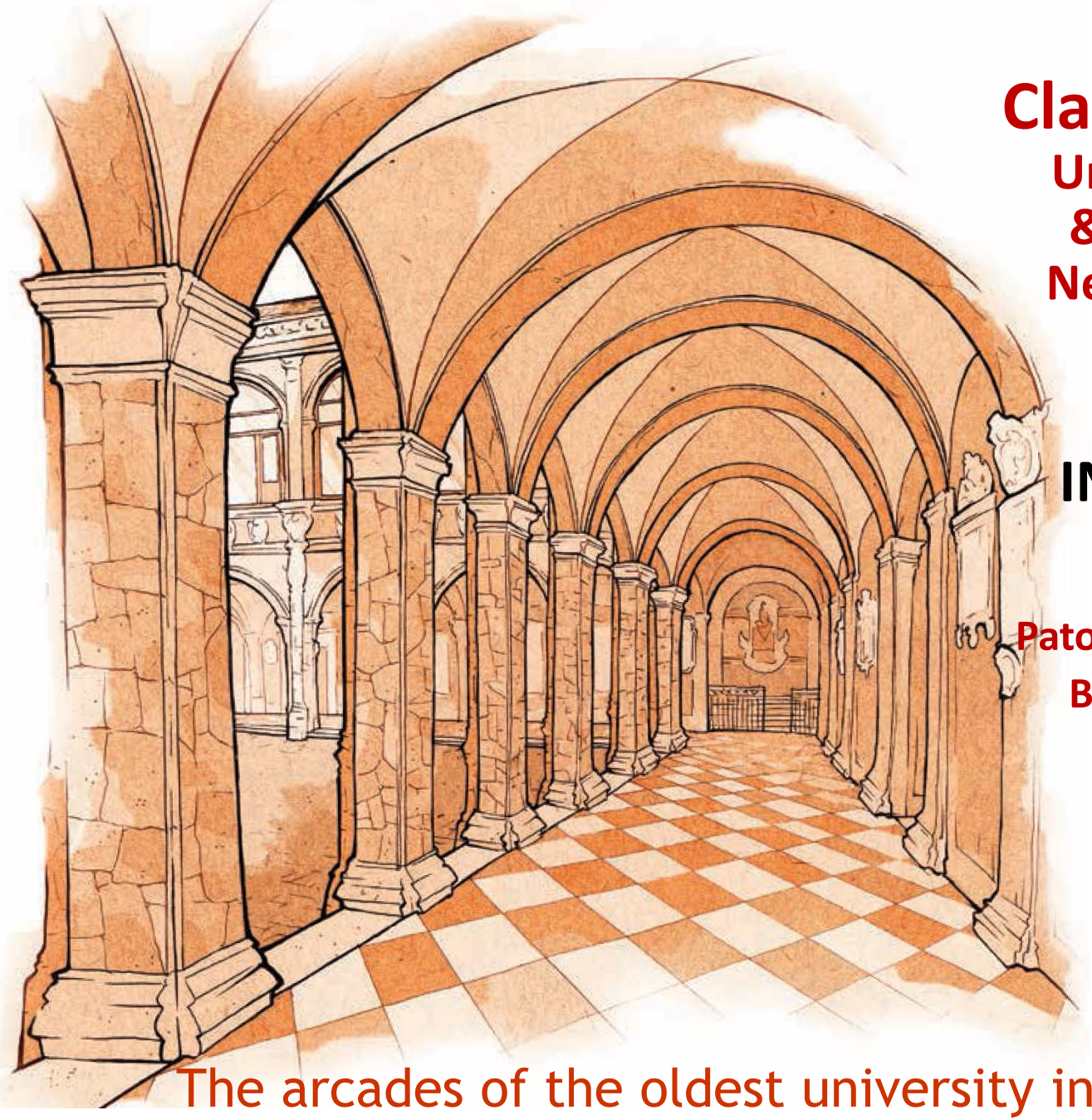

Claudio Franceschi

University of Bologna
& IRCCS Institute of
Neurological Sciences
Bologna, Italy

INFLAMMAGING

Patologie Mieloidi in Geriatria,
Bologna 6 Maggio 2016

The arcades of the oldest university in the Western world
(founded in 1080)

ELSEVIER

Experimental Gerontology 35 (2000) 879–896

Experimental Gerontology

www.elsevier.nl/locate/expgero

The network and the remodeling theories of aging: historical background and new perspectives

C. Franceschi[a,b,*,1], S. Valensin[a,1], M. Bonafè[a,1], G. Paolisso[c], A.I. Yashin[d], D. Monti[e], G. De Benedictis[f]

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[b]*Department of Gerontological Research, Italian National Research Center on Aging (INRCA), Ancona, Italy*
[c]*Department of Geriatric Medicine and Metabolic Diseases, Second University of Naples, Naples, Italy*
[d]*Max Plank Institute for Demographic Research, Rostock, Germany*
[e]*Department of Experimental Pathology and Oncology, University of Florence, Florence, Italy*
[f]*Department of Cell Biology, University of Calabria, Cosenza, Italy*

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

The phenotype of old people is the result of the capability of the body to respond / adapt to:

1. **the damaging stimuli we are exposed lifelong;**
2. **the unrepaired molecular and cellular damages continuously occurring in all tissues and organs, which have a signaling capacity**

↓

REMODELLING

(accumulation of damages/mutations +
local and systemic adaptive responses +
activation of the innate immune system)

An example of adaptation/remodelling: 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*

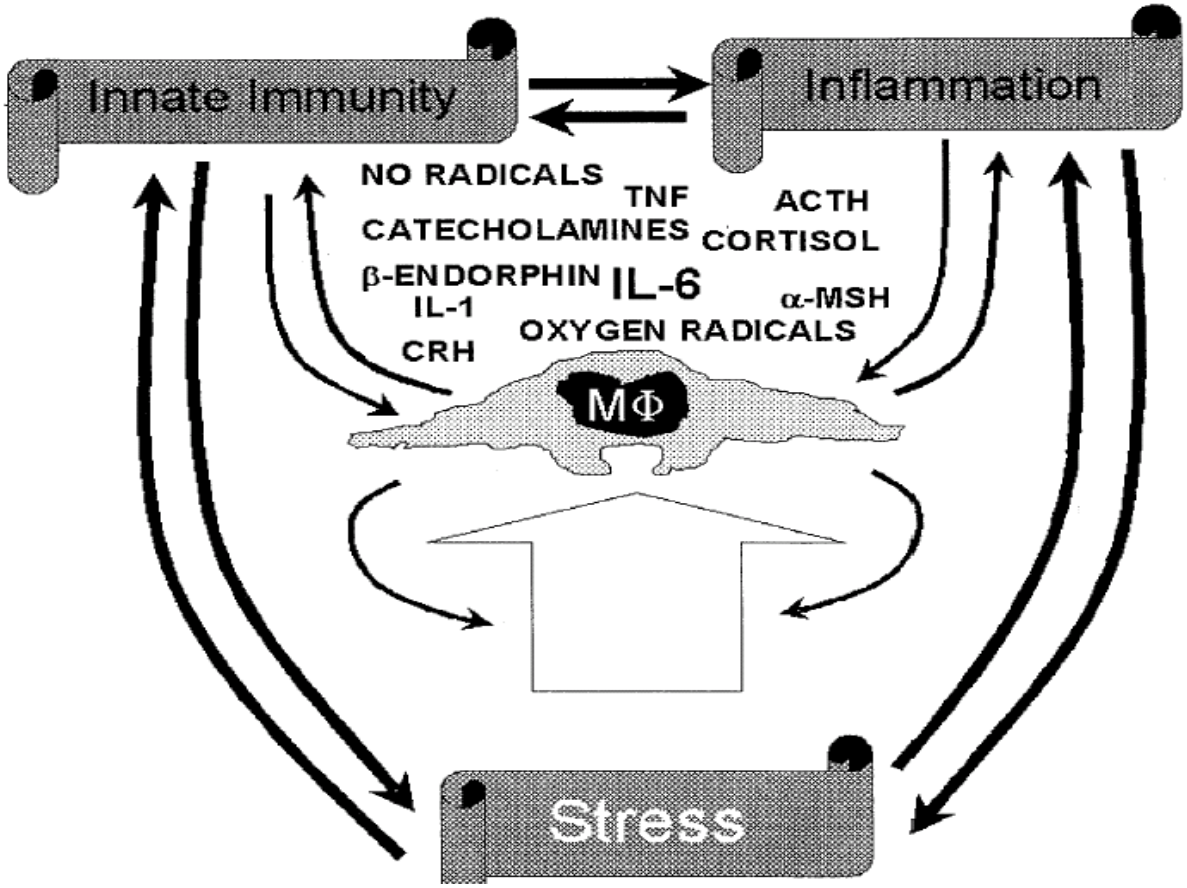
[d]*Department of Cell Biology, University of Calabria, Calabria, Italy*

"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

innate immunity, response to stressors & inflammation are evolutionary conserved from invertebrates to mammals, highly interconnected & macrophage-centered

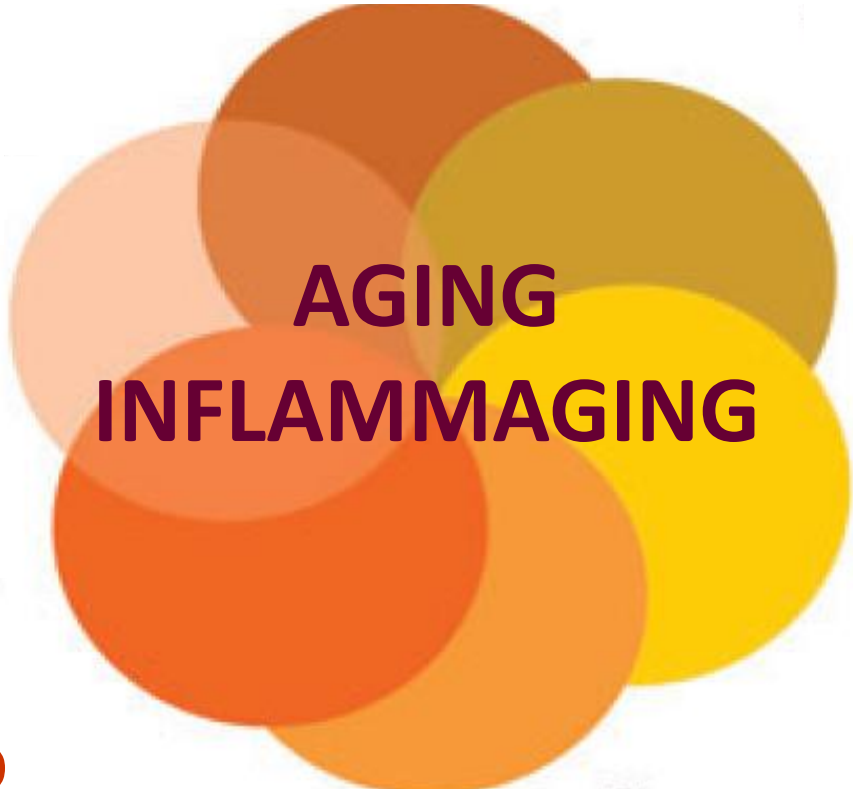


Franceschi et al., 2000

The Inflammaging Theory of Aging

Metabolic syndrome
Type 2 Diabetes

Cancer



Cardiovascular diseases

Alzheimer
PD
PO Delirium

Sarcopenia
Frailty

OA

COPD

Depression

The phenotype of CENTENARIANS
is an inextricable and dynamic mix of
<u>accumulating damages/functional decline</u>
and <u>adaptive mechanisms</u>

+ + +

Inflammaging

The phenotype of CENTENARIANS
is an inextricable and dynamic mix of
accumulating damages/functional decline
and adaptive mechanisms

Anti-inflammaging

+ + +
+ + +

+ + +
+ + +

Inflammaging

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

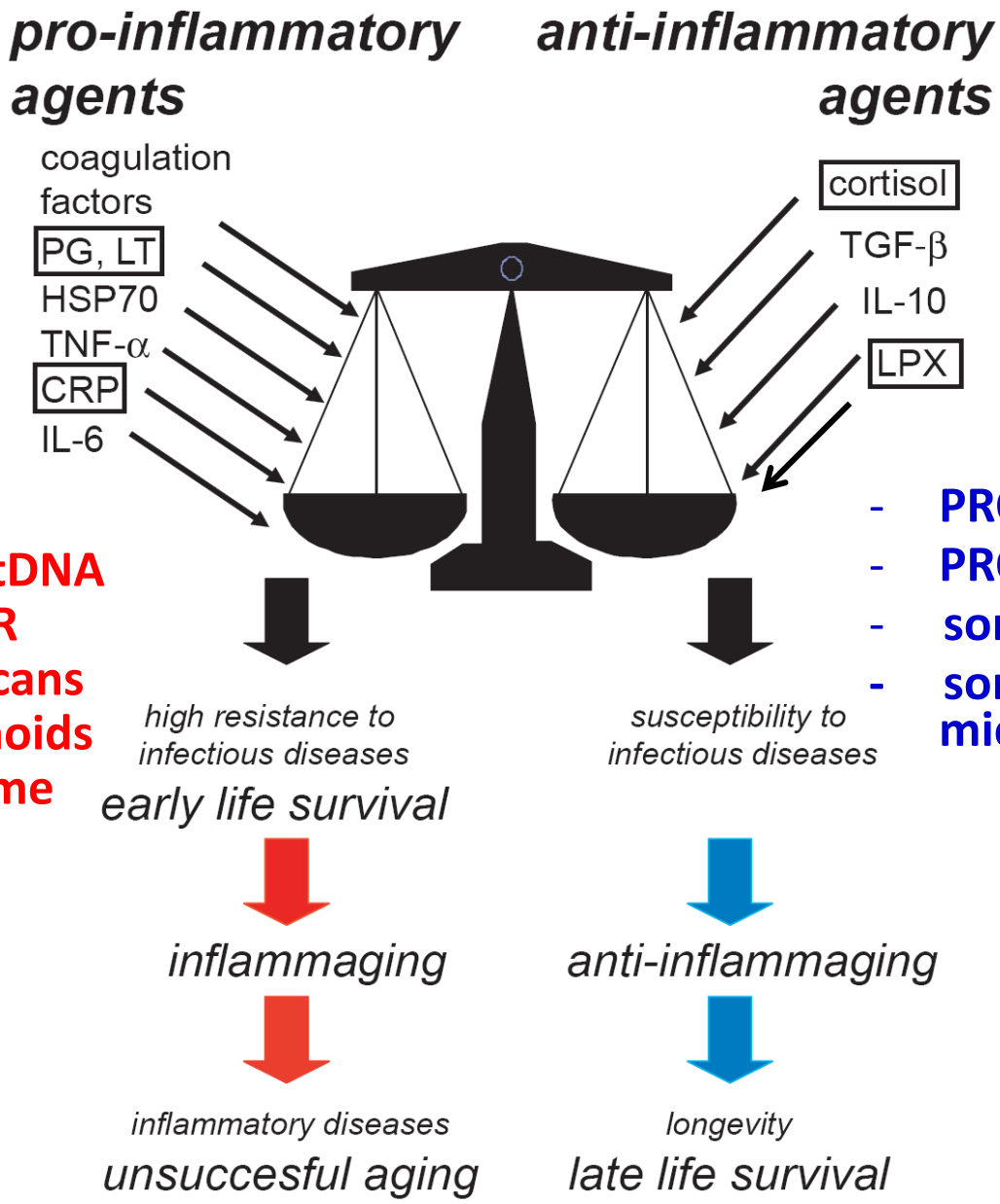
Claudio Franceschi [a,b,c,e,*], Miriam Capri [a], Daniela Monti [d], Sergio Giunta [e], Fabiola Olivieri [e], Federica Sevini [b], Maria Panagiota Panourgia [b], Laura Invidia [a], Laura Celani [b], Maria Scurti [b], Elisa Cevenini [b], Gastone C. Castellani [b,f], Stefano Salvioli [a,b,c]

