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## **HUMAN INDUCED PLURIPOTENT STEM CELLS REPROGRAMMED TO FORM THE PRECURSOR CELLS THAT BECOME EGGS AND SPERM**

### **Discovery May One Day Lead to New, Patient-Specific Treatments for Infertility**

For the first time, UCLA researchers have reprogrammed human induced pluripotent stem (iPS) cells into the cells that eventually become eggs and sperm, possibly opening the door for new treatments for infertility using patient-specific cells.

The iPS cells were coaxed into forming germ line precursor cells which include genetic material that may be passed on to a child. The study appears today in the early online edition of the peer-reviewed journal *Stem Cells*.

“This finding could be important for people who are rendered infertile through disease or injury. We may, one day, be able to replace the germ cells that are lost,” said Amander Clark, a Broad Stem Cell Research Center scientist and senior author of the study. “And these germ cells would be specific and genetically related to that patient.”

Theoretically, an infertile patient’s skin cells, for example, could be taken and reprogrammed into iPS cells, which, like embryonic stem cells, have the ability to become every cell type in the human body. Those cells could then be transformed into germ line precursor cells that would eventually become eggs and sperm. Clark cautioned, however, that scientists are still many years from using these cells in patients to treat infertility. There is still much to be learned about the process of making high quality germ cells in the lab.

In another important finding, Clark’s team discovered that the germ line cells generated from human iPS cells were not the same as the germ line cells derived from human embryonic stem cells. Certain vital regulatory processes were not performed correctly in the human iPS derived germ cells, said Clark, an assistant professor of molecular, cell and developmental biology.

So it’s crucial, Clark contends, that work continue on the more controversial human embryonic stem cells that come from donated, excess material from in vitro fertilization that would otherwise be destroyed.

When germ cells are formed, they need to undergo a specific series of biological processes, an essential one being the regulation of imprinted genes. This is required for the germ cells to function correctly. If these processes are not performed the resulting eggs or sperm, are at high risk for not working as they should. This has significant consequences, given that the desired outcome is a healthy child.

“Further research is needed to determine if germ line cells derived from iPS cells, particularly those which have not been created by retroviral integration, have the ability to correctly regulate themselves like the cells derived from human embryonic stem cells do,” Clark said. “When we looked at the germ cells derived from embryonic stem cells, we found that they regulated as expected, whereas those from the iPS cells were not regulated in the same way. We need to do much more work on this to find out why.”

Clark and her team plan to examine more iPS cell lines and evaluate the resulting germ cells derived from them to determine if the incorrect regulation remains a problem.

Creating germ cells from embryonic stem cells is challenging and the resulting proportions are low – about 10 percent of embryonic stem cells go on to become germ cells. Clark said creating germ cells from iPS cells proved just as challenging. Putting the iPS cells in an environment where germ cells thrive naturally, among fetal gonadal cells, proved to be the key.

Infertility affects about 15 percent of Americans. Current treatments include donor eggs and sperm and surrogacy. If germ cells can be derived from a patient's own adult cells using reprogramming followed by germ cell differentiation, this adds an important strategy into the tool box of options currently available to treat infertility, Clark said. A man with a low sperm count, for example, may be able to have more of his own sperm generated to fertilize his partner's egg.

The study took about 2 ½ years, first focusing on growing germ cells from human embryonic stem cells and then from iPS cells. It took just seven days to get germ line precursor cells from the iPS cells, once Clark and her team landed on the appropriate culture environment.

The stem cell center was launched in 2005 with a UCLA commitment of \$20 million over five years. A \$20 million gift from the Eli and Edythe Broad Foundation in 2007 resulted in the renaming of the center. With more than 150 members, the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research is committed to a multi-disciplinary, integrated collaboration of scientific, academic and medical disciplines for the purpose of understanding adult and human embryonic stem cells. The institute supports innovation, excellence and the highest ethical standards focused on stem cell research with the intent of facilitating basic scientific inquiry directed towards future clinical applications to treat disease. The center is a collaboration of the David Geffen School of Medicine, UCLA's Jonsson Cancer Center, the Henry Samueli School of Engineering and Applied Science and the UCLA College of Letters and Science. To learn more about the center, visit our web site at <http://www.stemcell.ucla.edu>.