

DEAN'S QUARTERLY



ACCELERATING SCIENCE – ADVANCING MEDICINE

Inspiring Success Through Mentorship

Greatness does not just happen. It must be recognized early, inspired to grow, and mentored, to truly succeed. Nor does greatness happen in isolation. It develops in the context of a group of individuals who are equally motivated, intelligent, ethical, and dedicated. That group, in turn, is led by someone who is visionary, passionate, creative, and ever willing to listen.

Creating great groups that drive epoch-making science that is translated into clinical applications is the overarching goal of the Mount Sinai School of Medicine. Today, biomedical science has the potential to transform the way medicine is practiced. Increased knowledge of the molecular pathways underlying disease will ultimately lead to personalized—rather than population-based—approaches to diagnosing, treating, and preventing human diseases.

To prepare our students to take advantage of the opportunities before us, we emphasize collaboration. More than 80 percent of Mount Sinai students are engaged in mentored research projects in the lab, the hospital, and the community. In every class

and clinic, students are encouraged to be both team players and independent thinkers, and to pursue their areas of interest far beyond what is required.

Such training ensures that Mount Sinai graduates will continue to be known worldwide for their scientific expertise and clinical skills. Our graduates' renown as professional leaders is secured through the strong mentoring relationships they develop during their time here. I like to refer to this as Mount Sinai Magic because the relationships that start here continue to thrive over life-long careers in science and medicine. These relationships provide our students, post-docs, and faculty with the support and opportunities they need to achieve greatness.



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.

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

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DISTINGUISHED BY SERVICE

Fifteen years ago, three residents at Mount Sinai School of Medicine were looking for a more compassionate and efficient way to treat older patients when they had an inspirational idea: provide care to the elderly in their homes. That idea led to the creation of the Mount Sinai Visiting Doctors Program, now the largest academic home-visiting program in the nation, with more than 6,000 visits each year to homebound elderly patients in Manhattan.

Recently, the program celebrated its 15th anniversary at an event honoring its founders, one of whom was David Muller, MD, Marietta and Charles C. Morchand Chair in Medical Education and Dean for Medical Education at Mount Sinai. Dr. Muller is now co-director of the Visiting Doctors Program, which partners with the Visiting Nurse Service of New York, and the Little Sisters of the Assumption Family Health Service.

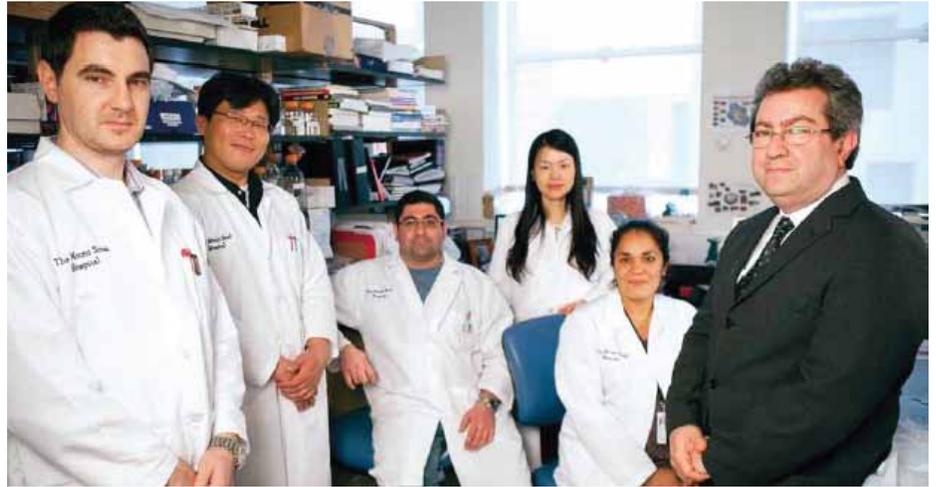
NEW GENE THERAPY PROVES EFFECTIVE IN TREATING SEVERE HEART FAILURE

Researchers at Mount Sinai School of Medicine have developed a new gene therapy that is safe and effective in reversing advanced heart failure. SERCA2a (sold as MYDICAR®), is designed to stimulate production of an enzyme that enables the failing heart to pump more effectively. In a Phase II study, SERCA2a was safe and showed clinical benefit in decreasing the severity of heart failure.

