Internship in Organic Chemistry – Master 2 or equivalent

Design of fluorinated Aib foldamers: synthesis, structural study and capacity to interact with amyloid proteins

Institution : CY Cergy Paris Université
Laboratory : BioCIS, ECB Team – Equipe de Chimie Biologique – UMR-CNRS-8076
Supervision : Pr. Grégory Chaume, Dr. Cillian Byrne and Marine Piétri (3rd year *PhD* student)
Duration : 5-6 months starting from January/February 2025
Application Deadline : Until filled

Context and Project objectives: Protein misfolding and aggregation and their subsequent "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 deposition of fibrillar species, thought responsible for cellular dysfunction and toxicity. α-helical and 3_{10} helical structures have been described for α-synuclein (α-Syn), amyloid β (Aβ) and human Islet Amyloid PolyPeptide (hIAPP) amyloid proteins. 3_{10} helices have been proposed as probable intermediates in the conversion of α-helix to β-sheet during $A\beta_{1\text{-}40}$ and hIAPP amyloidogenesis.[2] The rational design of peptidomimetic scaffolds capable of assuming a well-defined helical structure and interacting with monomeric or small amyloid protein oligomers to inhibit their aggregation constitutes a promising approach. Oligopeptides containing α-aminoisobutyric acid residue (Aib) have been reported as mimics of 3_{10}, mixed 3_{10}/α, or α-helical structure.[3] Our group has recently reported the synthesis of fluorinated Aib foldamers incorporating (*R*)- and (*S*)-α-trifluoromethylalanine (α-TfmAla) and demonstrated their ability to stabilize the 3_{10} helical conformation.[4] We are now focused on the engineering of a promising α-TfmAla-containing peptidomimetic template able to interact with amyloid proteins in their helical conformation and inhibit their aggregation.

Methodology: The first step of this internship will involve the peptide synthesis (in solution and/or on the solid phase) of a second generation of fluorinated peptides. This will be followed by conformational studies using NMR and CD spectroscopy as well as the study of their inhibitory activity by Thioflavin T assay.

Candidate's profile: The candidate must be preparing a Master 2 degree in a university or a 3rd year of engineering school with a specialization in organic chemistry, and 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.

To apply : Please send a CV, cover letter and Master 1 grades to gregory.chaume@cyu.fr and cillian.byrne@cyu.fr.

References:

[1] Ke, P. C. et al. *Chem. Soc. Rev.* **2017**, *46*, 6492–6531
[2] Bram, Y. et al. *Sci. Rep.* **2017**, *7*, 14031
[3] Jones, J. E. et al *J. Am. Chem. Soc.* **2016**, *138*, 688–695.
[4] Bodero, L. et al. *Chem. Eur. J. 2022*, e202103887; b) Picois, N. et al. *Chem. Eur. J.* **2024**, e202400540.