

Appel à manifestation d'intérêt - Chaire de professeur junior

Fiche projet type

Établissement/organisme porteur : Inserm

Nom du chef d'établissement/d'organisme : Gilles Bloch

Site concerné : Institut Mondor de Recherche Biomédicale, IMRB (INSERM U955-UPEC) _
Faculté de Santé. Créteil

Région académique : Val- de-Marne

Établissements/organismes partenaires envisagés : Université Paris Est Créteil (UPEC) and
CEA (MetaboHUB, CEA-INRA UMR 0496)

Nom du projet : Role of liver senescence in age-related diseases (Acronyme : LIVE-AGE)

Mots-clés : Senescence, cardiac aging, non- alcoholic fatty liver disease, diabetes mellitus, sarcopenia

Durée visée : 5 years

Scientific domain : Biology/Health/Metabolism/Senescence

Section (s) CNU/CoNRS/CSS correspondante (s) : CSS3 Inserm / CNU section 66

Strategy of the host institution: (15 lignes maximum)

"Aging /senescence /metabolism" is one of the priorities of the Inserm and our group is a partner of two dedicated programmes : Age-Med network and PEPR "Deep-Diab".

The chair also falls under the priority area "Health Environment" of our UPEC university and the priority axis "longevity, vulnerability and pathologies linked to aging" of our institute, the Mondor Institute for Biomedical Research (IMRB).

The recruited experienced researcher will benefit from an enriched environment to develop his project since these axes are enhanced by national and international projects that our team coordinates :

- 1) **RHU CARMMA (PIA2):** a project studying the impact of obesity on accelerated aging;
- 2) **EUR LIVE (PIA3):** University research school aiming to train master and PhD students for taking vulnerability into account, at the intersection of health/biology, health economics and health sciences;
- 3) **H2020 IMI CARDIATEAM:** a European project aiming to identify the specific mechanisms of diabetic heart disease from human cohorts to the development of preclinical models;
- 4) **FHU SENEC:** a project bringing together 19 hospital departments and 19 laboratories with the aim of targeting cellular senescence and assessing health trajectories in metabolic diseases.

Strategy of the host laboratory :(15 lignes maximum)

The Mondor Institute for Biomedical Research (IMRB, INSERM U955 – University of Paris Est Créteil) is one of the main biomedical research centres in eastern Ile-de-France with national and international influence. Its research teams develop high-level basic and translational research in a wide variety of fields with easy access to healthcare services and many patient cohorts.

The team that will host the candidate has dedicated its research efforts on "Cellular senescence, metabolism and cardiovascular diseases". The team is also deeply involved in the strategic theme of the IMRB "Environmental Diseases and Aggressions" as shown by the recent acquisition of an FRM/Environment grant on this topic. Furthermore, this team is developing an innovative research

exploring the inter-organ communication and the role of cellular senescence in the initiation and aggravation of cardiovascular, metabolic and lung diseases, Age- (FHU SENEC, RHU CARMMA, ANR DOXEPISEN, FRM Equipe). The host team participates in the INSERM Age-Med network, contributes to the development of the PEPR BioAgir and the PEPR Deep-DIAB. In addition, the host team is developing close collaboration with RHU QUIDNASH consortium and as such provides a ideal research milieu where the proposed studies can be performed.

Summary of the scientific project : 15 lignes maximum

LIVE-AGE is a project at the intersection of metabolism and senescence, relying on the breakthrough concept that diabetes-related hepatic and cardiac disorders and sarcopenia are causally interlinked through a senescence-like state of the liver that undermines key metabolic functions of the liver, including essential amino-acids catabolism. Based upon our recent data on age-related liver senescence acting as a key determinant of cardiac ageing through essential amino acid impaired catabolism, we hypothesize that liver senescence plays a key role in the context of diabetes-related alcoholic fatty liver disease (NAFLD) and represents an independent risk factor of cardiomyopathy and sarcopenia.

