Mount Sinai
MSSM
MOUNT SINAI SCHOOL OF MEDICINE

Dean's Quarterly

FALL 2011

ACCELERATING SCIENCE—ADVANCING MEDICINE

Transcending Limits in Science and Medicine

Five years ago, I unveiled the $2.25 billion strategic plan that laid the foundation for 15 translational research institutes at Mount Sinai School of Medicine *(see back page)*.Today, these institutes are hubs of scientific and clinical enterprise, working together to challenge the limits of science and medicine.

We are now poised to open a 550,000-square-foot Center for Science and Medicine, on schedule for completion next year, which will increase our research capacity by 30 percent and expand our cancer clinical footprint severalfold. To maximize interactions among clinical and basic-science researchers, each research floor will also contain workspace and offices for clinical investigators.

This next phase of our strategic plan will allow us to illuminate and realize the unprecedented opportunities of 21st century biomedicine. We have targeted five areas that represent the most pressing global disease burdens: cardiovascular disease, cancer, neuropsychiatric disorders, immune disorders, and virology/vaccines. We will expand our work in small-molecule drug discovery, monoclonal antibodies and purified proteins, high-content screening/RNAi, induced and embryonic pluripotent stem cell, and systems pharmacology and network analysis facilities.

Together with new pharmaceutical partners, we will facilitate the rapid translation of scientific findings from bench to bedside and into the community.

Breakthrough diagnostics and therapeutics in our chosen areas will ultimately save and extend lives, and could, in turn, reduce overall health care spending. A drug that delayed by 10 years the onset of diabetes or Alzheimer's disease—two of the largest health care expense drivers in the United States—would result in tremendous savings for our Medicare and Medicaid budgets. At the national policy level, Mount Sinai leadership is also promoting a range of measures to reduce health care spending. These efforts include support of a tax on fructose additives to help curb obesity, the condition that underlies hypertension, diabetes, and cardiovascular disease; a restructuring of patent policies to support and protect the development of truly innovative biomedical compounds; and the expansion of palliative care programs that have been proven to save money and improve end-of-life care for patients and their families.

Dennis S. Charney, MD, is the Anne and Joel Ehrenkranz Dean of Mount Sinai School of Medicine and the Executive Vice President for Academic Affairs of The Mount Sinai Medical Center.

These are among our priorities, as we reimagine what is possible and redefine the practice of modern medicine.

To learn more, visit www.mountsinai.org/Charney

INSIDE THIS ISSUE

DISTINGUISHED BY SERVICE

A Center Dedicated to Living Donors

Sander S. Florman, MD, Director of the Recanati/Miller Transplantation Institute

More than 110,000 Americans are waiting for an organ transplant. The demand for organs far exceeds the supply of deceased donors. Living donation is a critical means by which this discrepancy can be abated and more lives saved.

The Mount Sinai Medical Center's newly endowed Zweig Family Center for Living Donation at the Recanati/Miller Transplantation Institute (RMTI) is the first major multi-organ living donor center in the country that provides a full range of dedicated services specifically for living donors. Dianne LaPointe Rudow, DNP, a widely recognized advocate for living donors, serves as the Director of the Zweig Family Center. As a member of the board of directors of the Organ Procurement and Transplantation Network (OPTN)/ United Network for Organ Sharing (UNOS), Dr. LaPointe Rudow helped develop national and New York State standards for donor care.

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MEDICAL MILESTONES

Biobank Data Shows Importance of Personalized Medicine

Researchers at Mount Sinai School of Medicine, in collaboration with Loyola University Chicago Stritch School of Medicine, have found that the use of ethnic labels—African-American, Hispanic, and Caucasian—may no longer be helpful in predicting disease risk or determining how a patient will respond to certain medications. The study, which is the first of its kind, involved patients from the Mount Sinai Biobank and marks an important step in the clinical application of personalized medicine. The findings were published in May, in the online journal *PLoS One*.

The Biobank, a program of the Charles R. Bronfman Institute for Personalized Medicine, enrolls patients who represent the diverse communities surrounding The Mount Sinai Medical Center. Researchers used state-of-the-art genomic technology to determine the genetic make-up, or genotype, of nearly 1,000 Biobank participants who self-identified as European American, African-American, or Hispanic. They found that patients who considered themselves African-American or Hispanic had considerable parts of their genome coming from mixed-European or -African ancestry, respectively.

