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Deadline: February 27th, 2026

EUR CARe PhD program pre-proposal

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Research project title: Deciphering the Cellular and Epigenetic Mechanisms of Aging on native human Bone Marrow Mesenchymal Stem Cells

Research program abstract (max 500 words):

1. Introduction

Aging is a complex biological process characterized by a progressive decline in tissue function, increased susceptibility to diseases, and reduced regenerative capacity. Bone marrow mesenchymal stem cells (BM-MSCs) have a key role in maintaining skeleton homeostasis and hematopoiesis. However, aging in MSCs contributes to bone loss, impaired bone regeneration, metabolic disorders, altered immunity through inflammaging, and potentially dissemination of some cancer cells.

Despite extensive research, the molecular mechanisms underlying age-related dysfunction in human BM-MSCs remain incompletely understood, mainly because almost all reported studies use cultivated MSCs,
whose phenotype is altered compared to bone marrow residing native MSCs (nMSCs) which remain understudied.

Aging clocks emerged as promising tools for measuring the aging process. Artificial intelligence approaches can accurately estimate the age of an individual based on omics (epigenetics and transcriptomics) data. Thus, for the PhD project we plan to develop and apply aging clocks optimized for the evaluation of BM-nMSC aging and for modeling the impact of age on 3D ex vivo bone models, which we have generated in our ongoing ANR 3D-eMAGE project.

2. Research Objectives

By using multimodal experimental datasets and innovative computational approaches, we aim to:
1) map epigenetic modifications (DNA methylation, histone modifications) in young vs old BM-nMSCs to generate quantitative epigenomic descriptors (ageing clocks)
2) characterize the spatial structures of in vitro native BM generated by young vs old MSCs
3) employ image analysis and deep learning approaches to relate the cells' epigenomic descriptors to the spatial structures identifying quantitative metrics of bone aging.

3. Methodology

3.1. Sample characteristics (Restore, Toulouse)

Young (20-30 years) and aged (60+ years) human BM-MSCs directly isolated from bone marrow aspirates.
We will assess MSC proliferation and differentiation potentials. Characterization will be performed by flow cytometry, Colony-forming unit-fibroblast (CFU-F) assays will evaluate self-renewal capacity. All of these processes are carried out in our ongoing ANR granted project 3D-eMAGE.

3.2 Multiomics characterization and ageing clock construction (Restore, Toulouse & Budapest)

We aim to apply single-cell transcriptomics aging clock (i.e., AI-based age prediction models) and analyze the transcriptomics age of single-cells. We will then build cell type-specific protein-protein interaction networks and examine their aging using network science tools. We will apply various methylation aging clocks and then analyse

the epigenetic age differences. Experiments will be performed in Toulouse and all analyses will be carried out by the student.

3.3 Characterization of the 3D bone tissues from young and old MSCs (Restore, Toulouse)
We will perform deep learning classification of the images of 3D reconstituted bone models to identify structural features associated with ageing features found above.

4. Expected Outcomes
New key molecular pathways driving BM-nMSC aging from their deep multiomics characterization.
New biomarkers of BM-nMSC dysfunction in aging and demonstration of functional defects through imaging of bone microenvironments.
From a computational point of view, we will develop methods to relate cell phenotypes to characteristics of the multicellular structures that they produced in ex-vivo models.

Describe in 50 words max for each how this project fits the 3 defining criteria of the CARe graduate programme:

1) **Relation to CARe topics of Cancer, Ageing and/or Rejuvenation**
   MSCs produce bone forming cells, osteoblasts, chondrocytes, pericytes, and the hematopoietic stem cell microenvironment. MSCs ageing disturbs all of these compartments leading to osteoporosis, bone tumors, metabolic diseases, inflammaging, clonal hematopoiesis, and can induce cancer associated fibroblasts in tumours. Understanding aging of BM-MSCs is relevant for both cancer and aging.
2) **Multidisciplinary aspect**
   The project involves a new consortium with an AI lab, with a focus on mathematics informatics and deep learning for analysing aging-associated diseases, and a cellular and molecular biology research lab, with extensive expertise on MSCs. Experimental techniques used will span multiomics, advanced imaging and unique ex-vivo 3D cultures.
3) **International and/or industrial aspect(s)**
   The PhD programme will involve two labs, one in Toulouse, France, and one in Budapest University, Hungary, where the student will spend 6 months to develop advanced AI epigenetic clocks and image classification tools.

5 keywords in line with EUR CARe

Aging clock, Bone aging, Mesenchymal stem cells, Deep learning, Network analysis.

5 references of the teams, highlighting the co-signatory students:

*Lemenager, H., et al., Cell immaturity and white/beige adipocyte potential of primary human adipose-derived stromal cells are restrained by culture-medium TGFbeta1. Stem Cells, 2020. 38(6): p. 782-796.
*Fievet, L., et al., Single-cell RNA sequencing of human non-hematopoietic bone marrow cells reveals a unique set of inter-species conserved biomarkers for native mesenchymal stromal cells. Stem Cell Res Ther, 2023. 14(1): p. 229.
*Muralidharan C, Zakar-Polyák E, Adami A, Abbas AA, Sharma Y, Garza R, Johansson JG, Atacho DAM, Renner É, Palkovits M, Kerepesi C, Jakobsson J, Pircs K. Human Brain Cell-Type-Specific Aging Clocks Based on Single-Nuclei Transcriptomics.Advanced Science, Vol 12, Issue 43, e061092025 (2025)
*Zakar-Polyák E, Csordas A, Pálovics R, Kerepesi C. Profiling the transcriptomic age of single-cells in humans. Communications Biology, 7:1397 (2024).
*Kerepesi C, Gladyshev VN. Intersection clock reveals a rejuvenation event during human embryogenesis. Aging Cell, Vol 22, Issue 10 (2023).