SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Organic Chemistry

has the honor to invite you to the public defence of the PhD thesis of

Aurélie Honfroy

to obtain the degree of Doctor of Sciences

Joint PhD with CY Cergy Paris Université

Title of the PhD thesis:
Exploiting fluorine to control sustained drug release from peptide-based hydrogels

Promotors:
Prof. Dr. Charlotte Martin (VUB)
Prof. Dr. Steven Ballet (VUB)
Prof. Dr. Sophie Hernot (VUB)
Prof. Dr. Grégory Chaume (CY Cergy Paris Université)
Prof. Dr. Thierry Brigaud (CY Cergy Paris Université)

The defence will take place on

Friday, December 20, 2024 at 11 a.m. in the MIR auditorium (CY Cergy Paris Université, France)

Members of the jury

Prof. Dr. Damya Laoui (VUB, chair)
Dr. Nathalie Lensen (CY Cergy Paris Université, secretary)
Prof. Dr. Gilles Subra (Université de Montpellier, FR)
Dr. Elisabeth Garanger (Université de Bordeaux, FR)

Curriculum vitae

Aurélie Honfroy obtained her MSc in Chemistry from CY Cergy Paris University, France, in 2020. In October 2020, she joined the BioCIS group (CY Cergy Paris University) and the ORGC and MITH groups (Vrije Universiteit Brussel) as part of a joint EUTOPIA PhD program. During her PhD, she worked on the organic synthesis of fluorinated amino acids to be incorporated into peptide-based hydrogels for controlled drug release. She has published one international peer-reviewed article as first author and is preparing another for submission. She has presented her work at several conferences and has supervised three MSc and two BSc thesis students.

Abstract of the PhD research

The development of extended drug release systems has garnered significant interest in the last decades, leading to innovative formulations designed to overcome the limitations of conventional drug delivery systems. Hydrogels have emerged as promising matrices for the controlled release of drugs, such as opioid delivery for chronic pain treatments. Amphipathic peptide, which consist of alternating hydrophobic and hydrophilic amino acids, are able to self-assemble into hydrogels and these offer potential as injectable drug delivery platforms due to their ability to release pharmaceutical cargoes uniformly and over extended time windows. Notably, the amphipathic hexapeptide **P1** H-FQFQFK-NH_2 forms an injectable hydrogel with a drug release window of up to 4 days post-subcutaneous injection. However, this duration needs further refinement to be optimal for clinical use.

This thesis explores the enhancement of the release properties of peptide hydrogels through the incorporation of fluorinated amino acids. Fluorine is known to stabilize secondary structures, it is able to increase hydrophobicity and improve the pharmacological profiles of drug candidates. Three strategies were employed to investigate fluorine incorporation into peptide hydrogels based on the **P1** sequence: i) the first strategy focused on the incorporation of fluorinated amino acids along the hydrophobic face of the amphipathic peptide; ii) the second involved the design of β-hairpin hydrogelators and study the influence of incorporating various fluorinated turn motifs on the gelation process, and finally, iii) a side-project explored the design of (fluorinated) peptoid-based hydrogels.

The synthesis of multiple fluorinated amino acids was successfully achieved for incorporation into peptide hydrogelator sequences via solid-phase peptide synthesis. The impact of fluorinated groups on gelation, secondary structures and fiber network was assessed by means of dynamic rheometry, infrared and circular dichroism spectroscopy, as well as cryogenic electron microscopy, revealing, among others, that fluorine significantly enhances hydrogel stiffness when introduced in hexapeptide sequences. Similarly, the β-hairpin hydrogel analogue **P28** showed improved mechanical properties, although the incorporation of fluorine into the turn motif or strand of the β-hairpin sequence yielded a more nuanced effect on gelation. In vitro release studies of the optimized hydrogels, loaded with an opioid cargo, indicated enhanced stability. This improved stability was further validated *in vivo* using nuclear SPECT-CT imaging, where fluorinated hexapeptide and β-hairpin hydrogels demonstrated prolonged residence times post-injection. Overall, these findings underscore the value of fluorine incorporation and β-hairpin design in the development of advanced biomaterials for controlled drug release applications.