Claudio Franceschi

Alma Mater Studiorum
Università di Bologna;
IRCCS Institute of
Neurological Sciences
of Bologna, Italy;
Lobachevsky
State University,
Nizhny Novgorod, Russia

Biomarkers of biological age, chronic inflammation/ inflammaging

Healthy Life and Longevity
Centenarians in Italy and Israeli Lifestyle, Nutrition, Clinical, and Genetics
Monday 2nd December
The Steinhardt Museum of Natural History
Klausner St 12, Tel Aviv-Yafo , Israel

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

The Bologna team

University of Bologna & Inst Neurol Sci of Bologna

Claudio Franceschi - Professor Emeritus, MD
Stefano Salvioli – Associate Professor
Paolo Garagnani – Associate Professor
Miriam Capri – Senior Researcher
Aurelia Santoro - Researcher
Federica Sevini – Technician
Maria Giustina Palmas - Nurse
Massimo Izzi – Sanitary Assistant

PhD students
Maddalena Milazzo
Francesco Ravaioli
Salvatore Collura
Giulia Guidetti

Marie Curie Fellowships
Katarzyna Kwiatkowsa
Anna Carbó Meix

Postdocs
Maria Giulia Bacalini
Maria Conte
Cristina Giuliani
Elena Marasco
Morena Martucci
Cristina Morsiani
Chiara Pirazzini
Claudia Sala

Guest
Daniela Monti – Associated Professor
University of Florence

Aging
is NOT
a «simple»
decline
of all functions

THE "REMODELLING THEORY OF AGING"

(Franceschi et al., 1995; 2000)

The phenotype of old people is the result of the body's capability to respond/adapt to the unrepaired molecular/cellular insults continuously occurring lifelong in all tissues and organs (at a different rate !!!)

REMODELLING

a dynamic scenario characterized by a complex mixture of:

1. Progressive accumulation of damages/mutations
2. Chronic activation of local and systemic adaptive responses, including inflammation and adaptation to inflammation...

Usually it is difficult to distinguish between the two!

THE "REMODELLING THEORY OF AGING"
(Franceschi et al., 1995; 2000)

This lifelong remodelling
is a complex mixture of linear,
non-linear and stochastic
processes which generate
heterogeneity

Questions/Model

- **Why some people live consistently longer than others?**
- **Which is the biological basis of human longevity?**

Questions/Model

- **Why some people live consistently longer than others?**
- **Which is the biological basis of human longevity?**

Centenarians (100+)
and their offspring as a model

Centenarians (100+) as an exceptional model

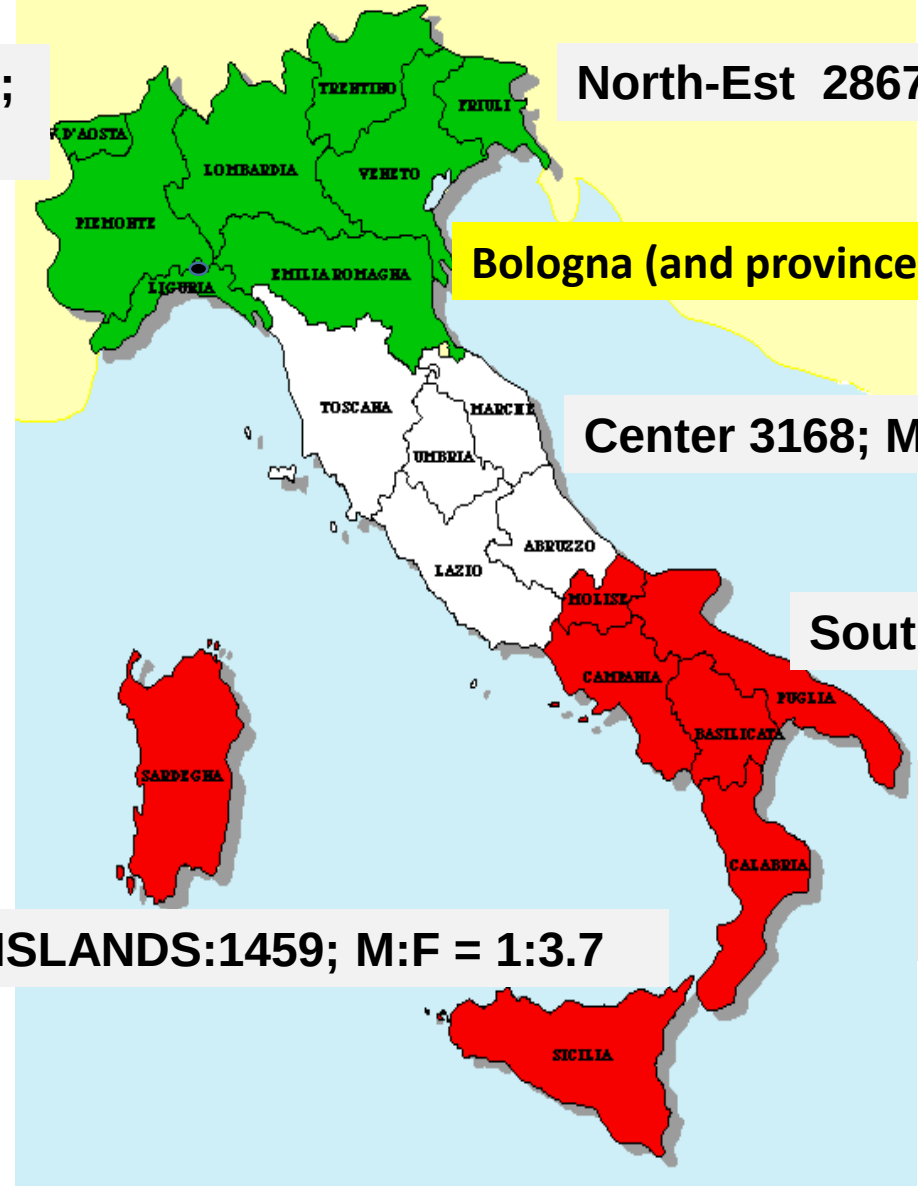
- They live 20-30 years more than members of the same demographic cohort
- Most of them avoided or largely postponed (20-30 years) the major age-associated diseases
- They die in few days!

100+ are the best model of human longevity and allow to identify biomarkers of healthy aging and protective factors (genetic, epigenetic…) *versus* the major age-associated pathologies

DEMOGRAPHY

CENTENARIANS IN ITALY (100+): 14,456;
M = 2,324; F= 12,132 105+ = 1,112 110+ = 21

North-West 3948;
M:F = 1:7.6



North-Est 2867; M:F = 1:6.8

Bologna (and province): 343; M:F = 1:6.8

Center 3168; M:F = 1:5

South: 3014; M:F = 1: 3.5

ISLANDS:1459; M:F = 1:3.7

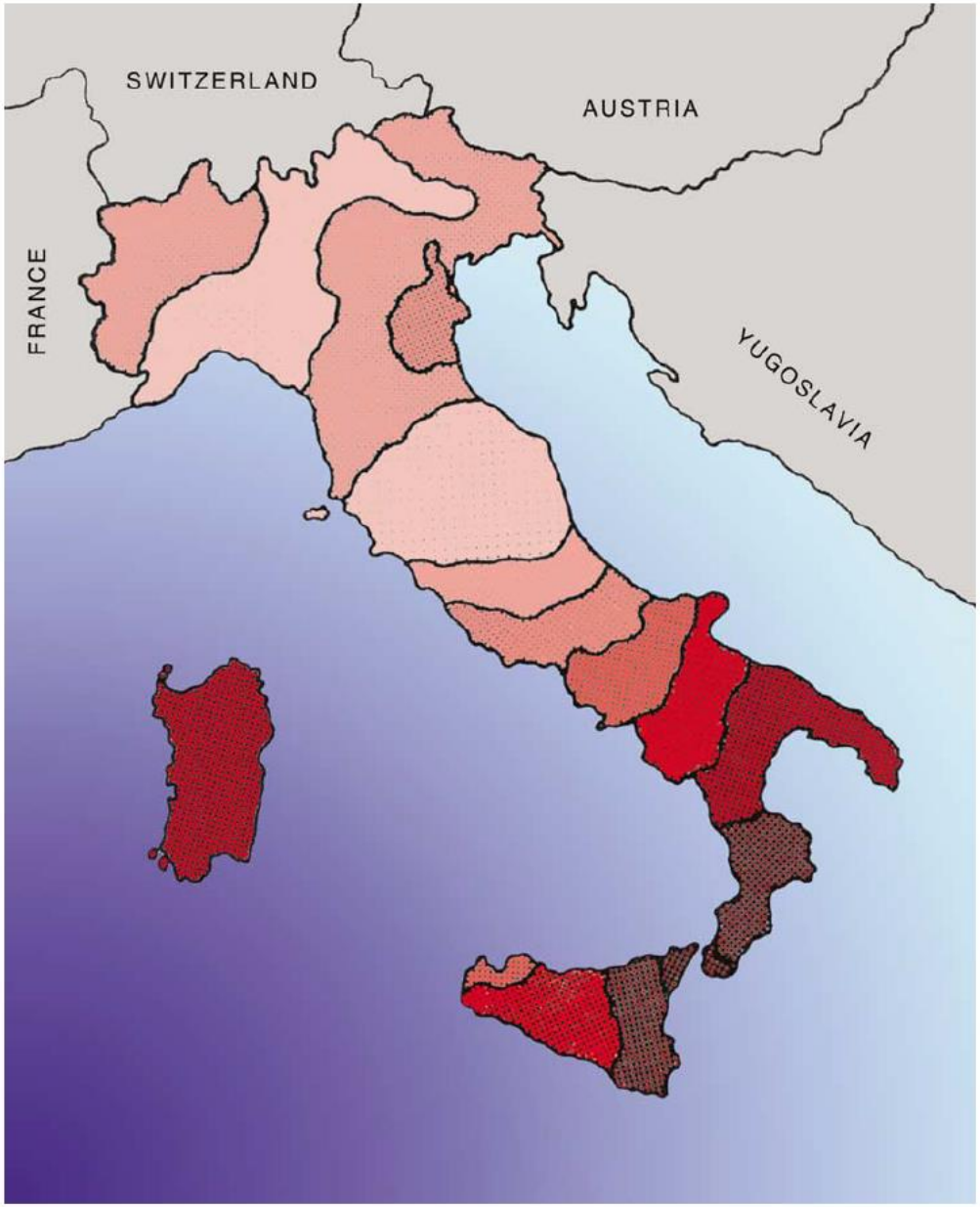
M:F
A North to South gradient (increase of male longevity)

Population: 60,359,546

ISTAT- up-dated January 1st 2019

Synthetic map of Italy representing the first principal component

from Cavalli Sforza et al. (1994)



2. CENTENARIANS AS MODELS OF LONGEVITY AND HEALTHY AGING

2.1. Longevity as a Recent, Historical, and Dynamic Phenomenon

Homo sapiens appeared on the stage about 300,000 years ago, and until about a century ago, life expectancy was about 50–55 years in developed countries, and it did not change much from that of hunter-gatherers until the twentieth century. Then a demographic revolution started, first in developed countries, but soon spreading worldwide. Life expectancy started to increase at about 3 months per year, and the average life expectancy at birth in developed countries is now more than 87 years for women and about 84 years for men (130). Thus, for hundreds of millennia longevity was a rare event, and extreme longevity was likely even more rare, apart from few exceptions that must be carefully investigated and validated. When we started studying centenarians in Italy in about 1990, the centenarians had been born at the end of the nineteenth century, and there were about 3,000 of them; two decades later, in 2017, they were born at the beginning of the twentieth century and there are 18,765 of them (of which 3,000 are men) (58). Thus, from a demographic standpoint, extreme longevity is a highly dynamic phenomenon, and the high number of centenarians worldwide currently (about 434,000) (131) must be considered a recent, largely unpredicted phenomenon. Centenarians undergo rapid changes not only regarding

Franceschi et al., Annual Reviews of Nutrition 2018

Sardinia as a demographic laboratory

ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Experimental Gerontology 39 (2004) 1423–1429

Experimental Gerontology

www.elsevier.com/locate/expgero

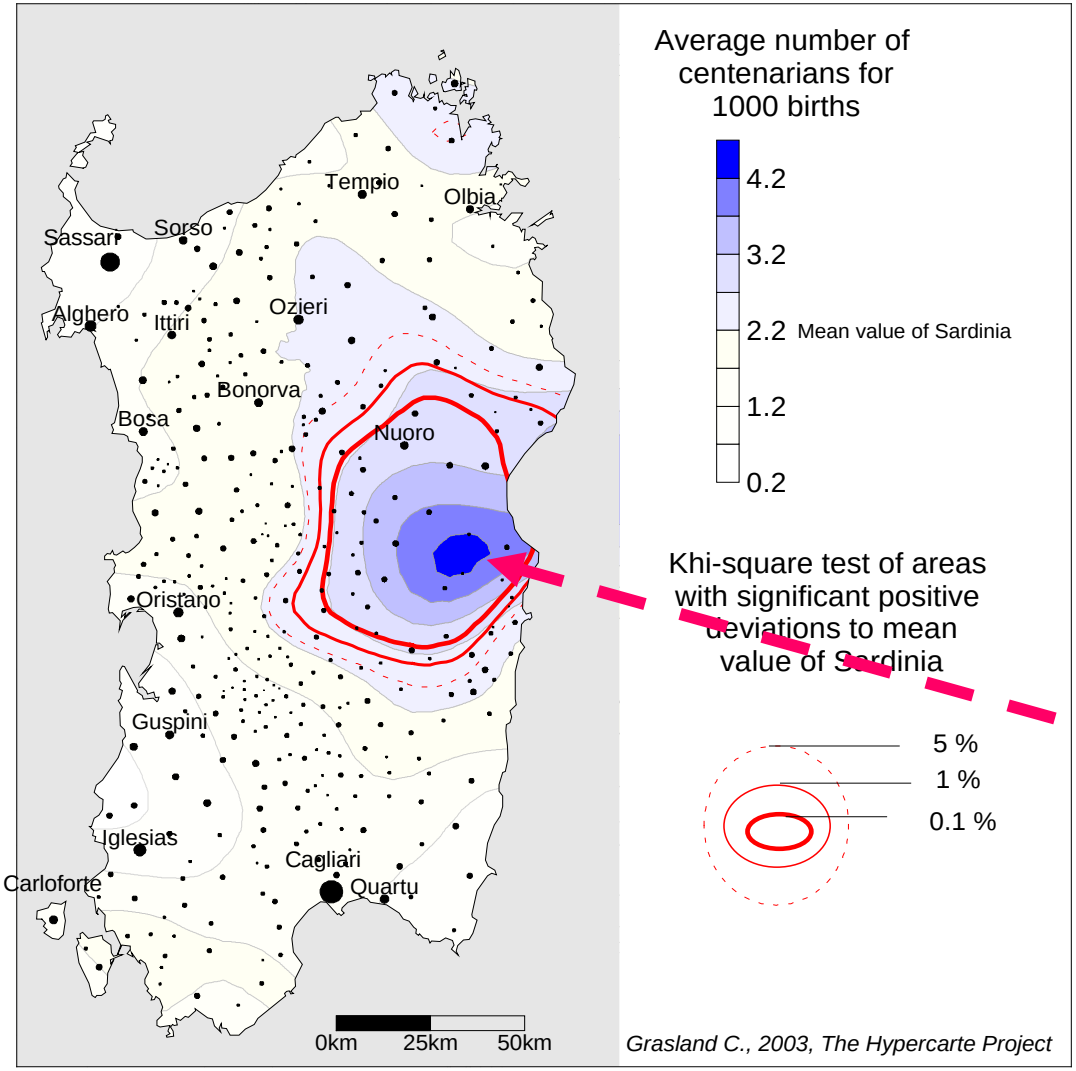
Identification of a geographic area characterized by extreme longevity in the Sardinia island: the AKEA study

Michel Poulain[a,*], Giovanni Mario Pes[b], Claude Grasland[c], Ciriaco Carru[b], Luigi Ferrucci[d,e], Giovannella Baggio[f], Claudio Franceschi[g], Luca Deiana[b]

[a]*FNRS-GéDAP, Groupe d'Etudes de Démographie Appliquée, Université Catholique de Louvain, Louvain-la-Neuve, Belgique*
[b]*Institute of Clinical Biochemistry, University of Sassari, Italy*
[c]*UMR Géographie-cités, University Paris 7, France*
[d]*Longitudinal Studies Section. Clinical Research Branch, National Institute on Aging, Baltimore, MD, USA*
[e]*Laboratory of Clinical Epidemiology, Geriatric Department, Italian National Research Centre on Aging (INRCA), Firenze, Italy*
[f]*Internal Medicine Unit, Azienda Ospedale-Università di Padova and University of Sassari, Italy*
[g]*Department of Experimental Pathology and C.I.G., University of Bologna, and INRCA, Department of Gerontological Research, Ancona, Italy*

Sardinia as a demographic laboratory

centenarians are non-randomly distributed
according to their place of birth



The discovery of the blue zone exceptional male longevity

M:F centenarian ratio 1:1

Deiana et al., Exp. Gerontol., 39:1423-9, 2004

Sardinia as a demographic laboratory

DEMOGRAPHIC RESEARCH

VOLUME 31, ARTICLE 42, PAGES 1275–1296
PUBLISHED 25 NOVEMBER 2014
http://www.demographic-research.org/Volumes/Vol31/42/
DOI: 10.4054/DemRes.2014.31.42

Research Article

Maternal longevity is associated with lower infant mortality

Graziella Caselli
Enrica Lapucci
Rosa Maria Lipsi
Lucia Pozzi
Giovannella Baggio
Ciriaco Carru
Luca Deiana
Claudio Franceschi
James W. Vaupel

DEMOGRAPHIC RESEARCH

VOLUME 32, ARTICLE 37, PAGES 1049–1064
PUBLISHED 21 MAY 2015
http://www.demographic-research.org/Volumes/Vol32/37/
DOI: 10.4054/DemRes.2015.32.37

Descriptive Finding

Demographic characteristics of Sardinian centenarian genealogies: Preliminary results of the AKeA2 study

Rosa Maria Lipsi
Lucia Pozzi
Ciriaco Carru
James W. Vaupel
Graziella Caselli
Giovannella Baggio
Claudio Franceschi
Luca Deiana

for centenarian women, 79 per 1000 of offspring died in the first year of life (infant mortality rate). In contrast, among the offspring of the controls in the same cohorts as the centenarians who died in their 60s or 70s, the infant mortality rate was 118–172 per 1000. Centenarian women also presented a lower infant mortality rate among their children than did women belonging to younger cohorts, particularly for those born between 1911 and 1916. A similar pattern was found for male counterparts (Lipsi et al. 2015). These results suggest a possible familial transmission of a lower mortality from parents to children, produced by shared genetic or socio-cultural factors

The female post-reproductive survival advantage is a relatively recent phenomenon observed only in the cohorts born towards the end of the 19th century, both in Italy and elsewhere.

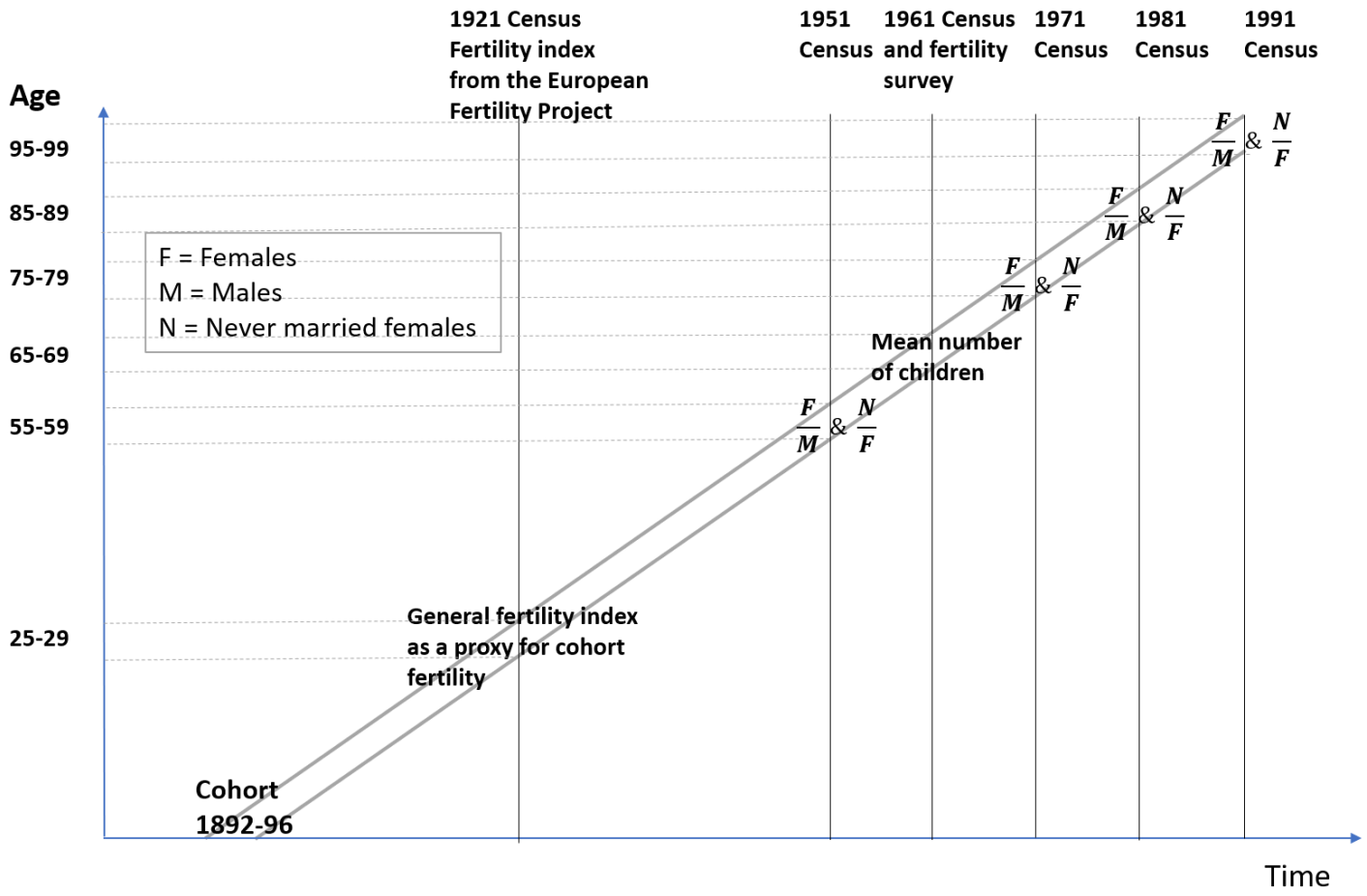
Sardinia as a demographic laboratory

Collaboration with Giambattista Salinari, Cristina Giuliani, Marco Breschi, Gustavo De Santis

- We used the data published by the Italian Institute of Statistics (ISTAT) to reconstitute the **demographic history of eight cohorts born in the years 1862-66, 1872-76, …, 1932-36** in 16 Italian administrative regions
- For each region and each cohort, we collected aggregate data on **cohort fertility, the probability of survival >59 and the FMR at various post-reproductive ages**, as well as and the proportion of ever-married women.

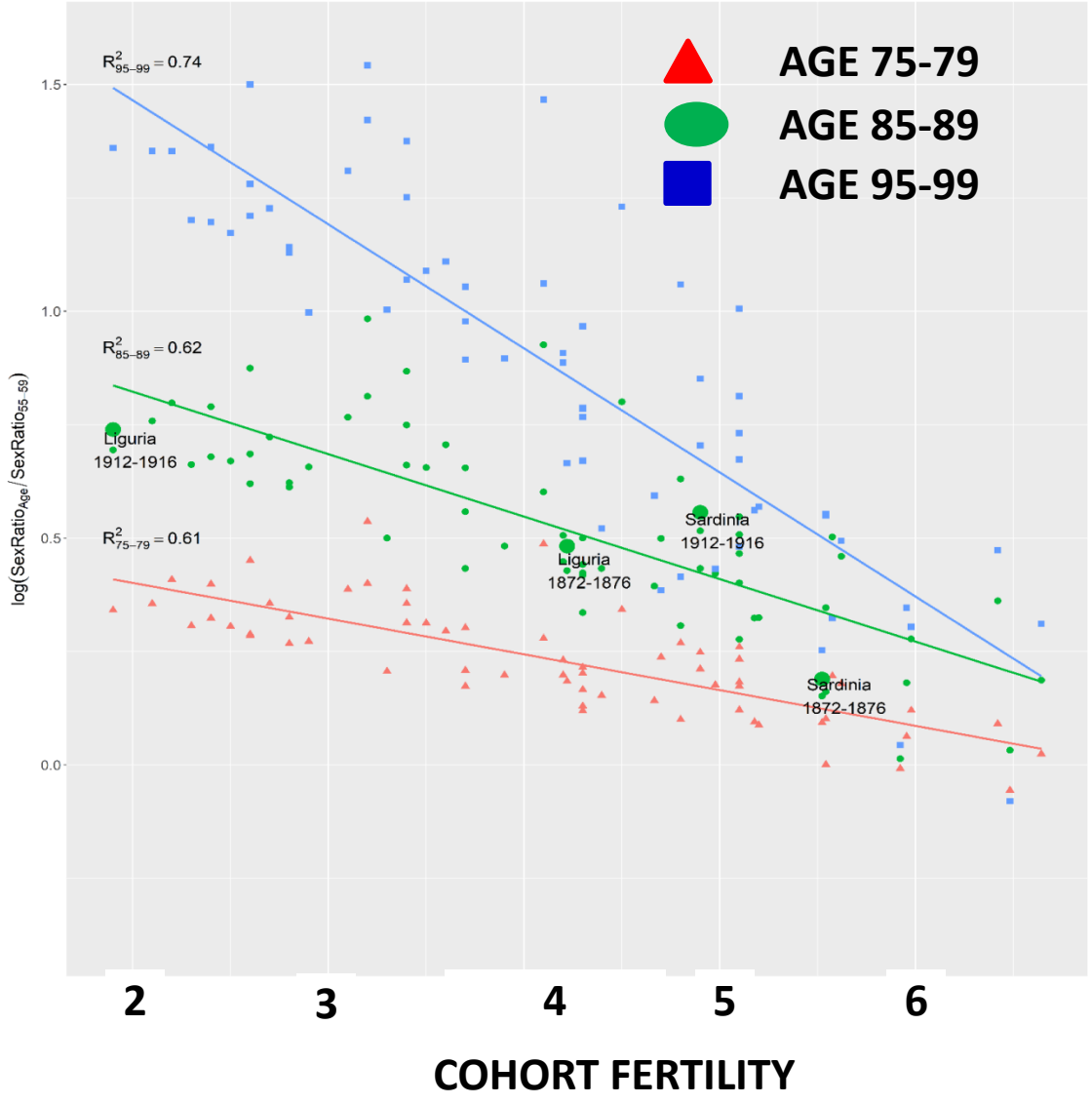
Sardinia as a demographic laboratory

Collaboration with Giambattista Salinari, Cristina Giuliani, Marco Breschi, Gustavo De Santis



Reconstitution of the demographic history of the cohort born in 1892-96

Effect of fertility on the post-reproductive sex ratio in Italy



- Liguria: the forerunner of the fertility transition in Italy.
- Sardinia: the last region to experience its fertility transition.

Salinari et al., submitted

Fertility and sex ratio

- Figure 2 highlights two main phenomena:

1. the sex-ratio underwent a temporal evolution, and the regions that had high values of this index in 2001 (north of Italy) had much lower values in the past, comparable to those recorded in Sardinia in 2001. **A low FMR at high ages was probably the norm in pre-transitional populations**.

2. the influence of fertility on the sex ratio becomes stronger with age. At high ages (95-99 years), fertility alone can explain about three quarter of the overall observed variance in RFS.

