Scientists replicate diseases in the lab with new stem cell lines

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A set of new stem cell lines will make it possible for researchers to explore ten different genetic disorders—including muscular dystrophy, juvenile diabetes, and Parkinson's disease—in a variety of cell and tissue types as they develop in laboratory cultures.

Researchers led by Howard Hughes Medical Institute investigator George Q. Daley have converted cells from individuals with the diseases into stem cells with the same genetic errors. These newly-created stem cells will allow researchers to reproduce human tissue formation in a Petri dish as it occurs in individuals with any of the ten diseases, a vast improvement over current technology. Like all stem cells, these disease-specific stem cells grow indefinitely, and scientists can coax them into becoming a variety of cell types.

Daley, who is at Children's Hospital Boston, worked with researchers from Harvard Medical School, Massachusetts General Hospital, and the University of Washington to create the disease-specific stem cell strains. The scientists will make the cell lines available to scientists worldwide through a core facility funded by the Harvard Stem Cell Institute. Daley and his colleagues published the details of the disease-specific stem cell lines in an advanced online publication of the journal *Cell* on August 7, 2008.

"Researchers have long wanted to find a way to move a patient's disease into the test tube, to develop cells that could be cultured into the many tissues relevant to diseases of the blood, the brain and the heart, for

example," he says. "Now, we have a way to do just that—to derive pluripotent cells from patients with disease, which means the cells can make any tissue and can grow forever. This enables us to model thousands of conditions using classical cell culture techniques."

Daley's team has created disease-specific stem cell lines for Duchenne muscular dystrophy; Becker muscular dystrophy; juvenile-onset (type I) diabetes; Parkinson's disease; Huntington's disease; Down's syndrome; ADA severe combined immunodeficiency (a form of the disorder commonly known as "boy-in-the-bubble disease"); Shwachman-Bodian-Diamond syndrome (which causes bone marrow failure and a predisposition to leukemia); Gaucher disease (an inherited metabolic disorder in which a fatty substance accumulates in several of the body's organs); and Lesch-Nyhan syndrome (an enzyme deficiency that causes a build-up of uric acid in body fluids). Many more cell lines are possible.

For years, researchers have grown human cells in the laboratory in an attempt to mimic various genetic diseases, but the available techniques had significant shortcomings. Cells taken directly from affected patients typically have a limited lifespan when grown in laboratory dishes, restricting the types of studies for which they can be used. Researchers often turn to cells that have been modified to make them live in a dish forever, but altering cells to make them immortal changes their physiology and can cast doubt on a study's results.

Recently, Daley's lab and others have demonstrated that adult cells can be converted to stem cells by introducing a set of genetic "reprogramming factors." To produce the disease-specific stem cells, Daley and his colleagues mixed cells from patients with the ten disorders with benign viruses to introduce the reprogramming factors into the cells. The resulting stem cells harbored the genetic diseases of the donors.

Once the researchers isolated the disease-specific stem cells, they analyzed the genes and confirmed that the stem cells had the same disease-causing defects as the original donor cells. The researchers also made sure that the stem cells were pluripotent—able to differentiate into many different tissue types.

Daley says that in many cases these new stem-cell cultures will mimic human disease more reliably than animal models. Despite the vast genetic similarities between humans and mice, physiological differences invariably affect the course of disease in a mouse. In some cases, the genetic defect that produces a disorder in humans—such as Down's syndrome—does not cause the same symptoms in mice. Therefore, human cell cultures are an essential complement to research with animal models, Daley says.

The most immediate application of the disease-specific stem cells will be to reproduce human diseases in culture to explore their development in different tissues, Daley says. The technique will even enable researchers to compare how the same disease varies among people, by generating disease-specific stem cell cultures from many individuals. The cells will also offer a proving ground for screening drugs to treat disease.

Over the longer term, Daley expects the technique will be applied clinically. For example, it may allow scientists to develop therapies using a patient's own cells--reengineering the cells to correct a disease-causing defect then re-introducing them into the body.

The Harvard Stem Cell Institute will make the stem cell lines available to the scientific community as quickly as possible, Daley says. The institute will also continue to work to generate cell lines for other diseases.

Daley and his colleagues' techniques for reprogramming adult cells are readily available so other researchers can generate their own disease-

specific stem cell lines. However, "Stem cells are quite finicky," Daley cautions. "They don't grow like weeds; they're more like orchids. You really have to tend to them." Therefore, he plans to collaborate with researchers at other institutions to help produce stem-cell lines for the diseases they want to study.

Source: Howard Hughes Medical Institute