“SERCA2a met the primary endpoints and appears to be safe and effective in people with advanced heart failure,” says trial investigator Jill Kalman, MD, Associate Professor, Medicine, Cardiology, Director of the Cardiomyopathy Program, Mount Sinai School of Medicine.

“There is a significant unmet need for treatments in this patient population, and these data indicate that SERCA2a is a promising option for them.”

The CUPID (Calcium Up-regulation by Percutaneous administration of gene therapy In cardiac Disease) trial is a randomized, double-blind, placebo-controlled study that enrolled 39 patients with advanced heart failure to study the safety and efficacy of SERCA2a. Patients were randomized to receive SERCA2a gene delivery in one of three doses or placebo, and were evaluated over six months. The treatment is delivered directly to the patient’s heart during a routine outpatient catheterization procedure.



LEFT TO RIGHT: Ioannis Karakikes, PhD, Postdoctoral Fellow; Dong Tak Jeong, PhD, Postdoctoral Fellow; Antoine H. Chaanine, MD, Postdoctoral Fellow (seated); Soojeong Kang, PhD, Postdoctoral Fellow; Lahouaria Hadri, PhD, Instructor in Medicine, Cardiology (seated); Roger J. Hajjar, MD, the Arthur and Janet C. Ross Professor of Medicine, Director, Cardiovascular Research Institute.

Patients in the SERCA2a group demonstrated improvement or stabilization in symptoms, heart function, and severity of heart failure. They also saw an increase in time between cardiovascular events and a decrease in frequency of events. SERCA2a was found to be safe, with no increases in adverse events, disease-related events, laboratory abnormalities, or arrhythmias compared to placebo.

SERCA2a was developed by a team led by Roger J. Hajjar, MD, Research Director of Mount Sinai’s Wiener Family Cardiovascular Research Laboratories and Professor of Cardiology, Medicine, and Gene and Cell Medicine, Mount Sinai School of Medicine.

“We are excited to offer patients with advanced heart failure the opportunity to reverse the disease, extend their lives, and enhance the quality of their lives,” says Dr. Kalman.

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LEFT TO RIGHT: Theresa Soriano, MD, MPH, celebrates with Visiting Doctors Founder Award recipients: David Muller, MD; Jeremy Boal, MD; Carmen Andujar, RN; and Laurent Adler, MD, MS.

The Mount Sinai Visiting Doctors Program, now the largest academic home-visiting program in the nation, makes more than 6,000 visits each year to homebound elderly patients in Manhattan.

“At the time, the hospital had many frail, elderly patients who were falling through the cracks in the system,” says Dr. Muller. “We wanted to feel as though we were making a difference.”

In the intervening years, Dr. Muller has formalized the program. All residents in Internal Medicine now spend a month as visiting doctors to see, firsthand, the everyday challenges that elderly patients face. Dr. Muller continues to make home visits, as well. “Every patient becomes a rich story, not just your 2:45 appointment,” he says.

NEW INSIGHT INTO POTENTIAL CAUSES OF PARKINSON'S DISEASE

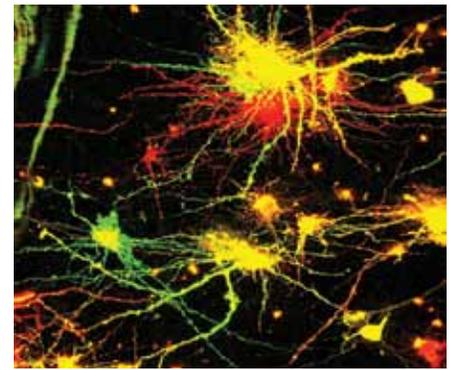
Using an advanced type of genetic engineering, researchers at Mount Sinai School of Medicine have created “mouse models” that allow them to see how mutations in a gene called LRRK2 may cause inherited Parkinson's disease, the most common form of the disease. The breakthrough, led by Zhenyu Yue, PhD, Associate Professor of Neurology and Neuroscience, and his colleagues, was recently published in *The Journal of Neuroscience*.

Up to now, it was clear that LRRK2 played a role in causing Parkinson's disease, but scientists had not been able to pursue the disease pathway of the gene mutation due to lack of a suitable animal model with abnormal forms of the gene. By using bacterial artificial chromosome (BAC) genetics, an advanced type of genetic engineering, Dr. Yue and his team had more control over

where and when a foreign gene is expressed in the target animal.

