



IHU HealthAge 1st SAB September 5-7, 2024

Unraveling the biological mechanisms of aging to prevent age-related diseases

Dr. Laure ROUCH, PharmD, PhD, HDR, Associate Professor

IHU HealthAge Center for Epidemiology and Research in Population Health, CERPOP UMR 1295 AGING Team, MAINTAIN







INSPIRE-OMICS. Machine learning-based multi-omics clocks of intrinsic capacity and organ function dynamics





Blood-based multi-omics clock to quantify changes in intrinsic capacity associated with aging







MESSIDORE 2023 not funded despite excellent scores \rightarrow resubmitted 2024

Organs/Tissues Brain Heart Muscle Kidney



Multi-omics clocks of organ-specific biological aging

03



Open Science collaborative platform for biological age predictions

Build a **BIOINFORMATICS TEAM** in Toulouse with Dr. Furman Laure's training at Buck planned

INSPIRE-OMICS. Deep learning-based multi-omics clocks of intrinsic capacity and organ function dynamics



A Novel Blood-Based Epigenetic Clock for Intrinsic Capacity Predicts Mortality and is Associated with Clinical, Immunological and Lifestyle Factors

 Matías Fuentealba, Laure Rouch, Sophie Guyonnet, Jean-Marc Lemaitre, Philipe de Souto Barreto, Bruno Vellas, Sandrine Andrieu, David Furman
 doi: https://doi.org/10.1101/2024.08.09.607252

> MESSIDORE 2023 call. Not funded despite excellent reviewers scores → resubmission MESSIDORE 2024 (NOA February 2025)

Posted August 12, 2024.

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Next achievements.

Next single omics clocks of intrinsic capacity Single omics organ-aging clocks DNAm IC clock validation in DO-HEALTH and other cohorts Build a **BIOINFORMATICS TEAM** in Toulouse in collaboration with Dr. Furman Laure's training at the Buck Institute planned





A Novel Blood-Based Epigenetic Clock for Intrinsic Capacity

Intrinsic Capacity

Construction of the IC clock, a DNA methylation-based predictor of IC trained on the clinical evaluation of cognition, locomotion, psychological well-being, sensory abilities, and vitality



b. Correlation between IC and the DNA methylation-based estimate of IC (DNAm IC) in the best model. **c.** Correlation between DNAm IC and chronological age.



e. Correlations between age acceleration from epigenetic clocks (i.e. age adjusted epigenetic age) and age-adjusted DNAm IC. **f.** Overlap between CpGs included in the IC clock (blue circles) and epigenetic clocks (yellow circles).

IC clock captures a distinct aspect of aging biology



e

A Novel Blood-Based Epigenetic Clock for Intrinsic Capacity

Calculation of DNAm IC clock in the Framingham Heart Study. Age-adjusted DNAm IC predicts all-cause mortality, and is strongly associated with changes in molecular and cellular immune and inflammatory biomarkers, functional and clinical endpoints, health risk factors, and diet



Framingham Heart Study Three Generations of Dedication

b. Top 20 biological processes enriched in aenes significantly associated with DNAm IC

> **b.** Cox proportional hazard models adjusting for chronological age for DNAm IC and firstand second-generation epigenetic clocks







b



Contributions of epigenetic and inflammatory aging to age-related diseases and syndromes



NIAGARA COG-HEART. Cognitive and cardiovascular health INSPIRE-T Study

Cross-sectional analyses completed - papers writing ongoing





Sex-specific associations accelerated epigenetic / inflammatory aging and cognition, added predictive value and potential synergistic effect



03

Sex-specific associations accelerated epigenetic / inflammatory aging and global cardiovascular health, cardiovascular risk factors/disease

Mediating effect of cardiovascular health in association biological aging and cognitive health

Function - intrinsic capacity
INSPIRE-T Study

Mild Behavioral impairment COGFRAIL and INSPIRE-T Studies Analyses ongoing paper milestone M12 2024 collaboration Pr. Philipe DE SOUTO BARRETO

Analyses to start - collaboration Pr. Maria SOTO

Unraveling the Geroscience Hypothesis of Alzheimer's Disease: From Aging Biology to groundbreaking AD therapeutics using the INSPIRE-T cohort



- 1 age greatest risk factor for Alzheimer's disease & related dementia
- Processes linked to ADRD gradually manifest across the lifespan



INSPIRE-T uniquely designed and phenotyped to address this research!

Identifying **upstream drivers** of AD pathogenesis and **targeting biological aging** → possibility of **disrupting foundational cause of AD** SASP-AMYLOID. Disentangling the role of cellular senescence in amyloid- β pathology burden and progression



Identify a set of plasma SASP proteins that can predict crosssectional and longitudinal plasma p-tau217 indicating amyloid-β burden and progression



Collaboration Dr. Nathan LeBrasseur





Investigate SASP added predictive performance over socio-demographic _____and clinical predictors



IHU HealthAge internal call 2024. FUNDED

Assessment of blood biomarkers of cellular senescence

SASP Cytokines Growth factors Proteases Extracellular matrix Senescent cell

28 candidates SASP biomarkers 500 μL of plasma for each participant Total estimated cost = 199.880 USD

SASP vs. exosomes?

Protein array to profile multiple SASP factors simultaneously vs. ELISA individual factors?