Implementing The Hallmarks Of Aging In The Inspire T-cohort

Felipe Sierra and Jean-Marc Lemaitre

Implementing The Hallmarks Of Aging In The Inspire T-cohort

- A human cohort has little value if researchers don’t mine the data
- The goal is to make the cohort more appealing to researchers
- The Inspire T cohort has a deep covering of clinical variables, and a rich biobank
- On the other hand, biological variables are explored only as a result of individual researcher’s interests

GOAL: To measure hallmarks of aging in the entire cohort, as they are being developed by the geroscience community

Implementing The Hallmarks Of Aging In The Inspire T-cohort

Cell

Leading Edge
Review

The Hallmarks of Aging

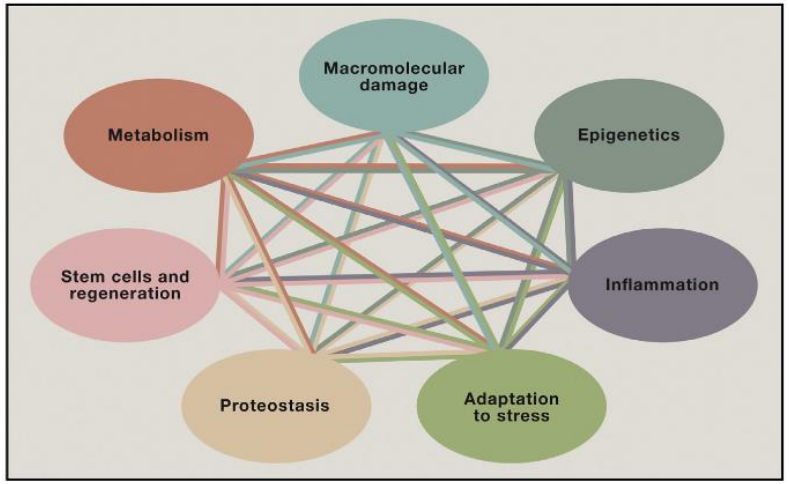
Carlos López-Otín,[1] Maria A. Blasco,[2] Linda Partridge,[3,4] Manuel Serrano,[5,*] and Guido Kroemer[6,7,8,9,10]

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]



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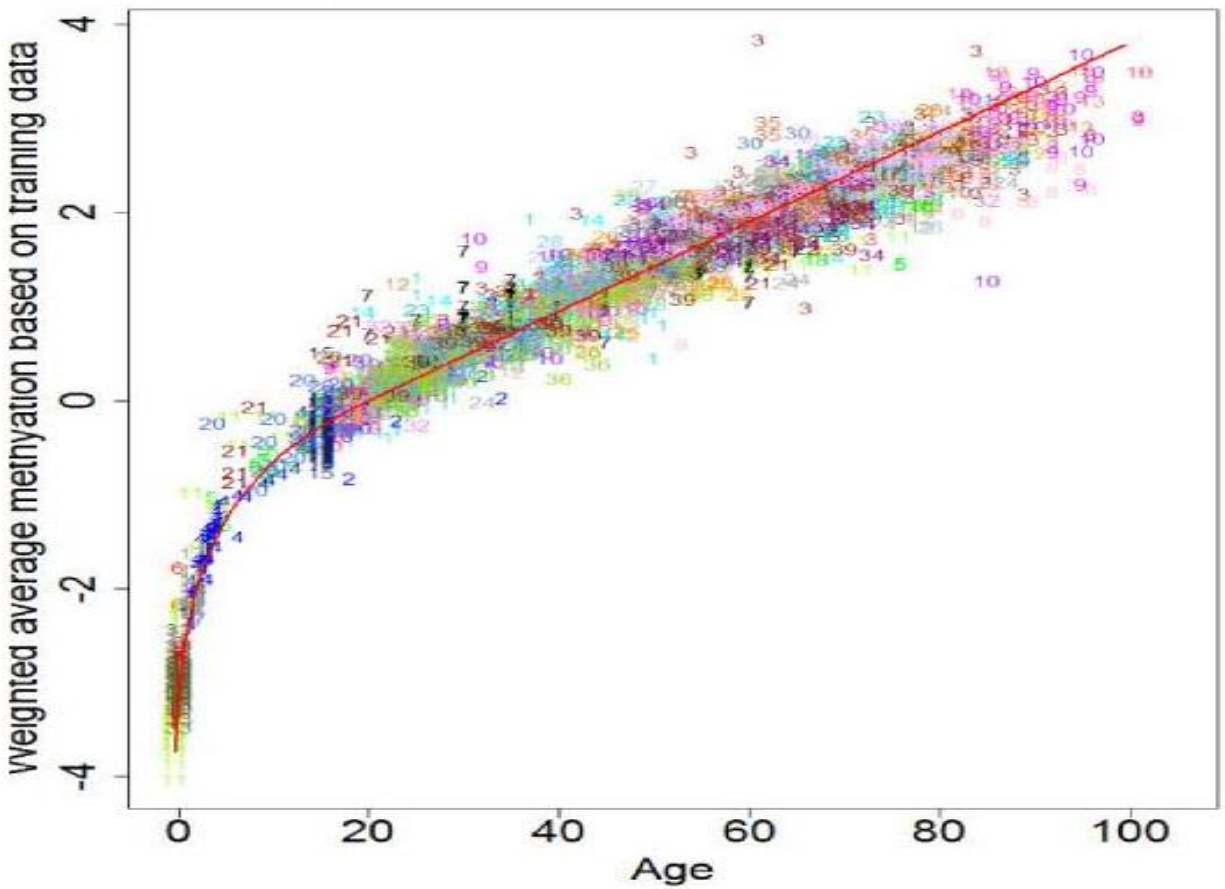
Clocks Are All The Rage

