



Icahn
School of
Medicine at
Mount
Sinai

Making an
Old Brain
More Plastic

Studying the
Epigenetic Basis
of Brain Disease

Finding the
Genetic Causes of
Movement Disorders

Using Molecular and
Electrophysiological
Approaches for
Emotional Memory

Mid-Pupal Eye
of the Fruit Fly
Drosophila

The Friedman Brain Institute

FALL 2013

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Compassionate Care, Pioneering Research

It is outstanding faculty in science and medicine who are the heart and soul of every medical center. They drive fundamental discoveries of disease pathogenesis into improved diagnostic tests and treatments, to ultimately offer state-of-the-art clinical care for all patients.

Since The Friedman Brain Institute (FBI) was founded five years ago, we have recruited more than 25 new basic science faculty and nearly as many new clinical science faculty, and brought in many new outstanding clinicians to staff our world-renowned outpatient and inpatient clinics. This growth would not have been possible without the recent opening of the new Leon

and Norma Hess Center for Science and Medicine and major renovations of older laboratories, all significantly generated through extraordinary philanthropy.

Growth of this magnitude is a once-in-a-generation opportunity to strengthen Mount Sinai's commitment to lead transformational advances in basic and clinical neuroscience. While many of our recruits are senior faculty who are tops in their fields with robust National Institutes of Health support, a small majority are junior faculty establishing new laboratories. They bring cutting-edge technologies, and innovative ideas and approaches. They have joined us from some of the best laboratories

around the world, attracted by Mount Sinai's strong collaborative opportunities, unparalleled resources, and mentors.

Highlighted in this issue are five stellar junior faculty recruits from neuroscience, neurology, ophthalmology, and psychiatry who are committed to transformational research at Mount Sinai.



Eric J. Nestler, MD, PhD

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YOUNG PIONEERS

Five Young Pioneers Drive Transformational Research at Mount Sinai

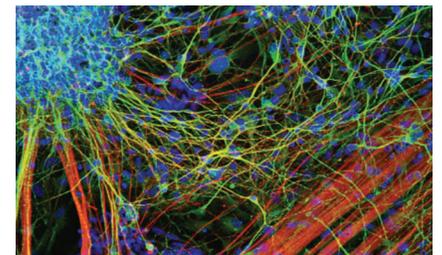
Kristen Brennand, PhD: Using Stem Cells to Study Schizophrenia

By combining expertise in stem cells and neurobiology, Kristen Brennand, PhD, is pioneering a new approach to studying psychiatric disease. Specifically, her focus is on schizophrenia, a disorder marked by genetic mechanisms that are highly complex and incompletely understood, and for which the precise nerve-cell types affected remain unknown. As well, only a few defining characteristics of the diseased cells have been identified, in part due to the lack of live brain tissue for study. Moreover, animal models of schizophrenia are particularly challenging given that many of its cardinal symptoms, such as hallucinations and delusions, are inaccessible in animals.

Dr. Brennand's novel approach is to obtain skin biopsies from patients with schizophrenia, and from family members or normal controls. She then reprograms these skin cells into induced pluripotent

stem cells, or iPSCs, which are subsequently differentiated into different types of neurons. By doing so, she has demonstrated several ways in which the induced neurons from patients with schizophrenia are abnormal, findings that are providing new insight into the neurobiological basis of schizophrenia. Moreover, these induced neurons are being used to screen for new treatments for the illness.

In the year since she joined Mount Sinai after postdoctoral training with Fred H. Gage, PhD, Professor, Laboratory of Genetics and Chair for Research on Age-Related Neurodegenerative Diseases at the Salk Institute for Biological Studies, Dr. Brennand has secured funding for her work from the National Institutes of Health and the Brain & Behavior Research Foundation. In 2013, she was named a Fellow at the Aspen Ideas Festival.



Confocal image of neuron-like cells derived from skin samples of patients with schizophrenia These cells express β III-tubulin (red) and the dendritic marker MAP2AB (green). Blue is a nuclear stain.



