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Developing Stem  
Cell Models of  
Schizophrenia

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# The Friedman Brain Institute

[www.mountsinai.org/fbi](http://www.mountsinai.org/fbi)

## Compassionate Care, Pioneering Research

A major challenge in brain research, by comparison to other medical disciplines, is the difficulty in obtaining brain biopsies, which has dramatically limited our ability to study disease pathogenesis. Another challenge is the unique difficulty in generating animal models, because key symptoms of most brain disorders cannot be accurately recapitulated in animals.

Additionally, the genetic complexity of these conditions—the likely involvement of many hundreds of genes even in a single patient—further complicates the ability of modeling human risk in animals.

This issue of The Friedman Brain Institute newsletter focuses on a complementary research approach—the ability to induce neurons and glial cells from a patient's skin biopsy or blood. While this technology is still in early stages of development, it offers great promise in better

understanding complex brain disorders and in generating improved treatments.

We also invite you to explore Mount Sinai's growing and vibrant neuroscience research and clinical community on our new website: [www.mountsinai.org/fbi](http://www.mountsinai.org/fbi).



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### RESEARCH FRONTIERS

## Understanding Disease Progression Using Induced Neurons from Patients

It is generally impossible—with the exception of brain cancer and rare infections—to obtain brain biopsies from patients with a range of central nervous system (CNS) disorders. Moreover, while postmortem material can reveal a great deal about the brain at the end of a long illness, it might teach us much less about the underlying causes that initiate a disease.

Now, technological advances have made it possible to generate neurons from a person's skin biopsy or blood. This involves culturing patient cells and reprogramming them into induced pluripotent stem cells (iPSCs), that is, stem cells that are capable of giving rise to virtually any cell type. The key discovery that has enabled this new approach was the observation that overexpressing a combination of four transcription factors—OCT3/4, SOX2, c-MYC, and KLF4 in almost any cell

type—yields iPSCs. Those iPSCs can then be differentiated into a cell type of choice, including a neuron or glial cell.

With these advances, scientists have gained the ability to make neurons or glia from patients who have genetically complex brain diseases that are particularly challenging to create in animal models. Such induced neurons or glia, in comparison to those from unaffected family members or control subjects, might make it possible to recapitulate aspects of disease progression in the laboratory (so-called "disease in a dish") and to test new strategies for disease treatment.

*Already, stem cell-derived neurons are being used in clinical trials of spinal cord injury or macular degeneration.*

Scientists at The Friedman Brain Institute—working in close conjunction with researchers in The Black Family Stem Cell Institute, led by Ihor Lemischka, PhD, whose own research program focuses on turning stem cells into blood and heart cells—have been among the first to employ these new technologies to study CNS diseases. While scientists have noted early advances, much work is needed to further improve these methods.

The cells that can be generated today from iPSCs or related approaches are relatively immature, being more similar to fetal human neurons or glia rather than adult

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## ► Understanding Disease Progression Using Induced Neurons from Patients *(continued from page 1)*

cells. Scientists at Mount Sinai and around the world are working to find new ways to rapidly mature induced neurons and glia and to develop methods to generate specific classes of cells, such as glutamatergic, or GABAergic, or dopaminergic neurons, which are particularly relevant to human disease.

Induced neurons and glia promise several transformative advances. They provide a novel means of studying disease

pathophysiology, as noted. Secondly, scientists are finding ways to generate functional 3D neuronal networks in the laboratory. These miniature “brains-in-a-dish” could conceivably be used for high-throughput screening to identify new therapies for complex CNS diseases. Induced neurons or glia could also conceivably be used as a cell therapy to replace or compensate for those damaged in disease. Already, stem cell-derived neurons are

being used in clinical trials of spinal cord injury or macular degeneration. We envision a time when induced neurons could be used in therapies for a range of disorders, such as Parkinson’s or Alzheimer’s disease.



**Ihor Lemischka, PhD**

Director, The Black Family Stem Cell Institute; and Lillian and Henry M. Stratton Professorial Chair

## Developing Stem Cell Models of Schizophrenia

Schizophrenia is a common and debilitating psychiatric disorder. No cure exists and the current treatments improve only some of the disabling symptoms of the syndrome. Moreover, schizophrenia cannot be accurately modeled in laboratory animals because core symptoms of schizophrenia, such as hallucinations and delusions, are inaccessible in animals, and because the syndrome—even in a single patient—results from hundreds of genetic variations.

