Engineering organoids to target kidney therapy

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ABSTRACT
Kidneys cannot naturally regenerate lost tissue, and few preventive medications exist, limiting treatment options to temporary salvages of dialysis or transplant with substantial side effects. We have developed a simple method to differentiate human pluripotent stem cells into intricately patterned, multi-segment organoids that resemble kidney tissues. These organoids form via a developmental pathway that induces the nephron progenitor cell, which gives rise to the epithelial lineages of the proximal nephron such as podocytes, proximal tubules, and distal tubules along a proximal-to-distal axis. While beautiful, how to translate organoids into innovative therapies for organs as complex as human kidneys remains a critical question. To address this challenge, we have applied CRISPR gene editing and high throughput automation to reveal disease mechanisms in organoids and test therapeutic interventions. Mutations associated with polycystic kidney disease or cilia cause organoid tubules to swell thousands of times in size, producing large, fluid-filled cysts of centimeter diameters. In contrast, mutations associated with podocytes, the filtering cells of the kidney, do not affect tubules but cause junctional deformities that explain urinary defects in vivo. To improve organoid function and seek therapies, thousands of organoids can be manufactured simultaneously in high throughput screening formats, and analyzed for multi-dimensional phenotypes of differentiation, toxicity, and disease. Screening reveals treatments that dramatically increase the vascular endothelium, and a surprising role for non-muscle myosin in cystogenesis, which can be targeted pharmacologically to modulate cystogenesis. Organoids with live fluorescence reporters and in microfluidic kidney-on-a-chip formats provide next-generation platforms for phenotypic screening and illumination of intracellular mechanisms at the tissue scale. Collectively, our findings delineate key strategies and focus areas for advancement of kidney therapeutics using human organoids as surrogates for drug discovery, gene therapy, and regeneration.

BIO
Benjamin “Beno” (pronounced Bee-no) Freedman is an associate professor of medicine at the University of Washington, in Seattle. He has studied the cell biology of vertebrate stem cells for over 20 years. Hallmarks of his career include: 1) the application of stem cells for studying disease and regeneration; 2) quantitative comparison of gene mutants; 3) functional assays providing stoichiometric insight into protein dynamics and activity; and 4) reconstitution of complex physiological phenomena in defined component systems in vitro. Freedman studied mammalian epimorphic regeneration after injury as an undergraduate at the University of Pennsylvania. Subsequently, he investigated cytoplasmic remodeling of germine nuclear DNA as a doctoral student at the University of California at Berkeley. These experiences provided Freedman with his fundamental training in the cell biology of stem cells. Several members of Freedman’s family suffer from kidney disease, which prompted him to investigate the potential of human pluripotent stem cells for this fascinating organ. At Harvard Medical School, he led a multi-institute collaboration to generate and characterize stem cells from polycystic kidney disease patients. This led to the identification of the first pluripotent stem cell phenotype relevant to kidney disease and a possible therapeutic approach. He subsequently developed protocols directing differentiation of stem cells into kidney progenitor cells and human kidney organoids that functionally model morphogenesis, physiology, and injury. Combining this with CRISPR/Cas9 genome-editing, Freedman has established kidney organoid models of several genetic and acquired kidney diseases. Currently, Freedman’s group is combining stem cells, bioengineering, and genome editing to model disease and therapy.