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## Stem cells represent a new area of kidney care

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Induced pluripotent stem (iPS) cells have the potential to play an important role in the future of kidney care. The 2012 Nobel Prize in Medicine was awarded for advances made in cellular reprogramming. Using this remarkable technology, somatic cells such as skin fibroblasts can be ‘reprogrammed’ into induced pluripotent stem (iPS) cells, with properties very similar to those of embryonic stem (ES) cells<sup>1</sup>. Like ES cells, iPS cells can replicate extensively, and are capable of differentiating into all of the body's cell types. These two qualities—self-renewal and pluripotency—make iPS cells a scalable source of cells and tissues, which could be produced “on demand.” Moreover, such tissues are expected to be immunocompatible with the patients from which they are derived. iPS cells therefore represent a new area of transplant.

### iPS use for kidney transplants

iPS has the potential to play an important role in the future of renal care. Thanks to improved graft survival rates, more patients are considered good candidates for kidney transplant today than ever before. Supply has not kept up with demand, however, creating a disparity between the need for organs and the number of available kidney donors. More than 75,000 patients await a kidney transplant in the United States every year, but only 17,000 transplants are performed, while more than 4,000 people die every year while waiting for a kidney. Even in patients fortunate enough to receive a transplant, graft acceptance and survival are not guaranteed. Immunosuppression is required for the lifetime of the graft to reduce the risk of acute or chronic rejection.

The side effects and infections that result from immunosuppression create significant quality of life issues for these patients. In contrast, iPS cell-derived kidney tissue could be produced on-demand, and would be unlikely to require immunosuppression.

### **Work still to be done for ESRD patients**

Challenges remain before iPS cells can be administered to patients as successful therapy for ESRD. Only recently has it become possible to differentiate kidney-like cells from ES and iPS cells<sup>2-5</sup>. The identification of these cells as kidney was based on gene expression, which resembles that of embryonic kidney tissue. It remains unclear the eventual complete maturation of these cells, whether they are capable of full function, duration of survival/regeneration (apoptosis), and whether all nephron cell types are represented in these cell cultures.

The embryo develops three types of kidney formation at different stages of development: the pronephros, mesonephros, and finally the metanephros, from which the adult kidneys are derived. Further in-depth characterization of ES and iPS-cell derived kidney tissues, using a broader set of markers and functional assays, is required to comprehensively understand which tissues they truly represent.

Therapeutic administration of iPS cells would require prior safety and efficacy testing, compared to the gold standards of dialysis and kidney transplant. To assess the potential of these cells for therapy, it is important to implant iPS cell-derived kidney cells into animal models of renal insufficiency, to test their ability to replace kidney function. Similar studies in non-kidney organs, such as the liver and pancreas, have been successful in demonstrating that iPS cell-derived tissues can confer functional benefit to animals. For the kidney, it remains an open question whether iPS-cell derived tissues will be able to engraft, vascularize, and integrate with the host circulatory system in such a way as to perform the functions of the native kidney. Earlier studies, using fetal kidney cells, have suggested that implantation of differentiating cells can prolong life in rodent models of kidney insufficiency<sup>6</sup>. Notably, immunocompatible cells also carry with them an increased risk of tumorigenicity. Safety is therefore a major concern with any iPS cell-derived tissue. Transplantation approaches must be tested and optimized in animals, starting with rodents, before taking the next step in humans. No clinical trial in any organ has actually tested therapeutic benefit of iPS-cell derived tissues implanted into patients. There are ongoing clinical trials relating to iPS cell therapy in the eye, and it is likely that additional organs will follow.

### **Generate, but do not duplicate**

If kidney tissue can be generated from patient cells and shown to be functional, one concern is that the new tissue may re-develop the disease, be it inherited or acquired (examples being autosomal dominant polycystic kidney disease or focal and segmental glomerulosclerosis). Well documented are cases of HLA-identical kidney transplants in which the graft shows an increased risk of acquiring the primary disease post-transplant. There are two possible approaches to alleviate this problem. The first is to replace progressively diseased tissue on-

demand with newer tissue, at needed time intervals. As iPS cells can self-renew extensively, this is a viable option, although it would involve multiple surgeries. The second approach is to correct the disease in the iPS cells before even implanting any tissue in the patient. Such an approach may be possible with new gene-corrective tools, such as CRISPR/Cas9 genome editing nucleases<sup>7</sup>. A limitation of this approach is that it requires pre-knowledge of the disease-causative mutations, which is not always available or even attainable.

