BioCIS Laboratory / Chemical Biology Team UMR 8076
CY Cergy Paris University
5 mail Gay-Lussac, Neuville-sur-Oise, 95000 Cergy-Pontoise France
https://biocis.cyu.fr/

PhD Position Available

Title: **Development of PROTACs targeting Cathepsin K as potential tools for cancer treatment.**

***Context and Project Objectives*:** Cathepsin K (Cat K) is a cysteine protease widely expressed in osteoclasts. It plays a crucial role in the degradation of type I collagen, which makes up the bone matrix. Several studies have shown the influence of this protease in diseases linked to the loss of bone mineral mass, such as osteoporosis,[1] but also in the development of breast or prostate cancer metastases. Several specific covalent inhibitors of CatK have been developed, and their efficacy has been demonstrated in experimental models.[2] However, serious side effects have halted their clinical development.

The PROTACs (Proteolysis-Targeting Chimaeras) strategy makes it possible to circumvent classic inhibition strategies by catalytically activating the proteolytic degradation of the target.[3] It is based on a bifunctional molecule (chimera) composed of two ligands, for the protein of interest and the E3 ubiquitin ligase, connected by a "linker" of variable size and nature. Using fluorinated pseudo peptides as ligands of the protein of interest has several advantages: it permits the modulation of the physicochemical properties of the PROTACs, it can increase the metabolic stability of the chimera (in comparison to peptide ligands), and it can improve the ligand affinity/selectivity (in contrast to nonpeptidic small molecules). Fluorinated ligands can also be employed as ^{19}F NMR probes.[4]

The Chemical Biology Team of BioCIS laboratory already has good experience developing PROTACs for anticancer purposes (ANR JCJC PRODIGE project).[5] The Team is also currently focused on developing a series of fluorinated ligands/inhibitors of cathepsin D and Pepsin (EMERGENCE FSI-PRO Project).[6] The context and the objectives of the project at the base of this Ph.D. thesis take advantage of these two areas of expertise of the Team. Therefore, the Ph.D. students will work on the:

- Design synthesis and characterisation of a family of fluorinated ligands of CatK.
- Synthesis of different PROTACS with a variable linker size/nature and "anchor points."
- Study the biological activity of PROTACS on the degradation of CatK.

***Candidate's Requirements*:** The candidate must have a Master's degree in Chemistry (or equivalent) and a very good theoretical and practical knowledge of organic synthesis and of the methods of analysis and characterisation of organic compounds. Experience in peptide synthesis and

peptidomimetics / pseudopeptides synthesis and/or in biological evaluation of organic compounds will be a plus.

Application Deadline: **25/05/2023**

To apply:

- CV and cover letter
- Master degree marks/evaluation
- Reference

Contact: please send the required documents to Julien Pytkowicz **julien.pytkowicz@cyu.fr**

References:

1] Mijanović, O. et al. Cathepsin K in Pathological Conditions and New Therapeutic and Diagnostic Perspectives. *Int. J. Mol. Sci.* **2022**, *23* (22).

[2] Langdahl, B. et al. Odanacatib in the Treatment of Postmenopausal Women with Low Bone Mineral Density: Five Years of Continued Therapy in a Phase 2 Study. *J. Bone Miner. Res.* **2012**, *27* (11), 2251–2258.

[3] a) Xiuyun Sun et al., *Signal Transduct Target Ther* **2019**, *4* ,64; b) M. Konstantinidou et al., *Expert Opin. Drug Discov.* **2019**, *14* 1255; c) P. P. Chamberlain et al., *Nat. Chem. Biol.* **2019**, *15*, 937; d) M. Scudellari, *Nature* **2019**, *567*, 298; e) A. Pandiella *J Exp Clin Cancer Res* **2020**, *39*, 189.

[4] a) Gillis, E. P. et al. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359; b) Inoue, M. et al. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5* (19), 10633–10640; c) O'Hagan, D. et al. Some Influences of Fluorine in Bioorganic Chemistry. *Chem. Commun.* **1997**, No. 7, 645–652; d) Devillers, E. et al. (R)-α-Trifluoromethylalanine as a 19F NMR Probe for the Monitoring of Protease Digestion of Peptides. *ChemBioChem* **2022**, *23* (1), e202100470.

[5] Meneghelli, L. et al. Design and Synthesis of Pin1-PROTACs as Potential Therapeutic Tools for Cancer Treatment *Proceedings of the 36th European Peptide Symposium* **2022**, 285-288.

[6] Terzani, F. et al. Design, Synthesis and Biological Evaluation of Fluorinated Cathepsin D inhibitors *Proceedings of the 36th European Peptide Symposium* **2022**, 83-85.