[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

increasing levels of pro-inflammatory markers with age stimulate a corresponding augmentation in anti-inflammatory markers

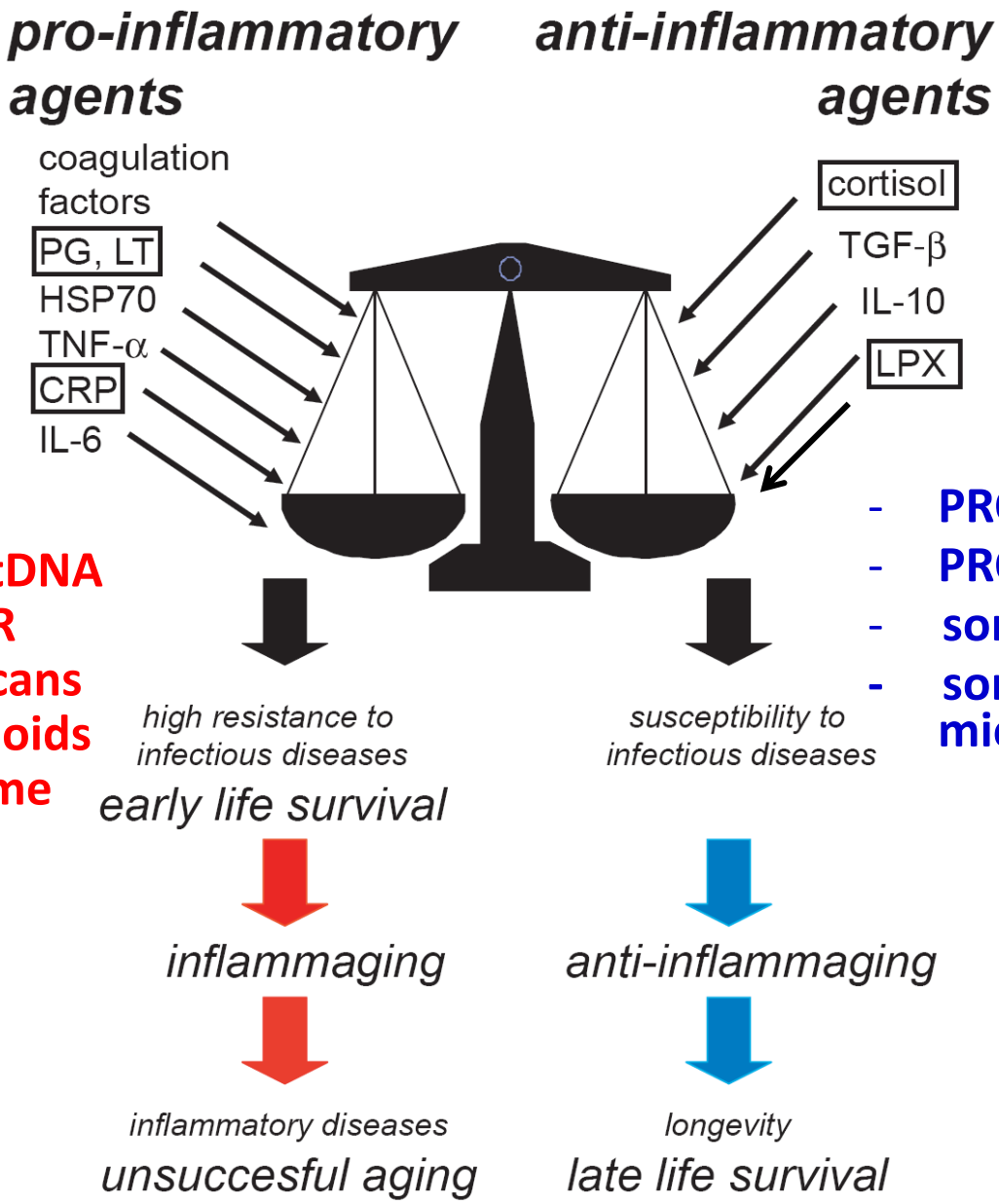
Inflammaging and Anti-Inflammaging: a systemic perspective… Franceschi et al., MAD 2007



- RISK ALLELES
- circulating mtDNA
- inflamma-miR
- agalact N-glycans
- some eicosanoids
- gut microbiome

- PROTECTIVE LIFESTYLE
- PROTECTIVE ALLELES
- some eicosanoids
- some bacteria of gut microbiome

Inflammaging and Anti-Inflammaging: a systemic perspective… Franceschi et al., MAD 2007



INFLAMMAGING as an Antagonistic Pleiotropy trait

- RISK ALLELES
- circulating mtDNA
- inflamma-miR
- agalact N-glycans
- some eicosanoids
- gut microbiome

- PROTECTIVE LIFESTYLE
- PROTECTIVE ALLELES
- some eicosanoids
- some bacteria of gut microbiome

Fulvia, 109 anni, Sarzana (Italy)

Centenarians are characterized by high levels of circulating pro- & anti-inflammatory molecules:
TGFβ, Cortisol, IL-1RA, Adiponectin

It is time to put Inflammaging within the «New Geroscience»

Leading Edge
Commentary

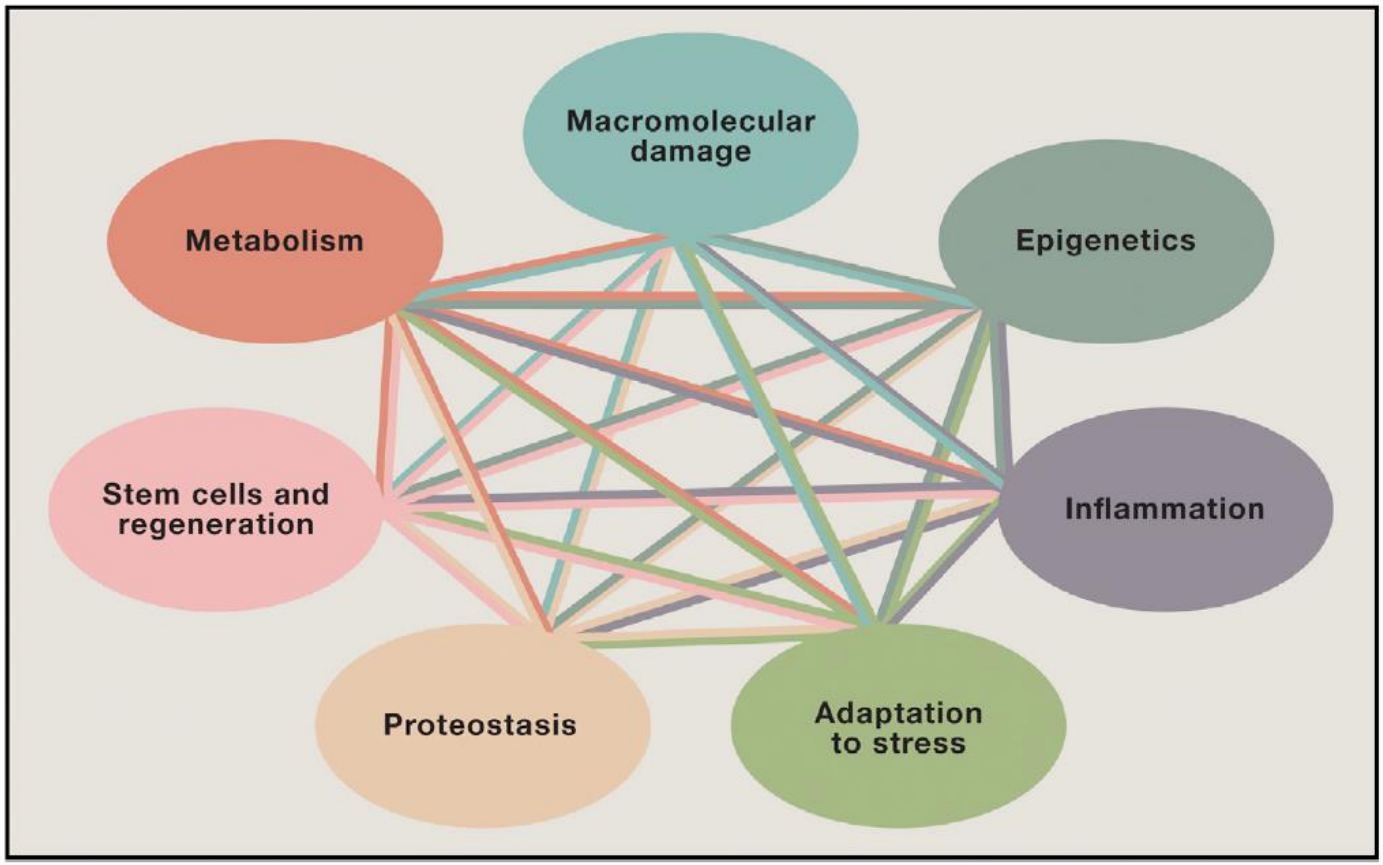
Cell

Geroscience: Linking Aging to Chronic Disease

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

Inflammaging within a larger, systems biology, networking perspective (striking connectedness)



THE SEVEN HIGHLY INTERTWINED PILLARS OF AGING

Kennedy et al., 2014

Journals of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci 2014 June;69(S1):S4–S9
doi:10.1093/gerona/glu057

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

"GARBAGING" and INFLAMMAGING

- **INFLAMMAGING is triggered by DAMAGE/GARBAGE,** i.e. by a variety of "***danger signals***"which can be:
- **1. *EXOGENOUS*** or **PAMPs**, *i.e.* **viruses** such as CMV or HIV, **bacteria** including the **gut/oral-nasal/respiratory- & genito/urinary-tract MICROBIOTA** and its products, **parasites** **("exogenous exposome")**
- ***2. ENDOGENOUS/SELF*** or **DAMPs**, *i.e*. damaged and **SENESCENT CELLS**, **CELL DEBRIS**, altered/modified proteins & lipids, heme, **ROS, extracellular mtDNA, cardiolipin,** AGE, **agalactosylated N-glycans**, extracellular ATP, uric acid, ceramides,HMGB1, resulting from **organelle/cell 3D: Damage/Death/Debris ("endogenous exposome")**

Franceschi & Campisi, 2014

- **Eukaryotic cells contain a plethora of INTRACELLULAR MOLECULES that are normally secured within the confines of organelles and the plasma membrane.**

When cells are stressed/damaged or die as a result of exposure to pathogens and pathogen-products, nutrient excess, heat, radiation, sterile cellular injury after trauma, ischemia, or toxin-induced cell rupture **these molecules, here collectively indicated as GARBAGE, can be actively liberated/secreted or passively released in two compartments:**

1. Within the cell

2. In the extracellular milieu

In both cases they act as Alarmins or **Danger-Associated Molecular Patterns (DAMPs)**

"GARBAGING" and INFLAMMAGING

THIS TYPE OF GARBAGING AND INFLAMMAGING IS PHYSIOLOGICAL AND PRODUCED ALSO BY YOUNG BODIES

Franceschi & Campisi, 2014

GARBAGE, DANGER SIGNALS & INFLAMMAGING

- **With increasing age INFLAMMAGING is fostered by:**

- **INCREASED EXPOSURE to exogenous PAMPs and "danger" signals** (*e.g.* altered **MICROBIOTA**, persistent **CMV**) related to immunosenescence
- **INCREASED GENERATION of endogenous/self DAMPs and "danger" signals** (*e.g.* increased number/amount of **SENESCENT CELLS, CELL DEBRIS, DYSFUNCTIONAL MITOCHONDRIA**)
- **DECREASED EFFICIENCY OF GARBAGE DISPOSAL**, i.e. **UPS/PROTEASOMES, AUTO- and MITO-PHAGY**
- **INCREASED ACTIVATION of NF-kB & INFLAMMASOMES**

Franceschi & Campisi, 2014

European Journal of Immunology

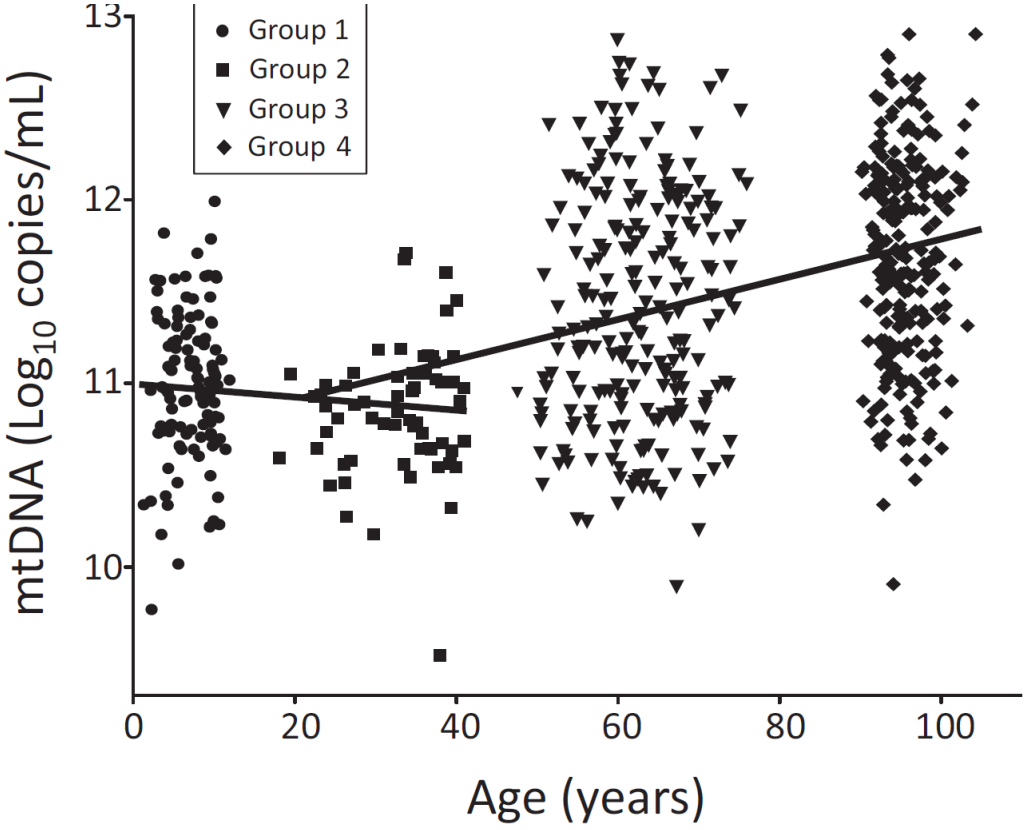
EJI 2014

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]