Epigenetic Clocks



DEVELOPING A FRAILTY CLOCK FOR PREVENTIVE INTERVENTIONS

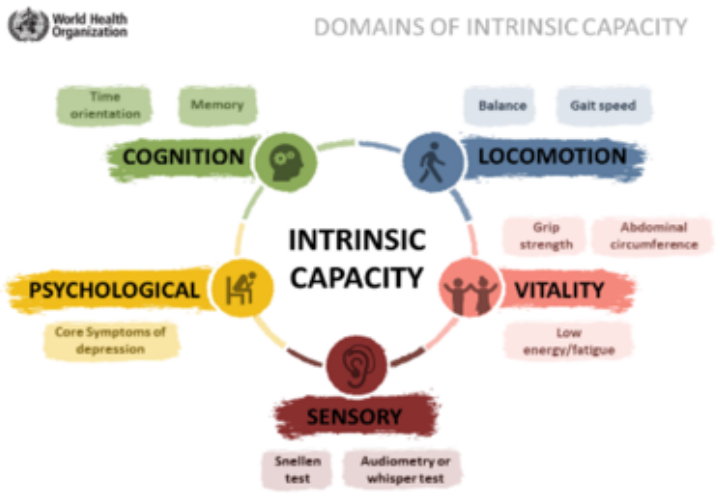
Jean-Marc Lemaitre

Genome and Stem Cell Plasticity in Aging

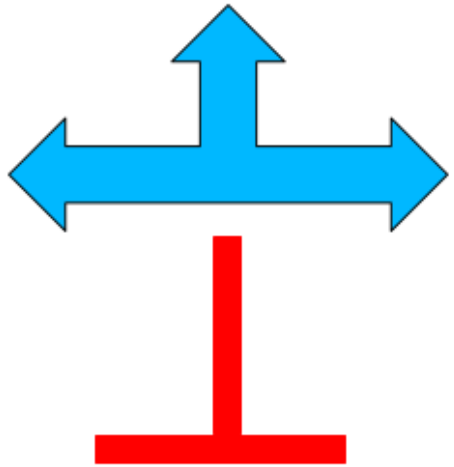
Co-Director IRMB Montpellier, France

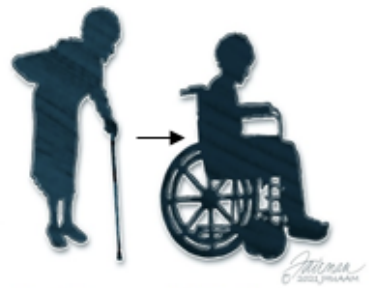
OBJECTIVES

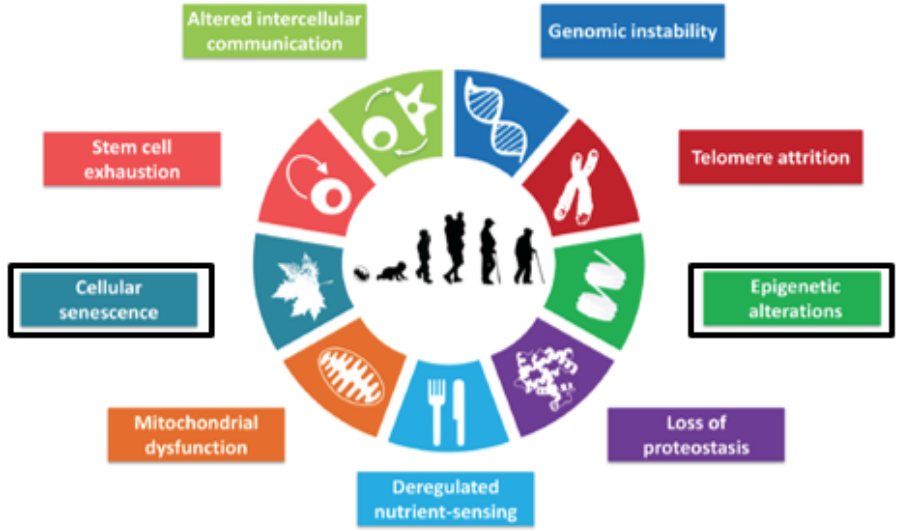