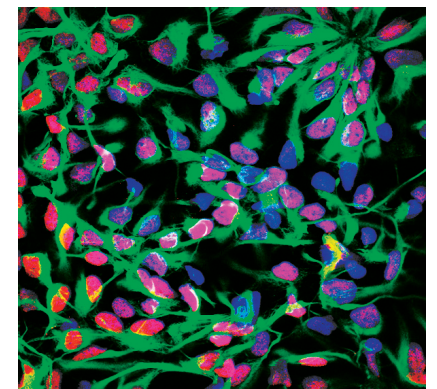
Friedman Brain Institute scientist Kristen Brennand, PhD, has led the field in developing stem cell models of schizophrenia, and has identified abnormalities in neuronal morphology, synapse formation, and migration in induced neurons from patients. Today,

Dr. Brennand and colleagues are using global measures of gene expression and synaptic function to understand the complex genetic architecture contributing to overall genetic risk for schizophrenia, as well as genetic contributions to treatment responsiveness. The team is also using modern genome engineering technologies, which make it feasible to swap risk-associated alleles into and out of iPSC lines to test the functional effects of individual genes, work that may pave the way for individualized treatment strategies based on a patient’s genotype.



**Kristen Brennand, PhD**

Assistant Professor, Psychiatry, and Neuroscience



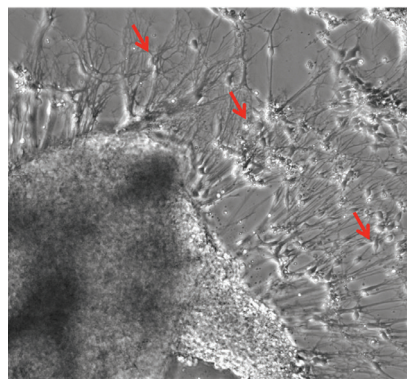
**Neural progenitor cells derived from patients with schizophrenia**

iPSC neurons are shown expressing the neural stem cell proteins SOX2 (red) and NESTIN (green). Nuclei are stained with DAPI (blue). Magnification is 630X.

## Changing the Field of Stem Cell-Based Research in Parkinson’s Disease

A philanthropic commitment of \$5 million has enabled Thomas Zwaka, MD, PhD, to launch the Huffington Foundation Center for Cell-Based Research in Parkinson’s Disease at Mount Sinai. The grant will allow Dr. Zwaka and colleagues to pursue several lines of investigation, including the development of a novel *ex vivo* model of the human central nervous system (midbrain organoids) and the study of engrafted cells in this system.

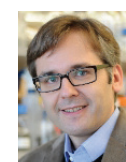
This multifaceted approach will encompass work on several different cell types—direct reprogramming of adult stem cells, iPSCs, and, most importantly, patient-specific embryonic stem cells—and the use of these cells to improve differentiation methods and to screen both drugs and genomes for factors that influence cell behavior and disease.



**Differentiation of human iPSCs into neuronal cells**

The development of the depicted cells (noted by red arrows) is biased toward midbrain neurons, which degenerate in Parkinson’s disease.

The Houston-based Huffington Foundation’s gift to Mount Sinai will enable Dr. Zwaka’s team to leverage Mount Sinai’s collaborative culture to fundamentally change the field of stem cell-based research and therapies in Parkinson’s disease. Because Parkinson’s disease is caused by the relatively selective death of a single type of neuron in the brain—midbrain dopamine neurons—it may be particularly amenable to stem cell therapies where induced neurons replace the dying cells.



**Thomas Zwaka, MD, PhD**

Senior Faculty, Developmental and Regenerative Biology

## Using a “Big-Data” Approach to Studying Stem Cells in Alzheimer’s Disease

A consortium of Mount Sinai laboratories, supported through the new “Accelerated Medicines Partnership” of the National Institutes of Health, is focused on the use of induced neurons to better understand and treat Alzheimer’s disease. The consortium includes Eric Schadt, PhD; Bin Zhang, PhD; and their colleagues in the Icahn Institute of Genomics and Multiscale Biology; Sam Gandy, MD, PhD, in the Department of Neurology, and Psychiatry; and Vahram (Harry) Haroutunian, PhD, in the Department of Psychiatry, and Neuroscience.

The investigators are utilizing a multifaceted approach to identify previously unappreciated

mechanisms of disease pathogenesis. This is accomplished by obtaining DNA sequence information from hundreds of patients, coupled with global gene expression patterns in the same patients’ induced neurons and glial cells. These data are further enhanced by comparisons to gene expression profiles in Mount Sinai’s large collection of postmortem brains of people with Alzheimer’s disease, coupled with studies of new induced neurons from those same postmortem samples. Together, this “big-data” approach has already revealed new insight into the range of biochemical pathways that are abnormal in Alzheimer’s disease. For example, it has helped uncover the involvement of particular

immune-related genes—TYROBP (TYRO protein tyrosine kinase-binding protein) and TREM2 (triggering receptor expressed on myeloid cells 2). Such discoveries are now driving novel approaches to therapeutics of this devastating disorder.



