SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Organic Chemistry

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

Morgane Mannes

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:
Discovery, design and synthesis of G protein peptidomimetics

Promotors:
Prof. dr. Steven Ballet (VUB)
Dr. Toon Laeremans (Confo Therapeutics)
Prof. dr. Charlotte Martin (VUB)

The defense will take place on
Friday, April 29, 2022 at 17h00

in auditorium D0.08 on the Campus Humanities, Sciences and Engineering of the Vrije Universiteit Brussel, Pleinlaan 2, 1050 Elsene, and will be followed by a reception.

Members of the jury
Prof. dr. Jan Steyaert (VUB, chair)
Dr. Oleksandr Volkov (VUB, secretary)
Prof. dr. Sophie Hernot (VUB)
Prof. dr. Jean-Louis Banères (University of Montpellier)
Prof. dr. Christa Müller (University of Bonn)
Prof. dr. Antonios Kolokouris (National and Kapodistrian University of Athens)

Curriculum vitae

Morgane Mannes graduated as Master in Bioengineering Sciences - Chemistry and Bioprocess Technology - at the Vrije Universiteit Brussel (VUB) in 2017. Next, she obtained an Innoviris scholarship to start a semi-industrial PhD in the Research Group of Organic Chemistry (ORGC) of the VUB in collaboration with Confo Therapeutics, a drug discovery company.

During her PhD, she focused on G protein peptidomimetics to stabilize G protein-coupled receptors in an active signaling conformation. Her research has led to a patent application on G_s mimetics, a review and a first author publication in one of the most influential chemistry journals (*Angew. Chem. Int. Ed.*). Besides teaching practicals and exercise sessions, she supervised a Master and Bachelor thesis student.

Abstract of the PhD research

G protein-coupled receptors (GPCRs) represent an important family of membrane receptors that play a central role in modern medicine. Unfortunately, it is quite challenging to gain insights into the structure and functioning of GPCRs due to their intrinsic dynamics and high instability when extracted from the cell membrane. Along these lines, conformational promiscuity hampers the full therapeutic exploitation of GPCRs, since the largest population of the receptors will adopt a basal conformation, subsequently challenging screens for agonist drug discovery programs. In past years, Confobodies (Cb) were discovered to lock GPCRs in active signaling states and these have been recognized to be of extreme value in the search of specific orthosteric GPCR agonist ligands. Yet, even though Cbs are crucial tools for structural biology and drug discovery, their use shows some limitations in terms of development costs, including the discovery and purification of the Cbs.

To overcome the drawbacks associated to Cbs, a set of peptidomimetic ligands stabilizing the active state conformation of the β_2 adrenergic receptor (β_2AR) and the dopamine 1 receptor (D1R), both signaling through the G_s protein, was developed. Of note, the developed peptidomimetics equalled the stabilization capacity of Cb80, a reported Cb of β_2AR. During fragment-based screening efforts, the (un)constrained peptide analogues of the α_5 helix in G_s proteins allowed to, gratifyingly, identify agonism pre-imprinted fragments for the examined GPCRs. Having the proof-of-concept that the designed G_s peptidomimetics act as a generic toolset to stabilize active conformations of G_s GPCRs, their fusion to the receptors represents a promising approach to standardize ligand screenings for all G_s-mediated receptors. To this end, different methods were considered to covalently conjugate a G_s peptidomimetic to the β_2AR. However, despite the promising results obtained for the covalent linkage of the G_s peptidomimetics to the membrane-embedded β_2AR, application of the envisaged receptor-peptidomimetics conjugates in drug discovery programs needs further research.