

THE RESEARCH INSTITUTES

ACCELERATING
SCIENCE

ADVANCING
MEDICINE



MOUNT SINAI
SCHOOL OF
MEDICINE

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PASSION

Fierce Competition

Fierce Cooperation

We intend to create a research environment
that encourages collaboration and rewards
work that challenges conventional wisdom.

— DENNIS S. CHARNEY, MD

MESSAGE FROM THE DEAN



DENNIS S. CHARNEY, MD

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

Where Does the Future Happen?

I am very proud to introduce Mount Sinai School of Medicine's vision for its twelve translational research institutes. These institutes embody our mission as a leader in basic and clinical research and lie at the heart of the larger strategic plan for The Mount Sinai Medical Center.

Translational medicine has been synonymous with Mount Sinai since the founding of the Hospital in the mid-nineteenth century, when our doctors turned to their microscopes to better understand the conditions they had just encountered in their patients.

The halls of our medical school are lined with portraits of Mount Sinai pioneers who first described clinically complex disorders, including Crohn's disease, Churg-Strauss disease, Tay-Sachs disease, and Brill's disease.

This passion for patient-focused research inspired another generation of physicians, who created Mount Sinai School of Medicine. Today, we are building upon this legacy with a research model that moves beyond the conventional departmental structure that typically governs medical schools.

Our plan originated in 2005, when I invited over 100 of Mount Sinai's leading researchers to form twenty-two working groups that would address our future. Together, we agreed that Mount Sinai had an unparalleled opportunity to transform itself into an even more powerful translational medical institution.

The basic infrastructure of The Mount Sinai Medical Center, a medical school embedded in a hospital, is tailor made for collaborative projects that can progress rapidly, unencumbered by a complex bureaucracy. In fact, Mount Sinai is unique among academic medical centers in not being accountable to either a university administration or a governmental organization.

During two years of intense study and discussion, we identified areas of research where Mount Sinai can truly be a world leader. This analysis formed the basis of the twelve research institutes that you will learn more about in subsequent chapters.

Each institute is designed to facilitate breakthrough science. We intend to create a research environment that encourages collaboration and rewards work that challenges conventional wisdom. Scientists from different departments and disciplines will be provided the intellectual freedom, the physical space, and the financial support they need to pursue their best ideas. Further, these research institutes will be characterized by organizational flexibility in order to maximize our capacity to respond quickly to scientific advances.

As the medical sociologist Rogers Hollingsworth observes, the most successful scientists possess “high cognitive complexity,” which gives them the capacity to see important relationships among disparate fields of knowledge. Both the physical design and intellectual atmosphere of our institutes reflect this insight, by encouraging the constant and open exchange of ideas. I believe we have greatly increased the potential for major discoveries at Mount Sinai by designing our research model to reflect Hollingsworth’s findings.

Seven of our institutes are disease oriented, focusing on the brain, cancer, child health and development, the heart, immunology, metabolism, and emerging pathogens.

Five institutes will complement and advance the work of the disease-oriented institutes: experimental therapeutics, molecular imaging, personalized medicine, stem cell research, and disease prevention and public health.

Our decision to target areas where Mount Sinai can excel also governs research priorities within the institutes, which build upon established clinical and research strengths, the expertise of our new recruits, our unique location at the intersection of New York’s most and least affluent zip codes, and our long-standing commitment to all of the communities that Mount Sinai serves.

Above all, Mount Sinai will continue to encourage and support the bold thinking and disciplined science that can fundamentally

change the face of medicine. Heart and brain researchers, for example, are working toward restoring tissue and repairing functions thought to have been lost forever. Experts in children's health are uncovering the genetic and environmental underpinnings of asthma, the primary cause of school absenteeism in New York City. Diabetes researchers are unraveling the complex web of factors that contributes to a national health crisis. Cancer investigators are using new knowledge of stem cells to fundamentally transform the fight against one of the leading causes of death worldwide.

These and myriad other investigations will take place on a campus invigorated by the new Center for Science and Medicine, which is designed to promote translational research. This 450,000-foot facility will house six full floors of laboratory space built to encourage scientists to share ideas and findings on an informal basis.

The Center will also be home to our cancer clinics and labs, and our new imaging center. This will facilitate communication between researchers and their clinical partners and will enable patients and doctors to take full advantage of the latest technologies. Overall, the Center for Science and Medicine, scheduled to open in 2012, will increase our research capacity by 30 percent.

Mount Sinai School of Medicine is a magnet for visionary scientists and clinicians, and I am honored to be working with such a passionate and productive group of colleagues.

VISION

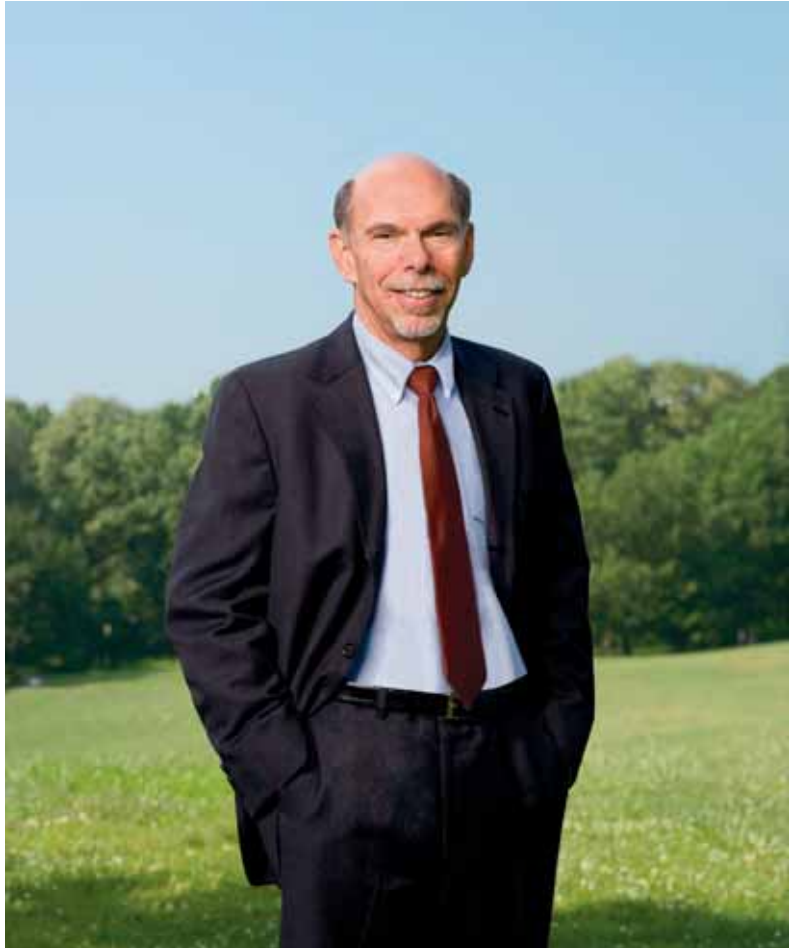
Rigorous Thinking

Revolutionary Medicine

Many discoveries are now within our grasp, including those that will increase the plasticity of the human brain, rejuvenate damaged heart tissue, and protect society from devastating pandemics.

— KENNETH L. DAVIS, MD

MESSAGE FROM THE PRESIDENT AND CEO



KENNETH L. DAVIS, MD
President and Chief Executive Officer of The Mount Sinai Medical
Center and the Gustave L. Levy Distinguished Professorship

A Portrait of the Future

We are living at a watershed moment in medical science. The elaboration of the human genome has created a revolution in biology that is equivalent to the revolution in physics that occurred in the early years of the twentieth century. Between 1890 and 1920 a sequence of basic discoveries set the stage for nuclear energy, transistors, and rapid communication, transforming life to such an extent that someone living a century ago could not have imagined the world of today.

The current revolution in the biomedical sciences reflects an increased understanding of how genes are controlled and how proteins are made and can be changed, and it presents unprecedented opportunities for the development of new classes of drugs and diagnostic tools. Armed with such new innovations, the medical profession can treat and cure some of the most serious diseases and conditions known to humanity, improving outcomes and extending millions of lives.

Those of us at the leading edge of research in the life sciences, especially at academic medical institutions, see extraordinary opportunities before us every day. I am particularly proud that The Mount Sinai Medical Center has both the intellectual and financial resources to deliver on these opportunities.

Our new institute structure, as envisioned by my colleague Dennis Charney, will accelerate the pace of breakthrough ideas. We have carefully chosen the areas of research in which we can excel, and we have recruited world-renowned scientists and clinicians to join our distinguished faculty. Many discoveries are now within our grasp, including those that will increase the plasticity of the human brain, rejuvenate damaged heart tissue, and protect society from devastating pandemics.

Financially, The Mount Sinai Medical Center is in sound condition, giving us the capacity to recruit world-renowned talent, support young scientists, build new facilities, and fund novel ideas.

Furthermore, successful translational medicine, by its very nature, promises to increase intellectual property and royalties, hospital revenues from new treatments and therapeutics, National Institutes of Health funding, and future philanthropy.

Our success and our stability as an academic medical institution reflect both the wisdom of the institute plan and the strength of the entire Mount Sinai team. Thanks to their efforts and foresight, we have every reason to be optimistic about the future of Mount Sinai and the future of medical science.

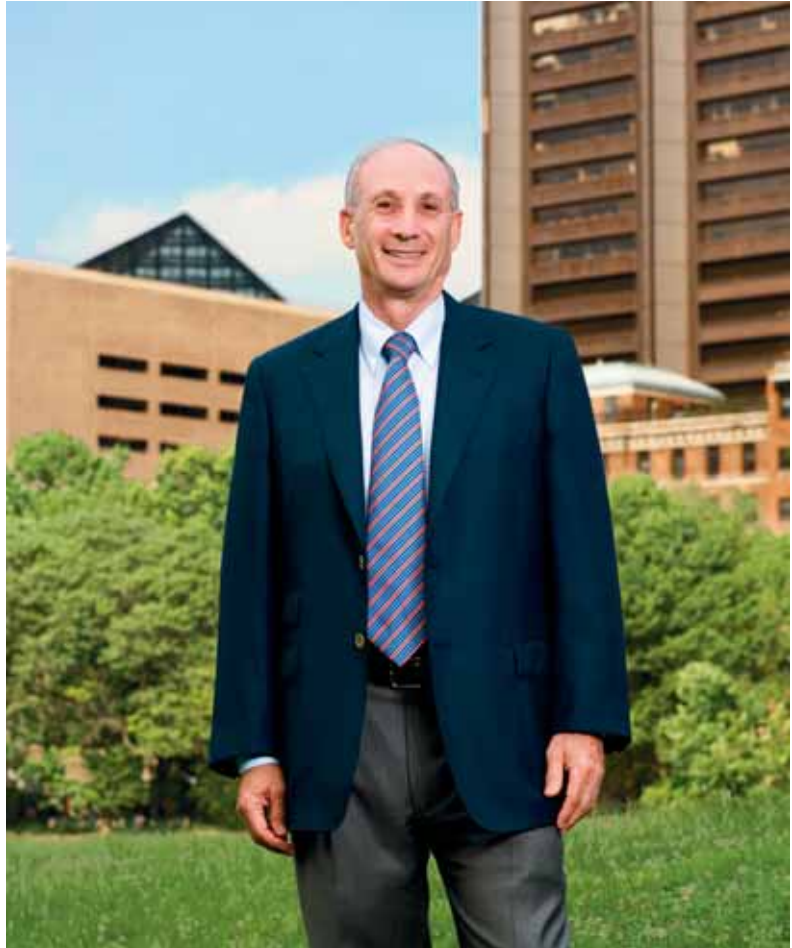
Breaking Ground

Building Greatness

The creation of twelve translational
research institutes is a bold move forward and a
natural evolution of Mount Sinai's legacy.

— PETER W. MAY

MESSAGE FROM THE CHAIR



PETER W. MAY
Chair of the Boards of Trustees

Building the Right Place at the Right Time

For over 150 years, Mount Sinai physicians have advanced science, and accelerated the pace at which research breakthroughs have been developed into novel therapies that benefit our patients. The creation of twelve translational research institutes is a bold move forward and a natural evolution of Mount Sinai's legacy.

Today, the revolution in the biological sciences is opening new avenues for investigation and even greater opportunities to improve patient care. At this critical moment, Mount Sinai is ideally positioned to shape the future of medicine.

Our endowment has grown to \$1.1 billion. This important measure of stability reflects both sound financial management and the long-term generosity of so many of our supporters.

Last year alone, Mount Sinai raised a record \$147 million in philanthropy, and soon we will launch a \$1 billion capital campaign to fuel Mount Sinai's comprehensive strategic plan. Many of the families responsible for our extraordinary growth are continuing a tradition that dates to the founding of the Hospital in the nineteenth century.

We are about to break ground for the new Center for Science and Medicine, a state-of-the-art facility that will serve as a focal point for our translational research efforts. The Center will include six full floors of laboratory space and will house all of Mount Sinai's cancer-related research, clinics, and advanced imaging technologies. With almost a half million square feet of space, the Center will increase our overall research capacity by a full 30 percent.

