The Cellular Pathology of Early Kidney Disease

Oxford supervisors: Dr Katherine Bull[1] and Professor Richard Cornall[1]

Novo Nordisk supervisor: Dr Ramneek Gupta[2]

Departments: 1. Nuffield Department of Medicine
2. Novo Nordisk Research Centre Oxford (NNRCO)

Project outline

Background

Deaths due to chronic kidney disease have doubled since 1990, in large part due to the global epidemic of type 2 diabetes, and a limited understanding of the underlying cellular pathological processes hampers the development of effective targeted renal therapies. Cell transcriptomic (scRNA-seq) studies in human kidney tissue are beginning to highlight cell specific differences in renal diseases, including diabetic nephropathy (DKD). However, renal damage is often asymptomatic until 85% of renal clearance is lost, and so it is proving difficult to distinguish between the dysregulated pathways driving renal damage and later tissue responses to injury. Moreover, comparisons between human disease tissue and healthy controls are confounded by genetic and environmental heterogeneity, and there is a need to validate transcriptomic insights with spatial cellular relationships at the protein level.

Over 200 kidney transplants are performed in the Oxford Transplant Unit each year, including in patients with a known risk of disease recurrence in the donor kidney post transplantation. These conditions include IgA nephropathy, some forms of focal segmental glomerulosclerosis (FSGS) and systemic diseases, of which DKD is the most common, contributing over 40% of patients on the transplant waiting list. FSGS recurs in 25% of cases, sometimes within hours or days post transplantation, DKD recurs histologically within 2 years, while IgA recurs in over 50% of patients by 4 years post-transplant. Access to paired pre- and post-implantation transplant kidney biopsy samples presents a unique opportunity to study the very earliest pre-clinical stages of active renal disease in previously normal kidneys.

Hypothesis

The cellular transcriptomic and proteomic signatures in early renal disease recurrence will identify disease specific modulators and novel therapeutic targets.

Aims

We will use the cellular transcriptomic and proteomic signatures of early renal disease to:

- Identify cellular pathways causative in renal disease, including interactions between glomerular cells and infiltrating immune cells, proteins or small molecules.

- Develop multiplex imaging panels which will be applicable to larger datasets of biopsy tissues, addressing heterogeneity and increasing the power of clinical trials.
- Illuminate early modulators of renal disease with potential as drug targets

Description of Work

Through the Oxford Transplant Biobank (led by Prof Rutger Ploeg, NDS) we have access to pre-implantation renal tissue from all living donors in Oxford, and 90% of all UK kidney donors via the QUOD biobank, with ethical approval to seek consent for a research biopsy post transplantation.

1. We will recruit 20 patients in Oxford undergoing work up for living donor renal transplantation, with a biopsy proven recurrent kidney disease due to DKD, IgA, MPGN and FSGS (with negative genetic screening for intrinsic podocytopathy). Routine pre- and post- clinical histology (Prof Ian Roberts, Renal Histopathologist) will define recurrence and exclude rejection or pre-implantation disease. **On each paired sample, we will perform**:

(i) **scRNA-seq** of renal cortex, comparing pre-implantation healthy donor tissue to samples from the same kidney post-transplantation, with spike-in and computational correction for batch effect. Comparisons across those with and without histological disease recurrence and between the disease states will be used to adjust for effects of immunosuppression (Dr Katherine Bull).

(ii) **Cellular podocyte and glomerular proteomics** using laser capture micro-dissection and mass spectrometry of over 4000 proteins (with Dr Roman Fischer, TDI).

(iii) **Multiplex Imaging**. Combined analysis of these datasets will inform the design of disease specific 40+ marker panels for tissue imaging (Hyperion-iCytof, Codex and CellDive platforms available in Oxford).

2. Disease associated signatures will be validated by studying further renal samples including existing biobank tissue, and used to identify potential drug targets and early biomarkers of recurrence or treatment response.

Supervisor's recent relevant publications:

1. Abeler-Dörner, L., Laing, A.G., Lorenc, A., Ushakov D.S,, Clare S., Spea' A.O., Duque-Correa M.A, White, Ramiro Ramirez-Solis, J.K., Saran, N., **Bull, K.R.,** Morón, B., Iwasaki, J, Barton, P.R., et int. **Cornall RJ**, Maloy K, Grencis R, Griffiths GM, Adams D, Hayday AC,. High-throughput phenotyping reveals expansive genetic and structural underpinnings of immune variation **Nature Immunol.** In Press 2019.
2. Yamamoto, A., Hester, J., Macklin, P. S., Kawai, K., Uchiyama, M., Biggs, D., Bishop, T., **Bull, K**.,Cheng, X., Cawthorne, E., Coleman, M. L., Crockford, T. L., Davies, B., Dow, L. E., Goldin, R., Kranc, K., Kudo, H., Lawson, H., McAuliffe, J., Milward, K., Scudamore, C. L., Soilleux, E., Issa, F., Ratcliffe, P. J., and Pugh, C. W., 2019. Systemic silencing of PHD2 causes reversible immune regulatory dysfunction. **J Clin Invest**, 130 (9), 3640–3656,2019.
3. Anzilotti, C., Swan, D. J., Boisson, B., Deobagkar-Lele, M., Oliveira, C., Chabosseau, P., Engelhardt, K. R., Xu, X., Chen, R., Alvarez, L., Berlinguer-Palmini, R., **Bull, K. R.,** Cawthorne, E., Cribbs, A. P et int... ***Cornall, RJ**, *Conley, ME, *Hambleton, S. (*Co-senior and corresponding authors). An essential role for the Zn2+ transporter ZIP7 in B cell development. **Nat Immunol**, 20 (3), 350–361, 2019.
4. Cheng, D, Deobagkar-Lele, M, Zvezdova, E, Choi, S, Uehara, S, Baup, D, Bennett, SC, **Bull, KR**,

Crockford, TL, Ferry, H et al 2017, Themis2 lowers the threshold for B cell activation during positive selection et int. **Cornall RJ**. **Nat Immunol**, 18, (2), pp. 205– 213, 2017.

5. **Bull, KR**, Mason, T, Rimmer, AJ, Crockford, TL, Silver, KL, Bouriez-Jones, T, Hough, TA, Chaudhry, S, Roberts, IS, Goodnow, CC and **Cornall, RJ** 2014, Next-generation sequencing to dissect hereditary nephrotic syndrome in mice identifies a hypomorphic mutation in Lamb2 and models Pierson's syndrome, **Journal of Pathology**, 233, (1), John Wiley & Sons, Ltd, pp. 18–26. 2014