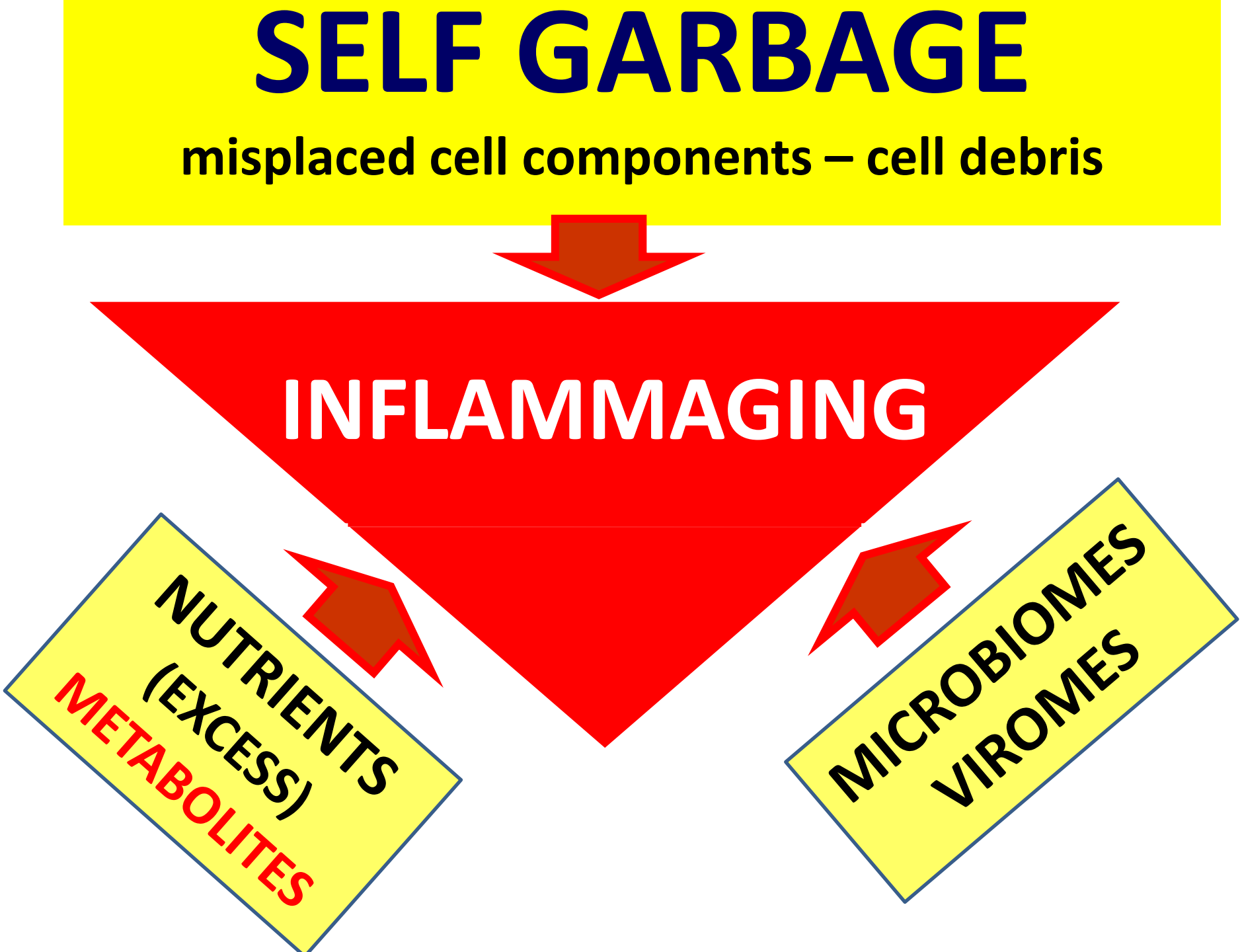
- **Circulating mtDNA increases with age and is a powerful inflammatory stimulus** contributing to inflammaging.
- The number of copies of circulating mtDNA is significantly correlated between siblings, suggesting that **it is a familial/genetic trait**.

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.



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


SELF GARBAGE
misplaced cell components – cell debris
INFLAMMAGING
NUTRIENTS
(EXCESS)
METABOLITES
MICROBIOMES
VIROMES

GARBAGE, DANGER SIGNALS & INFLAMMAGING

This perspective assumes that there is

a CONTINUUM between:

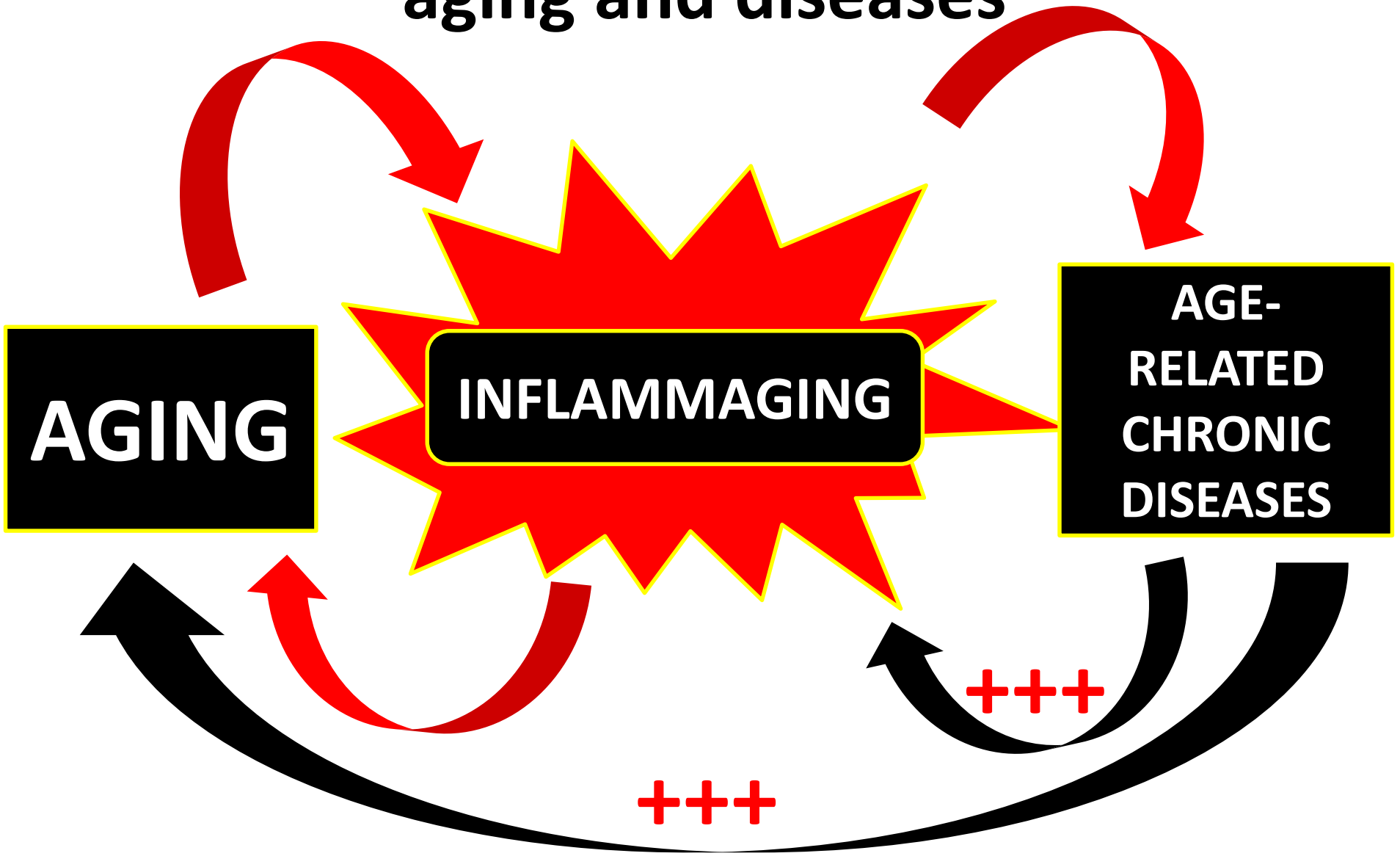
- young and old bodies

- aging physiology and pathology

Inflammaging would represent the progressive impairment with age of the physiological garbage disposal.

Franceschi & Campisi, 2014

The complex relationship between aging and diseases



INFLAMMAGING & age-related diseases

HYPOTHESIS:

All/most age-associated diseases can be conceptualized as "segmental" accelerated aging syndromes, involving/affecting (for genetic and/or lifestyle reasons) specific organs/pathways (more than others), where the aging process and inflammaging propagated faster

Aging and the blurring of the distinction between self and not self

INFLAMMAGING and AGE-RELATED DISEASES

can largely be conceptualized as the result of a low grade, progressive/slow, systemic, lifelong

AUTO-INFLAMMATORY PROCESS

- driven by a peculiar type of chronic stimulation,

- triggered by external and internal EXPOSOMES

- favored by the functional decline of immune responses, *i.e.* by what Roy Walford called *"immunosenescence"*.

"IMMUNOBIOGRAPHY"
& the "**Liquid Immunological Self**"

frontiers in IMMUNOLOGY

HYPOTHESIS AND THEORY ARTICLE
published: 09 April 2014
doi: 10.3389/fimmu.2014.00153

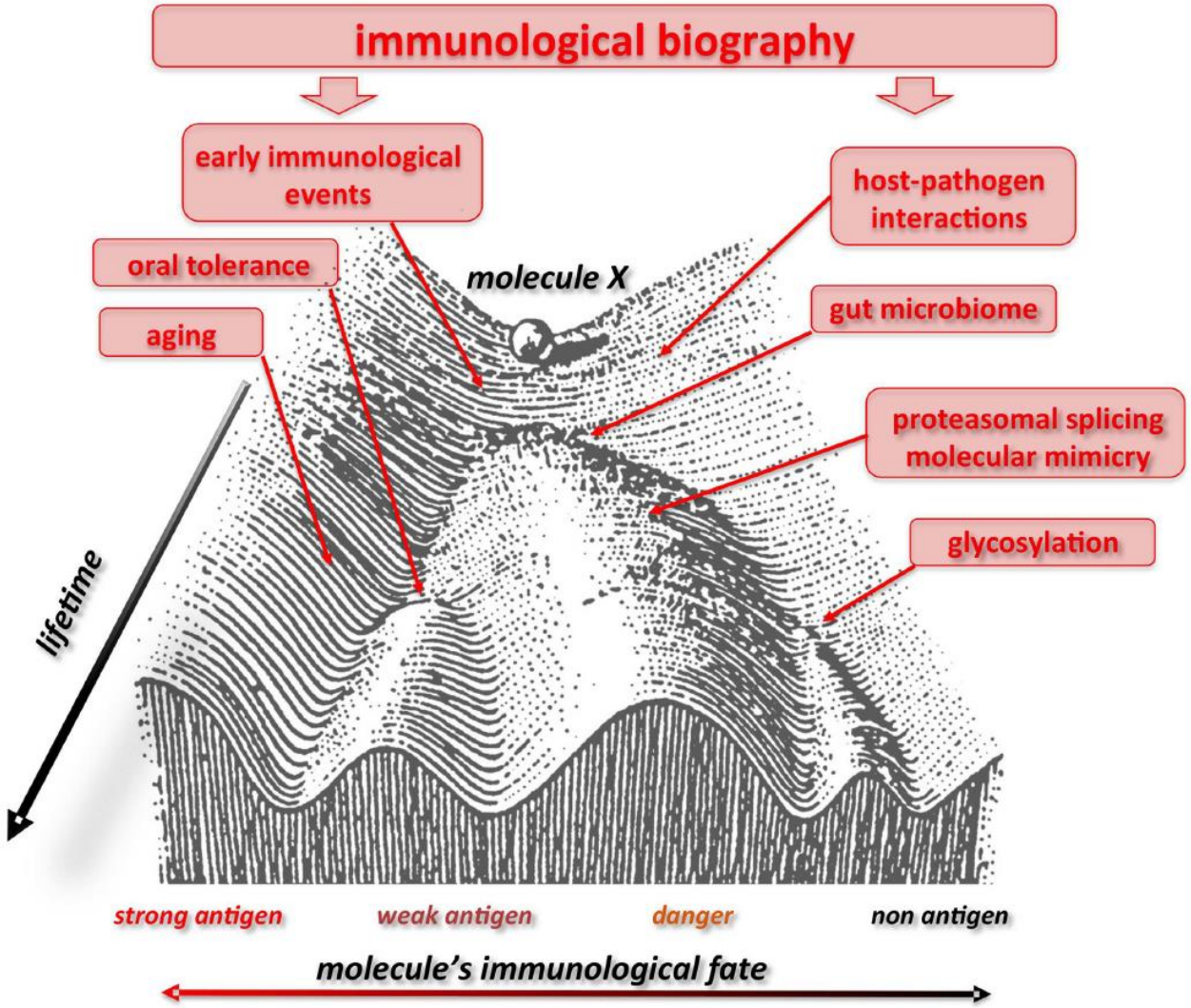
Towards a liquid self: how time, geography, and life experiences reshape the biological identity

Andrea Grignolio[1]*†, Michele Mishto[2,3]†, Ana Maria Caetano Faria[4], Paolo Garagnani[5], Claudio Franceschi[1,5,6,7] and Paolo Tieri[8]*

[1] *Interdepartmental Center "Luigi Galvani" for Bioinformatics, Biophysics and Biocomplexity, University of Bologna, Bologna, Italy*
[2] *Centro Interdipartimentale di Ricerca sul Cancro "G. Prodi", University of Bologna, Bologna, Italy*
[3] *Institut für Biochemie, Charité – Universitätsmedizin Berlin, Berlin, Germany*
[4] *Departamento de Bioquímica e Imunologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil*
[5] *Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy*
[6] *IRCCS of Neurological Science, Bologna, Italy*
[7] *Institute of Organic Synthesis and Photoreactivity, National Research Council, Bologna, Italy*