Recently, The Mount Sinai Hospital and Mount Sinai School of Medicine received an "A"-category rating from Moody's Investors Service. This is a tremendous achievement and represents the fruition of all of our financial improvement efforts. Among our particular strengths, Moody's praises our "focused and driven management team committed to financial success."

Of course, the most important component of Mount Sinai's growth is the superb quality of our scientists and physicians. Over the past two years, Mount Sinai has recruited scores of world-renowned researchers and clinicians who have chosen an environment that offers the freedom to explore new avenues of inquiry and the opportunity for cross-disciplinary collaboration.

As Board Chair, I am proud that Mount Sinai is in a position to fully support the unified vision of Dr. Davis and Dr. Charney, and encourage the work of so many remarkable medical pioneers.

THE CENTER FOR SCIENCE AND MEDICINE

The new Center for Science and Medicine will be a state-of-the-art, modern facility that will house both clinical care and basic research programs. Designed to increase interaction and collaboration among faculty and staff practicing a variety of disciplines, the building will feature wide open spaces, significant laboratory and clinical care space, as well as a roof lounge.



Construction for the Center for Science and Medicine is scheduled to begin in 2008 and is expected to take approximately three to four years. The 450,000-square-foot facility will increase Mount Sinai School of Medicine’s research capacity by about a third.



BRAIN INSTITUTE

Eric J. Nestler, MD, PhD

Director

Not
above
our
heads.

The Brain Institute is an interdisciplinary hub for defining the mechanisms underlying brain and nervous system diseases and for translating those findings into preventative or restorative interventions. The Institute is focused on three major areas of investigation where Mount Sinai can be truly transformative: neural injury and repair, cognition, and neuropsychiatry. The Institute will be judged by its success in advancing brain repair, developing new ways to advance cognition, and improving the treatment of neuropsychiatric disorders.

Building on Mount Sinai's Strong History

The Brain Institute's work spans basic molecular and genetic research of nervous system disorders, from animal models to investigations of human populations in the clinic. New knowledge from animal studies will drive clinical investigations, while new insight from clinical studies will help guide more basic exploration into the underlying mechanisms. This broad-based approach incorporates a wide range of state-of-the-art methodologies and coordinates efforts among numerous departments at Mount Sinai School of Medicine, including neuroscience, neurology, psychiatry, neurosurgery, pharmacology, geriatrics, and rehabilitative medicine.

Among the most common and devastating disorders we face today are those that involve the degeneration and death of nerve cells. Prominent examples include Alzheimer's and Parkinson's diseases.



Mount Sinai has been recognized as a leader in brain research and treatment for over a century. It has been at the forefront of the rapidly evolving discipline of basic neuroscience, while its long-standing reputation for excellence in clinical neurology, psychiatry, and rehabilitative medicine has continued to grow.

“The important contributions of Mount Sinai researchers and clinicians cover the human lifespan — from pediatrics to geriatrics. Mount Sinai’s world-renowned programs in Alzheimer’s disease, Parkinson’s disease, spinal cord injury, stroke, multiple sclerosis, schizophrenia, autism, and related areas give us a tremendous advantage,” says Eric J. Nestler, MD, PhD, Director of the Brain Institute, Nash Family Professor, and Chair of the Department of Neuroscience.

Neural Injury and Repair

Among the most common and devastating disorders we face today are those that involve the degeneration and death of nerve cells. Prominent examples include Alzheimer’s and Parkinson’s diseases. Additionally, traumatic injury of the brain and spinal cord, loss of brain tissue due to stroke, or damage to nerve cells due to loss of myelin sheaths in multiple sclerosis afflict large segments of the population.

The adult brain, and in particular the cerebral cortex, has much more neural plasticity than was once believed. Brain Institute members plan to translate this new understanding into a strategy for asking and answering questions that will benefit patients. Accordingly, they pose the question: “How can we help the afflicted individuals gain — or regain — greater independent function in their lives?”

Whether the disorder in question is depression, obsessive-compulsive disorder, stroke, or schizophrenia, the emphasis of this new translational medicine institute is on the retraining, recovering, and restoring of those processes controlled by the cortex.

“Depression, addiction, and so many other psychiatric disorders involve the altering of brain circuits; so to treat them, you have to tap into synaptic plasticity and shift these brain circuits back to their normal function,” says John Morrison, PhD, Dean of Basic Sciences and the Graduate School of Biological Sciences, and the W.T.C. Johnson Professor of Geriatrics and Adult Development (Neurobiology of Aging).

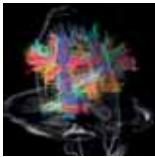
New treatments could range from the use of drugs to enhance neural plasticity to cognitive training or transcranial magnetic stimulation. “Deep brain stimulation (DBS), for example, is a revolutionary technology that is reshaping the field of neurosurgery. Rather than simply destroying or removing abnormally functioning tissue, DBS works with the brain, modulating neural function in discreet brain regions. As we increase our understanding of the physiological mechanisms underlying the effects of DBS, we can realize its promise not just for the treatment of neurologic disorders like Parkinson’s disease, dystonia, and epilepsy but also for mood disorders like depression and obsessive-compulsive disorder,” says Ron L. Alterman, MD, Director of Functional and Restorative Neurosurgery and Associate Professor of Neurosurgery.

Enhancing Cognitive Function

Over the past decade, scientists at Mount Sinai and elsewhere have unraveled many of the basic molecular, cellular, and nerve-circuit mechanisms that govern the brain’s remarkable capacity for plasticity. The Brain Institute is expanding on these advances in its efforts to develop treatments that will strengthen cognitive function in people of advancing age, the most rapidly growing segment of our population.

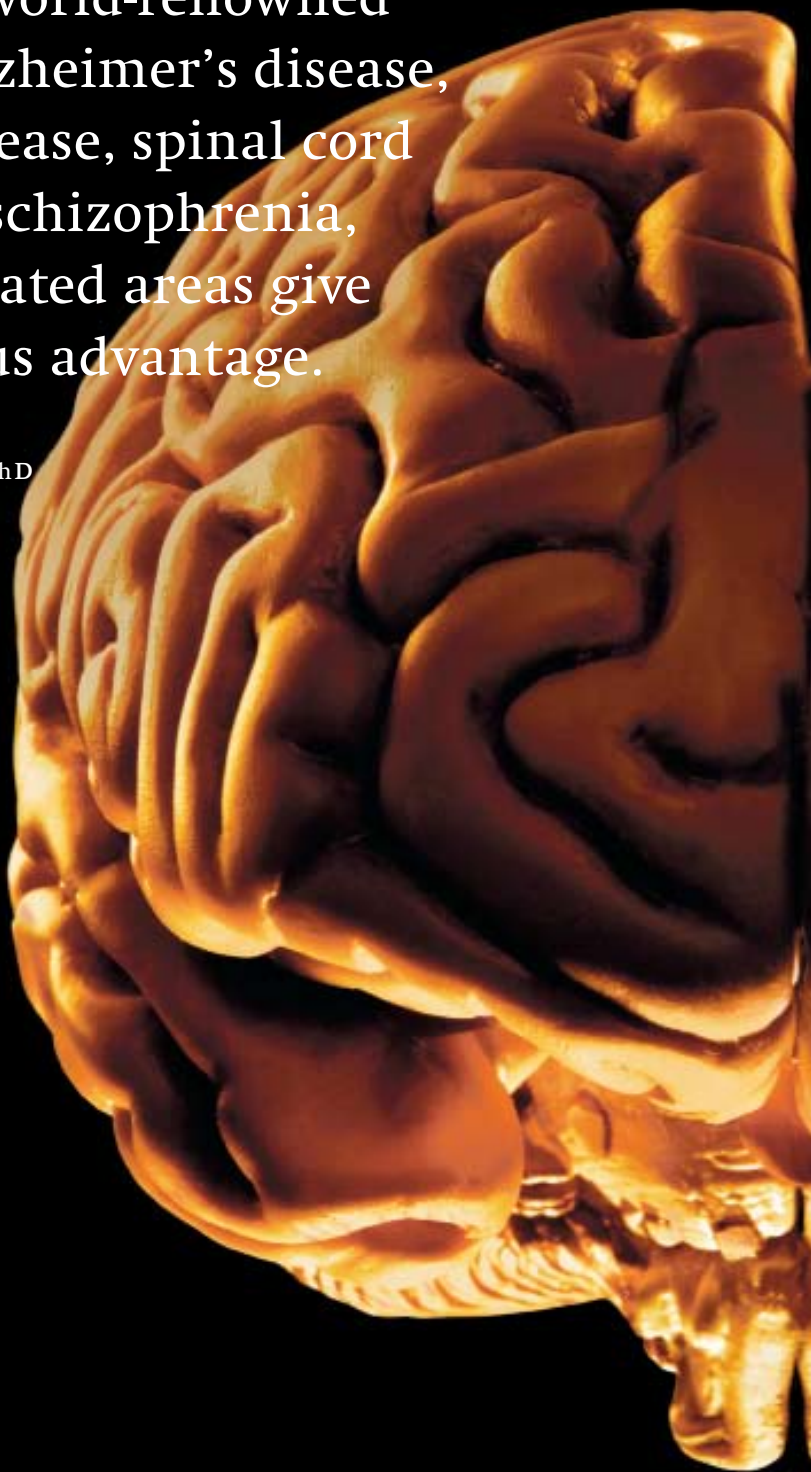
A prime example is the program being developed at the interface of geriatrics and neurodegenerative diseases. “Our research on brain and molecular pathways has led to fundamental discoveries of specific populations of neurons that are at heightened risk of degenerating in dementia. We know their morphomolecular phenotype, and this information is crucial to help us and others to design therapeutic means aimed at restoring or protecting these particular cells,” says

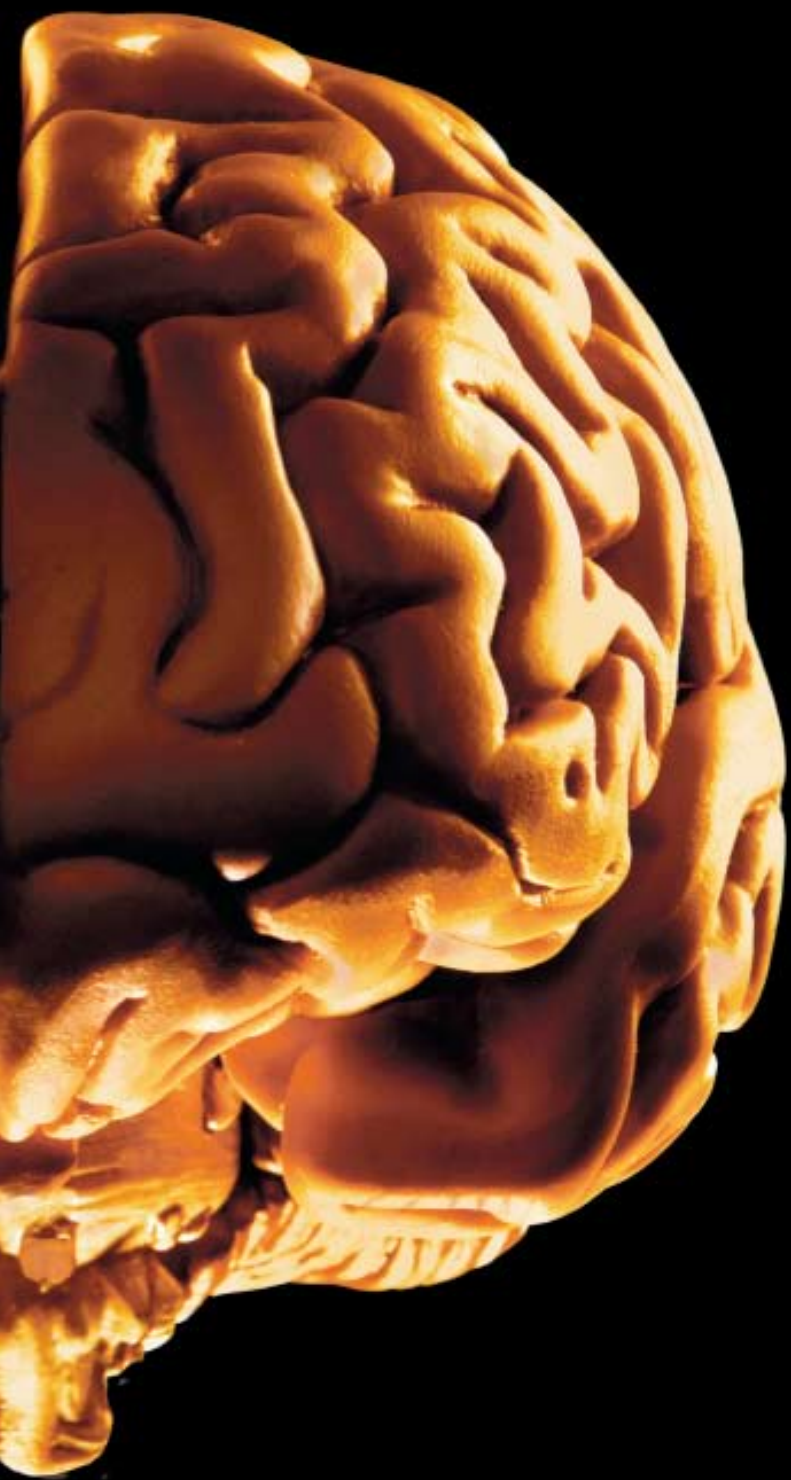
An illustration of axonal fiber tracking using Diffusion Tensor Imaging, a type of magnetic resonance imaging.



