ImmunoTools IT-Box-Cy55M-Award 2013

Supatra (Patty) Sachamitr

PhD Supervisor: Dr. Paul Fairchild

Sir William Dunn School of Pathology, University of Oxford
South Parks Road, Oxford OX1 3RE

Investigating the use of induced pluripotent stem cell-derived dendritic cells in HIV-1 immunotherapy

HIV-1 infection progressively diminishes the number of $CD4^+$ T cells, which are crucial for the immune response against exogenous antigens. This cripples the immune system, resulting in the high morbidity and mortality associated with the disease. Combination anti-retroviral therapy (CART) has been shown to substantially alleviate the viral load of HIV-1 infected individuals and ameliorate disease symptoms but requires indefinite treatment due to the persistence of replicating viruses in the various cellular reservoirs. Therapeutic vaccines that utilize autologous monocyte derived DCs (moDcs) pulsed with HIV antigens have been demonstrated to be effective in the SIV-Macaque model. However, clinical trials involving the use of moDC from HIV-1 infected individuals have proven less successful in humans. This may be due to the limited capacity of moDCs to cross-present exogenous HIV antigen to $CD8^+$ T cells, known to be essential for an effective immune response against the virus.

The recent identification of the human cross-presenting dendritic cells promises to facilitate the translation of the knowledge accrued from the study of mouse DC biology into clinical practice. These cells express the cell surface marker CD141 (BDCA-3) and the chemokine receptor XCR1. Although these cells are an attractive target for use in HIV-1 immunotherapy, their trace numbers in peripheral blood hampers their full exploitation in the clinic.

Recent work in the Fairchild laboratory has shown that $CD141^+XCR1^+$ DCs can be successfully derived from human induced pluripotent stem cells (iPSCs) using an approach compatible with their downstream clinical application. Since these DCs have

the ability to cross-present exogenous antigen via MHC I to CTLs, they might circumvent the limitations restricting the effective use of moDCs as a therapeutic vaccine for HIV-1. We aim to investigate the use of these induced pluripotent stem cell-derived DCs in HIV-1 immunotherapy.

Interleukin-10 (IL-10) is an anti-inflammatory cytokine which is involved in the regulation of the immune system. It has been shown to suppress macrophage function, render DCs pro-tolerogenic and, like TGF-β, to steer the development of T cells towards a regulatory phenotype that might undermine the success of vaccination. Since we have shown that cross-presenting DCs differentiated from human iPSC secrete high levels of IL-10, we wish to investigate whether this might pose a barrier to their ability to prime CTL responses, for which an appropriate murine model will be required. We have therefore, derived iPSC lines from wild type and IL-$10^{-/-}$ mice and demonstrated their capacity to differentiate into conventional DCs *in vitro*. In order to determine whether we can also direct differentiation into $CD8\alpha^{+}$ cross-presenting DCs, the murine equivalent of the human $CD141^{+}$ $XCR1^{+}$ subset, we require a broad panel of growth factors and cytokines to determine their effect on the differentiation of iPSC in culture, for which the *IT-Box-Cy55M* would be invaluable.