

# Human Skin Cells Converted Directly into Functional Neurons

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Technique moves researchers closer to replacement cell therapy for Alzheimer's and other neurodegenerative diseases; the cells may prove useful for testing new therapeutic leads.

NewsWire — (NEW YORK, NY, (August 4, 2011) – Columbia University Medical Center researchers have for the first time directly converted human skin cells into functional forebrain neurons, without the need for stem cells of any kind. The findings offer a new and potentially more direct way to produce replacement cell therapies for Alzheimer's and other neurodegenerative diseases. Such cells may prove especially useful for testing new therapeutic leads. The study was published in the August 4 online issue of the journal *Cell*.

In another first, the researchers used this method — called direct reprogramming — to generate neurons from skin cells of patients with familial (early-onset) Alzheimer's disease. The induced neurons were found to differ significantly from those made from healthy individuals, providing new insights into the development of the disease, reports study leader Asa Abeliovich, MD, PhD, associate professor of pathology & cell biology and neurology in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University Medical Center (CUMC).

In the 1980s and 90s, scientists realized that embryonic stem cells, because of their pluripotency (ability to develop into any kind of cell) and capacity for self-renewal, might be useful in regenerating or replacing tissue after injury or disease. However, the use of cells from human embryos raised ethical issues, triggering a search for alternatives.

A breakthrough came in 2007, when researchers determined how to genetically reprogram human skin cells to become induced pluripotent stem (iPS) cells, which are similar to naturally pluripotent cells. Although this advance allowed researchers to avoid using embryonic stem cells, iPS technology remains complex, inefficient, and time-consuming. Moreover, the pluripotent stem cells by their nature are capable of forming tumors, leading to potential safety concerns.

In 2010, Stanford University researchers reported turning mouse skin cells directly into neurons using transcription regulators (proteins that switch genes on or off), bypassing the need to create iPS cells.

Building on that work, Dr. Abeliovich and his team used a different combination of transcription regulators, plus several neuronal support factors, to convert human skin cells into forebrain neurons. The induced neurons appear to be the same as ordinary neurons, judging from electrophysiological testing and gene expression profiling. The researchers also showed that the neurons are able to send and receive signals in laboratory culture and when transplanted into the central nervous system of mice. These findings indicate that the induced neurons are capable of neuronal activity.

"Direct reprogramming is fundamentally different from making neurons with iPS technologies," says Dr. Abeliovich. "Using direct reprogramming, you could, in theory, take someone's skin cells and in a couple of weeks have fully functional neurons ready for replacement cell therapy."

"Although the project is still at early stages and certainly not ready for clinical applications, therapies based on direct reprogramming seem more realistic than those based on iPS technology. "What is particularly exciting," says Dr. Abeliovich, "is that direct reprogramming is broadly applicable to the study and treatment of a host of neurological diseases."

In the second part of the study, Dr. Abeliovich compared neurons made from skin cells of healthy individuals with neurons made from patients with early-onset Alzheimer's disease. The latter cells exhibited altered processing and localization of amyloid precursor protein (APP) and increased concentration of amyloid beta, a component of APP (Alzheimer's is thought to develop when abnormal amounts of amyloid beta accumulate in the brain, eventually killing neurons.) APP was found to collect in the cells' endosomes, cellular compartments that sort molecules for degradation or recycling. These findings suggest that this form of Alzheimer's is caused, at least in part, by abnormal endosomal function, the researchers report.

Dr. Abeliovich's paper is entitled, "Directed Conversion Of Alzheimer's Disease Patient Skin Fibroblasts Into Functional Neurons." His coauthors are Liang Qiang, Ryoujoke Fujita, Toru Yamashita, Herve Rhinn, David Rhee, Claudia Doege, Lily Chau, and William B. Vanti at CUMC and Sergio Angulo and Herman Moreno at the State University of New York Downstate Medical Center, Brooklyn, N.Y.

The New York State Stem Cell Science (NYSTEM), among others, provided funding for the study.

The authors declare no financial or other conflicts of interest.

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The Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University Medical Center is a multidisciplinary group that has forged links between researchers and clinicians to uncover the causes of Alzheimer's, Parkinson's and other age-related brain diseases and discover ways to prevent and cure these diseases. It has partnered with the Gertrude H. Sergievsky Center at Columbia University Medical Center which was established by an endowment in 1977 to focus on diseases of the nervous system. The Center integrates traditional epidemiology with genetic analysis and clinical investigation to explore all phases of diseases of the nervous system. For more information about these centers visit: <http://www.cumc.columbia.edu/dept/taub/>  
<http://www.cumc.columbia.edu/dept/sergievsky/>

Columbia University Medical Center provides international leadership in basic, pre-clinical and clinical research, in medical and health sciences education, and in patient care. The medical center trains future leaders and includes the dedicated work of many physicians, scientists, public health professionals, dentists, and nurses at the College of Physicians and Surgeons, the Mailman School of Public Health, the College of Dental Medicine, the School of Nursing, the biomedical departments of the Graduate School of Arts and Sciences, and allied research centers and institutions. Established in 1767, Columbia's College of Physicians and Surgeons was the first institution in the country to grant the M.D. degree and is among the most selective medical schools in the country. Columbia University Medical Center is home to the largest medical research enterprise in New York City and State and one of the largest in the United States.

## Channels:

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## Description

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## Citations

*Cell*