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CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Updates by the California Institute for Regenerative Medicine about news and events in stem cell research.

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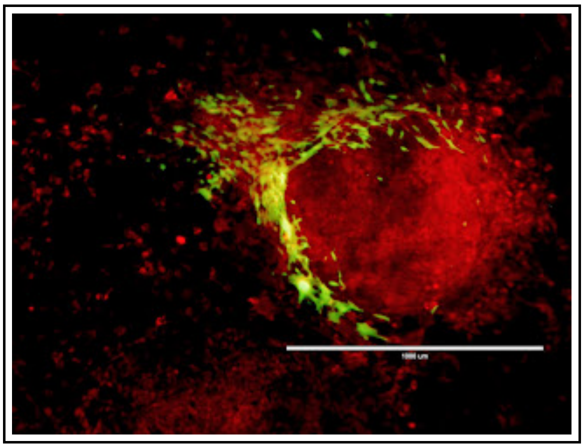
Pulling the Strings that Reprogram Cells



It was 2012, and the worldwide scientific community was laser focused on two scientists—separated by decades of research but together comprising two halves of a groundbreaking discovery: that mature, adult cells can be 'reprogrammed' back into a stem cell, or 'pluripotent' state.

The scientists, John B. Gurdon and Shinya Yamanaka, were awarded the Nobel Prize that year for this discovery, a discovery that has in recent years spurred the field of regenerative medicine forward in exciting new directions. But despite the fact that Yamanaka's 2007 seminal research proved that cellular reprograming was in fact possible, the process is far from perfect. It is notably inefficient with very few cells you push down the path toward pluripotency making it to the end.

This is in large part because the series of chemical reactions, or 'molecular pathways' that guide a cell from a stem cell to a mature cell—and back again—aren't fully understood. As researchers work towards realizing their goal of using this so-called induced pluripotent stem cell (iPS cell) technology for therapies, there is still more to learn.

Fortunately, scientists at the Centre for Genomic Regulation (CRG) in Barcelona have discovered the key role of a particular molecular pathway that guides this cellular transformation. But more importantly, the team has identified a way in which they can manipulate it.

Reporting in the latest issue of *Stem Cell Reports*, the research team announces new information on the Wnt signaling pathway—knowledge that could hold the key to improving the reprogramming process. The Wnt pathway is a series of carefully timed chemical reactions involved

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in the growth and production of cells. It is common to almost all animals, but there's a key difference in how the pathway behaves in frogs and lizards—and how it behaves in mammals.

Frogs and lizards use the Wnt pathway to help regenerate parts of their body lost to injury, which is why these animals are able to regrow limbs or a tail in adulthood. The Wnt pathway in mammals (including humans), by contrast, remains largely inactive once the mammal has reached adulthood. But previous research had shown that Wnt signaling must be switched on in the adult cell in order for it to be reprogrammed back into a stem cell-like state. So the CRG team took a closer look at this pathway's behavior.

In so doing, the researchers found that, during the reprogramming process, Wnt activity oscillated—alternating between the 'on' and 'off' position, similar to flicking a light switch on and off. As Ida Theka, one of the study's co-authors, explained in today's news release:

> "We have seen that there are two phases [of Wnt activity] and that in each one of them, Wnt fulfills a different function."

But more important was what happened when the team artificially manipulated the signal. As Theka continued:

> "We showed that by inhibiting [Wnt signaling] at the beginning of the [reprogramming] process, and activating it at the end, we can increase the efficiency of reprogramming and obtain a larger number of pluripotent cells."

In effect, the team acted like a puppeteer, artificially pulling the strings that altered the timing and strength of Wnt signaling. They did so with the help of a molecule called Iwp2. Iwp2 is a natural Wnt inhibitor—it normally blocks Wnt activity at specific intervals during development. And by manipulating Iwp2, the team could manipulate Wnt.

Notably, the team observed that manipulating Iwp2 did not have any sort of permanent effect on the cells—making it ideal for manipulating Wnt. As Theka continued in the same news release:

> "Until now [generating iPS cells] was a very inefficient process. There are many groups trying to understand the mechanism by which adult cells become pluripotent, and what blocks that process. We are providing information on why it happens."

While still a nascent field, the promise of iPS cell technology has spurred the hopes of scientists and patients alike, desperate for cures. As outgoing CIRM President Alan Trounson stated in 2012 regarding Yamanaka's Nobel Prize win:

> "There are few moments in science that are undisputed as genuine elegant creativity and simplicity. Shinya Yamanaka is responsible for one of those. The induced pluripotent stem cells he created will allow us to interrogate and understand the full extent and variation of human disease, will enable us to develop new medicines and will forever change the way science and medicine will be conducted for the benefit of mankind."

And now, with critical progress such as today's announcement from the team at CRG, we are that much closer to achieving that goal.

Photo: Cells with activated Wnt that can no longer be reprogrammed (in green) are located on the periphery; cells that can be reprogrammed are aggregated and can be seen in the center of the image (in red) [Credit: CRG]

Anne Holden

Posted by Anne Holden at 9:53 AM

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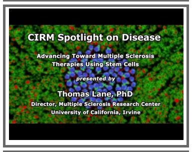

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