

Board of examiners

**Prof. Dr. José V. Castell**

Unidad Hepatología Experimental  
Instituto de Investigación, Hospital Universitario de La Fe

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Institute of Experimental and Clinical Research  
Université Catholique de Louvain

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Department of Morphology and Molecular Pathology  
Katholieke Universiteit Leuven

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Department of In Vitro Toxicology and Dermato-Cosmetology  
Vrije Universiteit Brussel

**Prof. Dr. Sophie Hernot**

In vivo Cellular and Molecular Imaging Lab  
Vrije Universiteit Brussel

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

Department of Pharmaceutical Chemistry and Drug Analysis  
Vrije Universiteit Brussel

**Promoters**

**Prof. Dr. Joery De Kock**

Department of In Vitro Toxicology and Dermato-Cosmetology  
Vrije Universiteit Brussel

**Prof. Dr. Tamara Vanhaecke**

Department of In Vitro Toxicology and Dermato-Cosmetology  
Vrije Universiteit Brussel

**Prof. Dr. Vera Rogiers**

Department of In Vitro Toxicology and Dermato-Cosmetology  
Vrije Universiteit Brussel



**PhD in Pharmaceutical Sciences  
2016-2017**

INVITATION to the Public defence of

**Karolien BUYL**

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

**Characterization and reprogramming of umbilical cord-derived mesenchymal stromal cells towards the hepatic lineage.**

**Tuesday 28 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>

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## Summary of the dissertation:

Drug-induced liver injury is one of the major causes for the discontinuation of drug development and post-market drug withdrawal. Thus, it is of utmost importance to screen out hepatotoxic compounds during the early preclinical phases of the drug development process. For this purpose, primary human hepatocytes are seen as the gold standard. However, these are very scarce since human donor livers are intensively used for transplantation purposes. Consequently, the search for alternative sources of primary human hepatocytes is still ongoing. In this context, stem cell technology holds great promise. Although a lot of hurdles still need to be overcome, important advances have been made over the last years. The current doctoral research could demonstrate that the human umbilical cord is an important source of mesenchymal stromal cells (MSC) that intrinsically express a set of liver-enriched transcription factors (LETFs) and other fetal and adult hepatic markers. Consequently, it was suggested that human umbilical cord-derived MSC (hUC-MSCs) could represent an important source to generate human hepatocyte-like cells. However, in order to imply these cells for *in vitro* hepatotoxicity testing, hUC-MSCs need to be obtained in a standardized and reproducible way. As such, a robust isolation protocol could be developed, allowing the isolation of hUC-MSCs within the short period of three hours. Using this procedure, hUC-MSCs could be obtained that retain the typical characteristics of MSCs. These hUC-MSCs also maintained the intrinsic expression of the aforementioned LETFs and fetal and adult hepatic markers and therefore could qualify as a plausible cell source to generate functional hepatocyte-like cells. However, we also found that hUC-MSCs lack the expression of other key LETFs (e.g. hepatocyte nuclear factor 1 alpha; Hnf1a) that are mandatory for hepatocytes to obtain and maintain their functional properties. We hypothesized that over-expression of these missing LETFs could support the hepatic differentiation of hUC-MSCs. Therefore, as a proof-of-principle, a lentiviral hepatic reprogramming protocol was established over-expressing one key LETF, i.e. Hnf1a, in order to investigate this hypothesis. It was found that over-expression of Hnf1a improves the hepatic differentiation of hUC-MSCs compared to a standard hepatic differentiation protocol. As such, hUC-MSC-derived hepatic cells could be obtained that significantly express several phase I and phase II biotransformation enzymes. Altogether, it is our firm belief that this PhD thesis delivers an important contribution in the search for plausible cell sources to generate functional human hepatocytes using stem cell technology.

## Curriculum Vitae:

Karolien Buyl was born on the 2<sup>nd</sup> of January 1988 in Ninove, Belgium. She completed secondary school, orientation science-mathematics, in 2006 after which she started her academic career at the Vrije Universiteit Brussel (VUB). In 2011 she obtained her degree as pharmacist and master in drug development with high distinction. She joined the research group of *In vitro* Toxicology and Dermato-Cosmetology at the faculty of Medicine and Pharmacy of the VUB, where she was mainly involved in the generation of hepatocyte-like cells from human umbilical cord-derived mesenchymal stromal cells, in this way contributing to the development of new *in vitro* models for drug toxicity testing. This work was done under the promotership of Prof. Joery De Kock, Prof. Tamara Vanhaecke and Prof. Vera Rogiers. The results obtained during her doctoral research work were presented at several national and international scientific conferences. Karolien was also involved in other scientific projects and her work has resulted in 11 scientific publications in international and peer-reviewed journals and books, of which 6 as first author. During her PhD, she successfully obtained the certificate of 'expert laboratory animal leader (FELASA C) and of the 'Intensive Course in Dermato-Cosmetic Sciences'. Karolien has also supervised the bachelor thesis and master thesis work of students of the Erasmushogeschool Brussel and VUB, respectively. Further, she assisted several practical courses and PO-projects of both the bachelor and master years in pharmaceutical sciences. She also received the 'Wetenschappelijk Fonds Willy Gepts of the UZ Brussel' in order to complete the last stages of her doctoral research. Upon completion of her PhD, she will carry on postdoctoral research (VLAIO Innovatiemandaat) at the IVTD lab in cooperation with the firm Galapagos NV. The postdoctoral research focuses on the hepatogenic differentiation of human skin-derived stem cells and their application in drug discovery.