THE EFFICACY AND SAFETY OF STEM CELL THERAPIES IN MOUSE MODELS OF KIDNEY DISEASE

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The prevalence of end-stage renal disease (ESRD) has been rising dramatically over the last decade and it is now recognised as a worldwide public health problem with major social and economic implications1. In ESRD, both kidneys are so damaged that they cannot sustain life, so that dialysis or renal transplantation, both with significant morbidity and mortality, are the only treatment options. Thus, we need to devise interventions that prevent or delay the onset of ESRD, which itself usually develops from a worsening of chronic kidney disease (CKD), associated with atrophy of glomerular and tubular epithelia, fibrosis, and a reduced glomerular filtration rate (GFR). This progression of disease is a well-documented phenomenon in humans and in several animal models, including the ischemia reperfusion (IR) and adriamyin (Adr)-induced injury models we will use in this Project 2,3. Over recent years, severa l studies have shown that stem cell-based therapies involving kidney-derived stem cells (KSCs) and mesenchymal stem/stromal cells (MSCs) can have beneficial effects when administered to rodents with kidney disease4-10. Whilst encouraging, these studies collectively have the following shortcomings, which must be addressed before such therapies could be used in the clinic: (i) variability in study design -the vast differences in cell-types, dosing regimes, administration routes, disease models and types of analyses used, makes it difficult to compare studies, and consequently, it is not possible to say which (if any) of these many forms of cell-based therapies would be most appropriate for clinical use; (ii) potential safety issues -due to limitations in in vivo imaging technologies, the extent to which the administered cells integrate into non-target organs and tissues tends not to be addressed, thus precluding any attempt to monitor the potential adverse effects of the cells on the surrounding tissues, the most common effects being inflammation, fibrosis, maldifferentiation or tumourigenesis; (iii) lack of knowledge regarding mechanism -in most cases, it is not clear how the administered stem cells ameliorate kidney damage. Knowledge of the mechanisms involved could allow such therapies to be improved or refined so that they are more efficacious and safer.