**Sam Gandy, MD, PhD**  
Mount Sinai Professor in Alzheimer’s Research; and Associate Director, Mount Sinai Alzheimer’s Disease Research Center



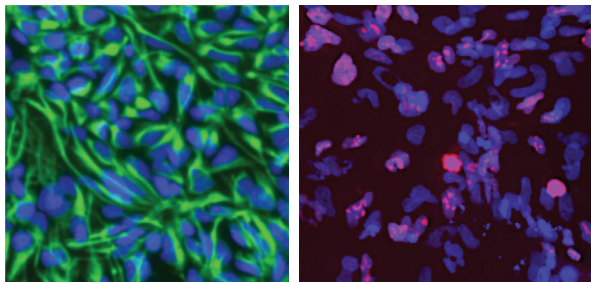
**Harry Haroutunian, PhD**  
Professor, Psychiatry, and Neuroscience



**Eric Schadt, PhD**  
Director, Icahn Institute for Genomics and Multiscale Biology; Chair, Genetics and Genomic Sciences; and Jean C. and James W. Crystal Professor of Genomics



**Bin Zhang, PhD**  
Associate Professor, Genetics and Genomic Sciences



Left: Immunostaining of neural progenitor cells from skin fibroblasts of a 38-year-old man with a mutation in the PSEN1 gene, which causes Alzheimer’s Disease. Green, NESTIN (a marker of neural progenitor cells); blue, DAPI (a marker of nuclei)

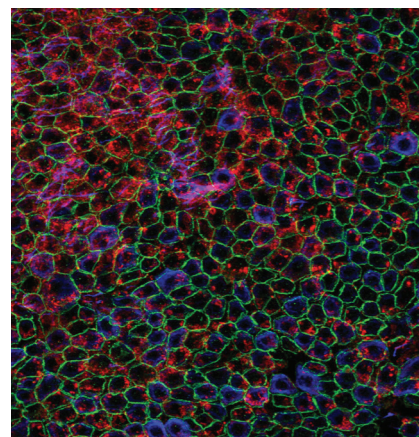
Right: Immunostaining of neural progenitor cells from an 18-year-old unaffected brother stained for the cell cycle marker Ki67 (pink) and nuclei (blue)

Images courtesy of Sam Gandy, MD, PhD; and Andrew Sproul, PhD, and Scott Noggle, PhD, of the New York Stem Cell Foundation

## Discovering Unique Genetic and Epigenetic Alterations in Glioblastomas

Glioblastomas, the most common adult primary brain tumors, are universally fatal. In recent years, we have learned a lot about the molecular characteristics of glioblastomas, yet the pathobiology of these deadly tumors is still unclear. One reason for this gap of knowledge is our poor understanding of the endogenous, preneoplastic precursors to glioblastomas.

A major research interest of Nadejda (Nadia) Tsankova, MD, PhD, is to better define the cellular and molecular phenotype of stem cells present in normal brain and their role in gliomagenesis. The Tsankova laboratory has developed unique, translational methodology for isolating glial progenitor (stem) cells from human brain, and is now working to isolate endogenous neural progenitors from pediatric and adult human brain tissue by use of fluorescence-activated cell sorting.



Photomicrograph of adult human subventricular zone showing cobblestoning of ependymal cells (β-catenin in green) in intimate association with glial cells (GFAP in blue, CD44 in red), a subpopulation of which may represent quiescent glial progenitor cells

Dr. Tsankova and colleagues are defining the epigenetic and transcriptional signatures of these progenitor cell types and studying their functional properties. They have found distinct epigenetic changes at specific developmentally regulated gene promoters, which might predispose a subset of glial progenitors in the subventricular zone in the brain toward a neoplastic fate. Discovering unique genetic and epigenetic alterations in such preneoplastic glia within their *in vivo* niche will allow the group to identify biomarkers for early detection and more effective treatment of human gliomas, including glioblastomas.



**Nadia Tsankova, MD, PhD**  
Assistant Professor, Pathology, and Neuroscience

PHOTO ESSAY

## Confocal Images of Neurons Derived from Patients with Schizophrenia

Such induced neurons express  $\beta$ 3-tubulin (red) and the dendritic marker MAP2AB (green). DAPI (blue) marks cell nuclei. 400x magnification

Image from the lab of Kristen Brennand, PhD, Assistant Professor,  
Psychiatry, and Neuroscience

