

Board of examiners

**Prof. dr. Raymond Hupperts**

Zuyderland Medisch Centrum Sittard, Academisch MS Centrum Limburg  
Department of Clinical Neurosciences  
Maastricht University Medical Center, Maastricht University

**Prof. dr. Niels Hellings**

Biomedical Research Institute, Faculty of Medicine & Life Sciences  
University Hasselt

**Prof. dr. Jan Versijpt**

Department of Clinical Sciences, Center for Neurosciences  
Vrije Universiteit Brussel

**Prof. dr. Veronique Bissay**

Department of Clinical Sciences  
Vrije Universiteit Brussel

**Prof. dr. Ann van Eeckhout**

Department of Pharmaceutical Sciences, Laboratory of Pharmaceutical Chemistry  
Drug Analysis and Drug Information, Center for Neurosciences  
Vrije Universiteit Brussel

**Prof. dr. Dimitri De Bundel, Chair**

Department of Pharmaceutical Sciences, Laboratory of Pharmaceutical Chemistry  
Drug Analysis and Drug Information, Center for Neurosciences  
Vrije Universiteit Brussel

**Prof. dr. Ron Kooijman, Promoter**

Department of Pharmaceutical Sciences, Laboratory of Pharmaceutical Chemistry  
Drug Analysis and Drug Information, Center for Neurosciences  
Vrije Universiteit Brussel

**Prof. dr. Miguel D'haeseleer, Promoter**

National MS Center Melsbroek and Department of Neurology, Universitair Ziekenhuis  
Brussel and Department of Clinical Sciences, Center for Neurosciences  
Vrije Universiteit Brussel

**Prof. em. dr. Jacques De Keyser, Promoter**

Vrije Universiteit Brussel



PhD in Medical Sciences  
2019-2020

INVITATION to the Public defence of

**Stéphanie HOSTENBACH**

To obtain the academic degree of '**DOCTOR OF MEDICAL SCIENCES**'

**Astrocytic endothelin-1 and cerebral hypoperfusion  
in multiple sclerosis.**

The defense will take place digitally on

Thursday, 16 July 2020 at 4 p.m.

via Zoom meeting, accessible through the following link:

[https://gf.vub.ac.be/redirects/PhD\\_defense\\_Stephanie\\_Hostenbach.php](https://gf.vub.ac.be/redirects/PhD_defense_Stephanie_Hostenbach.php)

---

## Summary of the dissertation

Multiple sclerosis is a chronic inflammatory and neurodegenerative disorder of the central nervous system characterized by inflammatory demyelinating lesions and progressive axonal degeneration. The underlying pathophysiology of the progressive axonal degeneration is not completely understood, but there is increasing evidence that axonal mitochondrial energy failure is involved in this process. Decreased levels of N-acetylaspartate (NAA) are found in the cerebral normal-appearing white matter (NAWM) in MS patients, which is considered as a marker for axonal mitochondrial activity. Furthermore, the cerebral blood flow (CBF) seems also to be globally impaired in the NAWM. In animal models, decreased CBF leads to mitochondrial energy failure and axonal degeneration. An increased cytokine-induced astrocytic endothelin-1 (ET-1) production seems to be involved in the reduction of the CBF, as a study with a single 62.5 mg dose of bosentan (ET-1 receptor antagonist) in MS patients restored CBF to levels similar to healthy controls. In this thesis, we wanted to explore the underlying mechanisms for astrocytic ET-1 upregulation in MS, as well as to find drugs that can suppress this upregulation. We found that simvastatin and resveratrol were able to reduce the ET-1 expression *in vitro*, however these effects cannot be achieved in humans when pharmacologically tolerated doses are used. The effect of fluoxetine on the ET-1 production was rather modest and probably not sufficient enough to be clinically relevant. A 4-weeks trial with bosentan was set up in MS patients, to explore if prolonged restoration of the CBF could improve axonal mitochondrial metabolism. This trial showed no effect on the CBF and NAA-levels, probably because of the mild disease courses and minimal local inflammatory activity. It seems plausible that only MS patients with decreased CBF benefit from therapies suppressing astrocytic ET-1 production or blocking its effect, but further clinical trials are necessary.

## Curriculum Vitae

Stéphanie Hostenbach was born on the 24th of February 1988 in Ukkel. In 2013 she obtained her medical degree at the Free University of Brussels, summa cum laude. Afterwards, she started her residency in neurology (Prof. Dr. Em. Jacques De Keyser and Prof. Dr. Bas Engelborghs) and will obtain her degree as neurologist in July 2020. In 2014, she started her PhD on the role of cerebral hypoperfusion in the pathophysiology of multiple sclerosis. From 2014 till 2018, she was an FWO fellow (Fonds voor Wetenschappelijk onderzoek) and also obtained funding from the Belgian Charcot Foundation. During her PhD, she published 4 first author manuscripts of which 2 papers in a Q1 journal. Besides her medical and PhD activity, she has been committed to the medical world since 2013 as vice-president of the national medical congress "Symposium Medische Wereld", organized on a yearly basis at the Free University of Brussels.