Erwin P. Bottinger, MD, Director of the Bronfman Institute

"A spectrum of mixed ancestry is emerging in the largest U.S. minority groups," explains Erwin P. Bottinger, MD, Director of the Bronfman Institute, and the Irene and Dr. Arthur M. Fishberg Professor of Medicine. "These findings validate the importance of considering the unique genotype of the individual patient rather than grouping patients by self-reported ethnicity."

Researchers are now evaluating the potential clinical use of hundreds of genetic markers for major diseases, such as heart disease, kidney disease, liver disease, and diabetes, and various drug responses, in all 20,000 Biobank samples. The goal is to identify the genetic markers that may be useful to predict disease risk in people with mixed genetic backgrounds.

"Now that we can determine the genotypic breakdown of our patients, we can begin to develop tests and tailor therapies for the diverse community we serve," says Dr. Bottinger. "This will allow us to provide highly effective, personalized care."

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A Center Dedicated to Living Donors, *continued from page 1*

Prospective donors are evaluated and informed about the benefits and risks of organ donation by a multidisciplinary team of experts. Marcelo Facciuto, MD, Surgical Director of Living Donor Liver Transplantation, and Juan Pablo Rocca, MD, Surgical Director of Living Donor Kidney Transplantation, lead the medical teams that ensure that potential living donors are well cared for during their entire experience. The team educates recovering donors about how to maintain their health and recognize the importance of adhering to long-term monitoring. Special programs, including counseling, support groups, yoga classes, and nutritional guidance enable living donors to develop vital skills for maintaining their health long-term. After surgery, the RMTI staff monitors each patient for potential complications, and provides support on key issues including patient safety, patient advocacy, and psychological concerns.

A new program starting this fall will match prospective donors with a past donor who will serve as a mentor.

Construction is currently under way on the five inpatient hospital rooms that will accommodate these heroes who, as philanthropist Martin Zweig has pointed out, "are giving the most that a person can give." Dr. Zweig has also commented that "The Zweig Family Center for Living Donation will honor that gift by providing exceptional care."

The key to reducing mortality among transplant candidates is to raise awareness about the pressing need for organ donation. The information below, from the OPTN, illustrates the need for more living donors.

NUMBER OF TRANSPLANT CANDIDATES ON THE OPTN WAITING LIST AS OF SEPTEMBER 2, 2011

112,080

TRANSPLANTS PERFORMED JANUARY - JUNE 2011

13,969

FROM LIVING DONORS

2,958

FROM DECEASED DONORS

11,011

Source: U.S. Organ Procurement and Transplantation Network

RESEARCH FRONTIERS

Protein Mutation Related to Parkinson's Disease Discovered

Zhenyu Yue, PhD, Associate Professor of Neurology and Neuroscience

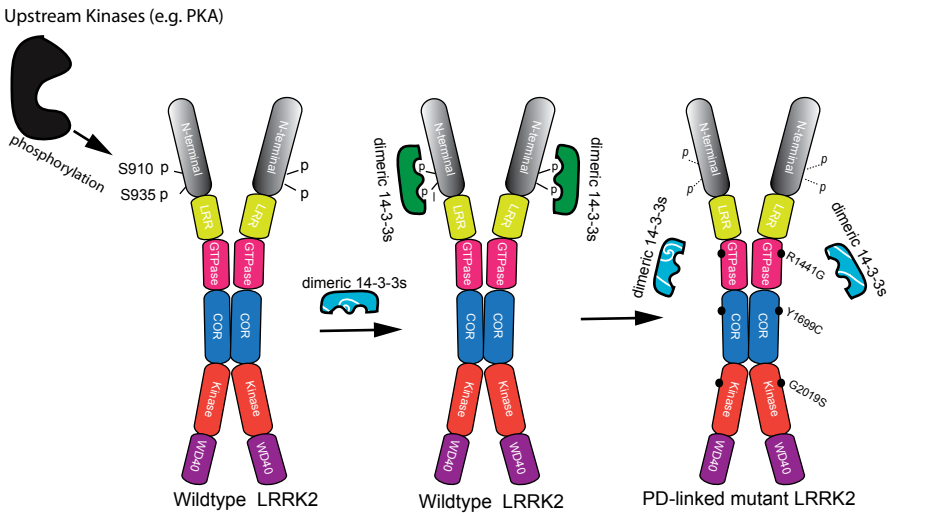
Researchers at Mount Sinai School of Medicine have uncovered how mutations in a protein, leucine rich repeat kinase 2 (LRRK2), may cause the most common inherited forms of Parkinson's disease (PD). Zhenyu Yue, PhD, Associate Professor of Neurology, and Neuroscience, and his colleagues published their findings in March, in the online journal *PLoS One.*

