Investigating the role of immune cell-mediated steroidogenesis in regulating cancer inflammation and immunity

Principal supervisor's name: Dr **Bidesh Mahata**
Principal supervisor's email address: bm562@cam.ac.uk

Principal supervisor's CRUK CC theme: Cancer Immunology Programme

Department for student registration: Pathology
Department or institute where research will take place: Division of Immunology, Department of Pathology, Tennis Court Road.

Co-supervisor's name (if applicable): Mr Amit Agrawal
Co-supervisor's email address (if applicable): amitagrawal@doctors.org.uk

Postgraduate scheme: **MRes + PhD (1 + 3-year non-clinical applicants only)**

MRes project outline:

The immune cell steroidogenesis pathway is maladapted in cancer. In established tumours, steroid-producing immunocytes suppress antitumour immunity and promote tumour growth. In addition, in inflammation-driven cancers such as inflammation-driven colorectal, liver and lung cancers, preliminary observations predict that immune cells secrete steroids to resolve cancer inflammation. Further studies are required to understand the role of local steroid biosynthesis and steroid signalling within the tumour microenvironment. In this MRes rotation study, the candidate will identify and characterise the differentially regulated steps of the pathway in the immune cells compared to adrenal and gonadal steroidogenesis. The results from this rotation project will constitute the foundation for the PhD project. The ultimate aim of this study is to find a specific target to modulate the pathway therapeutically.

MRes experimental plan:

To predict the differentially regulated steps of immune cell steroidogenesis the candidate will compare the transcriptomes (single cell as well as population level) of different steroidogenic cells including steroid-producing immune cells. Once predicted, the candidate will confirm the prediction experimentally by genetically or pharmacologically inhibiting the pathway. The candidate may extend the project to test the in vitro results in mouse models in collaboration with other lab members.

This is an overview of the experimental plan. The candidate would have the independence to show creativity in designing detailed experiments and finalising experimental logistics in agreement with supervisors.

PhD project outline:

Systemic steroid hormones regulate immune cell function. Interestingly, immune cells such as T helper 2 lymphocytes, mast cells and basophils, de novo synthesise and secrete immunoregulatory steroids. Little is known about this newly discovered immunoregulatory pathway (i.e., immune cell steroidogenesis). Importantly, the pathway is maladapted in cancer. In established tumours, steroid-producing immunocytes suppress antitumour immunity and promote tumour growth. In inflammation-driven cancers, such as inflammation-driven colorectal, liver and lung cancers, preliminary observations predict that steroidogenic immune cells secrete steroids to resolve cancer inflammation. Further studies are required to understand the role of local steroid biosynthesis and steroid signalling within the tumour microenvironment during carcinogenesis. The overarching aim of this project is to find targets that are differentially regulated in immune cells compared to glandular steroidogenesis and exploit that knowledge to develop a new therapeutic strategy. In this study, we will identify and characterise the molecular signals that induce immune cell steroid biosynthesis and determine the mechanisms that regulate the pathway. Special emphasis will be given to the differential induction and regulation of the pathway in the immune cells compared to the glandular steroidogenesis. We will determine the mechanisms of how steroid-producing immune cells regulate distinct stages of inflammation-driven carcinogenesis. Finally, we will exploit the steroidogenesis pathway to innovate immunotherapeutic strategies for inflammation-driven cancers.

PhD experimental plan:

We will test our hypothesis in the genetically modified experimental mouse model of cancer. Immune cell steroidogenesis is a type 2 immune phenomenon. Therefore, to identify and characterise the molecular signals that induce immune cell steroid biosynthesis, we will test the effect of type 2 cytokines, both in vivo and in vitro, by measuring the functional presence of steroids. To determine the mechanisms that regulate the pathway we will undertake genetic approaches. Genetically modified conditional knockout mouse models will be used to determine the role of predicted factor(s). First, we will abrogate the step genetically and compare the consequences in steroid production as well as cancer inflammation and anti-tumour immunity. Differential regulation of immune cell steroidogenesis will be charted by comparing transcriptomes of in vivo and in vitro steroidogenic immune cells and glandular steroidogenic cells. Finally, small molecule inhibitors of the differentially regulated steps will be employed in vitro and in vivo preclinical mouse models to test their safety, specificity, and efficacy in modulating immune cell steroidogenesis and tumour restriction.

This is an overview of the experimental plan. The candidate would have the independence to show creativity in designing detailed experiments and finalising experimental logistics in agreement with supervisors.

Main techniques:

We will undertake multidisciplinary approaches to test our hypothesis. The most useful tools and techniques we will use are mass-spectrometry, multiparameter flow cytometry, RNA sequencing (bulk and single-cell), proteomics, gene editing (CRISPR/Cas9), molecular cloning, ELISA, microscopic imaging, in vivo genetically modified mouse models of cancer, human patients' samples, and co-culture assays.

Key references:

1. Mahata, B. et al. Tumors induce de novo steroid biosynthesis in T cells to evade immunity. Nat Commun 11, 3588, doi:10.1038/s41467-020-17339-6 (2020).
2. Acharya, N. et al. Endogenous Glucocorticoid Signaling Regulates CD8(+) T Cell Differentiation and Development of Dysfunction in the Tumor Microenvironment. Immunity 53, 658-671 e656, doi:10.1016/j.immuni.2020.08.005 (2020).
3. Obradovic, M. M. S. et al. Glucocorticoids promote breast cancer metastasis. Nature 567, 540-544, doi:10.1038/s41586-019-1019-4 (2019).
4. Binnewies, M. et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med 24, 541-550, doi:10.1038/s41591-018-0014-x (2018).