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## Building a Better Cell

*Gladstone scientists report new method to make large numbers of cells from stem cells; could speed studies of embryonic development and congenital disease*

BY ANNE D. HOLDEN, PHD

A lot can go wrong during the earliest stages of pregnancy. For the newly fertilized egg to grow and mature requires a complex choreography of genes, proteins and signaling pathways that together guide the egg towards maturation. And while built-in redundancies protect the developing embryo during any missteps, some embryos are not so lucky, resulting in a devastating congenital birth defect or, in some cases, a miscarriage.

Scientists have long sought to understand how problems early in embryonic development lead to such defects. And while recent advances have filled in many gaps, there is much left to learn. But in a recent issue of the [American Journal of Stem Cells](#), scientists from the Gladstone Institutes describe a method they have developed to quickly and accurately generate a type of early-stage cell called *neural crest cells*. Problems with the development of these cells have been implicated in congenital birth defects. Importantly, these findings could pave the way for new research programs to understand how defects develop: day-by-day and cell-by-cell.

### Congenital Abnormalities and the Neural Crest

Neural crest cells play a starring role in early embryonic development. This class of cells, called ‘multipotent,’ are similar to stem cells in that during development they grow and differentiate into many types of cells, such as muscle, cartilage and bone cells. The healthy and timely maturation of neural crest cells into one of these cell types—and their physical migration to the appropriate location of the developing embryo—are critical. Abnormal development of neural crest cells has been linked to such birth defects as cleft palate and malformations of the heart and intestine.

But exactly how and why abnormal neural crest-cell development leads to such defects is an active area of scientific investigation, and is why many scientists are seeking new, powerful tools to study this link. Researchers in the laboratory of Gladstone cardiovascular and stem cell scientist [Bruce Conklin, MD](#) believe they have found a solution.

“When studying neural crest-cell development, it’s important to generate them in large quantities, but the recent advances in stem cell technology this was difficult to do,” said Dr. Conklin. “Even early stem-cell based methods were labor-intensive and produced low yields. But we’ve created a new method that lets us produce comparatively vast quantities of neural crest cells—and produce them quickly.”

## The LSB-Short Method

Dr. Conklin and his team developed their method by first building upon the work of their Gladstone colleague, Shinya Yamanaka, MD, PhD. In 2007, Dr. Yamanaka discovered how to transform human adult skin cells into cells virtually identical to embryonic stem cells—a discovery that earned him the [2012 Nobel Prize in Physiology or Medicine](#).

These so-called *induced pluripotent stem cells* or “iPS cells” represent an entirely new platform for fundamental studies of human disease. Rather than using models made in yeast, flies or mice for disease research, iPS cell technology allows human stem cells to be created from adult cells, such as skin cells. As a result, the iPS cells contain a complete set of the genes from that person—and thus represent the potential of a far-superior model for studying disease, testing new drugs and developing new treatments.

In this study, Dr. Conklin and his team harnessed iPS cell technology and developed a method that generates neural crest cells significantly faster than in previous methods.

This method, dubbed the “LSB-short” method, is similar to a previously published method called LSB, which induces the formation of neural crest cells from stem cells over about two weeks. However, recent research suggested that once the stem cells were primed, they didn’t need as much time to be coaxed into becoming neural stem cells. So the team shortened this second step by half.

“In this way, we could generate bona fide, fully functional neural crest cells—both from human iPS cells and human embryonic stem cells—in just eight days,” explained Faith Kreitzer, PhD, the paper’s lead author.

Neural crest cells must not only grow and differentiate into specific cell types as the embryo matures. They must also physically migrate—often great distances—to the appropriate location where they can continue to develop into a muscle, bone or cartilage cell. Drs. Conklin and Kreitzer, therefore, had to ensure that the neural crest cell they generated *looked* like a natural neural crest cell and that it behaved like one.

“Luckily, the newly generated neural crest cells responded to the appropriate chemical cues at the appropriate times,” said Dr. Conklin. “For all intents and purposes, these cells were indistinguishable from natural ones.”

There are many applications of this new LSB-short technology, but importantly the research team hopes that this method can serve as a resource for those looking to produce large quantities of neural crest cells for research into their basic cell biology and for regenerative medicine.

Added Dr. Kreitzer, “We hope that our method can help researchers like us study the mechanisms behind neural crest biology and disease patient-by-patient to treat—and someday even prevent—neural crest-related congenital defects.”