Dr. Yue's team found that in brain tissue, LRRK2 protein is modified by phosphorylation at multiple sites. The specific phosphorylation in LRRK2 creates a docking site for the binding of a family of proteins known as 14-3-3, which has regulatory function in cell signaling.

Dr. Yue's team also identified a potential enzyme, known as protein kinase A (PKA), responsible for phosphorylation. The serial molecular events reported in the study shed light on the signaling pathway related to LRRK2 biology. His team showed that several common PD mutations disturb the specific phosphorylation of LRRK2 and impair 14-3-3 binding.

Although the exact cellular functions disrupted by these changes are unclear, their study provides a starting point for understanding the molecular mechanism of the disease. Other recent studies have shown that 14-3-3 binds to other proteins implicated in inherited Parkinson's Disease, and has a neuroprotective function. When the binding is impaired, however, the protection is lost, triggering Parkinson's. The findings also demonstrate additional insight into the functional relevance of the LRRK2 and 14-3-3 interaction.

The presence of 14-3-3 in spinal fluid is currently used as a biomarker to test for Creutzfeldt-Jakob disease. Further applications of Dr. Yue's findings could point to its use in testing for Parkinson's.



PKA Phosphorylation, 14-3-3 binding of LRRK2, and the effect of common familial mutations of LRRK2 in 14-3-3 binding. A schematic model showing PKA (or other kinase) phosphorylation of S910/S935, dimeric14-3-3 binding of LRRK2 at pS910/pS935 sites in wild type LRRK2; PD-linked mutations R1441G, Y1699C or G2019S abolishes or reduces phosphorylation of S910/S935 and impairs 14-3-3 binding. In addition, we propose that dimeric 14-3-3 bind to pS910 and pS935 in the same LRRK2 molecule and binding of 14-3-3 plays little role in LRRK2 dimer formation.

YOUNG PIONEERS

Julie Magarian Blander, PhD, Receives Award

Julie Magarian Blander, PhD, Associate Professor of Medicine (Clinical Immunology), was recently honored with the prestigious Burroughs Wellcome Fund Award—a five-year $500,000 grant—for her investigations into the pathogenesis of infectious disease.

Dr. Blander, whose research appeared in the June 16 issue of *Nature*, discovered that the immune system has the capacity to sense microbial viability by detecting prokaryotic messenger RNA molecules. Her findings could lead to the creation of a new generation of vaccines that combine the safety of a dead vaccine with the efficacy of a live vaccine.

"We knew that the immune system could detect microbes and protect us from infection, but we did not know that it could further sense whether these microbes were dead or alive," she says. "This realization provides a simple explanation for the long-standing puzzle of why live vaccines work better than their dead counterparts."

The Burroughs Wellcome Fund Awards are given to the most promising researchers at their institutions. Dr. Blander's work has been supported by a two-year exploratory grant from the National Institutes of Health (NIH), and the prestigious Searle Scholar Award. She has received several other honors from the NIH, the American Cancer Society, and a 2010 Dr. Harold and Golden Lamport Award for basic research.

Lloyd F. Mayer, MD, Professor of Medicine, and Professor and Co-Director of the Immunology Institute at The Mount Sinai Medical Center, called Dr. Blander, "a rising star in the immunology community." He added that she "seeks to unravel the link between innate (primitive) and adaptive (antibodies and effector lymphocytes) immunity in a unique way."

