Icahn School of Medicine at Mount Sinai

The Friedman Brain Institute

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Compassionate Care, Pioneering Research

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An age-old debate is how to strike the right balance between basic research and translating that research into clinical advances. The human and financial costs of disease require the latter, yet those efforts are inherently limited by an incomplete knowledge of the basic biology involved. And, it can take many decades to establish the biological basis of a human disease.

A case in point is cancer. When I was in medical school 35 years ago, we were taught about molecular strategies to cure cancer, but it has taken three decades of very basic research to understand cancer's molecular basis, which at long last is guiding the first definitive treatments and cures. Conquering neurological and psychiatric illnesses, however, will take far longer, due to the brain's much greater complexity.

This issue of The Friedman Brain Institute (FBI) Report focuses on the importance of a sustained investment in basic, fundamental neuroscience in advancing our understanding, diagnosis, and treatment of brain diseases. Work by Scott Russo, PhD, and his laboratory has uncovered the involvement of inflammation in a subset of patients with depression, insights now being advanced into clinical trials for those individuals, which would have been impossible without the basic research. Mount Sinai is also proud of its team of researchers who work with non-human primates—macaque monkeys—to understand the neural mechanisms of higher brain function. Such functions are mediated by parts of the brain that are very rudimentary in rodents, and thus require primate models. This work is now beginning to inform conditions as diverse as epilepsy, aging, and dementia, among others.

Mount Sinai's FBI is committed to optimizing the pursuit of basic science investigation in the service of improvements in clinical care.

Targeting Inflammation to Treat Depression

Major depressive disorder (MDD) is the leading cause of worldwide disability with some reports estimating prevalence rates around 7 percent. A subset of depressed patients experience heightened inflammation, along with comorbid physical illness, such as cardiovascular disease, diabetes, metabolic abnormalities, asthma, and rheumatoid arthritis.

Scott Russo, PhD, and his team at the Icahn School of Medicine at Mount Sinai have set out to test whether overactive, unresolved inflammation might ultimately lead to the development of mood disorders. To achieve this goal, Dr. Russo partnered with a broad team of Mount Sinai specialists across Psychiatry, Immunology, and Vascular Biology. By adopting a "reverse translational" approach, they first identified elevations of the inflammatory cytokine IL-6 (interleukin-6) in humans with treatment resistant depression. His laboratory went on to show that, by neutralizing IL-6 in the periphery and preventing it

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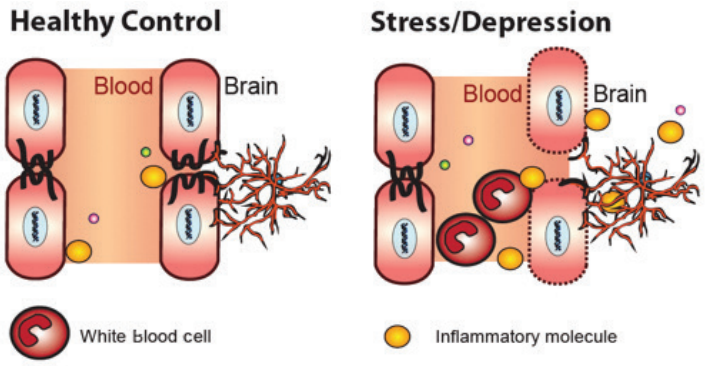


Stress/Depression induces neurovascular pathology and blood-brain barrier (BBB) leakiness in a subset of patients. Stress exposure causes abnormalities in the blood vessel endothelial cell lining and increases BBB permeability and infiltration of peripheral immune signals into the brain. Neurovascular changes then contribute to depression-related behavioral abnormalities, such as social avoidance, anhedonia, despair, and lack of self-care.

Understanding the Neural Basis of Cognition: Mount Sinai's Non-Human Primate Research Program

In order to effectively bridge the gap between basic studies in rodents and much-needed new treatments for psychiatric and neurological disorders, the Mount Sinai non-human primate neuroscience group aims to understand the neural basis of complex behavior and cognition by studying our close evolutionary relatives. Non-human primates have cognitive abilities not unlike our own and brain anatomy that bears striking homology to humans, making them an irreplaceable resource in brain and cognitive sciences. Mount Sinai's non-human primate research team consists of four laboratories led by: Mark Baxter, PhD; Paula Croxson, PhD; Peter H. Rudebeck, PhD; and Erin Rich, MD, PhD. The highly interactive, collaborative group employs a diverse array of cutting-edge research methods in macaque monkeys to understand the neural basis of higher cognitive function.