Salinari et al., submitted

PHENOTYPE

NERVOUS SYSTEM

- About 40% of centenarians reports good self-reported quality of life
- About one third of centenarians shows an unimpaired or mildly impaired cognitive status

ENDOCRINE SYSTEM

- Preserved glucose tolerance and insulin sensitivity;
- Lower levels of serum IGF-1
- Higher serum TSH levels compared to younger controls;
- Lower serum free T3 levels than elderly controls;

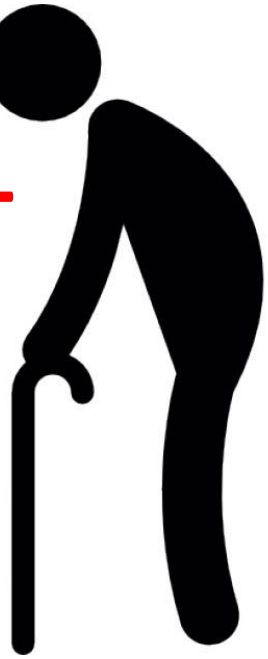
MUSCOLO-SKELETAL SYSTEM

- Vitamin D deficiency, low serum calcium;
- Hyperparathyroidism and osteopenia

SENSORY SISTEM

- About 80% of centenarians has visual or hearing deficits or both

100+



CARDIOVASCULAR SYSTEM

- Lower levels of triglycerides, total cholesterol and LDL;
- High Lipoprotein (a) serum level

GUT MICROBIOTA (GM)

- Enriched in "pathobionts" (e.g. Proteobacteria);
- Shrinkage of the core GM (dominant symbiotic bacteria)
- Increase in subdominant species (*Akkermansia, Bifidobacterium, Christensenellaceae*);
- Increased diversity in GM composition

IMMUNE SYSTEM

- Balance between pro- and anti-inflammatory markers;
- Well-preserved complement system
- Increase of memory T-cells;
- Strong decrease of naïve $CD95^-$ T-cells capable of mounting responses towards novel pathogens.

Giuliani, Garagnani & Franceschi, Circulation Res, 2018

The immunology of exceptional individuals: the lesson of centenarians

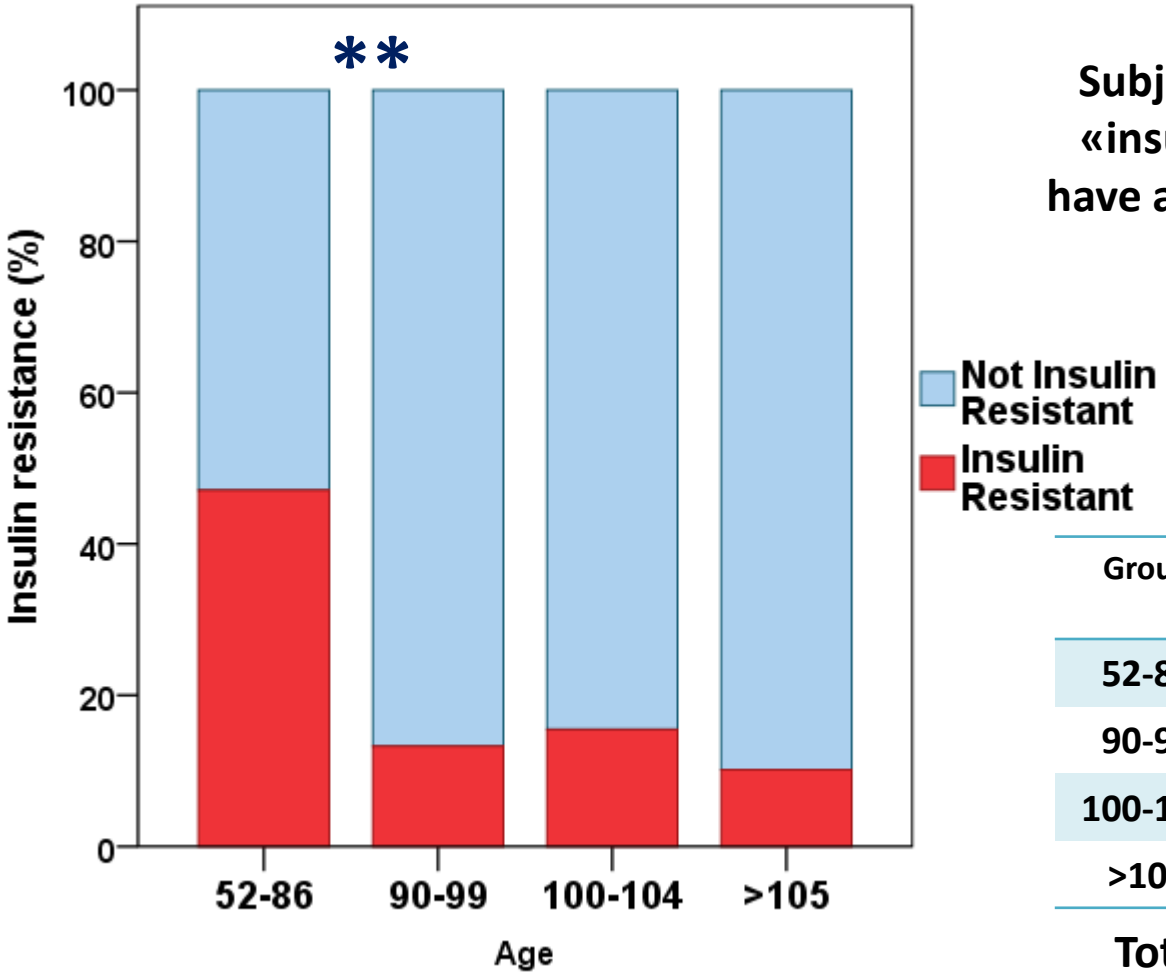
Claudio Franceschi, Daniela Monti,
Paolo Sansoni and Andrea Cossarizza

Centenarians are the best example of successful ageing, since they have escaped the major age-associated diseases, and most are in good mental and physical condition. Here, Claudio Franceschi and colleagues discuss how the study of their immune systems reveals that several immune parameters are well conserved, suggesting that a complex remodelling of most immune parameters occurs with age, rather than a unidirectional deterioration.

Immunology Today. 1995 Jan;16(1):12-6

AGE AND INSULIN RESISTANCE

In 419 subjects (52-113yrs)



Subjects were considered «insulin resistant» if they have an HOMA-IR index >2.5

Group	n	Men, n	Women, n
52-86	155	78	77
90-99	98	30	68
100-104	97	22	75
>105	69	15	54
Total	419	145	274

The percentage of subjects with insulin resistance decreases dramatically after the age of 90.

GENETICS

- **A meta-analysis of genome-wide association studies identifies multiple longevity genes.**

Deelen J, Evans DS, Arking DE, Tesi N, Nygaard M, Liu X, Wojczynski MK, Biggs ML, van der Spek A, **Atzmon G**, Ware EB, Sarnowski C, Smith AV, Seppälä I, Cordell HJ, Dose J, Amin N, Arnold AM, Ayers KL, Barzilai N, Becker EJ, Beekman M, Blanché H, Christensen K, Christiansen L, Collerton JC, Cubaynes S, Cummings SR, Davies K, Debrabant B, Deleuze JF, Duncan R, Faul JD, **Franceschi C**, Galan P, Gudnason V, Harris TB, Huisman M, Hurme MA, Jagger C, Jansen I, Jylhä M, Kähönen M, Karasik D, Kardia SLR, Kingston A, Kirkwood TBL, Launer LJ, Lehtimäki T, Lieb W, Lyytikäinen LP, Martin-Ruiz C, Min J, Nebel A, Newman AB, Nie C, Nohr EA, Orwoll ES, Perls TT, Province MA, Psaty BM, Raitakari OT, Reinders MJT, Robine JM, Rotter JI, Sebastiani P, Smith J, Sørensen TIA, Taylor KD, Uitterlinden AG, van der Flier W, van der Lee SJ, van Duijn CM, van Heemst D, Vaupel JW, Weir D, Ye K, Zeng Y, Zheng W, Holstege H, Kiel DP, Lunetta KL, Slagboom PE, Murabito JM.

Nat Commun. 2019 Aug 14;10(1):3669. doi: 10.1038/s41467-019-11558-2.

- **Genome-Wide Scan Informed by Age-Related Disease Identifies Loci for Exceptional Human Longevity.**

Fortney K, Dobriban E, Garagnani P, Pirazzini C, **Monti D, Mari D, Atzmon G**, Barzilai N, **Franceschi C**, Owen AB, Kim SK.

PLoS Genet. 2015 Dec 17;11(12):e1005728.

Cardiovascular Aging Compendium

Genetics of Human Longevity Within an Eco-Evolutionary Nature-Nurture Framework

Cristina Giuliani, Paolo Garagnani, Claudio Franceschi

Circulation Research 2018;123:745-772.

September 14, 2018

Longevity = G x E lifelong

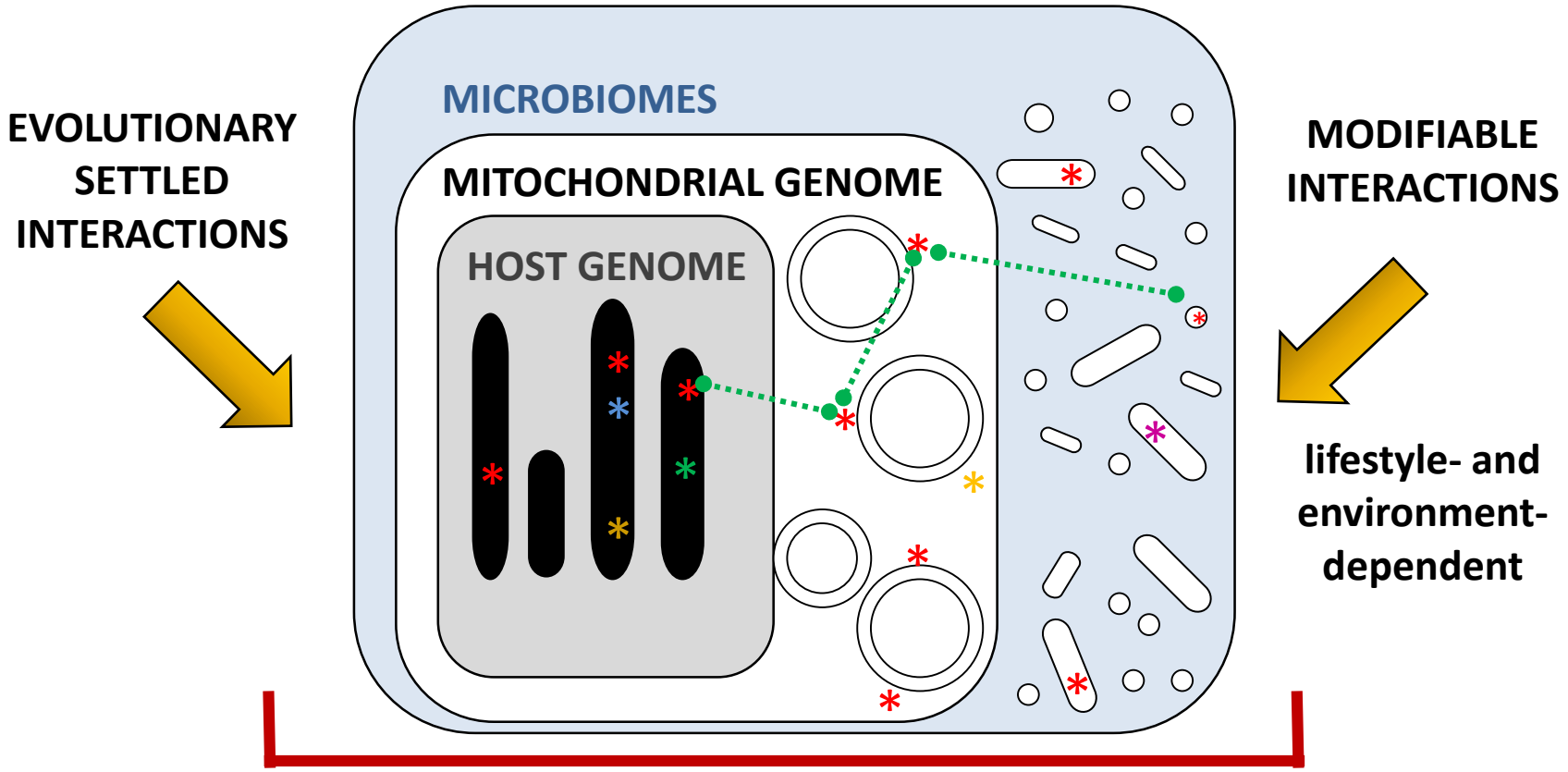
G = 3 = Nuclear and Mitochondrial genomes + Microbiomes

The capability to reach the extreme decades of human lifespan seems to be the result of an intriguing mixture of gene-environment interactions. Accordingly, the genetics of human longevity is here described as a highly context-dependent phenomenon, within a new integrated, ecological, and evolutionary perspective, and is presented as a dynamic process, both historically and individually. The available literature has been scrutinized within this perspective, paying particular attention to factors (sex, individual biography, family, population ancestry, social structure, economic status, and education, among others) that have been relatively neglected.

Circ Res. 2018;123:745-772.

Holobiont and metaorganism are terms coined within the framework of ecology, evolution and zoology

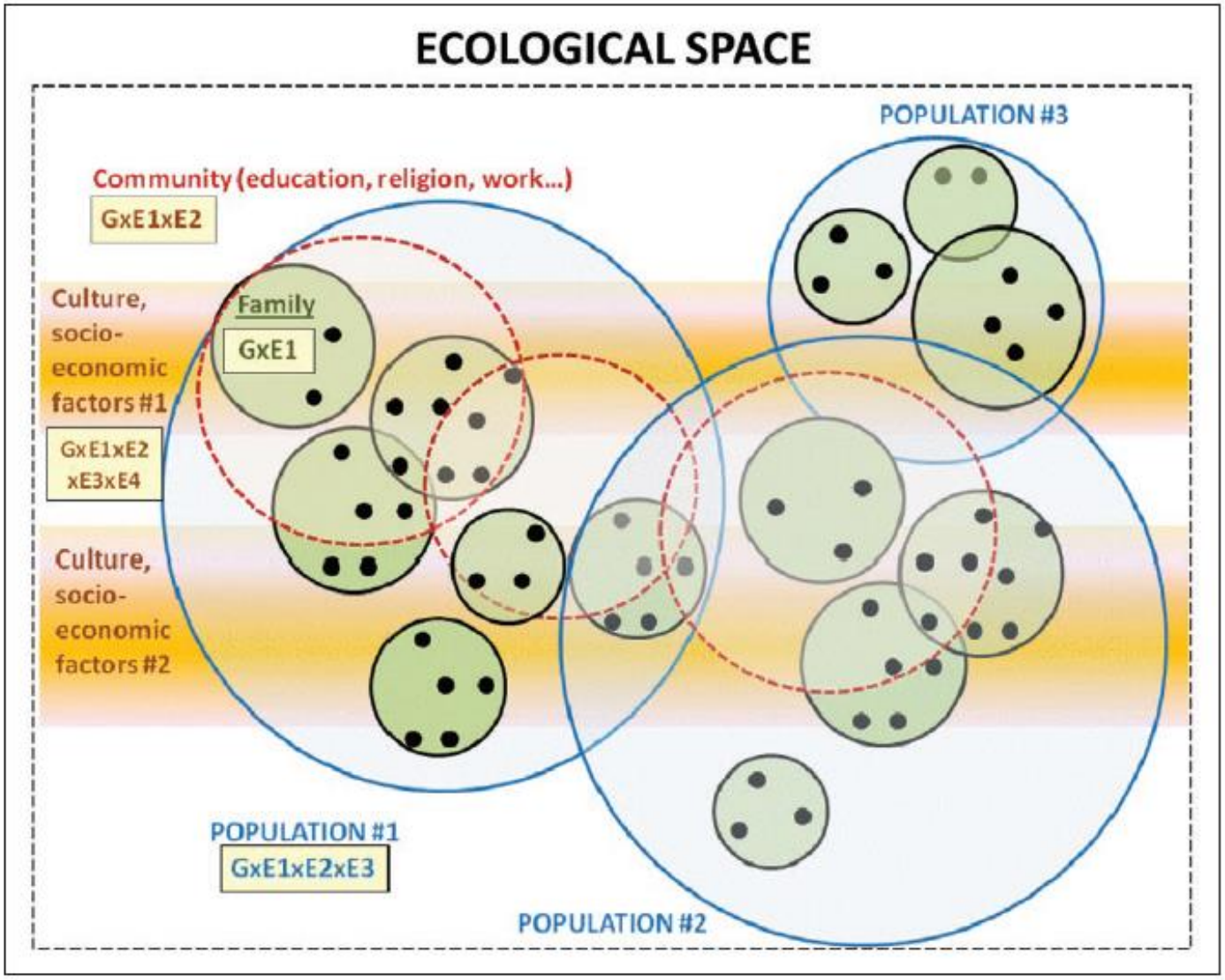
H. sapiens as HOLOBIONT/METAORGANISM



The genetics of longevity depends on the interaction among the 3 genomes of *H. sapiens* as a metaorganism, interacting lifelong with the environment

Giuliani, Garagnani & Franceschi, Circulation Res, 2018

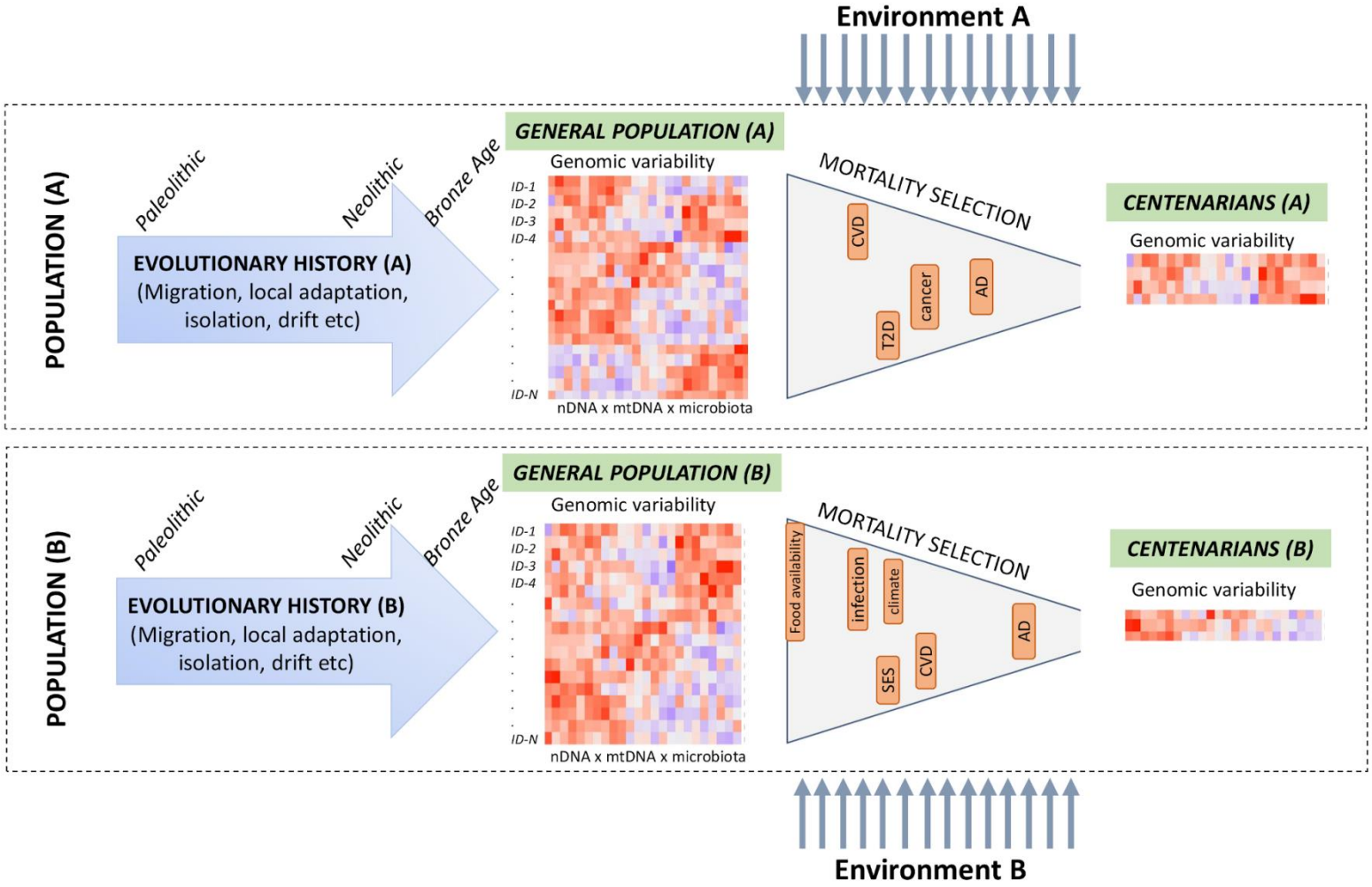
The complexity of GxE interactions in humans



Human longevity is highly context- & population-dependent

Giuliani, Garagnani & Franceschi, Circulation Res, 2018

The genetics of human longevity and the critical importance of evolution and context



Franceschi C, Garagnani P, Olivieri F, Salvioli S, Giuliani C. The contextualized genetics of human longevity. *Journal of the American College of Cardiologists*, submitted

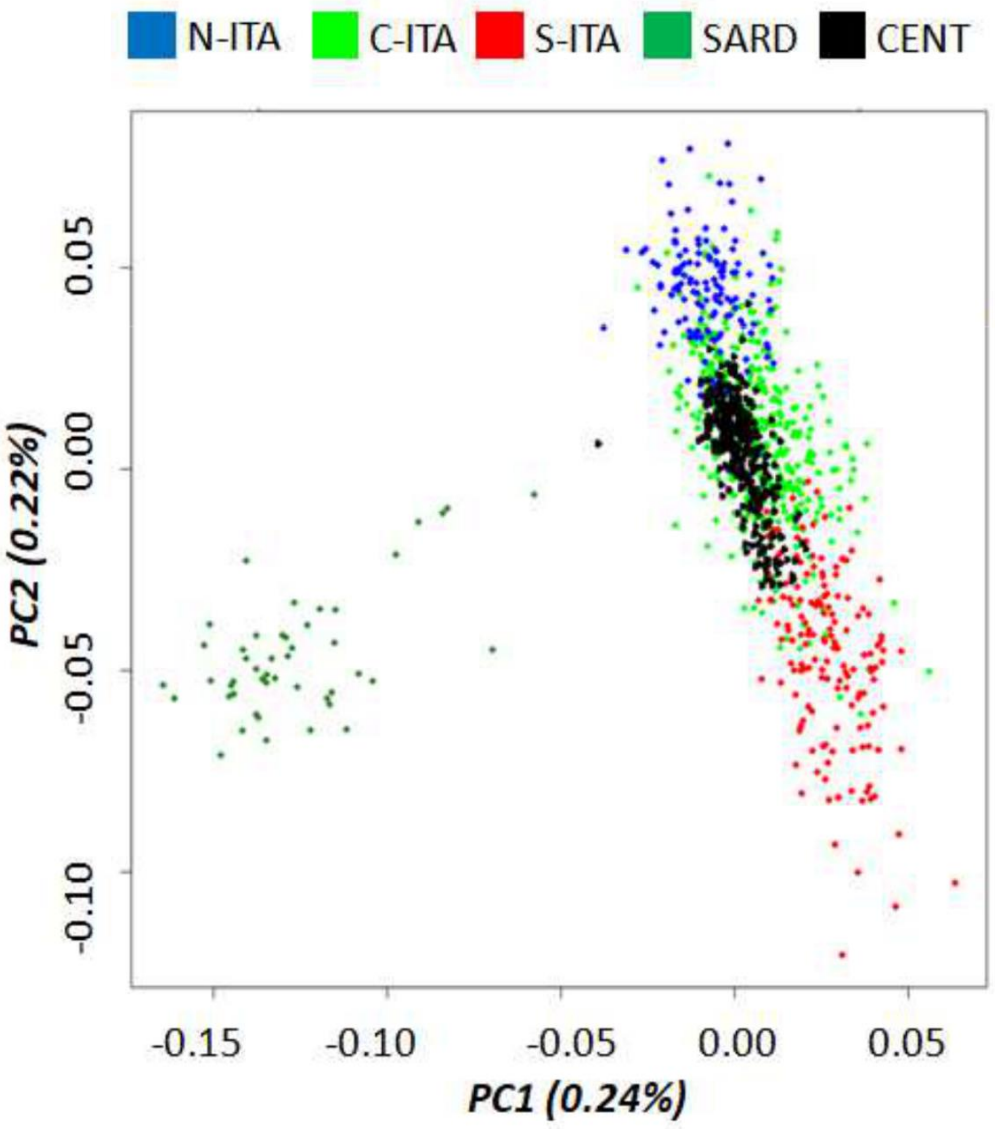
www.aging-us.com AGING 2018, Vol. 10, No. 8

Research Paper

Impact of demography and population dynamics on the genetic architecture of human longevity

Cristina Giuliani[1,2,3,*], Marco Sazzini[1,*], Chiara Pirazzini[4], Maria Giulia Bacalini[4], Elena Marasco[3,5,6], Guido Alberto Gnecchi-Ruscone[1], Fang Fang[7], Stefania Sarno[1], Davide Gentilini[8], Anna Maria Di Blasio[8], Paolina Crocco[9], Giuseppe Passarino[9], Daniela Mari[10,11], Daniela Monti[12], Benedetta Nacmias[13], Sandro Sorbi[13,14], Carlo Salvarani[15,16], Mariagrazia Catanoso[15], Davide Pettener[1], Donata Luiselli[17], Svetlana Ukraintseva[7], Anatoliy Yashin[7], Claudio Franceschi[4,21], Paolo Garagnani[5,18,19,20, 21]

Main results: **(i)** centenarian genomes are **enriched for an ancestral component** likely shaped by **pre-Neolithic** migrations; **(ii)** centenarians born in Northern Italy unexpectedly clustered with controls from Central/Southern Italy suggesting that **Neolithic** and Bronze Age **gene flow did not favor longevity** in this population; **(iii)** local past adaptive events in response to pathogens and targeting arachidonic acid metabolism became favorable for longevity.



