

Appel à manifestation d'intérêt - Chaire professeur junior Inserm

Établissement/organisme porteur : **INSERM**

Nom du chef d'établissement/d'organisme : **Gilles BLOCH**

Site concerné : **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)**

Unité de recherche : **Institut Mondor de Recherche Biomédicale, IMRB (INSERM U955-UPEC)**

Nom du projet : **Sarcopenia: role of phenylalanine in age-related diseases**

Éventuellement acronyme : « **SARCOPENIA** »

Mots-clés : *donner 5 mots-clés caractérisant le projet scientifique*
sarcopenia, senescence, phenylalanine, and aging

Durée visée : **5 to 6 years depending on the candidate's experience**

Thématique scientifique : **Biology/Health/Metabolism/Senescence**

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

Stratégie d'établissement : *décrire en quoi le recrutement est en lien avec la stratégie de l'établissement (15 lignes maximum)*

As for INSERM, this project conforms to one of the strategic themes of the establishment on "aging /senescence /metabolism" as shown by Age-Med network and PEPR "BioAgir" and "Deep-Diab" applications, in which our group is a partner. This research and teaching project falls under "Health Environment", one of the priority areas of our UPEC university in connection with the strategic areas of IMRB (longevity, vulnerability and pathologies linked to aging). These axes are enhanced by national (PIA) and international (H2020/IMI) projects that our team coordinates, such as : 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 addressing vulnerability in terms of health/biology, health economics and environmental sciences; 3) **CARDIATEAM (H2020 IMI)**: a European project aiming to identify the specific mechanisms of diabetic heart disease from human cohorts to the development of preclinical models; and 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. The recruitment of an experienced researcher would enrich the IMRB environment to be more competitive at the national and international level.

Stratégie du laboratoire d'accueil : *décrire en quoi le recrutement est en lien avec la stratégie du laboratoire d'accueil (15 lignes maximum)*

The Mondor Institute for Biomedical Research (IMRB, INSERM U955 – University of Paris Est Créteil) is a major biomedical research centre 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 innovative research exploring the inter-organ communication and the role of cellular senescence in the initiation and aggravation of cardiovascular, metabolic and lung diseases and age-related ones (FHU SENE, 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 an ideal research milieu where the proposed studies can be performed.

Résumé du projet scientifique : 15 lignes maximum

Sarcopenia is an age-related skeletal muscle disorder characterized by degenerative loss of muscle mass and strength, currently affecting more than 50 million people worldwide without approved treatment. A recent metabolomics study reported 30% higher phenylalanine (Phe: an essential amino acid) levels in gastrocnemius muscle of aged compared to young mice. Recently our team discovered that elevated circulating Phe levels – occurring through a hepatic senescence-induced decline in natural Phe catabolism – promote the development of a reactive cardiac Phe catabolism with cardiac aging (PMID 34162223, Circulation 2021).

Hypothesis: Abnormal hepatic Phe catabolism promotes the development of sarcopenia.

Method: C2C12 skeletal myoblasts and Pax7+ satellite cells (skeletal muscle stem cells lessening with age) will be exposed to Phe and cell death, senescence, proliferation, cell differentiation, energy metabolism and Phe metabolic fates will be evaluated. The *in vivo* role of Phe will be explored by subjecting 1) young (2-month-old) mice (WT & Pax7-GFP) to Phe overload (to prematurely induce sarcopenia) 2) aged (24-month-old) WT & Pax7-GFP mice to a dietary or pharmacological Phe restriction (to reverse sarcopenia). Different skeletal muscles (including oxidative, glycolytic, mixed muscles as well as diaphragm) will be studied for functional, structural, and molecular hallmarks.

Résumé du projet d'enseignement : 15 lignes maximum

The candidate 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 course 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, courses within the EUR LIVE target an international audience, hence, will be presented in English.

In addition to lecturing, the candidate 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 organise 3 to 4 seminars per year within the framework of the FHU SENE (ongoing activity), instruct Master 1 students of the Health Biology Program in a total of 6 lessons per year. He will have the mission to interact with the AURORA university network, which involved recently UPEC as a partner. He will be responsible for setting up an international doctoral network within the framework of AURORA.

