

Modeling genetic diseases in mini-kidney organoids

Harvard Stem Cell Institute researchers at Brigham and Women's Hospital have combined cutting-edge, gene-editing techniques with stem cell science to for the first time successfully model genetic kidney disease in lab-grown, mini-kidneys. The findings were published today in the journal *Nature Communications*.

"The study provides a proof-of-concept that we can use a genetic approach to make kidney disease in a dish," said Joseph Bonventre, MD, PhD, HSCI Principal Faculty, Chief of the Renal Division at Brigham and Women's Hospital at Harvard, and the study's senior author. "We were interested in creating disease models using these kidney organoids," he added.

Just last week, Bonventre and a team of HSCI/BWH investigators published research involving the creation of human kidney organoids, three-dimensional mini-organs grown in a lab dish, to model human kidney development and to test for drug toxicity. Now, using gene-editing tools, researchers can engineer these mini-kidneys with specific genetic diseases.

Using CRISPR technology, Bonventre and colleagues introduced into healthy human pluripotent stem cells either the gene mutations associated with polycystic kidney disease or those associated with glomerulonephritis.

The scientists then coaxed the stem cells to differentiate into mature kidney cells that self-assembled into functional organoids with the physical complications related to their genetic mutations; for example, organoids with polycystic kidney disease formed cysts, while organoids with changes in a protein that is implicated in glomerulonephritis displayed altered cell to cell interactions, which could ultimately lead to leaky filters in the mature kidney.

"Mutation of a single gene results in changes in kidney structures associated with human disease, allowing better understanding of the disease and serving as models to develop therapeutic agents to treat these diseases," Bonventre said.

Kidney disease costs the United States 40 billion dollars per year and affects 700 million people worldwide. Twelve million patients have polycystic kidney disease and two million people have complete kidney failure. Dialysis and kidney transplantation, the only options for kidney failure patients, can cause harmful side effects and poor quality-of-life.

"These genetically engineered mini-kidneys have taught us that human disease boils down to simple components that can be re-created in a petri dish," added the study's first author, Benjamin Freedman, PhD, who worked with Bonventre at BWH and has since taken a position as Assistant Professor at the University of Washington. "This provides us with faster, better ways of testing out drugs and therapies that might work in humans."