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Geneeskunde & Farmacie

GF

PhD in Medical Sciences
2015-2016

INVITATION to the Public defence of

Benedicte BRACKEVA

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

The quest for novel biomarkers of beta cell destruction: Potential of the neuroendocrine protein UCHL1

Thursday 2 June 2016
Auditorium **Brouwer**, 17:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

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Summary of the dissertation

The kinetics of immune-mediated destruction of pancreatic beta cells, during the natural course of type 1 diabetes (T1D) and after islet transplantation, are largely unknown. This fuelled the interest in innovative plasma tests for real-time detection of beta cell destruction. Dying beta cells in rat and human models of acute beta cell destruction release glutamic acid decarboxylase 65 kDa (GAD65) into the circulation. But the use of GAD65 is limited due to the interfering GAD65 autoantibodies in T1D patients, and its diagnostic sensitivity is limited.

This Ph.D. thesis aimed at the identification and step-wise clinical validation of novel protein-type biomarkers, as complement to GAD65. We used quantitative proteomics and tissue-comparative transcriptomics of rat and human beta cells for the bottom-up identification of intracellular proteins with high beta cell-selectivity and molar abundance. Among several candidates, we selected the neuroendocrine protein ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) for further study. First, we developed a sandwich immunoassay for UCHL1 quantification in cells and plasma, and used this to investigate its biomarker potential in standardized *in vitro* and *in vivo* models. *In vitro*, UCHL1 was superior to GAD65 to quantify both apoptosis and necrosis of rat and human beta cells. *In vivo*, UCHL1 was discharged along with GAD65 after diabetogenic streptozotocin-injection but its detection was inconsistent, likely attributed to a combination of rapid hepatic UCHL1 clearance and insufficient analytical sensitivity of our immunoassay. Our results support a diagnostic utility of UCHL1 to detect beta cell damage in islet transplantation trials, but illustrate the development of sensitive sandwich immunoassay methods as main bottle neck in biomarker selection algorithms.

Curriculum Vitae

Benedicte Brackeva was born on the 23rd of March 1984 in Zottegem, Belgium. From 2002-2007, she studied Biomedical Sciences at Ghent University (UGent). From 2007-2012, she worked as (Senior) Research Associate in the Pharmacology department of the biopharmaceutical company Ablynx. In 2012, she initiated her translational Ph.D. project at the Department of Clinical Chemistry and Radio-immunology (Universitair Ziekenhuis Brussel) and at the Diabetes Research Center (Vrije Universiteit Brussel), under promotorship of Prof. Dr. Geert Martens. During her Ph.D., she developed original methods, was first author and co-author of six scientific papers in peer-reviewed journals, presented her research on international and national conferences and supervised two master thesis students. As from June 2016, she will continue her professional career at Ablynx as Associate Scientist Pharmacology.