Synthèse financière : à réaliser à partir de la fiche financière jointe, décrire les besoins financiers et leur répartition pour mener à bien le projet scientifique (doctorant, post-doctorant, IT, équipement, ...)

Requested budget on CPJ grant (including ANR package)	380 000 €
- Salary of the candidate (total costs/ 3 years)	180 000 €
- Recruitment of a postdoctoral researcher (total costs /2 years)	120 000 €
- Consumables/animal husbandry	60 000 €
- Communication : congresses/outreach	10 000 €
- Publications	10 000 €
Co-financements (2022-2024)	75 000 €
- BQR 2021	10 000 €
- H2020 IMI CARDIATEAM	50 000 €
- FRM Equipe	15 000 €
Total budget	455 000€

Diffusion scientifique : préciser les résultats attendus en termes de diffusion scientifique (publications, communications,...)

The chairholder will aim to publish his major results in peer-reviewed journals of excellence targeting multidisciplinary scientific journals or specialised journals, as already performed in the host team. The chairholder will contribute to the scientific activities of the ITMO-PNM (physiopathology, nutrition, metabolism) and more specifically to the existing network on “diabetic cardiomyopathy” held under the auspices of ITMO-PNM.

Beyond his/her invitation and participation in seminars organized by the host institute as part of EUR LIVE and FHU-SENEC, the chairholder will participate in international congresses in the field of aging and promote the organization of scientific events in France (in the framework of PEPR-BioAgir and PEPR-Deep-Diab) and Europe.

Taking advantage of the host team’s collaborative network, the chairholder will promote collaborations and partnerships with the best universities and research institutes strengthening the international training actions at master’s / doctoral levels (EUR-LIVE Summer/winter Schools and FHU-SENEC) and promoting research projects and fellowship exchanges.

Science ouverte : le projet s’inscrit-il dans une démarche de science ouverte ? Si, oui décrire sa mise en œuvre.

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

This open science policy involves the deposition of manuscripts in the HAL open archive of articles in their final, accepted version and the support for the accessibility of manuscripts with our partners. Data management will benefit from the various existing data depositories and will be performed according to FAIR principles (findable, accessible, interoperable, reusable). The experiments will be recorded in the electronic laboratory notebook set up at the PRISM laboratory under the control of INSERM *via* the "labguru" interface.

Science et société : le projet envisage-t-il une communication auprès du grand public ? Si oui : préciser de quelle manière et à quelle échéance

Beyond clinicians, scientists and students, SARCOPHENIA’s dissemination and communication strategy is designed to reach many key stakeholders, including the general public, patients, pharmaceutical industry representatives, and decision-makers, to ensure maximum impact of SARCOPHENIA’s results and raise awareness of the risk of sarcopenia amongst age-related diseases.

Beyond a high-impact publication strategy, the dissemination activities of the SARCOPHENIA project will reach the members of the current programs (European, FHU, etc.) and will be extended beyond the borders as follows:

- 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

Indicateurs : préciser les indicateurs de suivi du déploiement du projet et la méthodologie de leur suivi

An in-depth annual evaluation will ensure the meaningful progress of the chair's project to offer all the guarantees for the sustainability of the position. As mentioned, it is also expected that this project will be deployed through the creation of collaborative partnerships (consortia or bilateral relations) giving rise to financial support (national then European calls for projects, etc.).

- **Scientific activities** in relation to the SARCOPHENIA project:
 - Milestone 1 (12 months): Completion of mechanistic studies on C2C12 cells and primary satellite cells
 - Milestone 2 (24 months): Completion of *in vivo* studies (murine models)
 - Milestone 3 (25 months): Patent filing
 - Milestone 4 (36 months): Publication in a high impact factor journal
- **Research activities** will be evaluated using traditional bibliometric indicators (number of publications, impact factor, communications, etc.) by a committee set up by IMRB/UPEC.
- **Teaching activities** will be evaluated by the executive committee and academic board members of EUR-LIVE once a year. To evaluate the innovative nature of international teaching the SAB will be consulted. An important aim of these evaluations will be to facilitate the successful integration of the chair holder.
- **Communication activities** will be evaluated once a year by a committee set up by IMRB/UPEC.