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Stem cell coup for Toronto; Mount Sinai team first to find way to reprogram adult cells without the cancer risk, raising new hopes for organ repair

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Illustrations: Dr. Andras Nagy made the breakthrough with team of scientists at Mount Sinai Hospital. ;

Toronto scientists have scored a major breakthrough in stem cell research, coming first in a worldwide race to find a safer way to make human skin cells act like embryonic stem cells. The discovery could well bring the promise of personalized organ repair within reach of patients.

Andras Nagy and his team of scientists at Mount Sinai Hospital are the first to reprogram adult human cells into embryonic-like stem cells without using potentially dangerous viruses that could cause cancer.

The finding overcomes one of the major hurdles in using the reprogramming technique in the search for new drugs, finding innovative cures for disease and creating personalized organs and tissue for patients.

Experts say the elegant discovery quickly will be adopted by labs around the world and will accelerate further advances in biology's hottest field.

"This is a significant contribution," says Alan Trounson, president of the California Institute for Regenerative Medicine, the state's stem cell funding body. "It's a very innovative way of delivering the gene products that are needed for reprogramming adult cells into embryonic stem cell-like cells. Well done to the Nagy group."

Scientists have been racing to find a safe and more efficient way to convert adult human cells into embryonic-like cells, called induced pluripotent stem cells, ever since the reprogramming technique was first reported in November 2007.

Nagy's coup is an indication that Ontario, particularly the researchers along Toronto's University Ave., remains at the forefront of stem cell research.

Embryonic stem cells are known as the body's master cells and can turn into any type of tissue or blood cell. Scientists want to harness that power for regenerative medicine, but groups opposed to the research say human embryos should not be destroyed to advance scientific study. Both scientists and opponents see reprogrammed cells as a way to get around that controversy.

Nagy and his team started to investigate the new reprogramming method in March last year. By April, he was collaborating with a British group, led by Keisuke Kaji at the University of Edinburgh, that was also on the same track. Their findings were reported yesterday in a pair of complementary papers in the

prestigious journal Nature.

Scientists are keen to use induced pluripotent stem cells, or iPS cells, in their research because the reprogramming method does not use human embryos or controversial cloning techniques - the two biggest ethical concerns dogging the field. The advent of the reprogramming method also means that, for the first time, scientists have a near endless supply of embryonic-like stem cells for their research. And, perhaps most importantly, iPS cells will allow scientists to generate embryonic-like stem cells from individual patients, a key component in personalized medicine.

McMaster University scientist Mickie Bhatia says reprogrammed stem cells are so promising, not only for their potential to generate new organs, but also because they bypass the rejection dangers that the use of tissues from other people always pose.

"The fact you can take someone's own cells and generate stem cells that can be transplanted back into them is wonderful," says Bhatia, the scientific director of the McMaster Stem Cell and Cancer Research Institute.

Until now, scientists have used viruses to reprogram cells. The virus acts as a vector to get extra copies of four genes, or growth factors, into a cell, which then genetically reprogram it back into an embryonic-like state. But the virus disrupts the cell's DNA and may trigger cancer.

Nagy, in collaboration with the British group, found a way around using viruses to reprogram cells. The teams identified a DNA sequence, called piggyBac, that can deliver the growth factors to a cell's chromosome and then, after the reprogramming, be removed with the growth factors all in one piece.

This double sequence of non-virus delivery and complete removal of growth factors is what makes the finding so important for future research on patients. Nagy likens the process to a space shuttle ditching its rocket once the fuel has burned up and the shuttle has reached space.

"The rocket has to be removed from the shuttle, otherwise it could create a problem," says Nagy, who is a senior investigator at the Samuel Lunenfeld Research Institute of Mount Sinai Hospital, investigator at the McEwen Centre for Regenerative Medicine and Canada Research Chair in Stem Cells

and Regeneration.

"It is the same with the reprogramming factors. They are potent, powerful factors so they can make stem cells. But they are needed for only three or four weeks ... If they remain, they could create a risk."

Other scientists have demonstrated a non-viral way to reprogram cells, but none have been efficient in human cells. And though much of Nagy's work was done using mouse cells, his team did show their virus-free method is an efficient way to generate human iPS cells. For Nagy, the next step is to refine the reprogramming technique and make it even more efficient.

Michael Rudnicki, scientific director of Canada's Stem Cell Network, called the study "a very important contribution" and says the new method will make iPS cells easier to generate and help scientists better understand the process adult cells must go through during reprogramming. And, he says, it also appears to eliminate the dangers associated with using viruses to transport reprogramming machinery into adult cell DNA.

"By making use of this ... technology, all of the introduced genes can be removed in their entirety, leaving behind no modifications, says Rudnicki, a Canadian Institutes of Health Research scientist, and whose group helped fund the research.

"It's an elegant advance in the technology. Conceivably, the use of this technology will generate iPS cells that could go into patients because they would have no genetic modifications whatsoever."

The Ontario iPS Cell Facility, based in Toronto, is working with Nagy to refine the new reprogramming method, says Bill Stanford, the facility's co-director. Researchers at the facility have generated 10 disease-specific cell lines, including one for cystic fibrosis using the original iPS technology.

"Once we have adapted the new technology," says Stanford, "we will be able to increase our efficiency and increase speed of generation with new disease lines."

McMaster's Bhatia says Nagy's work helps cement Ontario's position as the world leader in stem cell research.

"If you look at the planet in terms of who is doing what in terms of stem cells, there's a heavy concentration in Canada certainly, but a very heavy concentration in Ontario," says Bhatia, whose group has done groundbreaking work on coaxing embryonic stem cells to grow into new tissues.

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