

The Research Group

Cellular and Molecular Immunology

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

Ir. Karen De Vlaminck

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:
**Macrophages in the brain: key players in disease
and important therapeutic targets**

Curriculum vitae

Karen De Vlaminck obtained her Master degree in Bioengineering Sciences: Cell and Gene Biotechnology in 2016 at the Vrije Universiteit Brussel. Immediately after, she started her PhD in the myeloid cell immunology lab under the supervision of Prof. Dr. Ir. Kiavash Movahedi and Prof. Dr. Ir. Jo Van Ginderachter. Her work was realized with the financial support of Kom op tegen Kanker, and a personal finishing grant by Wetenschappelijk Fonds Willy Gepts (UZ Brussels). Karen De Vlaminck is co-author of ten scientific papers published in international peer-reviewed journals, among which two times as first author. She presented her work at several (inter)national conferences and received two awards for her master thesis in 2016 (IE-net, BrEA) and a conference poster award in 2022 (f-TALES). Finally, she guided one master thesis student.

Promotors:

Prof. Dr. Ir. Kiavash Movahedi (VUB)
Prof. Dr. Ir. Jo Van Ginderachter (VUB)

The defense will take place on
Thursday, March 30, 2023 at 16h in the U-Residence

Members of the jury

Prof. Dr. Joske Ruytinx (VUB, chair)
Prof. Dr. Carl De Trez (VUB, secretary)
Prof. Dr. Jan Gutermuth (VUB)
Prof. Dr. Bénédicte Machiels (ULiège)
Dr. Rejane Rua (Aix Marseille University)

Abstract of the PhD research

The brain plays a pivotal role in the normal functioning of the body, and is thereto organized in specialized compartments that combine brain accessibility with protection. Permissive border regions –including meninges and choroid plexus– allow communication with the periphery, while sophisticated barriers block unwanted cells and molecules from entering the functional parenchyma. Each compartment harbors brain-resident macrophages, i.e. microglia in the parenchyma and BAMs at the borders. They are crucial for brain development and homeostasis, and act as immune sentinels by scanning the brain and clearing harmful products. Upon disease, microglia undergo broad phenotypical changes and can play detrimental as well as tissue-healing roles, likely coordinated by context-specific cues. Yet, BAM responses upon disease remain elusive. Furthermore, monocyte-derived macrophages are often abundantly recruited to the diseased brain, but it remains incompletely understood how resident and recruited macrophages molecularly and functionally relate.

This PhD thesis characterizes microglia, BAM and recruited macrophage responses upon infection with the brain-invasive parasite *Trypanosoma brucei*. By combining cutting-edge technologies, we show that microglia and BAMs expanded and underwent strong phenotypical adaptations, allowing them to participate in initial parasite control and subsequent recruitment of peripheral help. Remarkably, microglia appeared to massively mobilize onto the choroid plexus epithelium. Recruited macrophages progressively accumulated in the infected brain, and adopted anti-microbial expression profiles with broader transcriptional plasticity than resident macrophages. Upon drug-induced parasite elimination, recruited macrophages rapidly disappeared and microglia underwent a gradual transition towards a homeostatic state. However, BAMs retained an altered phenotype for at least two months, suggesting that homeostasis may be affected long-term after disease resolution.

As researchers are gradually uncovering brain-disease-driving macrophage functions, macrophage-centered immunotherapies pose important new treatment strategies. Glioblastoma (GBM) –the most prevalent and aggressive brain tumor– is standardly treated by tumor resection, radiotherapy and/or chemotherapy, but always recurs and inevitably results in patient death. GBM macrophages play tumor-promoting roles and are correlated with poor prognosis. Hence, reprogramming them towards an anti-tumoral state may greatly ameliorate disease outcome. As cancer cells overexpress CD47 to propagate a “do-not-eat-me” signal to SIRP α -expressing macrophages, blocking this interaction could promote cancer cell phagocytosis. Here, we used SIRP α -targeting nanobodies, i.e. antigen-binding antibody fragments with a theoretically high tumor- and brain-penetrating capacity. We show that anti-SIRP α nanobodies bind primary mouse GBM macrophages and give a first proof-of-concept that they target mouse GBM *in vivo*. Finally, we elaborate on their promising potential as diagnostic and therapeutic tools in the future.