



The Friedman Brain Institute

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Compassionate Care, Pioneering Research

The Friedman Brain Institute is one of the world's premier institutions dedicated to advancing our understanding of brain and spinal cord disorders, and driving innovative approaches to new treatments and diagnostic tests, through translational research.

It is impossible to overstate the impact of diseases of the brain and spinal cord on society. The World Health Organization has determined that five out of the top ten causes of disease burden worldwide are brain disorders: depression; Alzheimer's disease and other dementias; psychosis (schizophrenia and bipolar disorder); stroke; and addictions. This preponderance of nervous system illnesses is likely to grow as scientists around the world improve treatments for other common medical conditions, such as cancer and cardiovascular disease. In medicine, nothing can have a greater positive impact on humanity than conquering brain and spinal cord disorders.

The Friedman Brain Institute (FBI) at Mount Sinai is committed to making a profound difference in advancing treatments through translational research. For too long, academic investigators have been content to publish their findings in scientific journals and to leave the translational potential of their discoveries to others. However, after six decades with few advances in diagnostics and therapeutics for nervous system disorders, we need a new paradigm. Academic investigators must take ownership and responsibility for this process and work with industry colleagues on ensuring the effective translation of basic research findings into clinical improvements. The complexity of the nervous system means that

this task will be far more difficult for brain and spinal cord than for most other organ systems. Yet, if we are not able to achieve this goal, who will?

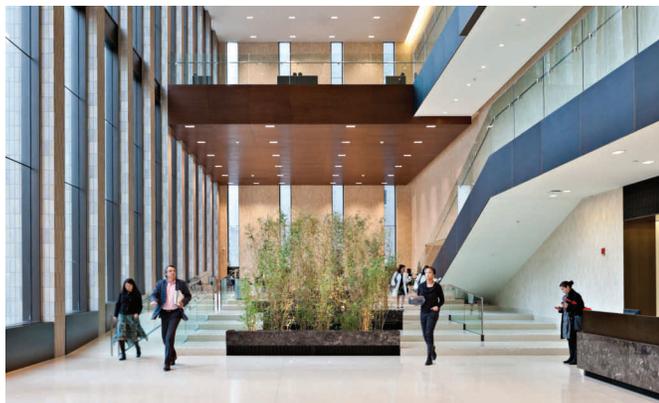
This issue of the FBI newsletter will focus on a great milestone for Mount Sinai and the FBI: the opening of the Leon and Norma Hess Center for Science and Medicine, which will facilitate a once-in-a-generation expansion of neuroscience research at Mount Sinai. We will highlight how the Hess Center and key senior faculty recruits, such as Schahram Akbarian, MD, PhD, and Paul Slesinger, PhD, will lead us to greater success in translating basic science into transformative clinical treatments.



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MILESTONES IN SCIENCE AND EDUCATION

A New Center, a New Name, a Bold New Mount Sinai



The opening of the Leon and Norma Hess Center for Science and Medicine has allowed The Friedman Brain Institute to greatly increase its capacity for basic science and clinical research.

December 13, 2012, marked a great day for Mount Sinai: the opening of the Leon and Norma Hess Center for Science and Medicine, as well as the unveiling of a new logo and the rebranding of The Mount Sinai Medical Center. This coincided with the renaming of Mount Sinai School of Medicine to the Icahn School of Medicine at Mount Sinai, in recognition of transformational support by long-time Mount Sinai Boards of Trustees member, Carl C. Icahn. These milestones further develop Mount Sinai's commitment to being one of the nation's premier institutions to study and treat human disease.

The Friedman Brain Institute (FBI) occupies the top two floors of the Hess Center, which together comprise approximately 55,000 square-foot of laboratory and office space. This increases the research footprint of the FBI by about one-third, and will have a significant impact in helping us achieve our goal of building the FBI into one of the nation's

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Paul A. Slesinger, PhD, Joins Mount Sinai to Lead Addiction Research

The complex communication among the approximate 100 billion neurons that form a single human brain depends upon minute electrical signals that are generated in each neuron. For more than 15 years, Paul A. Slesinger, PhD, recruited to Mount Sinai in

