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PhD in Medical Sciences
2014-2015

INVITATION to the Public defence of

Eric BALTI VOUNZIA

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

Biological prediction of rapid progression to type 1 diabetes: Preparing for immune intervention trials in the preclinical disease phase

Tuesday 30 June 2015

Auditorium **Vanden Driessche**, 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>



Vrije Universiteit Brussel

Summary of the dissertation

Observations from immune intervention studies at clinical onset of patients with type 1 diabetes (T1D) suggest that a better therapeutic response is obtained in subgroups characterized by young age and relatively preserved functional beta cell mass. One can therefore reasonably hypothesize that the preclinical disease phase, where the beta cell function is even better preserved, could offer a window of opportunity for the launch of secondary prevention trials. However, starting such trials in asymptomatic individuals will require: 1) the identification of a limited number of biological markers that are suitable for large scale screening in order to minimize the costs for rapidly identifying individuals with a subclinical disease process and 2) the selection of participants at sufficiently high risk of progression to clinically overt disease short-term to justify exposure to the potential adverse events related to the intervention.

To comply with these requirements, we aimed to develop a cost-effective and efficient screening strategy to identify such high risk individuals among offspring and siblings of patients with T1D at increased risk on the basis of the persistent presence of islet autoantibodies.

We explored if testing for autoantibodies against insulinoma-associated protein 2 (IA-2A) and zinc transporter 8 (ZnT8A) is as efficient as screening for the four main molecularly defined diabetes autoantibodies (insulin autoantibodies [IAA], glutamate decarboxylase autoantibodies [GADA], IA-2A and ZnT8A) in identifying individuals at high risk of T1D. We found that the progression rate to T1D was higher in the presence if IA-2A and/or ZnT8A irrespective of age. In relatives above age 10, the target group for immune intervention trials, testing for IA-2A and ZnT8A identified relatives with about 50% risk of T1D within 5 years with the same efficiency as screening for all four autoantibody types. However, in relatives younger than 10 years, testing for additional autoantibodies (such as IAA) would be needed for maximal screening efficiency.

Next, we investigated the predictive ability of functional and metabolic parameters derived from hyperglycemic clamp in comparison to oral glucose tolerance test (OGTT)-derived markers for prediction of rapid progression to overt diabetes. Using both univariate and multivariate survival analysis, we observed that low first- and/or second-phase C-peptide release during hyperglycemic clamp were associated with rapid progression to T1D and outperformed OGTT-derived parameters in this respect. Among all prediction models tested, the combination of first-phase C-peptide release during clamp and fasting blood glucose provided the best prediction of impending T1D as judged from the highest area under the receiver operating characteristic curve and the lowest Akaike information criterion. Performing a short hyperglycemic clamp (first-phase release only) in persistently islet autoantibody positive relatives allowed to identify individuals with 50-70% risk of developing T1D within 3 years.

Our findings offer a rationale for a cost-effective and age-independent stepwise approach for identifying individuals at sufficiently high risk of impending diabetes short-term for enrolment in immune intervention trials at the preclinical disease phase.

Curriculum Vitae

Eric Balti Vounsia was born on July 16, 1981 in Garoua, Cameroon. In 2007, he graduated as medical doctor (MD) at the Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Cameroon, and started working as clinician and research associate at the Endocrine and Diabetes Unit and at the National Obesity Center of Yaounde Central Hospital, Cameroon. In combination with his clinical activities, Dr Balti Vounsia also participated in several research projects including, among others, the Essential Non-communicable diseases Health Intervention Project (ENHIP) in the rural health area of Bafut (North-West region, Cameroon), the international multicentric HbA1c-Derived Average Glucose (ADAG) study and the Type 1 diabetes genetic consortium. In 2009, Dr Balti Vounsia obtained a scholarship to pursue a master degree in Biomedical Sciences-Cell and Gene Therapy (Former master in Medical and Pharmaceutical Research) at the Vrije Universiteit Brussel (VUB). After completing the two-year master programme (*magna cum laude*), he started (in October 2011) his doctoral (PhD) studies at the Diabetes Research Center (Diabetes Pathology and Therapy Research Group) under a VUB fellowship. His research focused on biological prediction of rapid progression to diabetes in first-degree relatives of patients with type 1 diabetes in preparation of immune intervention trials in the preclinical disease phase. So far, Dr Balti Vounsia is (co)author of 16 publications in international peer-reviewed PubMed indexed journals. Dr Balti Vounsia presented his work at several national and international conferences. In 2013, he received the "Young Investigator Award" of the Belgian Endocrine Society for his work on prediction of impending clinical onset of type 1 diabetes by means of hyperglycemic clamp test in individuals at risk of the disease, based on their family history and the presence of diabetes-associated autoantibodies.