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### **Prof. Dr. Frans K. Gorus, Promotor**

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Vrije Universiteit Brussel, Brussels, Belgium  
Department of Clinical Biology, Universitair Ziekenhuis Brussel, Brussels, Belgium



PhD in Medical Sciences  
2016-2017

INVITATION to the Public defence of

### **Olivier COSTA**

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

**Development of advanced immunoassays for subpicomolar detection of plasma GAD65 as biomarker of beta cell destruction.**

### **Wednesday 22 February 2017**

Auditorium **P. Brouwer**, 16:00  
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

The kinetics of immune-mediated beta cell destruction during the natural course of type 1 diabetes and after islet transplantation are poorly understood, and mostly derived from indirect evidence, indicating a need for biomarkers capable of real-time detection of ongoing beta cell destruction. This project covers further validation of the candidate-protein biomarker glutamic acid decarboxylase 65 kDa (GAD65). Previous studies have established GAD65 as specific indicator of human and rat beta cell destruction *in vitro* and *in vivo*. It was thus shown that disproportionately high circulating GAD65 levels shortly after intraportal implantation of an islet allograft associated with poor graft function two months later. The used time-resolved fluorescence immunoassay (TRFIA) was, however, insufficiently sensitive to consistently detect graft-derived GAD65 in all graft recipients, limiting its use as research and clinical diagnostic tool.

We built more sensitive immunoassays using innovative platforms: the Cytometric Bead Array (CBA) from Becton Dickinson®, the electrochemiluminescence immunoassay (ECLIA) from Mesoscale Discovery®, and digital ELISA on the single molecule array (SIMOA) platform from Quanterix®. A detailed method comparison indicated CBA and SIMOA as two highly sensitive platforms with subpicomolar sensitivity, who were able to achieve a more than 30-fold increase in analytical sensitivity as compared with TRFIA, allowing the new methods to consistently measure GAD65 up to two days after intraportal islet allotransplantation.

In the second part of this project, an in-depth comparison was performed between the newly developed GAD65 immunoassay (GAD65-CBA) and a novel, nucleotide-type biomarker: miR-375. We found a correlation between both biomarkers in samples drawn one hour after Tx. These novel sensitive assays provide useful tools to further guide innovative transplantation trials exploring the potential of alternative beta cell sources and implantation sites.

## Curriculum Vitae

Olivier Costa was born on the 16<sup>th</sup> of January 1985 in Liège, Belgium. After completing secondary school at KA Grimbergen (option « Latin-Mathematics ») he enrolled as a medical student at the Vrije Universiteit Brussel. During the course of his education, Olivier developed an interest in laboratory medicine. He also got involved as an active member in several students' organizations. In 2010, he graduated *Magna Cum Laude* as a Medical Doctor and got accepted for training as a clinical pathologist under supervision of Prof. Dr. Frans Gorus.

During his training, Olivier became particularly interested in the area of Clinical Chemistry, and interrupted it to pursue a PhD at the Diabetes Research Center of the VUB in the Clinical Biology of Diabetes unit under the guidance of Prof. Dr. Geert Martens and Prof. Dr. Frans Gorus with financial support of an IWT research grant. This resulted in the present work, as well as eight manuscripts, comprising two as first author, one as shared first author and five as co-author. Posters related to his research and clinical training were presented at seven national and three international scientific meetings. In 2010 he received the prize for best poster in clinical chemistry at the annual meeting of the Royal Belgian Society for Laboratory Medicine. Olivier will finish his training as a clinical pathologist in September 2017 and intends to continue subspecializing in the field of Inherited Metabolic Diseases, in combination with assistance in the coordination of the Belgian Diabetes Registry.