Unravelling which kidney cell types are affected in Renal Cyst and Diabetes Syndrome caused by HNF1B mutation using Single Cell RNAseq of stem cell kidney organoids

Many individuals are born with kidney problems because they carry faulty genes. Often this leads to a need for dialysis or kidney transplant at a young age. The gene HNF1B is the commonest of these faulty genes seen in the paediatric clinic and acts from very early in development. It is a key regulator controlling many other ‘lesser’ regulators in the kidney, both directly and indirectly. Because of this it has critical roles in making kidneys develop properly and it affects the function of many different kidney cell types. If this gene doesn’t work properly kidneys may develop cysts in different parts of the kidney even in utero: these cysts are a symptom that the kidney does not have the normal organisation and complement of molecules that regulate and drive its function. We can take stem cells which have mutations in HNF1B and differentiate them to kidney organoids, similar to a mini kidney. We are starting to pull out some of the key molecules that are disrupted, but we need to know where in the many different cell types of the kidney the main regulators (below HNF1B in the ‘governing hierarchy’) that are disrupted by HNF1B malfunction are. In this proposal we plan to identify all the genes that are active in each cell and type of cell in the kidney organoid and compare this between HNF1B mutant and unaffected organoids. This will allow us to find out which cells and which molecules contained within the organoids are most affected by HNF1B mutation allowing us to find early drug targets for potential therapy.