“Not having a mouse model had been a significant barrier to bringing the LRRK2 breakthrough from bench to bedside,” says Dr. Yue. “The new model likely replicates the earliest stage of Parkinson's disease, giving us the opportunity to understand the biochemical and molecular events that cause the disease.” The researchers have developed assays that allow them to measure the enzymatic activity of LRRK2 in the brain, and the mouse models will provide valuable tools in the preclinical development of drug compounds that target aberrant LRRK2 activity.

Dr. Yue and his team showed that mutant LRRK2 produces too much kinase activity in



Confocal image of nerve and glial cells in the mouse brain.

the brain. They are now looking into whether the increased kinase activity accounts for the reduced dopamine levels that subsequently lead to neurodegeneration.

NIH GRANT OF NEARLY \$10 MILLION SUPPORTS IMPROVED LAB SPACE

The Mount Sinai School of Medicine has received nearly \$10 million from the National Center for Research Resources, part of the National Institutes of Health (NIH), to expand and improve laboratory facilities. The grant will enable Mount Sinai to increase active research space by more than one-quarter, and strengthen collaborations now under way and those in the future, among principal investigators, post-doctoral students, research fellows, and research coordinators who will be consolidated on one floor of the medical center. Renovations, slated to begin in fall 2011, will affect 18,621 net square feet of space, and are expected to create space for an additional 42 research staff members. More than 85 staff members currently work on the floor.

Mount Sinai's physicians and scientists will utilize these state-of-the-art laboratory facilities to continue their tradition of conducting groundbreaking translational research. HIV-associated nephropathy is one example of the shared focus of all of the researchers who will be housed on the floor.

The NIH grant was awarded through the American Recovery and Reinvestment Act, the federal government stimulus package designed to encourage new discoveries in science, and attract new students to the field.

Young Pioneers

EMILY BERNSTEIN, PHD



Emily Bernstein, PhD

The long-term goal of Emily Bernstein, PhD, Assistant Professor, Oncological Sciences and Dermatology, and her colleagues at Mount Sinai School of Medicine, is to find new therapies for melanoma, which is very aggressive and resistant to the standard treatments for other cancers. Their work in epigenetics—a way of regulating genes without changing the DNA sequence—has enabled them to see chromatin changes that take place during melanoma progression. Chromatin is the control center of the epigenome.

Dr. Bernstein's research has yielded promising results that focus on the role of a molecule called macroH2A, a core part of the chromatin template that packages the DNA. By examining melanoma tissues from patients,

Dr. Bernstein and her colleagues found that macroH2A was absent from approximately 80 percent of the metastatic melanomas. Using RNAi technology, which allows for the manipulation of a specific molecule, Dr. Bernstein and colleagues found that loss of macroH2A promotes melanoma growth and metastasis. The lack of this molecule, she says, seems to go hand-in-hand with the development of the most dangerous kinds of melanoma. “This suggests that macroH2A is a suppressor of melanoma progression,” says Dr. Bernstein. “So it's there to protect the cells.”

She and her colleagues will continue to examine the role of macroH2A and other chromatin-associated molecules to better understand, and treat, the metastatic progression of melanoma.

Dr. Bernstein was the recipient of a 2009-2010 New York State Stem Cell Science (NYSTEM) grant to understand chromatin regulation in embryonic stem cells, a 2008-2012 New Scholar Award from the Ellison Medical Foundation, and a National Institutes of Health R21 grant to study the epigenome of melanoma.



Kenneth Rosenzweig, MD

KENNETH ROSENZWEIG, MD

Kenneth Rosenzweig, MD, a renowned physician-scientist who specializes in treating lung cancer and malignant mesothelioma, has joined Mount Sinai School of Medicine as Chair of the Department of Radiation Oncology.

Dr. Rosenzweig has developed novel techniques in radiation oncology. His work has led to new methods for delivering precise doses of radiation to lung tumors during certain points in the respiration cycle, an advancement that allows physicians to safely increase the radiation dose, shorten treatment, and spare healthy tissue. He has also worked to incorporate positron emission tomography (PET) into the radiation treatment. PET is an imaging procedure that produces advanced three-dimensional images of the body. Dr. Rosenzweig was the principal investigator for a critical-dose escalation study that established the maximum tolerated

dose of radiation therapy that can be safely delivered to patients.

