Using Human Pluripotent Stem Cells to Develop New Treatments for Cystinosis

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Pluripotent stem cells are powerful cells that give rise to all of the body's cell types and organs. With support from the CRF and a dedicated group of patients, our lab has established a new biobank of human pluripotent stem cells derived from patients with cystinosis. These cells provide a new way to study how cystinosis affects the body, and to develop therapies to protect against the effects of cystinosis or replace damaged tissues.

What does cystinosis look like in a petri dish? Under the right conditions, we observe that cystinosis stem cells accumulate more than 100 times as much cystine as stem cells without cystinosis. Subsequently, cystinotic cells become sick and die, while non-cystinosis cells remain healthy. Cysteamine protects against these symptoms, and prevents the cystinosis cells from getting sick.

Now that we know what cystinosis looks like, we are testing whether other therapeutics besides cysteamine can also protect these cells. In addition to drug treatments, one of the avenues we are exploring is gene therapy. By using a gene editing technique called CRISPR, we are able to supply cystinosis stem cells with a healthy copy of the CTNS gene. We expect that this will restore cystine levels in these cells and prevent them from getting sick.

The kidneys are highly sensitive to the effects of cystinosis, resulting in renal Fanconi syndrome and eventually kidney failure. To study the kidneys, we have coaxed cystinosis stem cells to change into kidney organoids – tiny structures that resemble kidney tissue. This process resembles the way kidneys form when we are in the womb. In our initial experiments, we have found that cystinosis stem cells can form kidney organoids. We are now examining these structures for signs of nephropathic cystinosis, such as crystal formation.

Kidney transplantation is a lifesaver, but there is a long waiting list, and even a 'perfect match' will eventually wear out. In the future, we seek to grow new kidney tissue 'on-demand' from pluripotent stem cells, which would be a true perfect match. Towards this goal, we have made the exciting discovery that cystinosis kidney organoids become more mature when implanted inside a living mouse host, forming filter units that integrate beautifully with the host's blood supply. We are now taking this one step further, to test whether such grafts can also form in mice with cystinosis, and whether they improve symptoms observed in these animals such as Fanconi syndrome, as a prerequisite for more advanced studies in human patients.