Mount Sinai's world-renowned programs in Alzheimer's disease, Parkinson's disease, spinal cord injury, stroke, schizophrenia, autism, and related areas give us a tremendous advantage.

— ERIC J. NESTLER, MD, PhD





Patrick R. Hof, MD, the Irving and Dorothy Regenstreif Professor of Neuroscience and Vice Chair for Translational Research of the Department of Neuroscience.

Similarly, Institute clinicians and basic scientists dealing with the causes and consequences of inflammatory reactions in the brain are working with researchers investigating protein folding and misfolding, a problem in neurodegenerative diseases, setting the stage for studying the impact of inflammatory reactions on protein misfolding.

As researchers gain greater understanding of the molecular and neural basis of synaptic plasticity and cognition, it will also be possible to enhance cognitive function in normal individuals. In this way, advances in basic and clinical neurosciences will help ensure that each individual reaches his or her full potential.

Neuropsychiatry

Neuropsychiatric conditions exact an enormous toll on human society. Disorders such as depression, drug addiction, schizophrenia, bipolar disorder, traumatic stress, and autism afflict more than 20 percent of the population and together represent a burden of illness that surpasses that of cancer and heart disease. Moreover, neuropsychiatric conditions affect our most human traits – emotions and feelings – and are most challenging to understand and to cure. Despite these obstacles, researchers have gained new knowledge of the genetic and nongenetic causes of these conditions that will guide their ability to treat the disorders in the years ahead and lead to major advances. The Institute is playing a principal role in identifying the causes of neuropsychiatric conditions, developing objective diagnostic tests for these disorders, and generating novel and more effective treatments.

“For instance, we know that addiction disorders have a large genetic predisposition that is impacted by the environment, so we must work to understand these interactions. In one recent study, the majority of people with a specific gene mutation were heroin abusers,” says Yasmin Hurd, PhD, Professor of Psychiatry and Pharmacology and Systems Therapeutics.

“Dr. Hurd’s work on genetics and epigenetics – looking at how the environment changes genetic regulation – could have an important practical impact on prevention and early intervention with our patients and their families,” says Dr. Nestler.

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20%

Innovation and Advances in Neurotherapeutics

The success of the Mount Sinai Brain Institute relies on its ability to develop and apply innovative approaches to scientific investigation — both in laboratory animals and in human treatments. For example, the Institute is manipulating genes in mouse models and establishing mice-harboring genetic mutations that cause disease in humans. Thus, for the first time, investigators can consider correcting or compensating for genetic abnormalities in the brain and spinal cord.

Experimental therapeutics will significantly surpass today's medicines, which now target fewer than 100 of the tens of thousands of gene products that compose the nervous system, resulting in new medications of expanded reach and effectiveness.



In fact, the use of viral vectors and other gene-therapy tools to treat disease is a major area of collaboration with the Experimental Therapeutics Institute. This work also involves the Translational and Molecular Imaging Institute, as researchers will need to validate the efficacy of these gene-therapy tools. And the collaboration will extend to the Institute for Personalized Medicine because in some cases, researchers will tailor gene therapies to an individual's particular pathological processes.

Similarly, nerve stimulation techniques show promise for correcting a range of brain and spinal cord abnormalities. For the first time, imaging technologies will make it possible to examine the functioning and chemical constituents of the human brain. The results will not only help gain critical insight about the causes of nervous system diseases but also lead to definitive diagnostic tests.

Experimental therapeutics will significantly surpass today's medicines, which now target fewer than 100 of the tens of thousands of gene products that compose the nervous system, resulting in new medications of expanded reach and effectiveness.

The Brain Institute is already playing a primary role in bringing revolutionary change to the study and application of clinical neuroscience. "We are working toward a day when individuals with symptoms of a nervous system disorder go to the doctor and, through a combination of genetic and imaging tests, obtain a definitive diagnosis — and toward a time when that precise diagnosis will guide the use of medication and non-medication treatments that specifically target an individual's underlying pathology, giving patients new hope for a better life," concludes Dr. Nestler.

CANCER INSTITUTE

Steven J. Burakoff, MD

Director

A
sharper
focus.

The Cancer Institute is dedicated to changing the reality of one of the leading causes of death worldwide. Any Mount Sinai researcher or clinician whose work touches cancer in any way will be connected to the Institute. Investigators — full-time members as well as members of a larger matrix organization— will work together to integrate Mount Sinai’s expanding research capacity in developmental and molecular biology, stem cells, cancer biology, and pharmacology with its current clinical programs, including those in liver, breast, prostate, head and neck, and hematological malignancies.

Rethinking the Strategy and Focus

“There is a shift in our understanding of cancer, and there needs to be a corresponding shift in our research infrastructure,” says Steven J. Burakoff, MD, Director of the Cancer Institute and Professor of Medicine (Hematology and Medical Oncology) and Oncological Sciences. “Although we have had success moving many cancers from a death sentence to a chronic disease, we have underestimated the complexity of this illness. Now we are unraveling these complexities with the goal of developing more targeted, effective treatments and, ultimately, prevention strategies. And this requires the thinking of investigators from many different and sometimes unexpected disciplines. That is why I believe in a large matrix organization that reaches out to all the best minds and ideas.”

Not only is Mount Sinai recruiting some of the world’s most renowned cancer researchers, but over 40 percent of the new Center for Science and Medicine building will be devoted to cancer research and treatment. “Mount Sinai’s unified structure is perfectly suited to forming the close collaborations between basic and clinical researchers and clinicians that will lead to breakthrough science,” adds Dr. Burakoff.

The Next Era of Cancer Research

The thinking on cancer is changing. Formerly, it was believed that cancer cells mutate and become resistant to chemotherapy. Today, there is a growing belief that a cancer stem cell begins to send out offspring cancer cells that cannot be detected clinically until they reach a sufficient number of cells to create a tumor.

“Cancer treatments typically focus on killing the tumor and on the end stage of cancer development, but we still need to get to the root of the problem – to the stem cell,” says Dr. Burakoff. “Ihor Lemischka is certainly one of the best-known scientists in the area of understanding stem cells. And you have to understand stem cells to know how they went awry to become cancer stem cells,” he continues.

“In recent years, it has become clear that at least in certain cancers, a small cellular subpopulation of the tumor sustains the disease and its progression,” says Dr. Lemischka. “These cells, commonly termed cancer stem cells, behave like tissue stem cells in that they give rise to the entire tumor mass and can also self-renew. Often this subpopulation is not sensitive to the common therapeutic agents that are used to treat the disease. Therefore, it will be imperative to

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40%

use paradigms obtained from studies of normal stem cells in order to develop novel therapies that specifically target the cancer stem cells.”

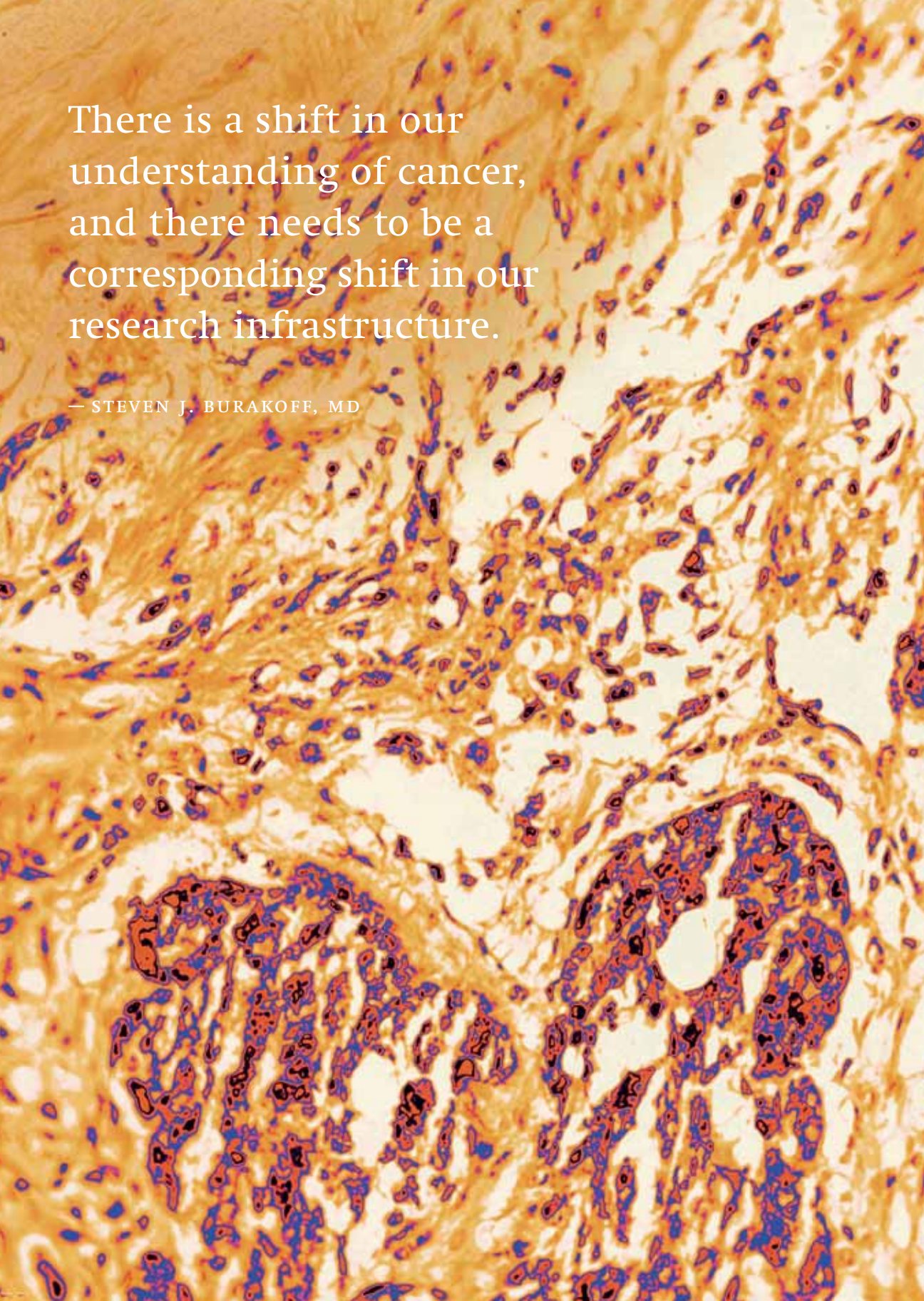
A New Avenue of Drug Discovery

Ross Cagan, PhD, Professor of Developmental and Regenerative Biology, has developed a method for screening the fruit fly *Drosophila* for therapeutic drugs. “We grow the flies in microwells using robotics to add food, drug, and flies to each well. We then use a bottom-line screen: the ‘tumors’ we build into the flies must diminish in size while the flies remain healthy. That is, we screen for efficacy and toxicity,” he explains.

One example of Dr. Cagan’s efforts with fly models is breast cancer. “Targeting oncogenes linked to breast cancer in the fly, we identified 39 compounds that slowed the tumor growth and metastasis that are so devastating in breast tumors,” Dr. Cagan says. “After ‘curing’ our flies, we tested several of these compounds in mouse breast cancer models. Four out of six drugs blocked proliferation of a murine breast cancer cell line in a dish. We then injected one of our compounds into mice and found that it could stop breast cancer metastasis to the lung in a standard breast cancer model. This compound inhibits activity of the Hedgehog signaling pathway, and we went on to show, in both flies and mice, that the Hedgehog pathway is linked to the Src oncogene that in turn promotes breast cancer metastasis. Most breast cancer fatalities are due to metastasis — migration of breast cancer cells to second sites such as the lung — and our work makes a connection between these two pathways. Further, we have identified candidate therapeutics and validated our fly approach as a new avenue of drug discovery.”

Stuart A. Aaronson, MD, the Jane B. and Jack R. Aron Professor of Neoplastic Diseases, is focused on the discovery and functions of cancer genes. While working at the NIH, he identified the first normal function of a cancer gene as that of a growth factor, PDGF, and cloned *erbB2*, a novel growth receptor-related gene he found to be amplified in a human breast carcinoma. This discovery and his subsequent studies paved the way to a diagnostic test for screening breast cancer patients for this lesion and to the development of targeted therapies directed against this alteration.

Dr. Aaronson also discovered KGF (FGF7), a growth factor with novel epithelial cell specificity, and demonstrated its involvement in wound repair. These findings have led to FDA approval for use of this growth

A microscopic image of tissue, likely a histological section, showing a dense network of cells and fibers. The tissue is stained with a combination of blue and brown dyes, highlighting cellular structures and possibly specific protein markers. The overall appearance is that of a complex, interconnected tissue structure.