Kristen Brennand, PhD

Assistant Professor, Psychiatry, and
Neuroscience

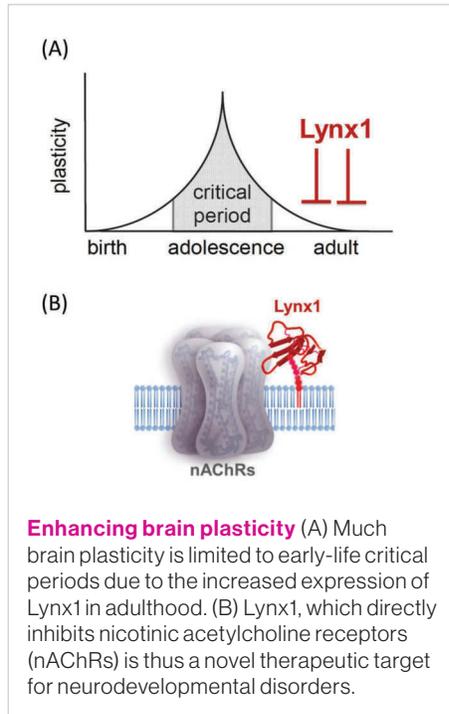
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<http://icahn.mssm.edu/departments-and-institutes/psychiatry/divisions/psychiatric-genomics>

Young Pioneers profiles continued on page 2 >

Hirofumi Morishita, MD, PhD: Making an Old Brain More Plastic

As a physician-scientist with training in psychiatry, Hirofumi Morishita, MD, PhD, has a long-term goal to provide new insight into the causes and treatment of neurodevelopmental disorders. Until recently, major forms of neural plasticity—the ability of the brain to adapt and change—was thought to be limited to a critical period in childhood, rendering many neurodevelopmental disorders difficult to treat in adulthood. Dr. Morishita, who joined Mount Sinai after postdoctoral research in the laboratory of Takao Hensch, PhD, Professor of Molecular and Cellular Biology, and Neurology, at Harvard University, has recently identified molecular mechanisms that control this window of neuroplasticity and discovered new ways of making an adult brain once again more plastic.

Today, his laboratory is studying a protein called Lynx1, which acts as a brake to limit neuroplasticity. In earlier investigations, Dr. Morishita studied mouse models of the visual



disorder, amblyopia, also known as lazy eye, and established that removing Lynx1 reintroduces plasticity and restores normal vision. The Morishita laboratory is now evaluating whether loss of Lynx1 can similarly induce plasticity in mouse models of other neurodevelopmental disorders, such as autism and schizophrenia, and exploring how these mechanisms can be utilized for therapeutic intervention.

Dr. Morishita received a 2012 Travel Award from the American College of Neuropsychopharmacology, as well as funding from the Whitehall Foundation, Brain & Behavior Research Foundation, and March of Dimes Foundation.



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Anne Schaefer, MD, PhD: Studying the Epigenetic Basis of Brain Disease

The research of Anne Schaefer, MD, PhD, focuses on epigenetic mechanisms of psychiatric and neurodegenerative disorders and their correction by targeting the molecular building blocks that control the expression of genes, namely, chromatin-dependent transcriptional regulatory processes. In past research with Paul Greengard, PhD, Professor, Laboratory of Molecular and Cellular Neuroscience at The Rockefeller University, Dr. Schaefer established the central role of microRNAs (miRNAs)—newly discovered small RNA

molecules that do not encode proteins but instead regulate the expression of other genes—in neuronal survival, as well as in the control of motor behavior and drug addiction. She also demonstrated a causal role played by the deficiency of the epigenetic regulators, G9a and GLP (Ehmt1 and Ehmt2), both histone methyltransferases, in the pathogenesis of a severe neurodevelopmental disorder, Kleefstra syndrome, in humans.

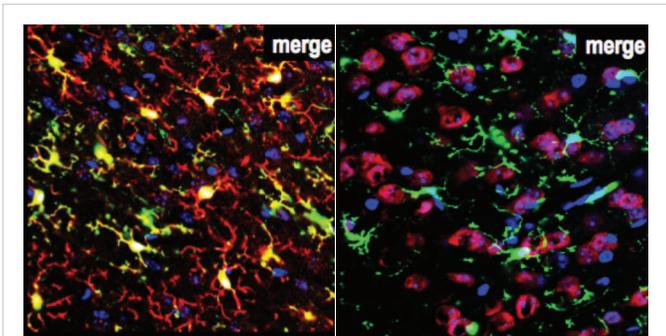
Dr. Schaefer has established an independent research program at Mount Sinai that aims to identify key epigenetic mechanisms of microglia-neuron interactions and their crucial involvement in brain inflammation. Microglia are specialized glial cells that represent the brain’s “immune system.” The Schaefer laboratory relies on cutting-edge technologies, including cell-type specific analysis of mRNAs, miRNAs, and chromatin modifications that occur selectively in neurons versus glia *in*

in vivo. The objective of this work is to add fundamentally new dimensions to a central problem in brain physiology: How are functionally distinct types of neurons surveyed by microglia, and what is the role of this surveillance in the regulation of brain homeostasis? Beyond the implications of this work for basic neuroscience, Dr. Schaefer’s research has the potential of advancing novel strategies for controlling inflammation in the brain and for treating a range of brain diseases, including autism, Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease.

