Elucidating the importance of PPARγ signalling in the podocyte in the development of diabetic kidney disease.

Diabetic nephropathy (DN) is the leading cause of kidney failure in the world and is closely linked with systemic insulin resistance. It is increasing at alarming rates due to obesity prone lifestyles. There is an urgent need to find new therapeutic targets for DN patients, as they do very badly. Indeed the average life expectancy of a 43-year old type-2 diabetic patient on dialysis is only 3-years. The natural history of DN is progressive albuminuria starting with microalbuminuria and progressing to macroalbuminuria. A key cell in preventing albuminuria is the podocyte. We have previously shown that the podocyte is an insulin sensitive cell (1) and when rendered insulin resistant a number of features of DN occur but in a normoglycaemic environment (2).

Thiazolidinediones drugs, including Rosiglitazone, activate the peroxisome proliferator activating receptor gamma (PPARγ) and have been shown clinically to be beneficial in treating early DN. They are insulin-sensitising. These drugs were initially thought to be exerting their beneficial actions by modifying adipocyte function however it now clear that they also directly modify PPARγ biology in the kidney.

This PhD project will define if modulating PPARγ specifically in the podocyte therapeutically prevents diabetic nephropathy from progressing, and importantly the cellular mechanisms underlying this. It will use a robust genetic murine model of podocyte-specific PPARγ knockdown in the setting of type-2 diabetes (on the db/db background), which we have generated over recent years. This model develops albuminuric kidney disease which correlates closely with systemic insulin resistance (**In press**- American Journal of Physiology). It will also generate murine and human podocyte cell lines and using CRSPR-Cas9 technology will manipulate PPARγ, and then identify the key pathways it modulates using RNA seq and proteomics to define new therapeutic targets in the podocyte to prevent this devastating complication of diabetes.

This project will be performed in the academic renal (ARU) unit in Bristol University which is a vibrant and world-leading center for glomerular biology research. The ARU is a blend of over 40 clinical and non-clinical scientists who work closely together in a highly supportive manner. It has a superb record in training PhD students. It will equip the student with excellent *in vitro* and *in vivo* scientific techniques.

1. Coward RJ, Welsh GI, Yang J, Tasman C, Lennon R, Koziell A, Satchell S, Holman GD, Kerjaschki D, Tavare JM, et al. The Human Glomerular Podocyte Is a Novel Target for Insulin Action. *Diabetes.* 2005;54(11):3095-102.
2. Welsh GI, Hale LJ, Eremina V, Jeansson M, Maezawa Y, Lennon R, Pons DA, Owen RJ, Satchell SC, Miles MJ, et al. Insulin signaling to the glomerular podocyte is critical for normal kidney function. *Cell Metabolism.* 2010;12(4):329-40.

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