Aging and the blurring of self/non-self discrimination

Waddington landscape of the "liquid immunological self"



Grignolio et al., 2014

“inflammaging is a fire”

There is evidence that:

- **The aging phenotype is maintained by the aged micro/macro-environment.**
- **Inflammaging can propagate from cells to cells (and from organs to organs ?)**

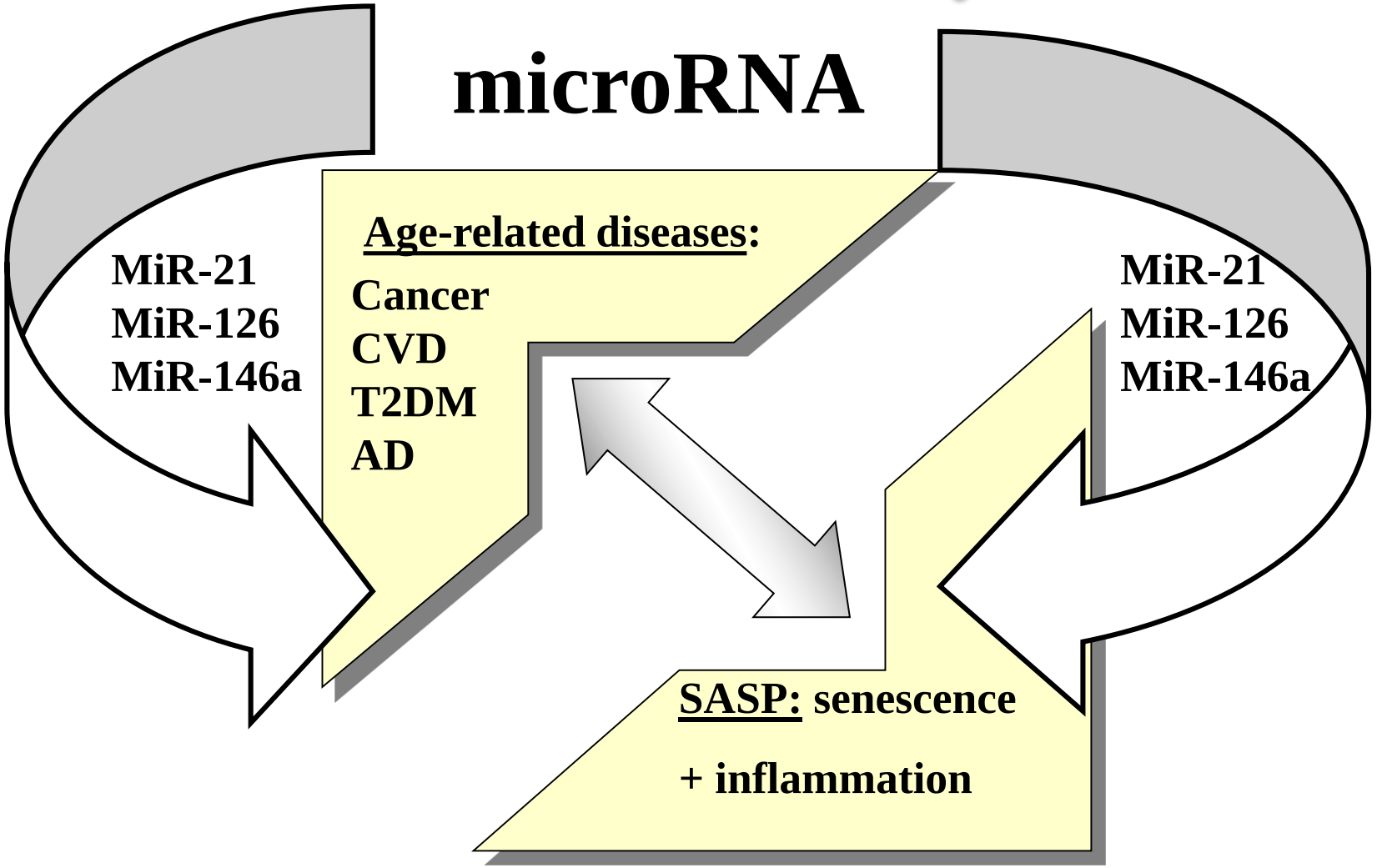
Circulating inflamma-miR

MicroRNAs linking inflammaging, cellular senescence and cancer

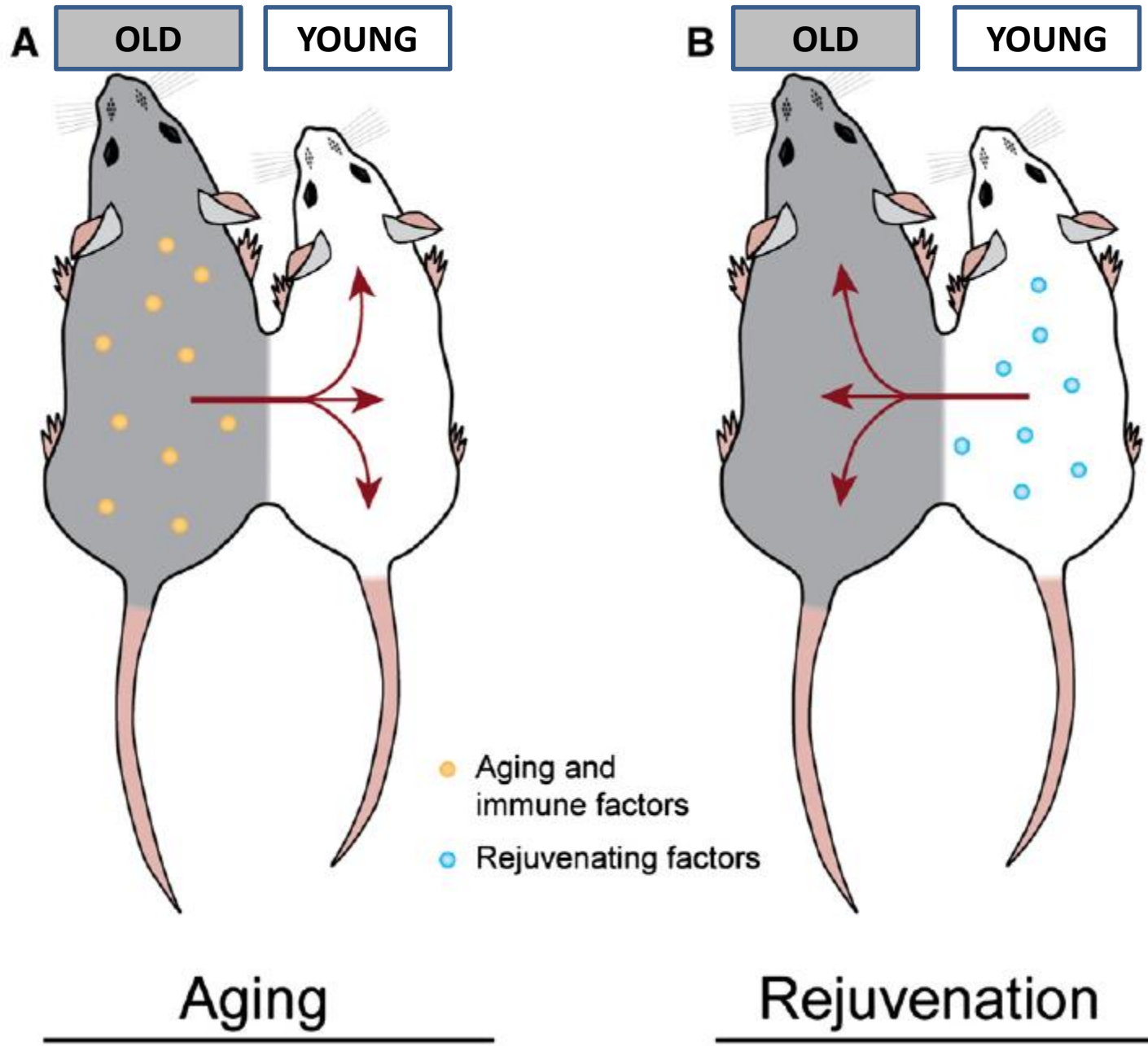
Olivieri F, Rippo MR, Monsurro V, Salvioli S, Capri M , Procopio AD and Franceschi C

Aging Research Reviews, 2013

Pro-inflammatory microRNA



Circulating Inflamma-miRs

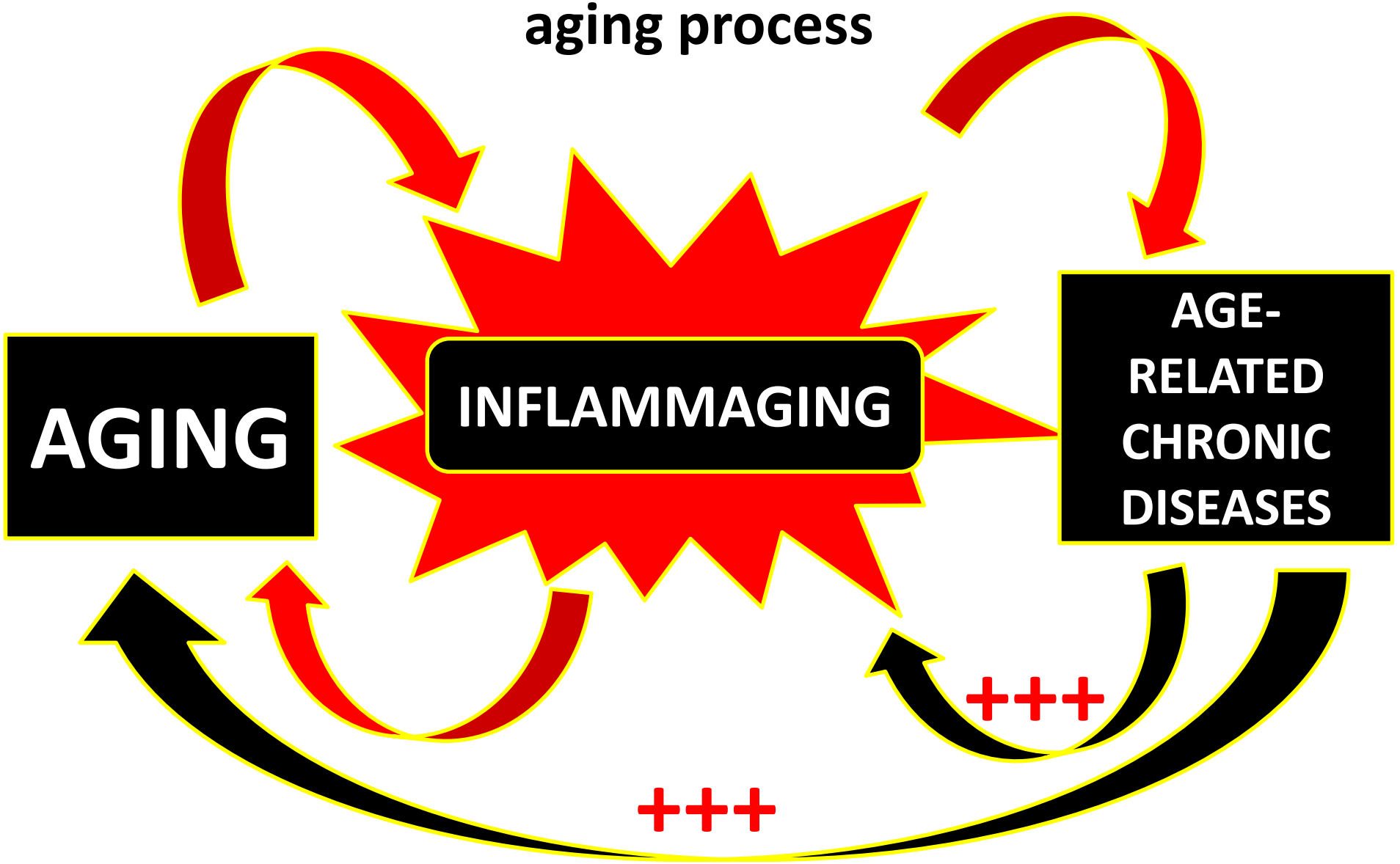


The model of heterochronic parabiosis

A PROPAGATING VIEW OF AGING & INFLAMMAGING

- **UNIBO-studied candidate stimuli present in the blood (circulating) which could maintain and propagate aging and inflammaging:**
- **circulating mtDNA**
- **agalattosylated N-glycans**
- **inflamma-miR**
- **gut microbiota products and metabolites**
- **lipid metabolites**

The «communicome» of an age-related disease likely contribute to propagate and accelerate the aging process



