SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Structural Biology Brussels

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

Ella Martin

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:

The Presynaptic Phosphoinositide Phosphatase Synaptojanin 1: From Structural Insights to Therapeutic Targeting

Supervisor:
Prof. dr. ir. Wim Versées (VUB)

The defence will take place on

Monday, November 3, 2025 at 4 p.m.

VUB Etterbeek campus, Pleinlaan 2, Elsene, Promotiezaal D.2.01

Members of the jury

Prof. dr. ir. Damya Laoui (VUB, chair)
Prof. dr. Ulrich Hennecke (VUB)
Prof. dr. Anastassia Vorobieva (VUB)
Prof. dr. Shehab Ismail (KU Leuven)
Prof. dr. Elisa Greggio (University of Padova, IT)

Curriculum vitae

Ella Martin obtained a Master degree in Biochemistry and Molecular and Cellular Biology at Université Libre de Bruxelles in 2018. After her master thesis about the functional and structural characterization of the bacterial protein Rel, she started her PhD as FWO fellow. Here, she combined enzymology, bioinformatics and structural biology to study the human protein Synaptojanin1.
Throughout her doctoral study, she published five papers in peer-reviewed international journals, of which two as first author. She also presented her findings at several international conferences and workshops, with one award for the best poster presentation, and supervised three master thesis students.

Abstract of the PhD research

Synaptojanin 1 (Synj1) is a dual-activity lipid phosphatase enriched at the nerve endings, where it specifically acts upon signaling lipids called phosphoinositides or PIPs. The enzyme bears two catalytic domains: a Sac1 domain that predominantly dephosphorylates PI(3)P and PI(4)P, and a 5-phosphatase domain dephosphorylating $PI(4,5)P_2$ and $PI(3,4,5)P_3$ at the 5-position of the inositol ring. Synj1 has previously been implicated in the manifestation of diseases including Parkinson's disease, Down syndrome and Alzheimer's disease, and has been proposed as a promising drug target for the latter disease. Additionally, its 5-phosphatase domain has been identified as a drug target to treat TBC1D24-related forms of epilepsy. However, insights into disease mechanisms at atomic scale and the development of potent inhibitors specifically targeting Synj1 were hampered by the lack of structural information and detailed biophysical / kinetic studies.

In the present PhD thesis, we describe the crystal structure of the apo and diC8-$PI(3,4,5)P_3$-bound form of the 5-phosphatase domain of Synj1, as well as an analysis of the contribution of the different inositol phosphate groups to catalysis. Together, these data provide important new insights in the catalytic mechanism of Synj1. We also analyze the effect on catalysis of three homozygous patient mutations in the 5-phosphatase domain (p.Y793C, p.R800C and p.Y849C), revealing the molecular mechanism underlying Synj1-associated diseases, and allowing to define a therapeutic window to target Synj1.

In a second part of the thesis, we present the results of a combined experimental and virtual screening approach to identify novel inhibitors of Synj1 5-phosphatase activity. The mechanism of action of the inhibitors as well as their specificity for Synj1 were investigated, allowing us to report the first potent and selective inhibitor of Synj1 5-phosphatase activity, with potential future therapeutic applications for Alzheimer's disease and TBC1D24-associated epilepsy.

Finally, we present a detailed characterization of the two Synj1 catalytic activities in the context of the full-length protein, as well as initial (low resolution) cryo-EM models of the full-length Synj1 protein alone as well as in complex with a pro-macrobody.

Altogether, this work delivers new insights into the working mechanism of Synj1 by providing structural and enzymatic data, while also presenting a potentially new therapeutic route for Alzheimer's disease and TBC1D24-related form of epilepsy through inhibition of the Synj1 5-phosphatase activity.