SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Structural Biology Brussels

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

Ivica Odorčić

to obtain the degree of Doctor of Bioengineering Sciences

Joint PhD with KU Leuven

Title of the PhD thesis:
Structural insights into the catalytic mechanism of γ-secretase APH-1B isoform

Supervisors:

Prof. dr. Rouslan Efremov (VUB)
Prof. dr. Lucía Chávez-Gutiérrez (KU Leuven)

The defence will take place on

Wednesday, September 10, 2025 at 4:30 p.m.

VUB Etterbeek campus, Pleinlaan 2, Elsene, auditorium I.2.01

The defence can be followed through a live stream: …

Members of the jury

Prof. dr. Han Remaut (VUB, chair)
Prof. dr. Joost Schymkowitz (KU Leuven, secretary)
Prof. dr. Colin Adrain (Queen's University Belfast, UK)
Dr. Irene Vercellino (Research Center Julich, DE)

Curriculum vitae

Ivica Odorčić obtained his Master degree in Medicinal Chemistry at the University of Rijeka in 2016. Following a short research stay that resulted in a published paper, in 2017 Ivica started his PhD training funded by the VIB international training program within the laboratories of Rouslan Efremov (VUB) and Lucía Chávez-Gutiérrez (KU Leuven).
During his PhD, Ivica presented his work at different international conferences and workshops, with one award for the best poster presentation. His research resulted in a first-author paper published in Nature Communications and contributed to the founding of a spin-off company.
Additionally, Ivica guided a Bachelor student on an international funded internship, who won the best presentaion award for presenting his work.

Abstract of the PhD research

Deposition of amyloid-β (Aβ) peptides in the brain is the first step in a cascade of molecular events that leads to Alzheimer's disease. Aβs are generated through sequential proteolysis of the amyloid precursor protein (APP) by the β-secretase and the γ-secretase complexes (GSECs). The aggregation potential and toxicity of Aβs, leading to pathogenicity, is determined by their length, which is, in turn, determined by the efficiency of sequential proteolysis by GSECs (processivity). In humans, two homologues of the GSEC subunits Presenilin (PSEN1/PSEN2) and anterior pharynx-defective 1 (APH-1A/APH-1B) constitute four distinct GSEC complexes with distinct processivities.
During my PhD, I sought to better understand, on the structural and mechanistic levels, how sequential cleavage of Aβs happens in GSECs and how the APH-1B subunit modulates this process.
In the first part of the PhD project, we established a robust protocol to express and purify human PSEN1/APH-1B GSEC (termed GSEC1B) as well as reconstitute it into lipid nanodiscs, which mimic lipid membranes. Next, we optimised the preparation of cryogenic samples of GSEC1B for high-resolution cryogenic electron microscopy (cryo-EM).
In the second part, we used cryo-EM to reconstruct the 3D structure of both GSEC1B in the apo form, and in complex with the intermediate Aβ46 substrate. This revealed that: (i) three divergent in sequence APH-1 loops exhibit different conformations between the homologues; (ii) one of these APH-1 loops is involved, together with PSEN1, in structural rearrangements that happen upon substrate binding; and (iii) Aβ46 is bound to PSEN1 in a conformation similar to that of the full-length substrates. The partially unwound Aβ46 helix is stabilised by several polar interactions which were functionally validated in cell assays.
Based on these findings, we proposed a mechanism of sequential catalysis of Aβs by GSECs and the mechanism of processivity modulation by the APH-1 subunit. Ultimately, this research may aid further development of GSEC inhibitors for cancer treatment and GSEC modulators for the treatment of Alzheimer's disease.