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Internship - Proposition de stage de stage

Understanding the neuroprotective roles of macrophages at the brain surface

Recent data indicate that immune responses at the surface of the central nervous system (CNS) are linked with inflammatory and age-related neurodegenerative diseases. The surface of the CNS is connected to the periphery by layers of highly vascularized membranes, the meninges (**Figure 1**). Similar to other barrier surfaces, they are populated by a myriad of resident immune sentinels (such as macrophages) that control tissue homeostasis and block threatening pathogens. Due to their strategic location at the interface between the periphery and the brain, the **meninges function as the first line of protection of the CNS** and represent a major site of immune cell recruitment to block microbial neuroinvasion. **A breach in this protective system can allow the spread of neuroinvasive pathogens (e.g. HIV, Zika)** and subsequent CNS damage. Meningeal macrophages are organized in a vast network that constantly monitor and scan the entire brain surface.

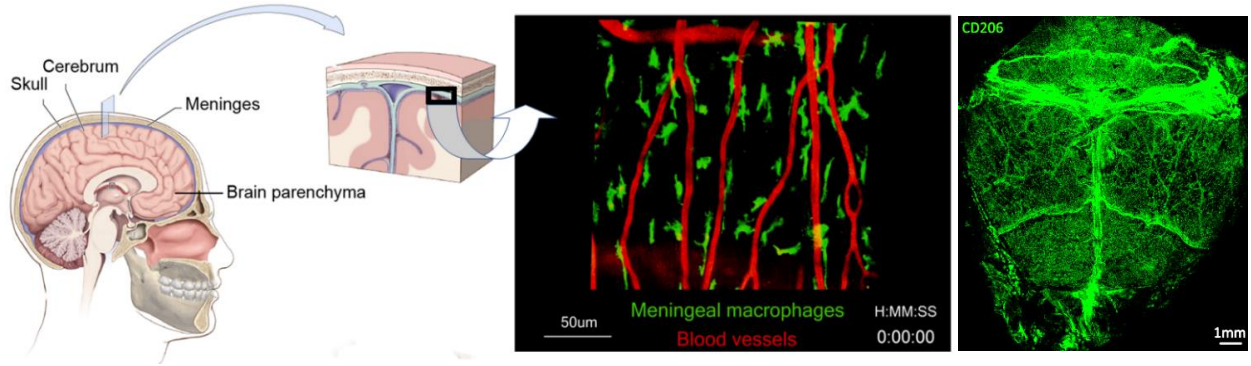

Figure 1. Location of the meninges at brain surface (left). Image extracted from an intravital movie of CX3CR1-GFP mouse showing a top-down view of meningeal macrophages (green) along the vasculature (red) (middle). Bone-in meningeal whole mounts showing the vast network of meningeal macrophages (identified by the mannose receptor CD206) covering the brain surface (right).

Even though meningeal macrophages represent the most promising sentinel candidates, virtually nothing is known about their heterogeneity and functions. **The objective of this project is to understand how macrophages at the brain surface prevent microbial spread into the CNS.** We hypothesize that meningeal macrophages are heterogeneous and that distinct macrophage subpopulations differ in the magnitude and quality of their antimicrobial response. To address these questions, we will combine multiparametric flow cytometry, state-of-the-art single-cell transcriptomics, CRISPR-Cas9 technology and intravital imaging approaches to analyze the heterogeneity and functions of meningeal macrophages following a microbial challenge.

Selection of recent publications

1. **Rua R, et al.** *Infection drives meningeal engraftment by inflammatory monocytes that impairs CNS immunity*. **Nat Immunol. 2019**
2. **Rua R**, McGavern DB. Advances in Meningeal Immunity. **Cell Press Trends Mol Med. 2018**
3. Kwong B*, **Rua R*** et al. *T-bet-dependent NKp46+ innate lymphoid cells regulate the onset of TH17-induced neuroinflammation*. **Nat Immunol**. **2017**
4. **Rua R,** McGavern DB. *Elucidation of monocyte/macrophage dynamics and function by intravital imaging.* **J Leukoc Biol. 2015**