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VRIJE UNIVERSITEIT BRUSSEL

UNIVERSITEIT GENT

Joint PhD VUB & UGent
2021-2022

INVITATION to the Public defence of

Eva GIJBELS

To obtain the academic degree of

'DOCTOR OF PHARMACEUTICAL SCIENCES' - VUB
'DOCTOR OF HEALTH SCIENCES' - UGENT

Modelling and prediction of chemical-induced human cholestatic liver injury: a mechanistic approach

The defence will take place on

Wednesday, 1 December 2021 at 5 p.m.

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

ADMITTANCE: Due to Covid restrictions, please contact the PhD candidate if you want to attend the public defence in person.

The public defence can also be followed online
via Zoom meeting, accessible with following link:

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

Summary of the dissertation

Cholestatic liver insults constitute a major manifestation of drug-induced liver injury. Current *in vivo* and *in vitro* approaches poorly detect drug-induced cholestatic liver injury, which is partly due to gaps in the mechanistic understanding of this type of hepatotoxicity. This doctoral project tackles this hurdle by providing a state-of-the-art scenario of the established as well as novel mechanisms that drive drug-induced cholestatic liver injury. In a first study, a liver-based *in vitro* system was optimized to mechanistically study cholestasis, namely human hepatoma HepaRG cell cultures exposed to different cholestatic drugs and bile acids. This *in vitro* system has shed new light on the mechanisms underlying drug-induced cholestasis and has unveiled differences between different types of cholestasis as well as between the *in vitro* and *in vivo* situation. In a second study, the newly developed *in vitro* system in combination with other tools to predict cholestatic potential was evaluated for its application to chemicals outside the pharmaceutical area, in particular industrial chemicals, cosmetics ingredients, herbicides and food additives. It was found that further fit-for-purpose optimization is required for general use of the *in vitro* setting. A third study investigated liver samples of cholelithiasis-induced cholestasis patients and cholestatic mice by means of transcriptomic analysis in order to elucidate the mechanistic framework of different types of cholestasis and simultaneously characterize the human relevance of mouse models of cholestasis. Overall, this doctoral project has provided an important contribution to the elucidation of mechanisms underlying chemical-induced cholestasis, based on both *in vitro* as well as *in vivo* studies, and has yielded an *in vitro* setting fit for detecting drug-induced cholestasis.

Curriculum Vitae

Eva Anne Dirk Gijbels was born on 12 December 1994 in Wilrijk, Antwerp. Eva followed the discipline mathematics and sciences at the secondary school Regina Pacis in Hove, Antwerp. She pursued her academic career with obtaining a bachelor's degree (cum laude) in Pharmaceutical Sciences, followed by a master's degree (magna cum laude) in Drug Development at the UAntwerpen. She spent 3 months at the department of Biological Sciences at Colombia University, New York-USA to perform research in the context of her master thesis dissertation. This experience aroused considerable interest in scientific research, which resulted in her next phase, the PhD journey. As such, she joined the research group of *In Vitro* Toxicology and Dermato-Cosmetology at the Faculty of Medicine and Pharmacy at the VUB, where her promotor was Professor Mathieu Vinken and co-promoter Professor Tamara Vanhaecke. After 1 year of gaining experience and maturity, she obtained a fellowship grant in Strategic Basic Research of the Research Foundation–Flanders that funded her further study. During the course of her PhD, she initiated a joint PhD with UGent that nicely complemented her study with an *in vivo* point of view. She was supervised by Professor Lindsey Devisscher from the research group Gut-liver Immunopharmacology at the Faculty of Medicine and Health Sciences. Eva contributed to 19 publications in international peer-review journals, of which 10 as first author and 1 under review. Eva assisted in at least 5 practical courses for bachelor and master students of Pharmaceutical Sciences at the VUB and supervised 3 master dissertations in addition to 2 bachelor dissertations. Finally, Eva had the privilege of being a jury member for the master theses of Pharmaceutical Sciences at the VUB in 2021.