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After Stem-Cell Breakthrough, the Work Begins

ANDREW POLLACK

If stem cell researchers were oil prospectors, it could be said that they struck a gusher last week. But to realize the potential boundless riches they now must figure out how to build refineries, pipelines and gas stations.

Biologists were electrified on Tuesday, when scientists in Japan and Wisconsin reported that they could turn human skin cells into cells that behave like embryonic stem cells, able to grow indefinitely and to potentially turn into any type of tissue in the body.

The discovery, if it holds up, would decisively solve the raw material problem. It should provide an unlimited supply of stem cells without the ethically controversial embryo destruction and the restrictions on federal financing that have impeded work on human embryonic cells.

But scientists still face the challenge of taking that abundant raw material and turning it into useful medical treatments, like replacement tissue for damaged hearts and brains. And that challenge will be roughly as daunting for the new cells as it has been for the embryonic stem cells.

“Even though we have this nice new sources of cells, it doesn’t solve all the downstream problems of getting them into the body in useful form,” said James A. Thomson of the University of Wisconsin, who led one of the teams that developed the stem cell substitutes. Dr. Thomson was also the first to isolate human embryonic stem cells, about a decade ago.

Still, the new discovery should accelerate progress — if only because with the ethical issues seemingly out of the way, more scientists and money will be drawn to the field.

There are two ways that stem cells can lead to treatments for diseases. Making replacement tissues for ailing organs is the direct way. But many scientists say the biggest impact of the new cells will be on the indirect way: using the cells to learn about diseases and then applying that knowledge to develop conventional drugs.

Using the new technique, scientists could take a skin cell from a person with a certain disease and generate stem cells. Those cells could then be turned into other cells, allowing the scientists to look at neurons from a person with Alzheimer’s disease, say, or heart cells from a person with heart failure. And a pharmaceutical company might get an early read on a new Alzheimer’s drug by trying it out on the newly created neurons.

“You cannot really go to a patient and say, ‘I want to study your brain,’” said Dr. Lorenz Studer, who works on neural stem cells at the Memorial Sloan-Kettering Cancer Center. “For the first time it gets us access to these cells.”

Some scientists have been trying to make disease-specific embryonic cells by creating a cloned embryo of a person with the disease. But that effort requires women to undergo sometimes risky treatments to donate their eggs.

Some diseased cells, like those from a tumor biopsy, are already available for study, but those are from a person already sick. The new approach would allow scientists to watch the disease as it developed and potentially design drugs not just to treat it but to prevent it.

“This is a whole new way of thinking about how we might investigate human disease,” said Kenneth S. Zaret, program leader for cell and developmental biology at the Fox Chase Cancer Center in Philadelphia.

Just this month, Israeli scientists reported in the journal Cell Stem Cell that they had created stem cell lines from embryos donated by families with a history of fragile X syndrome, a disease that leads to mental retardation and is caused by the silencing of a particular gene. Studying the stem cells, they got a better understanding of when and how this silencing occurred.

Still, it is not yet clear how useful this new approach will be. Will a neuron from an Alzheimer’s patient have to sit in a petri dish for 70 years before it becomes diseased? Or, as is the case with some diseases, will the neurons have to interact with other types of cells?

Moreover, scientists already have many tools to figure out causes of disease — imaging systems that can peer into cells, knockout mice, genome studies. But it is not always easy to translate knowledge about a disease into a treatment. And even if it were, it still takes years of testing in animals and people before a drug can reach the market.

The gene responsible for Huntington's disease was discovered in 1993, but there is still no cure. And the decoding of the human genome, contrary to some early expectations, has not led to a burst of new drugs, at least not yet.

When it comes to the direct approach, creating replacement cells and tissues for transplants, there are many challenges for both cells. Scientists do not envision transplanting embryonic stem cells themselves, either the real ones or the new close imitations, because they could turn into tumors inside the body.

So the idea is to differentiate the stem cells into specific types of cells. Scientists have made progress in creating some cell types, like the dopamine-producing neurons that might treat Parkinson's disease. Other cell types are proving more difficult, like insulin-producing islet cells to treat diabetes.

The transplanted cells must be very pure, because any remnants of the original stem cells might turn into tumors, said Dr. Steven A. Goldman, a neurologist at the University of Rochester. He and colleagues implanted dopamine-producing neurons derived from human embryonic stem cells into mice with Parkinson's disease. While their symptoms improved, they all got brain tumors.

Another challenge is to get the cells to hook up correctly with what is already in the body. Scientists at the Karolinska Institute in Sweden injected neural stem cells into rats with spinal cord injuries. The rats' motor ability improved, but the implant prompted nerve growth in a way that made even a slight touch painful.

Despite the challenges, two biotechnology companies hope next year to begin the first clinical trials of therapies derived from human embryonic stem cells. Geron plans to test a type of neural cell as a treatment for spinal cord injuries, and Advanced Cell Technology wants to plant retinal epithelium cells into the eye to treat retina diseases.

The new cells have a big strike against them. They were made by inserting four genes into skin cells, causing the cells to revert back to a blank slate.

But the viruses used to carry the genes into the cells incorporate themselves into the cells' DNA at random places, potentially causing mutations and cancers. And one of the genes used by the Japanese team is known to cause cancer.

The Food and Drug Administration "would never allow us to use those virally modified cells in patients," said Dr. Robert Lanza, the chief scientific officer of Advanced Cell Technology.

Scientists are exploring ways to reprogram the skin cells without those viruses. But any genetically engineered cell is likely to face scrutiny from the drug agency.

On the other hand, the new cells have one advantage over the embryonic cells. Stem cells can be derived from a patient's own skin cells, so tissue made from those stem cells would not be rejected by the immune system. Trying to do that with embryonic stem cells would require cloning.

Another possible advantage could be fewer intellectual property restrictions. Some scientists working with embryonic stem cells say their work has been encumbered by the requirement to get a license from the patent holder, the University of Wisconsin.

Wisconsin is applying for patent protection on the new technique but does not intend to require academic scientists to get a license.

"They can do it in their own lab," said Carl E. Gulbrandsen, the managing director of the Wisconsin Alumni Research Foundation, the university's patenting arm. "They don't have to tell me about it, and I don't really have to know."

Despite all the remaining challenges, scientists say there is no denying the magnitude of the advance made last week. "It's exciting, it's seminal, it's major — quite frankly I think it's potentially Nobel-level," said Dr. Kenneth R. Chien, director of the cardiovascular disease program at the Harvard Stem Cell Institute. "But there's still a lot more work to do."