

Scientists home in on chemicals needed to reprogram cells

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Scripps Research Institute scientists have made a significant leap forward in the drive to find a way to safely reprogram mature human cells and turn them into stem cells, which can then change into other cell types, such as nerve, heart, and liver cells. The ability to transform fully mature adult cells such as skin cells into stem cells has potentially profound implications for treating many diseases.

In research published in the December 3, 2010 issue of *Cell Stem Cell*, Scripps Research Associate Professor Sheng Ding, PhD, reports a novel cocktail of drug-like small [molecules](#) that, with the assistance of a gene called Oct4, enables reprogramming of human [skin cells](#) into stem cells.

"Our ultimate goal is to generate induced [pluripotent stem cells](#) with defined small molecules," Ding said. "This would offer a fundamentally new method and significant advantages over previous methods, such as [genetic manipulation](#) or more difficult-to-manufacture biologics."

Using small-molecule compounds to reprogram adult human cells back to their pluripotent state — able to change into all other cell types — avoids the ethical controversy around embryonic stem cell research, and paves the way for the large-scale production of [stem cells](#) that could be used inexpensively and consistently in drug development. Cures for Alzheimer's, Parkinson's, and many other diseases might be possible if new cells could be created from a patient's own cells to replace those that have succumbed to disease or injury.

Substituting Chemicals for Genes

Scientists discovered in 2007 that fully differentiated mature cells, such as skin cells, could be "reprogrammed" to become pluripotent by using four transcription genes. One problem with this technique is that these genes, once inserted into a cell, permanently alter the host cell's DNA.

"There are many concerns when the host cell's genome is manipulated," Ding says. "One major worry is that since the four genes are [cancer-causing] oncogenes, they could induce tumors or interrupt functions of other normal genes."

Because of this danger, scientists have been searching for methods that could induce reprogramming without the use of these cancer-causing genes. The method the Ding lab has been pioneering — using small, synthetic molecules — represents a fundamentally different approach from the previous methods.

"We are working toward creating drugs that are totally chemically defined, where we know every single component and precisely what it does, without causing genetic damage," Ding says.

Breaking New Ground

Scientists have known for at least 50 years that a cell's identity is reversible if given the right signal — cells go forward to become mature, functional cells or they can go backward to become primitive cells. In order for cellular reprogramming to be safe and practical enough to use in cell therapy, researchers have sought an efficient, reliable way to trigger the reprogramming process.

In 2008, the Ding lab reported finding small molecules that could replace

two of the required four genes. Now, two years later, through extraordinary effort and unique screening strategy, the lab made a major leap forward by finding a way to replace three out of the four genes.

"We are only one step away from the ultimate goal, which would represent a revolutionary technology," Ding says.

The new study also revealed that the novel compound facilitates a novel mechanism in reprogramming: the metabolic switch from mitochondrial respiration to glycolysis, an important mechanism for tissue regeneration. The small molecules Ding and his colleagues found promote reprogramming by facilitating such metabolic switching — an entirely new understanding of reprogramming.

A future goal is to replace Oct4, a master regulator of pluripotency, in the chemical cocktail. "That would be the last step toward achieving the Holy Grail," Ding says. "Our latest discovery brings us one step closer to this dream."

More information: The first author of the paper, "Reprogramming of Human Primary Somatic Cells by OCT4 and Chemical Compounds," is Saiyong Zhu of The Scripps Research Institute.

Provided by The Scripps Research Institute

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