Briefings in Bioinformatics Advance Access published August 24, 2015

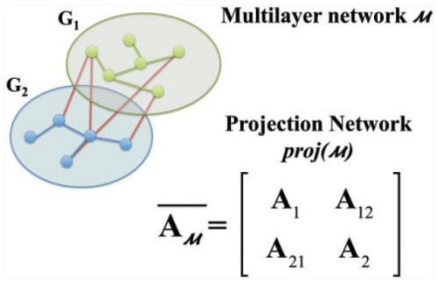
Briefings in Bioinformatics, 2015, 1–14

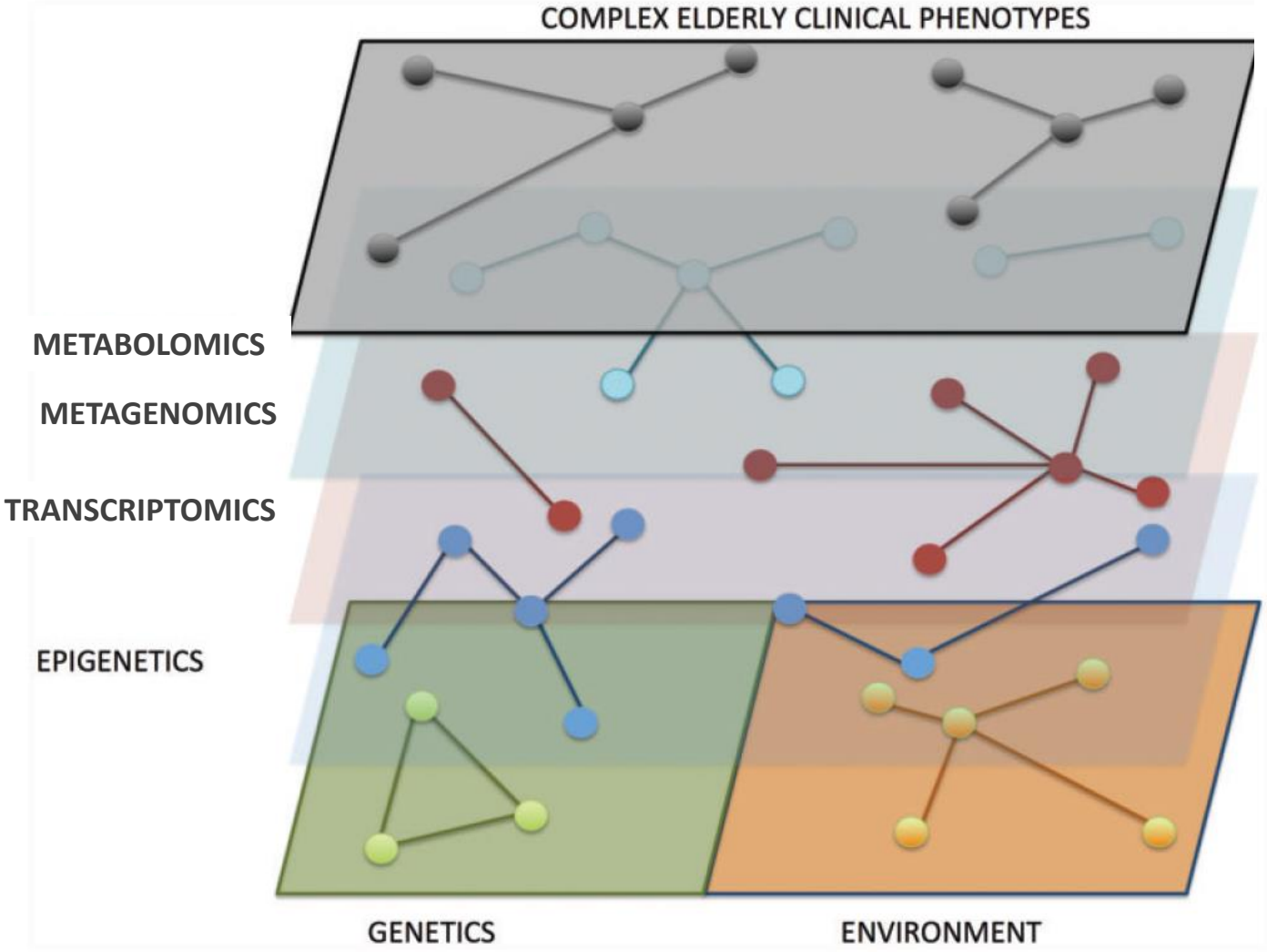
Systems medicine of inflammaging

Gastone C. Castellani*, Giulia Menichetti*, Paolo Garagnani, Maria Giulia Bacalini, Chiara Pirazzini, Claudio Franceschi, Sebastiano Collino, Claudia Sala, Daniel Remondini, Enrico Giampieri, Ettore Mosca, Matteo Bersanelli, Silvia Vitali, Italo Faria do Valle, Pietro Liò and Luciano Milanesi

"INFLAMMAGING is a unifying Biomedical Hypothesis particularly attractive for Systems Medicine as it is multi-scale, multi-organs and propagating among multiple spatial and temporal scales. INFLAMMAGING can be mapped onto a **MULTILAYER NETWORK** capable to model and quantify the endogenous and exogenous interactions"

A SYSTEMIC APPROACH TO AGING/INFLAMMAGING

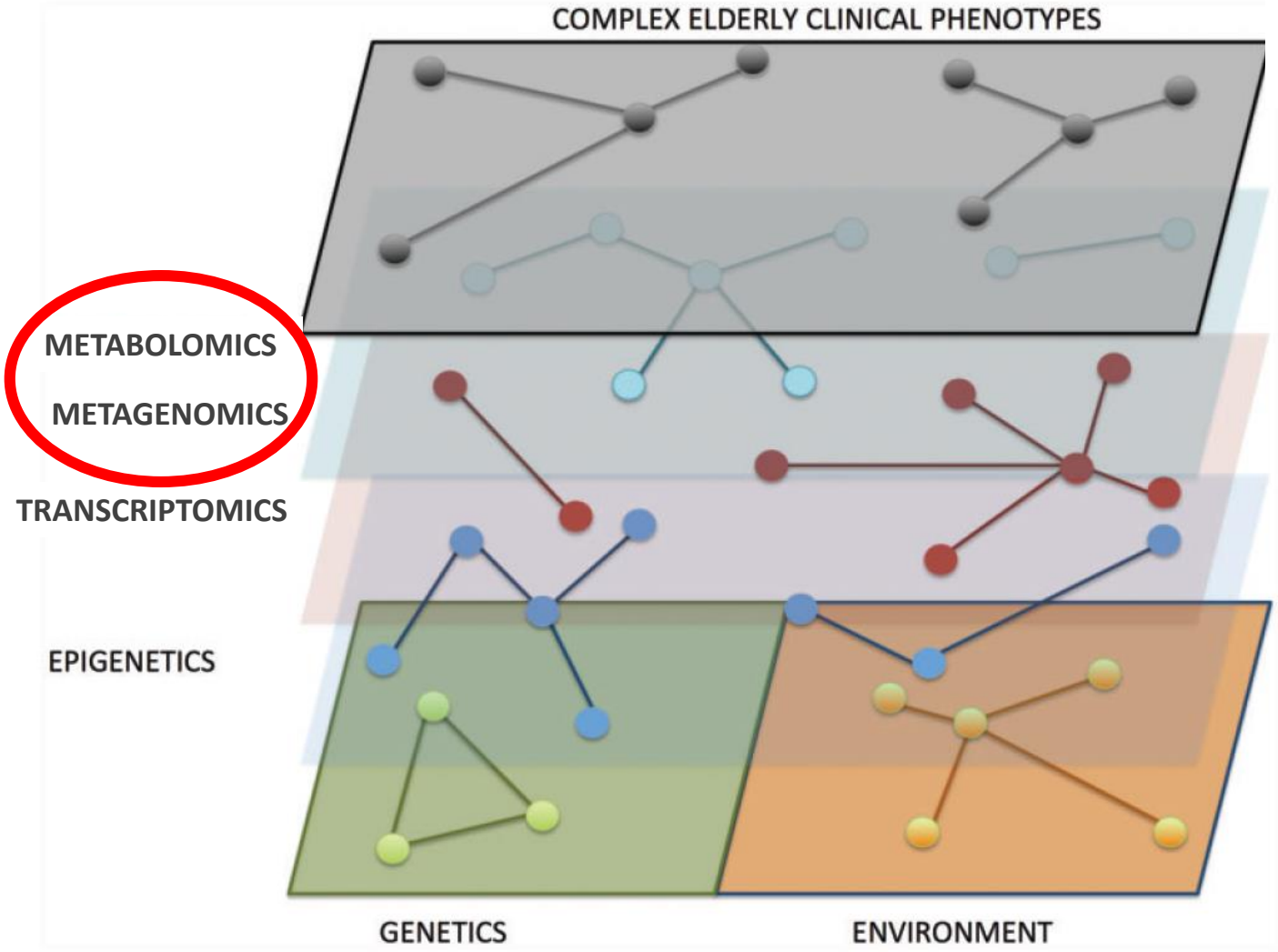


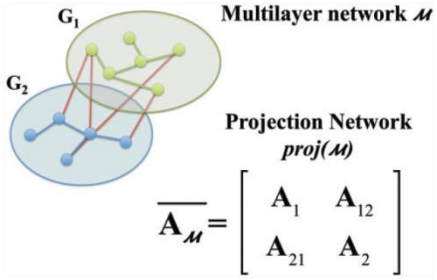


A MULTIPLEX is a set of networks or layers with common nodes.
Each layer corresponds to a given OMIC.
Intra and inter-layers links are treated with ***the new concept of MULTI-LINKS*** *are (correlation and causal relationships).*
The basal layer is divided into ***GENETICS*** *and* ***ENVIRONMENT*** *to quantify their relative role in a given phenotypical trait*

Briefing in Bioinformatics 2015

A SYSTEMIC APPROACH TO AGING/INFLAMMAGING





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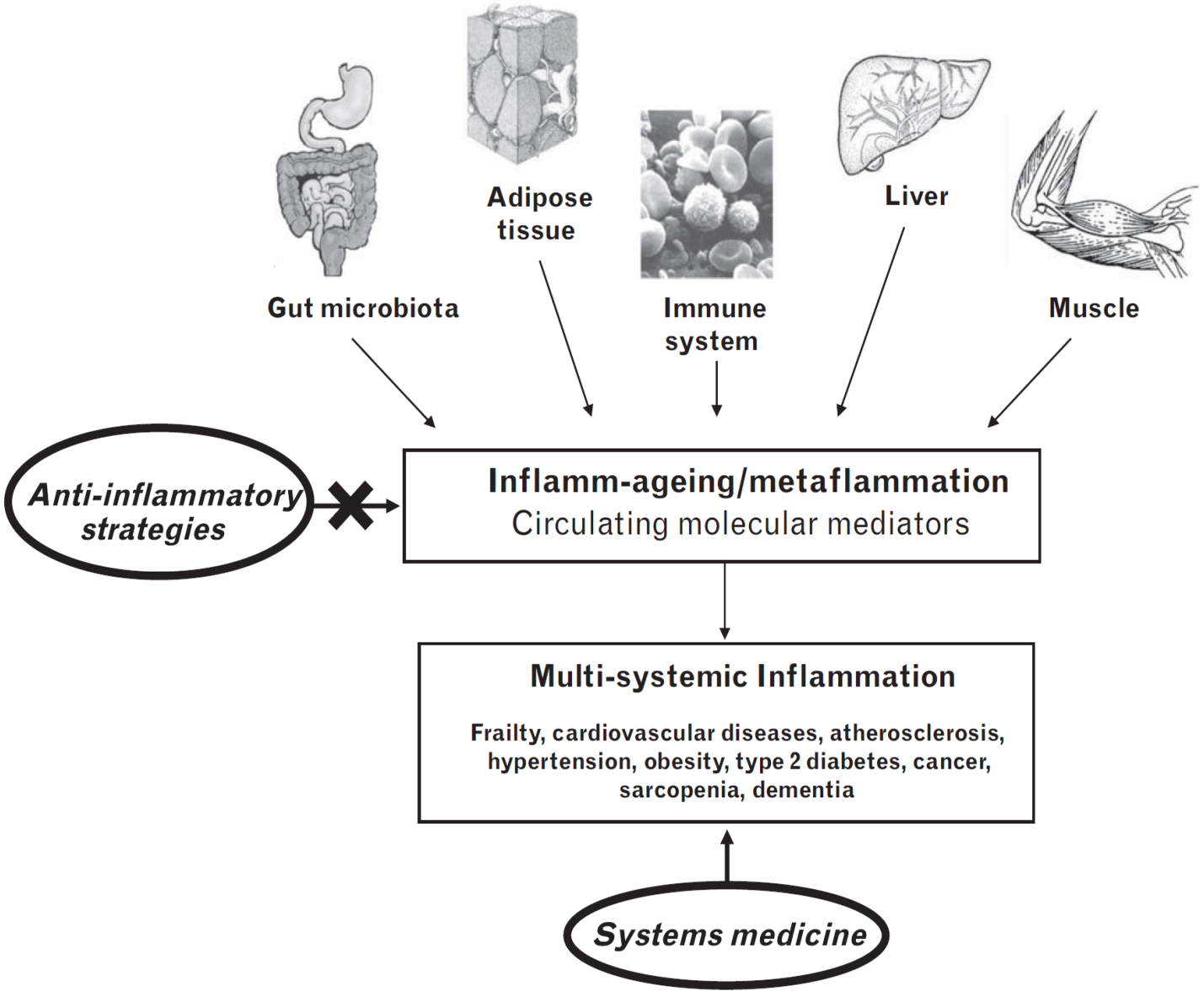
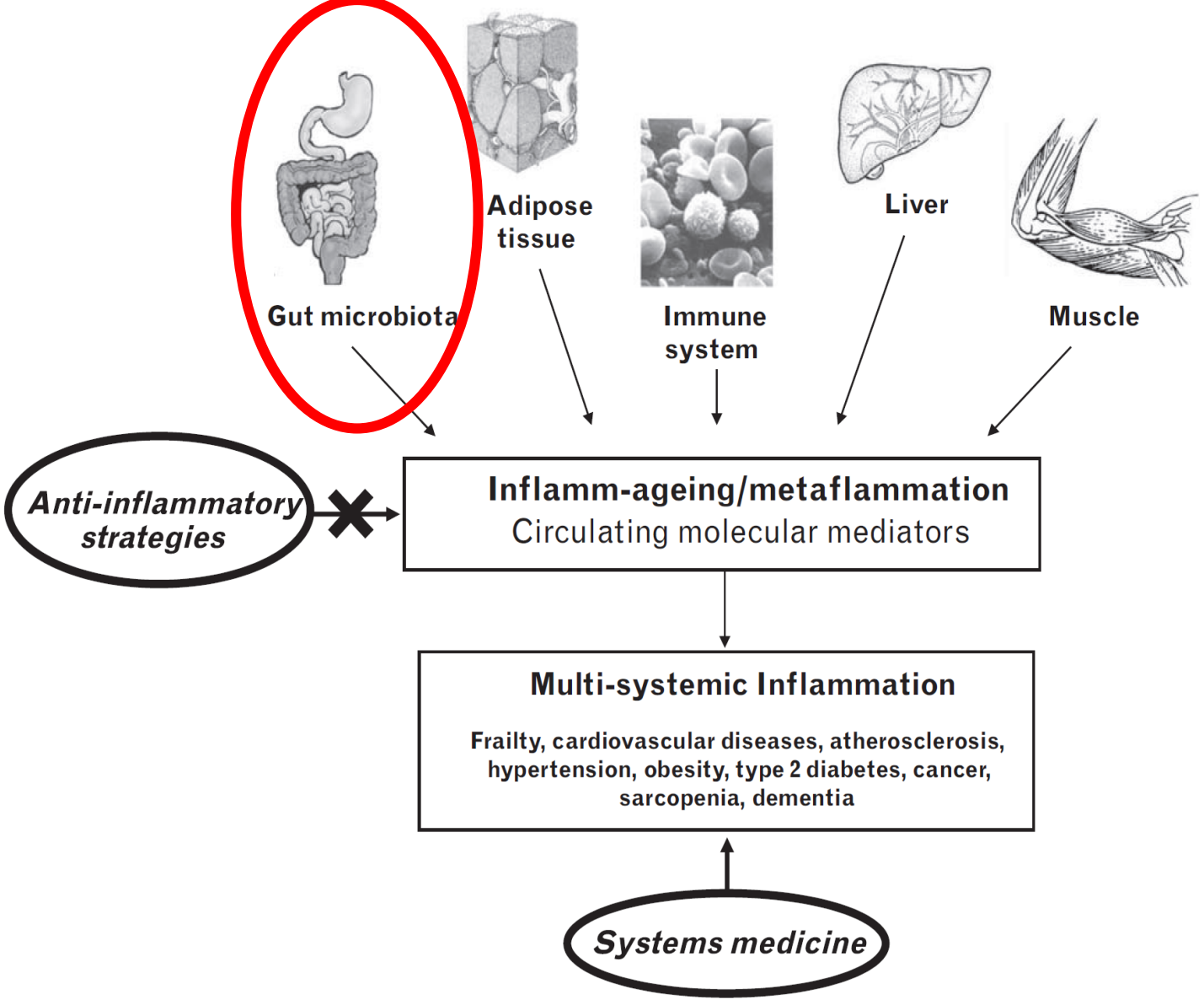
Briefing in Bioinformatics 2015