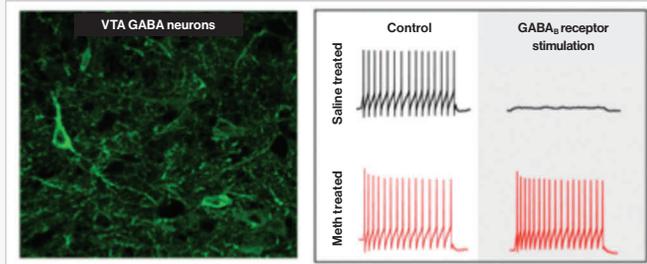


Figure generated by Dr. P.A. Slesinger (modified from Padgett et al., *Neuron* 2012)

Figure: Acute effect of methamphetamine on the brain's reward pathway

Left: GABA inhibitory neurons (labeled green) in the VTA; *Right:* electrical activity of VTA GABA inhibitory neurons from a saline-injected or methamphetamine-injected mouse. Activation of the GABA_B receptor normally silences electrical activity of these neurons, but has no effect in a mouse 24 hours after receiving methamphetamine.

2012 from the Salk Institute for Biological Studies in La Jolla, California, has been studying the function of small proteins, known as ion channels, which are essential for controlling the electrical properties of neurons. Dr. Slesinger recently joined Mount Sinai as Professor of Neuroscience, and he also will direct a new Center of Excellence on Addictions.

The Slesinger laboratory is focusing on one of the fundamental pathways for inhibition in the brain, crucial for all brain functions.

This inhibition is mediated in part by neurotransmitters that activate G protein-coupled receptors (GPCRs), which, in turn, activate G protein-gated potassium ion channels, referred to as "GIRK" channels. Dr. Slesinger and colleagues have uncovered

novel principles in G protein signaling, pioneering the concept of a macromolecular signaling complex, in which the channel partners directly with the GPCR and other signaling proteins. These findings challenged the prevailing view that proteins freely diffuse in the plasma membrane and have become a new, accepted paradigm for G protein signaling.

In recent years, the Slesinger laboratory translated this basic knowledge into new insight for the biology of addiction.

The central components of the brain associated with drugs of abuse are the ventral tegmental area (VTA), nucleus accumbens, medial prefrontal cortex, amygdala, and hippocampus, which are all part of the brain's natural reward pathway. The acquisition of addictive behaviors involves neuroadaptations within this pathway. In the VTA, certain

receptors for the neurotransmitter GABA (γ -aminobutyric acid), termed GABA_B receptors, and GIRK channels comprise a prominent inhibitory pathway. Recently, Dr. Slesinger and coworkers discovered that brief exposures to psychostimulant drugs of abuse in mice produce a profound depression of GABA_B-GIRK signaling that remains evident for at least a week, long after the drug has been cleared from the brain. This depression is selective for GABA-containing neurons in the VTA and is not seen in VTA dopamine neurons or GABA neurons in other brain regions. These VTA GABA neurons lose the ability to regulate their firing (see Figure) and release more than the usual amount of their inhibitory neurotransmitter. The Slesinger laboratory found that psychostimulants produce this persistent cellular memory trace in VTA GABA neurons by regulating a key protein phosphatase that alters the phosphorylation state of the GABA_B receptor. Current efforts are directed at understanding the consequences of this suppressed GABA_B-GIRK signaling in addiction-related behaviors with the goal of translating this discovery into a new treatment.



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➤ A New Center, a New Name, a Bold New Mount Sinai *(continued from page 1)*

foremost brain-science institutes. In total, the Hess Center has nearly a half million square-feet of outpatient clinical space, research laboratories across numerous disciplines, and advanced diagnostic imaging technology, and it uniquely brings together physicians and scientists in one location to facilitate multidisciplinary research and foster innovative translational discoveries.

Since the FBI's founding in 2008, we have recruited 25 basic neuroscience research faculty and 17 clinical neuroscience research faculty to Mount Sinai, greatly enabled by the Hess Center and generous philanthropic support. Major areas of growth have included efforts in genetics, epigenetics, neurophysiology, cognitive neuroscience, and neural stem cells, as applied to a wide range of nervous system conditions, including aging, Alzheimer's

disease, depression, drug addiction, multiple sclerosis, Parkinson's disease, schizophrenia, and spinal cord injury. We will complete this major recruitment phase over the next two years, by focusing on building a world-class brain-imaging center and strengthening our efforts still further in cognitive neuroscience and stem-cell biology.

