Treating a genetic kidney disease in a human stem cell model

Worldwide, half a million children and young adults have such severe kidney failure that they need dialysis or transplantation; half of them were born with abnormal kidneys. Sadly, dialysis does not maintain normal health, and kidney transplants are in short supply. So, we urgently need to understand why kidneys do not grow properly before birth to help design new treatments. A key gene that makes kidneys grow before birth is called ‘HNF1B’. It is a ‘conductor of the orchestra’, switching on many other kidney genes. In Paediatric Nephrology clinics, HNF1B is the commonest faulty gene we found in people born with abnormal kidneys. A problem is that we can rarely obtain tissues from affected fetuses or children and so can’t directly study these abnormal kidneys. We have got round this research road-block by using both healthy and mutant stem cells to grow mini-kidneys in the laboratory. Excitingly, mini-kidneys made from HNF1B mutant cells grow abnormally, similar to the patients' own kidneys. They contain malformed tubules, tiny tubes through which urine flows and is processed. These tubules are larger than normal but they do not function properly. We have found that a specific biological process called ‘glutamate signalling’ appears overactive in the mutant mini-kidney. In this laboratory project, we will test drugs that act on ‘glutamate receptors’ to correct the defective maturation of these human mini-kidneys. Our results will be a stepping-stone towards new treatments for people born with malformed kidneys.