CoreExomeChip (Illumina)

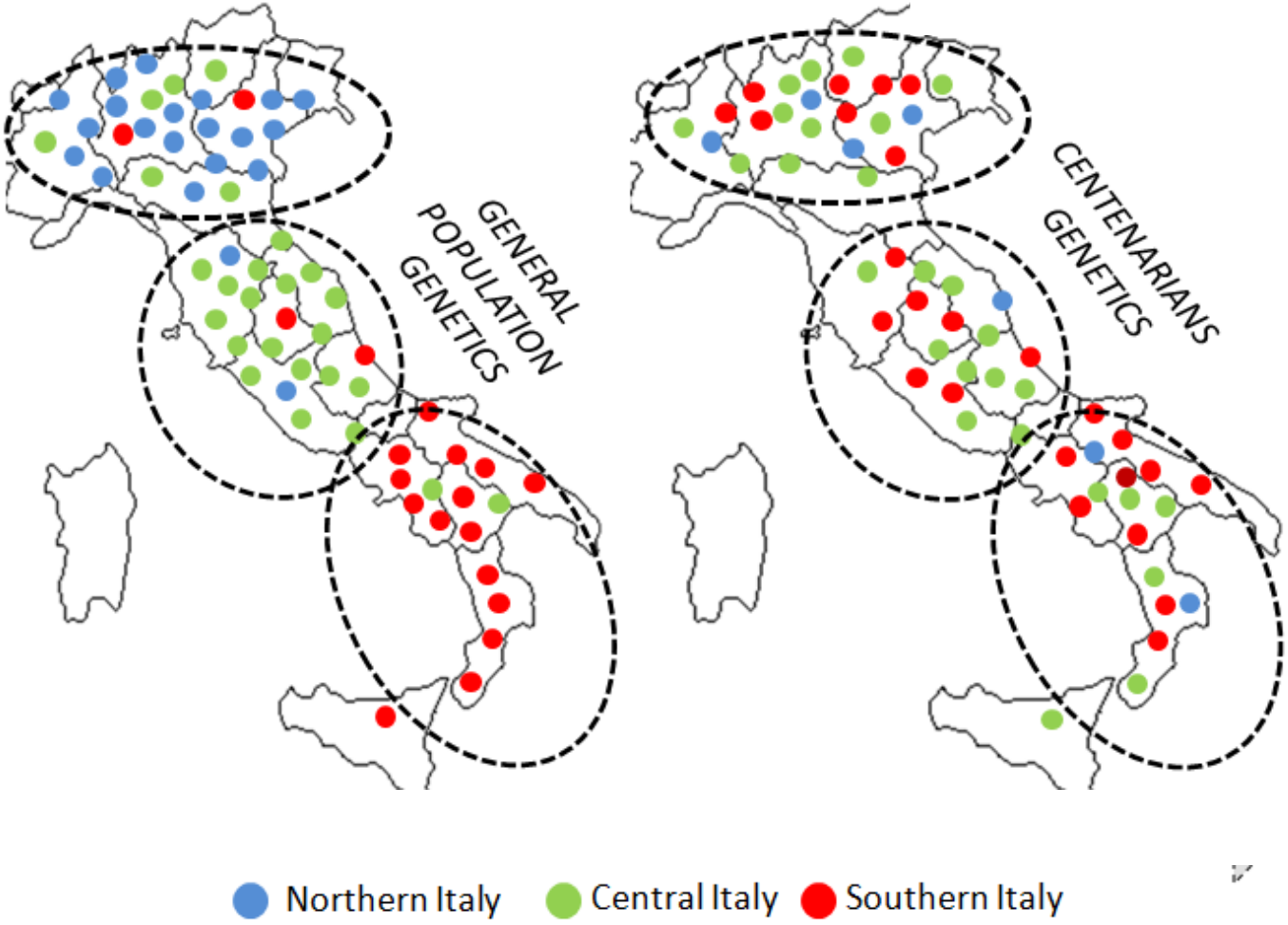
279k *genome-wide tag SNPs*
245k *exomic variants*
19k *disease-associated variants*

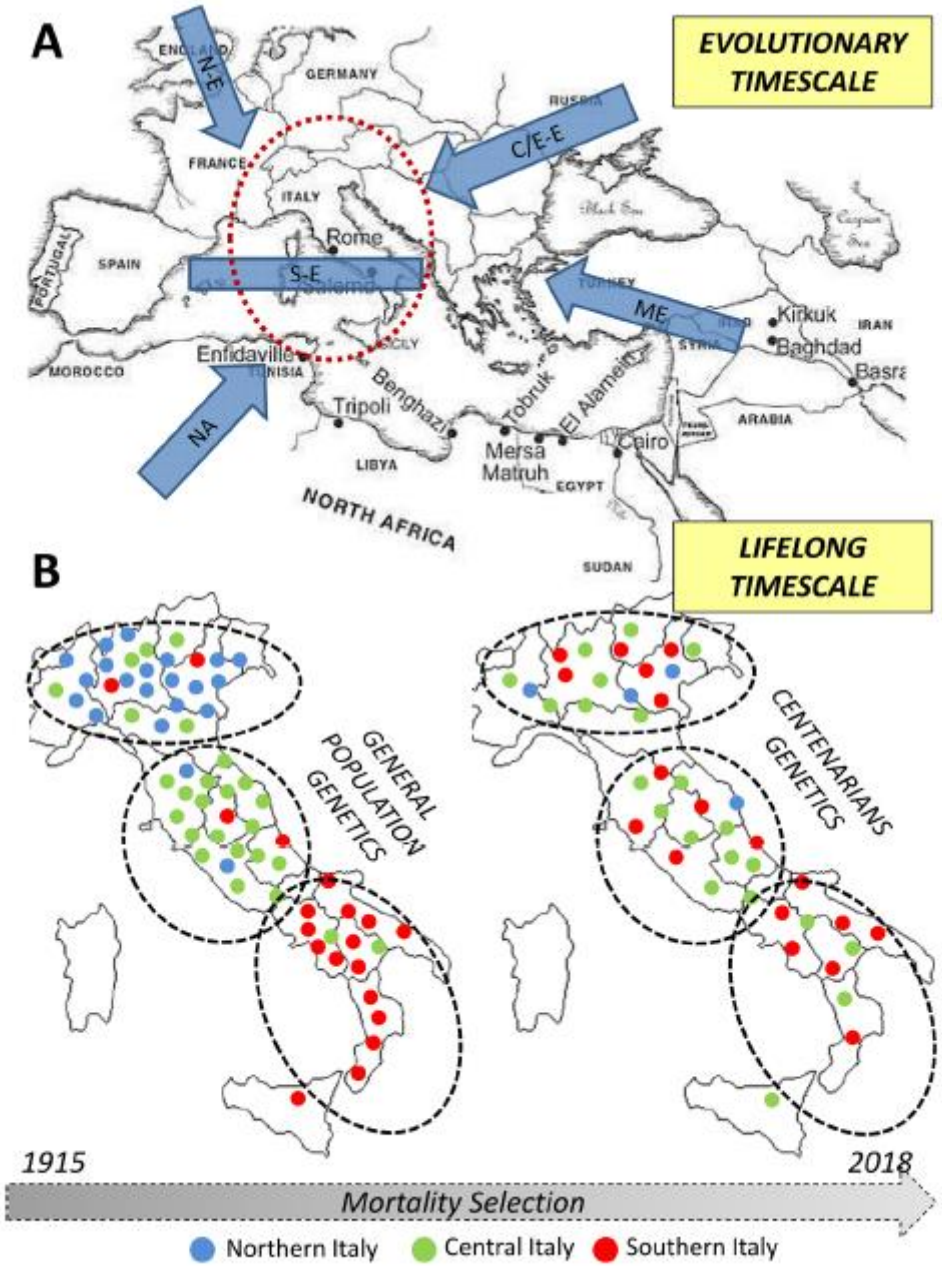
333 centenarians *from the whole Italian peninsula*

773 geographically-matched healthy young *Italian samples*

Unexpected position of centenarians in the Italian cline *(regardless of their micro-geographic origins)*

Centenarians are enriched for an ancient ancestry component equally represented along the peninsula




A
EVOLUTIONARY TIMESCALE
N-E
C/E-E
S-E
ME
NA
GERMANY
FRANCE
ITALY
Rome
SPAIN
PORTUGAL
MOROCCO
Enfidaville
TUNISIA
Tripoli
Benghazi
Tobruk
El Alamein
Cairo
Mersa Matruh
LIBYA
EGYPT
NORTH AFRICA
SUDAN
ARABIA
Kirkuk
Baghdad
IRAN
B
LIFELONG TIMESCALE
GENERAL POPULATION GENETICS
CENTENARIANS GENETICS
1915
2018
Mortality Selection
Northern Italy
Central Italy
Southern Italy

Sci Rep. 2016; 6: 21243.
Published online 2016 Feb 25

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Novel loci and pathways significantly associated with longevity

Received: 25 August 2015
Accepted: 20 January 2016
Published: 25 February 2016

Yi Zeng[1,2,†], Chao Nie[3,*], Junxia Min[4,*], Xiaomin Liu[3,*], Mengmeng Li[5], Huashuai Chen[1,6], Hanshi Xu[3], Mingbang Wang[3], Ting Ni[7], Yang Li[8], Han Yan[8], Jin-Pei Zhang[8], Chun Song[8], Li-Qing Chi[8], Han-Ming Wang[8], Jie Dong[8], Gu-Yan Zheng[8], Li Lin[5], Feng Qian[5], Yanwei Qi[3,9], Xiao Liu[3], Hongzhi Cao[3], Yinghao Wang[3], Lijuan Zhang[3], Zhaochun Li[3], Yufeng Zhou[3], Yan Wang[3], Jiehua Lu[10], Jianxin Li[10], Ming Qi[4], Lars Bolund[3,11], Anatoliy Yashin[12], Kenneth C. Land[12], Simon Gregory[13], Ze Yang[14], William Gottschalk[15], Wei Tao[16], Jian Wang[3,17], Jun Wang[3,18], Xun Xu[3], Harold Bae[19], Marianne Nygaard[20], Lene Christiansen[20], Kaare Christensen[20], Claudio Franceschi[21], Michael W. Lutz[15], Jun Gu[16], Qihua Tan[20], Thomas Perls[22], Paola Sebastiani[23], Joris Deelen[24], Eline Slagboom[24], Elizabeth Hauser[13], Huji Xu[5], Xiao-Li Tian[8,†], Huanming Yang[3,17,†] & James W. Vaupel[25]

GENETICS
of Chinese, European and USA 100+

- **2178 Han Chinese centenarians** (mean age 102.7 years) and **2299 mid-age controls** (mean age 48.4 years)
- **Compared with European 90+ sibs** of EC-funded GEHA project (Genetics of Healthy Ageing 2005-2010; Coordinator: C. Franceschi) and **100+ of New England Centenarian (NEC) study**

Two top loci emerged as significant

- **rs2069837** (chr 7p15.3**, *IL-6***, *P* =1.80x10−9)
- **rs2440012** (chr 13q12.12, ***ANKRD20A9P***, *P* =3.73x10-8)

rs2069837- *IL-6* alone explained 1.0% of the variance

rs2149954 (T) in chr 5q33.3 was confirmed

ANKRD20A9P

is a pseudogene that is affiliated with the long non-coding RNAs (lncRNA) class.

A gender–dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity

Massimiliano Bonafè[1], Fabiola Olivieri[2], Luca Cavallone[2], Simona Giovagnetti[2], Francesca Marchegiani[2], Maurizio Cardelli[2], Carlo Pieri[2], Maurizio Marra[2], Roberto Antonicelli[2], Rosmarie Lisa[2], Maria Rosaria Rizzo[3], Giuseppe Paolisso[3], Daniela Monti[4] and Claudio Franceschi[1],

Current literature indicates that elevated IL-6 serum levels are associated with diseases, disability and mortality in the elderly. In this paper, we studied the IL-6 promoter genetic variability at –174 C/G locus and its effect on IL-6 serum levels in a total of 700 people from 60 to 110 years of age, including 323 centenarians. We found that the proportion of homozygotes for the G allele at –174 locus decreases in centenarian males, but not in centenarian females. Moreover, we found that, only among males, homozygotes for the G allele at –174 locus have higher IL-6 serum levels in comparison with carriers of the C allele. On the whole, our data suggest that those individuals who are genetically predisposed to produce high levels of IL-6 during aging, *i.e.* –174 locus GG homozygous men, are disadvantaged for longevity.

CENTENARIANS AS SUPER CONTROLS

www.impactaging.com AGING, May 2013, Vol. 5 No 5

Research Paper

Centenarians as super-controls to assess the biological relevance of genetic risk factors for common age-related diseases: A proof of principle on type 2 diabetes

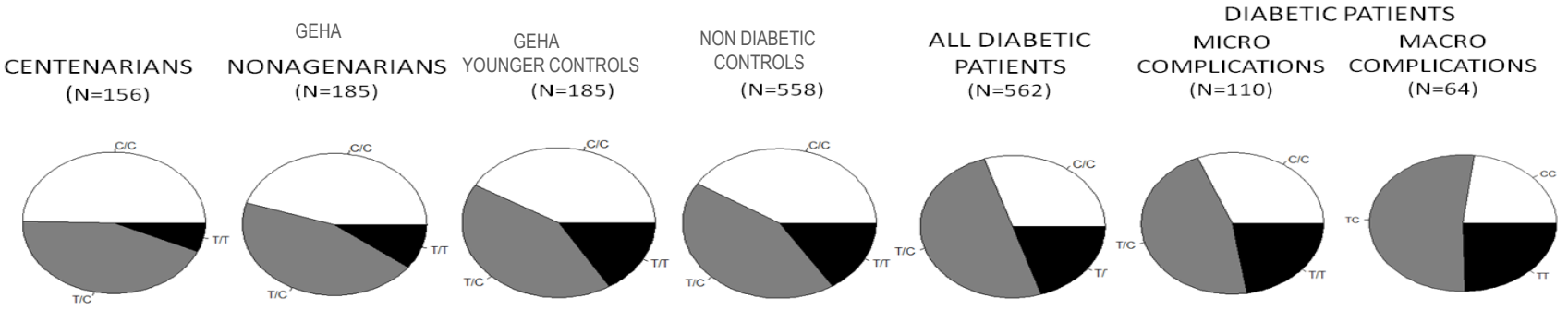
Paolo Garagnani[1,2,3 *], Cristina Giuliani[4 *,] Chiara Pirazzini[1,2], Fabiola Olivieri[5,6], Maria Giulia Bacalini[1,2], Rita Ostan[1,2], Daniela Mari[7], Giuseppe Passarino[8], Daniela Monti[9], Anna Rita Bonfigli[10], Massimo Boemi[10], Antonio Ceriello[11,12], Stefano Genovese[13], Federica Sevini[1,2], Donata Luiselli[4], Paolo Tieri[14], Miriam Capri[1,2], Stefano Salvioli[1,2], Jan Vijg[15,17], Yousin Suh[15,16,17,18], Massimo Delledonne[19,20], Roberto Testa[21], and Claudio Franceschi[1]

100+ supercontrols for T2D

in a total of 1,646 subjects, including n.156 100+ and n.185 90+

TCF7L2, DDAH1, IRS1, TERC, IGF2BP, APM1, hTERT, EPO, CAT, KCNJ11, KCNQ1, HIF-1α, FTO

rs7903146 in the TCF7L2 gene



rs 7903146 – TCF7L2							
	Genotypes frequencies (%)						
CC	49.7	45.1	41.6	41.1	30.0	29	23.4
TC	43.6	44.6	42.2	43.0	50.0	50	53.1
TT	6.7	10.3	16.2	15.8	20.0	21	23.4
	Allele frequencies (%)						
C	71.5	67.4	62.7	62.6	55	54.3	51.8
T	28.5	32.6	37.3	37.4	45	45.7	48.2

SCIENTIFIC REPORTS

OPEN

Explicating heterogeneity of complex traits has strong potential for improving GWAS efficiency

Received: 11 January 2016
Accepted: 28 September 2016
Published: 14 October 2016

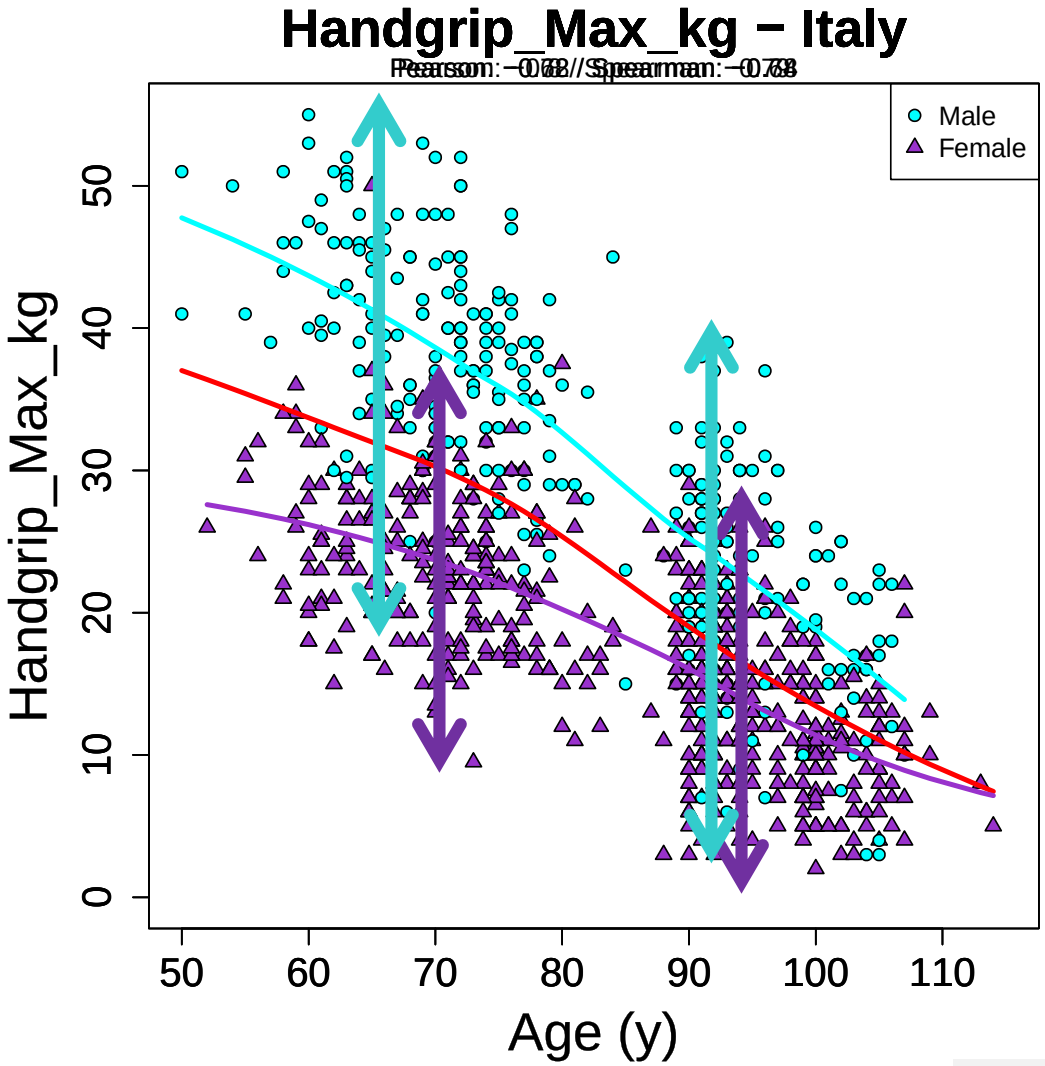
Alexander M. Kulminski, Yury Loika, Irina Culminskaya, Konstantin G. Arbeev, Svetlana V. Ukraintseva, Eric Stallard & Anatoliy I. Yashin

HETEROGENEITY

Heterogeneity of Handgrip in elderly and centenarians (males and females)

Accumulating variability with age

Maybe this parameter is the best marker of biological age



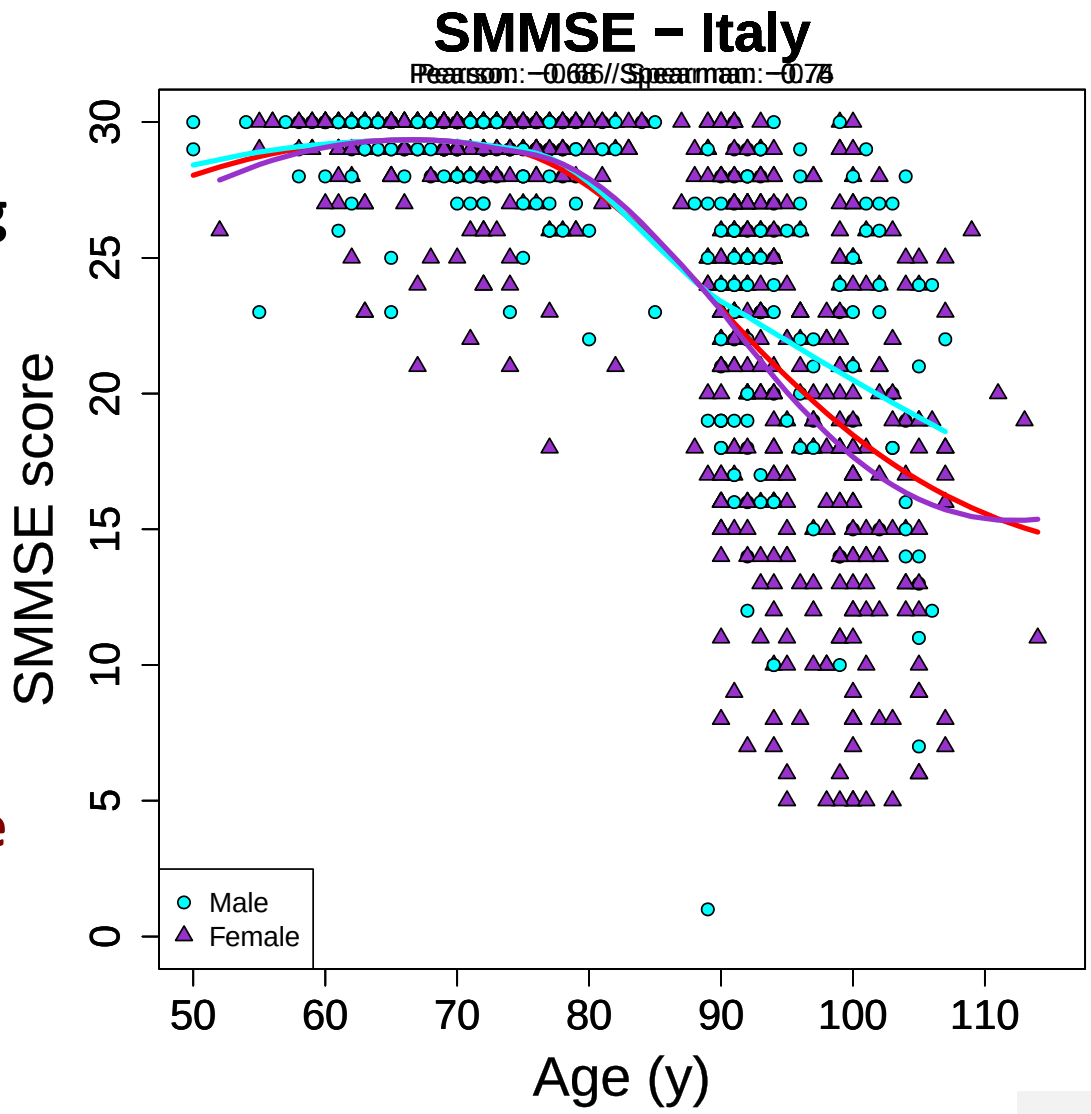
Selection on hidden heterogeneity or stochasticity?

PERSONALIZED REMODELLING?

Heterogeneity of SMMSE in elderly and centenarians (males and females)

Accumulating variability with age

Maybe this parameter is the best marker of biological age



Selection on hidden heterogeneity or stochasticity?

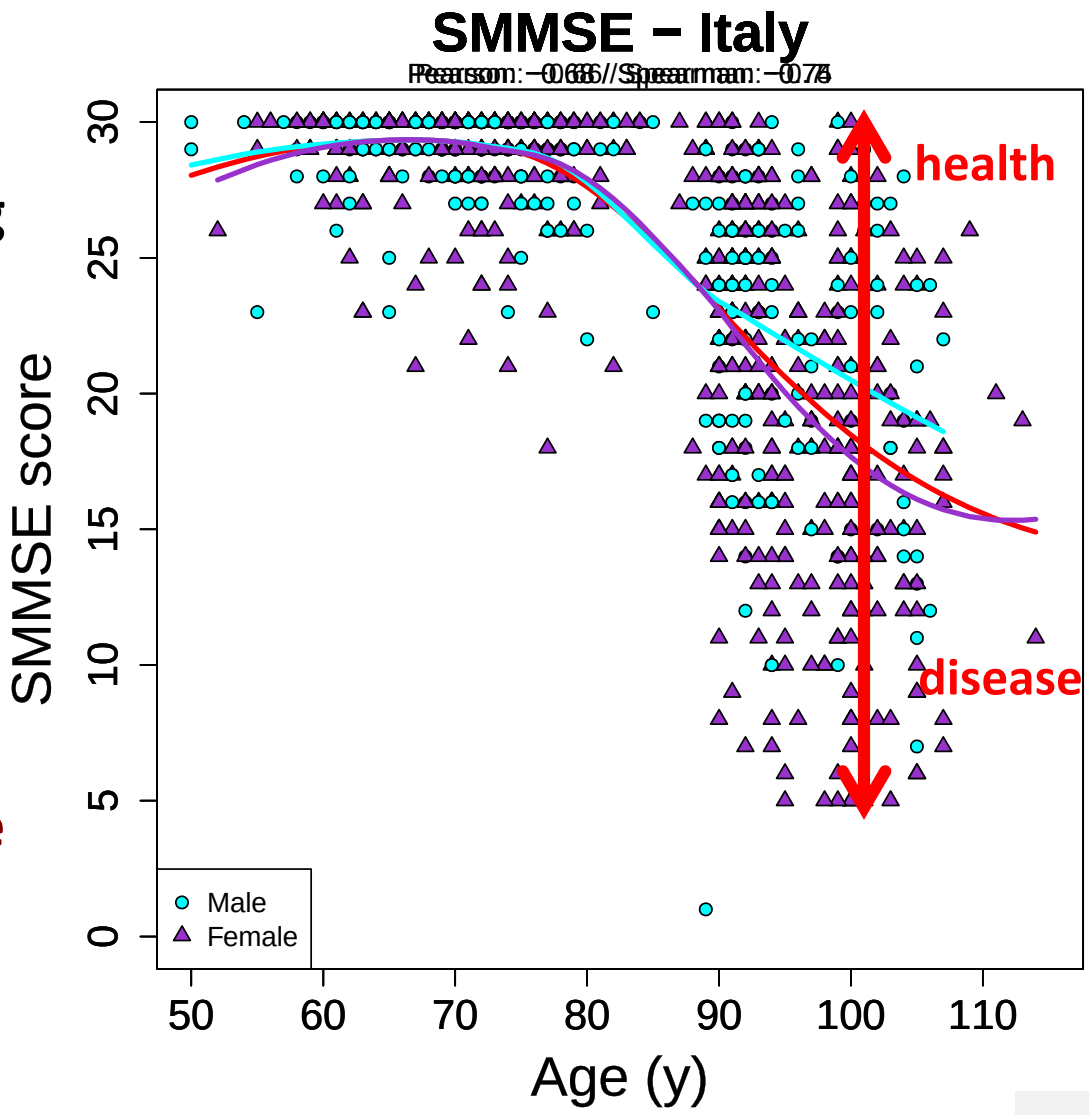
PERSONALIZED REMODELLING?

SMMSE= Standardized Mini Mental State Examination

Heterogeneity of SMMSE in elderly and centenarians (males and females)

Accumulating variability with age

Maybe this parameter is the best marker of biological age



Selection on hidden heterogeneity or stochasticity?

PERSONALIZED REMODELLING?

SMMSE= Standardized Mini Mental State Examination

Age-related diseases can be conceptualized as "accelerated aging"

frontiers in Medicine

REVIEW
published: 12 March 2018
doi: 10.3389/fmed.2018.00061

Check for updates

The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates

Claudio Franceschi[1], Paolo Garagnani[2,3,4,5], Cristina Morsiani[2], Maria Conte[2], Aurelia Santoro[2,6], Andrea Grignolio[7], Daniela Monti[8], Miriam Capri[2,6†] and Stefano Salvioli[2,6†]*

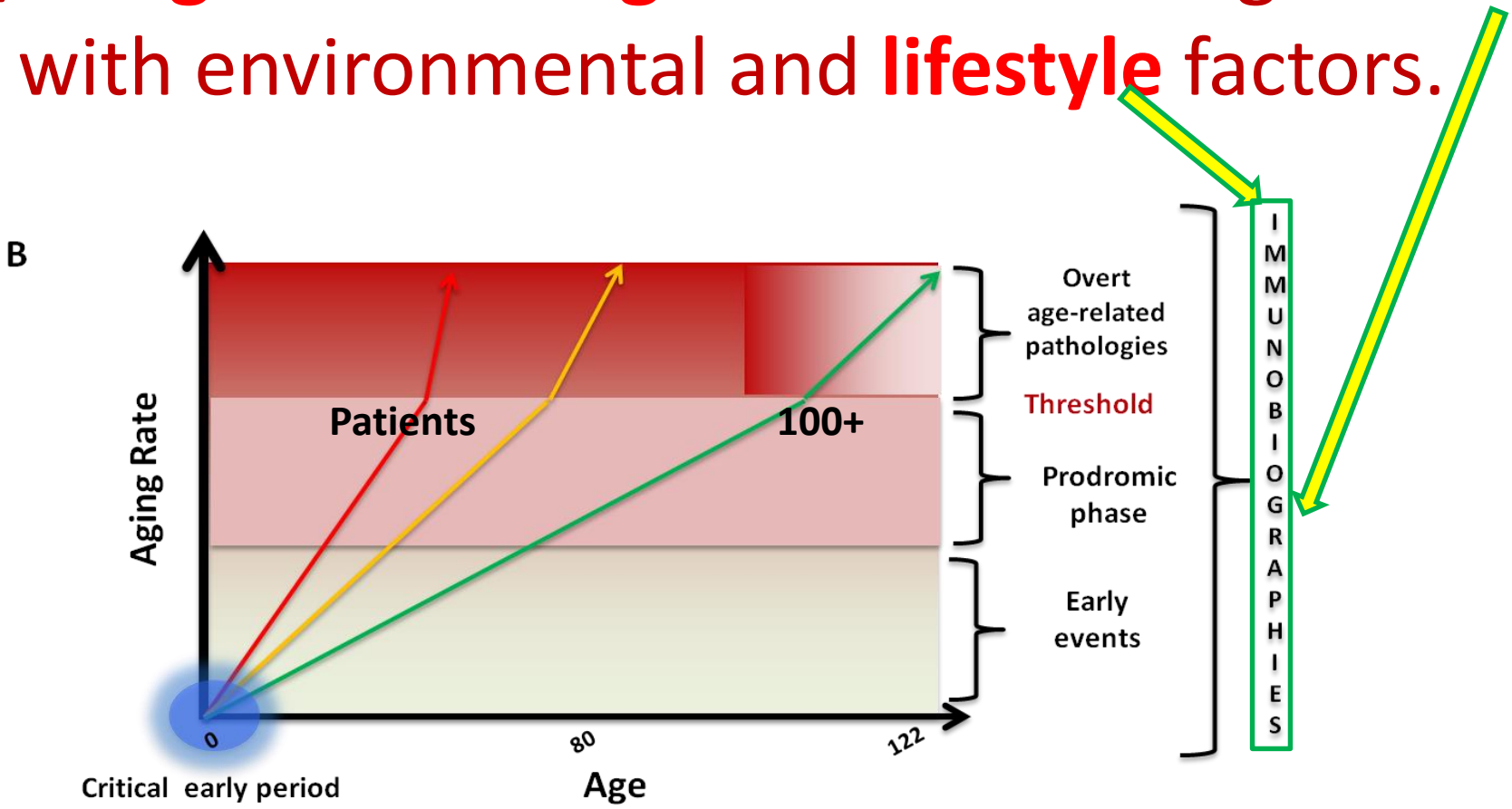
[1] Institute of Neurological Sciences, University of Bologna, Bellaria Hospital, Bologna, Italy, [2] Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy, [3] Clinical Chemistry, Department of Laboratory Medicine, Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden, [4] Applied Biomedical Research Center (CRBA), S. Orsola-Malpighi Polyclinic, Bologna, Italy, [5] CNR Institute of Molecular Genetics, Unit of Bologna, Bologna, Italy, [6] Interdepartmental Center "L. Galvani" (CIG), University of Bologna, Bologna, Italy, [7] Unit and Museum of History of Medicine, Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy, [8] Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy

Is aging a disease?

