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Study advances use of stem cells in personalized medicine

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Johns Hopkins researchers report concrete steps in the use of human stem cells to test how diseased cells respond to drugs. Their success highlights a pathway toward faster, cheaper drug development for some genetic illnesses, as well as the ability to pre-test a therapy's safety and effectiveness on cultured clones of a patient's own cells.

The project, described in an article published November 25 on the website of the journal *Nature Biotechnology*, began several years ago, when Gabsang Lee, D.V.M., Ph.D., an assistant professor at the Johns Hopkins University School of Medicine's Institute for Cell Engineering, was a postdoctoral fellow at Sloan-Kettering Institute in New York. To see if induced pluripotent stem cells (iPSCs) could be used to make specialized disease cells for quick and easy drug testing, Lee and his colleagues extracted cells from the skin of a person with a rare genetic disease called Riley-Day syndrome, chosen because it affects only one type of nerve cell that is difficult if not impossible to extract directly from a traditional biopsy. These traits made Riley-Day an ideal candidate for alternative ways of generating cells for study.

In a so-called "proof of concept" experiment, the researchers biochemically reprogrammed the skin cells from the patient to form iPSCs, which can grow into any cell type in the body. The team then induced the iPSCs to grow into nerve cells. "Because we could study the nerve cells directly, we could for the first time see exactly what was going wrong in this disease," says Lee. Some symptoms of Riley-Day syndrome are insensitivity to pain, episodes of vomiting, poor

coordination and seizures; only about half of affected patients reach age 30.

In the recent research at Johns Hopkins and Memorial Sloan-Kettering, Lee and his co-workers used these same lab-grown Riley-Day nerve cells to screen about 7,000 drugs for their effects on the diseased cells. With the aid of a robot programmed to analyze the effects, the researchers quickly identified eight compounds for further testing, of which one—SKF-86466—ultimately showed promise for stopping or reversing the disease process at the cellular level.

Lee says a clinical trial with SKF-86466 might not be feasible because of the small number of Riley-Day patients worldwide, but suggests that a closely related version of the compound, one that has already been approved by the U.S. Food and Drug Administration for another use, could be employed for the patients after a few tests.

The implications of the experiment reach beyond Riley-Day syndrome, however. "There are many rare, 'orphan' genetic diseases that will never be addressed through the costly current model of drug development," Lee explains. "We've shown that there may be another way forward to treat these illnesses."

Another application of the new stem cell process could be treatments tailored not only to an illness, but also to an individual patient, Lee says. That is, iPSCs could be made for a patient, then used to create a laboratory culture of, for example, pancreatic cells, in the case of a patient with type 1 diabetes. The efficacy and safety of various drugs could then be tested on the cultured cells, and doctors could use the results to help determine the best treatment. "This approach could move much of the trial-and-error process of beginning a new treatment from the patient to the petri dish, and help people to get better faster," says Lee.

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