Cohort Inspire -T



Geriatrics

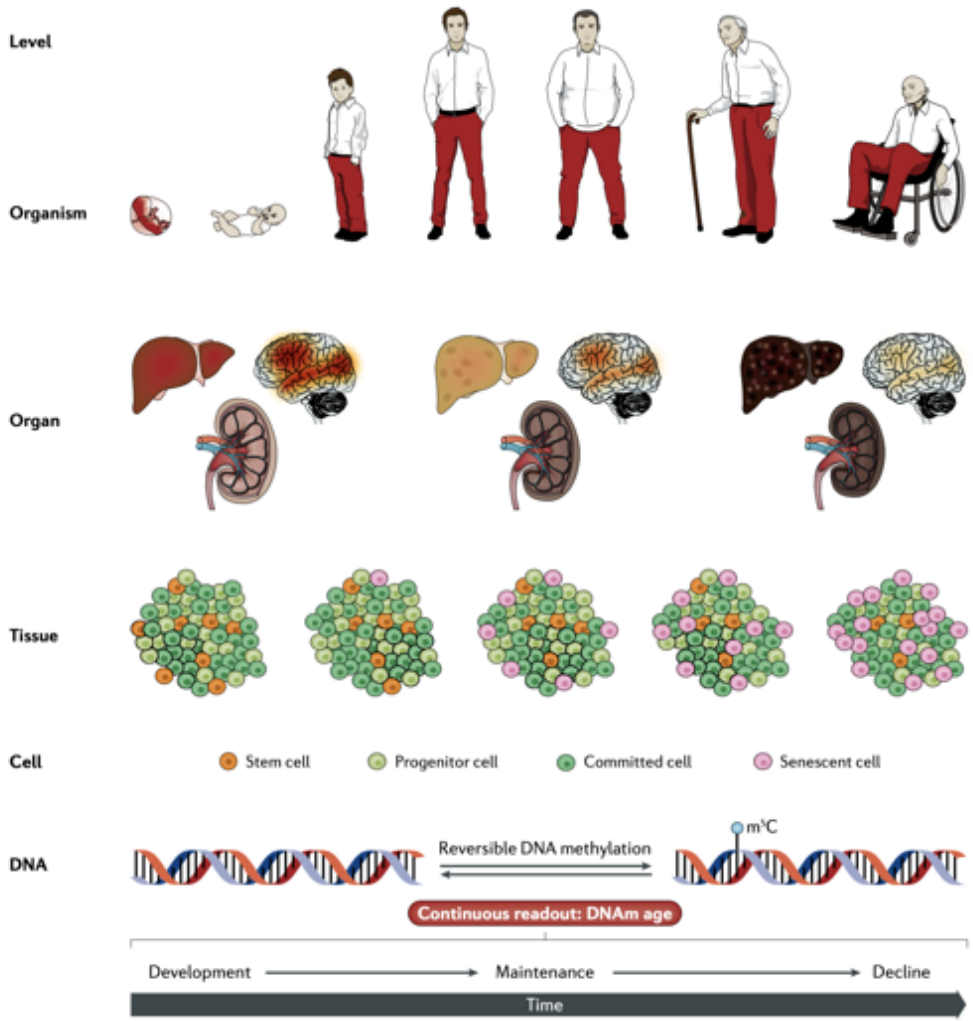






Geroscience

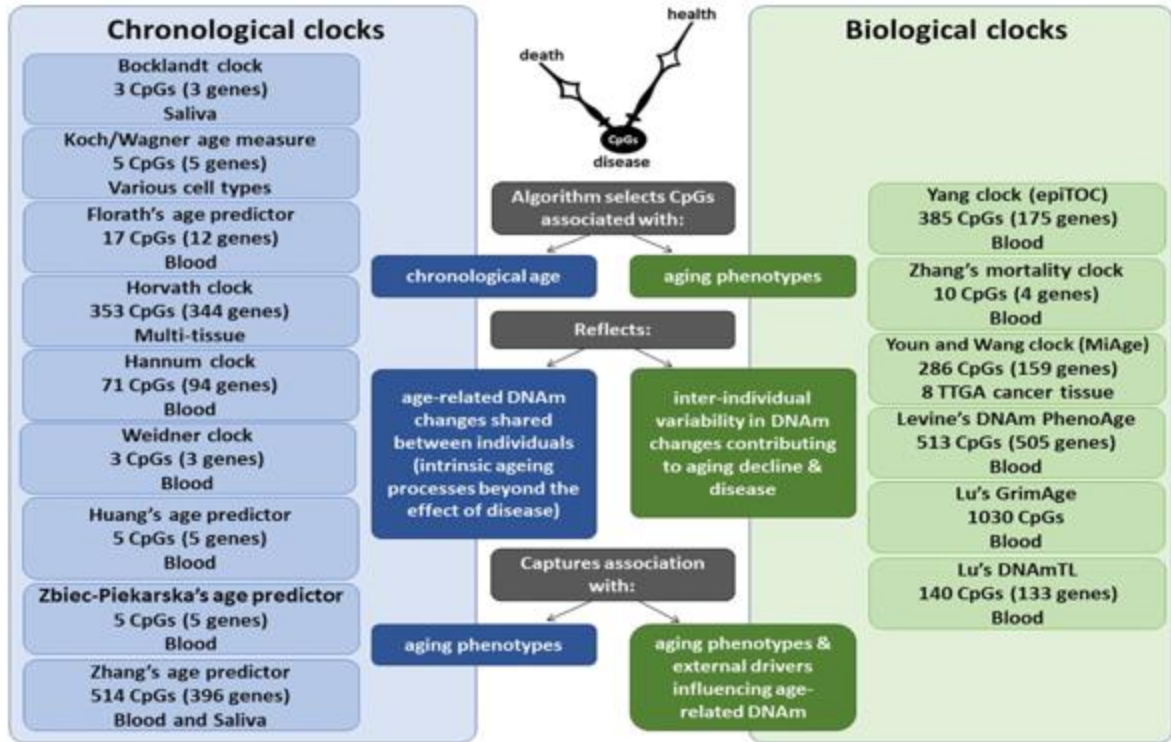
Senescence accumulation and epigenetic drift as potential readouts to evaluate aging progression



Adpated from Horvath et al., 2018

DNA methylation clocks diversity

AGE RANGE	SAMPLE SIZE	TISSUE	PLATFORM
18-70	68	Saliva	Illumina 27K
16-72	130	Various cell types	Illumina 27K
50-75	400	Blood	Illumina 450K
0-101	8000	Various cell & tissue types	Illumina 27K & 450K
19-101	656	Blood	Illumina 450K
0-78	575	Blood	Illumina 27K & 450K
9-75	89	Blood	Pyrosequencing
2-75	420	Blood	Pyrosequencing
2-104	13566	Blood & saliva	Illumina 450K & EPIC