- Aging, Age-Related Diseases (**ARDs**) and Geriatric Syndromes (**GSs**) are part of **a continuum** without precise boundaries.
- The two extremes are:
  - i) **centenarians** characterized by **decelerated** aging
  - ii) **ARDs/GSs patients** characterized by **accelerated** aging.
- **ARDs and GSs can be considered manifestation of accelerated aging.**

Franceschi et al., Front Med 2018

Whether an individual will follow a trajectory of accelerated or decelerated aging will depend on his/her **genetic background** interacting **lifelong** with environmental and **lifestyle** factors.



Franceschi et al., Nat Rev Endocrinol, 2018

frontiers in Immunology

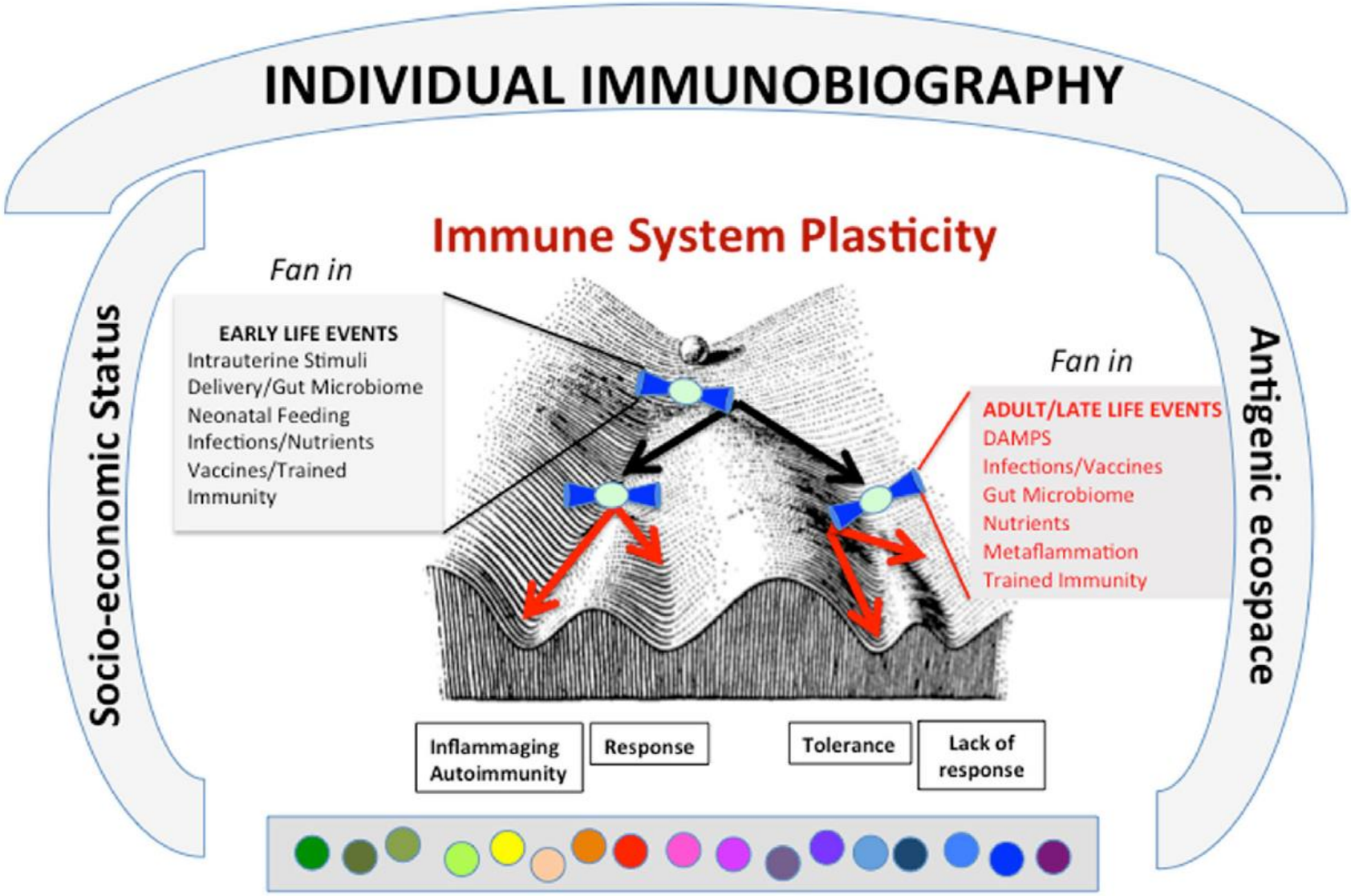
REVIEW
published: 15 August 2017
doi: 10.3389/fimmu.2017.00982

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*

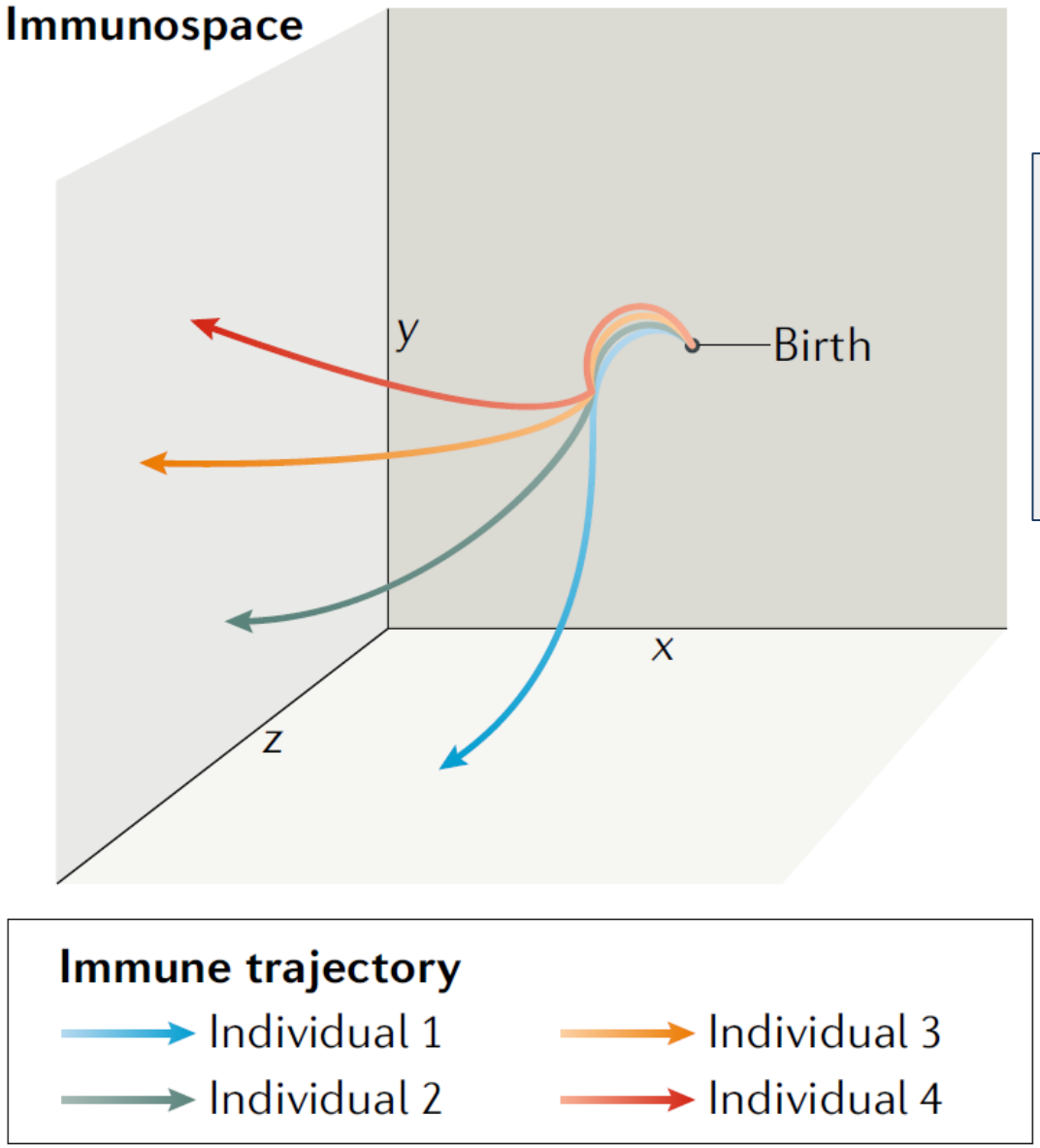
Aging/Inflammaging beyond chronological age



Heterogeneity of Immune Responsiveness & Inflammaging at Population Level

Franceschi et al., Front Immunol 2017

Diverging trajectories of immune system with age



This divergence
is in part explained
by epigenetic changes

Brodin P, Nat Rev Immunol 2019

HETEROGENEITY

Aging beyond chronological age

EPIGENETICS
GLYCOMICS
PROTEOMICS

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,§]

THE EPIGENETIC CLOCK

Steve Horvath (UCLA) in 82 databases on **DNA methylation data** obtained by Illumina platforms 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

Whole genome DNA methylation profile of 105+

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

	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, ECOLOGIA E SCIENZE DELLA TERRA, UNIVERSITÀ DELLA CALABRIA

DATA ANALYSIS:

Paolo Garagnani, Chiara Pirazzini, Steve Horvath

DNAmeth age *versus* Chronological age in 105+ and their offspring

According to the Horvath's DNAmet clock:

- semi-supercentenarians are on average **8.7 years younger** than expected based on chronological age;

- **105+ offspring are 5.2 years younger than age-matched controls (p=0.00051)**
- **In offspring' controls** DNAmethyl age and chronological age overlap

Horvath et al., AGING 2015

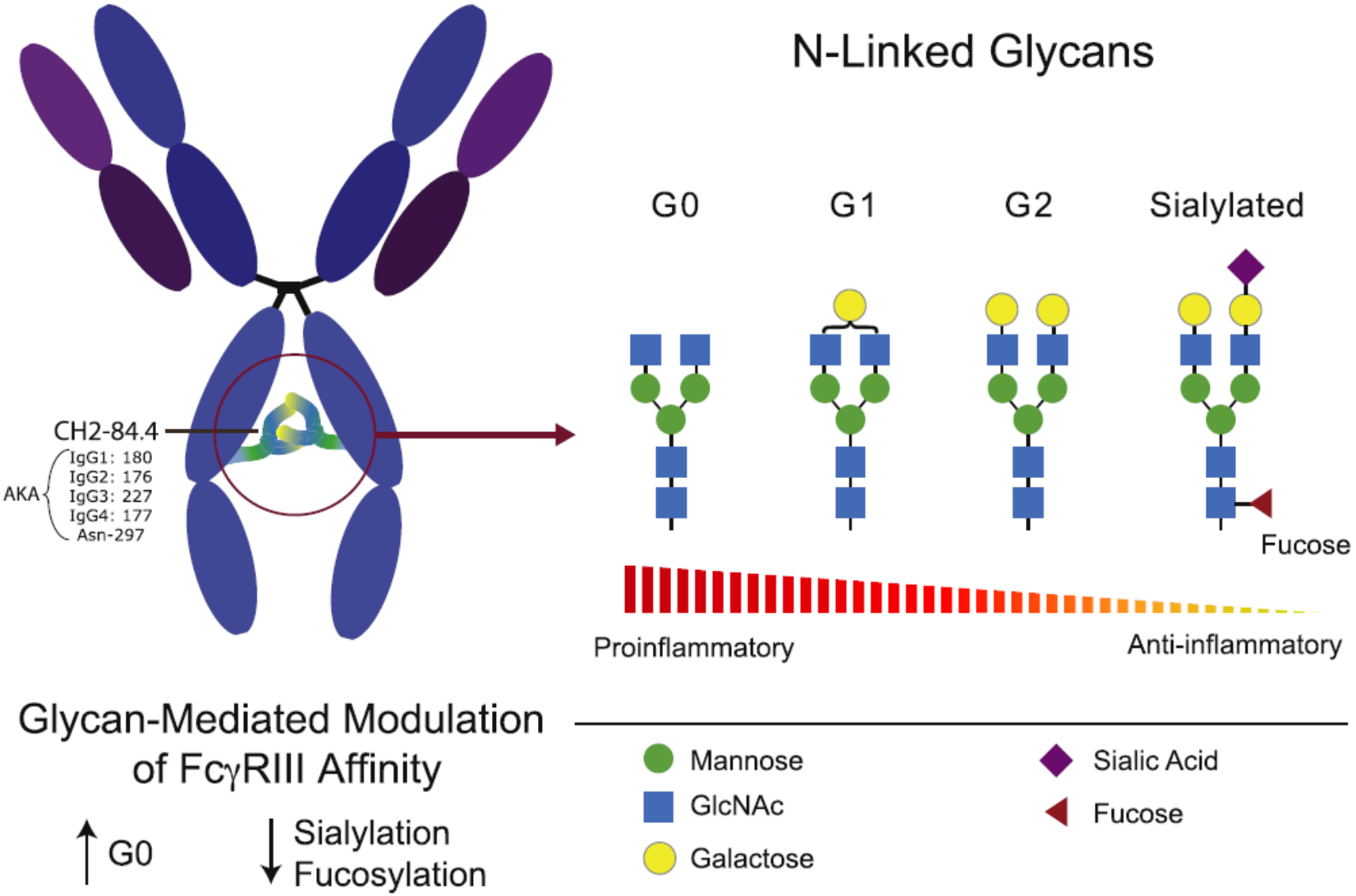
GLYCOMICS

N-glycans profiling appears to be one of the most robust biomarker of biological age

N-Glycomic biomarkers of biological ageing and longevity: a link with inflammaging

Fabio Dall'Olio, Valerie Vanhooren, Cuiying C Chen, P. Eline Slagboom, Manfred Wuhrer & Claudio Franceschi

Ageing Research Reviews 2012



Maverakis et al., 2015

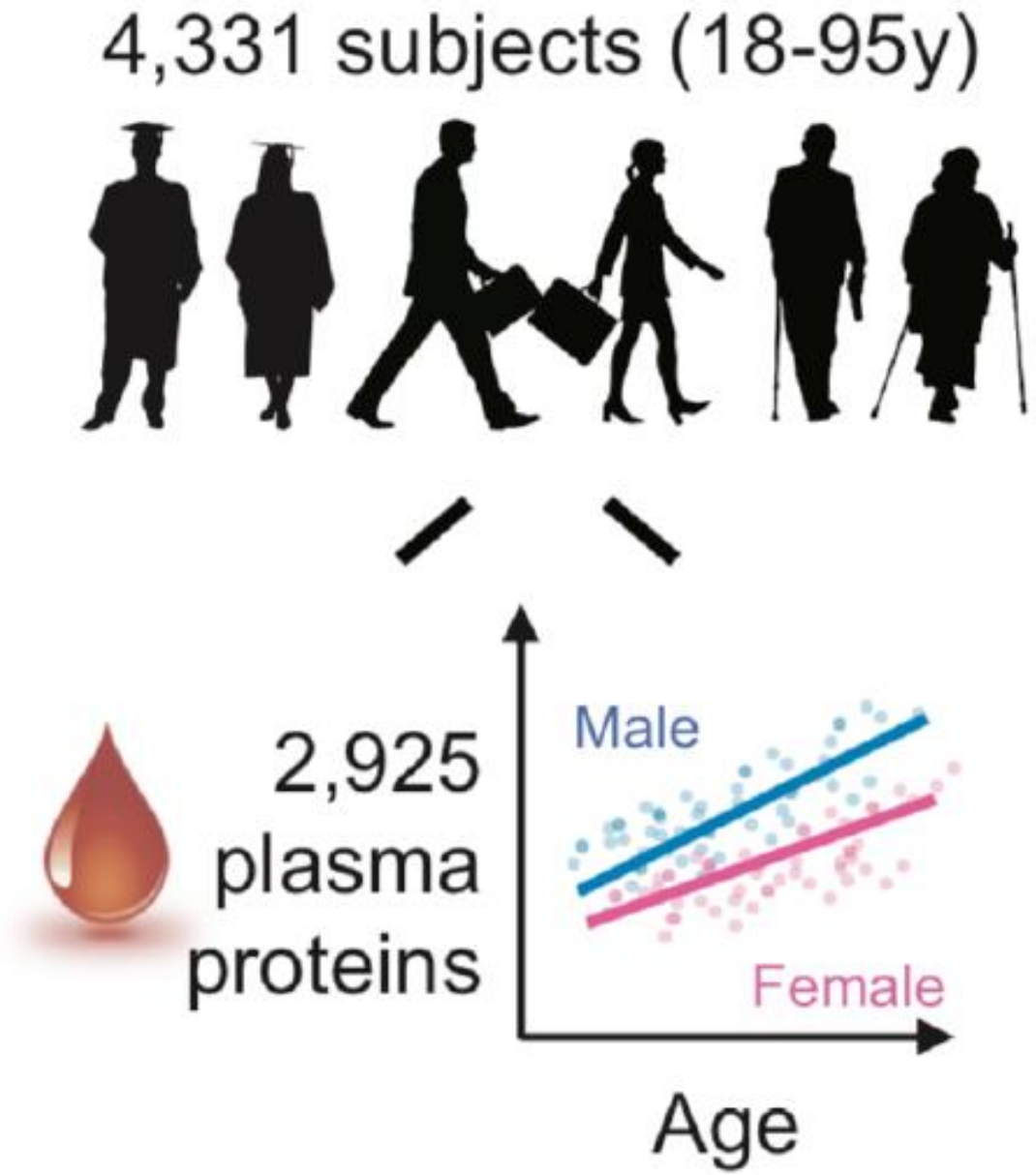
Heterogeneity and non-linearity of the human proteome

Undulating changes in human plasma proteome across lifespan are linked to disease

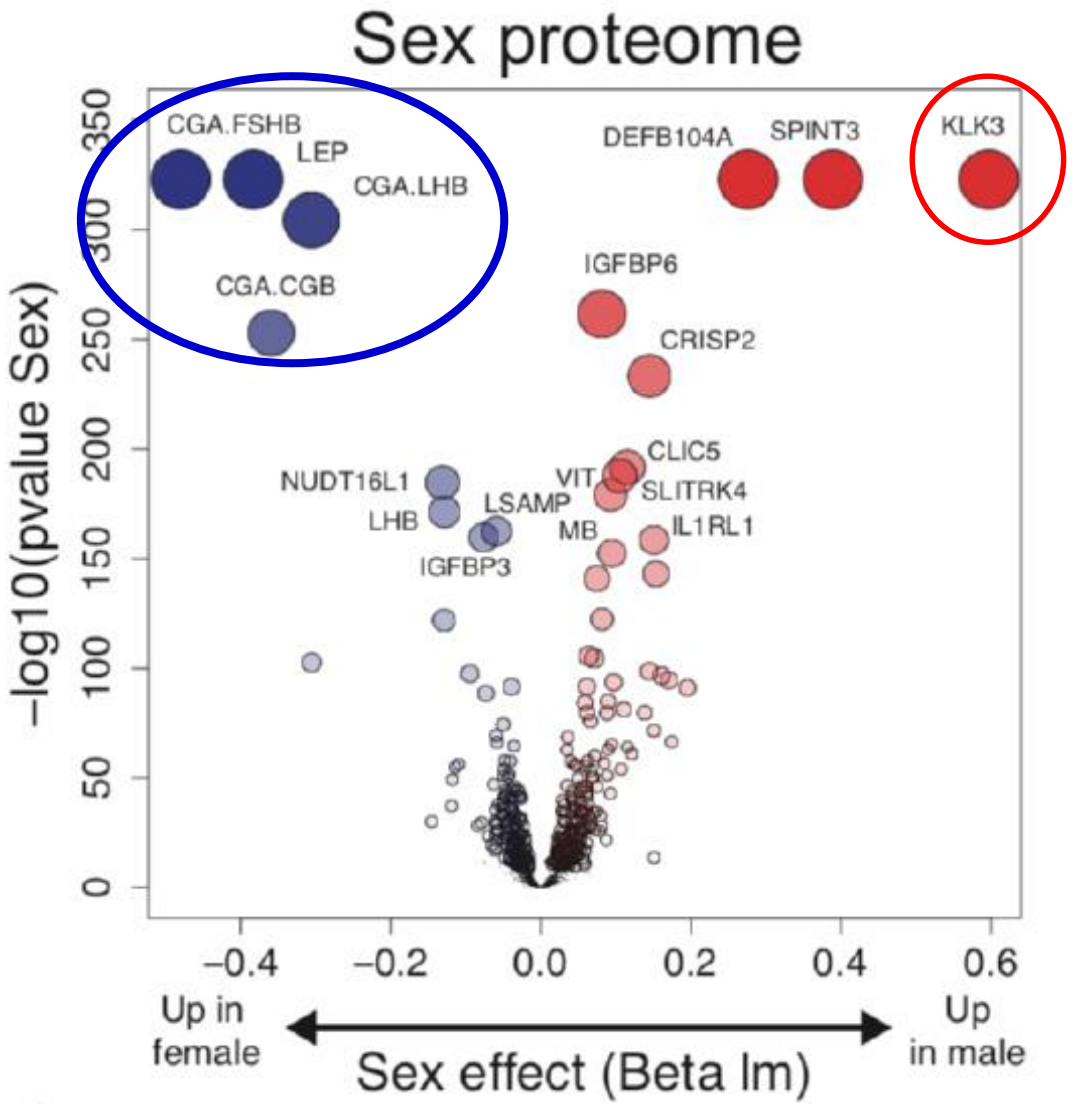
Benoit Lehallier[1,2,3*], David Gate[1,2,3,4], Nicholas Schaum[5], Tibor Nanasi[1,2,3,6], Song Eun Lee[1,2,3,4], Hanadie Yousef[1,2,3,4], Patricia Moran Losada[1,2,3], Daniela Berdnik[1,2,3,4], Andreas Keller[7], Joe Verghese[8,9], Sanish Sathyan[8,9], Claudio Franceschi[10,11], Sofiya Milman[8,12], Nir Barzilai[8,12], Tony Wyss-Coray[1,2,3,4*]

[1]Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA
[2]Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA, USA
[3]Paul F. Glenn Center for the Biology of Aging, Stanford University, Stanford, CA, USA
[4]Department of Veterans Affairs, VA Palo Alto Health Care System, Palo Alto, CA, USA
[5]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University, Stanford, CA, USA
[6]Institute of Cognitive Neuroscience and Psychology, Hungarian Academy of Sciences Research Centre for Natural Sciences, Budapest, Hungary
[7]Clinical Bioinformatics, Saarland University, Saarbrücken, Germany.
[8]Institute for Aging Research, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA
[9]Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA
[10]University of Bologna, Bologna, Italy
[11]National Research Lobachevsky State University of Nizhny Novgorod, Russia
[12]Department of Genetics, Albert Einstein College of Medicine, Bronx, NY, USA

Nature Medicine, accepted


4,331 subjects (18-95y)
2,925
plasma
proteins
Male
Female
Age

Proteins most strongly changed with sex included well-known follicle stimulating hormone (CGA FSHB), human chorionic gonadotropin (CGA CGB), luteinizing hormone (CGA LHB) and prostate-specific antigen (KLK3).

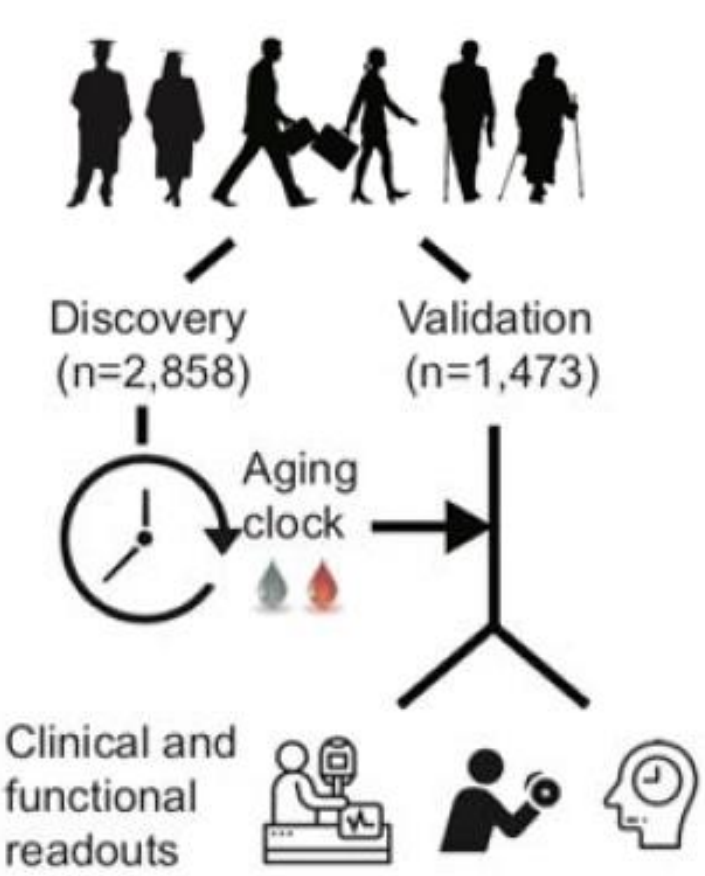


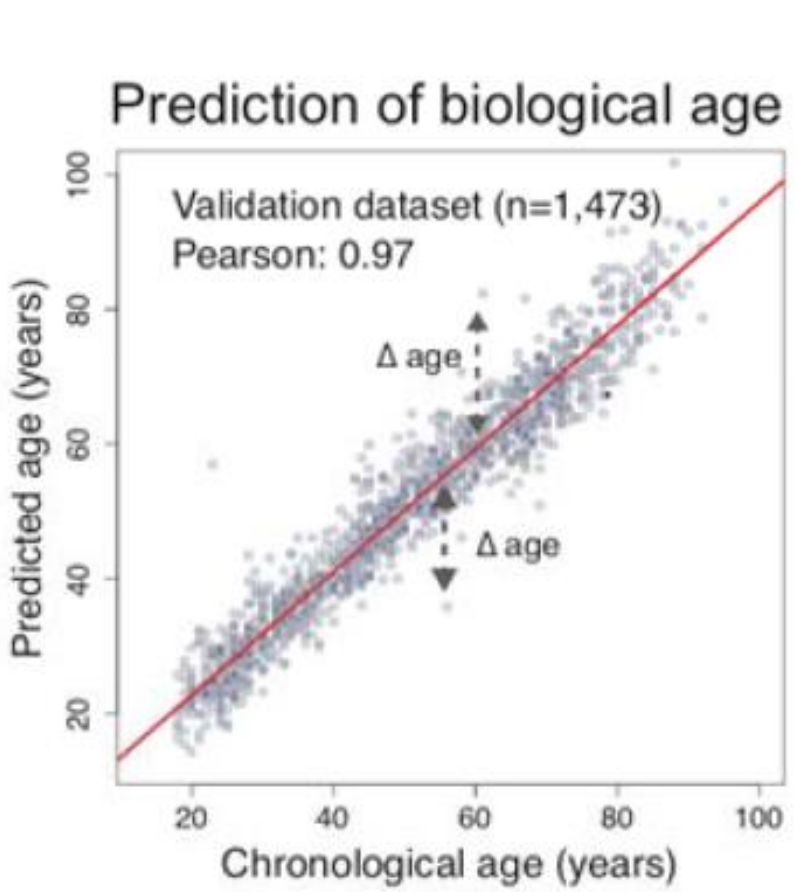
The proteins most strongly associated with age also changed significantly with sex. 895 proteins out of the 1,379 proteins altered with age were significantly different between males and females.

