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VRIJE UNIVERSITEIT BRUSSEL

PhD in Medical Sciences
2020-2021

INVITATION to the Public defence of

Eva DE SMEDT

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

Epigenetic reprogramming of malignant plasma cells: the therapeutic potential of RASSF proteins and G9a/GLP targeting in Multiple Myeloma.

The defence will take place on **Thursday, 1 July 2021 at 5 p.m.**

and will be organised **online** accessible through the following link:

Please click here to join the public defence:

Klik hier om aan de vergadering deel te nemen

Summary of the dissertation

Multiple myeloma (MM) is a neoplasia of mature plasma cells in the bone marrow. Despite improvements in disease management, virtually all patients relapse and succumb to refractory disease. Next to genetic defects, epigenetic aberrations play a pivotal role in MM pathogenesis. These reversible modifications are attractive targets for therapeutic intervention. However, clinical trials analyzing epigenetic modifying agents, so-called epi-drugs, are mostly disappointing. An essential objective for optimizing these trials is identifying *in vivo* relevant targets predictive for epidrug sensitivity. Aberrant Ras signaling is dominantly present in MM. Interestingly, RAS also mediates anti-tumoral effects through the tumor-suppressive Ras-Association Domain Family (RASSF) proteins. In this thesis, we identify RASSF4 as the main RAS death effector in MM. Epigenetic silencing of RASSF4 occurs during disease progression, correlating with a bad prognosis. Histone deacetylase inhibitor (HDACi) treatment restores RASSF4 expression. RASSF4 overexpression results in potent anti-myeloma effects and increased sensitivity to bortezomib and the specific MEK1/2 inhibitor trametinib.

Deregulated histone methylation modifiers (HMTs) also emerged as promising targets in MM. In a second project, we focused on elucidating the role of the HMT G9a in MM. High G9a expression levels correlate with a bad prognosis. G9a targeting induces apoptosis in human and murine cell lines and reduces primary samples' viability. These anti-MM effects are mediated by induction of autophagy-associated apoptosis and decreasing c-MYC levels. G9a targeting moreover sensitizes MM cells to proteasome inhibitor (PI) treatment. Thus, G9a targeting is a promising strategy to improve PI-based treatment in patients with high G9a levels.

Curriculum Vitae

Eva De Smedt was born on 17/02/1989 in Brussel. She studied Biomedical Sciences at the Vrije Universiteit Brussel (VUB). In 2013 she graduated with great distinction.

In August 2013, she started her Ph.D. research in the laboratory of Hematology and Immunology (HEIM) at the Vrije Universiteit Brussel (VUB) under the supervision of Prof. Dr. Elke De Bruyne and Prof. Dr. Karin Vanderkerken. Her research focussed on investigating the involvement of the epigenetic machinery in multiple myeloma pathogenesis. From 2016 onwards, she was a teaching assistant for the practical courses 'experimentele cellulaire en moleculaire biologie I en II ». Her scientific research resulted in 3 first-author and 4 co-author publications in international peer-reviewed journals.