Julie Magarian Blander, PhD, Associate Professor of Medicine (Clinical Immunology)

Eric E. Schadt, PhD

Eric E. Schadt, PhD, one of the world's foremost experts in computational biology, has been appointed Director of the Institute for Genomics and Multiscale Biology at The Mount Sinai Medical Center. The Institute is being set up in partnership with Pacific Biosciences of California (PacBio) where he will continue to serve as Chief Scientific Officer.

An expert in large-scale sequence variation, molecular profiling, and clinical data in disease populations, Dr. Schadt's research has provided novel insights into how massive amounts of data can be used to understand the complexity of diseases and lead to more informed decisions about drug discovery. He has also contributed to a number of important findings on the genetic basis of diabetes and obesity.

In his dual role at Mount Sinai and PacBio, Dr. Schadt will oversee a hub of genomics research, which will be at the forefront of the revolution in genetics and genomic sciences, and ultimately change the practice of medicine. He will foster multidisciplinary collaboration in areas such as newborn screening for rare genetic disorders, infectious diseases, and cancer.

Dr. Schadt is a founding member of Sage Bionetworks, an open-access genomics initiative. Before joining PacBio in 2009, he was Executive Scientific Director of Genetics at Rosetta Inpharmatics, a subsidiary of Merck & Co., Inc.

Pamela Sklar, MD, PhD

Pamela Sklar, MD, PhD, a leading expert in the genetic causes of psychiatric disorders, has joined The Mount Sinai Medical Center as the founding Chief of the Division of Psychiatric Genomics and Professor of Psychiatry. Dr. Sklar will help build a world-class psychiatric genomics division that works in collaboration with numerous departments and institutes at Mount Sinai.

A groundbreaking investigator, Dr. Sklar's research focuses on identifying the genes that put individuals at risk for developing psychiatric diseases. She has made substantial contributions to the understanding of gene variants and structural variants, which are linked to bipolar disorder and schizophrenia.

By understanding genetic risk factors, physicians can target psychiatric diseases at their roots and intervene earlier with treatments. Many patients do not develop psychiatric symptoms until adolescence.

Dr. Sklar has led genetic studies of bipolar disorder through the Systematic Treatment Enhancement Program for Bipolar Disorder Network, and has completed genome-wide association analyses in bipolar disorder.

Previously, Dr. Sklar served as Director of Genetics for the Stanley Center for Psychiatric Research at the Broad Institute of the Massachusetts Institute of Technology and Harvard University, and Associate Professor of Psychiatry at Harvard Medical School.

Carlos Cordon-Cardo, MD, PhD

Carlos Cordon-Cardo, MD, PhD, a renowned physician-scientist, and pioneer in oncologic molecular pathology, has been appointed Chair of the Department of Pathology at The Mount Sinai Medical Center.

Dr. Cordon-Cardo is a distinguished leader in the mechanism of tumor suppression, particularly in bladder cancer, prostate cancer, and soft-tissue sarcomas. His research focuses on understanding the cooperative effects of mutations of cell-cycle regulation, and genes that prevent cell death in cancer patients.

Dr. Cordon-Cardo helped create the systems pathology platform, which uses systems biology to create mathematical models of the interaction and behavior of cancer cells. This helps scientists determine tumor pathogenesis and predict clinical outcomes.

In his new position, Dr. Cordon-Cardo will draw upon his experience as an investigator, administrator, and educator, and work to enhance the Pathology Department's clinical and research programs in cancer.

Prior to joining Mount Sinai, Dr. Cordon-Cardo was Vice Chair of Pathology, Professor of Pathology and Urology, and Associate Director for Infrastructure at the Herbert Irving Comprehensive Cancer Center at Columbia University College of Physicians and Surgeons.

Charles A. Powell, MD

Charles A. Powell, MD, an acclaimed lung cancer researcher who helped recategorize the disease, has been appointed Chief of the Catherine and Henry J. Gaisman Division of Pulmonary, Critical Care and Sleep Medicine at The Mount Sinai Medical Center. In his new position, Dr. Powell will build on the division's strong foundation by strengthening its specialties in cardiothoracic surgery, radiology, and radiation oncology.

With clinical and research interests in lung cancer and mesothelioma, Dr. Powell's work centers on understanding the genetic and susceptibility factors that are involved in these types of cancers. He also studies the molecular events that are important in the early stages of lung cancer development and progression.

