PI profile

## **Rachael Bashford-Rogers**

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|   | **Dr. Rachael Bashford-Rogers****Titles**: Group Leader**Location**: Wellcome Centre for Human Genetics**Department**: Nuffield Department of Medicine**Group**: Dr. Rachael Bashford-Rogers**Webpage**: https://www.well.ox.ac.uk/research/research-groups/bashford-rogers**Email**: rbr1@well.oc.ax.uk**PA**: |

### GMS themes:

* Genomic and –omic technologies
* Functional genomics
* Genome biology (genomes and genetic variation)
* Genomics of disease
* Genomic analysis (bioinformatics and statistical genetics)
* Application of genomics in the clinic (diagnostics and therapeutics)

### Research Overview

We aim to determine the development, regulation and function of B and T cell populations in health and immunological diseases. This will lead us to an understanding of why certain individuals are at greater risk of developing immunological disease, as well as to identify potential therapeutic targets or improved clinical management. This is achieved through the development and application of novel experimental and computational approaches, working in partnership with a global network of clinicians, immunologists and sample cohorts.

Immunological health relies on a balance between the ability to mount an immune response against potential pathogens and tolerance to self. B and T cells are key to the immune response by producing antibodies and cytotoxic T cells. B/T cell clones selectively expand following antigen recognition by B and T cell receptors (BCR and TCR) respectively. BCRs are the membrane-form of antibodies and are generated through DNA recombination resulting in the potential to recognise a vast array of pathogens. Defects in the ability to mount effective B cell or T cell responses have been implicated in infectious susceptibility, impaired surveillance of cancer and immunodeficiencies, whereas a breakdown of immunological tolerance has been attributed to autoimmune diseases such as through autoantibody production and reduced numbers of regulatory B/T cells.

Project areas:

* How are Different B Cell Populations Developmentally Linked in Human Health and Disease?
* Immuno-surveillance in Cancer
* How is B Cell Repertoire and Function Different in Health and Disease?
* What is the Effect of Genetic and Environmental Variation on B and T Cell Fate?
* Single cell and omics technology Development

### Specific project proposals:

* Investigating the B and T cell mediated pro- and anti-tumour mechanisms in cancers

Please contact directly for further information.

*These pages were reviewed/updated:* ***16/07/2021***

Project proposal

# **Title**: Investigating the B and T cell mediated pro- and anti-tumour mechanisms in cancers

Supervisors: Dr Rachael Bashford-Rogers

Wet/dry lab mix (approx): can be wet or dry lab work, or mixture depending on student preference

### Description:

B cell infiltration has prognostic significance in solid tumours, and ongoing studies are investigating their phenotypes through single cell transcriptomics and spatial imaging. Characterising the B cell response to tumour cells, particularly their antigenic specificities, will be key to developing more immunologically appropriate cancer therapies. However, currently, the B cell antibody (Ab) specificity cannot be coupled with the Ab sequence, phenotype or transcriptome in a high-throughput manner. Here we propose a DPhil studentship project to develop novel technologies to be able to bridge the gap between B cell populations and antibody reactivity, thus giving a unique perspective on the development of anti-self, anti-tumour and anti-non-self Ab responses. **This project will involve the development a novel high-throughput method to probe the antigen specificities of B cells, which will be coupled with single cell resolution of clonal phenotype and single cell transcriptome. This will be used to investigate the development and role of tumour-infiltrating B cells across a range of tumours with varying degrees of immunogenicity.** This study will provide a unique platform to understand the probe between tumour neo-antigen, B cell immune-surveillance and specificity, and B cell phenotype, with the overall aim of highlighting new therapeutic options. Furthermore, this method is not just broadly applicable to cancer, but will have wider applications in immunology and biotechnology. This will be achieved through the development and application of novel experimental and computational approaches, working in partnership with a global network of clinicians, immunologists and sample cohorts.This information may be used to develop potential biomarkers of resistance to therapy and to determine potential therapeutic interventions that could be combined with the current standard of care that could target persistent clones in autoimmune diseases.

**This project will apply novel single-cell genetic technologies, imaging and functional experiments to link the development, regulation and function of B and T cell populations in health and immunological diseases to the underlying host genetics.**

This project aims to investigate the B and T cell immune response of circulating and tumour-infiltrating B cells across a range of tumours with different levels of immunogenicity and neo-antigen expression, including pancreatic and renal cancers. This will be done within the context of the tumour, stromal and myeloid cell populations to gain a global understanding of key immune cell dependencies and modes of modulation. This will involve the development of a novel platforms and methodologies to answer key questions in the field of tumour immunology including:

* What are the key features defining B and T cell infiltration into the tumour and how may this be modulated?
* What are the functions and cell-cell interaction effects of tumour infiltrating B and T cells?
* What determines the balance of whether B and T cells serve a pro- or an anti-tumourigenic function?
* Do tumour-associated B cells produce Abs against tumour cells, and how does tumour cell neo-antigen variation and expression level dictate Ab response? Are tumour-associated Abs cross-reactive to other self or non-self antigen, poly-reactive, or highly specific to tumour cells?

Overall, this may help shed light on the B cell response to tumour cells, the specificity and breadth of response, and potentially highlight novel therapeutic targets. We envisage that this novel platform may be extended to the other areas of B cell biology, and could be a general tool that could be of great value other researchers.

### Training Opportunities:

The DPhil will gain experience and training in laboratory molecular biology and single cell methods, bioinformatics and immunology. These include:

* Single-cell RNA sequencing and analysis of patient samples.
* Integration of single-cell RNA sequencing and other “omics” datasets to associate information about the B/T cell receptor with the single-cell transcriptome.
* Development of novel functional, imaging and computational analyses to gain an understanding of the role ad communication of immune cells within the contexture of the tumour environment.
* Characterisation of B/T cell traits throughout development and tissues.
* Validation of associations using a wide range of immunological techniques.
* The project will work in partnership with a global network of clinicians, immunologists and sample cohorts.

### Background reading / references:

* **Double-jeopardy: scRNA-seq doublet/multiplet detection using multi-omic profiling *(Cell Reports Methods,*** *2021****).***

Bo Sun, Emmanuel Bugarin-Estrada, Lauren E. Overend, Catherine E. Walker, Felicia A. Tucci, **Rachael J. M. Bashford-Rogers**

* **Activated regulatory T-cells, dysfunctional and senescent T-cells hinder the immunity in pancreatic cancer***(****Cancers****, 2021)* (<https://doi.org/10.1101/2020.06.20.163071>)

Shivan Sivakumar, Enas Abu-Shah, David Ahern, Edward H Arbe-Barnes, Nagina Mangal, Srikanth Reddy, Aniko Rendek, Alistair Easton, Elke Kurz, Michael Silva, Lara R Heij, Zahir Soonawalla, **Rachael Bashford-Rogers**, Mark R Middleton, Michael Dustin

* **B cell receptor repertoire analysis in six immune-mediated diseases** (***Nature****, 2019*)

**RJM Bashford-Rogers,** L Bergamaschi, EF McKinney, DC Pombal, F Mescia, JC Lee, DC Thomas, SM Flint, P Kellam, DRW Jayne, PA Lyons, KGC Smith

Insert any additional project description(s) on subsequent pages if applicable. Please use the same template and use separate pages for each project.