He has published more than 70 articles in journals such as *Journal of Clinical Oncology*, *International Journal of Radiation Oncology Biology Physics*, and *Radiotherapy Oncology*. Dr. Rosenzweig has also authored numerous textbook chapters, including chapters in *Principles and Practice of Oncology*, the leading textbook of cancer medicine.

After receiving his medical degree from the Yale University School of Medicine in 1992, Dr. Rosenzweig continued his training as a medical intern at Beth Israel Hospital in Boston, and his residency at the Joint Center for Radiation Therapy at Harvard Medical School. Prior to joining Mount Sinai, he worked at the Memorial Sloan-Kettering Cancer Center.



Elisa R. Port, MD, FACS

ELISA R. PORT, MD, FACS

Elisa R. Port, MD, FACS, has returned to The Mount Sinai Medical Center as Chief of Breast Surgery and Co-Director of The Eva and Glenn Dubin Breast Care Center. Dr. Port is an expert in the use of breast MRI in high-risk patients, and in sentinel-node biopsy, a procedure that allows physicians to determine the patient's breast cancer stage.

Through a grant from Susan G. Komen for the Cure, Dr. Port has researched positron emission tomography (PET), an imaging procedure that produces advanced three-dimensional images of the body, and its use in pre-operative assessment of breast cancer. Through funding from the National Cancer Institute, she is conducting a Phase I study on the inhibition of the enzymes COX-2 and aromatase in breast cancer.

Dr. Port's research has been featured in numerous journals, including the *Journal of the American College of Surgeons*, *Annals of Surgery*, and *Cancer Research*.

After receiving her medical degree from Mount Sinai School of Medicine in 1992, she completed her general surgery residency at Long Island Jewish Medical Center. In 1999, she joined Memorial Sloan-Kettering Cancer Center and Memorial Hospital for Cancer and Allied Diseases, where she remained as an Associate Member and Associate Attending Surgeon until her recent Mount Sinai appointment.



Raja M. Flores, MD

RAJA M. FLORES, MD

Raja M. Flores, MD, a leading surgeon specializing in mesothelioma, lung cancer, and esophageal cancer, has joined The Mount Sinai Medical Center as Chief of Thoracic Surgery, and Director of the Thoracic Surgical Oncology Program.

A technically superb surgeon, Dr. Flores has one of the lowest complication rates with esophagectomy for esophageal cancer in the United States. He is also a leading international educator on VATS lobectomy, a minimally invasive approach that uses three small incisions in the treatment of lung cancer.

Dr. Flores has authored more than 150 peer-reviewed manuscripts, reviews, books, and book chapters, and has given over 100 lectures worldwide. In a landmark study, "Extrapleural Pneumonectomy versus Pleurectomy Decortication in the management of malignant pleural

mesothelioma," published in the *Journal of Thoracic and Cardiovascular Surgery*, Dr. Flores changed the surgical management of pleural mesothelioma cancer, which can develop in the lining of the lungs from asbestos exposure.

After earning his medical degree from the Albert Einstein College of Medicine in 1992, he spent five years at Columbia-Presbyterian Medical Center pursuing his General Surgery Internship and General Surgery Residency. Following that, he completed a Thoracic Oncology Clinical Research Fellowship at Brigham and Women's Hospital/Dana Farber Cancer Institute/CALGB in Boston, and his Cardiothoracic Surgery Residency at Brigham and Women's Hospital, Harvard Medical School. He also received a Masters in Biostatistics from Columbia University. Most recently, Dr. Flores was an Associate Professor of Cardiothoracic Surgery at Memorial Sloan-Kettering Cancer Center.

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST AWARDS \$25 MILLION TO MOUNT SINAI HEART

