

Report on the Young Renal Scientist Forum 2009 by Dr Julie Williams

This year's Young Renal Scientist Forum was another resounding success with all of the presentations of exceptionally high quality. The judges were Prof Bernhard Moser and Prof Alison Eddy.

Prof Moser kicked off the proceedings with a seminar on Chemokines and Inflammation in which he described a subset of T cells termed Follicular B Helper T Cells (T_{FH}). He has shown that these cells are $CXCR5^+$ and found in the lymph nodes. The cells are important in B cell responses and support the production of, in particular, IgG and IgA. T_{FH} cells are also capable of secreting IL21. The cells move from the T cell zone where they mature to the B cell zone. Prof Moser's group has shown that an abundance of these cells are present in SLE and T cell lymphoma whereas a dearth are seen in B cell immunodeficiency. Prof Moser also described a second subset of T cells termed peripheral immunosurveillance T cells (TPS). This subset comprises a large fraction of the memory T cell set. They looked at T cell trafficking in these cells in relation to CCL1 and CCR8 and showed that there was a high abundance of CCR8+ cells in the skin but very few in the peripheral circulation. The CCR8 levels on the surface of the cells were stable over time and the cells also co-expressed CD45RA. They could find no association with disease.

The first of the speakers for the Young Renal Scientist Prize was Clare Turner who spoke on P2X7 in experimental glomerulonephritis (GN). Clare described how these ligand-gated ion channels which were activated by ATP formed multimers which acted as cation channels. P2X7 is proinflammatory and instigates secretion of IL1 β , IL8, MCP-1, IL6 and TNF α as well as being responsible for cell death. She described how the receptor was found on cells of the immune system but was low in the kidney. In a model of GN induced by NTS she showed that P2X7 was increased in the kidney and this was due to monocytes and macrophages. Additionally in a rat model of GN mRNA for the receptor was expressed. Her presentation described her work involving the use of P2X7 $^{-/-}$ mice given NTS investigating effects on urine and tissue. The knockout mice exhibited less glomerular thrombosis than controls, decreased proteinuria and serum creatinine, a decrease in macrophage infiltration, less MCP-1 expression, decreased fibrin but unchanged C3 binding. The selective P2X7 inhibitor A438079 was then used in the rat model. At a high dose there was less fibrinoid necrosis, proteinuria, macrophage infiltration and MCP-1 levels.

The second speaker was Andrew Salmon who looked at the association of VEGF165b and albuminuria in diabetes. Andrew told us that VEGF had been implicated in diabetic nephropathy (DN) but the mechanisms were unclear. Knockout animals were embryonically lethal and had no glomeruli but overexpression also resulted in glomerulopathy. An adult knockout animal exhibited thrombotic microangiopathy whereas the adult onset overexpression led to an histology similar to DN. In a rat model of induced diabetes by administration of streptozotocin an anti-VEGF decreased the incidence of DN. In a mouse model induced in the same manner overexpression of sFlt-1 did the same. Andrew's work looked at the influence of VEGF165b on the process by expressing the molecule in the podocytes and then examining renal function and glomerular permeability. At 6 weeks plasma creatinine was the same in VEGF165b expressing and non-expressing mice. However urinary ACR was elevated in control animals but not in the VEGF165b mice. He then harvested glomeruli and subjected them to 8% BSA to form an oncotic gradient and measured water permeability by their degree of shrinkage. The diabetic mice showed an increase in water permeability whereas the VEGF165b mice were protected.

Our third speaker was Shuang Feng who had investigated the regions within polycystin which were important for formation of the ion-channel complex. Shuang told us that polycystic kidney disease is caused by mutations in the genes *pkd 1* and *2* which code for polycystins. Polycystin 2 (PC2) is a transient receptor potential channel which is mostly found in the endoplasmic reticulum and it is able to form a complex with polycystin 1 (PC1) and well as with itself. He investigated the C terminal region of PC2 and identified a novel coiled-coil domain which he showed was essential for homodimerisation and function by a number of assays. This region was also involved in heterodimerisation with PC1. No functional channels were able to be formed without the interaction of PC1 and PC2.

