SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Organic Chemistry

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

Julie Heremans

to obtain the degree of Doctor of Sciences

Title of the PhD thesis:

Development and molecular imaging of peptide-based hydrogels for controlled drug delivery

Promotors:
Prof. dr. Steven Ballet
Prof. dr. Charlotte Martin
Prof. dr. Sophie Hernot
Prof. dr. Vicky Caveliers

The defence will take place on

Wednesday, June 19, 2024 at 5 p.m.
in auditorium D.2.01

Members of the jury

Prof. dr. Charles Van der Henst (VUB, chair)
Prof. dr. Mike Sleutel (VUB, secretary)
Prof. dr. Nick Devoogdt (VUB)
Prof. dr. Sandra Van Vlierberghe (UGent)
Prof. dr. Gilles Subra (Université de Montpellier, FR)

Curriculum vitae

Julie Heremans (°1996) obtained her Master's degree in Drug Development (Pharmaceutical Sciences) at KU Leuven in 2019. After graduating, she started her PhD in the Research Group of Organic Chemistry, in collaboration with the Molecular Imaging and Therapy group (VUB). Her research resulted in two published peer-reviewed papers as a first author. She also presented her work at national and international conferences and meetings, and received an award for her poster presentation at EPS in Sitges (2022). During the PhD, Julie supervised three master students and one bachelor student.

Abstract of the PhD research

The sustained release of a drug by use of controlled delivery systems leads to a better therapeutic control with reduced side effects. This is of immense benefit in the treatment of chronic diseases. Hydrogels made of self-assembling peptides are of particular interest in this regard, considering their physical properties, mild gelation procedure, and tunability. Even though many advances have improved our understanding of hydrogel-forming amphipathic peptides, their *in vivo* hydrogel behavior and drug release performance is yet not fully understood. The Ballet group has developed a short amphipathic hexapeptide H-FQFQFK-NH_2 (**H6**), which, after gelation and encapsulation of analgesic molecules, demonstrated prolonged analgesia after subcutaneous injection in mice. The goal of this work was to further understand and improve its drug release behavior. Several cargoes were considered, including linear and cyclic peptides, but also a single-domain antibody (sdAb). Specifically, after structural characterization of the hydrogels and *in vitro* drug release studies, the hydrogel's stability and drug release behavior were evaluated in a biological environment using *in vivo* imaging modalities. Lastly, potential therapeutic applications were explored.

Aiming at extended intermolecular interactions, an elongation of the hydrogelator length was envisaged. The 12mer H-FQFQFKFQFQFK-NH_2 (**H12**) gave rise to a weaker gel, but a markedly enhanced *in vivo* stability, causing a slower cargo release. Further optimization of its polarity provided H-KFQFQFKFQFQFKK-NH_2 (**H12-KK**), an analogue with a better balance between *in vivo* stability and biodegradability, which opens doors for future drug release studies. When attempting to unravel cargo peptide fiber interactions, some designed cargo analogues showed that hydrophobic and electrostatic interactions are at play, providing the possibility to reach higher retention by the gel network. In view of therapeutic applications, the short circulation time of a sdAb immune checkpoint inhibitor could be extended via use of our hydrogel platform. Moreover, in the context of pain treatment, the hydrogel showed potential to further improve the beneficial effects of bifunctional opioids **KGFF09** and **KGNOP01**. Even though the above results suggest the potential of a hydrogel-based drug release in both cancer immunotherapy and chronic pain treatment, further pharmacokinetic and therapeutic studies will be needed.

Altogether, it is demonstrated that a broad range of cargoes can be released from our peptide hydrogels, whereas both hydrogel and cargo properties are determinant in the drug release behavior. In addition to an elongated hydrogelator length, pursuing interaction studies to scrutinize hydrogelator cargo couples could be a future strategy to further optimize the cargo release profiles.