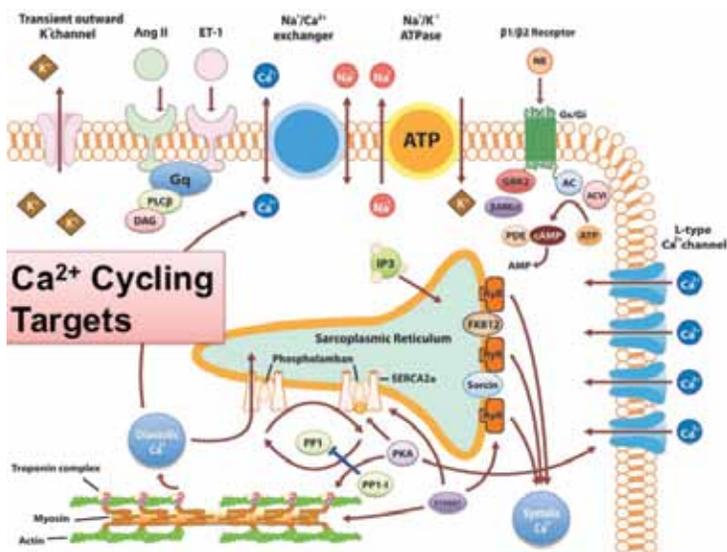
The Leona M. and Harry B. Helmsley Charitable Trust has awarded a \$25 million grant to The Mount Sinai Medical Center to establish The Helmsley Center for Cardiovascular Translational Research. The Helmsley Center, which will comprise The Helmsley Molecular Research Center and The Helmsley Clinical Investigation Center, will put Mount Sinai at the forefront of prevention, diagnosis, and the treatment of cardiovascular disease. The Helmsley Center will be a locus of exploration for novel methods including: using sophisticated gene therapy to repair damaged heart muscle; employing genetic tests to screen patients for risk assessment; and performing clinical trials to provide innovative patient therapies. The Center will accelerate the development of new drugs, devices, and protocols, and clinical trials that will allow promising interventions to move more quickly to the market and to the patient bedside. This gift will allow Mount Sinai to gain a critical

understanding of the leading cause of death among women—a disease that affects an estimated one in three American adults.

This major grant follows earlier gifts totaling \$37.5 million from The Helmsley Trust in 2009 to support Mount Sinai Heart and inflammatory bowel disease. The Helmsley commitment will support two critical areas:

The Helmsley Molecular Research Center, under the direction of Roger Hajjar, MD, will seek to understand congestive heart failure at the molecular level, target faulty genes, and use gene therapy to repair damaged muscle. Dr. Hajjar's laboratory has already made extraordinary strides in this area, showing that a new form of gene therapy—delivered directly to the heart through an outpatient procedure—can stimulate production of an enzyme that allows the heart to pump more effectively. The Center will also be working with Jean-Sebastian Hulot, MD, PhD, a world leader in pharmacogenomics. He is currently developing genetic tests that can predict which drug therapies and interventions will work in a given patient, and also what the likelihood of a re-occurrence of heart attack or disease may be.

The Helmsley Clinical Investigation Center will be directed by Valentin Fuster, MD, PhD, Director of Mount Sinai Heart, the Zena and Michael A. Wiener Cardiovascular Institute, the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, and Richard Gorlin, MD/Heart Research Foundation Professor of Cardiology. The Center will launch clinical trials that are fueled by the basic science discoveries of Dr. Hajjar's laboratory, with the intention of improving the care of patients with cardiovascular disease.



Excitation-Contraction Coupling of a Human Cardiac Cell Calcium cycling abnormalities are central to the progression of heart failure. Targeting proteins that regulate calcium movements has been the central focus of Dr. Hajjar's laboratory. Restoring one of these key regulatory proteins, the sarcoplasmic calcium ATPase pump (SERCA2a), to normal levels by gene therapy has reversed heart failure not only in experimental models but, now for the first time, in patients with advanced heart failure.

THE GLICKENHAUS FAMILY GIVES \$4 MILLION TO THE FRIEDMAN BRAIN INSTITUTE

Sarah and Seth Glickenhau, who have supported a variety of initiatives within the neurosciences in the past several years, recently committed a gift of \$4 million to the Friedman Brain Institute. This contribution will be used to establish the Glickenhau Neuroscience Laboratories, which will be dedicated to the work of researchers and clinicians who focus on cognition and neurodegenerative diseases. The gift allows The Mount Sinai Medical Center to create a state-of-the-art facility that will allow researchers to pursue work in cognition, autism, schizophrenia, Alzheimer's disease, and the genetics of Parkinson's disease.

"The Glickenhau family understands what we truly need to remain at the forefront of neurological discovery. Their support enables us

to continue to make strides in Alzheimer's disease, cognition, and a host of other areas," says Eric Nestler, MD, PhD, Nash Family Professor, Chair of Neuroscience and Director of the Friedman Brain Institute.

