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

Lina WAUTERS

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:

Biochemical, kinetic and structural characterization of the unusual GTPase cycle of Roco proteins

Promotors:

Prof. Dr. ir. Wim Versées (VUB)
Prof. Dr. Peter J.M. van Haastert (RUG)
Prof. Dr. Arjan Kortholt (RUG)

The defence will take place on

Friday November 16 2018 at 14:30h

in the Academiegebouw at the University of Groningen, Broerstraat 5 – Groningen – The Netherlands, and will be followed by a reception.

Members of the jury:

Prof. Dr. Egbert J. Boekema (RUG)
Prof. Dr. Jürgen Wendland (VUB)
Prof. Dr. Dirk J. Slotboom (RUG)
Prof. Dr. Veerle Baekelandt (KUL)
Prof. Dr. Kirsten Harvey (UCL)
Prof. Dr. Peter Tompa (VUB)
Dr. Maarten H.K. Linskens (RUG)

Curriculum vitae

Lina Wauters obtained a Master of Science in Bioengineering Sciences at the Vrije Universiteit Brussel (VUB) in 2013. Subsequently she started a joint PhD in Bioengineering Sciences at the research group Structural Biology Brussels of the VUB and the Department of Cell Biochemistry of the Graduate School of Science and Engineering of the University of Groningen. Her scientific research in the field of Structural Biology so far led to the publication of 4 papers and 1 review in peer-reviewed journals. In addition, she aided in the teaching of master students in laboratory practices and supervised a bachelor student.

Abstract of the PhD research

Since mutations in the gene coding for the human Roco protein LRRK2 were found to be the most frequent cause of familial Parkinson's Disease, the protein has been intensively studied. LRRK2 is a large multidomain protein harbouring both GTPase and kinase activity. Despite tremendous research efforts, and the discovery of several LRRK2 pathways and interaction partners, still many research questions remain unanswered. One important aspect of the working mechanism of LRRK2 that is still under debate, is the functioning of the central RocCOR module, responsible for the GTPase activity of the protein.

During my PhD research, I have unravelled the GTP hydrolysis mechanism of Roco proteins. In a first part of the study, I investigated the oligomeric state of the bacterial *Chlorobium tepidum* Roco protein (*Ct*Roco) upon nucleotide binding. We could show that the protein cycles between a monomeric and dimeric state upon nucleotide binding and hydrolysis and that monomerization is a characteristic feature of the GTP hydrolysis cycle. In a second part of the study, I have characterized the GTP hydrolysis mechanism of several prokaryotic Roco proteins and human LRRK2 via biochemical and kinetic experiments. I have shown that the GTP hydrolysis itself is the rate-limiting step in the GTP hydrolysis cycle and that Roco proteins do not require auxiliary proteins for the exchange of nucleotides, although additional factors might still regulate the moderate GTPase activity.

Based on these data, we have proposed a new working hypothesis for Roco proteins in general and LRRK2 in particular. In this way, this work provides valuable new insights in our endeavour to unravel the working mechanism of this protein family.