Dr. Schaefer is the recipient of a National Institutes of Health Director’s New Innovator Award and a Seaver Autism Foundation Fellowship, and she was named the Chrissy Rossi Investigator by the Brain & Behavior Research Foundation.



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Genetic tagging of microglia The left panel shows microglia-specific expression of a GFP-tagged ribosomal protein (green). Red is a marker of microglia; blue is a marker of all nuclei. The right panel shows lack of expression of this ribosomal protein in neurons (identified with a marker of neurons in red).

Five Young Pioneers Drive Transformational Research at Mount Sinai *(continued from page 2)*

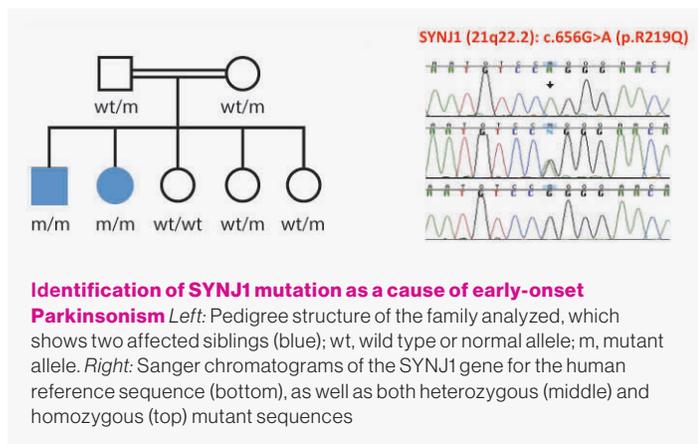
Coro Paisán-Ruiz, PhD: Finding the Genetic Causes of Movement Disorders

The laboratory of Coro Paisán-Ruiz, PhD, focuses on identifying the genes that cause Parkinson's disease, Parkinson's-like syndromes called Parkinsonism, and essential tremor. To accomplish this, her group employs state-of-the-art molecular genetic techniques, such as whole genome DNA arrays, as well as whole exome sequencing and targeted resequencing techniques. The Paisán-Ruiz laboratory has discovered mutations in several genes that cause subtypes of these various syndromes. For example, the group recently identified the first mutations in the gene that encodes synaptojanin 1, which are responsible for early-onset Parkinsonism with generalized seizures. Synaptojanin 1 plays an important role in trafficking neurotransmitter vesicles at synapses. The identified mutations

incapacitate certain functions of the protein, which now provide important new clues into the illness's pathophysiology.

To directly explore the molecular and cellular mechanisms by which the abnormal genes identified lead to Parkinson's disease and related syndromes, Dr. Paisán-Ruiz and her colleagues are characterizing the function of normal versus disease-associated mutant proteins in zebrafish. This approach enables a relatively high-throughput means of studying a protein's function and can be exploited to identify means of counteracting the pathological consequences of the abnormal protein to advance novel therapeutic approaches.

Dr. Paisán-Ruiz joined Mount Sinai after postdoctoral training with John Hardy, PhD, head of the Department of Molecular Neuroscience and Chair of Molecular Biology of Neurological Disease at University College London Institute of Neurology. Her Mount Sinai laboratory is supported by two recently awarded National Institutes of Health grants, as well as awards from private foundations. She is the recipient of the 2013 Dr. Harold and Golden Lamport Research Award, which is presented to tenure-track assistant professors at Mount Sinai whose research shows exceptional potential.



Identification of SYNJ1 mutation as a cause of early-onset

Parkinsonism *Left:* Pedigree structure of the family analyzed, which shows two affected siblings (blue); wt, wild type or normal allele; m, mutant allele. *Right:* Sanger chromatograms of the SYNJ1 gene for the human reference sequence (bottom), as well as both heterozygous (middle) and homozygous (top) mutant sequences



