Ecole Doctorale COMPLEXITE DU VIVANT – Fiche Projet CONCOURS

Fiche à nommer selon le format Nom_Prenom (sans accents ni cédilles), à enregistrer en format PDF et à renvoyer à l'adresse : edcdv@sorbonne-universite.fr

Nom et prénom du directeur de thèse (et si besoin du co-directeur) : Isabelle Petropoulos/ Chahrazade El Amri
Le directeur de thèse et le co-directeur doivent impérativement avoir l'HDR ou équivalent
Coordonnées Tel : **0144278167/0144276952**

E-mail : **isabelle.petropoulos@sorbonne-universite.fr/chahrazade.el_amri@sorbonne-universite.fr**

Nom et prénom du co-encadrant (*non HdR*) (s'il y a lieu) :
Coordonnées Tel :
e-mail :

Y-a-t-il un candidat déjà identifié pour le projet : OUI ~~NON~~

Nom et prénom du responsable de l'équipe : Bertrand Friguet

Intitulé de l'équipe : Integrated Cellular Aging (ICAI)

Nombre de chercheurs et enseignants-chercheurs statutaires de l'équipe titulaires d'une HDR (ou équivalent) : 4

Nom et prénom du responsable d'UMR ou de département : Bertrand Friguet

Intitulé et N° d'UMR ou de département : UMR 8256 Adaptation Biologique et Vieillissement

Titre du projet de thèse :

Senescence and iron dyshomeostasis in Alzheimer's Disease: deciphering potential role of neuropsin for the design of innovative multipathway's pharmacological agents

Signature du directeur d'UMR ou de département (vaut avis favorable pour le dépôt du projet) :

UMR 8256 - B2A - CNRS - SU
Professeur Bertrand Friguet
Sorbonne Université
Bât. A - 5ème étage - Case courrier 256
7 quai Saint Bernard, 75005 Paris

Spécialité :

Biologie cellulaire et Biochimie du vieillissement

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Résumé du projet de thèse *(1 page maximum, en anglais). Pour les thèses avec 2 co-directeurs, ou en partenariat entre 2 laboratoires ou structures, indiquer la participation de chaque co-directeur et structure dans la gestion du projet.*

In France about 900 000 people suffer from Alzheimer's disease, and 35 million patients worldwide. Alzheimer disease (AD) is a progressive brain disease with devastating effects on cognition, especially on memory function for which there is neither a treatment nor a pre-mortem diagnosis with perfect sensitivity/specificity. Early diagnosis of AD, before appearance of the first symptoms, represents an absolute imperative to set the proper treatment right from the onset of the disease before irreversible dissemination of brain lesions. To improve the management of AD it is necessary to identify the most suitable biomarkers and factors contributing to neurodegeneration that can be targeted in therapeutic strategy. In this PhD project, we propose to focus simultaneously on two features of AD, i.e. senescence-mediated iron accumulation and unopposed proteolysis mediated by KLK8/neuropsin a preponderant serine protease in the brain. The PhD student will benefit from strong established data within the team on both molecular and cellular mechanisms that drive neural senescence as well as strategies of design of pharmacological agents that fine-tune cell fate in neurodegenerative diseases by targeting central nervous system (CNS) kallikreins. Iron dyshomeostasis is a feature of AD. Iron chelators are currently being developed as effective drugs to prevent the effect of iron ions accumulation in AD and its consequences in production of reactive oxygen species (ROS) (1-3). The impact of iron on AD is attributed to its interactions with the central proteins of AD pathology (amyloid precursor protein and tau) and/or through the iron-mediated generation of prooxidant molecules (e.g., hydroxyl radicals). However, the source of iron accumulation in pathologically relevant regions of the brain and its contribution to AD remain unclear. **One likely contributor to iron accumulation is the age-associated increase in tissue-resident senescent cells that drive inflammation and contribute to various pathologies associated with advanced age.** Interestingly, senescence has been observed in brain cells from AD patients and AD mouse models (4) and is believed to promote neurodegeneration and cognitive impairments (5). Iron accumulation predisposes ageing tissue to oxidative stress that can lead to cellular dysfunction and to iron-dependent cell death modalities (e.g., ferroptosis). Further, elevated brain iron is associated with the progression of AD and cognitive decline (3). **Elevated brain iron presents a feature of AD that may be modified pharmacologically to mitigate the effects of age/senescence-associated iron dyshomeostasis and improve disease outcome (6-7).** Furthermore, different studies highlighted the involvement of serine proteases in the central nervous system (CNS) physiology and neurodegenerative diseases like AD. Amongst such proteases, the trypsin-like extracellular serine protease kallikrein 8 (KLK8 or neuropsin) has been identified as an emerging biomarker of AD. KLK8 is expressed in the hippocampus, the lateral nucleus of the amygdala as well as other areas of the limbic system that are all involved in learning and memory. Excessive cerebral KLK8 protein level has been detected at early stage of AD in patients and TgCRND8 murine model (9). Notably, elevated KLK8 levels have been found in Aß plaques as well as in both cerebrospinal fluid (CSF) and blood of AD patient in preclinical stages suggesting that KLK8 detection in these biological fluids may serve as a novel biomarker for early diagnosis of AD (10). In murine model of AD, the KLK8 inhibition attenuates AD physiopathology and restores normal cognitive functions directly by activating pathways of clearance of the Aβ peptide and by counteracting tau hyper-phosphorylation but also indirectly by promoting neuronal plasticity and neurovascular function. The high therapeutic potential of **KLK8 inhibition could thus lead to a causative treatment of the disease rather than a symptomatic therapy.** In the team ICAI, Isabelle Petropoulos is expert of cellular ageing and develops projects around molecular and cellular factors that trigger senescence particularly in the context of human skin ageing and neurodegeneration by using transgenic AD mice PS1M146Vki (PS1). Chahrazade El Amri animates the research axis "Pathological proteolysis in age-related diseases" has recently identified efficient dual compounds of interest in AD that both display iron chelating properties and KLK8 inhibition (patent in progress).

