Research Project Overview and Outline

Understanding immune cell dysfunction in the myeloproliferative neoplasms

Background

Myeloproliferative neoplasms (MPNs) are a group of rare bone marrow disorders characterised by the rapid and abnormal growth of blood cells (Cancer Research UK, 2021). Patients with more advanced forms of MPN are at a much higher risk of developing a life-threatening leukaemia. MPNs have an incidence of up to 5 in 100,000 and very little is known about the etiology and potential risk factors of these conditions (Anderson and McMullin, 2014). Haematopoietic stem cells (HSCs) are ultimately responsible for producing all the mature blood cell types required throughout life. MPNs and blood cancers are caused by mutations in HSCs that alter stem cell function. While mutant HSCs initiate and drive these disorders, immune cell populations arising from these abnormal stem cells are also thought to participate in various disease processes. What immune cell populations such as macrophages contribute to this inflammatory environment remains unclear.

The project aims

A more complete understanding of the behaviour (proliferation and expansion capacities) of mutant HSCs is crucial in understanding the disease progression of MPNs.

This proposed project aims to define characteristics of mutant immune cell populations in various mouse models of MPNs. To do this, I will be looking at and comparing characteristics of macrophages in mice samples which are normal (Wild-Type) and those which have tumours with the potential of becoming cancerous (TET2 Knockout). I will work to understand how those immune cells contribute to the microenvironment in diseased mice.

Methods outline

For this project, I will learn how to perform several lab-based techniques such as cell culturing as well as flow cytometry. Culturing immune cell populations (macrophages) will enable me to do functional assays such as stimulate the immune cell populations with certain cytokines or other proteins and see how these cells respond.

The data from multiple experiments on macrophages that I will be conducting over the course of the 6 weeks will be analysed qualitatively by describing the overall cell heterogeneity of a population by measuring cell surface proteins using fluorescently labelled antibodies. The macrophage populations within the samples will have specific combinations of cell surface proteins which means that only certain antibodies will bind to these cells. Flow cytometry can then be used to assess the cell surface profile of these macrophages.

The first 2 weeks of my project will involve being trained in the lab skills I will need to conduct the experiments and the following 4 weeks will involve me conducting the experiments and gathering data. The data will then be analysed using a qualitative approach where the overall cell heterogeneity of a population will be described by measuring cell surface proteins using fluorescently labelled antibodies. The results will be used to create a report to summarize the findings and key conclusions from the project.

Expected results

Following the data analysis, I will report the results and the most significant/interesting findings will be the focus of my report. The results expected upon preforming this study may involve gaining an understanding of whether immune cell populations differ in MPN mouse models. In the lab I will be specifically looking for changes in location, overall numbers, and cell surface marker expression. The main goal is to explore any interesting differences in those characteristics after generating the initial sets of data. Overall, this project would be contributing to our understanding of how the specific mutations in question may influence the function of immune cell populations in MPNs.

Wider implications

In the wider context, this research project will facilitate understanding of the underlying pathology through analysing the immunological mechanisms in MPNs. Particularly within cancer research, understanding the impacts of certain mutations and how immune cells behave accordingly may guide further research towards understanding the underlying mechanisms of MPNs.

A better understanding of the tumour microenvironment is important as it may facilitate understanding of how to manipulate specific factors within the disease microenvironment which can allow for advancements in management, and perhaps novel treatments of MPNs/MDS as well as other immune/haematological conditions.