

402 features were measured including **74 metabolomic features**, 34 clinical biochemistry features, 36 immune repertoire features, **15 body composition** features, 8 physical fitness features, 10 electroencephalography (EGG) features, **16 facial skin features,** and **210 gut microbiome features**

Graphical abstract



Authors

Chao Nie, Yan Li, Rui Li, ...,
Claudio Franceschi, Brian K. Kennedy,
Xun Xu

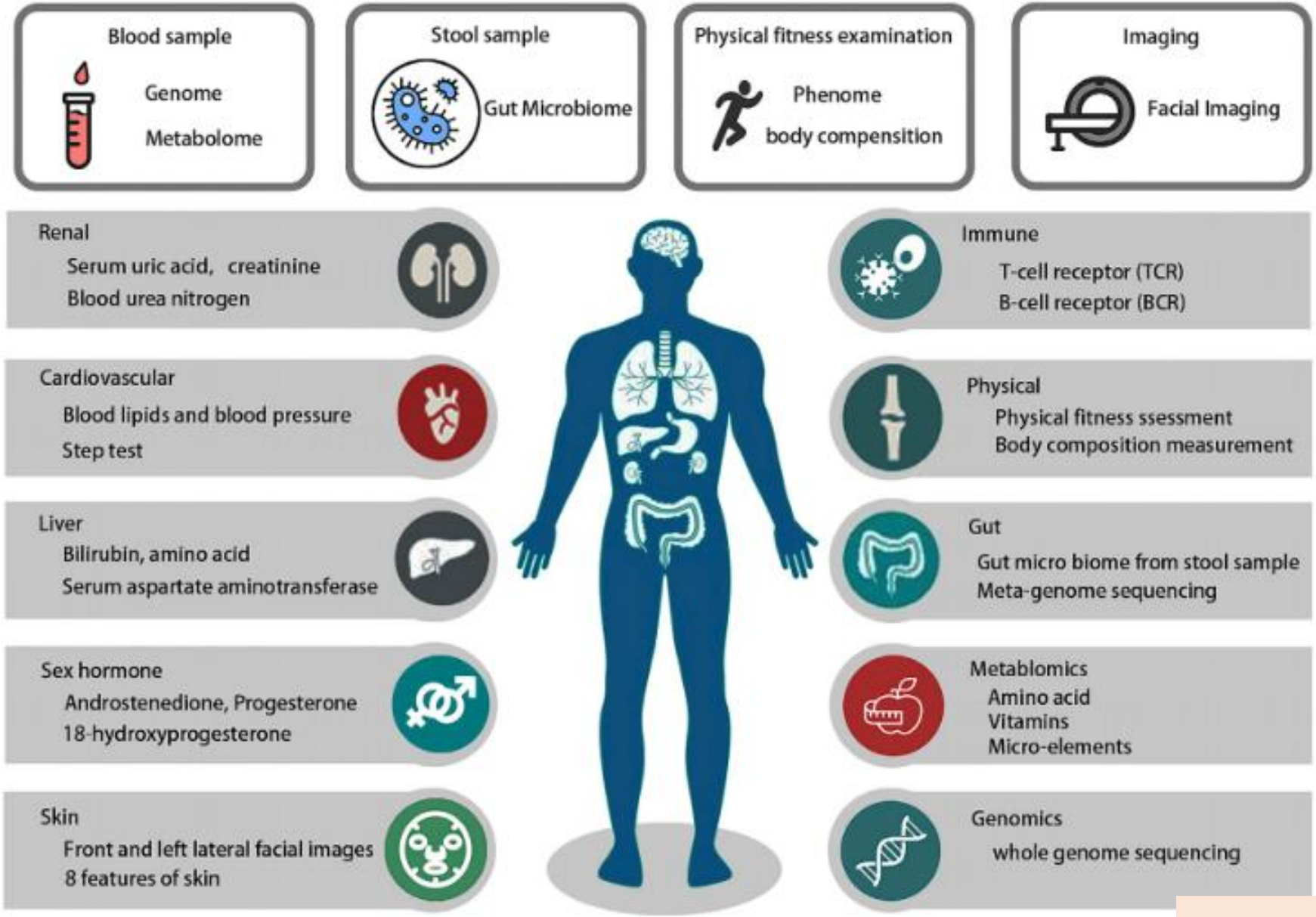
Correspondence

xuxun@genomics.cn (X.X.),
bkennedy@nus.edu.sg (B.K.K.),
claudio.franceschi@unibo.it (C.F.),
zhangxq@genomics.cn (X.Z.)