The complex, systemic nature of INFLAMMAGING

Cevenini et al., Curr Opin Clin Nutr Metab Care 2012

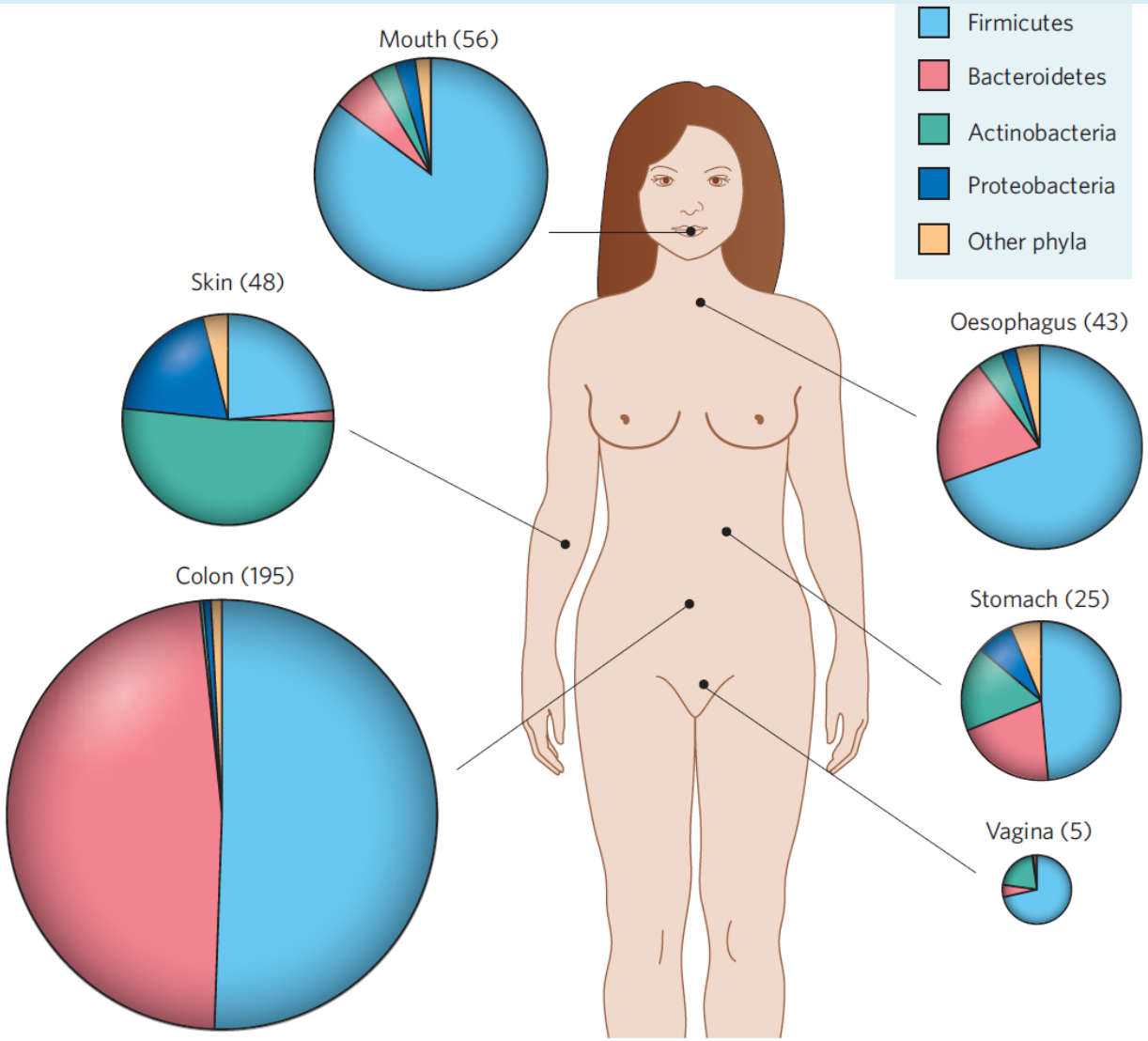


The complex, systemic nature of INFLAMMAGING

Cevenini et al., Curr Opin Clin Nutr Metab Care 2012

Invisible Partners

bacteria in the different body sites



Invisible Partners
bacteria in the different body sites

- **90% of bacteria reside within the gastrointestinal tract** which harbors more than 500 different bacterial species, and about **10^{11} bacteria per gram of luminal content.**
- The human gut microbiome is functional and exerts both **local and long-distance effects** involving hormonal intermediates, metabolites, and immunologic messengers .
- Host-microbe interactions thus have the potential to influence **carcinogenesis** and to promote the onset of others age-related diseases through mechanisms such as **chronic inflammation, induction of genotoxic responses, alteration of the microenvironment, and metabolism**

OPEN ACCESS Freely available online

PLoS one

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

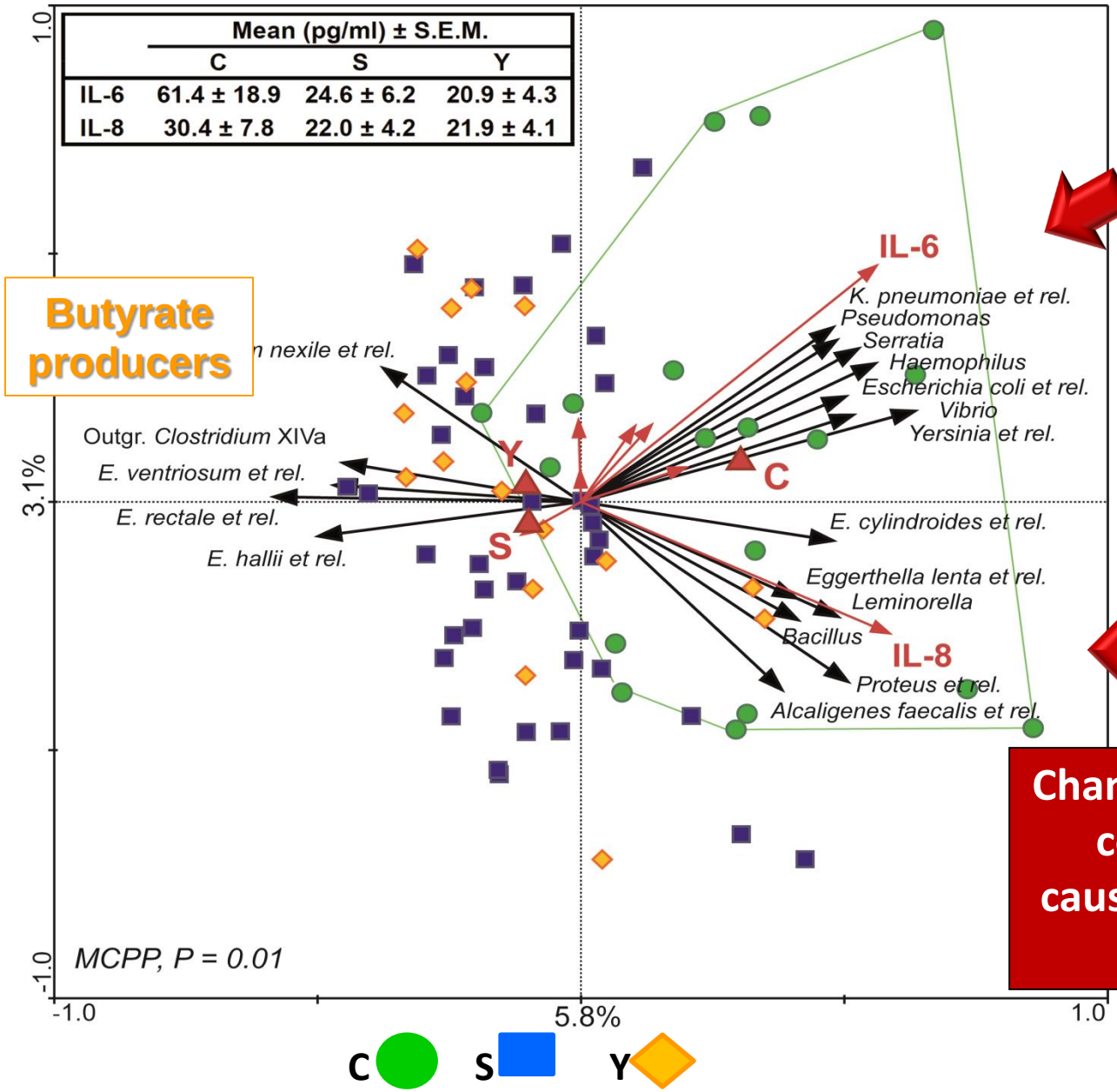
Elena Biagi[1]*, Lotta Nylund[2,3], Marco Candela[1], Rita Ostan[4], Laura Bucci[4], Elisa Pini[4], Janne Nikkïla[3], Daniela Monti[5], Reetta Satokari[2], Claudio Franceschi[4], Patrizia Brigidi[1], Willem De Vos[3,6]

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

CENTENARIAN MICROBIOTA AND INFLAMMATION

	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

8.9% of the total variability of the GM is correlated with the pattern of pro-inflammatory cytokines

Pathobionts

Changes in the microbiota composition can be caused by and contribute inflammaging

www.impactaging.com AGING, December 2013, Vol 5 N 12

Research Paper

Functional metagenomic profiling of intestinal microbiome in extreme ageing

Simone Rampelli [1], Marco Candela [1], Silvia Turroni [1], Elena Biagi [1],Sebastiano Collino[2], Claudio Franceschi [3], Paul W O'Toole [4], and Patrizia Brigidi [1]

By **Illumina shotgun sequencing** of the fecal microbial DNA from the centenarians, elderly and young people, we generated **a total of 214.6 million paired-end reads**, with **an average of 23.8 million reads per subject**.

Metagenome function analysis

- We found **an age-related reduction of the pathways involved in Short Chain Fatty Acids (SCFA) production** via proteolytic fermentation.
- Genes involved in SCFA production, showed an inverse association with aging.

Rampelli *et al*., AGING 2013

SCFA contribute to intestinal homeostasis

SCFA such as **acetate,n-propionate, and n-butyrate:**

- are end products of bacterial anaerobic fermentation of **dietary fibers**;
- are **secreted in high amounts by commensals bacteria** (*e.g.* clusters IV and XIV of Clostridia);
- can be found at **high concentrations in the large intestine** (*e.g.* 20mM n-butyrate in colonic lumen);
- are **an important energy source**
- have **strong anti-inflammatory properties**

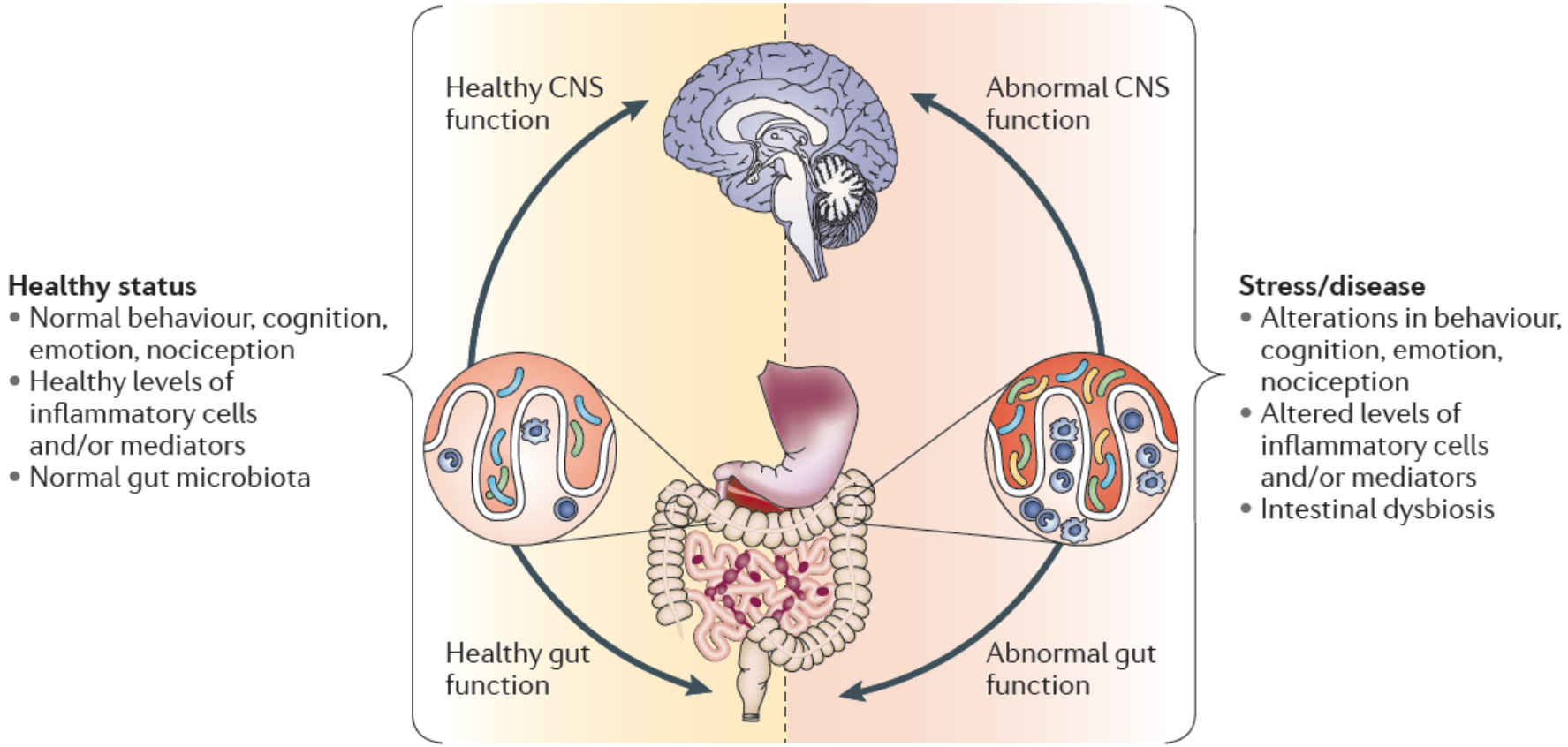
Butyrate is mainly produced by clusters IV and XIV of Clostridia and contributes to the maintenance of intestinal homeostasis:

