Insulin and insulin like growth factor (IGF) signalling control many aspects of metabolism, growth and survival in biological systems. They also exhibit significant homology in their structures and the receptors through which they signal [the insulin receptor (IR) and IGF1 receptor (IGF1R)]. Abnormailities in insulin signalling through the IR has previously been found to be critical for podocyte function (Welsh *et al.* Cell Metab. 2010 12(4) 329-340) and this study aims to define the physiological importance of the related IGF1R and combined IGF1R/IR in podocytes.

We initially generated podocyte IGF1R knockout (podIGF1RKD) mice by crossing IGF1R floxed mice with animals expressing Cre recombinase under the control of a podocin promotor. To increase the level of knockdown we also made one of the IGF1R allelles null. These podIGF1RKD mice had no renal phenotype at 9 months of age with no changes in renal histology or urinary albumin:creatinine when compared with littermate controls. When these mice were stressed at age 8 weeks utilising an Adriamycin glomerulopathy model and compared with littermate IGF1R sufficient controls we, surprisingly, found that podIGF1RKD mice were protected against kidney disease progression with improved glomerular histology and lower levels of albuminuria (p<0.005). Studies of primary cultured podocytes from podIGF1RKD mice revealed that despite 80% knockdown of the receptor, these cells are still able to signal and phosphorylate AKT and MAP kinase in response to IGF stimulation. We therefore knocked down the IGF1R further in conditionally immortilsed podocytes derived from podIGF1RKD mice by transduction with lentiviral Cre recombinase. This acheived > 95% cellular IGF1R knockdown and resulted in significant cell death relative to controls.

To understand if there was compensation within the IR/IGF1R axis we also generated podocyte specific IR/IGF1R double knockout (podDKO) mice using both conventional podocyte Cre drivers and a new podocyte Cre driver that is not subject to epigenetic degradation. Interestingly mice on the “conventional” Cre were healthy with no obvious albuminuric kidney disease. We subsequently discovered that their podocyte IR and IGF1Rs had been knocked down between 50-70 %. In contrast, the initial cohort of DKO mice on the “new” Cre driver developed severe kidney disease from 12 weeks of age, resulting in global sclerosis, renal failure and death.

Collectively this work reveals the critical importance of podocyte IGF/insulin signalling and that only a fraction of basal activity is required to maintain function. We also show that partial inactivation of podocyte IGF1R may be beneficial in some disease settings.