Aging is different in men and women

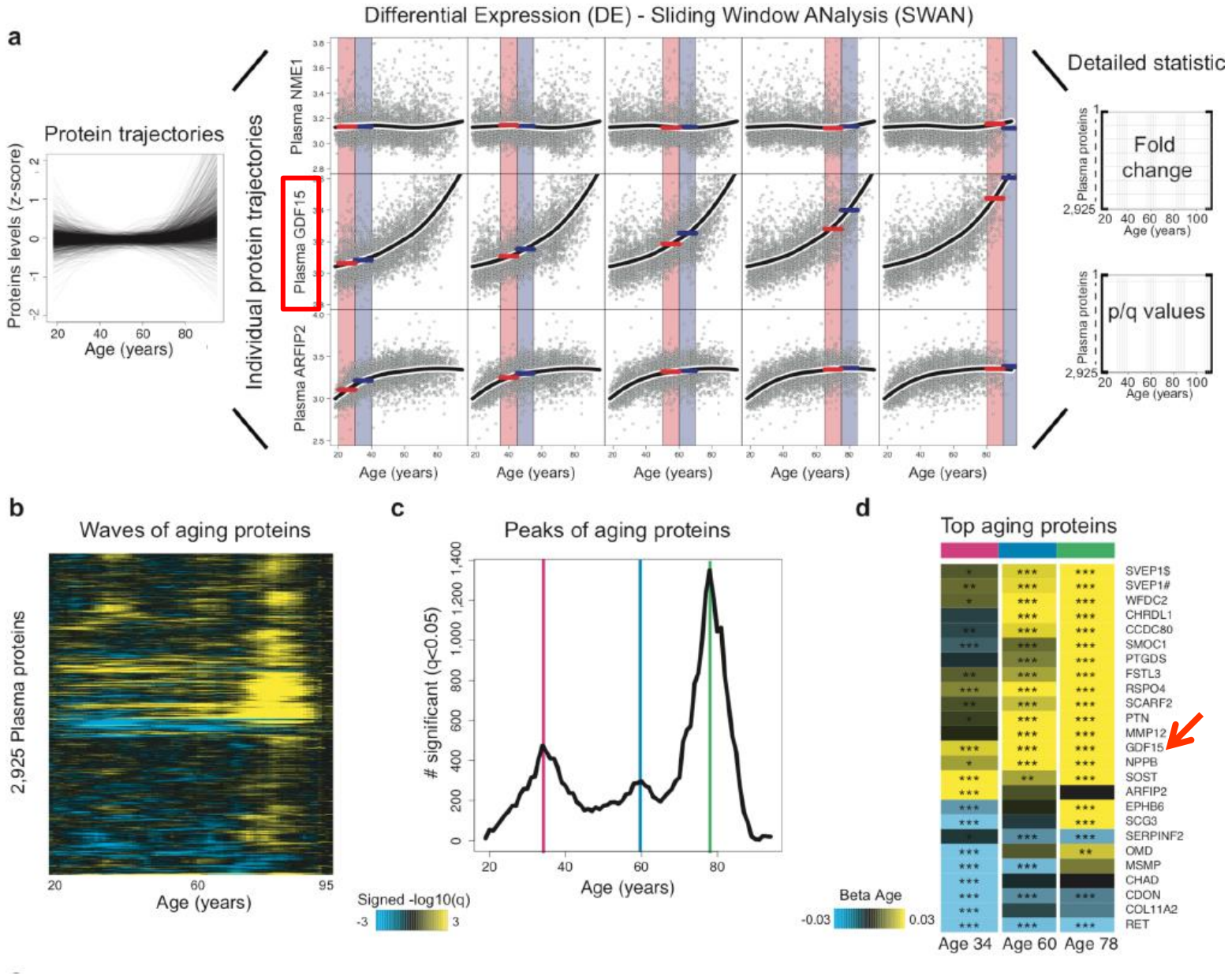
Our results are aligned with a growing number of studies demonstrating that males and females age differently

A sex-independent plasma proteomic clock consisting of 373 proteins

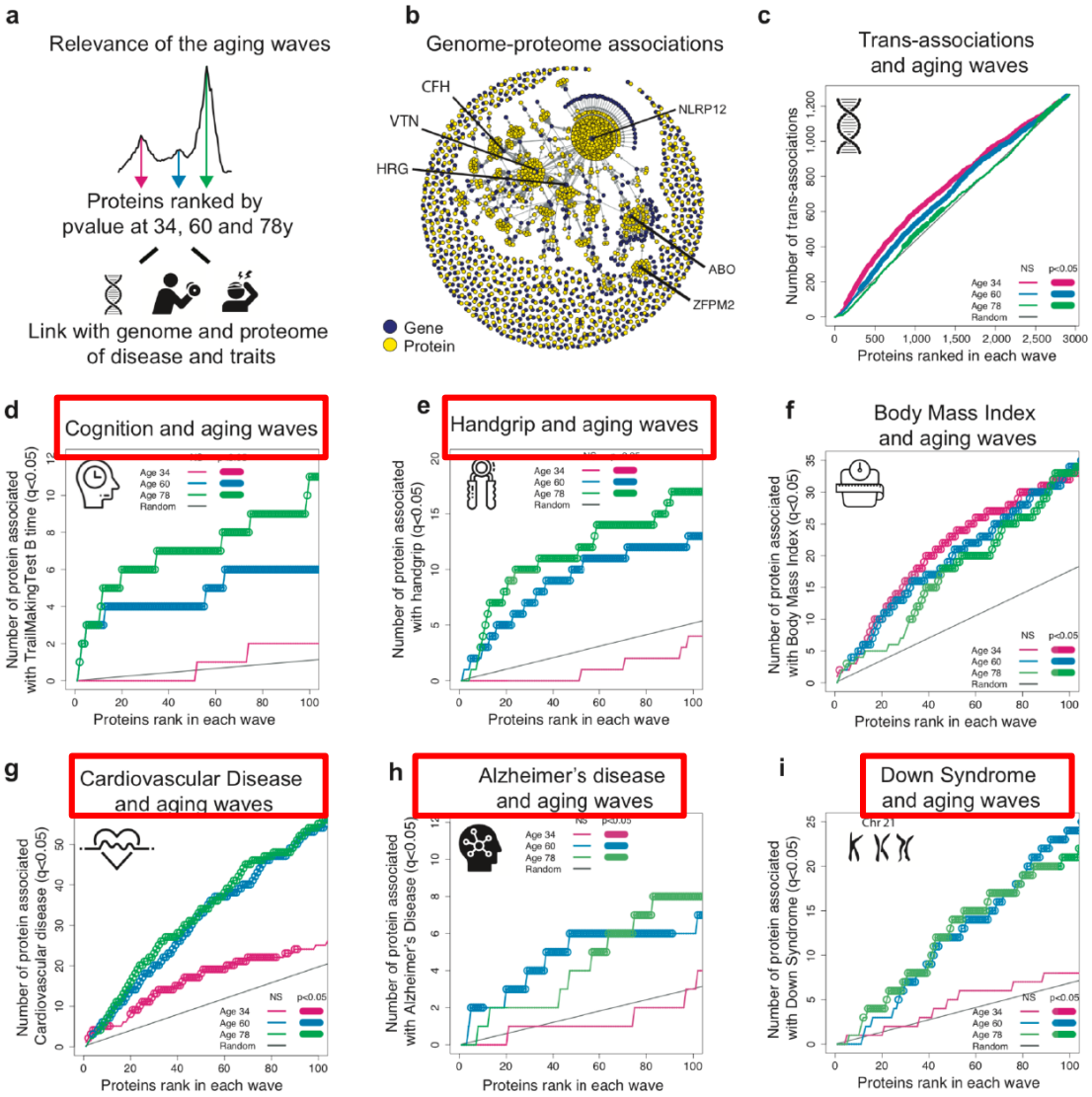




3 crests at ages 34, 60 and 78



Waves of aging proteins are differentially linked to the genome and the proteome of traits and disease



INFLAMMAGING:
an example of adaptation/remodeling

The Inflammatory Theory of Aging

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*

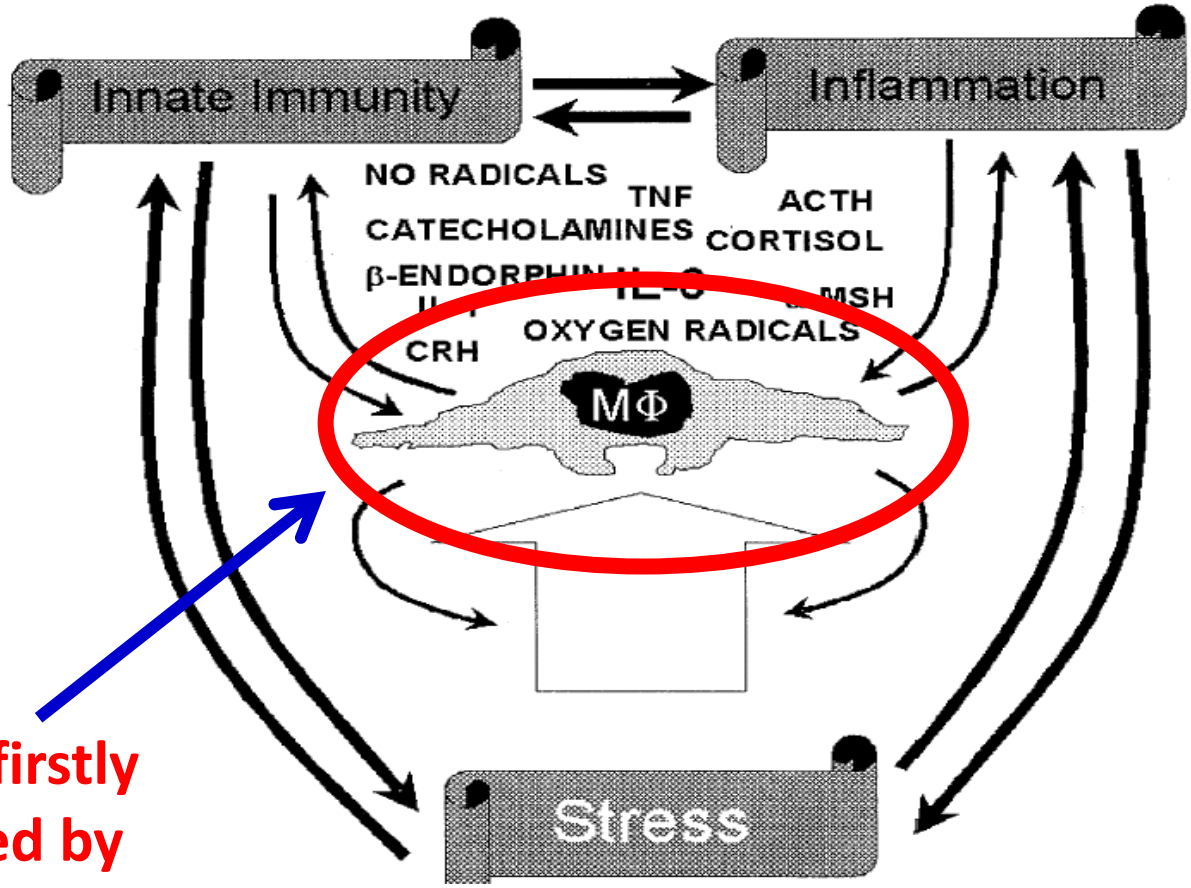
"chronic", "low grade", "sterile"

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

Inflammaging is based on studies on the evolution of immune response and stress from invertebrates to mammals

2645 citations (01/11/2019)

Inflammaging is macrophage-centered



The cell firstly described by Mechnikov

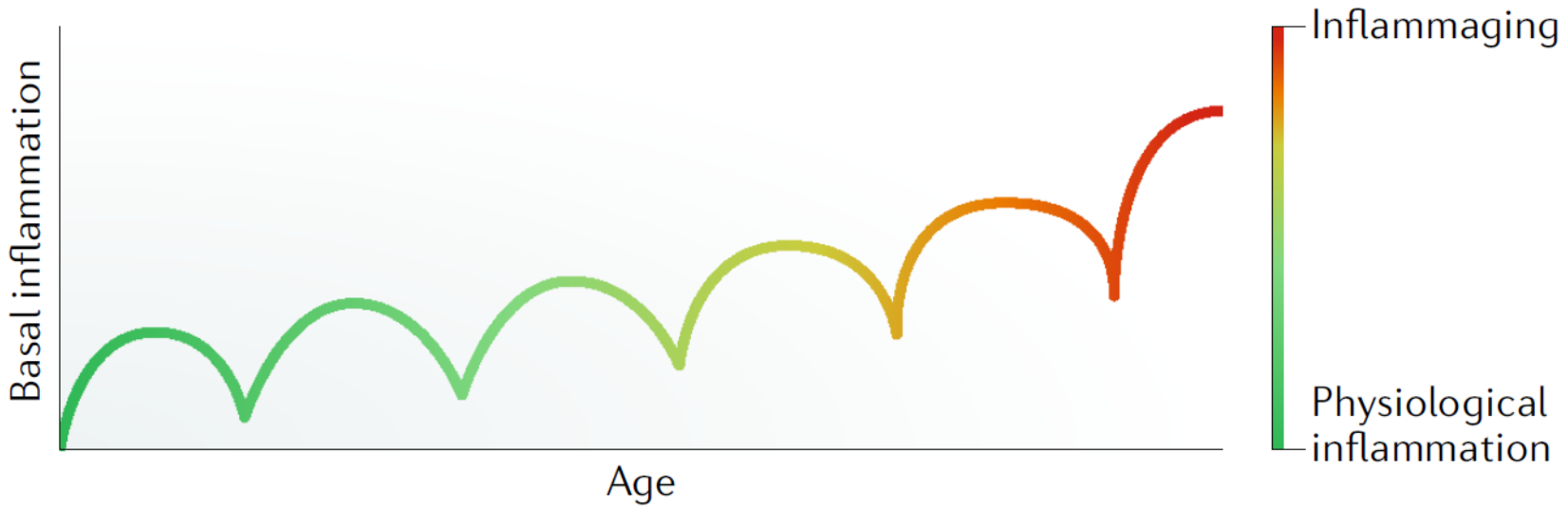
Franceschi et al., 2000

Inflammaging fits the Antagonistic Pleiotropy

Franceschi, Nutr Rev 2007

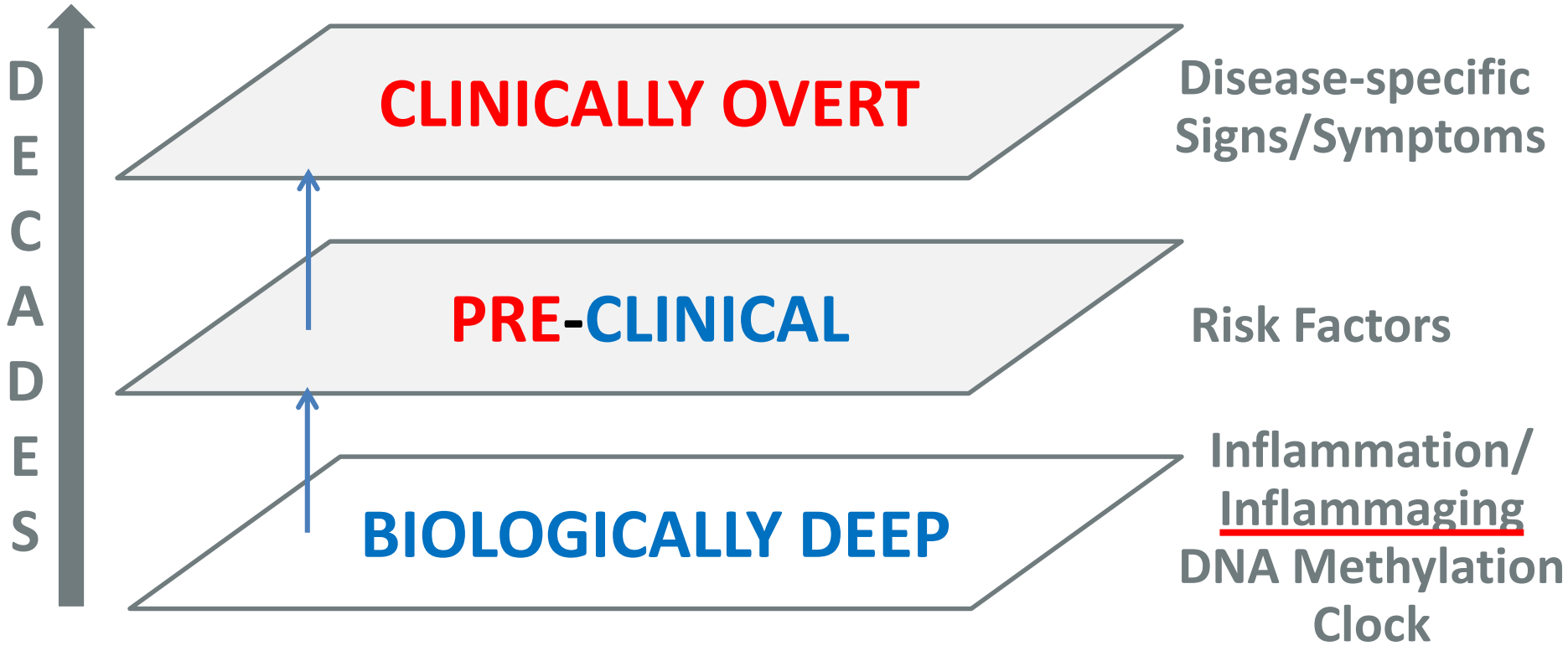
Inflammation is the most important/beneficial, adaptive, evolutionary-conserved response to «damage stimuli», and is crucial for repair/survival

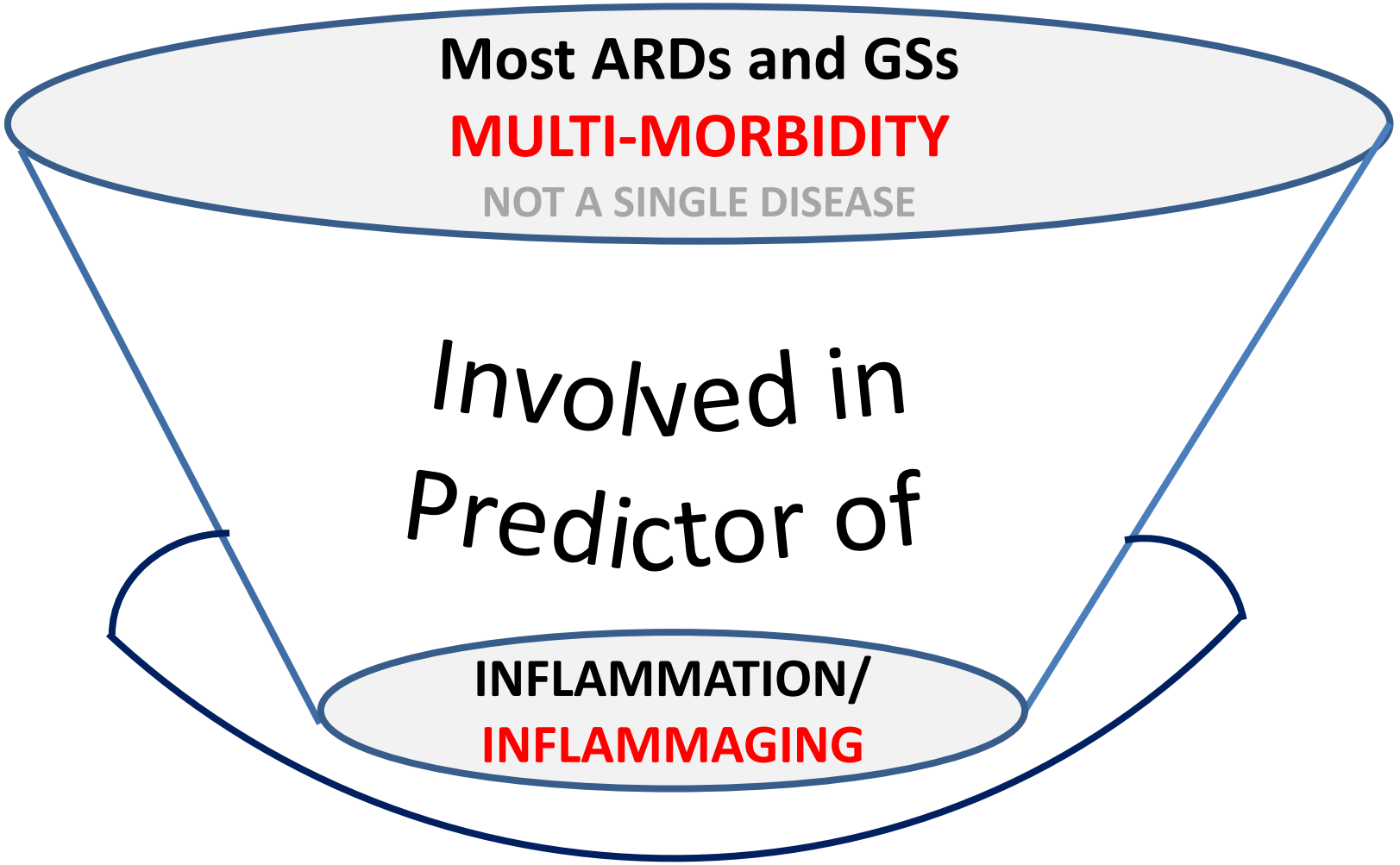
When overstimulated, particularly in the post-reproductive period of life, inflammation can become chronic and detrimental



Franceschi et al., Nat Rev Endocrinol, 2018

ARDs and GSs Layers





the most comprehensive conceptual framework for ARDs and GSs

Inflammaging and Age-Related Diseases (ARD)

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

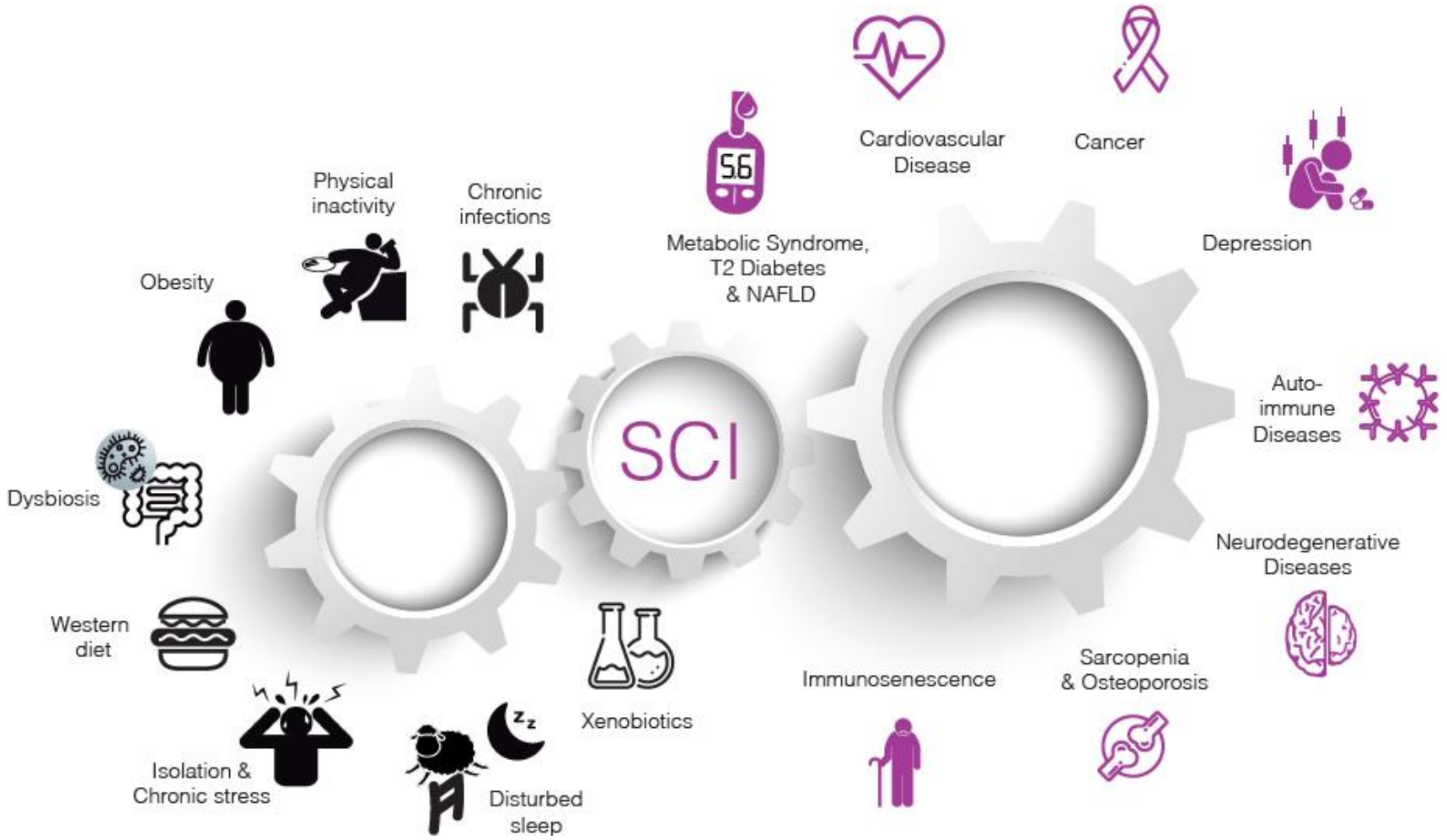
1290 citations (01/11/2019)

Chronic Inflammation in the Etiology of Disease Across the Lifespan

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

Nature Medicine, accepted

SCI=Systemic Chronic Inflammation
A variety of causes/triggers and outcomes (multimorbidity)



Furman et al., 2019

REVIEWS

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 Jul 25

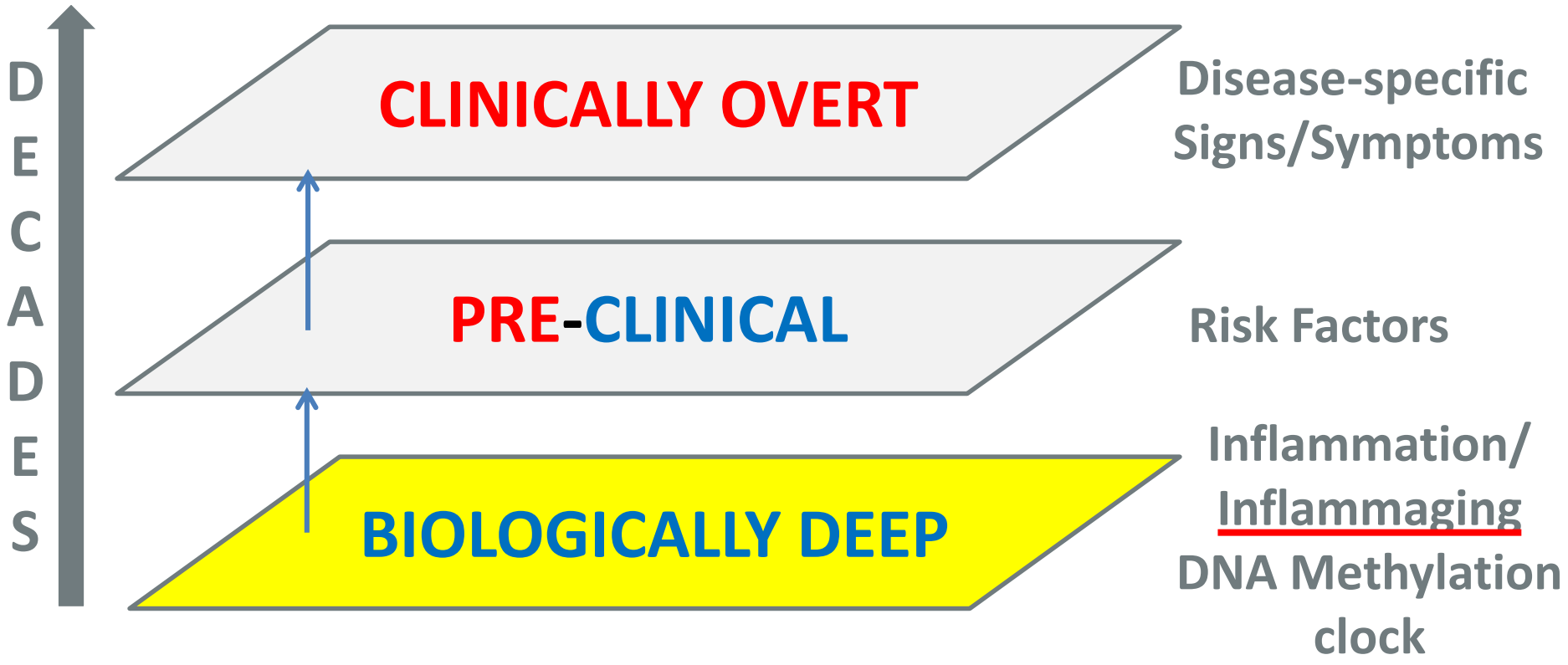
Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty

Luigi Ferrucci[1] and Elisa Fabbri[2]*

NATURE REVIEWS | CARDIOLOGY VOLUME 15 | SEPTEMBER 2018 | 505

Abstract | Most older individuals develop inflammageing, a condition characterized by elevated levels of blood inflammatory markers that carries high susceptibility to chronic morbidity, disability, frailty, and premature death. Potential mechanisms of inflammageing include genetic susceptibility, central obesity, increased gut permeability, changes to microbiota composition, cellular senescence, NLRP3 inflammasome activation, oxidative stress caused by dysfunctional mitochondria, immune cell dysregulation, and chronic infections. Inflammageing is a risk factor for cardiovascular diseases (CVDs), and clinical trials suggest that this association is causal. Inflammageing is also a risk factor for chronic kidney disease, diabetes mellitus, cancer, depression, dementia, and sarcopenia

Levels of ARDs and GSs



INFLAMMAGING & GARB-AGING

the role of molecular garbage

Major inflammatory stimuli

Non Self

- **Pathogens Nucleic Acids** viruses,
- bacteria, parasites and their products
- Pollutants

Quasi Self

- Nutrients and their metabolic products
- **Gut microbiota products**

Self

- Cell debris , AGEs
- Misplaced/Misfolded/Modified proteins
- **Misplaced Self Nucleic acids**

A change of paradigm: **the enemy from within**

Trends in Endocrinology & Metabolism 2017

Review

Inflammaging and 'Garb-aging'

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

CELLULAR AND MOLECULAR GARBAGE: cell debris (resulting from cell death), misplaced/altered/oxidized molecules, Gut Microbiota products , internal exposome metabolic products…

Endogenous/Self Molecular Garbage

- In human body over 50-70 billion cells die each day;
- NECROPTOSIS & PYROPTOSIS increase with age;

The overall result is:

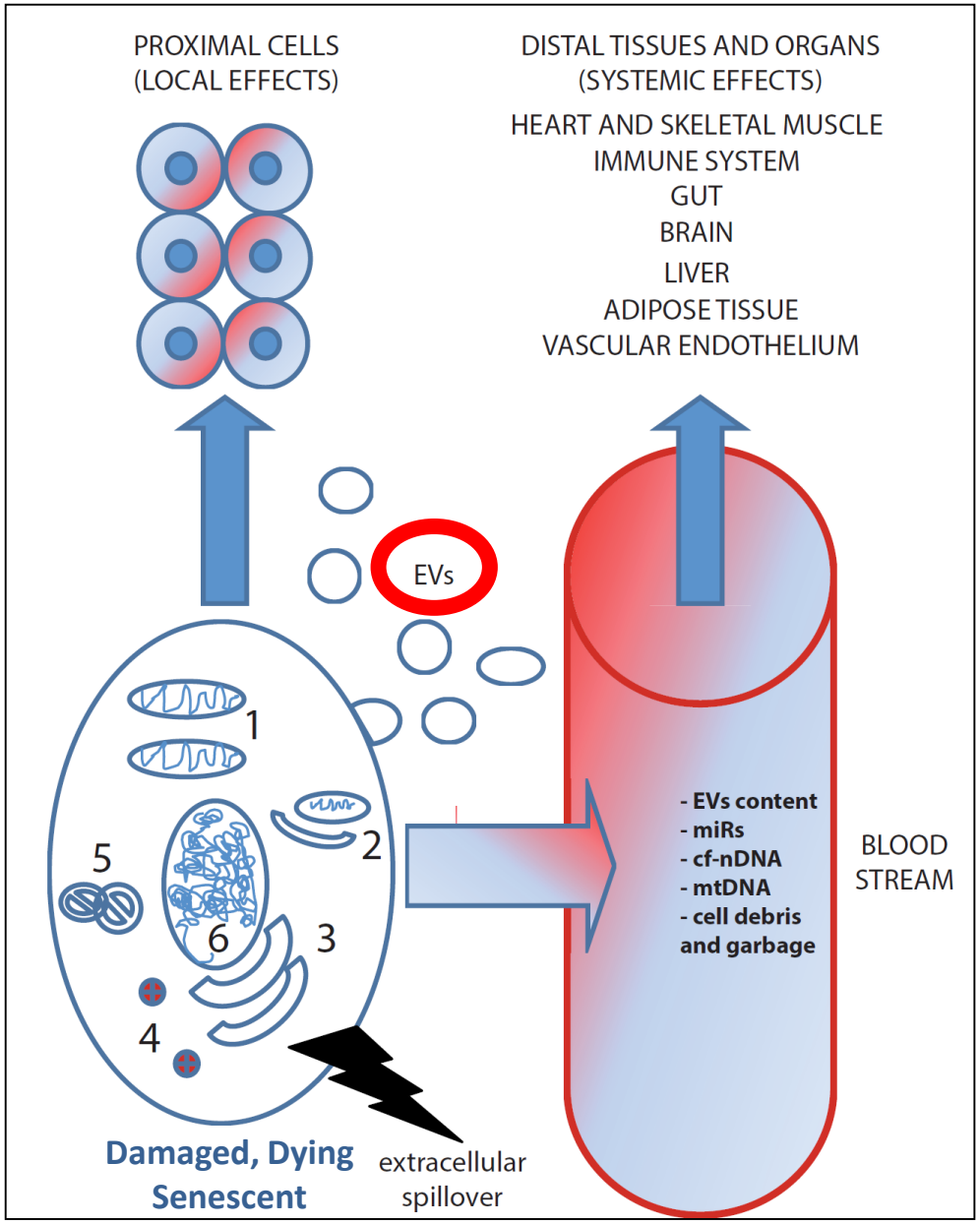
- an increased production of DAMPs (Damage-Associated Molecular Patterns);
- a large misplacing of proteins and nucleic acids.

The clearance of such molecular garbage is imperative!

Normal cell components (Self) sensed as inflammatory DAMPs when misplaced

DAMPS	Origin	Engaged receptors	REF
mtDNA	Mitochondria	TLR9, NLRPs	[53,54,58]
N-formyl peptides	Mitochondria	Formyl peptide receptor-1, NLRPs	[106]
Cardiolipin	Mitochondria	NLRPs	[56]
Histones	Nucleus	TLRs	[107]
High Mobility Group Box 1 protein (HMGB1)	Nucleus	RAGE, NLRPs, TLR4	[57,74]
Nuclear DNA (CpGs)	Nucleus	TLR9	[108]
Heat Shock Proteins (e.g. HSPA1A, HSP90AA1); ER chaperons (CRT, ERp57, GP96)	Cytoplasm, mitochondria, Endoplasmic reticulum	TLR2, TLR4, NLRPs	[45,109,110]
Cathepsin B	Lysosomes	NLRPs	[58]
Triphosphate nucleotides (ATP, UTP)	Cytoplasm	NLRPs	[45]
S100 proteins (including S100a8, a9 and a12)	Cytoplasm – granules (neutrophils)	RAGE, TLR4, TLR9	[57,75]
Lipids (fatty acids, ceramides)	Cytoplasm, membranes	TLR4, NLRPs	[58,111]
Crystals (e.g. monosodium urate, cholesterol crystals, calcium pyrophosphate dihydrate)	Cytoplasm	NLRPs, TLR2, TLR4, CD14	[45,57]
Hyaluronans	Extracellular matrix	NLRPs	[45]
Altered N-glycans	Serum proteins	DC-SIGN, MBR	[112]

Franceschi et al., Trends in Endocrinol. Metab. 2017



Inflammaging & aging propagate among cells and organs (like a fire or an infectious diseases)

EV= Extracellular Vesicles

Franceschi *et al.*, Trends in Endocrinology and Metabolism, 2017

European Journal of Immunology

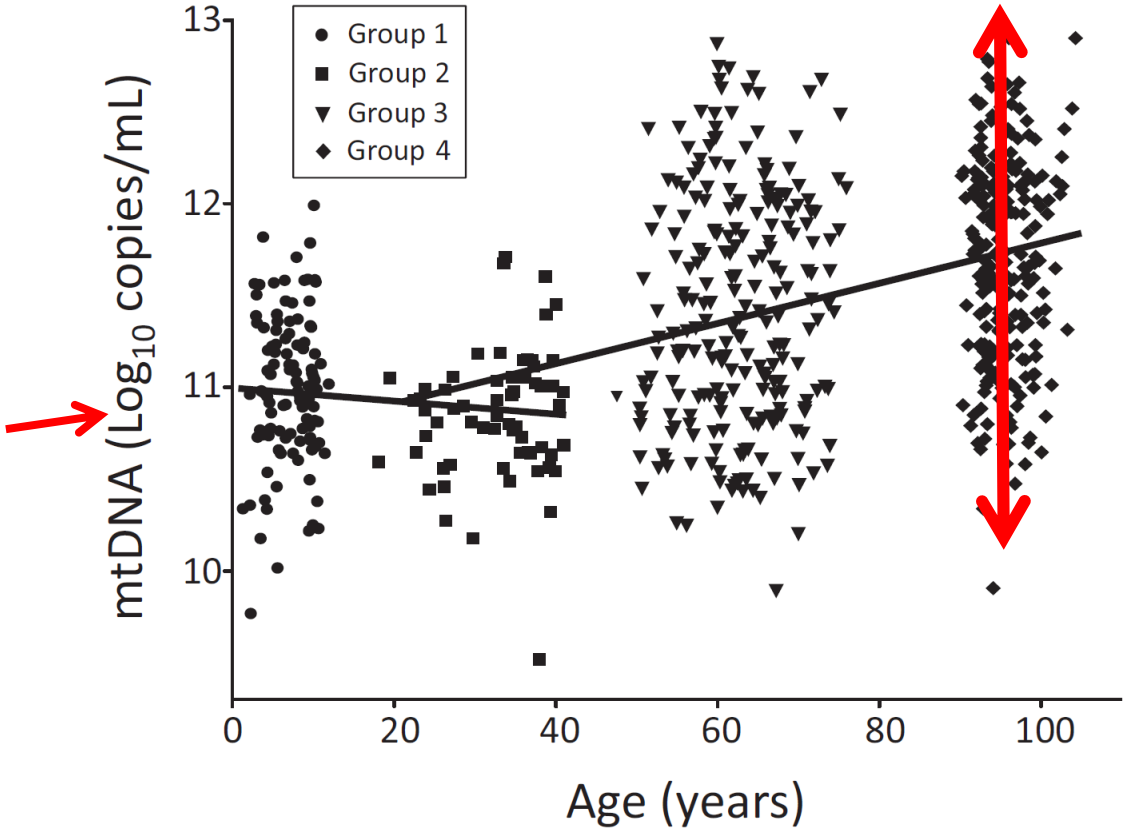
EJI 2014

Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for "inflamm-aging"

Marcello Pinti[*1], *Elisa Cevenini*[*2,3], *Milena Nasi*[4], *Sara De Biasi*[4], *Stefano Salvioli*[2,3], *Daniela Monti*[5], *Stefania Benatti*[1], *Lara Gibellini*[4], *Rodolfo Cotichini*[6,7], *Maria Antonietta Stazi*[6], *Tommaso Trenti*[8], *Claudio Franceschi*[2,3] *and Andrea Cossarizza*[4]

- **Circulating mtDNA is a powerful inflammatory stimulus** contributing to inflammaging.
- The number of copies of circulating mtDNA is significantly correlated between siblings, suggesting that **it is a familial/genetic trait**.

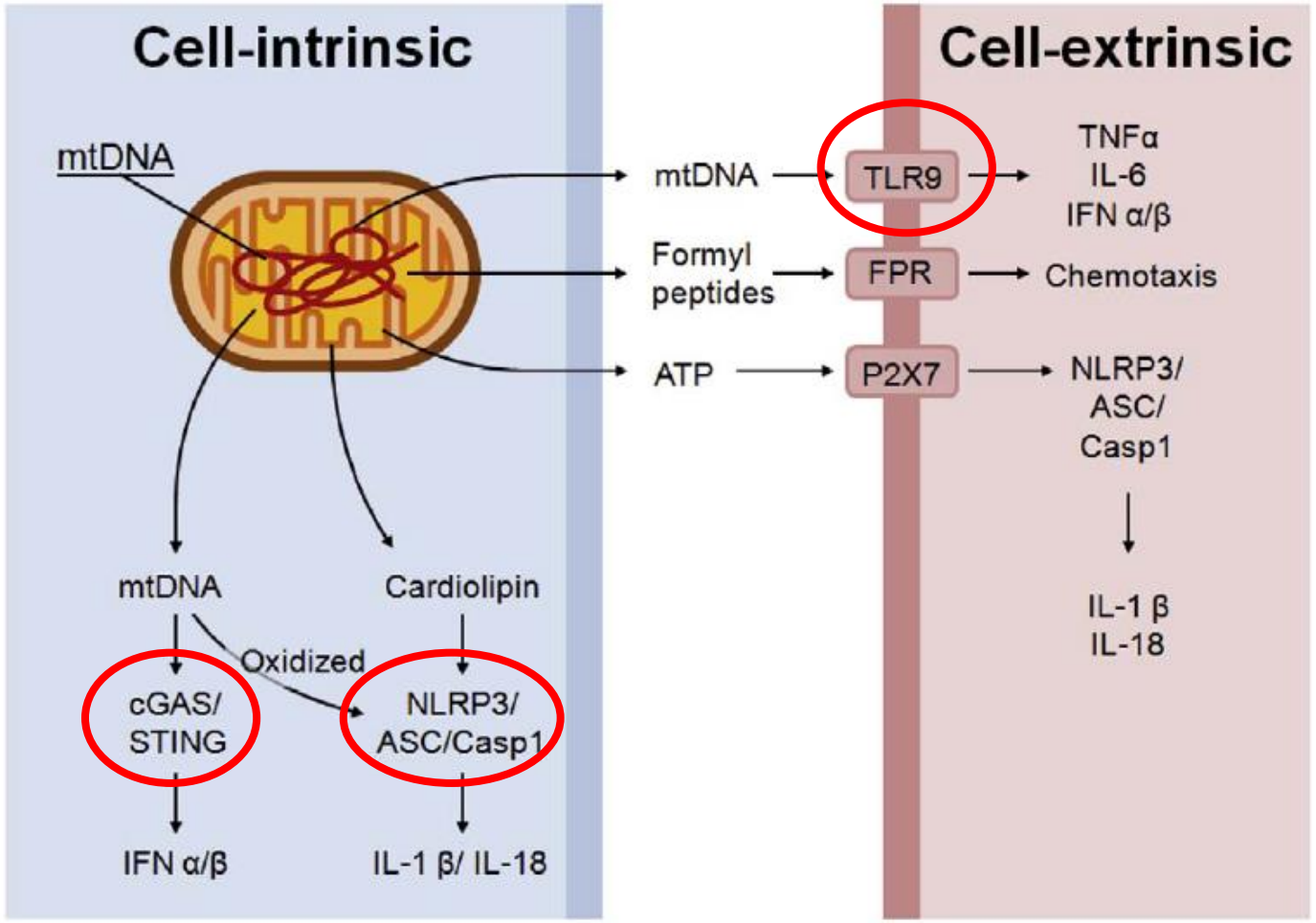
Age-related increase of circulating mtDNA plasma level in the different age groups. Data are generated from 831 samples, and are expressed as $\log_{10}$ mtDNA copies/mL of plasma.



90+ siblings belonging to 191 sibships

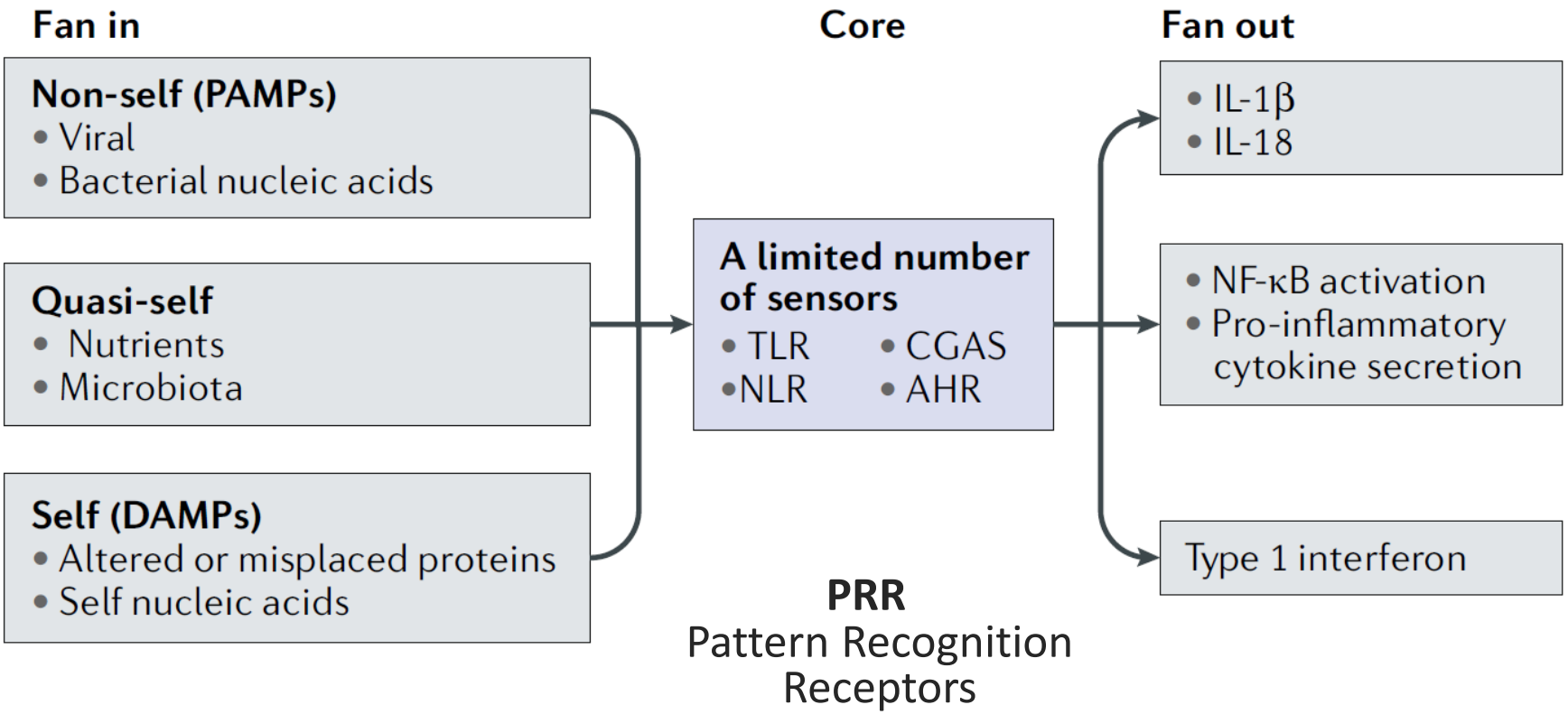
Linear Regression for log 10 mt DNA by age

Groups	Number of obs.	R-squared	Beta Co eff.	Age p	95% CI	
Group 1 and 2	171	0.0215	-0.0045	0.055	-0.0091	0.0001
Group 2, 3 and 4	516	0.1590	0.0115	<0.001	0.0092	0.0138

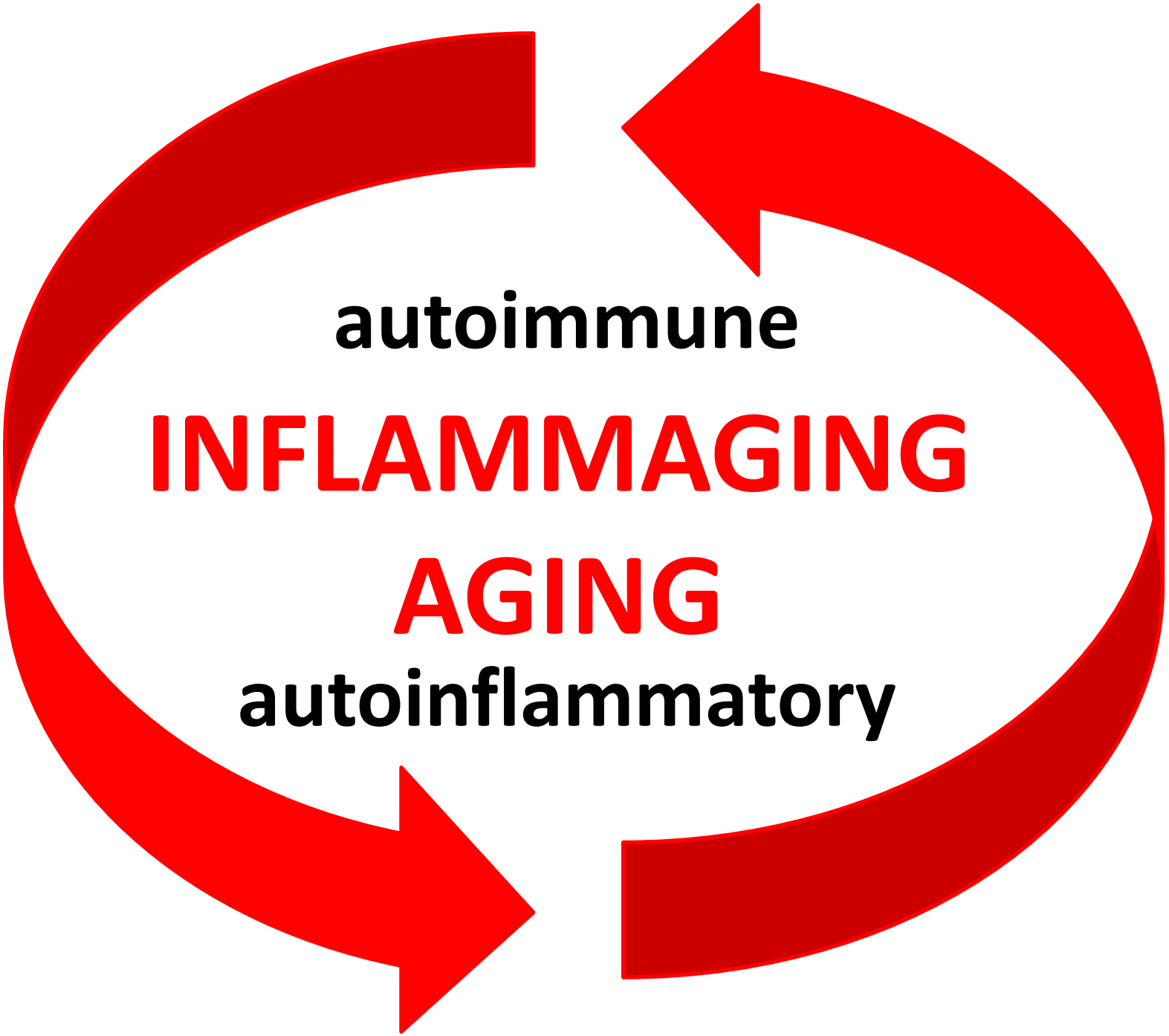


Rongvaux, A., *Mitochondrion* 2017

Molecular garbage converges on a limited number of DANGER/DAMAGE SENSORS characterized by a high degree of "DEGENERACY"



Franceschi et al., Nat Rev Endocrinol, 2018


autoimmune
INFLAMMAGING
AGING
autoinflammatory

Centenarians have a peculiar INFLAMMAGING

Fulvia, 109 years
Sarzana (Italy)

We surmised
that a possible main reason
why 100+ are 100+
is because they are
capable of reaching an
optimal balance between
pro- (CRP, IL-6, TNFα) &
anti-inflammatory (TGFβ,
Cortisol, IL-1RA,
Adiponectin) molecules

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 suggested that the age-related increase of pro-inflammatory molecules likely stimulates a corresponding adaptive increase of anti-inflammatory molecules

Cell Death Differ. 2019 Jan 8.

Cell Death & Differentiation

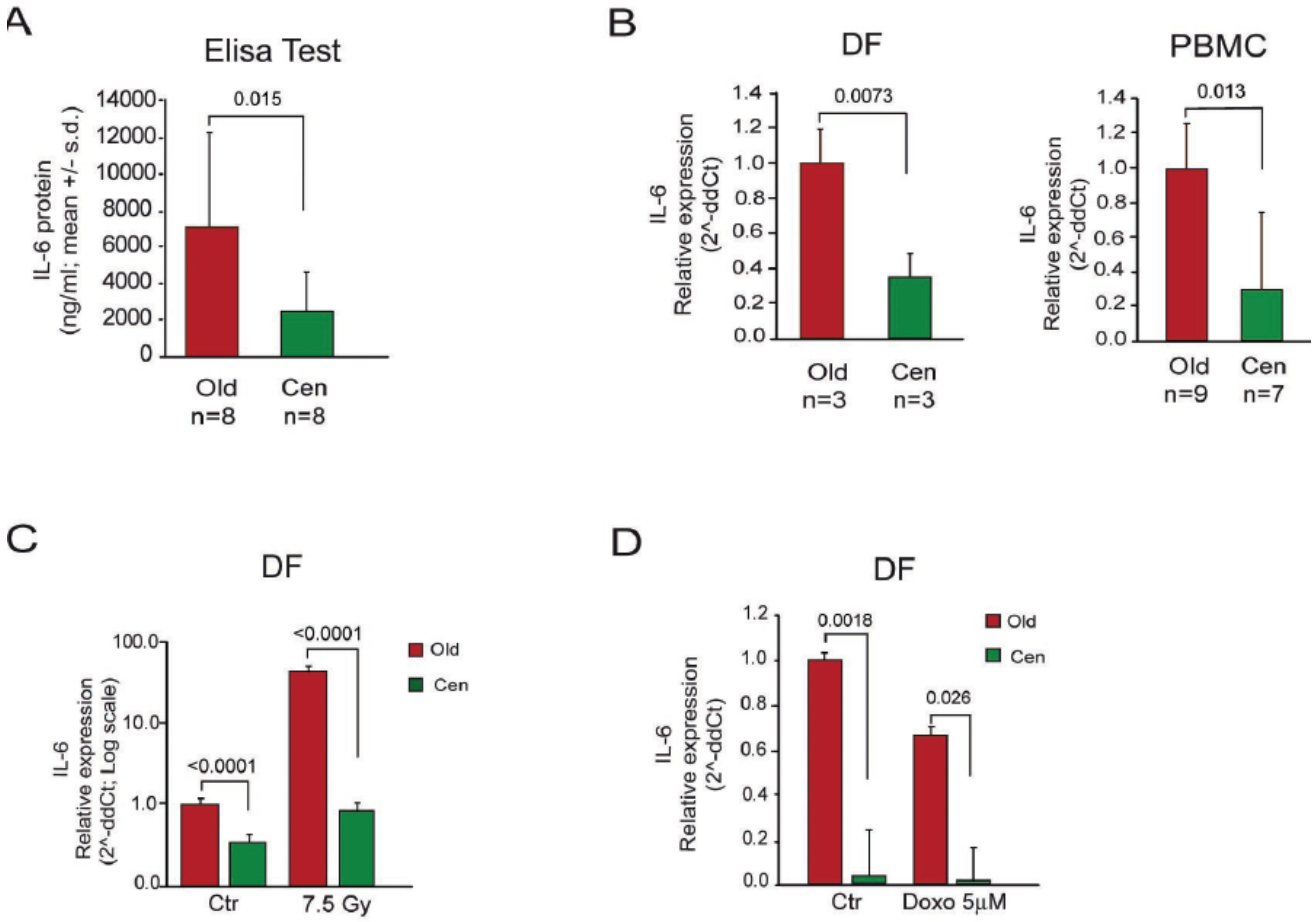
ARTICLE

Genomic stability, anti-inflammatory phenotype, and up-regulation of the RNAseH2 in cells from centenarians

Gianluca Storci[1,2,3] · Sabrina De Carolis[1,3] · Alessio Papi[4] · Maria Giulia Bacalini[5] · Noémie Gensous[1] · Elena Marasco[1] · Anna Tesei[6] · Francesco Fabbri[6] · Chiara Arienti[6] · Michele Zanoni[6] · Anna Sarnelli[7] · Spartaco Santi[8,9] · Fabiola Olivieri[10,11] · Emanuela Mensà[10] · Silvia Latini[10] · Manuela Ferracin[1] · Stefano Salvioli[1] · Paolo Garagnani[1] · Claudio Franceschi[5] · Massimiliano Bonafè[1,3,6]

Here, we report on the anti-inflammatory molecular make-up of centenarian's fibroblasts and PBMC (low levels of IL-6, type 1 interferon beta, and pro-inflammatory microRNAs), which is coupled with low level of DNA damage (measured by comet assay and histone-2AX activation) and preserved telomere length.