Coro Paisán-Ruiz, PhD

Assistant Professor of Neurology, Genetics and Genomic Sciences, and Psychiatry

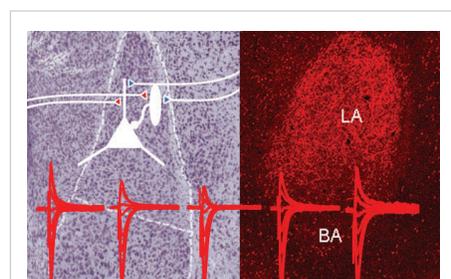
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Roger Clem, PhD: Using Molecular and Electrophysiological Approaches for Emotional Memory

Emotional experiences, both positive and negative, leave an enduring record in the brain by inducing structural and molecular remodeling of nerve cells and their interconnections, called synapses. While these modifications are essential for survival by helping an individual respond appropriately to rewards and threats, they can—in their extreme—also contribute to maladaptive states, like drug addiction and post-traumatic stress disorder. Many key characteristics of emotional memory mirror those of synaptic plasticity in simpler neuronal preparations, such as a brain slice from an animal that underwent such an experience, but such basic models do not capture the complexity of adaptations that underlie emotional memory storage, or update or inhibit memory, as behavioral conditions change.

The laboratory of Roger Clem, PhD, utilizes molecular and electrophysiological approaches, including optogenetic stimulation, where nerve cell activity is controlled by light, to identify how a fearful



Optogenetic regulation of the amygdala

Left: Photomicrograph of amygdala showing cartoon of a pyramidal neuron (triangle) and interneuron (oval) and their innervation by prefrontal cortical (PFC) neurons (red terminals) and other regions (blue terminals). *Right:* Red staining shows channelrhodopsin expressed in PFC nerve terminals in amygdala. This makes it possible to selectively stimulate those terminals to produce synaptic responses (red traces). *Credit:* Maithe Arruda-Carvalho

experience modifies individual neurons and neural pathways in limbic (emotion-related) brain regions of a mouse, such as the amygdala, hippocampus, and prefrontal

cortex. A major goal is to understand the mechanisms that lead to the very stable nature of these emotional memories, as well as to develop new ways of reinforcing adaptive (useful) memories or weakening maladaptive (pathological) ones through experimental molecular and behavioral interventions. The goal is to adapt such interventions as more effective treatments of psychiatric syndromes.

Dr. Clem came to Mount Sinai from Johns Hopkins University, where he completed postdoctoral training with Richard Haganir, PhD, Professor, and Director of the Department of Neuroscience. Dr. Clem is a past finalist of the Eppendorf & Science Prize for Neurobiology.



Roger Clem, PhD

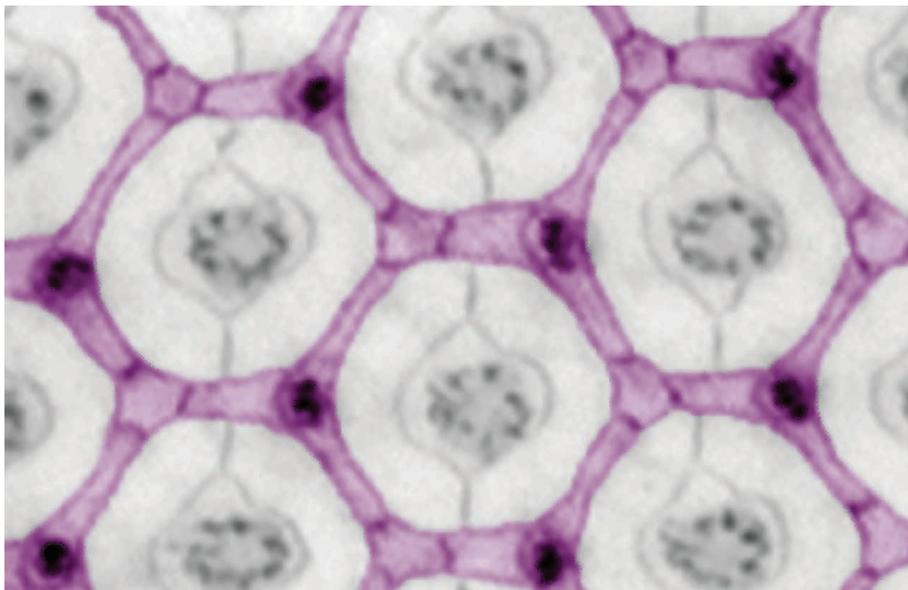
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PHOTO ESSAY

Mid-Pupal Eye of the Fruit Fly *Drosophila*



Mid-pupal eye of the fruit fly *Drosophila* showing visual units (ommatidia, gray) and glial-like support cells (magenta). The striking precision of the eye neuroepithelium permits an accurate view of the world.



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