Efficient model for generating human iPSCs developed

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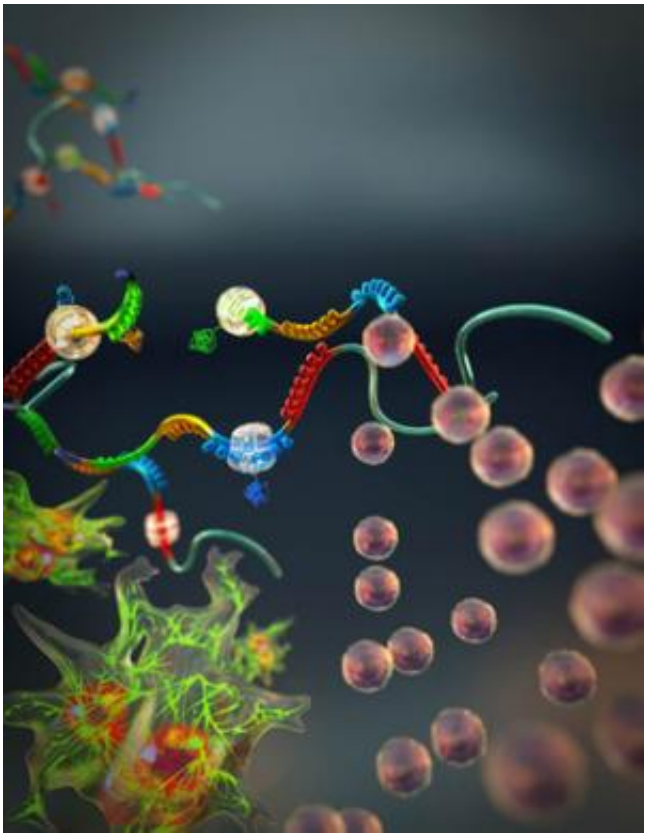

This graphic depicts single RNA generation of human iPS cells. Credit: Peter Allen, UC Santa Barbara.

Researchers at the University of California, San Diego School of Medicine report a simple, easily reproducible RNA-based method of generating human induced pluripotent stem cells (iPSCs) in the August 1

edition of *Cell Stem Cell*. Their approach has broad applicability for the successful production of iPSCs for use in human stem cell studies and eventual cell therapies.

Partially funded by grants from the California Institute for Regenerative Medicine (CIRM) and the National Institutes of Health (NIH), the methods developed by the UC San Diego researchers dramatically improve upon existing DNA-based approaches – avoiding potential integration problems and providing what appears to be a safer and simpler method for future clinical applications.

The generation of human iPSCs has opened the potential for regenerative medicine therapies based on patient-specific, personalized stem cells. Pluripotent means that these cells have the ability to give rise to any of the body's cell types. The human iPSCs are typically artificially derived from a non-pluripotent adult cell, such as a skin cell. They retain the characteristics of the body's natural pluripotent stem cells, commonly known as embryonic stem cells. Because iPSCs are developed from a patient's own cells, it was first thought that treatment using them would avoid any immunogenic responses. However, depending on methods used to generate such iPSCs, they may pose significant risks that limit their use. For example, using viruses to alter the cell's genome could promote cancer in the host cell.

Methods previously developed to generate integration-free iPSCs were not easily and efficiently reproducible. Therefore, the UC San Diego researchers focused their approach on developing a self-replicating, RNA-based method (one that doesn't integrate into the DNA) with the ability to be retained and degraded in a controlled fashion, and that would only need to be introduced once into the cell.

Using a Venezuelan equine virus (VEE) with structural proteins deleted, but non-structural proteins still present, the scientists added four

reprogramming factors (OCT4, KLF4, SOX2 with either c-MYC or GLIS1). They made a single transfection of the VEE replicative form (RF) RNA into newborn or adult human fibroblasts, connective tissue cells that provide a structural framework for many other tissues.

"This resulted in efficient generation of iPSCs with all the hallmarks of stem cells," said principal investigator Steven Dowdy, PhD, professor in the UC San Diego Department of Cellular & Molecular Medicine. "The method is highly reproducible, efficient, non-integrative – and it works."

Dowdy added that it worked on both young and old human cells. He explained that this is important since – in order to be used therapeutically in fighting disease or to create disease models for research – iPSCs will need to be derived from the cells of middle-aged to old adults who are more prone to the diseases scientists are attempting to treat. In addition, reprogramming factors can be easily changed.

Provided by University of California - San Diego

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