SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Structural Biology Brussels

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

Jone Paesmans

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:

Unraveling the structure and function of the synaptic proteins TBC1D24 and Synaptojanin1 and their role in neurological disorders

Promotor:
Prof. dr. ir. Wim Versées

The defense will take place on

Tuesday, June 29, 2021 at 17h00

The defense can be followed through a live stream. Contact Jone.Paesmans@vub.be for more information and the link.

Members of the jury

Prof. dr. Steven Ballet (VUB, chair)
Prof. dr. Janine Brunner (VUB, secretary)
Prof. dr. Ilse Smolders (VUB)
Prof. dr. Shehab Ismail (Chemistry Department, KU Leuven)
Prof. dr. Elisa Greggio (Department of Biology, University of Padova)

Curriculum vitae

Jone Paesmans obtained her Master of Science in bioengineering sciences: cell and gene biotechnology in 2014 at the Vrije Universiteit Brussel. Immediately after she started her PhD, funded by an FWO fellowship, within the lab of Prof. Dr. ir. Wim Versées (Structural Biology Brussels). She presented her work at different (inter)national conferences and published two high-impact peer reviewed papers as first author, and was co-author on two other publications. She is also co-inventor on a patent application. Finally, she guided and supervised four master thesis students.

Abstract of the PhD research

Neurological disorders, such as epilepsy, Parkinson's disease and Alzheimer's disease, are often considered to be idiopathic diseases, since the underlying causes or mechanisms are unknown. However, in recent years, mainly due to next-generation sequencing, these disorders are more and more linked to mutations in protein-encoding genes. As such, it turned out that, next to mutations in ion channels, also malfunctioning of the proteins and processes related to synaptic vesicle trafficking are a common underlying cause of these disorders, making them ideal targets for drug design. Two of these synaptic proteins are TBC1D24 and Synaptojanin1 (Synj1), both forming the subject of this PhD thesis.

We first focused on the TBC1D24 protein, which is found mutated in epilepsy and DOORS syndrome patients, and which consists of a TBC- and a TLDc-domain. The combination of these two domains is unique among human proteins, but an orthologous protein could be identified in fruit flies, where it is called Skywalker (Sky). Sky was used in this PhD thesis as a model system, and the crystal structures of its TBC- and TLDc-domains were determined. For the TBC-domain, we revealed an unexpected positively charged pocket that can bind to the phosphoinositides $PI(4,5)P_2$ and $PI(3,4,5)P_3$, membrane lipids that also play an important role in synaptic vesicle trafficking. Patient mutations found in the positively charged pocket hamper this binding and concomitantly lead to neurological defects and seizures in fruit flies. However, these defects could be reversed by genetically increasing the phosphoinositide levels through partial ablation of Synj1, a phosphoinositide 5-phosphatase that dephosphorylates the 5-position of $PI(4,5)P_2$ and $PI(3,4,5)P_3$ via its catalytic 5-phosphatase domain.

As a second part of this PhD research, we focused on the human Synj1 protein as it was identified as a potential drug target for TBC1D24-related epilepsy as well as for Alzheimer's disease and Down syndrome, while, on the other hand, inherited mutations in the gene encoding Synj1 cause Parkinson's disease and epilepsy. Despite its involvement in a range of diseases, structural and detailed mechanistic information on Synj1 is missing. Therefore, we solved the crystal structure of the catalytic 5-phosphatase domain of Synj1 with a trapped substrate ($PI(3,4,5)P_3$) in its active site. Together with a detailed biochemical analysis, we provided new insights in Synj1's catalytic mechanism. Finally, analysis of patient mutations showed a decrease in the catalytic performance of Synj1 and suggested a link between the magnitude of these effects and the severity and age-of-onset of the disease manifestations. In the future, these insights may guide structure-based drug development.