The investigative team is studying learning, memory, executive function, and decision-making, and how these processes fail in neuropsychiatric disease. These functions rely on the coordinated activity of widely distributed circuits in the brain, with key hubs in the prefrontal cortex, which is particularly enlarged in primates, as well as in the temporal lobe.

The Baxter laboratory focuses on questions concerning the relationship of these functions to the underlying brain systems by directly interfering with neural function in a defined circuit, and determining the consequences on behavior.

The Croxson laboratory investigates plastic and degenerative changes as the result of disruption to memory systems, using functional and structural imaging.

The Rudebeck laboratory focuses on understanding how neurons in the prefrontal cortex and interconnected structures control affective behavior, with the aim of delineating how these brain circuits function normally and what goes wrong when they fail in disease states.

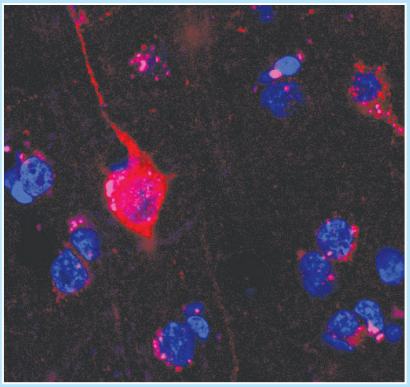


Figure 1. Inhibitory DREADD expression (red) superimposed on brain cell nuclei (blue) in dorsolateral prefrontal cortex of the macaque monkey brain. Activation of this receptor with a drug temporarily leads to disruption of spatial working memory function.

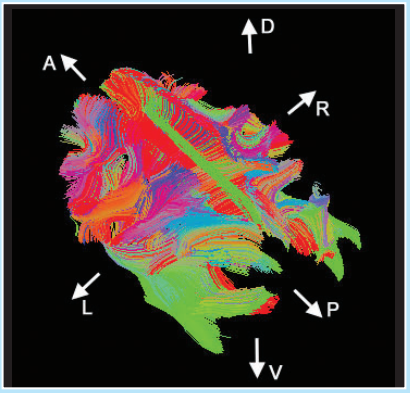


Figure 2. High-resolution imaging of a macaque brain showing the entire brain's connectome constructed from diffusion data acquired on a 3 Tesla MRI scanner with custom hardware. Tracts are color-labelled (red, left-right; blue, dorsal-ventral; green, anterior-posterior).

The Rich laboratory, which launches this spring, will use a combination of neurophysiological and computational approaches to simultaneously record large numbers of brain signals and map their neural dynamics onto cognition and other behaviors.

The non-human primate program is distinguished by several strengths, in particular the application of new technology and collaborations with rodent researchers and physicians. The group is using cutting-edge chemogenetic approaches to manipulate brain circuits. By introducing a modified receptor—Designer Receptor Exclusively Activated by Designer Drug—(DREADD) into a defined population of neurons, it is possible to temporarily modulate neuronal activity targeted to a specific brain circuit (see Figure 1). This has led to newly funded grants from the National Institute of Mental Health (Dr. Rudebeck) and the National Institute of Neurological Disorders and Stroke (Drs. Baxter and Croxson). The success of this work in monkeys will help to determine whether this technology has the potential to be used to target specific neurons and circuits to treat human psychiatric and neurological disorders, a potentially revolutionary development.

This effort has required our collective expertise in neurosurgery, neuroimaging (see Figure 2), behavioral analysis, neurophysiology, and neuroanatomy, as well as the expertise of many other Friedman Brain Institute investigators in viral vector design and use.

The non-human primate group has strong collaborations with researchers both within and outside Mount Sinai, sparking research into such diverse areas as drug addiction and psychosis, aging and dementia, epilepsy, mechanisms of anesthesia, spinal cord regeneration, and ultra-high-field-strength brain imaging. This has allowed the impact of the non-human primate research program to extend across multiple domains: having such access to a neural system that is highly similar to the human brain is essential for the ultimate development of treatments for a range of human disorders.

Mark Baxter, PhD, Professor, Neuroscience, Anesthesiology, and Geriatrics and Palliative Medicine

Paula Croxson, PhD, Assistant Professor, Neuroscience, and Psychiatry

Peter H. Rudebeck, PhD, Assistant Professor, Neuroscience, and Psychiatry

Erin Rich, MD, PhD, Assistant Professor, Neuroscience, and Neurology

Eric J. Nestler, MD, PhD, Becomes President of the Society for Neuroscience

Eric J. Nestler, MD, PhD, Nash Family Professor of Neuroscience, Director of The Friedman Brain Institute, and Dean for Academic and Scientific Affairs at the Icahn School of Medicine at Mount Sinai, was inaugurated as the 48th President of the Society for Neuroscience, the world's largest organization of brain and nervous system scientists and physicians, at the 2016 annual meeting held last fall in San Diego. Dr. Nestler will preside over the 2017 annual meeting to be held in November in Washington, DC. The nonprofit organization, founded in 1969, now has nearly 40,000 members in more than 90 countries around the world.

