GENEESKUNDE & FARMACIE

INVITATION to the Public defence of

Jonathan BASTOS

To obtain the academic degree of

'DOCTOR OF MEDICAL SCIENCES'

The dynamics of microglia replacement using autologous monocytes

The public defence will take place on

Friday, 10 October 2025 at 5 p.m.

In LIC.0.04 Learning Theatre
VUB Main Campus
Pleinlan 2, 1050 Brussels

Promotor

Prof. Dr. Kiavash Movahedi
Brussels Center for Immunology Research Group, VUB

Chair

Prof. Dr. Cleo Goyvaerts
Molecular Imaging and Therapy Research Group, VUB

Board of examiners

Prof. Dr. Katrin Kierdorf
Universitätsklinikum Freiburg, Germany

Prof. Dr. Renzo Mancuso
University of Antwerp, Belgium

Prof. Dr. Dimitri De Bundel
Experimental Pharmacology, VUB

Prof. Dr. Eva Hadadi
Brussels Center for Immunology Research Group, VUB

Summary of the dissertation

Microglial dysfunction contributes to neurodegenerative diseases like Alzheimer's, driving interest in therapeutic microglia replacement strategies to treat these diseases. In this thesis, we investigated the barriers to this microglia replacement approach and the requirements for successful transplantation.

We first addressed why resident microglia resist replacement. Our findings show that successful engraftment requires creating a "receptive niche" by specifically inhibiting the rapid self-renewal of endogenous microglia following their depletion. Next, we demonstrated that the developmental origin of the progenitor cell is critical. Fetal liver-derived monocytes successfully differentiate into microglia-like cells, capable of expressing key microglia identity genes like Sall1, which yolk sac-derived endogenous microglia naturally express. In contrast, adult bone marrow-derived monocytes fail to acquire this microglial identity. This unique potential is traced to the progenitor's epigenetic state, specifically the pre-existing chromatin accessibility of the Sall1 locus in fetal liver-derived cells.

Through xenotransplantation of human monocytes in mouse brains and Alzheimer's patient data, we identified human monocyte-derived microglia. Imaging of postmortem Alzheimer's brains indicated that human monocyte-derived microglia are found in association with amyloid plaques.

This work establishes the dual requirements for successful microglia therapy: preparing a receptive niche in the brain and that the origin of the chosen microglia progenitor alters the phenotype of the transplanted microglia-like cell.

Curriculum Vitae

Jonathan Bastos acquired his bachelor's degree in biology with great distinction and his master's degree in molecular and cellular life sciences with greatest distinction from the Vrije Universiteit Brussel. His master's degree thesis focused on fundamental research on microglia phenotypes within the circumventricular organs of the brain. Afterwards, he pursued a PhD education under the supervision of Prof. Dr. Kiavash Movahedi on the topic of microglia replacement in the brain using monocytes. His research delved into the fundamental understanding of what conditions drive microglia replacement and how different monocyte ontogenies affect the phenotype of the replaced monocyte-derived microglia. Using a xenotransplantation model, he identified the phenotype of human monocyte-derived microglia and discovered putative monocyte-derived microglia in Alzheimer's disease patients. His future interests involve developing novel therapeutical approaches to cure neurodegenerative diseases.