- Acts as an **energy source** for normal colonic epithelial cells (throphic effect)
- **Upregulates histone H3 acetylation** at regulatory regions of Foxp3 gene facilitating the **differentiation of CD4+ T cells into Treg cells**
- Induces **TGF-beta secretion** by epithelial cells
- Triggers the production of cytoprotective cytokine IL-18 and stimulate **IL-10 and retinoic acid production** by dendritic cells and macrophages
- Suppresses the proliferation of cancerous epithelial cells

Aging Microbiome, Inflammaging and tryptophan metabolism

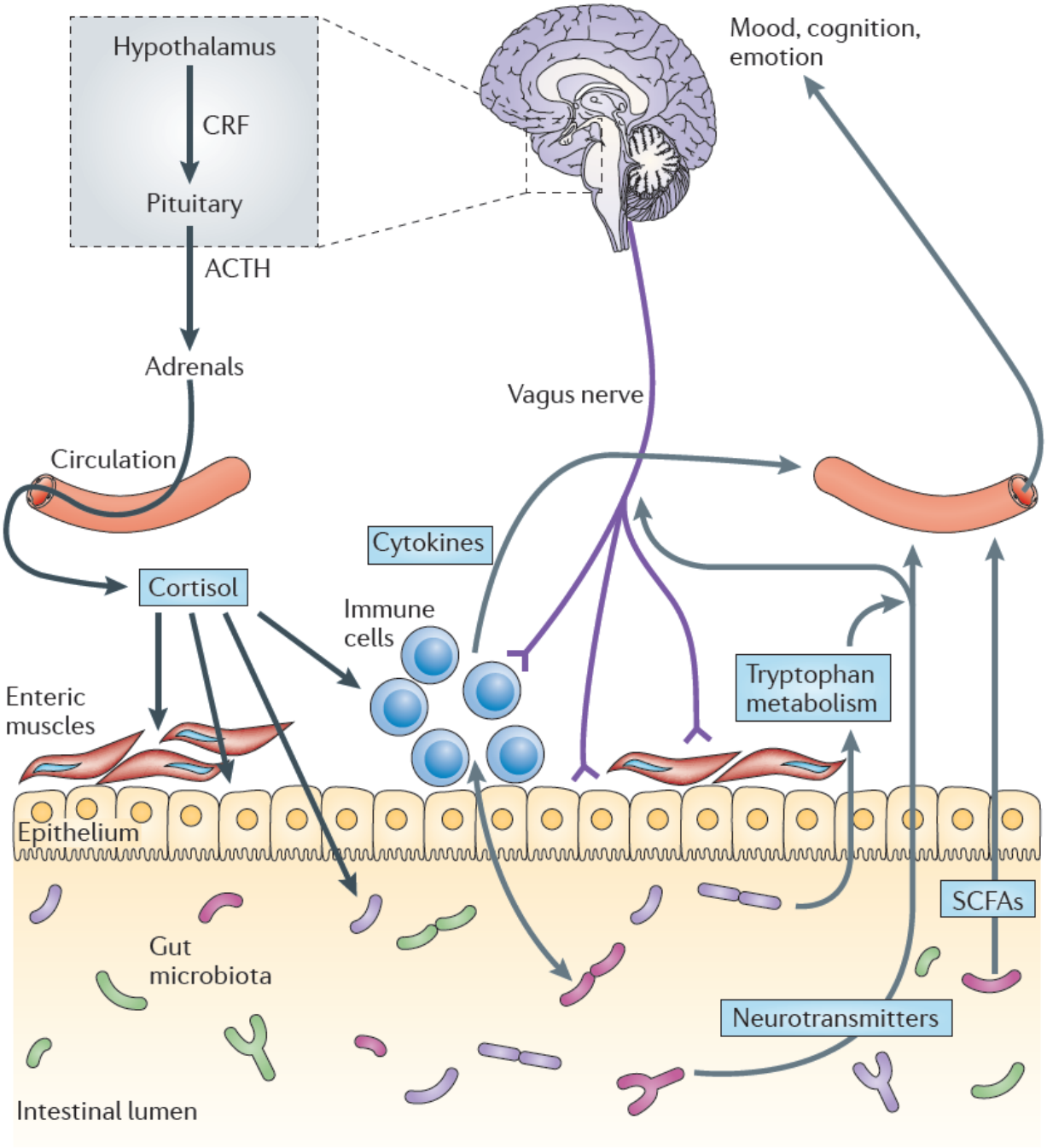
- We observed **an age-related increase of genes involved in the tryptophan metabolism pathway**
- This observation is in agreement with the **reduction of tryptophan in the plasma** of 100+
- Reduced plasma tryptophan levels are related to increase of **immune activation**.
- **The increased consumption of tryptophan by the gut microbiota**, affects its bioavailability within the host, and **can contribute to inflammaging.**

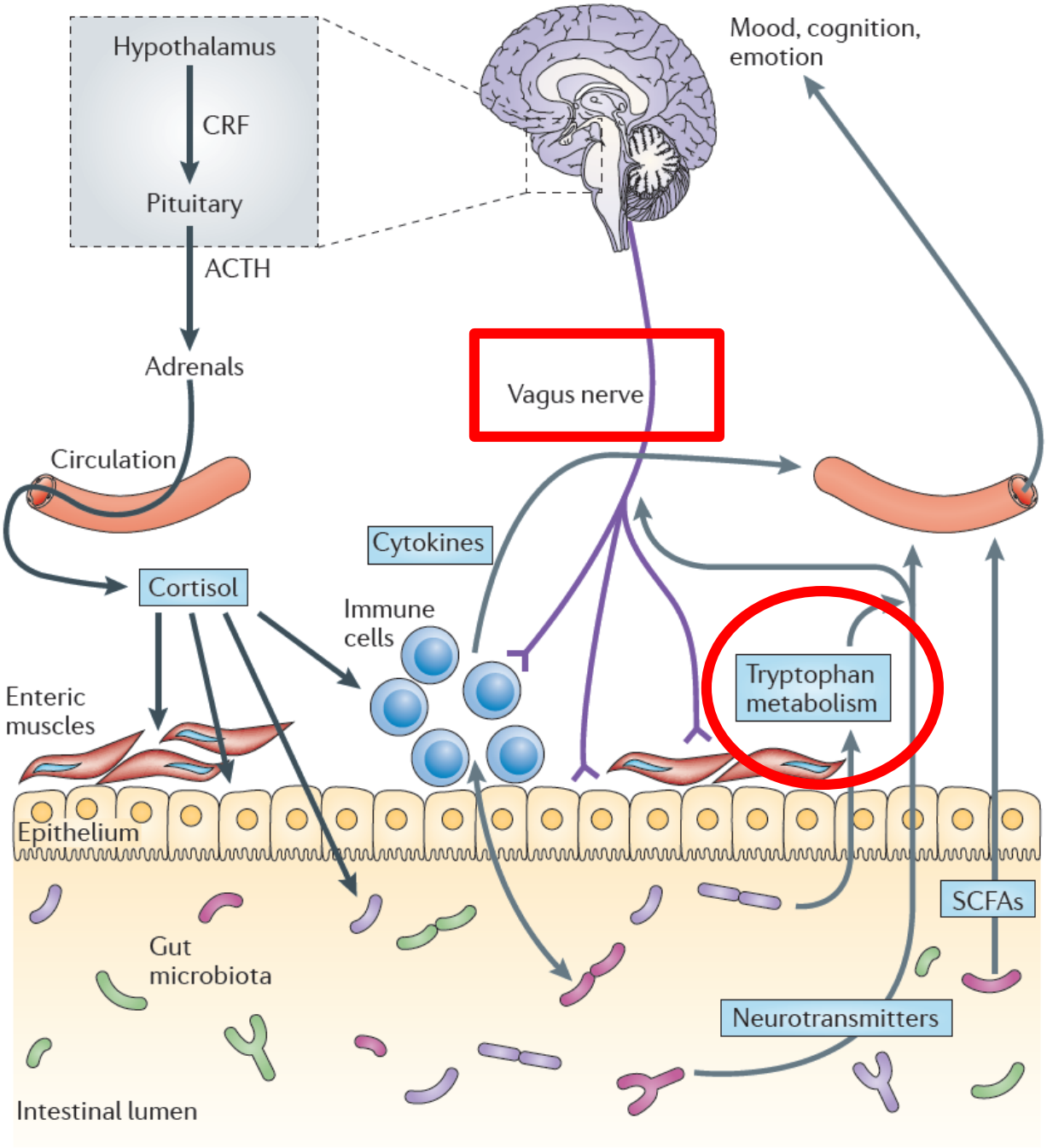
Rampelli *et al*., AGING 2013



The gut-brain axis

Cryan and Dinan, 2012


Hypothalamus
CRF
Pituitary
ACTH
Adrenals
Circulation
Cortisol
Mood, cognition, emotion
Vagus nerve
Cytokines
Immune cells
Tryptophan metabolism
Enteric muscles
Epithelium
SCFAs
Gut microbiota
Neurotransmitters
Intestinal lumen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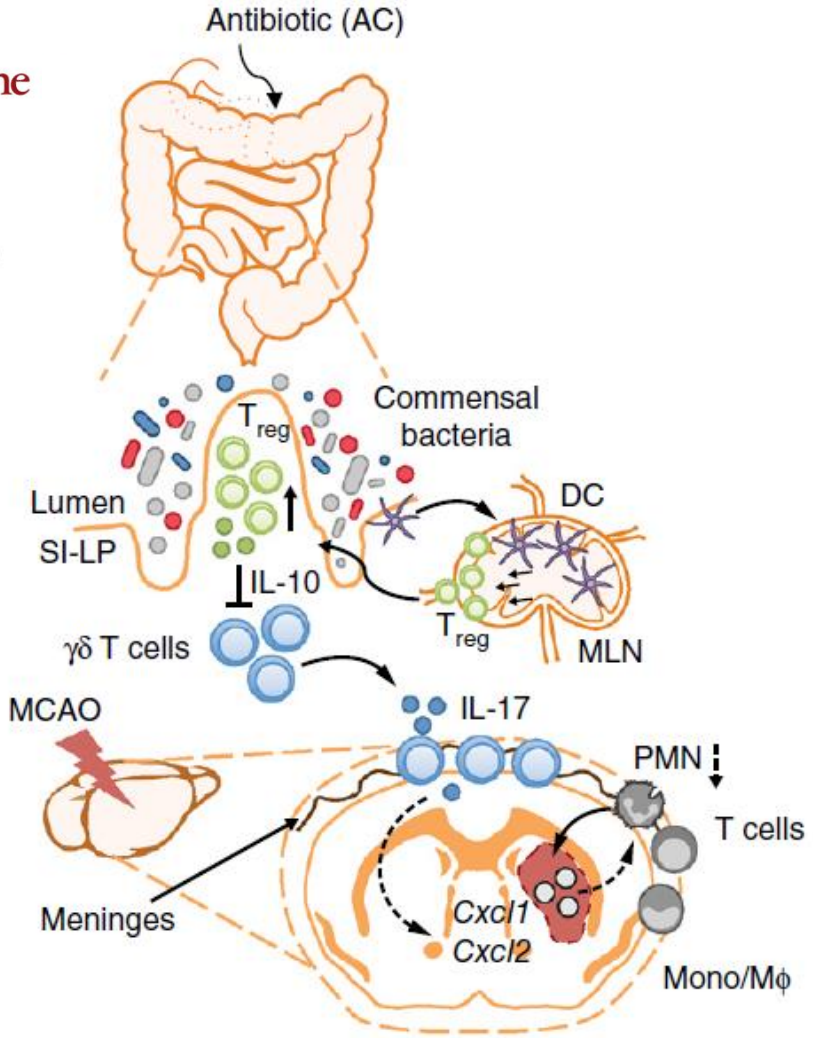
Neurotransmitters
Intestinal lumen

nature medicine

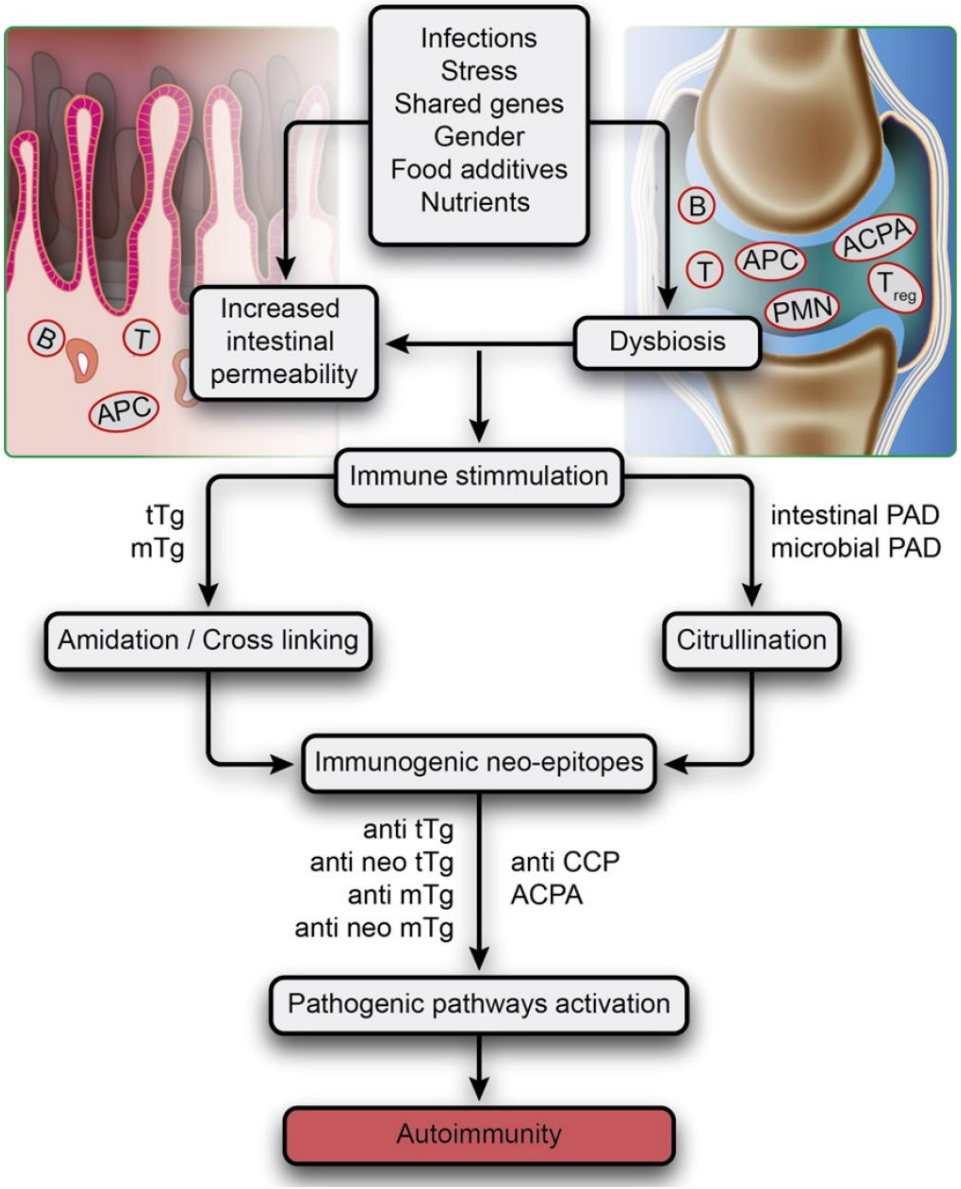
Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells

Corinne Benakis[1,5], David Brea[1,5], Silvia Caballero[2,3], Giuseppe Faraco[1], Jamie Moore[1], Michelle Murphy[1], Giulia Sita[1], Gianfranco Racchumi[1], Lilan Ling[4], Eric G Pamer[2–4], Costantino Iadecola[1] & Josef Anrather[1]



Commensal gut bacteria impact the host immune system and can influence disease processes in several organs, including the brain. However, it remains unclear whether the microbiota has an impact on the outcome of acute brain injury. Here we show that antibiotic-induced alterations in the intestinal flora reduce ischemic brain injury in mice, an effect transmissible by fecal transplants. Intestinal dysbiosis alters immune homeostasis in the small intestine, leading to an increase in regulatory T cells and a reduction in interleukin (IL)-17–positive γδ T cells through altered dendritic cell activity. Dysbiosis suppresses trafficking of effector T cells from the gut to the leptomeninges after stroke. Additionally, IL-10 and IL-17 are required for the neuroprotection afforded by intestinal dysbiosis. The findings reveal a previously unrecognized gut-brain axis and an impact of the intestinal flora and meningeal IL-17$^+$ γδ T cells on ischemic injury.