During his one-year term, Dr. Nestler will guide the venerable society to support the neurosciences in a number of ways. Some of the themes he plans to address during his tenure include promoting a diverse workplace in the neuroscience field, working with academic institutions and government agencies to reduce the administrative burden on the neuroscience research enterprise, and promoting optimal translation of basic discoveries into clinical advances, while recognizing the crucial importance of a strong investment in basic research.

›Targeting Inflammation *continued from page 1*

from entering the brain, they could produce antidepressant-like effects in a mouse model of depression (PMID: 25331895). As a result of this preclinical work, Janssen Pharmaceuticals has initiated a phase II clinical trial to test the efficacy of IL-6 neutralization in treatment of unipolar depression, with a particular focus on individuals with elevated levels of this cytokine; part of the study is being performed at Mount Sinai (https://clinicaltrials.gov/ct2/show/NCT02473289).

More recently, Dr. Russo and his team have investigated how peripheral inflammatory cytokines like IL-6 enter the brain and where they exert their effects. He has hypothesized that such cytokines diffuse more readily into the brains of stressed individuals because of neurovascular damage that weakens the brain's defense system, known as the blood-brain barrier (BBB) (PMID:26404713). The BBB is formed by endothelial cells sealed by tight junction proteins, pericytes, and astrocytes, which surround capillaries and prevent potentially harmful molecules in the blood from entering the brain. Recently, the Russo Lab presented preliminary work detailing the effects of chronic social stress on BBB integrity, which showed that chronic stress in rodents damages the endothelial cells lining blood vessels within brain regions important for mood and emotion. This enabled the entry of IL-6 into the brain, where it promoted depression-like behaviors (see figure, cover page). They also found evidence for a similar pathology in human brain tissue from depressed patients.

The expectation is that Dr. Russo and his team can now leverage these exciting data to screen for novel therapeutic agents that enhance repair of endothelial damage due to stress and prevent or reverse depression in the subset of individuals who display these abnormalities—an innovative example of individualized "Precision Medicine" being applied to Psychiatry.

Scott Russo, PhD,
Associate Professor of Neuroscience

FBI Research Scholars Partnership

Second Annual Awards Announced

The Philanthropic Leadership Council of The Friedman Brain Institute is pleased to announce the 2016 recipients of the FBI Research Scholars Awards.

Richard and Susan Friedman Research Scholar Award:

Rafael O'Halloran, PhD, Assistant Professor, Radiology, and Psychiatry

"Effect of methylphenidate on real-time cognitive neurofeedback training"

Nash Family Research Scholar Award:

Gang Fang, PhD, Assistant Professor, Genetics and Genomic Sciences

"Functions of a novel form of DNA methylation in neuronal development and schizophrenia"

Rosen Family Research Scholar Award:

Peter H. Rudebeck, PhD, Assistant Professor, Neuroscience, and Psychiatry

"Neural mechanisms of human higher cognitive function"

Elizabeth and Michael Fascitelli Research Scholar Award:

Nadejda Tsankova, MD, PhD, Assistant Professor, Pathology, and Neuroscience

"Characterization of astroglial pathology in pediatric human temporal lobe epilepsy"

Saint-Amand Research Scholar Award:

Andrew W. Varga, MD, PhD, Assistant Professor, Medicine (Pulmonary, Critical Care and Sleep Medicine)