Low production of IL-6 by centenarians' cells in basal conditions and after exposure to physical and chemical stressors

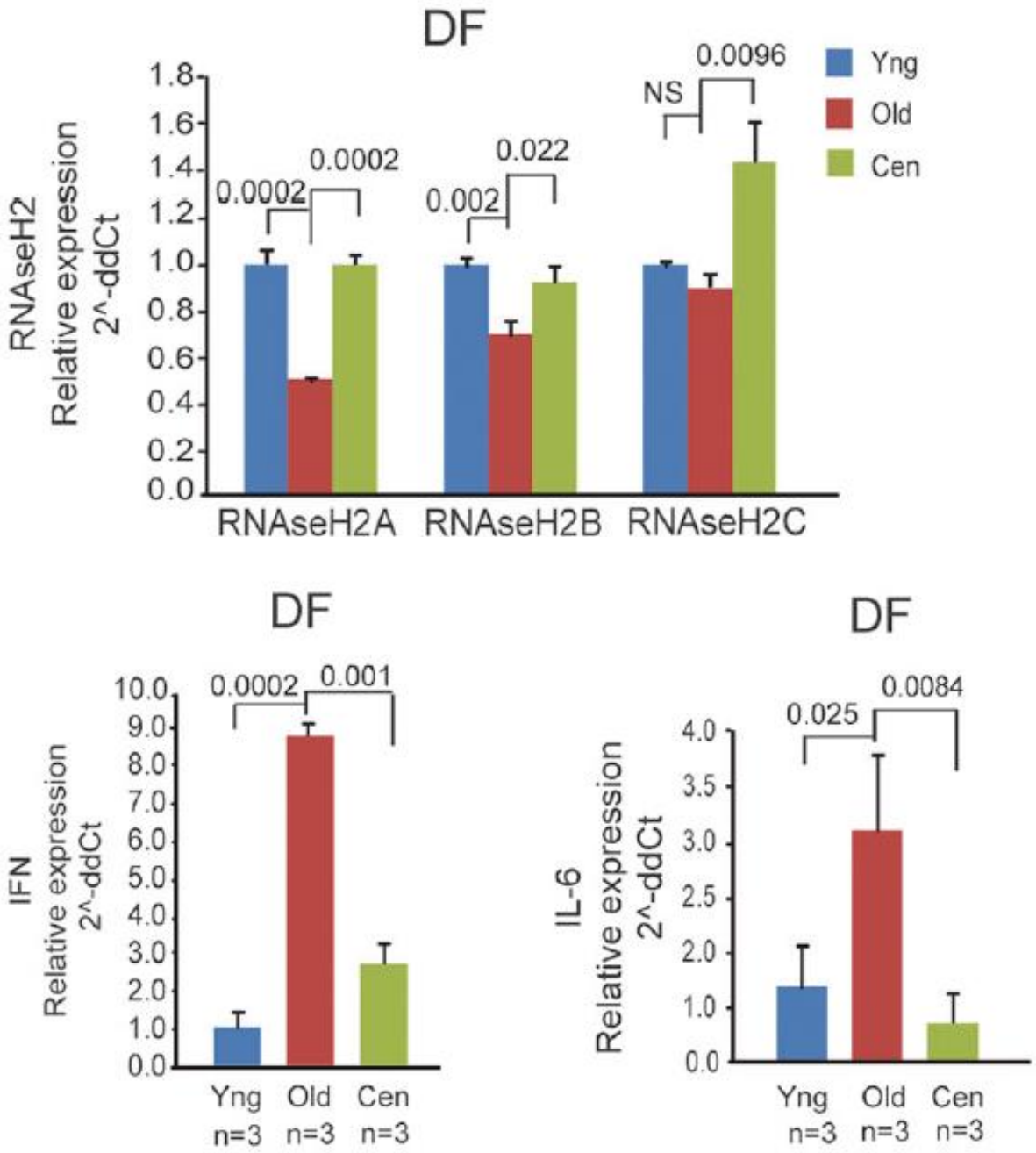


Storci et al., Cell Death & Differentiation, 2019

The anti-inflammatory phenotype of 100+

- **High levels of the RNAseH2** enzyme subunit and low amounts of RNAseH2 substrates, i.e. inflammatory cytoplasmic RNA:DNA hybrids, are present in centenarian's fibroblasts, .
- **Extracellular vesicles from centenarian's cells propagate their anti-inflammatory phenotype** to fibroblasts, myeloid, and cancer cells up-regulating RNAseH2C expression

Storci et al., CDD 2019


DF
RNAseH2
Relative expression
2^-ddCt
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0002
0.0002
0.002
0.022
NS
0.0096
Yng
Old
Cen
RNAseH2A
RNAseH2B
RNAseH2C
DF
IFN
Relative expression
2^-ddCt
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.0002
0.001
Yng
n=3
Old
n=3
Cen
n=3
DF
IL-6
Relative expression
2^-ddCt
4.0
3.5
3.0
2.5
2.0
1.0
0.0
0.025
0.0084
Yng
n=3
Old
n=3
Cen
n=3

AGS as a model

- The Aicardi–Goutières syndrome is a genetic encephalopathy that is associated with childhood illness and death. The syndrome is hypothesized to be due to **misidentification of self-derived nucleic acids as nonself** and the sub-sequent induction of a type I interferon–mediated response that simulates an antiviral reaction.
- **Endogenous retroelements**, mobile genetic elements that can be transcribed to RNA and then to DNA by reverse transcription, **constitute 40% of the human genome and represent a potential source of immunostimulatory nucleic acid** in patients with this syndrome

RNase H2 catalytic core Aicardi-Goutières syndrome–related mutant invokes cGAS–STING innate immune-sensing pathway in mice

Vladislav Pokatayev,[1,2*] Naushaba Hasin,[3*] Hyongi Chon,[3] Susana M. Cerritelli,[3] Kiran Sakhuja,[3] Jerrold M. Ward,[4] H. Douglas Morris,[5] Nan Yan,[1,2**] and Robert J. Crouch[3**]

J Exp Med. 2016 Mar 7;213(3):329-36.

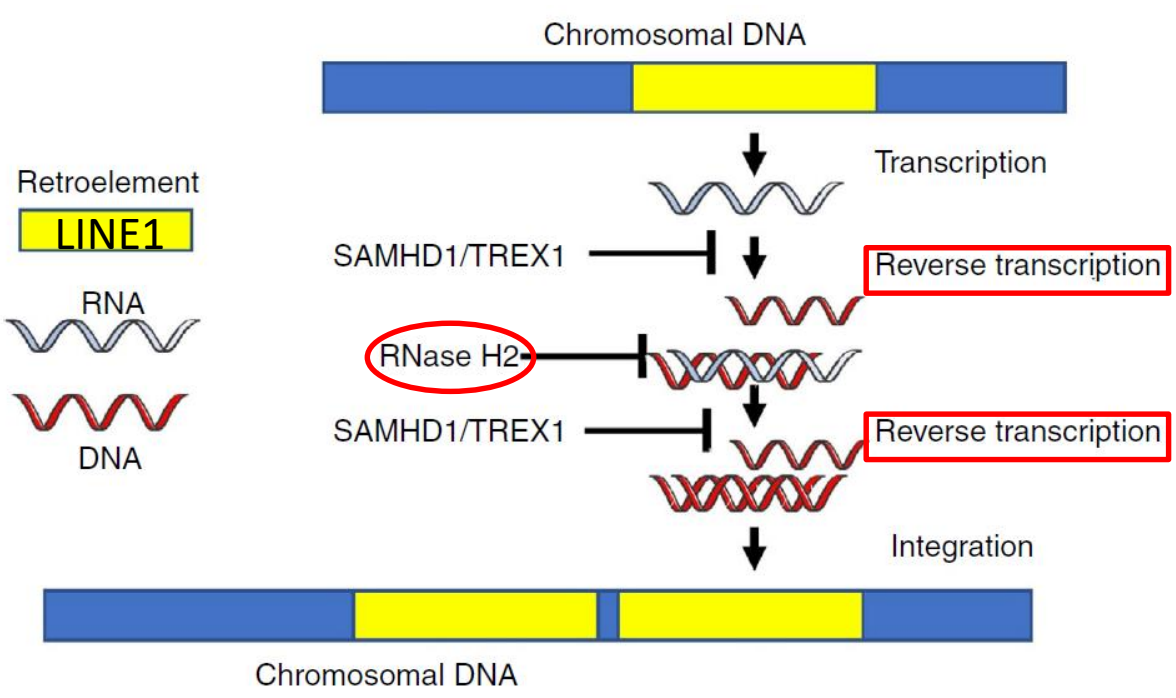
- The neuroinflammatory autoimmune AGS develops from mutations in genes encoding several nucleotide-processing proteins, including **RNase H2**.
- Defective RNase H2 induce **accumulation of self-nucleic acid** species that trigger chronic type I interferon and inflammatory responses, leading to AGS pathology.

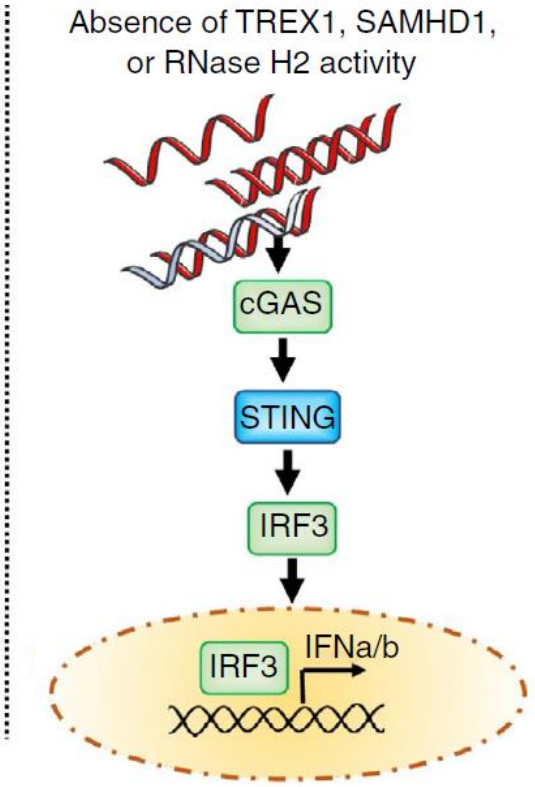
The autoinflammatory autoimmune disease Aicardi-Goutières Syndrome (AGS)

- AGS arises from mutations in seven different genes: *RNASEH2A, RNASEH2B, RNASEH2C*, *TREX1*, *SAMHD1*, *ADAR1*, and *IFIH1*, all of which are nucleic acid–transacting/processing enzymes.
- AGS is believed to result from activation of the innate immune pathway by nucleic acids accumulating in the cytosol when an AGS-associated gene is defective.

Retroelement control by enzymes mutated in AGS.

LINE-1 retroelement propagation involves a copy and paste' cycle of transcription, reverse transcription, and integration.





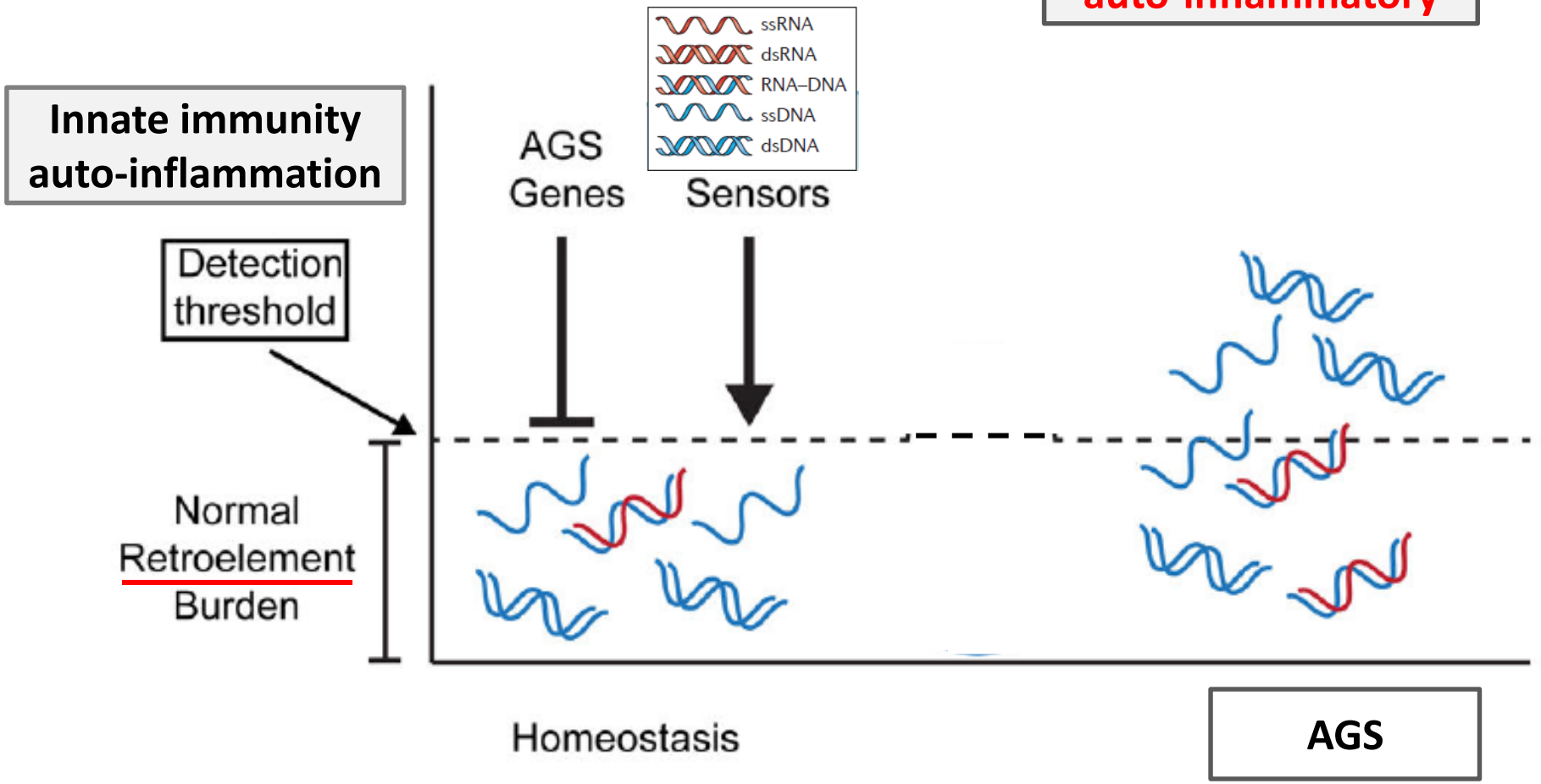
Nucleoside reverse transcriptase inhibitors (NRTIs)

AGS Genes = RNaseH2
TREX1, STING, IRF3
+ type 1 IFNs

mutations →

AGS = Aicardi-Goutieres syndrome
autoimmune
auto-inflammatory

Innate immunity
auto-inflammation



AGS

There is an intricate network of enzymes that prevent the accumulation of IMMUNE-STIMULATING NUCLEIC ACIDS FRAGMENTS from ERs transcription and reverse transcription

Inspired by Volkman & Stetson 2014

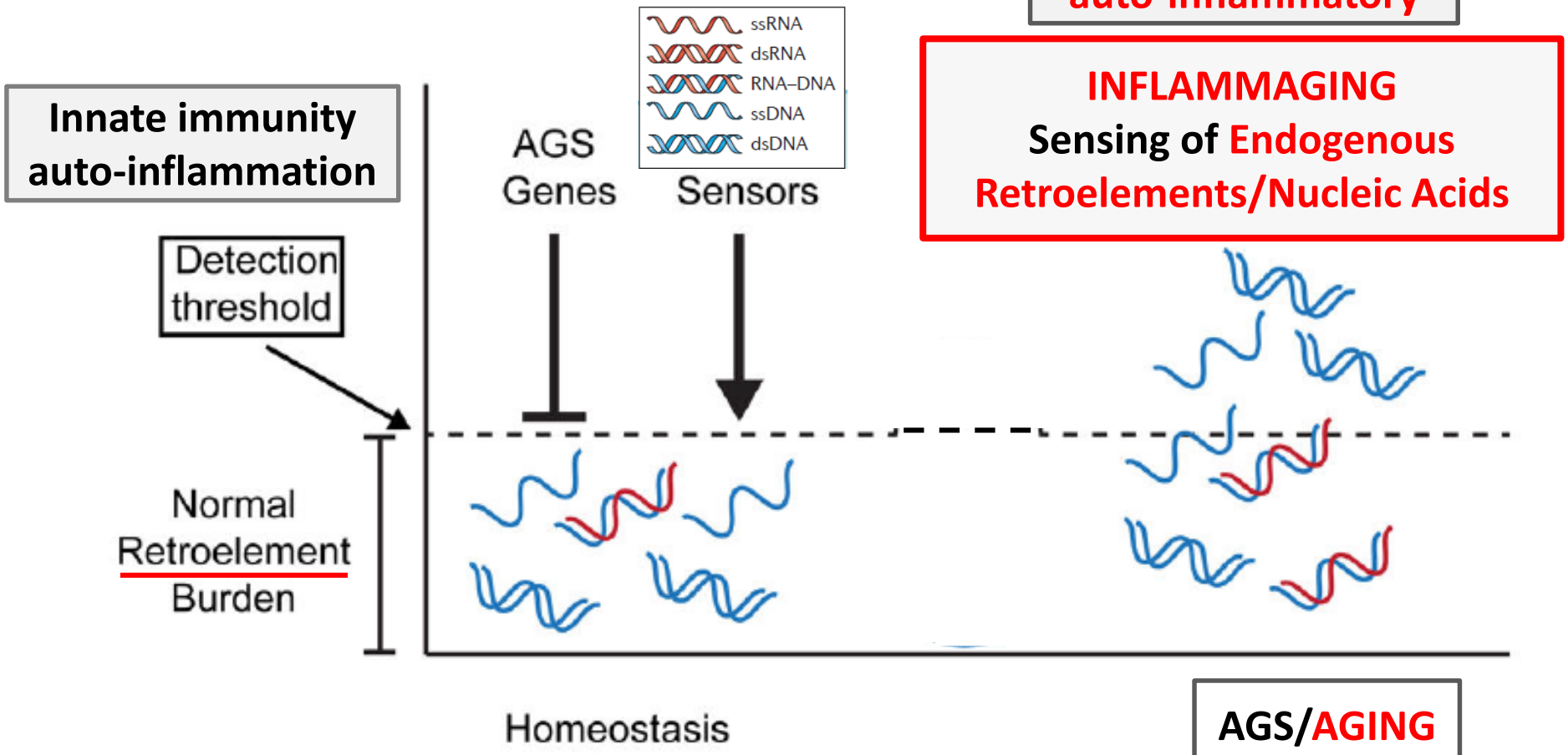
AGS Genes = RNaseH2
TREX1, STING, IRF3
+ type 1 IFNs

mutations

AGS = Aicardi-Goutieres syndrome
autoimmune
auto-inflammatory

Innate immunity
auto-inflammation

INFLAMMAGING
Sensing of Endogenous Retroelements/Nucleic Acids



AGS/AGING

There is an intricate network of enzymes that prevent the accumulation of IMMUNE-STIMULATING NUCLEIC ACIDS FRAGMENTS from ERs transcription and reverse transcription

Inspired by Volkman & Stetson 2014

The NEW ENGLAND JOURNAL of MEDICINE

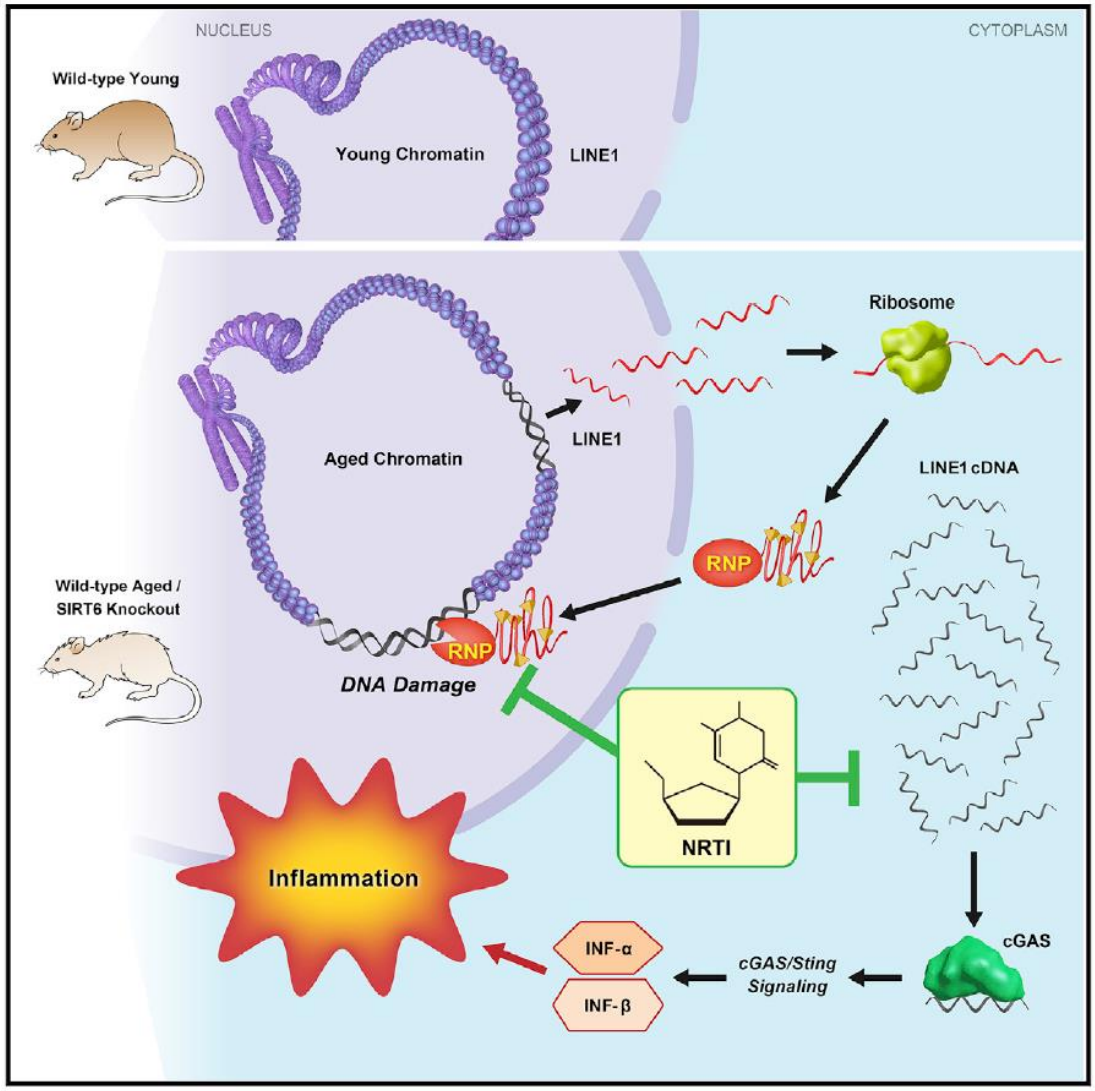
CORRESPONDENCE

Reverse-Transcriptase Inhibitors in the Aicardi–Goutières Syndrome

Rice et al., N Engl J Med. 2018 Dec 6;379(23):2275-7

Abacavir (Ziagen), lamivudine, and zidovudine (ZDV), also known as azidothymidine (AZT)

LINE1 Derepression in Aged Wild-Type and SIRT6-Deficient Mice Drives Inflammation



Simon et al., 2019, Cell Metabolism 30, 871–885 April 2, 2019

Highlights

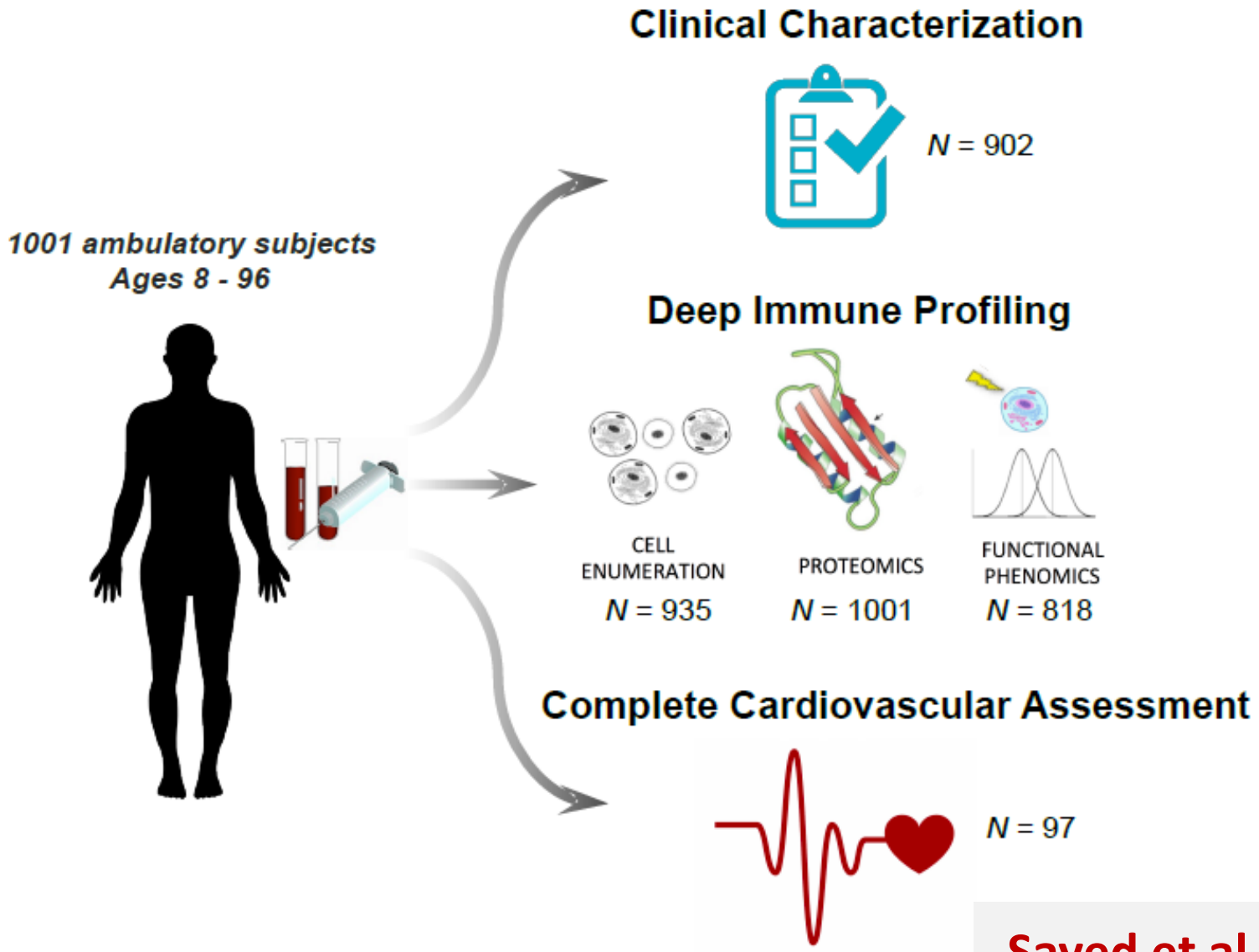
- SIRT6 KO mice accumulate L1 cDNA, triggering interferon response via cGAS pathway
- Wild-type aged mice accumulate L1 cDNA and display type I interferon response
- Reverse-transcriptase inhibitors rescue type I interferon response and DNA damage
- Reverse-transcriptase inhibitors extend lifespan and improve health of SIRT6 KO mice