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— STEVEN J. BURAKOFF, MD

factor in the treatment of mucositis, a debilitating side effect of many cancer therapies. His discoveries of other critical components in growth factor signaling pathways – including erbB3, the alpha PDGF receptor, and HGF as the ligand for MET – and their implications in cancer have also led to preclinical and clinical development of therapies targeting these molecules in tumors.

At Mount Sinai, Dr. Aaronson has made new discoveries implicating other signaling pathways in human cancer with the goal of extending the number of novel therapies for cancer patients.

Building on Mount Sinai’s Disease-Based Programs

Liver Cancer

Liver cancer is the fifth most common cancer in the world and is the third most common cause of cancer-related death. For years, Mount Sinai investigators have worked to understand the pathogenesis of liver cancer, and their work has yielded immense insight into the biology of the disease and how to treat it.

“Mount Sinai’s hepatocellular cancer program is one of the best in the country,” says Dr. Burakoff. “The program has outstanding surgeons and investigators who are conducting exciting research, such as Dr. Josep Llovet’s work.”

Josep Llovet, MD, Director of Liver Cancer Research at Mount Sinai and a Professor of Research at the Liver Unit of the Hospital Clinic in Barcelona, Spain, has spearheaded several studies that have ranged in focus from identifying new molecular markers, to understanding cancer cell signaling, to finding new uses for existing drugs.

Most recently, Dr. Llovet and his team discovered that a drug used to treat advanced kidney cancer – Nexavar (sorafenib) – helps patients with advanced liver cancer live 44 percent longer compared with patients who do not receive the anticancer drug.

Breast Cancer

George Raptis, MD, MBA, is Director of Mount Sinai’s new Eva and Glenn Dubin Breast Care Center, and he also serves as the new Associate Chief for Solid Tumors in the Division of Hematology-Oncology and is an Associate Professor of Medicine. The Eva and Glenn Dubin Breast

Cancer Center houses a comprehensive, highly integrated program that brings together the best minds in breast radiology, medical oncology, surgery, radiation oncology, pathology, clinical genetics, psychosocial support, and clinical translational research to provide patients with seamless care and access to clinical research.

Additionally, epidemiological research is integral to Mount Sinai's work in breast cancer. Nina A. Bickell, MD, Associate Professor of Health Policy and of Medicine (General Internal Medicine), is a principal investigator of studies funded by the Agency for Healthcare Research and Quality and the National Cancer Institute. Focusing on the reduction of racial disparities in breast cancer, Dr. Bickell has conducted several studies that examined access to medical care, breast cancer disparities among minority women, and even the quality of early-stage breast cancer treatments.

Prostate Cancer

Mount Sinai's Barbara and Maurice A. Deane Prostate Health and Research Center links multiple disciplines to bring patients with prostate cancer a comprehensive and coordinated approach to care. The most recent addition to the Center is David B. Samadi, MD, Chief of the Division of Robotics and Minimally Invasive Surgery in the Department of Urology. A leading urologic oncologist, Dr. Samadi specializes in the use of the da Vinci® robotic surgical system, a revolutionary technology that magnifies the surgical field significantly and gives surgeons greater visualization, dexterity, and precision during surgery.

While treatments for prostate cancer continue to improve, researchers are also exploring a type of gene therapy that uses cytotoxic genes and cytokines to treat patients with advanced prostate cancer. Simon Hall, MD, Chair of the Department of Urology, is collaborating with researchers in the Department of Gene and Cell Medicine to study the use of vesicular stomatitis virus in therapy. This viral therapy works by targeting and preferentially eliminating prostate and bladder cancer cells while sparing normal cells, and it is being investigated as a treatment for locally advanced or recurrent prostate cancer. Dr. Hall and his colleagues are also working on a Phase I clinical trial using an adenovirus expressing interleukin-12 in patients with locally advanced, recurrent cancer, in an effort to stimulate immune responses against local cancer as well as microscopically present metastatic disease.

Researchers are exploring a type of gene therapy that uses cytotoxic genes and cytokines to treat patients with advanced prostate cancer.



In the Department of Radiation Oncology, investigators have focused on two main research endeavors in prostate cancer. The first is a longitudinal study that follows the clinical outcomes of prostate brachytherapy patients. The second is a translational study that correlates genetic mutations with clinical outcomes following brachytherapy.

“We are looking for small mutations in various genes to see whether patients with these genetic alterations are more likely to develop radiation-related side effects,” says Richard G. Stock, MD, Professor and Chair of the Department of Radiation Oncology, “The long-term goal of this work is to create individualized treatments where specific radiation doses and targets are tailored to a patient’s personalized genetic profile.”

Hematological Malignancies

Ronald Hoffman, MD, the Albert A. and Vera G. List Professor of Medicine, the Director of the Myeloproliferative Disease Program, and Professor of Medicine (Hematology and Medical Oncology) and of Gene and Cell Medicine, is advancing Mount Sinai’s research initiatives in myeloproliferative disorders, a group of diseases in which bone marrow cells produce excessive numbers of red cells, white cells, and platelets.

Mount Sinai serves as the lead clinical site for an international, multicenter study directed by Dr. Hoffman and funded by the National Cancer Institute. The study will also examine the origins of myelofibrosis.

“We seek to answer two key questions,” explains Dr. Hoffman. “First, what is the nature of the stem cell defect that leads to myelofibrosis? And second, stem cells need to stay in the bone marrow, but in myelofibrosis, stem cells are inappropriately being released from the marrow into the circulation. We want to learn whether we can interrupt this defect and retain the stem cells inside the bone marrow, and then develop targeted therapies for these disorders.”

All of these programs, Dr. Burakoff notes, will benefit from one another: “It is easy to talk about translational research, but it is difficult to do,” he says. “Mount Sinai is not just talking about it – we are doing it, and the infrastructure and architecture of the new Cancer Institute will bring together the best in cancer care and research, greatly increasing the potential for major discoveries.”

CARDIOVASCULAR RESEARCH INSTITUTE

Valentin Fuster, MD, PhD

Director

A
change
of
heart.

The past two decades have produced critical knowledge that has led to new insights into heart and cardiovascular disease, dramatically changing our thinking about the fundamental nature of the disease and our approach to its prevention, diagnosis, and treatment. By integrating three corresponding disciplines – molecular cardiology, regenerative cardiology, and cardiac imaging – the Institute has made great headway with new approaches that enhance patient care.

A Strong Foundation and New Paradigm

Cardiovascular disease is a growing global public health threat and the leading cause of death in the industrialized world. To respond to this epidemic, Mount Sinai leveraged its already well-established translational research program with the creation of the Cardiovascular Research Institute, which traces its roots back to another institute. Over a decade ago, the Zena and Michael A. Wiener Cardiovascular Institute was created to more closely connect Mount Sinai's research advances with the clinical practice of medicine. In 2006, the Zena and Michael A. Wiener Cardiovascular Institute joined forces with the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, forming Mount Sinai Heart. Today, the Cardiovascular Research Institute is the translational research hub of Mount Sinai Heart.

Our new research and clinical paradigm is promoting health not only of individuals but of the cardiovascular system, to prevent it from becoming diseased.



“The Cardiovascular Research Institute has served as a destination for an extraordinary group of world-renowned scientists and clinicians who are fundamentally changing how we think about heart disease,” says Valentin Fuster, MD, PhD, Director of the Institute, the Zena and Michael A. Wiener Cardiovascular Institute, and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health; and the Richard Gorlin, MD/Heart Research Foundation Professor. “Our new research and clinical paradigm is promoting health not only of individuals but of the cardiovascular system, to prevent it from becoming diseased. Our approach is radically different and distinct from that of previous decades, when we focused on treating disease.”

Clinical Research

Advances in the prevention and treatment of vascular disease will require focused cooperation from Mount Sinai's established multiple interdisciplinary cardiology research teams that include cell and molecular biologists, immunologists, clinical researchers, and physicians. Understanding the prevention and treatment of vascular disease will also come from the \$25 million, five-year FREEDOM trial, sponsored by the National Institutes of Health (NIH) and led by Dr. Fuster as principal investigator and Michael E. Farkouh, MD, Associate Professor of Medicine (Cardiology), as co-principal investigator. The FREEDOM trial has reached the 1,000-patient milestone, thus creating the largest database of diabetic patients with multivessel coronary disease to date and allowing analysis of the surgical versus interventional (eluted stents) approach.

Jonathan L. Halperin, MD, the Robert and Harriet Heilbrunn Professor of Medicine (Cardiology), served as the principal cardiologist responsible for the design and execution of the Stroke Prevention in Atrial Fibrillation clinical trials, which received over \$25 million in grant support from the NIH. Dr. Halperin also directed the SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation) clinical trials, which evaluated the first oral direct thrombin inhibitor for prevention of stroke in patients with atrial fibrillation. Furthermore, Dr. Halperin served on the International Committee chaired by Dr. Fuster to set up the current guidelines on how to manage atrial fibrillation.

The award-winning research of Bruce Gelb, MD, the Director of the new Center for Molecular Cardiology, the Arthur J. and Nellie Z. Cohen Professor of Pediatrics, and Professor of Genetics and Genomic Sciences, focuses on the development of the heart and the genes that lead to congenital heart defects. Furthermore, Dr. Gelb and Roger Hajjar, MD, the Arthur and Janet C. Ross Professor of Medicine (Cardiology) and Director of the Cardiovascular Research Center, served as the co-principal investigators of the recently awarded NIH training grant.

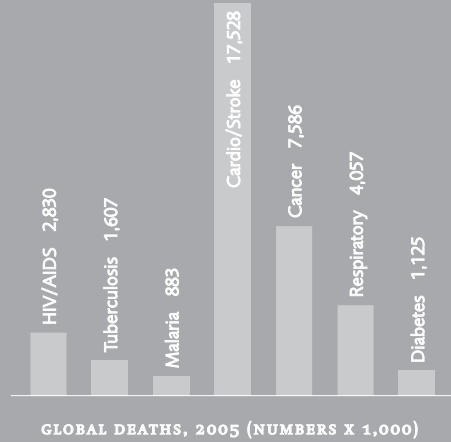
Juan J. Badimon, PhD, Professor of Medicine (Cardiology), is internationally recognized for his work on the role of lipids and thrombosis in cardiovascular disease.

Jeffrey W. Olin, DO, Professor of Medicine (Cardiology), is a renowned clinical investigator in the field of vascular medicine and has served as the lead investigator in numerous clinical trials that addressed therapeutic angiogenesis.

Linking Imaging and Clinical Trials for Improved Drug Development

Today, safe, coordinated, high-throughput imaging, including state-of-the-art magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET), provides options that are used more routinely in the clinic. Institute investigators are also using these types of imaging techniques in cardiovascular basic and clinical outcomes research in collaboration with faculty in the Translational and Molecular Imaging Institute. Specifically, Dr. Fuster; Zahi A. Fayad, PhD, Interim Director of the Translational and Molecular Imaging Institute and Professor of Radiology and Medicine (Cardiology); and Dr. Farkouh are coordinating three major national projects, which include eight

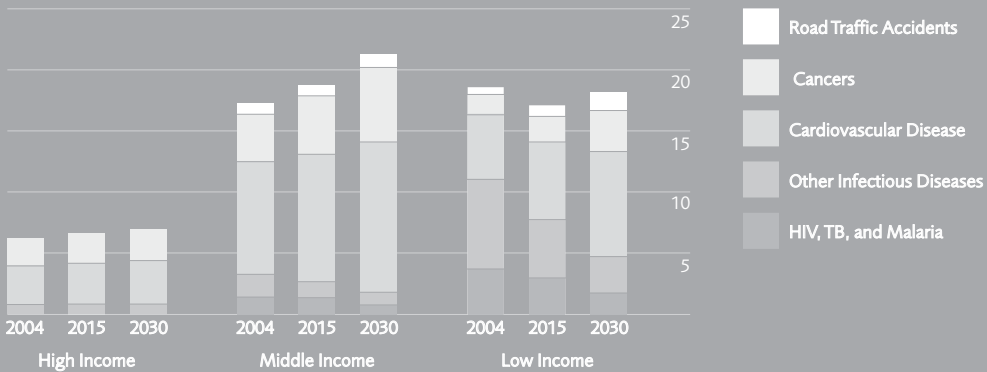
THE INSTITUTE
IS REPLACING
OLD RESEARCH
PARADIGMS WITH
NEW PARADIGMS
THAT ARE SHAPING
THE FUTURE OF
PATIENT CARE.



