Board of examiners

Prof. dr. Krista Rombouts
Centre for Tissue Repair and Regeneration
Institute for Liver and Digestive Health
Regenerative Medicine and Fibrosis group
University College London

Prof. dr. Isabelle Colle
Department of Gastroenterology-hepatology
Ghent University

Prof. dr. Karine Hellemans
Diabetes Pathology & Therapy (DIAB)
Vrije Universiteit Brussel (VUB)

Prof. dr. Robim Marcelino Rodrigues
Experimental in vitro toxicology and dermato-cosmetology (IVTD)
Vrije Universiteit Brussel (VUB)

Prof. dr. Karine Breckpot, Chair
Laboratory for Molecular and Cellular Therapy (LMCT)
Vrije Universiteit Brussel (VUB)

Promoters:

Prof. dr. Leo van Grunsven
Liver Cell Biology Research Group (LIVR)
Vrije Universiteit Brussel (VUB)

Prof. dr. Inge Mannaerts
Liver Cell Biology Research Group (LIVR)
Vrije Universiteit Brussel (VUB)

VRIJE UNIVERSITEIT BRUSSEL

PhD in Medical Sciences
2021-2022

INVITATION to the Public defence of

Vincent De Smet

To obtain the academic degree of

'DOCTOR OF MEDICAL SCIENCES'

Hepatic Stellate Cell Transcriptional Dynamics in Liver Fibrosis

The public defence will take place on

Monday, **20 June 2022 at 5 p.m.**

In Auditorium Vanden Driessche
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

and can be followed online, accessible through the following link**:**

https://gf.vub.ac.be/redirects/PhD_defense_Vincent_De_Smet.php

Summary of the dissertation

Chronic liver disease (CLD) is a global health burden accounting for an estimated 2million deaths per year worldwide. One of the characteristics of CLD is the development of fibrosis (i.e. scarring of the liver). The extent of liver fibrosis has been shown to be the main prognostic determinant of CLD, irrespective of CLD etiology. At the cellular level, liver fibrosis is caused by hepatic stellate cells (HSC) that activate from a quiescent, retinoid-storing, phenotype to an activated, myofibroblast-like, phenotype. At this point, no treatment options exist for CLD other than treating the underlying cause or transplanting livers in end stage disease state. These options are often not feasible however. Thus, there currently is an unmet need for the treatment of CLD. To tackle this unmet need, we used transcriptomics to investigate the process of HSC activation during the very first moments of activation (called initiation). We hypothesized that these insights would allow us to identify new putative antifibrotic candidates. The results obtained in this thesis show that, while initiation is historically defined as being limited to early events, initiation characteristics remain present throughout all stages of liver disease, from acute liver injury to end stage liver disease. From this data, we were able to identify GPR176, an orphan G-protein coupled receptor with enriched expression in HSCs that is associated with the extent of HSC activation and liver fibrosis. Blocking of GPR176 expression reduced HSC activation and liver fibrosis in mice. In conclusion, by analyzing HSC transcriptional dynamics, we were able to show that HSC initiation can be considered a previously unexplored entity for the treatment of CLD on the one hand and we were able to identify a new putative antifibrotic candidate on the other. Evidence provided in this thesis further broadens our understanding of HSC biology and might fuel new fundamental and translational research in pursuit of new CLD therapeutics.

Curriculum Vitae

Vincent De Smet was born on the 25th of April, 1992 in Jette, Belgium. He lived and completed his schooling in Aalst, going on to attend the Vrije Universiteit Brussel (VUB) for his medical studies. He completed his studies in 2017, graduating with greatest distinction with a Master in Medicine. During the course of his studies, Vincent participated in a diverse range of internships across many different hospitals in Belgium - additionally completing an international internship in Mumbai, India and passing Step 1 of the USMLEs.

His final year of medical studies, Vincent was introduced to the Liver Cell Biology group through his master thesis. The group, led by prof. Van Grunsven, awoke his passion for research and he would go on to obtain funding for a PhD fellowship through the Research Foundation Flanders (FWO). The doctorate would focus on transcriptional analysis of liver cells, with a strong focus on hepatic stellate cells in liver fibrosis. Combining his work with clinical rotations as well as the supervision of biomedical students, Vincent's research had led to two peer-reviewed publications as first author. Furthermore, it has been well-received at oral and poster presentations at national and international conferences – one presentation going on to receive the 'best abstract' award.

At the time of writing, he is preparing to defend his doctorate while completing a residency in Internal Medicine with the intent of specializing in Gastro-Enterology.