Fluorinated foldamers: synthesis, structuration and capacity to interact with amyloid proteins and biomembranes. FluFOLD

Establishment: Université Paris Saclay
Doctoral school: Innovation Thérapeutique : du fondamental à l'appliqué (n°569)
Research unit: BioCIS, Team FLUOPEPIT - UMR 8076
Thesis supervision: Pr. Sandrine Ongeri
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Keywords
foldamers, peptidomimetics, fluorine, amyloid, neurodegenerative diseases, cell penetrating peptides, biomembranes

Profile and skills required
Organic chemistry
Medicinal chemistry

Project description
This project is part of an ANR PRC 2022 funding and brings together teams from Paris Saclay (BioCIS laboratory - UMR 8076) and Sorbonne University (LBM laboratory - UMR 7203). Secondary structures of proteins, such as β-sheets, α-helices, polyproline II helices (PPII) are often stabilized by NH...O=C hydrogen bonds and by interactions between side chains such as hydrophobic interactions. Peptides capable of mimicking these secondary structures are very promising candidate molecules to modulate protein-protein and protein-membrane interactions. Unfortunately, their use in therapy remains very limited due to their low resistance to proteolysis. Peptidomimetic foldamers are a class of compounds capable of adopting well-defined secondary structures with the advantage of being very stable against proteases. At the same time, the use of fluorinated compounds in medicinal chemistry has become widely popular, with the incorporation of fluorine atoms being of major interest to modulate their physicochemical and therapeutic properties. Although the combination of fluorine and foldamers appears to be an innovative strategy for the development of new drugs, fluorinated foldamers remain to date unexplored compounds in medicinal chemistry.

Objectives: In this thesis project, we propose to study the effect of introducing specific fluorinated motifs into foldamers mimicking α/310 helix, beta-strands and beta-hairpin. We will study the influence of fluorinated moieties on (i) their structuring, (ii) their stability against proteolysis, (iii) their ability to interact with amyloid proteins to inhibit their aggregation, (iv) their ability to cross biomembranes as cell-penetrating peptides (CPP).

Methodology: The first aspect of the thesis will be devoted to the synthesis of fluorinated scaffolds and their self-coupling and/or coupling with specific natural amino acids in solution and/or solid-phase strategies. The choice of the fluorinated scaffolds and of the peptide

sequences will be rationnally designed to interact with specific amyloid proteins and to cross biomembranes.
The second aspect of the thesis will be dedicated to the structural study of the synthesized foldamers by NMR and circular dichroism and will be supported by molecular modelling studies. The PhD student will be also involved in the third aspect of the project i.e. the studies of the biological properties of the synthesized foldamers (inhibition of amyloid protein aggregation, membrane interactions, proteolytic stability). These parts will be carried out both in our and in the consortium laboratories.

Valorization/diffusion of the research results
Poster and Oral communications in international congress, high impact factor publications and potentially patents are expected.

Candidate profile: Holder of Master 2 degree (or international equivalent), the candidate must have a good theoretical and practical knowledge of organic synthesis as well as of the methods of analysis and characterization of organic compounds. A first experience in peptide chemistry and good knowledge in NMR conformational analyses could be a plus.

To apply: please send a detailed CV, a letter of motivation and your M1 and M2 scores to sandrine.ongeri@universite-paris-saclay.fr
A letter of recommendation from your two M1 and M2 internship supervisors must be sent by e-mail also directly by your supervisors to Prof. Sandrine Ongeri.

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Representative Publications

-1- Designed Glycopeptidomimetics Disrupt Protein−Protein Interactions Mediating Amyloid β-Peptide Aggregation and Restore Neuroblastoma Cell Viability. J. Kaffy, D. Brinet, J-L Soulier, I. Correia, N. Tonali, K. F. Fera, Y. Iacone, A. R. F. Hoffmann, L. Khemtemourian, B. Crousse, M. Taylor, D. Allsop, M. Taverna, O. Lequin, S. Ongeri, *J. Med. Chem.* **2016**, *59*, 2025−2040.

-2- β-Hairpin mimics containing a piperidine-pyrrolidine scaffold modulate the β-amyloid aggregation process preserving the monomer species, S. Pellegrino, N. Tonali, E. Erba, J. Kaffy, M. Taverna, A. Contini, M. Taylor, D. Allsop, M. L. Gelmi, S. Ongeri *Chem. Sci.* **2017, *8***, 1295 - 1302.

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