

Board of examiners

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School of Molecular and Cellular Biology
Faculty of Biological Sciences
University of Leeds, UK

PhD in Pharmaceutical Sciences
2015-2016

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Rega Institute for Medical Research
University of Leuven

INVITATION to the Public defence of

Lise SCHOTTE

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

Single-domain antibody fragments against poliovirus: mechanisms of neutralization and use in research and eradication

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Auditorium **Brouwer**, 17:00

Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

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Vrije Universiteit Brussel

Summary of the dissertation

Poliovirus, as the causative agent of poliomyelitis, has plagued mankind throughout history. The development and implementation of two successful vaccines against the virus in the 1950s has since impressively decreased the number of polio-patients. However, to complete the last phases of polio-eradication and to protect people afterwards, the development of multiple anti-polioviral drugs and certain tools (e.g. standards in vaccine-control) is needed. As an interesting approach, single-domain antibody fragments (VHHs or Nanobodies®) can be thought of. Five *in vitro* neutralizing VHHs against poliovirus type 1 were previously developed at our department. The current work describes the mechanisms of neutralization of these VHHs in detail, as well as the epitopes targeted on the polioviral capsid and the structural changes involved at the VHH-poliovirus interface. Interestingly, the VHHs were found to bind the capsid at sites that extensively overlap the binding site of the natural poliovirus receptor, and at structures that are known to move during the expansion of the metastable capsid during its natural replication cycle. Binding with these residues explains the stabilizing activity of the VHHs against heat-induced degradation of the capsid and the multi-level mechanisms of neutralization of the five VHHs. As a second part of the work, neutralization escape mutants resistant against the VHHs have been selected, identified and characterized. This is important in the context of developing the VHHs as anti-viral drugs and provides knowledge on the implications of these mutants and, concurrently, on strategies to limit therapy-resistance. Additionally, the possibility to format the VHHs into constructs and to use them as probes in research and eradication was explored.

Curriculum Vitae

Lise Schotte was born on December 19th, 1986 in Mechelen. After five years of pharmacy studies at the Vrije Universiteit Brussel, she graduated as a Pharmacist and Master in Pharmaceutical Care in 2009 with highest distinction. During the internship for her masters thesis at the Department of Pharmaceutical Biotechnology and Molecular Biology, she worked on the fluorescent labeling of poliovirus which introduced her into the interesting world of Picornavirology. After her graduation, she proceeded in poliovirus-research and obtained a grant from the Research Foundation Flanders (FWO) to start her PhD in October 2009, under the promotership of Prof. Bart Rombaut and Bert Thys. In 2013 she was appointed as a teaching assistant at the same department and continued her research in combination with teaching pharmacy students the practical skills in biochemistry, microbiology and biotechnology. During the preparation of her PhD, she collaborated with Prof. Jim Hogle and his research team at Harvard Medical School in Boston (MA., USA) and she had the privilege to visit the Hogle lab several times. After the sudden and unfortunate passing of Prof. Bart Rombaut in January 2014, Prof. Hogle and his team, together with Prof. Ann Massie, engaged themselves to guide Lise in the last phases of her PhD-research. Lise is author of six publications in international peer-reviewed journals (three as first author), currently preparing two more papers and presented her research on several international and national conferences and meetings. The poliovirus-nanobody research has also been financially supported by the World Health Organization. Her next challenge for the upcoming years is to become a clinical biologist.