4,066 individuals aged between 20 and 45 years of age

In brief

Nie et al. estimate biological ages of organs and systems using 402 multi-omics features from 4,066 individuals and demonstrate several applications. They find that organs and systems are aging at different rates, and biological ages could be utilized for population stratification, mortality prediction, and phenotypes of genetic association studies.

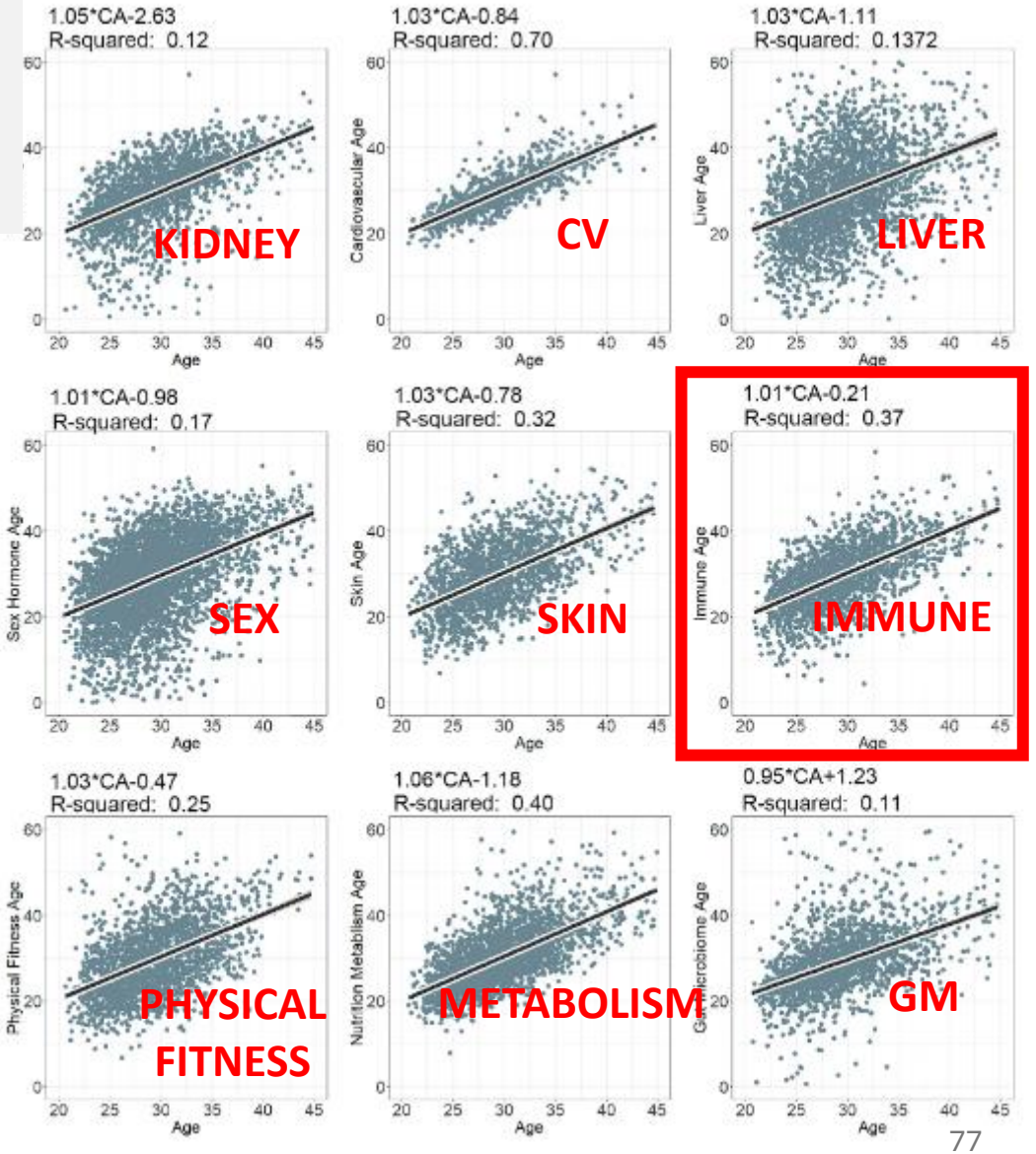


Nie et al., CR 2022

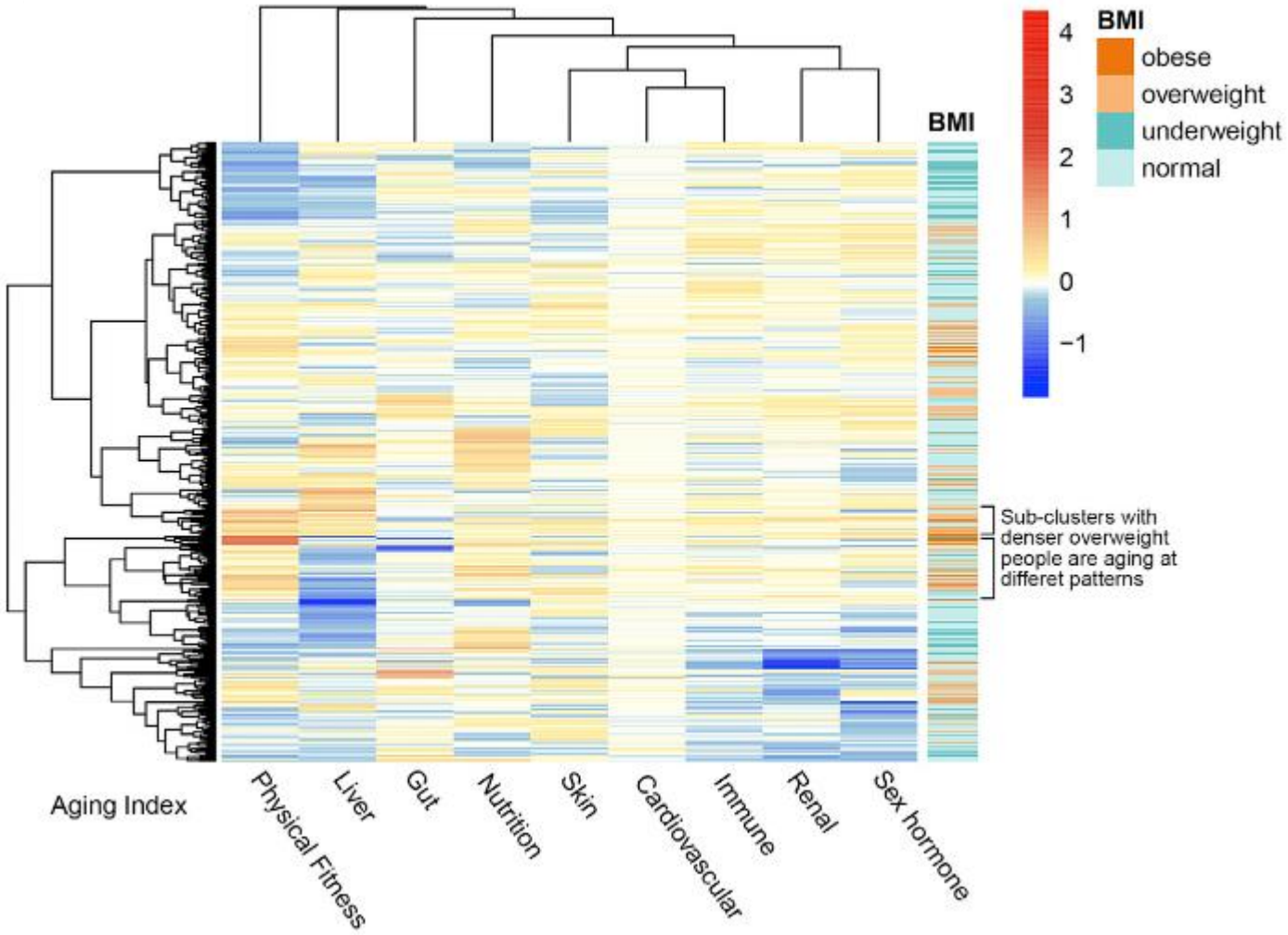
Individual variability of the aging rates of organs and systems

The body as a mosaic of clocks

- One possible explanation is the presence of **multiple cellular clocks**, being organs and system composed of a mixture of different cell types.
- In addition, this phenomenon can be **different in each person**.



Extraordinary complexity and individual variability of organ biological age according to BMI



Clustering heatmap of **481 individuals** according to different biological ages.

- The color gradient represents the aging rates.
- Red indicates faster and blue indicates slower aging rates relative to the person's chronological age.
- For instance, if the biological age is larger than his/her chronological age, the person is aging faster.

