SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Brussels Center for Immunology

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

Mohamed Amer Musrati

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis

The impact of infection on Kupffer cell fate and function

Promotors:
Prof. dr. ir. Jo Van Ginderachter
Prof. dr. ir. Kiavash Movahedi

The defence will take place on

Wednesday, January 22, 2025 at 3.30 p.m. in auditorium I.0.01

Members of the jury

Prof. dr. ir. Eveline Peeters (VUB, chair)
Prof. dr. ir. Damya Laoui (VUB, secretary)
Prof. dr. Leonardus van Grunsven (VUB)
Prof. dr. Andreas Schlitzer
(Universität Bonn, DE)
Prof. dr. Alexandre Boissonnas
(Sorbonne Université, FR)

Curriculum vitae

Mohamed Musrati obtained his bachelor degree in Biological Sciences and Bioengineering with honors from the International University of Sarajevo, Bosnia and Herzegovina. He then gained his Master's degree in Molecular Biology with great distinction from the joint programme of the VUB, KU Leuven, and University of Antwerp, Belgium. His Master's research focused on studying myeloid cells in hepatic inflammation. He then pursued his PhD studies on the role of hepatic macrophages during infection. Mohamed also has post-graduate certificate (PGCertMedEd) in Medical Education from the University of Dundee, United Kingdom. His research areas of interest are infectious and liver immunology, and myeloid cells.

Abstract of the PhD research

Macrophages are highly versatile cells present in most organs of the body. Most tissue-resident macrophages are established prenatally, and sustained throughout life by different mechanisms, ranging from self-renewal to replenishment by monocytes. Maintenance of tissue-resident macrophage homeostasis and identity requires a continuous exposure to local micro-environmental cues and interactions with the cellular components of their hosting niches. Hence, events that provoke perturbations to the basal physiological conditions, including inflammatory insults, can interfere with these regulatory circuits and consequently reshape macrophage identity and function. Recent studies have shown that pathogenic insults can result in long-lasting effects on tissue-resident macrophages. This phenomenon, known as trained immunity, may alter macrophage responses to secondary challenges in a context-dependent manner. Hence, an intriguing possibility is that macrophage function is constantly reshaped throughout life by inflammation and disease.

This is of particular importance for tissues regularly exposed to pathogens, such as the liver. Although the liver is commonly targeted during pathogenic insults, and despite serving important immunological functions by being home to one of the largest macrophage populations in the body, it is currently unclear whether infections can durably alter hepatic macrophages. This is particularly relevant for Kupffer cells (KCs), which reside in the hepatic vasculature and continuously monitor sinusoidal blood for microbes, damaged erythrocytes, and are implicated in metabolic tasks. In this PhD work, the possibility that KCs are altered by infection history, as well as the effect of ontogeny on KC function, was explored. A murine model of a curable chronic infectious disease, induced by the extracellular protozoan parasite *Trypanosoma brucei brucei*, was employed to study changes to the KC pool during and after infection. KC biology was dissected using a combination of fate mapping, cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq), single nuclei RNA- and ATAC sequencing, epigenetic analysis and a series of *in vivo* functional assays. This work mainly demonstrates that a prior exposure to infection imprints long-lasting transcriptional, epigenetic and functional changes to post-resolution KCs which associate with an enhanced resilience to a subsequent infection with an unrelated pathogen, and also sheds light into the heterogeneity of KCs. Given the wide relevance of liver pathologies and the implication of hepatic macrophages in various liver diseases, these results could provide insight in how infection history reshapes the identity and function of hepatic macrophages and their functional contribution to health and disease, thereby affecting preventive and therapeutic strategies.