As Chair of the Thoracic Oncology Section of the American Thoracic Society, Dr. Powell is an internationally recognized authority on lung cancer. He is an elected member of the Fleischner Society, and a recipient of the American Cancer Society Research Scholar Award.

Before joining Mount Sinai, Dr. Powell was Associate Professor of Medicine and Associate Division Chief of the Division of Pulmonary, Allergy and Critical Care Medicine at Columbia University Medical Center. He also served as Director of the Pulmonary and Critical Care Medicine Fellowship and Medical Director for the High Risk Lung Assessment Program at New York Presbyterian Hospital.

PHILANTHROPY

Advancing Stem Cell Research in Heart Disease

Mount Sinai Trustee Joseph Plumeri recently donated $2 million to the President's Strategic Initiative Fund to support programs in stem cell research leading to innovative treatments for heart disease.

Joseph Plumeri

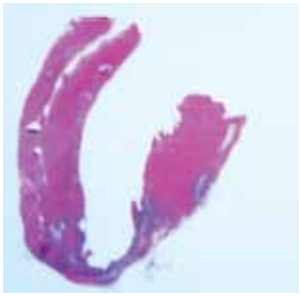
"Stem cells are one of the most promising lines of heart disease research today," says Roger J. Hajjar, MD, Director of Mount Sinai's Cardiovascular Research Institute and the Arthur & Janet C. Ross Professor of Medicine. "Meaningful support such as this has a real impact in expanding our knowledge of stem cell-derived treatments."

Mr. Plumeri was inspired to make his donation after learning about the promising multidisciplinary collaboration between Dr. Hajjar and Ihor R. Lemischka, PhD, Director of the Black Family Stem Cell Institute and Professor of Developmental and Regenerative Biology at The Mount Sinai Medical Center. Dr. Hajjar's laboratory is exploring how gene therapy can be used to prevent heart failure and other cardiovascular diseases, while Dr. Lemischka's work focuses on understanding the molecular and cellular mechanisms that control the fate of undifferentiated stem cells.

"Discovering new stem cell treatments requires complete teamwork and a shared vision," Mr. Plumeri says. "Mount Sinai has both of these qualities in abundance. I look forward to seeing the next wave of discoveries from Dr. Hajjar's and Dr. Lemischka's laboratories."

The gift will play a critical role in furthering research. "Stem cell researchers are discovering new possibilities all the time," says Dr. Lemischka. "The support of our philanthropic partners is essential to that endeavor."

> "Discovering new stem cell treatments requires complete teamwork and a shared vision. Mount Sinai has both of these qualities in abundance."
>
> — JOSEPH PLUMERI, TRUSTEE



Slides from Mount Sinai's Cardiovascular Research Institute show, TOP: Heart tissue that is dying due to an obstruction of blood to the tissue; and BOTTOM: Heart tissue that has been regrown through genetic therapies derived from stem cells.

