

The Research Group
Cellular and Molecular Immunology

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

Ana Rita Pombo Antunes

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:

Multi-omic analysis of glioblastoma-associated myeloid cells across species and disease stages

Curriculum vitae

Neuroimmunologist focusing on the study of brain cancer. Ana Rita obtained in 2012 her bachelor degree in Biochemistry and in 2015 her master degree in Cellular and Molecular Biology in the University of Coimbra, Portugal. She did her master thesis project at the Lab for Experimental Brain Research in the University of Lund, Sweden. From 2016 she has been a Ph.D. Candidate in Bioengineering at VIB-VUB Cellular and Molecular Immunology, Brussels, Belgium. Ana Rita's work resulted in three first-author publications, of which two research articles and one a review.

Abstract of the PhD research

Cancer immunotherapy has proven its great potential by saving the lives of a proportion of late-stage patients with immunogenic tumor types. However, other tumor types, including glioblastoma, remain largely refractory. Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. Despite the available treatment options, the life expectancy following GBM diagnosis is 15 months. Hence, there is a large unmet need for new therapeutic strategies to target this deadly disease. The glioblastoma immune microenvironment is recognized as highly immunosuppressive, posing a major hurdle for inducing immune-mediated destruction of cancer cells. Scattered information is available about the presence and activity of immunosuppressive or immunostimulatory cell types in glioblastoma tumors, including tumor-associated macrophages, and tumor-infiltrating dendritic cells. These cell types are heterogeneous at the level of ontogeny, spatial distribution and functionality within the tumor immune compartment. Unraveling their heterogeneity and dynamics may yield next generation molecular targets for therapeutic intervention.

A major aim of this PhD thesis was to characterize the glioblastoma immune landscape, both in human and mouse. By relying on cutting-edge technologies, including single-cell RNA sequencing (scRNA-Seq) and cellular indexing of transcriptomes and epitopes by sequencing (CITE-Seq), we characterized the tumor-infiltrating immune populations at the molecular, protein and functional levels. This revealed a large and diverse myeloid compartment, with dendritic cell and macrophage populations that were conserved across species and were dynamic across disease stages. Tumor-associated macrophages (TAMs) consisted of microglia- or monocyte-derived populations, with both exhibiting additional heterogeneity, including subsets with conserved lipid and hypoxic signatures. Interestingly, microglia-derived TAMs (Mg-TAMs) were predominant in newly diagnosed tumors but were outnumbered by monocyte-derived TAMs (Mo-TAMs) upon recurrence, especially in hypoxic tumor environments. Using *ex vivo* assays, we showed that GBM TAMs are an immunosuppressive population with poor T-cell activation potential. Moreover, Mg- and Mo-TAMs showed different capabilities of cytokine secretion and T-cell suppression and activation. Finally, we show that microglia- and monocyte-derived TAMs were self-renewing populations that competed for space and could be depleted via CSF1R blockade.

Promotors:

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

The defense will take place on

Thursday, April 22, 2021 at 16h00

The defense can be followed through a live stream. Contact

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Members of the jury

Prof. dr. Stefan Weckx (VUB, chair)
Prof. dr. ir. Wim Versées (VUB, secretary)
Prof. dr. Joeri Aerts (VUB)
Prof. dr. Sophie Janssens (UGent)
Prof. dr. Evelien Smits (UAntwerpen)