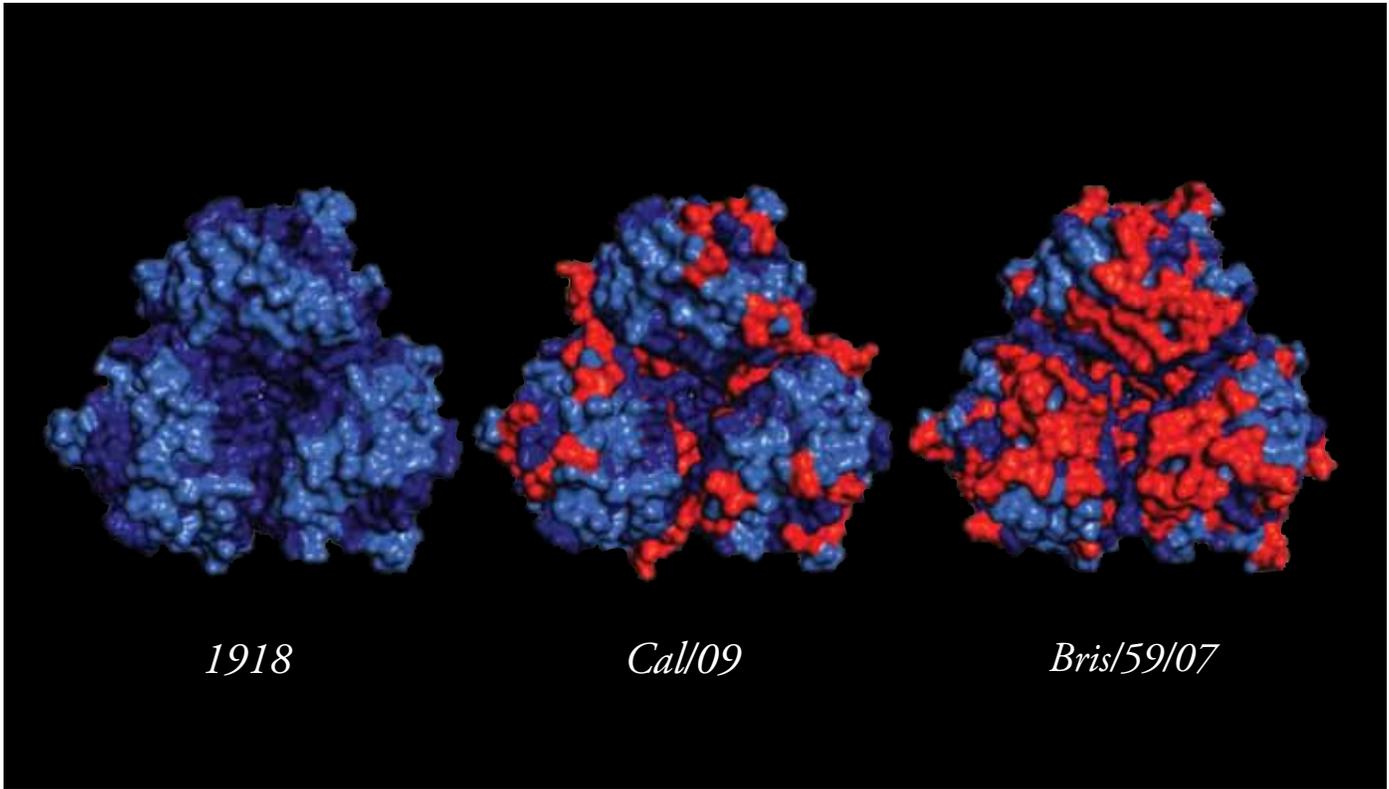
Key initiatives that the Glickenhau family has funded at Mount Sinai include a named



professorship and chairmanship for the Department of Neurology, held by Stuart C. Sealfon, MD, Sarah B. and Seth M. Glickenhau Professor and Chair of the Department of Neurology; Director of the Center for Genomics, Proteomics and Bioinformatics; Director of the Center for Translational Systems Biology, and Professor of Neurobiology and Pharmacology and Systems Therapeutics.

Mr. and Mrs. Glickenhau's children, Jim and Nancy, have also been actively engaged in philanthropy to Mount Sinai. Their granddaughter, Katie, is currently studying at Mount Sinai School of Medicine.