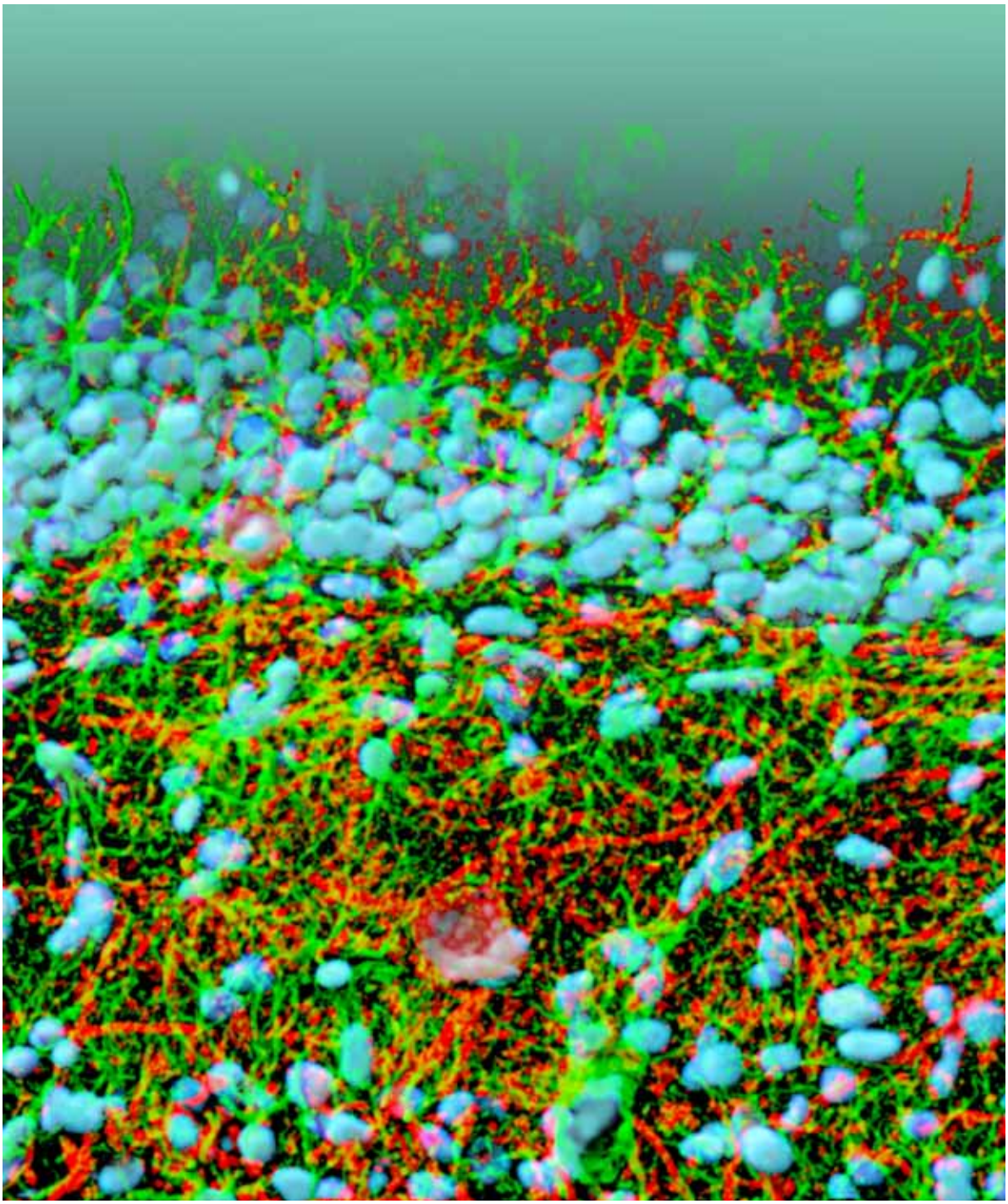
Ihor R. Lemischka, PhD, Director of the Black Family Stem Cell Institute and Professor of Developmental and Regenerative Biology

Roger J. Hajjar, MD, Director of Mount Sinai's Cardiovascular Research Institute and the Arthur & Janet C. Ross Professor of Medicine

PHOTO ESSAY

Long-term Memory Formation

Mount Sinai researchers, led by Cristina Alberini, PhD, Professor of Neuroscience, found that the interaction between brain cells known as astrocytes (stained in green), and neurons (in red), is essential during long-term memory formation. (Cell nuclei are in blue.)



To learn more, visit www.mountsinai.org/inside, March 21 - April 3, 2011 Issue of *Inside Mount Sinai*

PHOTO: Image of rat hippocampus by Rumana Huq, and visual design by Alberini lab, Mount Sinai School of Medicine; and Laura Gibson, TheVisualMD

COMMENTARY

Promote Clinical Trials
Unblock the Road to Biomedical Advancement

Remarkable advances have been made recently in our understanding of disease. But turning our scientific findings into better patient care—and, ultimately, improved health—requires careful clinical studies involving humans. Without such trials, medical science would have never realized the great value of antibiotics for peptic ulcer disease, intensive care unit checklists to prevent major infections, and alpha receptor blockers for benign prostate disease.


