DOCTORAT BIOLOGIE BRETAGNE SANTE LOIRE

Year 2022

THESIS TOPIC

Subject N° (to be completed by the ED):	FUNDING: ☐ Requested ☒ Acquired	Funding origin: Région Bretagne/ IMT Atlantique
Thesis title: **Approche "théranostique" de la maladie d'Alzheimer par des hexapeptides.**		3 keywords: Alzheimer, Tau protein, Theranostic
Unit / team: **Irset, équipe 6, DREAM / Laboratory of Subatomic Physics and Associated Technologies**		
Supervisor's name: **Cyrille GARNIER/Sandrine HUCLIER**		Phone number: 02232 36824 Email address: cyrille.garnier@univ-rennes1.fr/sandrine.huclier@subatech.in2p3.fr

Socio-economic and scientific context (approximately 10 lines):
Alzheimer's disease (AD) is a neurodegenerative disease that was first described in 1906 by Aloïs Alzheimer. Today the prevalence of Alzheimer's disease is increasing mainly in developed countries. According to predictions, the number of cases is expected to quadruple by 2050, making Alzheimer's disease a major public health issue at a cost of € 140 billion per year. Most Alzheimer's disease appears sporadically, the causes remain poorly understood. The consequence is that two proteins, AAP and Tau, acquire new structural properties leading to their self-assembly in the form of amyloid fibers / plaques. APP undergoes cleavage generating an Aβ peptide aggregating as senile plaques. Tau self-associates and forms structures called PHF for "paired helical filaments". These structures colonize the central nervous system and are the cause of its dysfunction. Since their identification, APP and Tau have been considered prime targets for developing treatments against Alzheimer's disease. More than a century after the discovery of the pathology and more than thirty years after the identification of the responsible proteins two problems persist: i) the diagnosis of the disease is late and is not definitive until post-mortem and ii) it is not there is still no effective treatment.

Working hypothesis and aims (approximately 8 lines):
AD therefore comes up against two major problems: i) the impossibility of making a reliable and early diagnosis allowing good patient management and ii) no treatment has shown at least effectiveness in stopping or even reversing the accumulation of protein aggregates in the brain. To overcome these shortcomings, we are developing a "theranostic" approach consisting in producing, in the same tool, molecules which can be used i) for therapeutic purposes in the treatment against AD and ii) as a molecular probe for early diagnosis. The basic skeleton of these molecules are hexapeptides whose target is to inhibit the formation of Tau PHFs. From 42 proposed hexapeptides and after selection on different in vitro and in vivo models, one or two sequences should emerge as therapeutic "leader" peptides. For diagnostic purposes, these leader hexapeptides will then be coupled to innovative multimodal nanoparticles chelating metals of interest for monitoring by PET molecular imaging (positron emission tomography) allowing early diagnosis, improved prognosis and implementation. place of therapy adapted to each patient.

Main milestones of the thesis (approximately 12 lines):
The PhD project is structured around two main steps. A first step will lead to the selection of leader hexapeptides and to the characterization of their effect on Tau protein self-associative process. A second step will consist in the coupling of these leader hexapeptides with chelating nanoparticles of radionuclides of interest for PET molecular imaging on small animals (rat/mouse MA). Hexapeptides are chosen by a dual in silico-vitro approach combined with a decision-making approach. These peptides will be preselected based on their biochemical characteristics and their safety as a future drug. Once preselected, they will be tested alone or in tandem on in vitro assembly models, two new models are to be developed. Peptides inhibitory capacities, interaction parameters, and induced structures will be studied. The candidates will then be tested on cell models of neuroblastomas and on zebrafish. For diagnostic purposes, and in collaboration with the Nantes team, candidate therapeutic hexapeptides will be coupled to innovative multimodal nanoparticles chelating radionuclides of interest with a short half-life ($^{64/67}$Cu, $^{43/44/47}$Sc) for monitoring by PET. This type of imagery is particularly well suited and has proven its effectiveness in the exploration of brain functions and neurodegenerative diseases. Its use in AD will allow early diagnosis, improved prognosis and the implementation of therapy adapted to each patient. Each modification made on peptides will require will require an in vitro/vivo reassessment of their inhibitory effect on Tau PHF.

Scientific and technical skills required by the candidate (2 lines):
The PhD student should have a solid understanding of biochemistry / molecular biology and / or cell biology. He will be interested in the molecular, structural and medical aspects of the project

3 publications from the team related to the topic (last 5 years):

- **C. Garnier**, F. Briki, B. Nedelec, P. Le Pogamp, A. Dogan, ..., L. Martin, M. Delpech, F. Bridoux, G. Grateau, J. Doucet, P. Derreumaux, and S. Valleix. VLITL is a major cross-ß-sheet signal for fibrinogen Aa-chain frameshift variants. (2017), Blood, 130(25): 2799-2807
- **C. Garnier**, F. Devred, D. Byrne, R. Puppo, A. Yu. Roman, S. Malesinski, A. V. Golovin, R. Lebrun, N. N. Ninkina, and P. O. Tsvetkov. Zinc binding to RNA recognition motif of TDP-43 induces the formation of amyloid-like aggregates. (2017) Scientific reports, 7(1): 6812
- C. Schirmer, E. Lepvrier, L. Duchesne, O. Decaux, D. Thomas, C. Delamarche, and **C. Garnier**. Hsp90 directly interacts, in vitro, with amyloid structures and modulates their assembly and disassembly (2016) Biochim. Biophys. Acta General Subjects 1860: 2598-2609
- **C. Garnier**: Inhibitory Peptides for the Diagnostic and/or Treatment of Tauopathies. 2021, European patent office, EP21211241

National and international collaborations:
1- Dr. Christel Marquette member of the 1292 BIOsanté research unit, DS / IRIG / DRF Commission for Atomic Energy and Renewable Energies of Grenoble and 2- Dr. Johnny Vercouillie (MCU) Inserm U1253, Ibrain team. This project is also part of a context of European international collaborations 3- Dr. Renata Mikolajczac (Associate Professor) National Center for Nuclear Research, Radioisotope Center POLATOM, poland 4- Dr. Dana Niculae, Horia Hulubei National Institute for Physics and Nuclear Engineering , Radiopharmaceutical Research Center, Romania 5- Dr. Petr Hermann (Professor) Department of Inorganic Chemistry, Charles University (Universita Karlova), Czech Republic. 6- Tomasz Dziel, Centrum Wysokich Technologii w Świerku Hitec Świerk Sp. Z o.o, Poland.

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