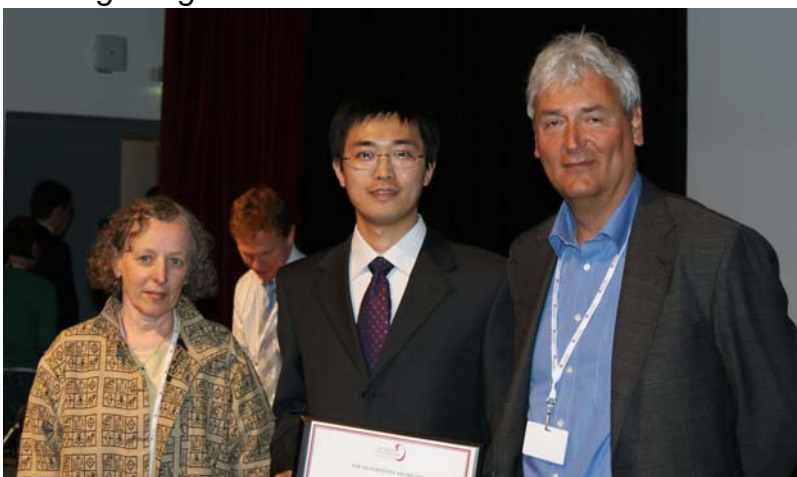
The fourth speaker was Heather Bevan who presented work on NO production in glomerular endothelial cells in shear stress and its dependency on eNOS. She pointed out that endothelial cells are constantly exposed to shear stress which leads to intracellular signals and the release of mediators such as NO. Shear stress leads to activation of PI3K, Akt and phosphorylation of eNOS and there is also involvement of AMPK and PKA, but this had not been confirmed in glomerular endothelial cells. Shear stress was induced in these cells by rotation, which led to actin skeletal alignment. Western blotting showed that eNOS became phosphorylated at all shear levels. This was apparent by 10min and remained for 24h. Nitrate levels were also elevated. Akt phosphorylation was increased in an identical manner. AMPK phosphorylation had disappeared by 24h but was raised initially with a similar time course to the other molecules.

Our fifth speaker was James Browne who spoke about how ERK5 was involved in the non-fibrotic outcomes of TGF β in renal epithelial cells. James told us that DN was associated with glomerulosclerosis and tubulointerstitial fibrosis. TGF β leads to fibrosis and epithelial mesenchymal transformation (EMT) in proximal tubular epithelial cells (PTEC) and had been shown to activate ERK5. James investigated the role for ERK5 by using siRNA. Down regulation of ERK5 followed by TGF β in PTEC led to a retention of E-cadherin and less increase in fibronectin. Alpha smooth muscle actin increased in the cells. He concluded that ERK5 was involved in the TGF β induced E-cadherin loss and fibronectin secretion and may be involved in early EMT.

The final talk was given by Y Zhou on how podocyte injury giving rise to progressive renal damage may be modified by ACE inhibitors. She described how proteinuria was toxic and podocyte loss was either a symptom or cause. As podocyte injury was important in many diseases could proteinuria be used as a sign of stress to predict and prevent disease and would ACE inhibitors be useful in treatment? Angiotensin II was formed during stress and gave rise to podocyte damage, proteinuria, a decrease in cell number, foot effacement and fibrosis. If Angiotensin II was blocked this led to rescue. The research in the presentation used Transgenic mice expressing podocyte-DTR. Mice were given DT and developed proteinuria in days with glomerular damage. At one month chronic damage was observed. The proteinuria peaked at 2 weeks and then decreased at 5weeks and the same was observed for urea and albuminuria. Glomerular histology showed a continuous injury to glomeruli over the 6 months of the model with a decrease in podocytes. The ACE inhibitor captopril was given for 8 weeks. This led to a decrease in blood pressure over control animals, decreased scarring, less sclerosis and decreased ACR but there was no difference in serum creatinine, urea or albumin.

After a short deliberation due to the constraints of time Shuang Feng was awarded the prize for the best presentation of 2009. Well done Shuang!

The Judges and Winner – Left to right Prof Alison Eddy, Shuang Feng and Prof Bernhard Moser



The announcement of the winner by Prof Eddy (and our chairmen behind her)



All of the presenters for 2009

