

The Research Group

Cellular and Molecular Immunology

has the honor to invite you to the public defense of the PhD thesis of

Aleksandar Murgaski

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:
Understanding the effect and mechanisms of CD40 agonist therapy on tumour growth and dendritic cell vaccination strategies

Promotor:

Prof. dr. ir. Damya Laoui (VUB)

Prof. dr. ir. Jo Van Ginderachter (VUB)

The defense will take place on
Tuesday, December 20, 2022 at 15h00 in auditorium E.0.05

The defense can be followed through a live stream, please contact murgaski.aleksandar@vub.be for more information

Members of the jury

Prof. dr. ir. Wim Versees (VUB, chair)

Prof. dr. Carl De Trez (VUB, secretary)

Prof. dr. Karine Breckpot (VUB)

Prof. dr. Karim Vermaelen (UGent)

Dr. Jan Böttcher (Technical University of Munich)

Curriculum vitae

Aleksandar Murgaski obtained the degree of Master of Science in Biomolecular Sciences at the VUB in 2017. Afterwards he started as a PhD student in the lab of Cellular and Molecular Immunology under the promotorship of Prof. Damya Laoui and Prof. Jo Van Ginderachter.

During his PhD, Aleks was supported by predoctoral fellowship funding from Fonds Wetenschappelijk Onderzoek and Kom Op Tegen Kanker. Aleks has been a co-author of five research papers published in peer-reviewed journals.

Abstract of the PhD research

The way we think about treating cancer has been revolutionised by the clinical success of therapies that release the brakes on the immune system. Understanding the possible functions of diverse immune populations during successful and unsuccessful therapy can be used to inform new, more successful, combination therapies that prolong survival. Within most tumours exist rare populations of conventional dendritic cells (cDCs) that specialise in generating and maintaining antitumour T-cell responses. By stimulating cDCs we hope to re-energise T cell-mediated killing of cancer cells and slow tumour growth.

In order to activate cDCs, this PhD made use of an agonistic antibody that targets the CD40 receptor that is expressed by cDCs, as well as multiple other cell types. We observed contrasting effects on tumour growth with some models displaying profound tumour growth delay, while others were completely unaffected by anti-CD40 therapy. In responsive models, we found that a subset of cDCs called cDC1 was required before any therapy was administered. However, the presence of cDC1s was not necessary during the actual therapeutic window. The critical cell during the therapeutic window was identified as another subset of cDCs, called cDC2s, which became hyperactivated after CD40 ligation and activated antitumour CD8⁺ T cells. We then were able to sensitise the non-responsive model to CD40 therapy by using a combination of chemotherapy and suppressive macrophage depletion that resulted in delayed tumour growth. Finally, we wondered whether anti-CD40 stimulated cDCs could induce an immune response that could protect against metastasis. To answer this question we created a model of complete removal of the primary tumour resulting in later spontaneous lung metastasis. Interestingly, we found that anti-CD40 pre-treated mice that received cDC2 isolated from resected tumours had delayed lung metastases and extended survival compared to control mice.

Overall, this PhD contributed to further unravelling the complex and dynamic responses of the immune system to anti-CD40 immunotherapy. We showed how understanding and fine-tuning the tumour microenvironment prior to drug administration can be employed to improve therapeutic outcome and how anti-CD40 immunotherapy can be used to activate cDCs in a personalized therapy against metastasis.