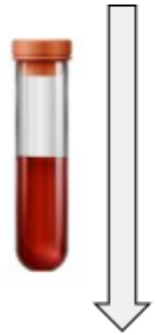
AGE RANGE	SAMPLE SIZE	TISSUE	PLATFORM
19-101	656	Blood	Illumina 450K
31–82	1000	Blood	Illumina 450K
NA	4020	8 TTGA cancer cells	Illumina 450K
>20	9926	Blood	Illumina 27K, 450K & EPIC
NA (mean 66)	1731	Blood	Illumina 450K & EPIC
22-93	2256	Blood	Illumina 450K & EPIC

INSPIRE-T cohort for physiological aging evaluation

INSPIRE
VIEILLIR EN BONNE SANTÉ

20 yo -100 yo
1000 volunteers

Year 1



Year 10

OPPORTUNITIES

PBMC DNA methylation Clocks

. Chronological age

. Biological age

FRAILTY

. Predicted age for co-morbidities

. Predicted age of death

Hôpitaux de Toulouse

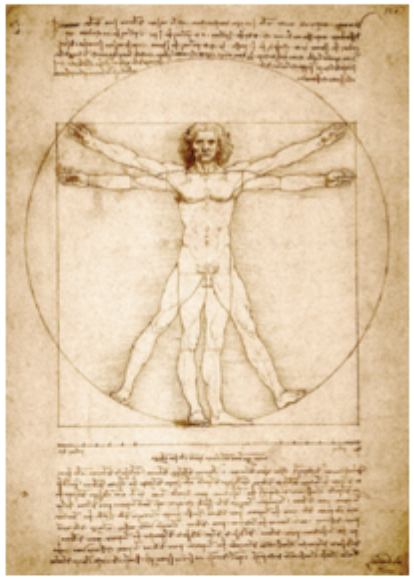
Toulouse GÉRONTOPÔLE

Centre Collaborateur OMS pour la Fragilité, la Recherche Clinique et la Formation en Gériatrie

Road map for developing INSPIRE-T Clock

INSPIRE
VIEILLIR EN BONNE SANTÉ

20 yo -100 yo
1000 volunteers



Year 1

Year 10

DNA methylation
illumina 850 K

Initial step
available clocks

Horwath pan tissue
Horwath skin + blood
Hannum
Levine

INSPIRE-T FRAiLTY Clock

PBMC DNA methylation Clocks

. Chronological age

. Biological age

FRAILTY

. Predicted age for co-morbidities

. Predicted age of death

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Clocks Are All the Rage

- Clocks are based on the analysis of omics signatures: DNA methylation, transcriptomics, proteomics, lipidomics, etc.

- A potentially productive view is to do the entire omics as we go along, rather than specialized subsets useful for available clocks:
    - Total DNA methylation: Horvath, but also others
    - Total transcriptome for iAGE, but also other analyses
    - Total proteome for Wyss-Coray's clock… and others
    - Et cetera

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HALLMARK	Elements	Elements	Elements	Elements
Epigenetics	DNA Methylation	ncRNA	Histone modif	Transposable
Stem Cells	Proliferation	Plasticity	Regeneration	
Inflammation	Senescence	Cytokines	Resident macrophages	Microbiome
Metabolism	Mitochondria	Nutrition	Circadian	Energetics
Quality Control	DNA repair	Telomeres	Proteostasis	Autophagy
Plasticity	Stress response	Resilience	Regeneration	