To explore the induction of liver senescence across a range of NAFLD severity and study the molecular mechanisms between senescence (p21) and decline in hepatic function, we will use an *in vivo* approach (two distinct rodent models of NAFLD induced by high fat diet +/- CCL4) and an *in vitro* approach (cultured hepatocytes incubated +/-glucose/palmitate to mimic diabetes). Human liver slices (control or NAFLD patients) will corroborate findings. To establish the senescence-induced impairment of liver to the noxious liver-heart and liver-skeletal muscle crosstalk, we will feed high-fat diet (HFD) to hepatocyte-restricted p21 deficient mice.

We expect mice with liver-restricted p21 deletion to be protected from HFD-induced decline in hepatic metabolic function, diabetic cardiomyopathy, sarcopenia and hepatic pathology but without altering systemic glucose homeostasis, which will outline a novel diagnostic and therapeutic target. Human samples with the full spectrum of NAFLD will support rodent studies.

Summary of the teaching project : 15 lignes maximum

The recruited researcher will be engaged in the teaching mission of his environment, through lectures within EUR LIVE (University Research School or Graduate School “Life trajectories and health VulnErability”, UPEC). Specifically, he will develop his original teaching portfolio in the framework of a "Biology of Aging and Vulnerability" course (28 hours of lectures) as part of the EUR LIVE Master 2 course. This EU will be the extension to a Master 1 course as part of the Health License already launched by the Faculty of Health with the title "Longevity and vulnerability". Importantly, lessons within the EUR LIVE target an international audience, hence will be presented in English.

In addition to lecturing, the recruited researcher will actively participate in supervising students at Master 1 and 2 level (started as part of EUR LIVE in 2021) as well as a biology bachelor and doctoral students.

At the Faculty of Health, he will also organize 3 to 4 seminars per year within the framework of the FHU SENEC (ongoing activity), instruct Master 1 students of the Health Biology Program in a total of 6 lessons per year. He/she will have the mission to interact with the AURORA university network, which involved recently UPEC as a partner. He/she will be responsible for setting up an international doctoral network within the frame work of AURORA.

Funding :

Requested budget (including ANR package = 200 K€)	500 000 €
- Salary of the candidate (total costs/ 5 y)	300 000 €

- Recruitment of a postdoctoral researcher (total costs /2y)	120 000 €
- Consumables/animal husbandry	60 000 €
- Communication : congresses/outreach	10 000 €
- Publications	10 000 €
Co-funding (2023-2025)	80 000 €
- BQR 2022	15 000 €
- H2020 IMI CARDIATEAM	50 000 €
- FRM Equipe	15 000 €
Total project	580 000 €

*source et montant

Scientific communication and dissemination :

Publication in journals of excellence targeting multidisciplinary scientific journals or specialized journals

Presentations at congresses focusing on aging

Seminars organized by the institution as part of EUR LIVE and FHU SENEK

Open Science :

Yes, with publications in HAL with Open Access option secured.

Science and society :

LIVE-AGE's dissemination and communication strategy is designed to reach many key stakeholders, including the general public, patients, clinicians, scientists, industry, and decision makers, to ensure maximum impact of LIVE-AGE's results and raise awareness of the risk of sarcopenia in age-related diseases.

Beyond a high-impact publication strategy, the dissemination activities of the LIVE-AGE project will include:

- A social media strategy to share results with patient associations and organizations online
- Press releases to share results via scientific and specialized media
- A strategy for organizing symposia and participating at conferences dedicated to the general public

Teaching

EUR LIVE Master 2 course "Biology of Aging and Vulnerability" : Teaching 6 hours /year

EUR LIVE Master 2 course "Biology of Aging and Vulnerability" : Organization of one seminar /year

EUR LIVE annual Summer school : participation and organization

Indicators :

Research // Knowledge transfer

Milestone 1 (12 months): Completion of mechanistic studies on cell cultures

Milestone 2 (24 months): Completion of in vivo studies (murine models)

Milestone 3 (25 months): Patent filing

Milestone 4 (36 months): Number of papers published in peer-reviewed journals

Milestone 5 (48 months): Completion of the clinical study in diabetic patients with NASH

Milestone 6 (60 months) : Number of papers published in peer-reviewed journals