The gut-joint axis



A. Lerner, T. Matthias / Autoimmunity Reviews 14 (2015) 1038–1047

Gut microbiota and extreme longevity

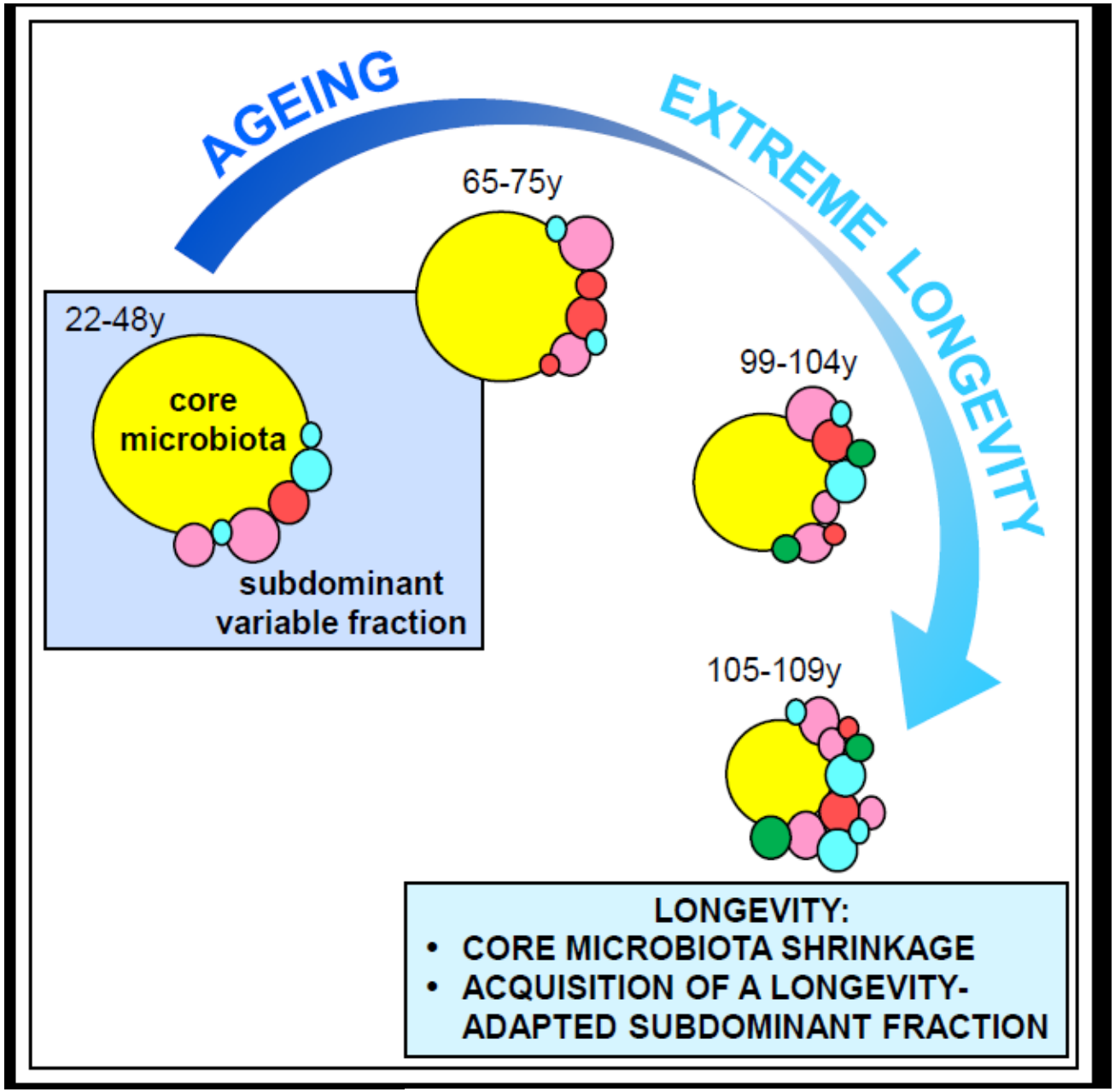
Biagi Elena[1,*], Franceschi Claudio[2,3,4], Rampelli Simone[1], Severgnini Marco[5], Ostan Rita[2,3], Turroni Silvia[1], Consolandi Clarissa[5], Quercia Sara[1], Scurti Maria[2,3], Monti Daniela[6], Capri Miriam[2,3], Brigidi Patrizia[1], Candela Marco[1,*].

Biagi et al., *Curr Biol* in press

- We highlighted the presence of **a core microbiota** of highly occurring, symbiotic bacterial groups (mostly belonging to the Ruminococcaceae, Lachnospiraceae and Bacteroidaceae families), that represented the majority of the intestinal ecosystem in terms of relative abundance in all samples, but **with a cumulative percentage decreasing along with age**.
- The ageing microbiota is characterized by **an increasing contribution of subdominant species**, as well as a rearrangement in their co-occurrence network.

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	↗



Another example of age-related re-modelling

Biagi et al., *Curr Biol* in press

OPEN ACCESS Freely available online

PLOS ONE

Metabolic Signatures of Extreme Longevity in Northern Italian Centenarians Reveal a Complex Remodeling of Lipids, Amino Acids, and Gut Microbiota Metabolism

Sebastiano Collino[1]*, Ivan Montoliu[2], François-Pierre J. Martin[1], Max Scherer[1], Daniela Mari[3,4], Stefano Salvioli[5,6], Laura Bucci[5,6], Rita Ostan[5,6], Daniela Monti[7], Elena Biagi[8], Patrizia Brigidi[8], Claudio Franceschi[5,6], Serge Rezzi[1]

1 Proteomics and Metabonomics, Nestlé Institute of Health Sciences SA, Campus EPFL, Quartier de l'innovation, Lausanne, Switzerland, **2** Applied Mathematics, NESTEC SA, Nestlé Research Center, Lausanne, Switzerland, **3** Department of Medical Sciences, University of Milan, Milan, Italy, **4** Geriatric Unit Ca' Grande Foundation Maggiore Policlinico Hospital, Milan, Italy, **5** Department of Experimental Pathology, University of Bologna, Bologna, Italy, **6** Interdepartmental Centre L. Galvani, University of Bologna, Bologna, Italy, **7** Department of Experimental Pathology and Oncology, University of Florence, Florence, Italy, **8** Department of Pharmaceutical Sciences, University of Bologna, Bologna, Italy

PLOS ONE March 2013 | Volume 8 | Issue 3 | e56564

A total of 457 individuals:
N= 143 centenarians
N= 220 offspring of centenarians
N= 73 offspring of non long-lived parents
N= 21 young subjects

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Research Paper

Serum profiling of healthy aging identifies phospho- and sphingolipid species as markers of human longevity

Ivan Montoliu[1], Max Scherer[2], Fiona Beguelin[2], Laeticia DaSilva[2], Daniela Mari[3,4], Stefano Salvioli[5,6] ,François-Pierre J. Martin[2], Miriam Capri[5,6], Laura Bucci[5,6],Rita Ostan[5,6],Paolo Garagnani[5,6], Daniela Monti[7], Elena Biagi[8], Patrizia Brigidi[8], Martin Kussmann[2,9,10], Serge Rezzi[2], Claudio Franceschi[5,6], and Sebastiano Collino[2]

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[7]Department of Clinical, Experimental and Biomedical Sciences, University of Florence, Viale Morgagni 50, 50134 Florence, Italy;
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[9]Faculty of Life Sciences, Ecole Polytechnique Fédérale Lausanne (EPFL), Lausanne, Switzerland;
[10]Faculty of Science, Interdisciplinary NanoScience Center (iNANO), Aarhus University, Aarhus, Denmark;

DNA methylation profile of 105+

Semi-supercentenarians (105+), their Offspring and age- and sex-matched Controls

Illumina *Infinium* HumanMethylation450 BeadChip

	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

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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

Using data of more than 8000 samples present in 82 databases on DNA methylation data obtained by Illumina platforms (**Infinium 450K and 27K**) Steve Horvath (UCLA) identified in the whole genome **353 CpGs** whose methylation level is a

MULTI-TISSUES PREDICTOR OF AGE

which allows to estimate

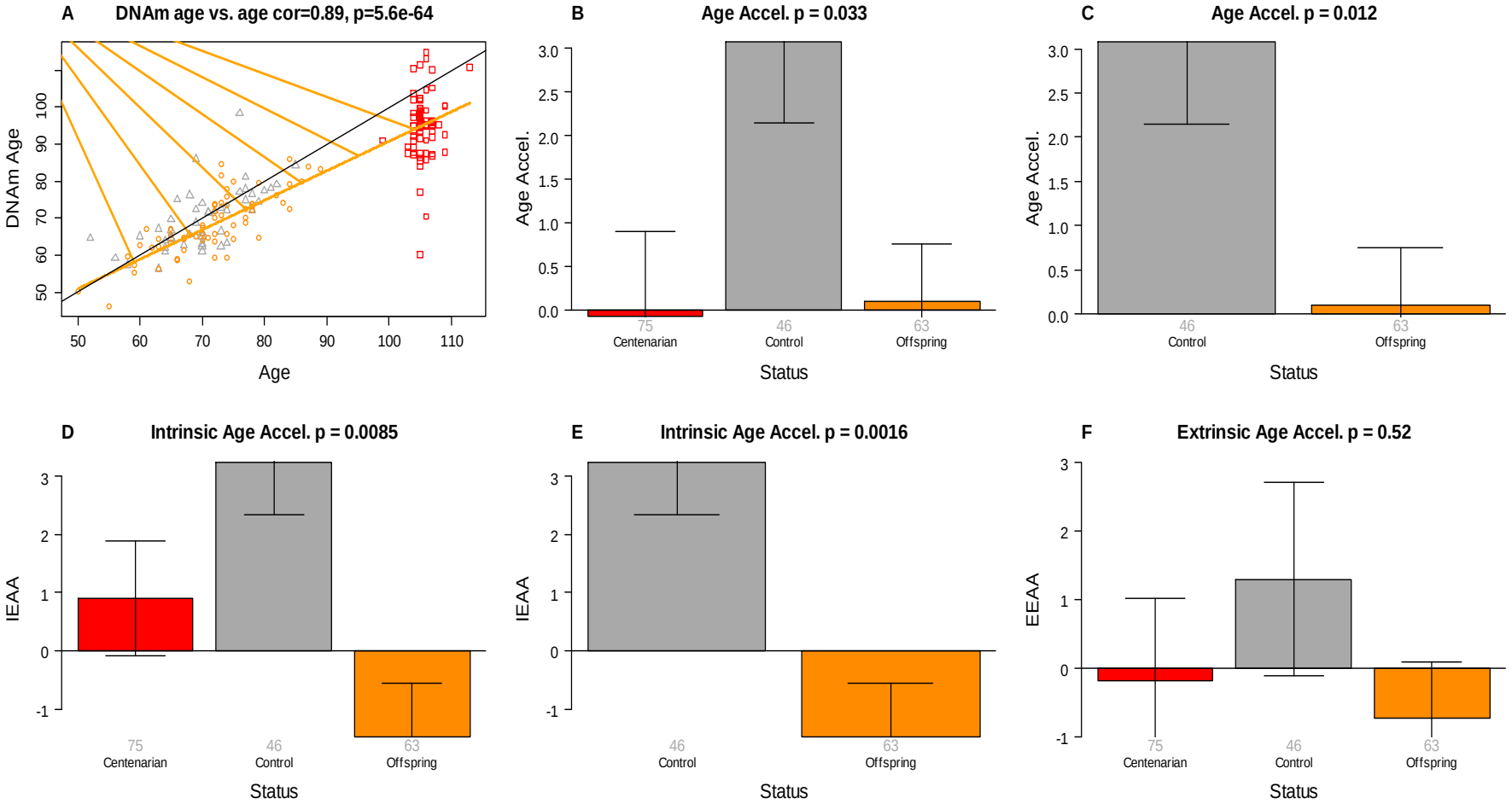
EPIGENETIC AGE *VERSUS* CHRONOLOGICAL AGE

***i.e.* the DNA METHYLATION AGE (DNAm Age)**

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

Correlation between DNAm age and chronological age = 0.97, error = 2.9 years

Measures of epigenetic age acceleration/deceleration



Horvath et al., AGING 2015

105+ and their offspring age more slowly than expected based on their chronological age

According to this model, **semi-supercentenarians are on average 8.7 years younger than expected based on chronological age**, and **offspring of 105+ are 5.2 years younger (p=0.00051) than age- matched controls** even after adjusting for sex and blood cell counts.

Horvath et al., AGING 2015

Thanks for your attention

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