SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Structural Biology Brussels (SBB)

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

Egon DEYAERT

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:

Unravelling and modulating the Roco protein activation cycle

Promotor:

Prof. Dr. ir. Wim Versées

The defence will take place on

Friday November 24 2017 at 17:00h

in Auditorium D.0.05 at 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. Jürgen Wendland (chairman)
Prof. Dr. ir. Remy Loris (secretary)
Prof. Dr. Nick Devoogdt
Prof. Dr. Sergei Strelkov (KUL)
Prof. Dr. Elisa Greggio (Univ. of Padova, Italy)

Curriculum vitae

Egon Deyaert obtained a Master of Science in Chemistry at the VUB in 2011. Subsequently he became teaching assistant in the Structural Biology Brussels (SBB) research group. Alongside his educational tasks he performed scientific research in the field of structural biology. This research contributed to the publication of 5 papers in international peer-reviewed journals and he presented his results at international conferences.
In addition he supervised 3 students during their Master thesis.

Abstract of the PhD research

Mutations in the gene coding for the LRRK2 protein are the most common cause of the inherited form of Parkinson's disease. LRRK2 is a large multidomain protein bearing both kinase and GTPase activity. As a results, both academia and industry are trying to understand the complex structure and regulatory mechanism of LRRK2, as a potential target for drug design.

Since biochemical studies with LRRK2 are notoriously challenging, homologous proteins from the Roco family are used as model systems. One important aspect of the mechanism of LRRK2 and related Roco proteins that is still under debate concerns the relation between the function and oligomerisation of these proteins. During my PhD research, I have characterized the effect of nucleotide (GTP/GDP) binding on the oligomeric state of the bacterial *Chlorobium tepidum* Roco protein (CtRoco). We could show unequivocally that the CtRoco protein cycles between a monomeric and dimeric state during nucleotide binding and hydrolysis. Our data also suggests a direct link between oligomerization and disease-associated mutations in LRRK2. In a second part of the study, I solved the crystal structure of a domain construct of CtRoco consisting of the LRR, Roc and COR domains. Finally, nanobodies were generated against the CtRoco protein that recognize the protein in a conformation (nucleotide)-specific way. These nanobodies will prove valuable in directing further research.

In conclusion, this research throws a new light on the mechanism of the Roco proteins, including LRRK2, and in particular on the long-standing discussion regarding their oligomeric state. Our insights might open new avenues for future drug discovery in Parkinson's disease.