In addition to their potential for transplantation, iPS cells derived from chronic kidney disease (CKD) patients have applications as laboratory models for human kidney disease. Human cellular models, where they exist in a limited capacity, are obtained from patients who have established and/or advanced disease, and tissue is obtained via biopsy or surgical specimen. Genetic information is rarely available, and the primary kidney epithelial cells de-differentiate rapidly in cell culture. iPS cells from patients can be used as a new type of laboratory model, to better understand pathophysiology and develop treatments. iPS cells can be derived non-invasively from fibroblasts, blood, and even urine<sup>1, 8, 9</sup>. They provide a safe and reproducible source of human tissue for laboratory analysis – a “clinical trials in a dish” approach. The key feature of this approach is to identify a cellular phenotype in patient iPS cells that represents some aspect of disease pathophysiology. As controls, disease iPS cells can be compared side-by-side to iPS cells without disease; for instance from unaffected siblings who do not exhibit the same phenotype. Gene therapy might also be administered to the cells to test whether correction of genetic mutations is capable of rescuing the phenotype. Candidate therapeutics could be applied at different stages and doses to determine the optimal treatments for slowing pathophysiology.

## Treating PKD with iPS cells

iPS cells have now been derived from patients with different kidney diseases, including autosomal dominant polycystic kidney disease (ADPKD), systemic lupus erythematosus (with renal involvement), and Wilms tumor.<sup>8–10</sup>

Our group is generating and studying iPS cell lines from patients with ADPKD. We identified a defect in PKD gene expression at the primary cilium, an antenna-like organelle, as the first phenotype relevant to kidney disease in patients' iPS cells<sup>8</sup>. Administration of a corrected copy of the PKD1 gene to these cells was sufficient to reverse the phenotype in derived epithelial cells. iPS cells from patients can provide a new type of human laboratory model for studying the pathophysiological consequences of naturally occurring kidney disease mutations.

We are currently conducting expanded studies in additional patients with varying phenotypic expression, to test whether features of human PKD can be faithfully reproduced in cell culture. In PKD, cysts are the disease. Will PKD iPS cells differentiated into kidney cells show an increased tendency to form cysts in a dish? Will cysts form in an accelerated, same or slower manner? Observation might provide important insights into the earliest initiating stages of cyst formation, which remain to be defined.

PKD is a slowly progressive disease with patients, on average, exhibiting symptoms in middle age. Approximately 50% of the affected PKD population do not require renal replacement therapy. A drug which slows PKD progression by 10-15 years could therefore improve a patient's chances of avoiding dialysis. Despite high-profile clinical trials, such a drug remains elusive. One problem is that PKD appears to be easier to treat in mice than in humans. Development of specific iPS-cell models for PKD will enable 'clinical trials in a dish' in larger cohorts of iPS cells, with the intent of identifying treatments likely to reverse kidney disease in affected patients. Such 'clinical trials in a dish' can be used to complement pre-clinical studies in animal models, and guide clinical trials for human kidney disease. This is a general approach that can be applied to many different kidney diseases, in a manner similar to that initiated for patients with PKD.

## Summary

iPS cells from patients with kidney disease are a new tool with the potential to impact the future of renal care. They can be used in the laboratory to model the pathophysiology of human kidney disease, and have the potential to establish a new area of immunocompatible, on-demand renal transplantation. Critical challenges remain before the full potential of these cells can be accurately assessed. We need to understand whether the derived cell types are mature and can replace kidney function(s). To what extent can iPS cells model kidney disease in the simplified environment of cell culture? Ultimately, successful integration of these cells as autograft therapies will require demonstration of safety and efficacy equal or superior to the existing gold standards of kidney allograft transplantation and dialysis. Specific educational and infrastructural changes will be necessary if these specialized technologies are to be adopted as an accepted modalities in clinical medicine. Given these barriers, the first fruit of these labors is likely to be improved understanding of pathophysiological pathways in human iPS cell disease models, followed by drug discovery and testing. These experiments will lead naturally to improvements in differentiation and experiments in animal models testing function.

The time course to achieve the desired goals remains unknown, but the ultimate hope is that new, more effective and less expensive modalities for renal replacement therapy will occur in the foreseeable future. A new standard of care for patients is anticipated that addresses limitations of currently available treatments.

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