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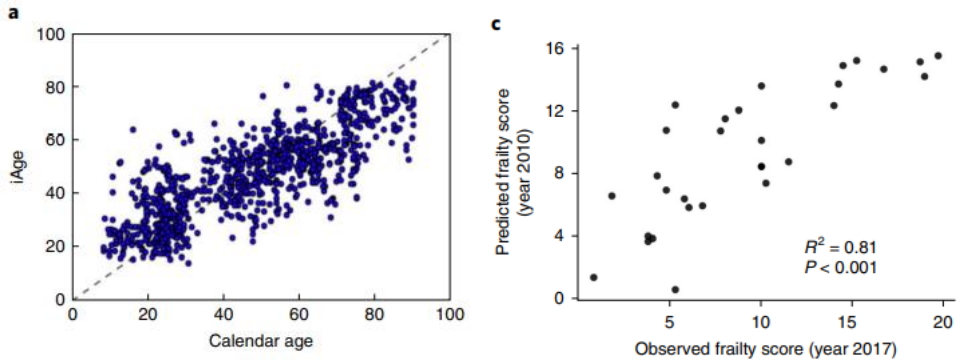
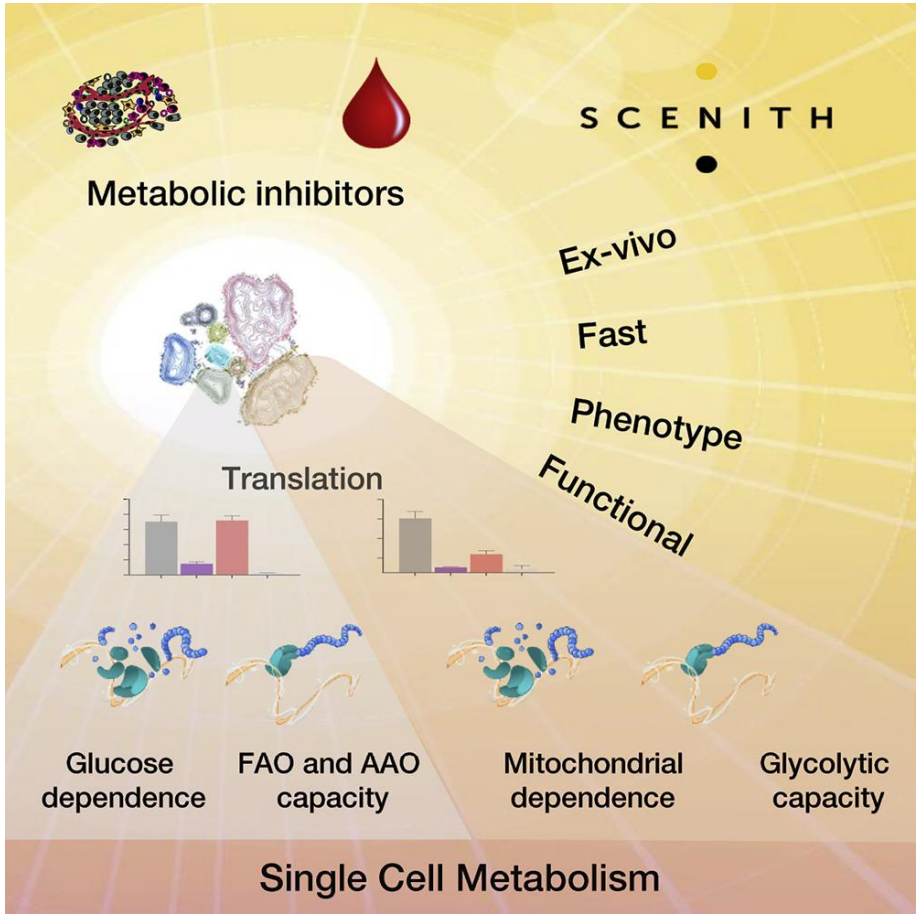
Looking to the Future

ARTICLES
https://doi.org/10.1038/s43587-021-00082-y
nature aging
Check for updates

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

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





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The Plan

- We are starting with the « low hanging fruit »: the epigenetic clock (DNA methylation), through a collaboration with Jean-Marc Lemaitre
- Immediately (because funds are available), we will also launch an effort on the inflammation clock (iAGE), through a collaboration with David Furman
- We are exploring a potential exploratory measurement on metabolism, using the Scenith technology. A collaboration between I2MC and INFINITy
- We are forming an international committee to help guide us on the selection of future hallmarks/measurements that could be of interest

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In Summary

- We are poised to measure epigenetics (DNA methylation)
- In the near future, we are considering:
  - Immunological aging (iAGE)
  - Mitochondrial function aging (Scenith)
- Later, we might consider:
  - Microbiome
  - Cell Senescence
  - Autophagy
  - Telomeres