Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Shaping monocyte/macrophage system to control HIV/AIDS pathogenesis: lessons from HIV-2

Synopsis:

Monocytes and macrophages are innate immune cells that play critical roles in the development and homeostasis of all tissues and, together with dendritic cells, initiate and shape immune responses, particularly inflammatory processes.

Persistent inflammation was demonstrated to be the main driver of disease progression in HIV/AIDS and a major cause of mortality, even in patients successfully treated with antiretroviral therapy (ART).

Thus, finding novel approaches to control inflammation in HIV/AIDS is of utmost importance, as HIV-1 infection is still a major global health concern, affecting more than 38 million people and resulting in 770,000 deaths per year.

Importantly, we have in Portugal a unique opportunity to study HIV-2, which is associated with a naturally attenuated disease with reduced mortality. Like HIV-1, HIV-2 establishes disseminated viral reservoirs, but the plasma viral load is usually undetectable even in the absence of ART, leading to low rates of transmission and to the confinement of HIV-2 infection to West Africa and historically connected countries. Notably, HIV-2 features a particular interaction with the molecular machinery of innate immune cells, despite the high degree of homology with HIV-1.

We hypothesize that monocytes and macrophages have a fundamental role in the distinct course and prognosis of HIV-1 and HIV-2 infections, which should inform the developing of new strategies for immunization and treatment.

To this purpose, our research plan combines an *ex-vivo* investigation of monocytes and macrophages from HIV-2- and HIV-1-infected patients and healthy subjects, using both high-dimensional conventional/spectral flow cytometry and transcriptomic/epigenetic data, with optimized *in-vitro* culture system of macrophage differentiation to investigate the impact of HIV-2 and HIV-1 as well as the pathways to be therapeutically targeted. Ultimately, co-culture systems with T and B cells will be developed to determine the macrophage potential to modulate the adaptive immune system activation, with possible application in immunization strategies. Ultimately, we will identify novel macrophage targets to modulate inflammation in HIV/AIDS, likely to be extended to other inflammatory clinical settings.

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The project will join the contribution of a supervisor with clinical immunology background and special experience in innate immunity in the context of inflammation driven diseases and a co-supervisor with a major experience in fundamental/translational immunology/immunotherapy and ; b) the internationally recognized expertise of the Human Immunodeficiency & Immune Reconstitution Lab for the study of both HIV-2 and HIV-1 associated immunodeficiency; c) the collaboration of infectious disease specialists from the Hospital Santa Maria, that provide access to large HIV-2 and HIV-1 patient cohorts, also including rare patients like HIV-1 anti-retroviral therapy naive seroconverters and HIV-1 elite controllers.

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Remunerated or volunteer training: *Volunteer training*