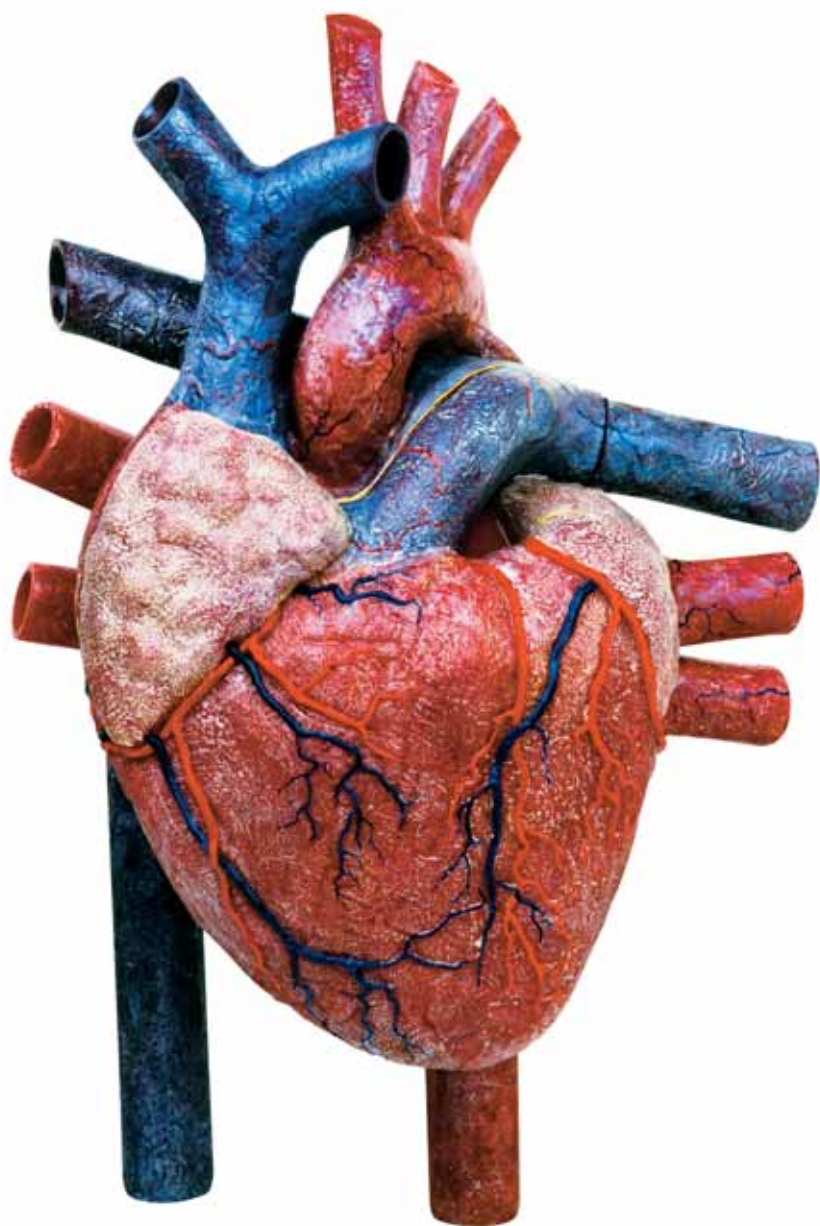
54%
GLOBAL
STROKES,
2008

47%
GLOBAL
HEART
DISEASE,
2008

BURDEN OF HYPERTENSION
About half of this
global burden is in people
with hypertension.



PROJECTED DEATHS BY CAUSE FOR HIGH-, MIDDLE- AND
LOW-INCOME COUNTRIES (DEATHS IN MILLIONS)
Data from World Health Organization's *World Health Statistics 2008*



noninvasive imaging technologies for identifying patients at high risk of cardiovascular disease.

Institute researchers, led by Mount Sinai's Mario Garcia, MD, Director of Non-Invasive Cardiology and Professor of Radiology and Medicine (Cardiology), are applying advances in heart and blood vessel image collection and analysis in a first-of-its-kind Imaging and Trials Unit. Investigators are gathering intermittent image data along with traditional end-point data in ongoing clinical trials, with the aim of identifying visible biomarkers of response to treatments. Such surrogate markers of disease progression and response to treatment could help identify successful and unsuccessful treatments more quickly during their development.

"The technology is exploding and revolutionizing the way we practice cardiology," says Dr. Garcia. "It was not long ago that we lacked a simple, economical, and noninvasive way to detect cardiovascular problems at the early stages. Now, we have the tools to be proactive."

Gene Therapy Treatment for Congestive Heart Failure

Congestive heart failure is now epidemic in the Western world and is the leading diagnosis at hospital discharge for patients 65 and older. Current treatments ameliorate the symptoms, but an optimal treatment would repair the damaged heart muscle cells. Institute researchers are pursuing two paths to restore cardiac function: gene therapy and stem cell therapy.

In gene therapy, Mount Sinai researchers are conducting animal studies demonstrating that overexpression of one such cardiac muscle gene has had restorative properties. Once a gene with these properties is identified, researchers will then develop viral-mediated gene therapy, first in animal models and then in humans, to restore expression of the gene in the diseased heart. Clinical trials are under way for one candidate gene, and the researchers intend to examine other candidate genes as well.

The Institute's interdisciplinary research in basic and clinical cardiovascular sciences includes cardiovascular development, function, pathophysiology, pharmacology, genetics, genomics, and proteomics, and investigators lead a number of key programs of research.

Dr. Hajjar focuses on understanding the molecular mechanisms of heart failure, especially as it relates to calcium cycling, and is

Dr. Hajjar focuses on understanding the molecular mechanisms of heart failure, especially as it relates to calcium cycling, and is developing novel molecular imaging techniques to better track gene transfer.



developing novel molecular imaging techniques to better track gene transfer. His laboratory is using both genomics and proteomics to identify new targets based on the restoration of contractile function following SERCA2a gene transfer.

Dr. Hajjar has assembled a team of young investigators focused on understanding the mechanisms of cardiac dysfunction and on developing novel therapies for various cardiovascular diseases. This team includes Hina Chaudhry, MD, Associate Professor of Medicine (Cardiology) and Director of Cardiovascular Regenerative Medicine, an NIH-funded physician-scientist whose basic research interests are focused on cardiac regeneration using both cell cycle regulation and endogenous cardiac progenitors; Fadi Akar, PhD, Assistant Professor of Medicine (Cardiology), who studies optical mapping of ventricular arrhythmias and mitochondrial control of ionic changes; Yoshiaki Kawase, MD, Assistant Professor of Medicine (Cardiology), who uses large animal models of arrhythmia caused by ischemic cardiomyopathy; Djamel Lebeche, PhD, Assistant Professor of Medicine (Cardiology), who investigates the genetic and cellular mechanisms underlying the pathophysiology of diabetic cardiomyopathy; and Thomas Weber, PhD, Assistant Professor of Medicine (Cardiology), Gene and Cell Medicine, and of Developmental and Regenerative Biology, whose laboratory looks at the biology of adeno-associated vector entry in cardiac cells.

Institute researchers are exploring new methods for repairing the damaged tissue using stem cell therapies.



Stem Cell Therapy, Imaging, and Cardiovascular Regenerative Medicine

Myocardial infarctions can damage the heart muscle, leaving it vulnerable to further and fatal deterioration. Institute researchers are exploring new methods for repairing the damaged tissue using stem cell therapies, starting with studies in rodents. One challenge involves the monitoring of changes that occur once cells are administered to the test animals.

Institute scientists, in collaboration with Ihor R. Lemischka, PhD, Director of The Black Family Stem Cell Institute and the Lillian and Henry M. Stratton Professorial Chair of Gene and Cell Medicine, and investigators from the Translational and Molecular Imaging Institute are devising ways to phototag the stem cells so that the cells can be noninvasively tracked in individual animals through the course of

Technology is exploding and revolutionizing the way we practice cardiology. It was not long ago that we lacked a simple, economical, and noninvasive way to detect cardiovascular problems at the early stages. Now, we have the tools to be proactive.

— MARIO GARCIA, MD

the experimental treatments. “With imaging we will be able to know exactly where the injected stem cells migrated,” says Dr. Fayad.

Another aspect of Institute research into cardiovascular regeneration involves investigation of the genes that regulate cell division in heart muscle cells. Dr. Hina Chaudhry has identified a gene that may be responsible for causing cardiomyocyte cell division in the embryonic heart. After birth, the gene, cyclin A2, undergoes complete silencing in mammalian species. “What we have found is that when the gene is turned on in mice and rats it is able to cause growth of new heart muscle cells. Now we are working on an adeno-associated virus that will deliver cyclin A2 into the infarcted heart of a pig, and will test whether it will cause heart tissue regeneration,” says Dr. Chaudhry.

Setting and Monitoring the Beat

Cardiac arrhythmias range from annoying to dangerous, and current treatments for them are less than optimal, typically treating the symptom but not the cause. Looking for better treatments has prompted the search for candidate pacemaker genes, in the belief that such genes might be used therapeutically.

To attack this problem, newly recruited bioengineers have devised a novel way of studying cardiac “pace making” in vitro, with a new optical monitoring method. Using that system, these Mount Sinai investigators have identified a candidate pacemaker gene. Now they plan to investigate whether manipulating expression of this gene will help in developing cardiac pacemaker stem cells. Such cells might one day be transferred into patients in order to permanently reverse and prevent arrhythmias.

Bioengineers have devised a novel way of studying cardiac “pace making” in vitro, with a new optical monitoring method. Using that system, these Mount Sinai investigators have identified a candidate pacemaker gene.



Tracking the Problem

As technological advances continue and treatments become more targeted and refined, the Cardiovascular Research Institute will take advantage of Mount Sinai’s expertise in epidemiology and biostatistics at the Disease Prevention and Public Health Institute and the extraordinary diversity of the New York population. Researchers will conduct extensive surveys of disease risk factors and responses to treatment. In addition to identifying the root causes of cardiovascular diseases, epidemiological studies will examine environmental factors that can aid in prevention and in improved treatment outcomes.

CHILD HEALTH AND DEVELOPMENT INSTITUTE

Philip J. Landrigan, MD

Interim Co-Director

Frederick J. Suchy, MD

Interim Co-Director

Fast
forward.

The Mount Sinai Child Health and Development Institute is organized around the principles of understanding, treating, and preventing diseases that represent critical health problems for an ever-growing number of children in New York and across the United States. These disease areas include: asthma and allergies, obesity and diabetes, and learning disabilities, such as attention deficit disorder, autism, dyslexia, and a broad spectrum of neurodevelopmental disorders. Mount Sinai's strong research programs and its access to a large patient population make this Institute particularly appealing to outstanding research faculty from around the world.

A Leader in Children's Health Research

Mount Sinai ranks first among New York's academic medical centers in National Institutes of Health (NIH) grants for pediatric research. Research areas of particular note include the molecular genetics of congenital heart disease, the developmental biology of liver and bile ducts, the pathophysiology of cholestatic liver disease, the factors affecting the progression of inherited kidney disease, the immunopathogenesis of food allergy, and the impact of the environment on children's health. Mount Sinai's vast resources and potential for philanthropic support and government funding, combined with the metropolitan area's immediate medical and public health needs, position the Child Health and Development Institute to become one of the world's leading centers of children's health research.

The Institute is the outgrowth of collaborative work in two highly regarded and research-intensive departments at Mount Sinai: Pediatrics and Community and Preventive Medicine. Researchers in both departments have long recognized that children are not small adults: Children have unique vulnerabilities with no counterpart in adult life, and their biology and vulnerability to illness evolve as they mature from infancy to adolescence.

The Department of Community and Preventive Medicine, chaired by Philip J. Landrigan, MD, the Ethel H. Wise Professor and Chair of the Department of Community and Preventive Medicine and Professor of Pediatrics, has been a national leader in studying the impact of environmental toxins on children and adolescents. The Environmental Protection Agency, the National Institute of Environmental Health Sciences, and the National Institute of Child Health and Human Development all contribute to funding research on children's health, both pre- and postnatal, and on how pesticides, lead, and endocrine disruptors affect children's physical and mental development.

The Department of Community and Preventive Medicine has played a pioneering role in planning and developing the highly acclaimed NIH-funded National Children's Study, a massive and prospective epidemiological investigation that will follow 100,000 American children from conception to age twenty-one, to identify the environmental exposures that cause disease in children and across the life span.

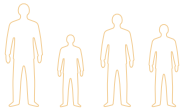
This National Children's Study is the pediatric equivalent of the famous longitudinal Framingham Heart Study, whose landmark

findings have brought about a nearly 60 percent reduction in incidence of heart disease and stroke among American adults. Because of the long-term nature of the project, epidemiologists in training will eventually become the leaders of this landmark study, and much of that future leadership is expected to come from the cadre of pediatricians and scientists now in training at Mount Sinai.

Looking at Complex Factors

Institute research is being guided by epidemiological studies that track groups of New York City children in order to identify factors in the urban environment that cause and aggravate public health concerns, such as asthma and obesity. The Institute works collaboratively with Mount Sinai's new Disease Prevention and Public Health Institute to study urban epidemics.

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“Currently we are looking at perfluorooctanates and neurodevelopment in children, focusing on possible neurological and intellectual effects. We are also addressing the effects of environmental pollutants on the onset of puberty,” says David A. Savitz, PhD, Director of the Disease Prevention and Public Health Institute, and the Charles W. Bluhdorn Professor of Community and Preventive Medicine and Professor of Obstetrics, Gynecology, and Reproductive Science.

Researchers will continue to build on interdisciplinary collaborations with faculty in the Departments of Psychiatry, Neuroscience, and Medicine (Endocrinology), as well as many of the other translational research institutes, focusing on the brain, metabolism, immunology, and personalized medicine.