Scientific objectives of the PhD

The objective of this project is to provide a comprehensive view of the role of senescence-associated iron dyshomeostasis and KLK8 deregulation in the development of AD pathophysiology and to decipher whether KLK8 inhibition could protect from brain senescence. The specific aims of the PhD project at the interface of cellular ageing and molecular pharmacology are: i) **Aim 1:** to study the impact of neural senescence on iron homeostasis and particularly to study the putative role of KLK8 on senescence associated secretory phenotype and neuron ferroptosis in cultured neurons and in *in vivo* AD mice models. Primary neurons and human neuroblastoma cell line in culture will be challenged with Aβ oligomers. SASP profiling senescence and ferroptosis markers will be evaluated. KLK8 will be inhibited by using pharmacologic agents or siRNA to assess whether senescence and iron dysregulation could be prevented by KLK8 disruption. Brain alterations i.e. cellular senescence, inflammation ferroptosis, Aβ loads, KLK8 expression, synaptic loss will be analyzed using histochemistry, biochemistry and biomolecular approaches in AD mice brain tissues. ii) **Aim 2** to optimize, in-depth depict the mechanism of action and pharmacological profiling of dual agents that simultaneously target iron accumulation and KLK8 based on initial chemical scaffolds identified in the team. Pharmacomodulations and chemical synthesis will be conducted in collaboration with ChemBio Team (IPCM, Sorbonne Université). For this specific task, kinetics assays using fluorogenic substrates, molecular modelling and biophysical tools will be conducted.

Our ultimate goal is to derive from these findings a new class of senomodulators/neuroprotectors that simultaneously impact several pathways involved in AD physiopathology that may be used at early stages of the disease.

References

1. Masaldan S, Belaidi AA, Ayton S, Bush AI. Cellular Senescence and Iron Dyshomeostasis in Alzheimer's Disease. *Pharmaceuticals*. 2019 Jun 19;12(2):93.
2. Jakaria M, Belaidi AA, Bush AI, Ayton S. Ferroptosis as a mechanism of neurodegeneration in Alzheimer's disease. J Neurochem. 2021 Dec;159(5):804-825.
3. Zeidan RS, Han SM, Leeuwenburgh C, Xiao R. Iron homeostasis and organismal aging. Ageing Res Rev. 2021 Dec;72:101510.
4. Gonzales MM, Krishnamurthy S, Garbarino V, Daeihagh AS, Gillispie GJ, Deep G, Craft S, Orr ME. A geroscience motivated approach to treat Alzheimer's disease: Senolytics move to clinical trials. Mech Ageing Dev. 2021 Dec;200:111589. doi: 10.1016/j.mad.2021.111589. Gonzales MM, Garbarino VR, Marques Zilli E, Petersen RC, Kirkland JL, Tchkonia T, Musi N, Seshadri S, Craft S, Orr ME. Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD): A Pilot Clinical Trial. J Prev Alzheimers Dis. 2022;9(1):22-29. doi: 10.14283/jpad.2021.62.
5. Baker DJ, Petersen RC. Cellular senescence in brain aging and neurodegenerative diseases: evidence and perspectives. J Clin Invest. 2018 Apr 2;128(4):1208-1216. doi: 10.1172/JCI95145.
6. Masaldan S, Clatworthy SAS, Gamell C, Meggyesy PM, Rigopoulos AT, Haupt S, Haupt Y, Denoyer D, Adlard PA, Bush AI, Cater MA. Iron accumulation in senescent cells is coupled with impaired ferritinophagy and inhibition of ferroptosis. Redox Biol. 2018 Apr;14:100-115.
7. Parella KJ, Manhardt C, Capucilli D, Moyer B, Colegrove H, Moody KJ, Sleeper M, Banas A, Rebbaa A, Wolfe AJ. Fluorescence-Based Detection of Ferrous Iron in Senescent Cells. Rejuvenation Res. 2021 Dec;24(6):456-463.
8. Münster Y, Keyvani K, Herring A. Inhibition of excessive kallikrein-8 improves neuroplasticity in Alzheimer's disease mouse model. Exp Neurol. 2020 Feb;324:113115.
9. Teuber-Hanselmann S, Rekowski J, Vogelgsang J, von Arnim C, Reetz K, Stang A, Jöckel KH, Wiltfang J, Esselmann H, Otto M, Tumani H, Herring A, Keyvani K. CSF and blood Kallikrein-8: a promising early biomarker for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2020 Jan;91(1):40-48.

