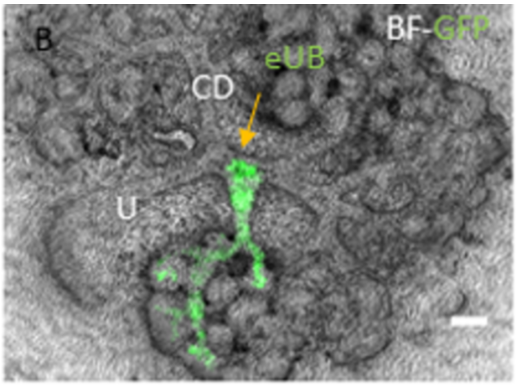
Making a connection

I have mentioned before, in these blogs, the challenge of providing tissue-engineered kidneys with a ureter to drain urine from them. In *Chris takes the you-know-what*, I described Chris Mill's success in turning a kidney tube into a basic ureter (albeit one without muscles) and in *From ES cells to urothelium*, I described May Sallam's success in developing a way of making ureter tissue from embryonic stem cells. In a paper just accepted for publication in *Organogenesis*, May has now gone on to develop a method for attaching these engineered ureters to host kidneys in culture.

This paper arose through the combination of a happy accident, and a student who was observant enough to notice it and curious enough to want to follow it up. Work for her previous paper had included experiments in which May had grafted engineered ureteric buds (the progenitors of ureters) into cultured embryonic mouse kidneys, to see how they would develop. These experiments indicated that the choice of developing into kidney-type urine collecting ducts or developing into a ureter depended on what type of cells surrounded the graft. May noticed, though, that in a couple of examples in which grafting had not gone well and the host was damaged, the graft seemed to connect to a tube in the host. She never saw this in the experiments that went well.

It is moments like this that reveal the difference between a mediocre student and an excellent one. A mediocre student would either have failed to make the observation at all, or would have ignored it on the grounds that these were damaged anyway and there was plenty of good data for a paper from the undamaged examples. But, while working on the main paper, May brought the issue to my attention and we discussed how to follow it up carefully. The obvious experiment was to culture host foetal kidneys and to injure half of them deliberately, by 'nicking' one of their collecting duct tubes or their ureter, then to graft an engineered ureteric bud close-by. The control, un-nicked examples received similar grafts.



The results were striking: in half of the experiments, the grafted engineered ureteric bud (green in the image) made a connection with the nicked host tube (the non-green 'tree'). No connections were made in the un-nicked controls. In general, grafts that connected to collecting ducts turned into collecting ducts themselves, and those that connected to ureters turned into ureters

themselves. This was not surprising, as we already knew that their developmental trajectory was set by the cells ('kidney-type' or 'ureter-type') that surrounded them. Where the graft was orientated so that one end met a nicked ureter but the other projected up into the 'kidney-type' surrounding cells, its two ends took on different fates: the end up in the kidney was fully kidney-like while that near the ureter turned into ureter itself and connected to the ureter of the host. Peristaltic waves of contracting muscle ran along both the graft and the host.

The business of the 50% success rate is intriguing. As May pointed out, she has to cut her engineered ureteric buds off the structure that produces them, and they are so tiny that it is not practical to keep track of which of their ends is the cut one. Therefore there is a 50% chance of the cut end of the engineered ureter being the one that meets the nicked host. Perhaps the 50% success rate emerges directly from this.

There is no natural developmental event that this mimics, in the sense that the ureter-and-collecting-duct system does not assemble from separate parts that join. And it is clear that the nicking is needed, though it is not clear why. The reason might be entirely mechanical - that the nick separates cells in the wall of the host and makes it possible for them to join the graft instead of each other as they heal. But I am sceptical about this - the opposite side of the nick will be nearer than most grafts so simple healing would be expected to dominate, with no joining. Injury changes the profile of growth factors released by cells, and perhaps this creates attraction, or least blocks repulsion between the epithelia as they meet. The truth is, we really don't know what is going on.

Why are we excited by these observations at all? So far, there have been two main ideas for using stem cells to help people with failing kidneys. One, the one that appears most often in these blogs, is to try to make complete new kidneys. The other is to introduce simple suspensions of stem cells into the kidney, typically via blood, so that they might be able to settle and produce new tissue or repair what was there before. The observation that engineered kidney tissue might be able to join on to existing kidney tissue may open up a third possibility - that sections of new kidney might be engineered and then grafted into a damaged host kidney where they would connect to its systems and take over (some of) its function. Right now, this remains science fiction, but it might be worth exploring whether we can gain these connections even to adult kidney, which would be one step in the direction of making this fiction true.

Jamie Davies, East Lothian, March 2021