Researchers at the Child Health and Development Institute are searching for cellular, molecular, and genetic mechanisms that underlie common yet complex diseases in children. Investigators are also searching for environmental causes of disease and for the relationships between genes and the environmental factors that make some children especially susceptible. This research includes studying contextual and psychosocial factors that modulate a child's vulnerability, as well as epigenetic, chromatin-based influences, which may interact with particular DNA sequences to shape individual biological responses to environmental exposures.

Along with establishing new research programs, the Child Health and Development Institute will continue to emphasize training in

Mount Sinai ranks first
among New York's academic
medical centers in NIH
grants for pediatric research.



basic, clinical, and translational aspects of children’s health. Mount Sinai has a long-standing tradition of translating new knowledge into treatment. Research on childhood allergens, for example, led Mount Sinai investigators to develop and receive approval for the use of a new vaccine against peanut allergy. Similarly, research on the harmful effects of fetal pesticide exposure has led to community outreach programs that help pregnant mothers avoid these chemicals.

These initiatives build on Mount Sinai’s fundamental strengths in pediatrics and community and preventive medicine, where recent awards include new NIH funding for the Mentored Physician Scientist Training Program (K12) for training in molecular and developmental biology in pediatric research.

Core Institute Research Areas

Asthma and Allergy

Rates of asthma and allergy have increased sharply. Asthma is now the leading cause of hospital admissions and the leading cause of school absenteeism among American children. “Asthma is multifactorial, and to treat it, we need to look at the genetic, environmental, and even social components that impact individual patients,” says Frederick J. Suchy, MD, the Herbert H. Lehman Professor, Chair of the Department of Pediatrics, and Pediatrician-in-Chief at Mount Sinai School of Medicine.

Research conducted at the Institute will identify subtle differences in genes that control the immune response or determine the response to standard medications in a large group of affected children, leading to individualized therapy. There is real promise that vaccines against allergic disease or even novel medications based on herbal preparations will be developed as a result of this research.

Diabetes and obesity disorders have tripled in frequency in the past decade. A staggering 41 percent of school-age children in New York City, particularly in the neighboring East Harlem community, are overweight or obese. Institute programs are investigating the causes of this significant increase.

3x

Diabetes and Obesity

Diabetes and obesity disorders have tripled in frequency in the past decade. A staggering 41 percent of school-age children in New York City, particularly in the neighboring East Harlem community, are overweight or obese, according to the New York City Department of Health. Institute programs are investigating the causes of this significant increase. Along with too much food and too little exercise, there is growing evidence that certain environmental endocrine disruptors

contribute to obesity as well as to precocious puberty. These questions are being addressed by faculty in the Department of Community and Preventive Medicine in tandem with researchers in the Division of Endocrinology, Diabetes, and Bone Disease; the Metabolism Institute; and the Disease Prevention and Public Health Institute who are developing the adult obesity and diabetes research program.

“The conventional view is to look at obesity strictly in terms of exercise and diet and not to think in terms of factors that may change the tipping point,” says Dr. Landrigan. “Obviously, the balance between diet and exercise is critical, but we all know that there are people who have faster metabolism, people who have slower metabolism, some people who just can’t stop eating, other people who never seem to have much trouble stopping eating — those are clearly biochemical factors. So the question is, how do you disentangle these factors? In conjunction with Dr. Derek LeRoith, Director of the Metabolism Institute, we will investigate certain chemicals in the environment. Some of the phthalates, which are some of the plasticizers, may actually reset the appetite threshold in the human body, in the hypothalamus of the brain, thus increasing the risk of obesity. This could accelerate the appetite, making people eat more.”

Neurodevelopmental and Neuropsychiatric Disorders

Neurodevelopmental and neuropsychiatric disorders, which include autism, dyslexia, attention deficit disorder, congenital abnormalities, and susceptibility to perinatal injury, affect 10 to 15 percent of the 4 million babies born each year in the United States. Some of these conditions appear to be increasing in frequency and cost the United States more than \$50 billion annually in direct medical costs and unrealized future productivity.

Research on neurodevelopmental disorders builds on existing collaborations, including those with the Department of Psychiatry’s Seaver and New York Autism Center of Excellence, a nationally recognized site for autism research and treatment. One such interdisciplinary effort investigates whether certain targeted environmental chemicals might increase the risk for autism. This research has the potential to identify preventable causes of autism and avenues for treatment, including genetic and behavioral modification counseling and new medications.

As part of this program, federal funding has recently been awarded by the National Institutes of Health for a grant to educate pediatricians and psychiatrists about potential environmental and genetic causes of autism. These training programs will help strengthen the connection between the research and the clinical objectives of the Institute. Moreover, they will develop an awareness among physicians-in-training of potential toxins and of the translational research under way at Mount Sinai aimed at minimizing exposure to such health risks.

EMERGING
PATHOGENS
INSTITUTE

Adolfo García-Sastre, PhD
Co-Director

Mary E. Klotman, MD
Co-Director

What's
next.

The Emerging Pathogens Institute is the nucleus of Mount Sinai's work on infectious diseases and the pathogens that cause them. The Institute builds on Mount Sinai's internationally recognized expertise in RNA virus research and encompasses ongoing research on the molecular pathogenesis of influenza, HIV, and dengue and Ebola viruses, as well as on hepatitis C.

Creating New Programs

The Emerging Pathogens Institute is expanding the translational aspects of Mount Sinai's antimicrobial research by creating programs in vaccine, antiviral, and antimicrobial drug development. This includes adding clinical resources and training programs that are needed to develop and test new agents.

The Institute is also developing research programs driven by local and global public health needs. One emerging area of interest is antibiotic resistance, which has become a serious threat to hospitalized patients. The Institute's proposed antibiotic resistance program will leverage Mount Sinai's abundant clinical and patient resources, and its global health initiatives will encompass training as well as basic and clinical research.

The Foundations of the Emerging Pathogens Institute

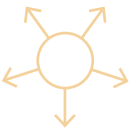
Mount Sinai has an exceptional record in emerging pathogens research. In the influenza virus field, Peter Palese, PhD, the Horace W. Goldsmith Professor and Chair of Microbiology; Chris Basler, PhD, Associate Professor of Microbiology; Adolfo García-Sastre, PhD, Co-Director of the Institute and Professor of Microbiology; and their teams reconstructed the devastating 1918 flu virus, confirmed its virulence, and showed that it was sensitive to currently available antiviral agents such as Tamiflu.

Additionally, Drs. Palese and García-Sastre created a new vaccine against avian influenza that is now used in the poultry industry throughout the developing world.

Researchers in the Department of Microbiology have also demonstrated expertise in the area of innate immune response to emerging infectious agents, most notably to influenza virus, Nipah virus, SARS coronavirus, Ebola and Marburg virus, dengue virus, and other hemorrhagic fever viruses.

The innate component of the immune response is a rapid one, in which the body recognizes and fights off general classes of infectious agents. Mount Sinai has been at the forefront of current research, identifying viral factors that inhibit innate immune responses and showing how such factors contribute to the pathogenesis of the virus. Mount Sinai researchers' expertise in virology will prove invaluable as they work to develop robust vaccines and antiviral drugs.

The Institute is expanding the translational aspects of Mount Sinai's antimicrobial research by creating programs in vaccine, antiviral, and antimicrobial drug development.



Significant contributions have also been made by basic scientists and clinical investigators in HIV pathogenesis. Researchers in the Divisions of Infectious Diseases and Nephrology in the Department of Medicine have uncovered a previously unrecognized ability of this virus to damage the kidney by direct infection of kidney cells, even in individuals in whom the virus may otherwise be dormant. Translating this finding into a hunt for a treatment, the researchers found a candidate target in the kidney for protecting the kidney from viral damage. Now, collaborating with members of the Experimental Therapeutics Institute, they are screening for small-molecule drugs that act against this target.

Researchers in the Emerging Pathogens Institute are also collaborating with scientists in the Department of Obstetrics, Gynecology, and Reproductive Science to develop topical microbicides that will safely prevent the spread of HIV that is transmitted sexually. The exciting work of young investigators in the Department of Medicine in HIV biology has recently been recognized with highly competitive awards from the National Institutes of Health and the Burroughs Wellcome Foundation.

Other examples of integrated, NIH-funded programs involving emerging pathogen researchers at Mount Sinai include the Northeast Biodefense Center, a collaborative effort among investigators from many academic medical schools in the Northeast; the Center for Research in Influenza Pathogenesis (CRIP), one of the six NIAID Centers of Excellence in Influenza Research and Surveillance; and the Center for Investigating Viral Immunity and Antagonism (CIVIA), which brings together researchers from the Departments of Microbiology, Medicine, and Neuroscience to share technologies across disciplines. CIVIA will be a particularly important resource in establishing a program to characterize human immune responses, which is needed for vaccine development. Specifically, CIVIA neuroscientists are expert at conducting miniaturized genomic and proteomic studies, approaches that are useful when only a small amount of each sample is available, as is the case for human immune reactions studies.

Finally, The Mount Sinai Hospital, with its growing base of tertiary care and quaternary and complex cases, can be a source for studying drug-resistant microbes. It is critical that clinicians and scientists recognize these newly resistant pathogens early, for clinical as well as

research purposes. The mix of basic and clinical researchers within the Institute provides the potential for rapid response and for testing new antimicrobial agents. The Institute's clinical strength is especially desirable for recruiting those researchers with special interest in initiating or continuing antimicrobial drug development programs.

"We are in a community with a tremendously diverse patient population. We have over half a million visits per year to our outpatient clinics. We have research programs that are organized around disease entities that affect our patient population, including HIV, hepatitis, and asthma. The community that we work in, the expertise of our physicians and basic scientists, and the way our clinics are organized all make for an exciting environment for translational research," says Mary E. Klotman, MD, Co-Director of the Institute and also the Irene and Dr. Arthur M. Fishberg Professor of Medicine (Infectious Diseases), Professor of Microbiology, and Associate Professor of Gene and Cell Medicine.

Proposed Areas for Growth in the Emerging Pathogens Institute

Pathogenesis of RNA Viruses

Recruitment to the Emerging Pathogens Institute in the area of RNA viral pathogenesis is focused on expanding Mount Sinai's world-renowned programs in RNA viruses. These programs are designed to answer a set of specific questions addressing how the viruses cause disease, including:

- *How does the virus get into cells, replicate, and spread in the body?*
- *What function does each of the viral proteins have?*
- *What structural features of the virus dictate the type of cells each virus infects?*
- *What structural features of the virus determine its pathogenicity?*
- *What features determine the virus's species specificity?*
- *What host responses are critical for altering the disease?*

CIVIA

CENTER FOR INVESTIGATING
VIRAL IMMUNITY AND ANTAGONISM

CIVIA is a particularly important resource in establishing a program to characterize human immune responses, which is needed for vaccine development. Specifically, CIVIA neuroscientists are expert at conducting miniaturized genomic and proteomic studies, approaches that are useful when only a small amount of each sample is available, as is the case for human immune reactions studies.

Researchers in the Emerging Pathogens Institute are also collaborating with scientists in the Department of Obstetrics, Gynecology, and Reproductive Science to develop topical microbicides that will safely prevent the spread of HIV that is transmitted sexually.

Mount Sinai's groundbreaking research reconstructed the devastating 1918 flu virus, confirmed its virulence, and showed that it was sensitive to currently available antiviral agents such as Tamiflu. Photos: The 1918 influenza virus (left) and masked policemen during the epidemic.



Mount Sinai has been a leading institution in identifying viral factors that inhibit innate immune responses and in showing how such factors contribute to the pathogenesis of the virus. The expertise will prove invaluable as researchers work to develop vaccines and antiviral drugs.

HIV
INFLUENZA
NIPAH
SARS
EBOLA
MARBURG
DENGUE

RNA

How does the virus get into cells, replicate, and spread in the body?

What function does each of the viral proteins have?

What structural features of the virus dictate the type of cells each virus infects?

What structural features of the virus determine its pathogenicity?

What features determine the virus's species specificity?

What host responses are critical for altering the disease?

This strategy also serves as a model for developing new programs to study other RNA viruses, such as hepatitis C. Hepatitis C is an obvious focus for expanding pathogenesis research given the growing prevalence of this infection, particularly within the patient populations served by Mount Sinai. Other viruses of possible interest include West Nile and certain RNA viruses on the lists of potential bioterrorist agents and of global health threats.

Vaccine and Antiviral Drug Development

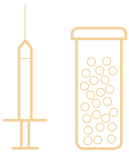
Developing a robust human vaccine program requires input from a variety of specialists, including clinical trialists and immunologists who focus specifically on humans. Such new recruits, who may also be affiliated with the Immunology Institute, will determine the immune responses of humans to each type of virus being investigated and then consider other issues, such as how humans respond differently to virulent and weaker strains of the same virus, the genetic basis of these responses, and what distinguishes a successful versus a failed fight against the virus. Having this type of information is essential for a comprehensive program in vaccine development.