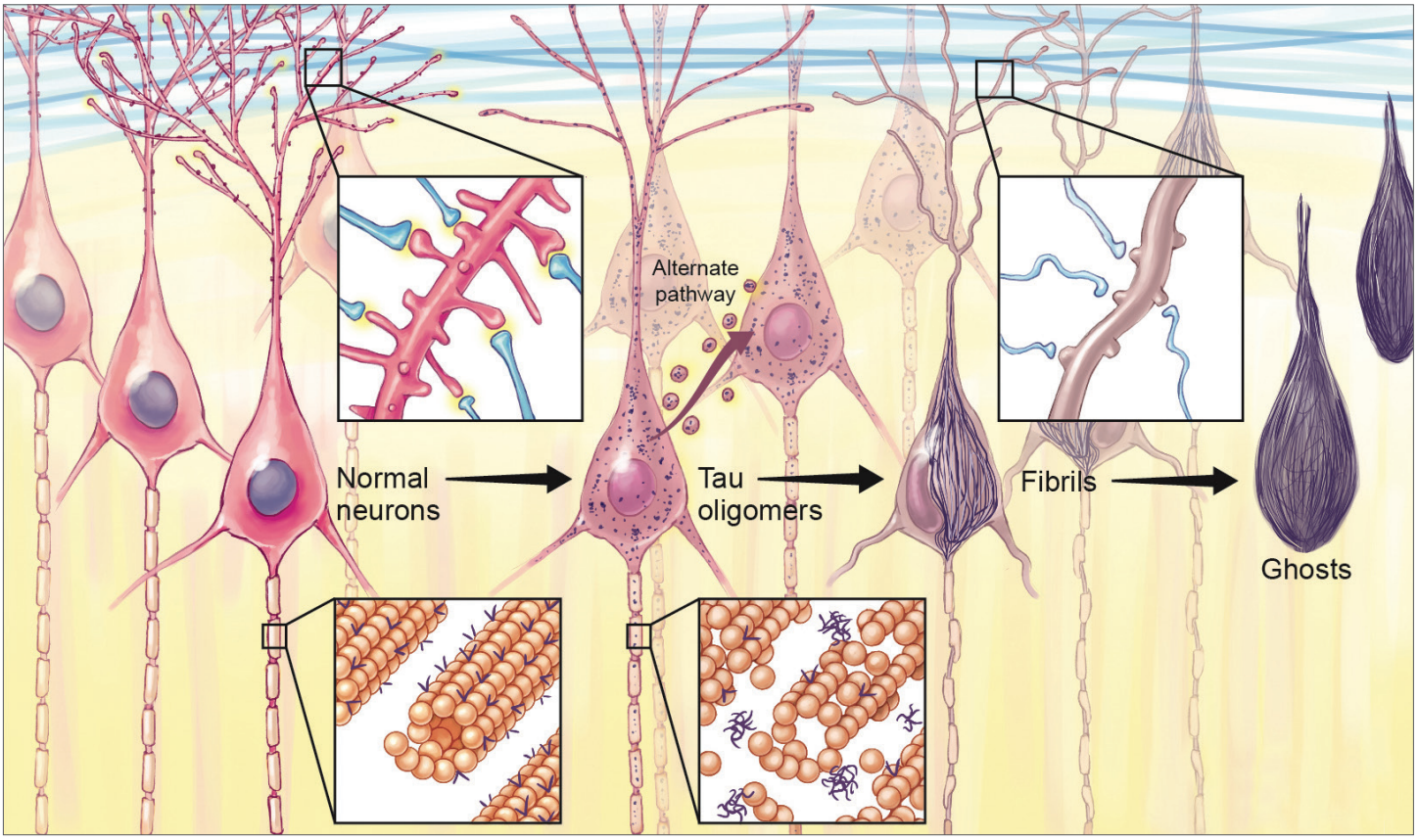
"Bidirectional sleep modulation and role of neuronal activity on tau neuropathology in a mouse model of dementia"

Funded entirely through philanthropy, the goal of the program is to encourage innovative brain research and to offer young pioneers who are venturing into a new area of investigation the freedom to follow their science.

Alison M. Goate, DPhil, Elected to National Academy of Medicine

Alison M. Goate, DPhil, Willard T.C. Johnson Research Professor of Neurogenetics and Director of the Ronald M. Loeb Center for Alzheimer's Disease, was elected to the National Academy of Medicine (NAM), the nation's highest honor for medical researchers. Dr. Goate's laboratory focuses on the genetic basis of dementias and other neurodegenerative disorders. Her election brings the number of Friedman Brain Institute faculty who are NAM members to seven, a major distinction for our neuroscience community. Other NAM members from the FBI are: Joseph D. Buxbaum, PhD; Dennis S. Charney, MD; Kenneth L. Davis, MD; Eric J. Nestler, MD, PhD; Pamela Sklar, MD, PhD; and Barbara G. Vickrey, MD, MPH.

Visual Essay: Development of Neurofibrillary Tangles



The development of neurofibrillary tangles, made of the microtubule-associated protein tau, within brain cells is a hallmark of Alzheimer's disease and other neurodegenerative brain diseases. This figure depicts the stages of neurofibrillary tangle development. Normally, tau is enriched in axons where it attaches to and stabilizes microtubules, structures that define the shape of neurons and transport material within cells. Early in the disease, small aggregates (oligomers) of abnormal tau appear, which are thought to be able to spread from cell to cell. In disease progression, these tau aggregates coalesce into mature neurofibrillary tangles that choke the cellular machinery, leading to synapse dysfunction, atrophy, and ultimately, cell death.

Illustration created to accompany the research of John F. Crary, MD, PhD, Associate Professor, Pathology, and Neuroscience.