Promotor

Prof. Ilse Smolders

Department of Pharmaceutical Chemistry
and Drug Analysis
Center for Neurosciences C4N
Vrije Universiteit Brussel

Copromotoren

Prof. Yvette Michotte

Department of Pharmaceutical Chemistry
and Drug Analysis
Center for Neurosciences C4N
Vrije Universiteit Brussel

Prof. Patrick Vanderheyden

Department of Molecular and Biochemical
Pharmacology
Vrije Universiteit Brussel

Leden van de examencommissie

Prof. Giuseppe Di Giovanni

Faculty of Medicine & Surgery
University of Malta, Malta

Dr. Govert Hoogland

School for Mental Health and Neuroscience
Maastricht Universitair Medisch Centrum
Universiteit Maastricht, Nederland

Prof. Vicky Caveliers

Nucleaire Geneeskunde UZ Brussel
Medical Imaging and Physical Sciences
Vrije Universiteit Brussel

Prof. Mathieu Vinken, voorzitter

Department of Toxicology
Vrije Universiteit Brussel

Vrije Universiteit Brussel

FACULTEIT GENEESKUNDE EN FARMACIE

Doctoraat Farmaceutische Wetenschappen
Academiejaar 2011-2012

UITNODIGING

Voor de openbare verdediging van het
doctoraatsproefschrift van

Ellen LOYENS

Donderdag 21 juni 2012

U wordt vriendelijk uitgenodigd op de openbare verdediging van het proefschrift van

Ellen LOYENS

'The role of insulin-regulated aminopeptidase and its substrates in mechanisms of epilepsy and antidepressant-like activity'

Op **donderdag 21 juni 2012** om **17 uur**
in auditorium **3** van de
Faculteit Geneeskunde & Farmacie
Laarbeeklaan 103, 1090 Brussel

Situering van het proefschrift

Since several years, our research group has been intrigued by the anticonvulsant effects of angiotensin IV (Ang IV), the hexapeptide that represents the end product of the renin-angiotensin system, in animal seizure models. Until now, its mechanism of anticonvulsant action remained speculative. Moreover, the involvement of its high affinity binding site insulin-regulated aminopeptidase (IRAP) in seizure models was never investigated directly. By using transgenic IRAP wild-type and knock-out mice, we unequivocally unraveled in this thesis that IRAP is involved in seizure generation since IRAP deletion decreased the susceptibility of the mice to chemically-induced seizures. Moreover, IRAP ligands exerted anticonvulsive effects in the rat focal pilocarpine model that were reversed by somatostatin 2 receptor (sst2R) antagonists. Although three hypotheses have been put forward to explain IRAP-mediated effects, our experiments pointed to a novel, indirect interaction mechanism between IRAP ligands and sst2Rs. Since IRAP ligand binding resulted in an increased sst2R recycling rate, we expect that the higher number of surface sst2Rs could be responsible for an increased sst2R signaling and hence anticonvulsive effects of the IRAP ligands. We also showed that the presence of IRAP is required for oxytocin, a proconvulsant substrate of IRAP, to exert antidepressant-like effects.
Taken together, as an enzyme or a regulator of sst2R trafficking, IRAP can be considered as a therapeutical target for the treatment of seizures and depression.

Curriculum Vitae

Ellen Loyens was born on the 14th of February 1983 in Hasselt, Belgium. In 2001, she acquired her diploma from secondary school at Koninklijk Atheneum I (Hasselt, Belgium). In September of the same year, she started to study Biomedical Sciences at the University Hasselt in Diepenbeek, Belgium, where she got her candidate diploma cum laude in 2003. She continued her education in Diepenbeek to obtain her Master (Licentiate) Magna Cum Laude in Biomedical Sciences at the transnationale Universiteit Limburg (tUL), a cooperation between University Hasselt and University Maastricht, in 2005. For this degree she performed an internship of 7 months at the department of Physiology in Diepenbeek, Belgium. Her master thesis was entitled 'Influence of simvastatin on oxidative stress in OLN-93 cells'.
During her internship, Ellen Loyens got interested to perform scientific research. Therefore, in 2008 she started to work as a PhD student at the department of Pharmaceutical Chemistry and Drug Analysis at the Vrije Universiteit Brussel under promotorship of Prof. I. Smolders. During this time, she mentored several master students during their internships, she is author and co-author of several international papers, and she participated to several national and international conferences where she was able to present her research by poster presentations.