The plan also calls for the development of mathematical models of virus-host interactions. This new area of research, coming through CIVIA collaborations with neuroscientists and immunologists, aims to understand how immune cells respond to differing but similar stimuli, such as different strains of a virus. Using a theoretical approach, the researchers can construct predictive models and test them experimentally, obtaining additional insight that will assist in vaccine and antiviral drug development.

Additionally, the successful development of vaccine and antiviral drug programs will call for investigators trained in specific aspects of clinical trial design and execution. In particular, researchers with expertise in the study of environmental factors that influence the spread of infections, as well as those with expertise in human genetics that will bring understanding of individual differences in disease severity and response to vaccination, will be recruited. These individuals will work closely with the Disease Prevention and Public Health Institute and the Institute for Personalized Medicine.

Plans for developing vaccines as well as antiviral therapy will draw upon the knowledge Mount Sinai investigators have amassed on

Plans for developing vaccines as well as antiviral therapy will draw upon the knowledge Mount Sinai investigators have amassed on how viruses disarm the host's innate immune system.



how viruses disarm the host's innate immune system. Institute faculty members are collaborating with one pharmaceutical company to explore the potential for harnessing the new knowledge about virus-host innate immune interactions, which will aid in the development of preventive or therapeutic agents. Moreover, Institute researchers plan to collaborate with faculty in the Experimental Therapeutics Institute, who have high-throughput assays that can screen for relevant innate immune-stimulatory compounds that could potentially become useful therapeutics.

“Not every pathogen causes the same disease in the host,” says Dr. García-Sastre. “For example, influenza may affect a lot of people differently. Some people have severe disease while other people have very mild disease or may even be asymptomatic. It depends not only on a person's past experience but also on a combination of genes. And to complicate things further, some genes may help to fight particular pathogens but encourage more serious disease with other pathogens.”

Antimicrobial Resistance

The problems of antibiotic and antiviral resistance are currently of serious, often life-threatening concern for patients, particularly immunocompromised patients, such as cancer and transplant patients and HIV-infected individuals. Accordingly, additional faculty will be recruited to develop a comprehensive research program in antimicrobial resistance. Recruiting will focus initially on basic research, since considerable work is needed to identify new targets for improved drugs. Once drug targets have been defined, the Institute will also recruit in the area of antimicrobial drug development. The Emerging Pathogens Institute's research will be well integrated with the expertise of faculty in the Experimental Therapeutics Institute, along with the clinical trials research faculty recruited for the vaccine and antiviral drug development.

IMMUNOLOGY INSTITUTE

Sergio Lira, MD, PhD

Co-Director

Lloyd F. Mayer, MD

Co-Director

Fighting
smarter.

The Immunology Institute fosters interdisciplinary, translational research in immunology, immunologic diseases, and transplantation. Mount Sinai's impressive contributions to immunological research and to the diagnosis and treatment of immune disorders have brought wide acclaim. Mount Sinai scientists and clinicians have gained international recognition in areas such as primary immunodeficiency, mucosal immunity, inflammatory bowel disease, allergic diseases, and liver transplantation. Today, Mount Sinai programs in the study and treatment of asthma, arthritis, multiple sclerosis, diabetes, hepatitis C, HIV, as well as organ transplantation are stronger than ever and still growing.

The Need for Integrative, Translational Immunology

Almost all human diseases have an immune basis as a component of their pathology. For example, severe bacterial and viral infections can arise when the host's immune response is not strong enough to fight invading microbes. Cancers may develop when the immune system fails to eliminate tumor cells from the body. Asthma, allergies, and autoimmune/inflammatory diseases, such as type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, and lupus, represent conditions in which components of the immune system are overreacting, either to foreign material or to the body's own cells. In contrast, immune deficiency leads to too many infections and unregulated inflammation. Cells and biochemical products of the immune system may even play key roles in the development of cardiovascular diseases such as atherosclerosis.

Since the immune system plays a central role in numerous diseases, medications to redirect, modify, or replace various aspects of immunity have become essential therapeutics for doctors in many specialties. Nonetheless, many immunotherapeutic drugs show limited effectiveness or carry their own unwanted side effects. Restoring the missing immune components has been successful in some cases, but more work is required. As we increase our understanding of the immune system's complex components, we will be better poised to develop effective and safe drugs for immune-mediated diseases.

Over the next few years, interdisciplinary and collaborative teams of clinicians, immunologists, geneticists, microbiologists, imaging scientists, cell biologists, and information technologists will be focused on harnessing the knowledge derived from the breakthroughs over the past several years and working toward the development of extremely valuable treatments. These efforts are the underpinnings of the new Immunology Institute.

Cells and biochemical products of the immune system may even play key roles in the development of cardiovascular diseases such as atherosclerosis.



Mount Sinai Resources

The Institute builds upon a strong foundation of basic research within the Immunobiology Center and an equally solid program of clinical research and practice in the divisions of Clinical Immunology within the Departments of Medicine and Pediatrics.

Traditionally, research has emphasized human immune-mediated diseases. More recently, this work has been balanced by the addition of

Mount Sinai was translational long before *translational* was a buzzword. One of our advantages has always been our focus on greater access to patient populations. That is the critical component.

— LLOYD F. MAYER, MD

investigators who create and manipulate rodent and other models of human immune-mediated diseases.

This balance is reflected in the leadership of the Institute's new co-directors: Lloyd F. Mayer, MD, Director of the Institute, the Dr. David and Dorothy Merksamer Professor of Medicine (Allergy and Immunology), Chief of the Divisions of Clinical Immunology and Gastroenterology, and Professor of Microbiology, who has a background in human-subject research and clinical practice, and Sergio Lira, MD, PhD, Director of the Institute and Professor of Medicine, who specializes in the animal modeling of human disease. This combination of complementary specialties encourages collaborative translational research.

Areas of Focus

Mount Sinai is maximizing the translational aspect of its research by focusing on major immune system functions and diseases. This strategy is designed to promote interdisciplinary collaboration and efficient transfer of results into new treatments.

"Mount Sinai was translational long before *translational* was a buzzword," says Dr. Mayer. "One of our advantages has always been our focus on greater access to patient populations. That is the critical component. For primary immunodeficiency, we are probably one of the largest centers in the world. For inflammatory bowel disease, we are one of the five largest in the United States. For food allergy, we are the largest in the United States. That means Mount Sinai sees more of these patients than any other center. That obviously helps us make inroads in our understanding of disease process and in identifying novel targets for therapy."

The role of immunity in disease processes can be grouped into four general areas: autoimmunity, host-pathogen interactions, inflammation and immunoregulation, and immunocompetence.

To build a world-class translational research Institute, researchers decided to focus on the last two areas, immunoregulation and immunocompetence, specifically during their early stages of development. This decision was based upon Mount Sinai's proven expertise in the fields of inflammation, immune deficiency, and immunoregulation; the existence of a robust patient population; the lack of strong competition within New York City for immunocompromised patients; and

substantial potential for extramural funding in these areas, both from NIH and from disease-oriented foundations.

“I believe the opportunities are enormous. The immune response and consequent inflammation are at the root of many diseases,” says Dr. Lira. “If we have a better understanding of these processes, we will have the ability to treat diseases as diverse as atherosclerosis, multiple sclerosis, and diabetes.”

The Immunology Institute will also be home to transplantation research. Jonathan S. Bromberg, MD, PhD, Chief of the Transplantation Institute, Surgical Director of the Kidney/Pancreas Transplantation Program, and Professor of Surgery, Immunology, and Gene and Cell Medicine, leads Mount Sinai’s research efforts in this area.

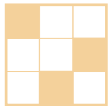
Inflammation, Immunoregulation, and Immunocompetence

Since immune-mediated inflammatory diseases share common pathways and targets for therapy across disease types, biotechnology companies have seized the opportunity to develop drugs that can have salutary effects in many different diseases. A prime example of such a target is tumor necrosis factor-alpha (TNF- α). Several biologic drugs that inhibit TNF- α action have been developed for treating conditions such as rheumatoid arthritis, psoriasis, and Crohn’s disease.

“Another area of intense investigation has been treatments to reinforce or reconstitute the immune system where important parts are missing,” says Charlotte Cunningham-Rundles, MD, PhD, Director of the Immunodeficiency Clinic, the David S. Gottesman Professor of Immunology, and Professor of Medicine and of Pediatrics. These treatments include use of blood, plasma, cytokines, and other therapies that replace or enhance the immune system.

Novel targets of this sort are being defined yearly, and all must be tested on tissue specimens from patients with various diseases. Since Mount Sinai has such patient material in abundance, it is well positioned to define, validate, and test these targets. Mount Sinai has already been a leader in testing many of the newer therapeutics in inflammatory bowel disease (IBD) and common variable immunodeficiency (CVID), and in developing and testing new treatments for peanut allergies. This rich source of test material will help to attract new faculty and commercial partners to translate novel findings into new treatments for immune-mediated diseases.

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— SERGIO LIRA, MD, PHD

Transplantation

Developing better immunosuppressive medication for use in organ transplantation and increasing the viability of pancreatic islet cells for transplantation into diabetics are particularly important areas within the transplantation program. Advances in the understanding of immunoregulation and immunocompetence will also have a direct impact.

“One of our strategies is to prevent graft-versus-host disease by concentrating on the events occurring during the immune response. This is obviously very important for malignancies, but also for organ transplantations in patients with severe autoimmune diseases,” says Miriam Merad, MD, PhD, Associate Professor of Gene and Cell Medicine and Medicine (Hematology and Medical Oncology).

METABOLISM INSTITUTE

Derek LeRoith, MD, PhD

Director

Life
in the
balance.

The Metabolism Institute was created in response to urgent and chronic health care needs of people with diabetes and obesity. The problems posed by these conditions are especially evident at The Mount Sinai Hospital, where approximately one-third of patients are diagnosed with diabetes. This chronic condition is also reaching epic proportions in our neighboring communities of East and Central Harlem and is on the rise worldwide. Underlying this epidemic is a complex relationship among metabolism, lifestyle, and genetics. Never before has the need been as urgent and the opportunity as great for breakthroughs in research and treatment.

The development and promotion of obesity- and diabetes-prevention programs are key areas of translational research in the Metabolism Institute.



Patient Populations

The Mount Sinai Medical Center straddles two communities that share an inverse relationship between income and obesity and diabetes rates. In East Harlem, which is primarily Hispanic and where many people live below the poverty level, obesity and diabetes rates are estimated to be about eight times higher than in the Upper East Side, which is largely Caucasian and affluent. Consequently, complications of stroke, cardiovascular diseases, cancer, kidney failure, and leg amputation occur more often and strike at an earlier age in the East Harlem community than in the Upper East Side.

Type 2 diabetes no longer affects just those in mid- and late-life; increasingly, this condition, along with obesity, appears in young adults, adolescents, and even children. Therefore, research aimed at helping people of all ages is part of the Metabolism Institute's strategic plan.

Many of those hit hardest by the dual epidemics of obesity and diabetes can least afford treatment, so when they finally come to the hospital, they often require the most extensive care. Thus, there is an urgent need to put effective prevention strategies into place that can benefit an entire community, perhaps even an entire generation, and potentially reduce health care costs associated with the treatment of these chronic conditions. The development and promotion of obesity- and diabetes-prevention programs are key areas of translational research in the Metabolism Institute.

Building on Existing Research

The Metabolism Institute emerged from the Department of Medicine's Division of Endocrinology, Diabetes, and Bone Disease. Among its first recruits was a diabetes epidemiologist with experience in clinical trial design. The Institute, while still recruiting, is currently collaborating with clinical investigators in many other departmental programs, including:

- *The Diabetes Center of Excellence, a New York State-funded program in the Department of Health Policy;*
- *The Metabolic Monitoring Program in the Department of Psychiatry, which tracks patients taking antipsychotic drugs;*
- *The Division of Experimental Diabetes and Aging in the Department of Geriatrics and Adult Development;*

- *The Neurobiology of Aging Laboratory in the Department of Neuroscience;*
- *The Division of Adolescent Health in the Department of Pediatrics;*
- *The Division of Transplantation in the Department of Surgery;*
- *The Program for Inherited Metabolic Diseases in the Department of Genetics and Genomic Sciences; and*
- *Mount Sinai Heart, which includes the Department of Medicine's Division of Cardiology as well as the Department of Cardiothoracic Surgery.*

Target Areas for the Metabolism Institute

Epidemiology of Obesity and Type 2 Diabetes

The epidemiology program is focused on identifying risk factors and protective factors for obesity and type 2 diabetes, including dietary, environmental, and behavioral variables, and on studying the interactions within the diverse populations that Mount Sinai serves.

Mount Sinai's catchment area offers opportunities for epidemiologic and genetic studies among ethnically diverse populations that few other academic medical centers in the world can claim.

This program has reported findings about the limited availability of fresh produce in the East Harlem neighborhood and has partnered with community members to initiate change.

