IMMUNOLOGY AND INFLAMMATION PROGRAM

Immunobiology Group
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Project 1: Characterising anti-viral immune responses in immunodeficiency: implications for the development of cancer

The overall incidence of malignancy in immunodeficient individuals is up to 300 times greater than in the normal population. This striking statistic underscores the critical role played by the immune system in tumour surveillance. Malignancies have been detected in patients with inherited and sporadic immunodeficiencies, acquired immunodeficiency due to HIV infection and those undergoing stem cell transplant. These malignancies often result from the uncontrolled expansion of cells infected with oncogenic viruses, such as Epstein-Barr virus, highlighting the severe impairment in mechanisms of tumour surveillance in immunodeficient hosts. EBV is a ubiquitous herpes virus that infects >90% of the population. Primary EBV infection is often asymptomatic. However, ~25% of infected individuals present with infectious mononucleosis (commonly known as glandular fever), a self-limiting acute infection. EBV was the first virus implicated in causing human cancer and to-date it has been associated with the development of at least 7 distinct types of human malignancies. The project involves the characterisation of T cell responses to EBV in various different human immunodeficiencies. The impact of specific immune defects on controlling EBV infection will be examined. In parallel, immune responses to other common viruses, such as CMV and Influenza will also be characterised to compare with anti-EBV responses and to identify specific defects that lead to EBV-driven lymphomas.

Project 2: Role of SAP in regulating $CD8^+$ T cell responses

X-linked lymphoproliferative disorder (XLP) is a rare x-linked immunodeficiency charactersied by a dysfunctional immune response to Epstein-Barr virus (EBV) as well as a range of other immune abnormalities. Following EBV infection the majority of patients die from fulminant infectious mononucleosis. XLP is caused by mutations in the gene encoding SLAM-associated protein (SAP). SAP is a small adaptor molecule that binds to members of the SLAM family of receptors. These SLAM-family receptors are widely expressed on a range of immune cells. Mice deficient in SAP have been generated as a model of the human disease.

Key to understanding what goes wrong during EBV infection in XLP patients is appreciating the role that SAP plays in regulating $CD8^+$ T cells responses. Previous work has shown that SAP-deficient mice show increased $CD8^+$ activation following viral infection, however the mechanism involved is still unclear. This project will analyse the in vivo activation of $CD8^+$ T cells in SAP-deficient mice looking at questions such as the role of SLAM family members and SAP expression in $CD8^+$ T cells, the role of altered $CD4^+$ T cell help and how this combines with different stimuli to alter the expansion and differentiation of $CD8^+$ T cells.

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Project: the role of GPR18, a novel chemoattractant receptor in the immune responses and autoimmune/inflammatory diseases

We believe that the best way to combat inflammatory diseases is to target cell migration molecules. GPR18 is a novel chemoattractant receptor that is selectively expressed on B cells and T follicular helper (T_{FH}) cells, a T cell subset helping B cells in long-term antibody responses. GPR18 thus may have important functions to regulate humoral immunity following infection or immunisation and control immunopathology in autoimmunity, inflammation and immunodeficiency.

We have generated mice deficient of GPR18. Using this mouse, the function of GPR18 will be studied in normal immune responses and various autoimmune and inflammatory diseases. Monoclonal antibodies specific to GPR18 will be made to dissect GPR18 functions, and possibly to use as new therapeutics.

Selected publications

New cell migration based therapeutics for inflammatory diseases and cancer. *Nature Immunology* (2008)

Roquin represses autoimmunity by limiting inducible T cell costimulator messenger RNA. *Nature* (2007)

Targeting dual-specificity phosphatases: manipulating MAP kinase signaling and immune response. *Nature Review Drug Discovery* (2007)

Human C5aR knock-in mice facilitate the production and assessment of anti-inflammatory monoclonal antibodies. *Nature Biotechnology* (2006)

Positive regulation of immune cell function and inflammatory responses by phosphatase PAC-1. *Nature Immunology* (2006)

Antibody Engineering Group
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Project: Antibody therapeutics

Our laboratory is working on the development of novel antibody therapeutics. Monoclonal antibodies have revolutionised the treatment of many conditions. In fact, they are the most common class among recently approved drugs, with more than 150 candidates currently in clinical trials. While early monoclonals were generated by immunisation of animals, they are now increasingly generated by genetic engineering and display technologies. These technologies have also allowed the development of small, highly engineered antibody fragments. Domain antibodies, consisting of a single variable chain, are a promising new class of such fragments. Domain antibodies can be produced in large quantities in bacteria and open up promising new routes for non- intravenous applications, imaging and therapy. We are applying our technology to targets in cancer and inflammatory diseases

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Project: Mechanisms of action of intravenous immunoglobulin (IVIG)

IVIG is a crude antibody preparation, isolated from plasma collected from large numbers of healthy donors. While it has traditionally been used for replacement therapy in immunodeficiencies (such as HIV), it is now increasingly used as a powerful immunomodulatory reagent in over 35 autoimmune and inflammatory conditions (such as ITP). The use of IVIG has increased dramatically over the past decade to a degree that its supply is now critically limited and its use represents a significant cost to the community.

However, despite its clear efficacy in the clinic, the mechanisms of action of IVIG remain unknown. To tackle this problem, we use cutting-edge biochemical techniques and models of disease. Our approach includes biochemical fractionation of IVIG components, their analysis in in-vitro and in-vivo models, and the development of antibody fragments as a recombinant substitute. Together, these studies will provide insights into the molecular mechanisms of immunomodulation and will allow a more efficient use of this costly form of therapy.