PhD offer in Bioorganic and Peptide Chemistry

Rational design of fluorinated peptides for the inhibition of amyloid protein aggregation

University : CY Cergy Paris Université **Doctoral school :** Sciences et Ingénierie (n°417)
Research Unit : BioCIS, Chemical Biology Team – UMR 8076
Thesis supervision : Pr. Grégory Chaume and Dr. Cillian Byrne
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Origin : MENRT
Deadline for application : 15 april 2025
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Context:

Protein misfolding and aggregation and the “gain of toxic function” are associated with more than 30 serious and incurable human diseases.[1] Amyloid protein aggregation occurs through misfolding, leading to oligomeric precursors and the deposition of fibrillar species, responsible for cellular dysfunction and toxicity. The design of peptides and peptidomimetics capable of interacting and inhibiting the oligomerization process of amyloid proteins by protein-protein interaction is a fast-growing therapeutic strategy.[2] Our laboratory has previously demonstrated the ability of short fluorinated peptides to inhibit the aggregation of the Aβ protein involved in Alzheimer's disease.[3] More recently, our team has developed a first series of fluorinated foldamers which have shown very promising preliminary results for the inhibition of amyloid protein aggregation (hIAPP and α-synuclein).[4] In parallel, we have initiated a new research axis focusing on understanding the biological mechanisms of tauopathies and developing peptide inhibitors of Tau protein aggregation.[5] This work has already identified non-fluorinated peptide sequences capable of preventing Tau protein aggregation, and some of the results are now the subject of a patent application.

Objectives:

The aim of this thesis project is now to develop a new generation of peptides capable of selectively inhibiting the aggregation of amyloid proteins. In this thesis project, we propose to carry out the rational design of peptide sequences to increase inhibitory activity and refine interactions with target amyloid proteins (Tau, Aβ, hIAPP).

Methods:

The first step of the the PhD project will involve the synthesis of peptides. We will study the effect of the incorporation of both chiral fluorinated amino acids and D- amino acids at key residue positions. The stereoselective synthesis of fluorinated amino acids will be developed for application to larger scale synthesis and Solid Phase Peptide Synthesis as has been optimized in our laboratory over many years.[4,6] New methods of peptide synthesis of fluorinated amino acids will also be established.
The second aspect of the thesis will be the study of the structure of the synthesized peptides by NMR, X-Ray, Circular Dichroism, and IR spectroscopy. These structural studies will be supported by modelling studies. In parallel, biophysical (proteolytic stability, cell permeability) and biological (inhibitory activity, cytotoxicity, target selectivity) experiments will be carried out on the peptides. High end equipment (High field NMR and cryo-EM, WAX) techniques will be done in collaboration with International and national collaborators who are experts in neurodegenerative disease.

Candidate profile:

Holder of Master 2 degree (or international equivalent) with a specialization in organic chemistry, the candidate must have an attraction for research at the interface with biology. Good theoretical and practical knowledge of organic chemistry is required. Knowledge of NMR analysis and peptide chemistry

would be highly appreciated. A good level of English is essential for bibliographical research and interaction within our European research team.

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