LEFT TO RIGHT: Seth and Sarah Glickenhau with Kenneth L. Davis, MD, President and Chief Executive Officer of The Mount Sinai Medical Center.



ANTIGENIC CHARACTERIZATION OF THE NOVEL H1N1 INFLUENZA VIRUS

Structural models of the viral Hemmagglutinin (HA) protein show that the Novel H1N1 influenza virus (middle), which caused the 2009 pandemic, is antigenically similar to the lethal 1918 Spanish influenza virus (left), but drastically different from recent seasonal H1N1 viruses such as Brisbane/59/07 (right). The known antigenic sites of the HA protein are depicted in light blue, and changes that occurred over time in these sites are depicted in red.

The Spanish influenza virus of 1918 killed more than 50 million people. Researchers at Mount Sinai School of Medicine determined that people who have been vaccinated against the 2009 H1N1 influenza virus, and those who were exposed to it, might be cross-protected against the 1918 Spanish influenza virus. The reconstruction of the formerly extinct 1918 influenza virus has greatly facilitated the study of other pandemic viruses.

PHOTO: Adolfo García-Sastre, PhD
Professor, Microbiology, Mount Sinai School of Medicine

FULFILLING THE PROMISE OF BIOMEDICAL RESEARCH

The signing of our nation's historic health care legislation should be just the beginning of a national discussion on how biomedical research can bend the cost curve of medical care through new therapeutics.

Debates leading up to this landmark event were characterized by a paucity of discussion on the potential impact of biomedical research on the health of individuals, our nation, health care costs, and the economy.

There is clear evidence that increases in biomedical research funding by the National Institutes of Health (NIH) have led to reduced mortality rates for chronic diseases including cancer, cardiovascular disease, stroke, AIDS, and diabetes. Today, the average life expectancy at birth in the United States is 78; 80 years ago it was 57. A good part of that increase is related to advances in biomedical science. Antibiotics, vaccines, cardiovascular drugs, anti-ulcer drugs, anti-inflammatory drugs, and bronchodilators have had major effects on mortality from common diseases. Most recently, anti-retroviral drugs have dramatically reduced deaths resulting from AIDS. Imagine the cost to our health care system if advances in AIDS treatment or cardiovascular disease had not been made. Even more to the point, imagine a health care system without a polio vaccine.

There is clear evidence that increases in biomedical research funding by the National Institutes of Health (NIH) have led to reduced mortality rates for chronic diseases including cancer, cardiovascular disease, stroke, AIDS, and diabetes.

Today, human genetic studies have the potential to transform the way clinical medicine is practiced. Increased knowledge of the molecular pathways underlying disease may reveal novel drug targets, leading to personalized—rather than population-based—approaches to diagnosing, treating, and ultimately preventing human diseases. Robust investments in biomedical research now would bring promising results within the next decade.

We also need a drug-development infrastructure that can handle the acceleration in biomedical research. The pace of approval for new drugs by the U.S. Food and Drug Administration remains unacceptably low. From 1950 to 2008, the agency has approved 1,222 new drugs—with the per annum number remaining flat. Given the promise that biomedical research holds, it is a tragedy that in 2008 only 21 drugs of novel mechanism were approved for use in the United States. This is well below the level required to dramatically enhance human health—and far beneath



the scientific community's capacity for drug discovery and development.

In addition to potentially changing the course of human health, the large-scale investments in biomedical research would also stimulate economic growth. A recent study demonstrated that in one year alone, NIH funding for New York State generated nearly 30,000 jobs and over \$4 billion in business activity. At the national level, more than 1.2 million people are employed in the biosciences, and the Bureau of Labor Statistics projects that employment in biosciences will grow at an annual rate that is 13 percent higher than the overall rate of employment. Additional investments would lead to even greater growth. If the United States does not increase its investment in biomedical research, the world's center for medical innovation and discovery will shift. In the context of a struggling economy, growing federal deficits, and the challenge of our intractable disease burden, the United States should consider the opportunities that could be generated by a major investment in biomedical research.

Dennis S. Charney, MD, is Dean of Mount Sinai School of Medicine at The Mount Sinai Medical Center in New York City. Kenneth L. Davis, MD, is President and Chief Executive Officer of The Mount Sinai Medical Center. One in a series of commentaries in *The New York Times* by prominent Mount Sinai physicians and scientists.



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