

Board of examiners

Prof. Dr. Wolfgang Löscher

Department of Pharmacology, Toxicology and Pharmacy
University of Veterinary Medicine Hannover, Germany

Dr. Corinne Roucard

Founder and CEO of SynapCell
France

Prof. Dr. Dimitri De Bundel

Pharmaceutical Chemistry and Drug Analysis
Vrije Universiteit Brussel

Prof. Dr. Mathieu Vinken

In Vitro Toxicology and Dermato-Cosmetology
Vrije Universiteit Brussel

Prof. Dr. Joeri Aerts, Chair

Pharmaceutical Biotechnology and Molecular Biology
Vrije Universiteit Brussel

Prof. Dr. Ilse Smolders (promotor)

Pharmaceutical Chemistry and Drug Analysis
Vrije Universiteit Brussel

Dr. Rafal Kaminski (co-promotor)

Neurosciences Research
Experimental Therapeutics, UCB Biopharma
Braine l'Alleud, Belgium



**PhD in Pharmaceutical Sciences
2016-2017**

INVITATION to the Public defence of

Karine LECLERCQ

To obtain the academic degree of '**DOCTOR IN PHARMACEUTICAL SCIENCES**'

**Development of preclinical models of drug-resistant
epilepsy for application in future antiseizure drug
discovery.**

Tuesday 21 February 2017

Auditorium **Piet Brouwer**, 17:00

Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

How to reach the campus Jette:

<http://www.vub.ac.be/english/infoabout/campuses>

Summary of the dissertation

Drug-resistant epilepsy represents an important unmet medical need. Consequently, preclinical strategies have to be revisited to deliver more effective antiseizure drugs (ASDs). In the present work, several novel experimental approaches applicable to the discovery of future ASDs were evaluated. We first compared the biochemical and electrophysiological endpoints after allylglycine-induced seizures in mice and zebrafish. The anticonvulsant efficacy and potency of five clinically used ASDs were compared in both species. Having demonstrated strong cross-species similarities in response to ASDs, we propose the use of zebrafish for high-throughput screening aiming to discover novel, more effective compounds. In the second experimental part, we report the development and pharmacological validation of the 6 Hertz (6 Hz) corneal kindling model in mice. Repeated electrical stimulations (kindling) led to a progressive sensitization and the development of generalized motor seizures. Several ASDs were compared between the 6 Hz and the conventional 50 Hz kindling models, revealing limited efficacy of drugs to protect against seizures in the 6 Hz paradigm. The influence of experimental conditions such as mouse strain and stimulation device on the response to ASDs was also assessed using acute 6 Hz corneal stimulation. The obtained results indicate that the genetic background of experimental animals is an important determinant of drug response, which may reflect resistance of human epilepsy to current ASDs. Finally, we studied the impact of a first inciting event (pilocarpine-induced status epilepticus) on the potency and efficacy of ASDs in the 6 Hz model, which collectively resembles clinical pathophysiology of temporal lobe epilepsy. The work reported in this thesis opens new avenues and provides much needed research tools for future ASDs discovery.

Curriculum Vitae

Nationality : Belgian

Date of birth : Dec 31st, 1965

Education: industrial engineer degree in biochemistry obtained in 1987 (HelHa, Charleroi), master degree in molecular biology and biotechnology in 1990 (ULB, Brussels)

Professional experience : research associate in in vivo pharmacology laboratory at UCB (Oct 1989-1997); research associate in in vitro cellular laboratory at UCB (1998-2003); scientist and team leader in in vivo epilepsy pharmacology at UCB (since 2004).

Opportunity to perform a PhD thesis under the promotorship of Prof. Ilse Smolders and co-promotorship of Dr. Rafal Kaminski. This work summarizes the most convenient and promising rodent models which could be implemented in preclinical research to identify new treatment for drug-resistant epilepsy.

Publications: author of four first-author publications and thirteen co-author publications in peer-reviewed journals.