This expansion of our research capabilities could not have been attained without Mount Sinai's commitment to recruiting a large number of leading clinicians and the subsequent growth and development of many associated clinical programs throughout the neurosciences, including those in the departments of neurology, neurosurgery, ophthalmology, psychiatry, and rehabilitation medicine.

Schahram Akbarian, MD, PhD, Heads New Division of Psychiatric Epigenomics

During the last several decades, researchers have examined the approximately 20,000 genes that comprise the human genome in an attempt to discover what causes disease. However, while psychiatric syndromes such as schizophrenia, bipolar disorder, depression, autism, and several dementias are all highly heritable, it has been difficult with currently available technology to identify the variations in DNA sequence that cause each illness.

There is a growing perception in the field that to understand both normal brain function and the mechanisms of psychiatric disease, researchers need to build upon studies of the linear sequence of DNA and consider changes in its organization within the cell nucleus, a process known as epigenomics.

Scientists in the new Division of Psychiatric Epigenomics at Mount Sinai are focusing on the material in a cell nucleus that molds and shapes the human genome into myriads

of gene expression and other units, what scientists call the *epi* (Greek for “over” or “above”) genome. The epigenome contains hundreds of different types of epigenetic marks, including many forms of DNA methylation (where the DNA is chemically modified by addition of a methyl group without changing the linear DNA sequence); histone modifications (where histone proteins, around which DNA is wrapped, are chemically modified by methylation or acetylation, for example); and chromosomal looping (where distant stretches of DNA are brought into close proximity to form a functional unit).

Led by Schahram Akbarian, MD, PhD, Professor of Psychiatry, and Neuroscience, the Division plans to study the epigenome in postmortem human brain, including changes during development and disease, as well as in genetically engineered mice that have mutations in key control genes that structure large portions of the genome. Dr. Akbarian was recruited

to Mount Sinai from the University of Massachusetts where he was Director of the Brudnick Neuropsychiatric Research Institute.

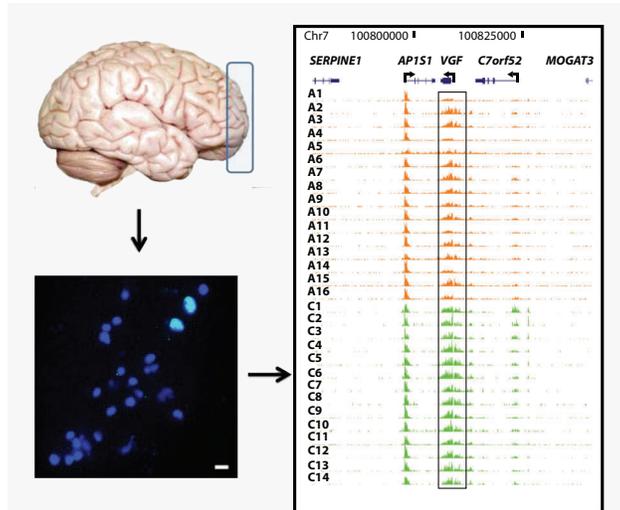
His team has constructed some of the first “epigenetic risk maps” for neurons from the brains of subjects diagnosed with schizophrenia or autism (see Figures). They were also the first to identify a histone methyltransferase enzyme (called “Eset” or “Setdb1”) that when overexpressed selectively in mouse neurons, conveys increased resilience to stressful environments, providing a novel target for antidepressant drug development. In a related project involving the United States, Switzerland, and Russia, Dr. Akbarian’s team has identified hundreds of short DNA sequences defined by epigenetic signatures and chromatin architectures unique to human neurons

and not shared with other primates. This work is important given that neurons, with their intricately complex circuitries, are ultimately at the core of our unique cognitive abilities and probably also our vulnerability for a range of “human-specific” conditions, such as autism and Alzheimer’s disease. The team’s findings, recently published in *PLoS Biology*, are significant because many human-specific epigenetic signatures are now providing researchers with new leads on the evolution of the human brain and the genesis of brain diseases.

For example, some of these human neuron signatures are absent even in the genomes of other Hominids (extinct species that are the closest relatives to humans, such as Neanderthal and Denisovan), whose genomes were recently sequenced as a follow-up to the human genome project. “Understanding how the epigenome of neurons and other brain cells is regulated during the course of normal development, and how they may be altered in disease, is the key to developing the next generation of therapies to treat psychiatric and neurological diseases,” says Dr. Akbarian.



