

Kim Irwin (kirwin@mednet.ucla.edu)
(310) 206-2805
Enrique Rivero (erivero@mednet.ucla.edu)
(310) 794-2273

Embargoed for Use
Until 1 p.m. EST
Wed., June 6, 2007

STEM CELL RESEARCHERS REPROGRAM NORMAL TISSUE CELLS INTO CELLS WITH THE SAME PROPERTIES AS EMBRYONIC STEM CELLS

Researchers at the Institute for Stem Cell Biology and Medicine at UCLA were able to take normal tissue cells and reprogram them into cells with the same unlimited properties as embryonic stem cells, the cells that are able to give rise to every cell type found in the body.

The work, done in mouse models, appears in the inaugural June 7, 2007 issue of *Cell Stem Cell*, published by Cell Press. UCLA researchers, working closely with stem cell scientists at Harvard, took mouse fibroblasts, cells that develop into connective tissue, and added four transcription factors that bind to special sites on the DNA. Using this process, they were able to turn the fibroblasts into pluripotent cells that, in every aspect tested, were identical to embryonic stem cells.

The implications for disease treatment could be staggering. Reprogramming adult stem cells into embryonic stem cells could generate a potentially limitless source of immune-compatible cells for tissue engineering and transplantation medicine. If the work can be replicated in human cells, it may mean that a patient's skin cells, for example, could be reprogrammed to become embryonic stem cells. Those embryonic stem cells could then be prodded into becoming various cell types – beta islet cells to treat diabetes, hematopoietic cells to create a new blood supply for a leukemia patient, motor neuron cells to treat Parkinson's disease.

“If we can recreate this in human cells, it has significant implications for regenerative therapies,” said Kathrin Plath, an assistant professor of biological chemistry, a researcher with the Institute for Stem Cell Biology and Medicine at UCLA (ISCBM) and co-lead author of the study. “Our reprogrammed cells were virtually indistinguishable from embryonic stem cells. We could find no evidence that they were different in any way. We were rather surprised at how well this reprogramming worked.”

The finding also is significant in that this new technique could potentially replace a controversial method used to reprogram cells, somatic cell nuclear transfer (SCNT), sometimes referred to “therapeutic cloning.” To date, SCNT has not been done successfully in human cells.

“If we can successfully reprogram a normal human cell into a cell with almost identical properties to those in embryonic stem cells without SCNT, it may have important therapeutic ramifications and provide us with another method to develop human stem cell lines,” said Dr. Owen Witte, ISCBM director and a Howard Hughes Medical Institute investigator. “Up until now, it's been unclear whether a cell could be reprogrammed back into

an embryonic stem cell state without the use of SCNT, so that makes this a very important finding.”

Studies published previously had shown that the four transcription factors, which regulate expression of downstream genes and either activate or silence their expression, could reprogram cells into cells with some pluripotent properties. But they differed from embryonic stem cells in that they could not differentiate into every cell type or support development of adult tissues.

“They had very limited developmental potential,” Plath said. “We took a different approach, carefully selecting from our pool of cells the reprogrammed cells that highly expressed two genes we know are essential in embryonic stem cells.”

Selecting cells that highly expressed the genes, Oct4 and Nanog, essential to giving embryonic stem cells their unique characteristics resulted in reprogrammed cells with much more powerful pluripotency, Plath said.

The reprogrammed cells were not just functionally identical to embryonic stem cells. They also had identical biological structure. In a cell nucleus, DNA - an organism’s unique map or instructions - wraps around histones, which serve as a kind of scaffolding for compaction of the long DNA molecule. Histones don’t merely package DNA. Chemical tags on histones determine which genes are expressed or shut off in the DNA. In the reprogrammed cells, the location of the chemical tags along the DNA chromosomes were identical to those found in embryonic stem cells and, just as importantly, dramatically different from those in the fibroblasts before reprogramming. The structure of the reprogrammed cells - down to the very small chemical tags that dictate gene expression - is highly similar to that of embryonic stem cells.

Plath and her colleagues are working now to recreate the cell reprogramming in human cells. It could take years to determine if the same results can be achieved.

The Institute for Stem Cell Biology and Medicine was launched in 2005 with a UCLA commitment of \$20 million over five years. The ISCBM 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 institute 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.

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To learn more about the Institute for Stem Cell Biology and Medicine at UCLA, visit our web site at <http://www.stemcell.ucla.edu/>.