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VRIJE UNIVERSITEIT BRUSSEL

UNIVERSITEIT GENT

Joint PhD VUB & UGent
2017-2018

INVITATION to the Public defence of

Mérédis FAVREAU

To obtain the academic degree of

'DOCTOR IN MEDICAL SCIENCES'
'DOCTOR IN SOCIAL HEALTH SCIENCES'

Immune therapy in multiple myeloma: Can iNKT cells be targeted?

Wednesday 4 October 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

Summary of the dissertation

In the plasma cell cancer multiple myeloma (MM) the invariant natural killer T cell (iNKT), an unconventional lipid antigen reactive T cell bearing an important role in anti-tumor immunity, is functionally and numerically impaired. Therefore, we aimed to unravel and overcome mechanisms causing iNKT deficiency in MM. We were the first to reveal the leptin – leptin receptor (LR) axis as an important iNKT-mediating pathway in MM and anti-tumor immunity. Increased leptin serum and LR expression levels on iNKTs were seen during MM progression and leptin was shown to profoundly inhibit iNKT functionality. iNKT anergy was strongly alleviated by blocking LR signaling and an almost complete tumor protection in the 5T33MM model was observed when iNKTs were stimulated in presence of a LR antagonist. Finally, we provided for the first time an intravital detailed time course of the iNKT dynamics in response to α-GalCer. Secondly, the implication of checkpoint molecule PD-1 in mediating iNKT deficiency and deficiencies in mucosal-associated invariant T cells (MAITs), another invariant T cell subset, was evaluated. Also MAITs proved to be numerically and functionally impaired in MM, a novel observation that hasn't been reported before. This deficiency was correlated with reduced iNKT numbers in MM patients. Moreover, MAITs showed poor activation by α-GalCer-stimulated iNKTs, illustrating a dysfunctional interaction between both. Remarkably, elevated PD-1 levels were found on both iNKTs and MAITs. A combination of PD-1 blockade and iNKT stimulation was able to significantly rescue iNKT and MAIT functionality and conferred superior tumor protection in the 5T33MM model. To conclude, we uncovered new very promising ways to restore the anti-tumor function of iNKTs in MM.

Curriculum Vitae

Mérédis Favreau was born on the 9th of June 1989 in Jette, Belgium. She attended secondary school at the Sint-Catherina College, Geraadsbergen where she majored in Latin - Sciences. In 2007, she started studying Biomedical Sciences at the faculty of Medicine and Pharmacy of the Vrije Universiteit Brussel (VUB), Belgium. She obtained her master degree in 2012 with great distinction together with the prize for student with the best study results. She started a JointPhD in Medical Sciences at the VUB and Social Health Sciences at the Universiteit Gent on the topic « Immune therapy in multiple myeloma: can iNKT cells be targeted? » under the guidance of Prof. Dr. Eline Menu, Prof. Dr. Karin Vanderkerken (Laboratory of Hematology and Immunology, VUB); Prof. Dr. Dirk Elewaut and Dr. Koen Venken (Laboratory for Molecular Immunology and Inflammation, VIB-Universiteit Gent Center for Inflammation Research). Part of her work was also carried out at the Institut pour la Recherche sur le Cancer de Lille in France under the guidance of Prof. Dr. Xavier Leleu and Nathalie Jouy. Her PhD has been supported by grants from Kom Op Tegen Kanker, Wetenschappelijk Fonds Willy Gepts, Fonds Stimulans, Belgian Hematology Society and the Doctoral School of Life Sciences and Medicine VUB. The results of her PhD project have been published in Leukemia (Nature Publishing group), number one of peer-reviewed papers in Hematology, and also in the peer-reviewed paper Haematologica.