Nie et al., CR 2022

Highlights

- Constructing biological ages of organs/systems using multi-omics features
- Organs and systems are aging at different rates
- Specific biological age could predict disease of corresponding organs
- Biological ages of organs and systems have diverse genetic architectures

Nie et al., CR 2022

The Biological Aging (BA) rates of organs and systems are diverse

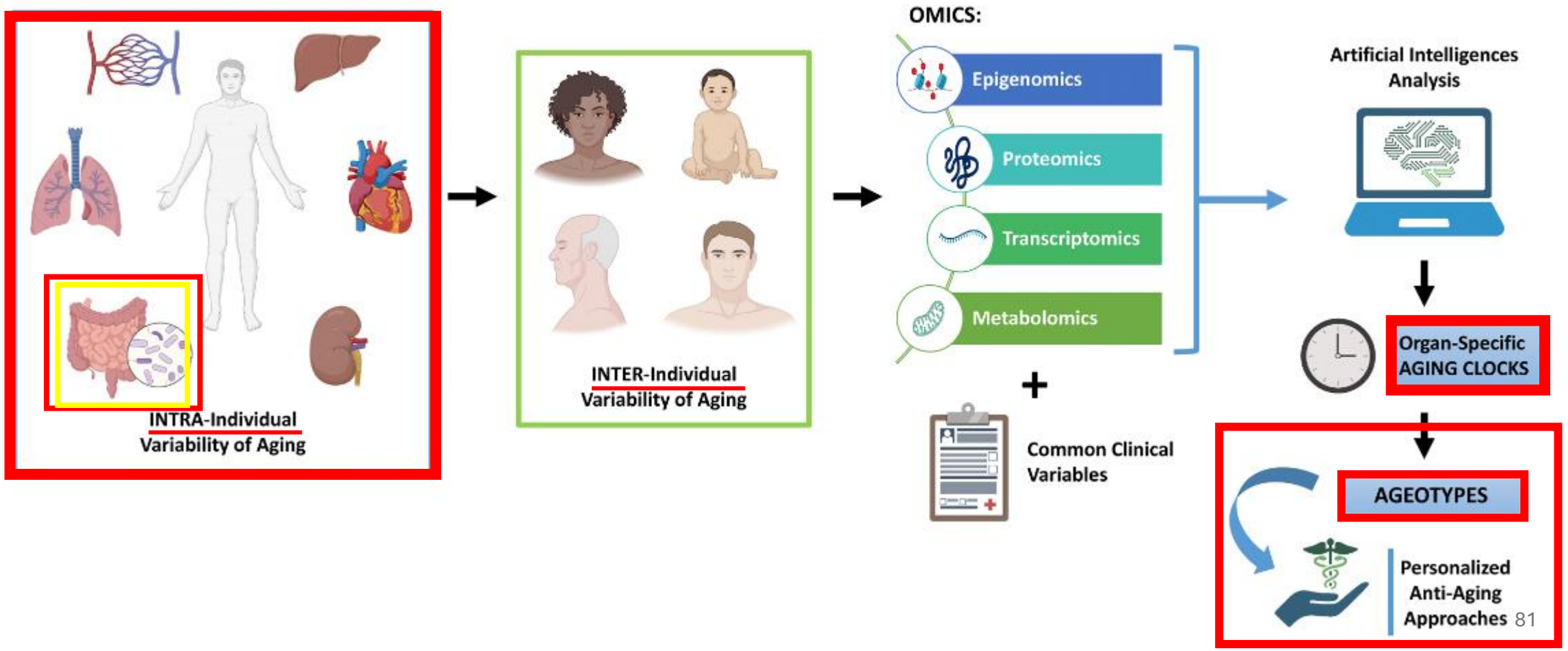
There are multiple "clocks" within the body

The identified BA predicts:

1. Mortality in the US National Health and Nutrition Examination Survey
2. Longevity in the Chinese Longitudinal Healthy Longevity Survey

Organ-specific biological clocks: Ageotyping for personalized anti-aging medicine.

Prattichizzo F, Frigé C, Pellegrini V, Scisciola L, Santoro A, Monti D, Rippo MR, Ivanchenko M, Olivieri F, Franceschi C. **Ageing Res Rev. 2024 Mar 4**;96:102253.



PERSONALIZED VACCINATION ?

Immunobiography

+

Personalized Inflammaging

+

eXplainable AI

Thanks
4 your
attention

BOLOGNA/UNIBO: the arcades of the oldest university in the Western world (founded in 1080)