Faisabilité du projet de thèse (*1/2 page maximum, en anglais)*

Expliciter la faisabilité du projet en terme d'expertise de l'équipe d'accueil, des collaborations potentielles qui pourront être mises en place pour certains aspects du projet, de la disponibilité des appareils nécessaires au bon déroulement du projet...

One of the main features of the Integrated Cellular Aging (ICAI) team is its pluridisciplinarity being composed of members from different disciplines, including biochemistry, biophysics, cell biology and physiology. Moreover, ICAI team has a long and established experience in cell biology and biochemistry of ageing. This pluridisciplinarity allows the emergence of innovative and disruptive projects that aim to decipher specific cellular ageing pathways and to design new therapeutics and molecular tools for tissue regeneration. Most equipment, biological models (*ex vivo* studies, geriatric and AD models) and know-hows (cell biology, proteomics, enzymology) dispensable for the PhD project are either available within the team or the Research Unit Biological Adaptation and Aging (B2A). AD models will be provided by our collaborator Prof Kiyoka Kinugawa (B2A-Charles Foix Hospital).

The goals of the PhD project are based on complementary expertise of both supervisors in senescence in one part and protease enzymology and drug design in another part. Moreover, the project will also take advantage of established and ongoing collaborations with medicinal chemistry teams such as the ChemBiol Team (Dr Candice Botuha; Institut Parisien de Chimie Moléculaire). ICAI team is currently involved in the ongoing ANR networks and COST action ProteoCure "A sound proteome for a sound body" (2021-2025) and in ageing research networks as INSERM AGEMED and GERONDIF that also guarantees enlarged opportunities to go further if necessary.

Thèses actuellement en cours dans l'équipe

Tous les encadrements doivent être indiqués (y compris les co-directions avec un autre HDR pour des doctorants d'une autre ED, et les encadrements dans le cadre de programmes doctoraux tels qu'IPV, FDV...)

Nom et Prénom du doctorant	Directeur(s) de thèse	Année de 1ère inscription	ED	Financement
Yoan Kovacs	Bertrand Friguet/Aurore L'honoré	2018	CDV	Fondation Leducq
Tania Medali	Bertrand Friguet	2019	CDV	Fondation MEB
Mazzarine Dotou	Chahrazade El Amri/Aurore L'honoré (HDR en cours)	2020	CDV	Initiave IBio
Remy Smith	Khadija El Hadri/Eric Duplus	2020	CDV	Allocation de recherche SU
Elodie David	Candice Botuha/Chahrazade El Amri	2020	Chimie Moléculaire	Initiative ISIM
Lauréline Urli	Kiyoka Kinugawa/Isabelle Petropoulos	2020	3C	GERONDIF
Jérémy Chantrel	Han Li/ Aurore L'honoré (HDR en cours)	2021	CDV	GERONDIF

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Trois publications récentes du directeur de thèse (du co-directeur ou du co-encadrant s'il y a lieu). Mettre en gras le nom du directeur de thèse.

Halkoum R, Salnot V, Capallere C, Plaza C, L'honoré A, Pays K, Friguet B, Nizard C, **Petropoulos I**. Glyoxal Induces Senescence in Human Keratinocytes through Oxidative Stress and Activation of the Protein Kinase B/FOXO3a/p27^{KIP1} Pathway. J Invest Dermatol. doi : 10.1016/j.jid.2021.12.022.