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Figures, with slight modifications, from Shulha et al., (2012) *JAMA Psychiatry* 69:314–324 and Cheung et al., (2010) *Proc Natl Acad Sci USA* 107:8824–8829.

Figures: Exploring neuronal epigenomes from human brain

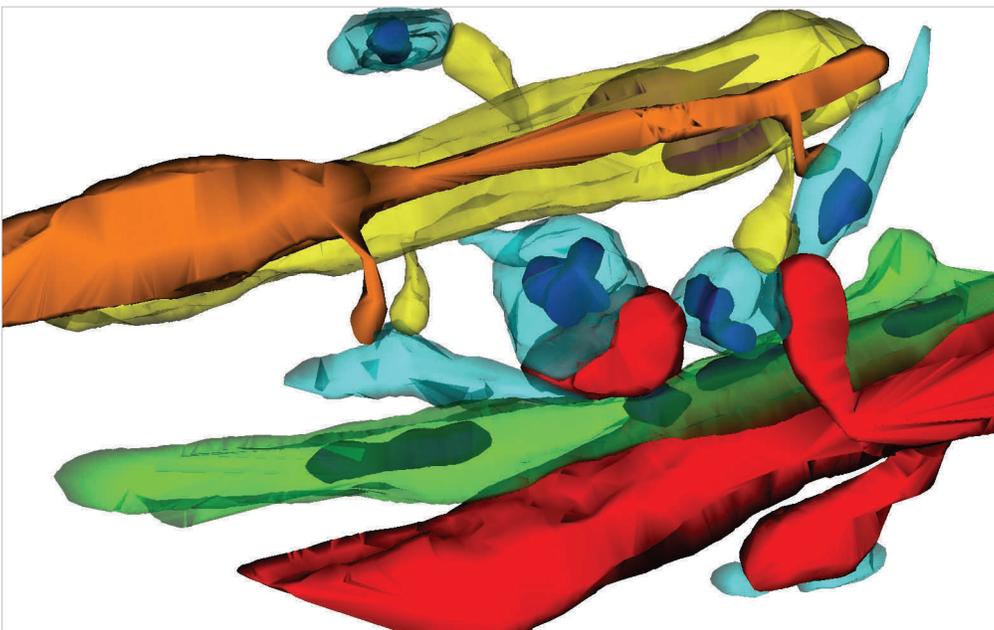
Left: Tissue from the frontal pole, a brain region associated with complex cognition and psychiatric disease susceptibility, is processed, and the nuclei of nerve cells isolated for epigenome analysis. *Right:* Histone H3-Lys4 trimethylation intensities at an important nerve growth factor gene (termed VGF) in chromatin fibers, which are the building blocks of chromosomes. Each green track is from a control brain, and each orange track is from a brain of a subject diagnosed with autism. Note: several autism cases exhibit a loss of histone methylation at the VGF gene locus. The VGF gene is of critical importance for maintenance of neuronal health and function, and its epigenetic dysregulation is likely to have contributed to the disease process in the affected individuals, based on studies in mouse models.

Glickenhau Family Creates New Center

Sarah and Seth Glickenhau recently established the Glickenhau Center for Successful Aging at Mount Sinai. The Center acknowledges Mount Sinai’s long and distinguished reputation in aging research, aimed at understanding how the brain ages, why some people remain cognitively intact despite very advanced age, and how medicine and science might intervene to maximize every individual’s brain function throughout life. A new neuroimaging center will be created as part of this gift to drive translational research on aging. The Glickenhau family’s new gift adds to a tradition of intellectual curiosity and philanthropy at Mount Sinai, which has totaled more than \$14 million during the last five years.

PHOTO ESSAY

Monkey Hippocampal Synapses



Three-dimensional reconstruction of dendrites, dendritic spines, and axonal boutons from the monkey hippocampal dentate gyrus. Red, orange, transparent yellow, and transparent green structures represent individual dendritic segments with dendritic spines; transparent blue represents axonal boutons; and dark blue/purple structures inside the dendrites and boutons represent mitochondria.



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Figure courtesy of Yuko Hara, PhD