Dennis S. Charney, MD


Hugh A. Sampson, MD


Annetine C. Gelijns, PhD


Deborah D. Ascheim, MD

Yet, despite the importance of clinical research, there is growing recognition that the clinical trial enterprise in the United States is failing, and that its shortcomings are limiting our ability to realize the benefits of scientific discovery and obtain the best value for our health care dollars. Fewer than 5 percent of all eligible adult patients are enrolled in therapeutic studies, and this percentage is even lower among the elderly, women, and racial and ethnic minorities. This, in turn, raises questions about whether trial results can be generalized. The Institute of Medicine also recently observed that 40 percent of cancer trials funded by the National Institutes of Health are never completed or published, and of those that made it to completion, many did not do so in a timely manner.

The lack of public awareness on the importance of clinical trial participation is the biggest roadblock to a robust trial enterprise. Another is the fact that some patients want only the new therapy and do not want to be randomized to the traditional or control treatment. This strong patient desire has undermined many trials, among them hormone therapy for postmenopausal women, antiarrhythmic drugs for atrial fibrillation, and high-dose chemotherapy with autologous bone marrow transplantation for advanced breast cancer. These therapies were all highly touted and widely used—before rigorous clinical trials could demonstrate that they posed more risks than benefits. Off-trial use of these untested therapies absorbed much of the candidate pool and, subsequently, the trials took longer than expected to complete.

Misunderstanding, or mistrust, of the research community also leaves some potential candidates cautious about enrollment. Cultural, linguistic, and literacy barriers, as well as financial obstacles due to insurance limits, also undermine enrollment. And too often, academic medical centers themselves—the very institutions that generate the science behind tomorrow's cures—do not invest in the infrastructure needed to conduct clinical trials, and physicians in community practices are often far removed from the trial enterprise.

The lack of public awareness on the importance of clinical trial participation is the biggest roadblock to a robust trial enterprise.

Addressing these barriers will require concerted effort among all physicians, policymakers, and the public. As a start, private payers should follow Medicare's lead and reimburse non-experimental treatment costs for patients participating in rigorously conducted clinical trials. Academic medical centers should also create innovative partnerships with referring physicians to expand enrollment and thwart off-trial use of unproven therapies. Public awareness campaigns should be developed with the dual purpose of promoting the altruism of participation—that trials improve care for future generations—as well as the reality that patients often get superior treatment and follow-up in clinical trials.

Achieving tomorrow's medical breakthroughs relies on an overhauled and revitalized clinical trial enterprise.

About the authors: **Dennis S. Charney, MD**, is the Anne and Joel Ehrenkranz Dean of Mount Sinai School of Medicine and Executive Vice President for Academic Affairs of The Mount Sinai Medical Center; **Hugh A. Sampson, MD**, is Dean for Translational Biomedical Research, Director of Conduits, Director of the Jaffe Food Allergy Institute, and Professor of Pediatrics and Immunology; **Annetine C. Gelijns, PhD**, is Co-Chair of the Department of Health Evidence and Policy, Co-Director of the International Center for Health Outcomes and Innovation Research, and Professor of Health Policy; **Deborah D. Ascheim, MD**, is an Associate Professor of Health Evidence and Policy, and Medicine (Cardiology) at Mount Sinai School of Medicine.

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Mount Sinai School of Medicine is home to 15 translational research institutes.

THE BLACK FAMILY STEM CELL INSTITUTE
Director: Ihor R. Lemischka, PhD

THE CHARLES R. BRONFMAN INSTITUTE FOR PERSONALIZED MEDICINE
Director: Erwin P. Bottinger, MD

CHILD HEALTH AND DEVELOPMENT INSTITUTE
Director: Bruce D. Gelb, MD

CONDUITS: THE INSTITUTES FOR TRANSLATIONAL SCIENCES
Director: Hugh A. Sampson, MD

DISEASE PREVENTION AND PUBLIC HEALTH INSTITUTE
Director: Paolo Boffetta, MD, MPH

EXPERIMENTAL THERAPEUTICS INSTITUTE
Director: Srinivas Iyengar, PhD

THE FRIEDMAN BRAIN INSTITUTE
Director: Eric J. Nestler, MD, PhD

GLOBAL HEALTH AND EMERGING PATHOGENS INSTITUTE
Director: Adolfo García-Sastre, PhD

IMMUNOLOGY INSTITUTE
Directors: Lloyd F. Mayer, MD; and Sergio A. Lira, MD, PhD

INSTITUTE FOR GENOMICS AND MULTISCALE BIOLOGY
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