Lourenço dos Santos S, L'honoré A, **Petropoulos I**. (2021). Reactive Oxygen Species and Protein Homeostasis in Skeletal Muscle Regeneration. In : Proteostasis and Proteolysis. Chondrogianni N, Pick E, Gioran A, Editors ; CRC Press, chapter 15 : p 197-212. doi: 10.1201/9781003048138-15

Aït Amiri S, Deboux C, Soualmia F, Chaaya N, Louet M, Duplus E, Betuing S, Nait Oumesmar B, Masurier N, **El Amri C**. Identification of First-in-Class Inhibitors of Kallikrein-Related Peptidase 6 That Promote Oligodendrocyte Differentiation. J Med Chem. 2021 May 13;64(9):5667-5688. doi: 10.1021/acs.jmedchem.0c02175.

Docteurs encadrés par le directeur de thèse ayant soutenu entre la date de dépôt de ce dossier et il y a 5 ans et publications relatives à leur sujet de thèse. Mettre en gras le nom du directeur de thèse et celui du docteur.

Nom Prénom : Halkoum Rym

Date de soutenance : 10/05/2021
Durée de thèse (en mois) : 39 mois (extension COVID)
Ecole Doctorale : CDV (Thèse CIFRE)

Publications :
Halkoum R, Salnot V, Capallere C, Plaza C, L'honoré A, Pays K, Friguet B, Nizard C, **Petropoulos I**. Glyoxal Induces Senescence in Human Keratinocytes through Oxidative Stress and Activation of the Protein Kinase B/FOXO3a/p27^{KIP1} Pathway. J Invest Dermatol. doi : 10.1016/j.jid.2021.12.022.

Nom Prénom : Ait Amiri Sabrina

Date de soutenance : 19/03/2021
Durée de thèse (en mois) : 40 mois (extension COVID)
Ecole Doctorale : CDV

Publications :
1. **Aït Amiri S**, Deboux C, Soualmia F, Chaaya N, Louet M, Duplus E, Betuing S, Nait Oumesmar B, Masurier N, **El Amri C**. Identification of First-in-Class Inhibitors of Kallikrein-Related Peptidase 6 That Promote Oligodendrocyte Differentiation. J Med Chem. 2021 May 13;64(9):5667-5688. doi: 10.1021/acs.jmedchem.0c02175.

2. Soualmia F, Bosc E, **Ait Amiri S**, Stratmann D, Magdolen V, Darmoul D, Reboud-Ravaux M, **El Amri C**. Insights into the activity control of the kallikrein-related peptidase 6: small-molecule modulators and allosterism. Biol Chem. 2018 Sep 25;399(9):1073-1078.

3 . Brevet B2690FR00/WO/2019/158859: Compounds and compositions to treat neurodegenerative diseases and inflammation. **El Amri C** , Soualmia F, Masurier, N., **Ait Amiri, S.**, Deboux, C, Nait Oumesmar, B.

Nom Prénom : Bosc, Elodie

Date de soutenance : 26/11/2018
Durée de thèse (en mois) : 38 mois
Ecole Doctorale : CDV

Publications :
1: **Bosc E**, Anastasie J, Soualmia F, Coric P, Kim J, Lacin G, Duplus E, Tixador P, Brugg B, Reboud-Ravaux M, Bouaziz S, Karin M, **El Amri C**, Jacotot E. Genuine Selective Caspase-2 Inhibition with new Irreversible Small Peptidomimetics bioRxiv 2021.12.13.472505; doi: https://doi.org/10.1101/2021.12.13.472505
2: **Bosc E**, Nastri J, Lefort V, Valli M, Contiguiba F, Pioli R, Furlan M, Bolzani VDS, **El Amri C**, Reboud-Ravaux M. Piperlongumine and some of its analogs inhibit selectively the human immunoproteasome over the constitutive proteasome. Biochem Biophys Res Commun. 2018 Feb 12;496(3):961-966.
3: Soualmia F, **Bosc E**, Amiri SA, Stratmann D, Magdolen V, Darmoul D, Reboud- Ravaux M, **El Amri C**. Insights into the activity control of the kallikrein- related peptidase 6: small-molecule modulators and allosterism. Biol Chem. 2018 Sep 25;399(9):1073-1078.
4: Arama DP, Soualmia F, Lisowski V, Longevial JF, **Bosc E**, Maillard LT, Martinez J, Masurier N, **El Amri C**. Pyrido-imidazodiazepinones as a new class of reversible inhibitors of human kallikrein 7. Eur J Med Chem. 2015 Mar 26;93:202-13.