Lamivudine, commonly called *3TC* Stavudine, called *d4T* (Zerit)

- **An Inflammatory Clock Predicts Multi-morbidity, Immunosenescence and Cardiovascular Aging in Humans**
- Nazish Sayed, Tianxiang Gao, Robert Tibshirani, Trevor Hastie, Lu Cui, Tatiana Kuznetsova, Yael Rosenberg-Hasson, Rita Ostan, Daniela Monti, Benoit Lehallier, Shai Shen-Orr, Holden T. Maecker, Cornelia L. Dekker, Tony Wyss-Coray, Claudio Franceschi, Vladimir Jojic, François Haddad, José G. Montoya, Joseph C. Wu and David Furman

submitted

Identification of an inflammatory clock of aging (iAge) which tracked with multi-morbidity and immunosenescence



Sayed et al., 2019

The inflammatory clock

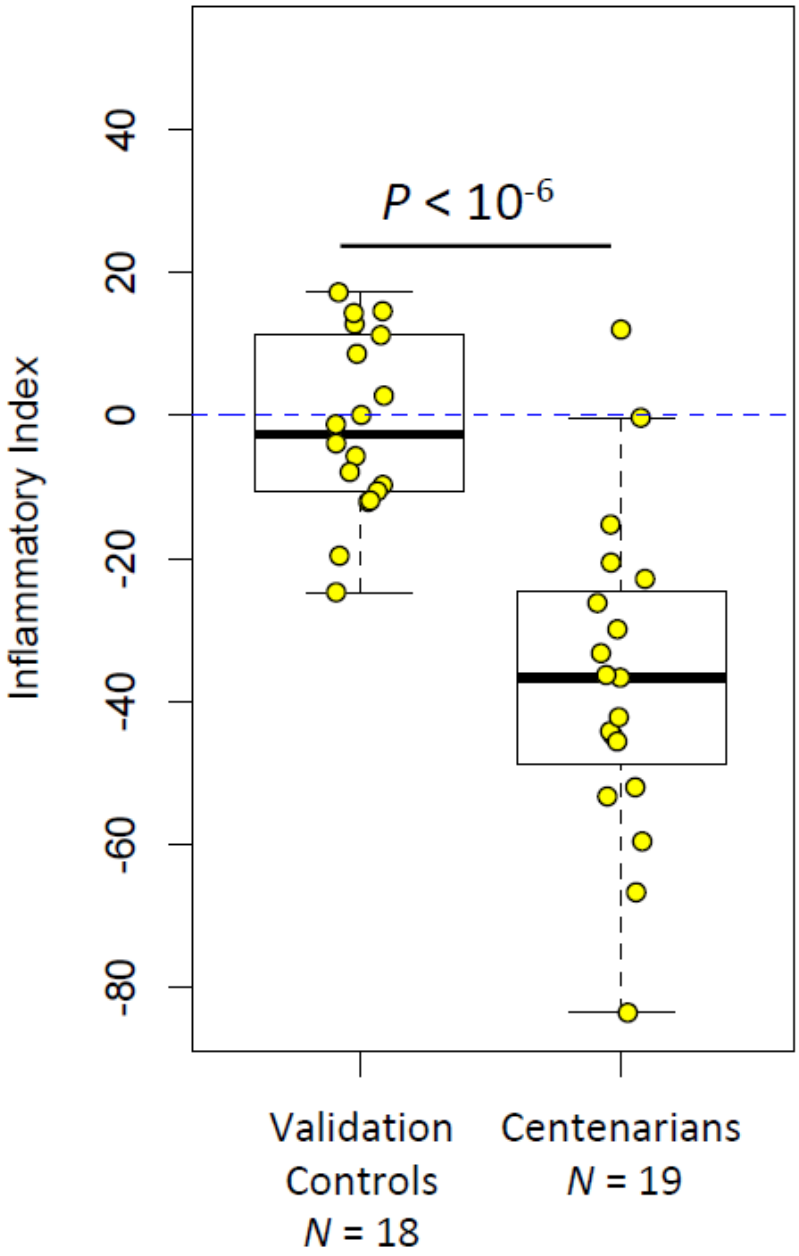
We observed a significant correlation between iAge and multi-morbidity in the older adults (*N* = 285, >60 years old), but not with any individual disease item, suggesting that the inflammatory clock is a metric for overall health linked to multiple diseases associated with aging.

Sayed et al., 2019

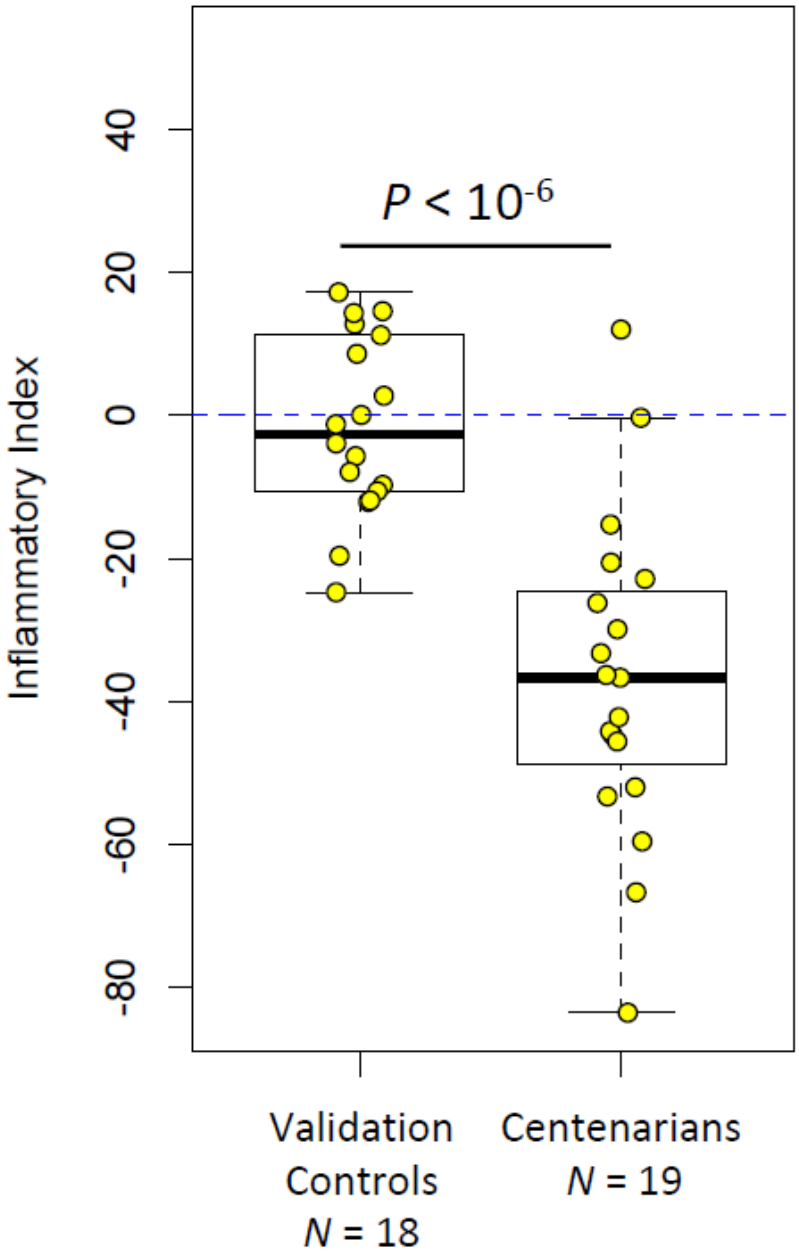
Inflammaging is non-linear

The phenomenon of low-grade chronic inflammation/inflammaging in humans is best modeled using non-linear methods, and based on these, one can derive a metric for chronic inflammation that accurately predicts chronological age in the population, while preserving the biological information related to the total inflammatory burden as measured by the level of circulating immune proteins.

Sayed et al., 2019



In centenarians, the **inflammatory clock index** (inflammatory clock minus chronological age) is on average, **40 years lower** than chronological age.



The large variance observed in 100+ suggests that there may be other mechanisms apart from inflammation/ inflammaging conferring them disease protection and long lifespan

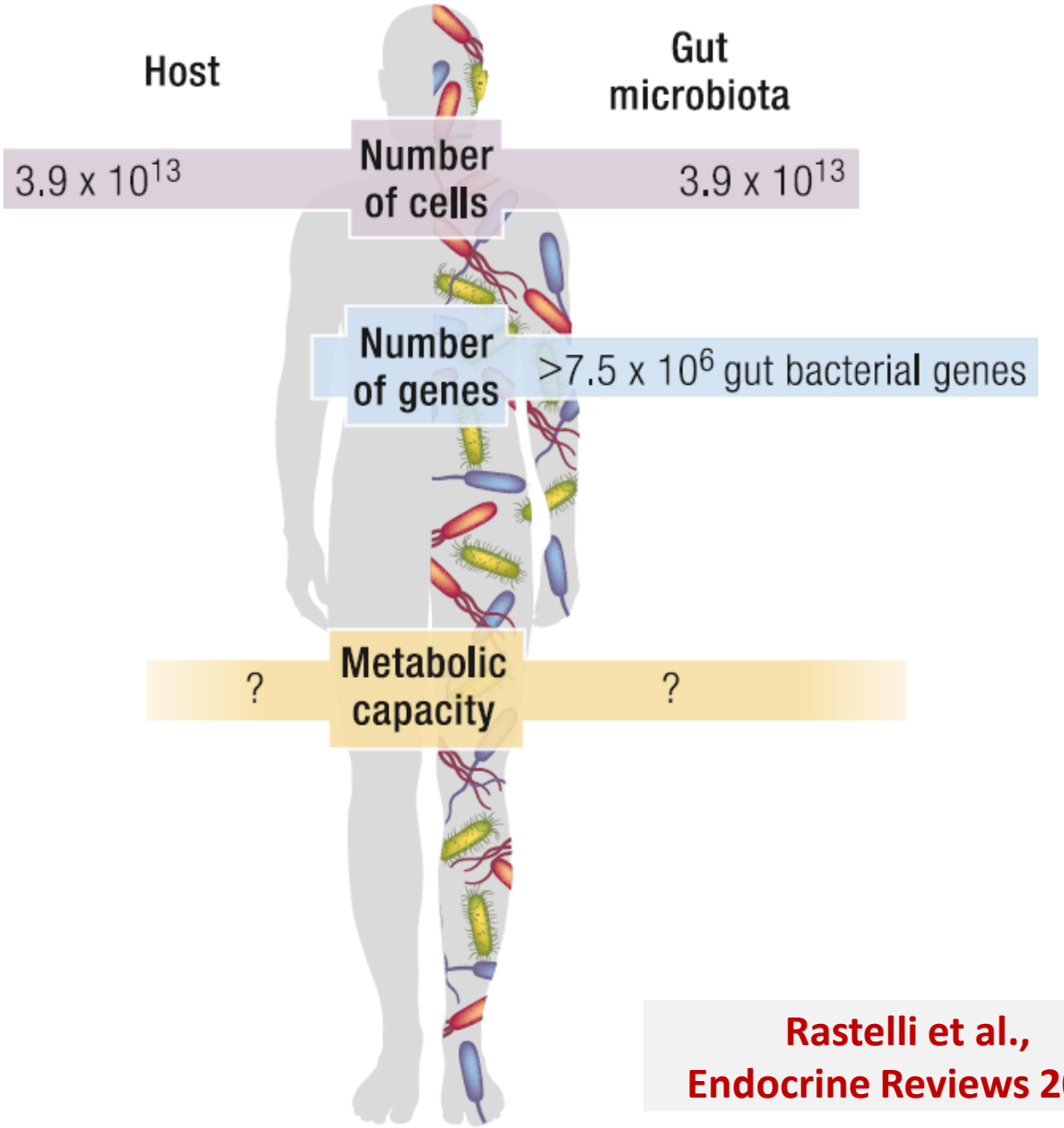
The age-related change of gut microbiota contributes to inflammaging …but within a profound adaptive remodelling

Host and gut microbiota in comparison

1:1 is the human cell:gut bacteria ratio

Gut bacteria: 38-fold more genes than the human genome

Metabolic capacity of gut bacteria exceeds host metabolic capacity



Rastelli et al., Endocrine Reviews 2019

GM, Aging/Longevity and Inflammaging

OPEN ACCESS Freely available online

PLoS one

Through Ageing, and Beyond: Gut Microbiota and Inflammatory Status in Seniors and Centenarians

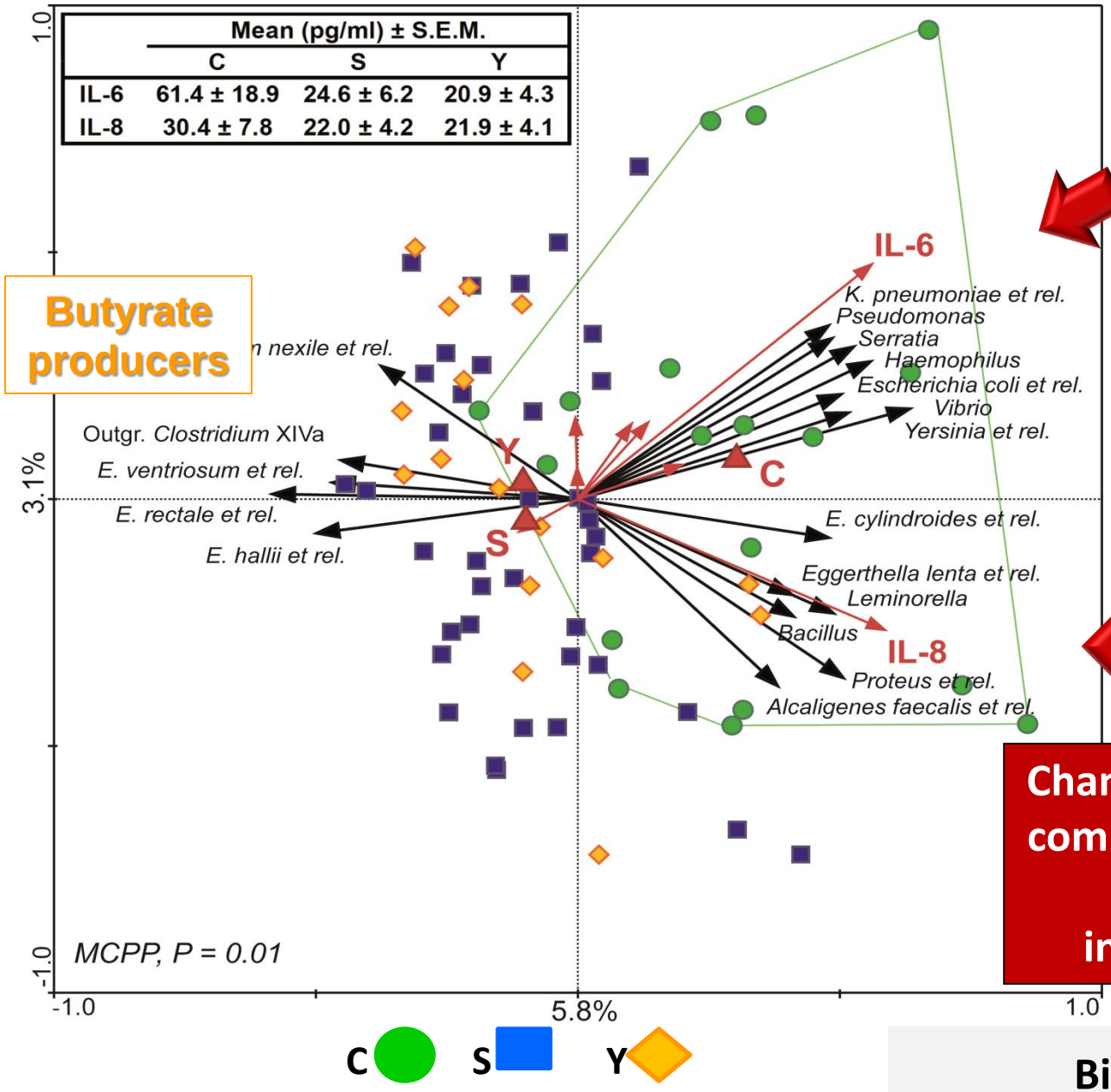
Elena Biagi[1]*, Lotta Nylund[2,3], Marco Candela[1], Rita Ostan[4], Laura Bucci[4], Elisa Pini[4], Janne Nikkïla[3], Daniela Monti[5], Reetta Satokari[2], Claudio Franceschi[4], Patrizia Brigidi[1], Willem De Vos[3,6]

1 Department of Pharmaceutical Sciences, University of Bologna, Bologna, Italy, **2** Functional Foods Forum, University of Turku, Turku, Finland, **3** Division of Microbiology and Epidemiology, Department of Basic Veterinary Medicine, University of Helsinki, Helsinki, Finland, **4** Department of Experimental Pathology and CIG-Interdepartmental Center L. Galvani, University of Bologna, Bologna, Italy, **5** Department of Experimental Pathology and Oncology, University of Florence, Florence, Italy, **6** Laboratory of Microbiology, Wageningen University, Wageningen, The Netherlands

PLoS One 2010

GUT MICROBIOTA AND INFLAMMAGING

	Mean (pg/ml) ± S.E.M.		
	C	S	Y
IL-6	61.4 ± 18.9	24.6 ± 6.2	20.9 ± 4.3
IL-8	30.4 ± 7.8	22.0 ± 4.2	21.9 ± 4.1



Butyrate producers

RDA shows that 8.9% of the total variability of the GM can be related to the pattern of pro-inflammatory cytokines

Pathobionts

Changes in the microbiota composition contribute to the age-related inflammatory status

Biagi et al., 2010

Current Biology
Report

The continuous remodeling with age of GM

Gut Microbiota and Extreme Longevity

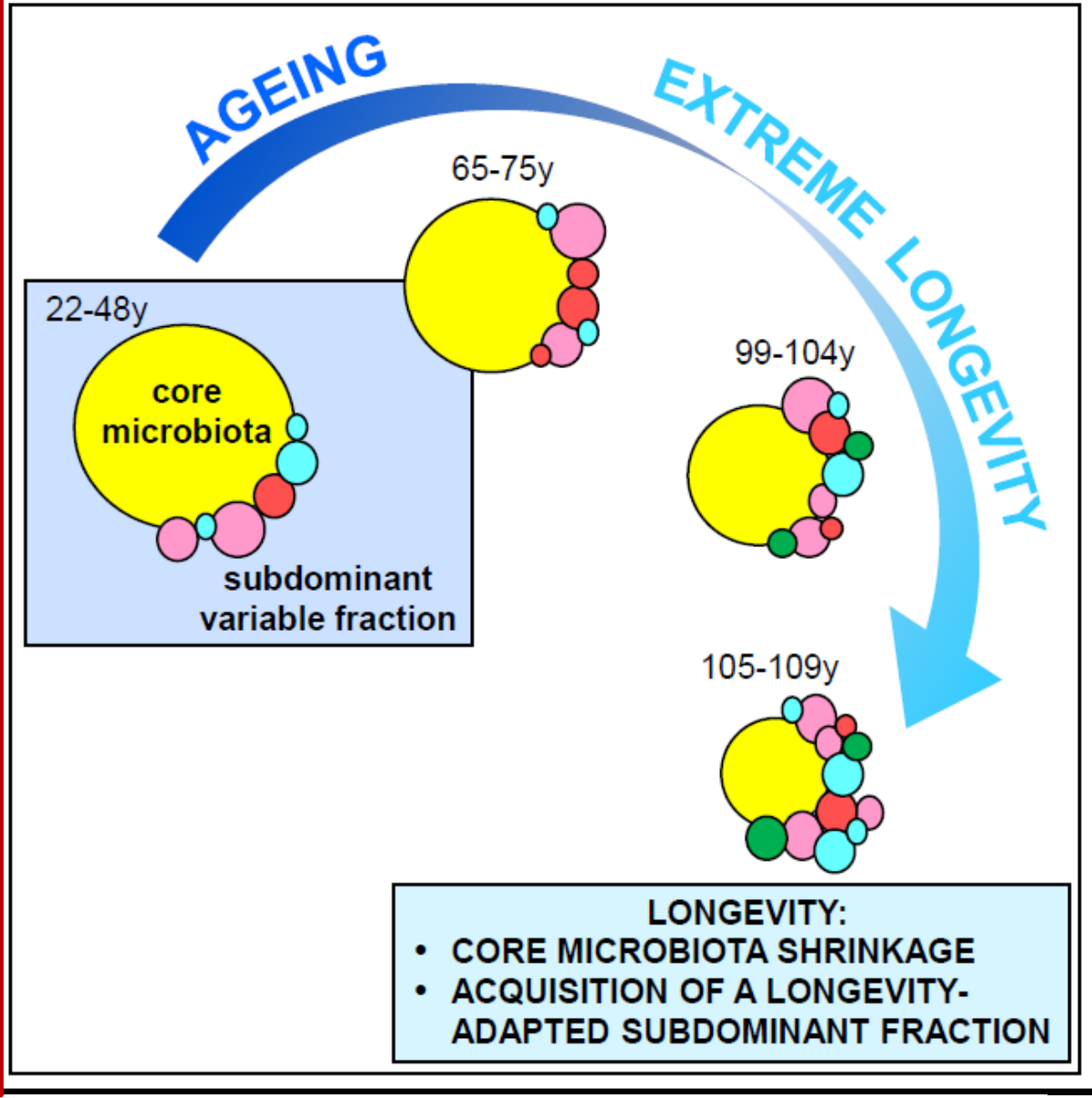
Elena Biagi,[1,*] Claudio Franceschi,[2,3,4] Simone Rampelli,[1] Marco Severgnini,[5] Rita Ostan,[2,3] Silvia Turroni,[1] Clarissa Consolandi,[5] Sara Quercia,[1] Maria Scurti,[2,3] Daniela Monti,[6] Miriam Capri,[2,3] Patrizia Brigidi,[1] and Marco Candela[1,*]

[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

Current Biology 26, 1–6 June, 2016

There is a GM signature of aging and longevity

Adaptive, balanced pro- & anti-inflammatory remodeling of GM with age from 22 to 109 years



Biagi et al., *Curr Biol* 2016

Table 1. Age-related trajectory of bacterial groups contributing to the sample separation.

Bacterial group	Average relative abundance (%)				Trajectory
	Group Y	Group E	Group C	Group S	
Coprococcus	8.4	5.4	4.9	3.3	↘
Roseburia	7.9	4.6	2.3	2.4	↘
Faecalibacterium	8.6	7.6	4.5	2.6	↘
Uncl. *Lachnospiraceae*	6.1	5.9	4.9	4.6	↘
Oscillospira	0.9	2.1	3.2	3.6	↗
Odoribacter	0.08	0.2	0.5	0.3	↗
Butyricimonas	0.03	0.07	0.2	0.1	↗
Eggerthella	0.07	0.1	0.1	0.3	↗
Akkermansia	1.1	2.3	2.6	4.0	↗
Anaerotruncus	0.01	0.03	0.05	0.1	↗
Bilophila	0.05	0.08	0.1	0.1	↗
Christensenellaceae	0.5	1.1	2.7	3.3	↗
Synergistaceae	0	0.2	0.6	0.9	↗

Biagi et al., *Curr Biol* 2016

Geriatric oncology 1

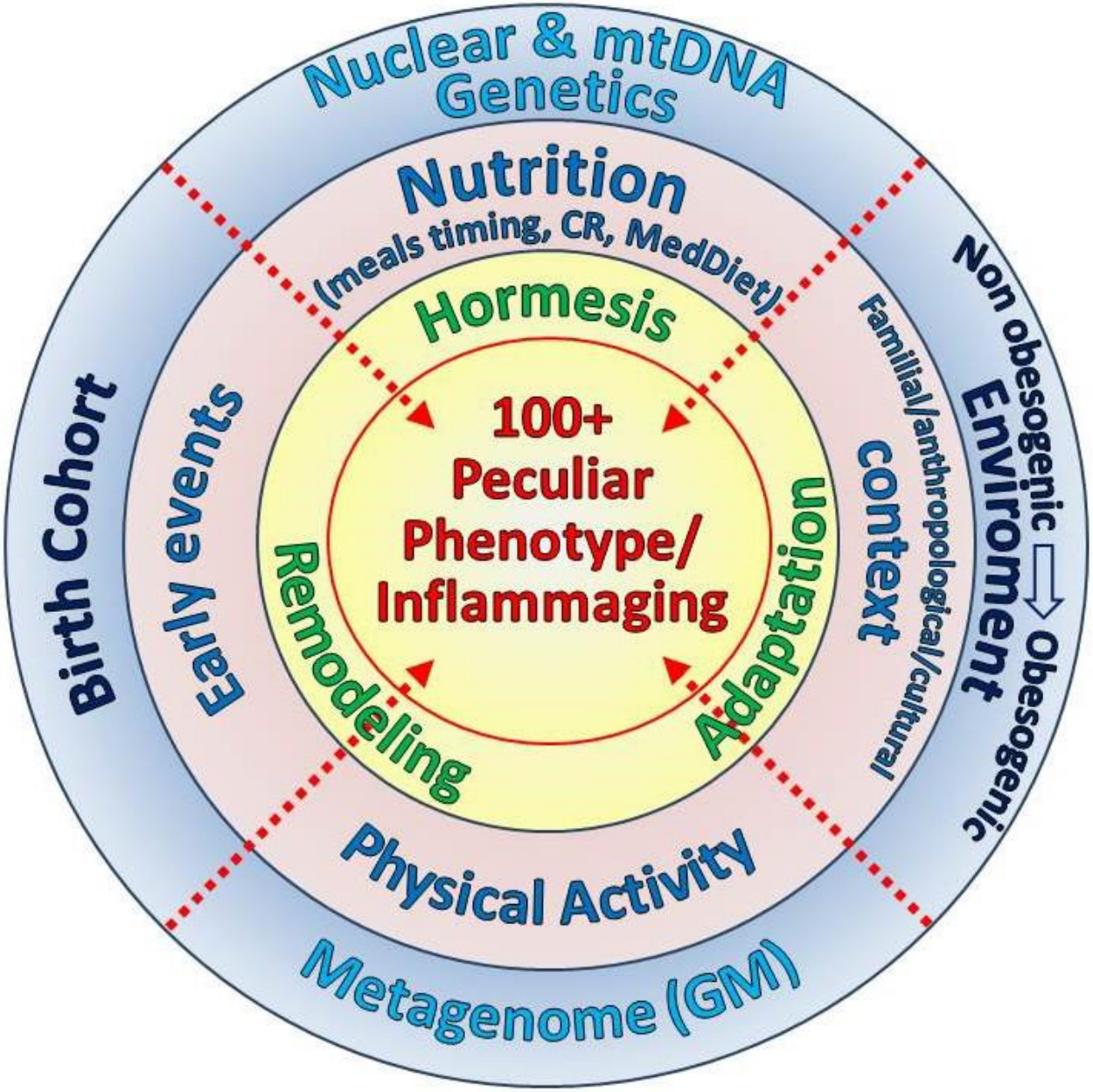
Gut dysbiosis: a potential link between increased cancer risk in ageing and inflammaging

Arya Biragyn, Luigi Ferrucci

thelancet.com/oncology Vol 19 June 2018

«Expansion of gut dysbiosis and leakage of microbial products contribute to the chronic inflammatory state [inflammaging], which negatively affects the immune system and impairs the removal of mutant and senescent cells, thereby enabling tumour growth»

The complex combination of «INGREDIENTS» to reach 100 years



an
ECOLOGICAL
VISION
of HUMAN
LONGEVITY

Franceschi *et al.*,
Annu Rev Nutr., 2018

Thanks 4 your attention

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