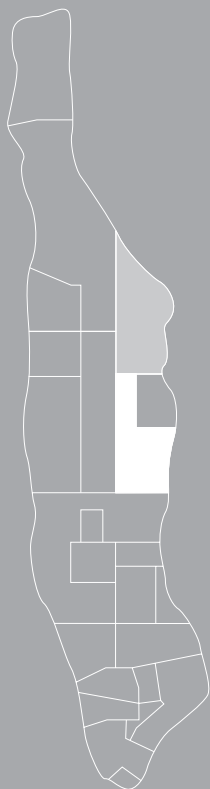


Furthermore, newly recruited faculty with expertise in epidemiology and clinical study design are providing guidance for expanding ongoing efforts, such as the Department of Health Policy's New York Center of Excellence Harlem Diabetes Program. This program has reported findings about the limited availability of fresh produce in the East Harlem neighborhood and has partnered with community members to initiate change, such as bringing a green market to the community and advocating for fresher, more nutritional foods at local stores. Ongoing collaboration with the Metabolism Institute will enable the Health Policy faculty to further expand its programs.

Genetics of Metabolic Disorders

The genetics of metabolic disorders program works to identify the critical genetic factors that increase or decrease the risks for various aspects of obesity and type 2 diabetes. Studies in this program are investigating genetic contributions to comorbid conditions such as kidney failure, given that only a subset of diabetics succumb to kidney failure.

MANHATTAN
New York City



OBSESITY



31%

EAST HARLEM



7%

UPPER EAST SIDE

DIABETES



15%

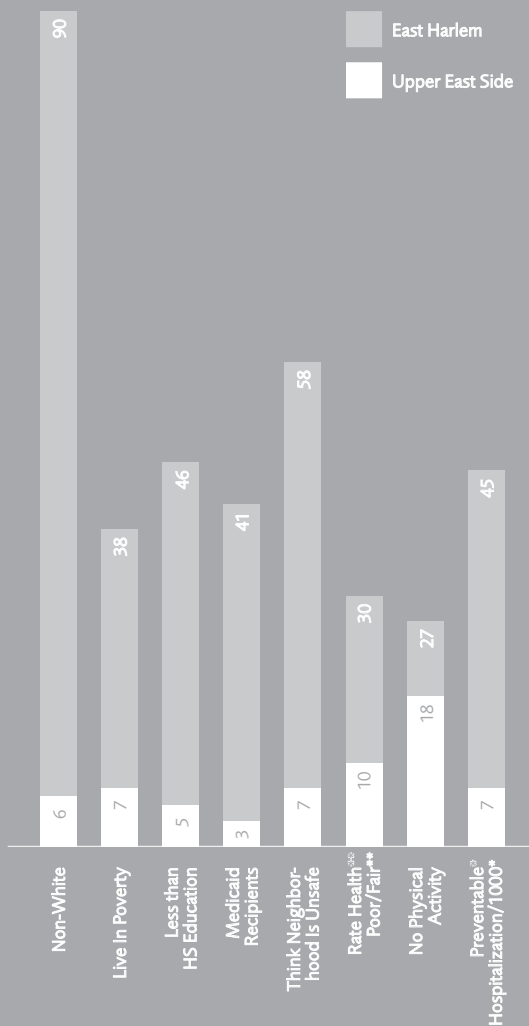
EAST HARLEM



2%

UPPER EAST SIDE

MOUNT SINAI SERVES
THE POPULATIONS WITH
NEW YORK CITY'S HIGHEST
AND LOWEST RATES OF
OBESITY AND DIABETES.



FAULT LINE (NUMBERS IN PERCENTS)

*EH has highest rate in NYC

** EH has highest rate in Manhattan

In the long term, this program will also look for hereditary factors that influence individual responses to new therapies for diabetes or obesity.

These studies apply in-depth, genome-wide scanning techniques, first to find informative polymorphisms and ultimately to identify candidate disease genes. Success requires large numbers of patients and controls, and sizeable numbers of families with and without the diseases. When candidate genes are found, the research will then move into cellular or animal – primarily rodent – models of the putatively defective genes.

Pathophysiology of Metabolic Disorders

The program in pathophysiology is researching and identifying the mechanisms that underlie these metabolic diseases. “One of the areas that’s really very hot, and that surprised us, is the role the hypothalamus plays not just on appetite but on the function of tissues like the fat cell, the liver, the muscle, the pancreas, all of which are important for obesity in type 2 diabetes,” says Derek LeRoith, MD, PhD, Director of the Metabolism Institute, the Lillian and Henry M. Stratton Professor of Molecular Medicine, and Chief of the Division of Endocrinology, Diabetes, and Bone Disease. “For a long time we focused on the pancreas, the liver, the muscle, and the fat cell, but now we are focusing on how the gut plays an important role and how the brain is probably very critical in controlling all of these systems.”

The Institute is also partnering with Helen Vlassara, MD, Director of the Division of Experimental Diabetes and Aging, and the Mount Sinai Professor in Diabetes and Aging, and her team to study issues surrounding diabetes and aging. “Our research has focused on the AGEs, the advanced glycation end products,” says Dr. Vlassara. “Underneath all chronic diseases is a dominating oxidative process that makes us slowly decline. We used to call it aging, normal aging. In fact, we are learning that there is no such thing. But younger people do acquire a lot of diseases, including diabetes, which used to be the companion of old age. This has made us tremendously interested in the concept of health-span as opposed to life span.”

The Institute is also investigating conditions such as progressive liver disease, non-alcoholic hepatosteatosis (NASH), and other specific disorders that frequently accompany obesity and diabetes. In the case of obesity, investigations will range from behavioral studies, such as on

eating disorders, to cellular studies for understanding abnormal rates of adipogenesis. In diabetes, investigations cover topics such as insulin secretory dysfunction and defects in insulin action. This research will use both human tissue biopsy specimens and animal models.

These studies require core facilities such as nuclear magnetic resonance (NMR) spectroscopy as well as magnetic resonance imaging (MRI) and computed tomography (CT) scanning and therefore will be done in collaboration with members of the Translational and Molecular Imaging Institute.

Translational Research on Metabolic Disorders and Treatments

Discoveries made at the bench will be introduced into the clinical arena, first by investigating their utility in a clinical research setting and then in clinical trials for such common disorders as childhood/adolescent obesity and type 2 diabetes; obesity and NASH; and type 2 diabetes and complications, such as cardiovascular disease and kidney failure.

As an example, Mount Sinai neuroscientists working with an already approved drug have evidence suggesting that the drug may be useful in treating obesity. Under the umbrella of the Metabolism Institute, they will collaborate with clinicians from the Division of Endocrinology, Diabetes, and Bone Disease to study a cohort of obese patients in a weight-reduction clinic, examining the feasibility of testing the drug in patients in the clinic.

As another example of interdisciplinary translational research, researchers in the Metabolism Institute are collaborating with faculty in Surgery to build a program in pancreatic islet-cell transplantation. Development of islet-cell transplantation strategies for treating type 1 diabetes has been under way for several years. However, it is increasingly apparent that people with type 2 disease also undergo pancreatic islet-cell shutdown over time. Given the epidemic proportions of type 2 diabetes and the decrease in age of disease onset, there is a need for creating a long-term treatment, such as islet-cell transplantation, which now seems a viable strategy for halting disease progression. The Metabolism Institute is developing a program to address this.

Extramural Collaborations

Some research in metabolism may be best served by joining forces with groups outside Mount Sinai. A prime example involves a joint effort with investigators at the State University of New York at Stony Brook. This basic research on rodent metabolism is leveraging a well-established facility for rodent metabolic studies at Stony Brook and exceptional computational strength at Mount Sinai.

The Metabolism Institute has also partnered with pharmaceutical companies to create a training program for endocrinology clinicians in key aspects of clinical drug testing. This allows a large number of endocrinologists to more quickly acquire critical expertise in the design and execution of clinical trial studies.

DISEASE PREVENTION AND PUBLIC HEALTH INSTITUTE

David A. Savitz, PhD

Director

Learn to
prevent.

The Disease Prevention and Public Health Institute is an outgrowth of Mount Sinai's highly regarded and well-established community and preventive medicine program, and it reflects the Medical Center's long-standing commitment to the health of our community. Since Mount Sinai serves one of the most ethnically diverse populations in America, opportunities exist for using epidemiology to study, prevent, and treat diseases. The new infrastructure of the Institute further enhances the ability of Mount Sinai's epidemiology team to collaborate with investigators from the other institutes and departments and makes epidemiological studies a major theme in clinical, translational, and basic research throughout Mount Sinai.

A Broad Mandate

At the Disease Prevention and Public Health Institute, researchers study the etiology of disease, addressing a combination of genetic, lifestyle, and environmental components with an eye toward developing preventive measures, examining the natural history of disease, conducting outcomes research to address the impact of therapy on the course of disease, using the tools of clinical epidemiology to evaluate methods for screening and diagnosis of disease, conducting community-based research to address the effect of health services and public health policy on the health of populations, and developing a comprehensive biostatistical support program to enhance all of the research at Mount Sinai.

Serving the Community in the Mount Sinai Tradition

The Institute embodies Mount Sinai's original mission of serving the medical and health care needs of its community. In fact, the first dean of the School of Medicine was a specialist in community medicine, and the formation of the medical school was an outgrowth of the Hospital's need to better serve its patients.

Historically, epidemiology has made critical contributions to disease prevention and management, from the eradication of smallpox and a 90 percent reduction in lead poisoning in American children to a significant reduction in sudden infant death syndrome (SIDS) and a 50 percent drop in the incidence of heart disease and stroke.

Mount Sinai researchers have played a pivotal role in numerous other areas of epidemiological inquiry. Irving J. Selikoff, MD, for example, conducted pioneering studies that revealed the role of asbestos in lung cancer and mesothelioma, research that led to a profound change in the regulation of asbestos.

More recently, Mount Sinai researchers contributed to a reduction of asthma among New York City residents by working with other medical centers to identify critical, modifiable risk factors, such as cockroaches, mold, mildew, and particulate air pollution.

Mount Sinai is now conducting epidemiological studies on industrial pollutants and pesticides, examining the impact of exposure perinatally and at different stages of life.

Most notably, Mount Sinai is a lead investigator in tracking the physical and mental health consequences of exposure to toxic gases

Historically, epidemiology has made critical contributions to disease prevention and management, such as a 50 percent drop in the incidence of heart disease and stroke.



50%

and particles, and documenting the trauma that occurred after the World Trade Center disaster.

The Institute has strong ties to the Department of Community and Preventive Medicine, where the disciplines of epidemiology and biostatistics have traditionally been housed. By bringing together faculty from the Departments of Medicine, Pediatrics, Psychiatry, Obstetrics, Gynecology, and Reproductive Science, Genetics and Genomic Sciences, the Institute will create a unique resource for understanding and preventing disease.

“As epidemiologists, we thrive on integration and collaboration, and Mount Sinai very much encourages that way of working,” says David A. Savitz, PhD, Director of the Institute, the Charles W. Bluhdorn Professor of Community and Preventive Medicine, and Professor of Obstetrics, Gynecology, and Reproductive Science.

Targeted Opportunities for Fighting Disease

The Institute has targeted several areas for its translational research efforts based on the strength of existing intellectual assets at Mount Sinai, overall medical need, the potential of current research collaborations, and the opportunities presented by Mount Sinai’s location on the fault line between the highest and lowest income neighborhoods in New York.

Eight principal areas of inquiry have been selected: cardiovascular disease, obesity and diabetes, cancer, genetics, infectious diseases, perinatal research, geriatrics, and psychiatry.

The major chronic diseases — cardiovascular disease, diabetes, and cancer — were selected because Mount Sinai excels at conducting research and providing clinical care for these conditions, and there is ample opportunity to link epidemiological research with established research and clinical programs.

For example, epidemiology can play a pivotal role in developing comprehensive programs that address the causes of obesity — a primary risk factor for diabetes — in the ethnically diverse communities served by Mount Sinai. Perinatal research is also a logical target for the Institute’s work. Besides addressing pregnancy outcomes, epidemiology can shed light on the perinatal origins of a range of childhood and adult health issues, such as obesity, metabolic disorders, and neurobehavioral outcomes. Collaborations with faculty from the Departments

NEW YORK CITY

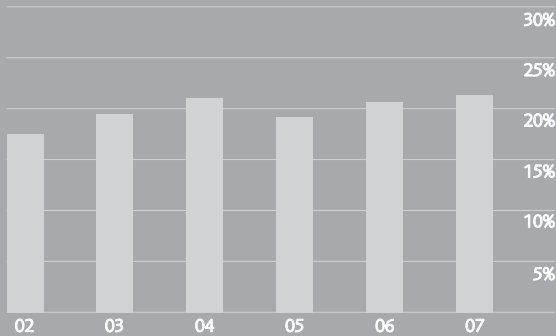
In addition to New York City being an important population for health research because of its size, the unique ethnic mix, urban environment, and interest in public health make it an extremely informative resource for studies of disease causes and prevention. There are health needs and research opportunities here that simply do not exist anywhere else in the US.

22%

OBESITY RATE IN NEW YORK CITY, 2007

8,008,278

POPULATION OF
NEW YORK CITY, 2000



OBESITY RATE IN NEW YORK CITY, 2007

9.5%

DIABETES RATE, 2006

UNITED STATES

Although many factors contribute to the development of diabetes, including genetics, the impact of obesity on risk is profound.

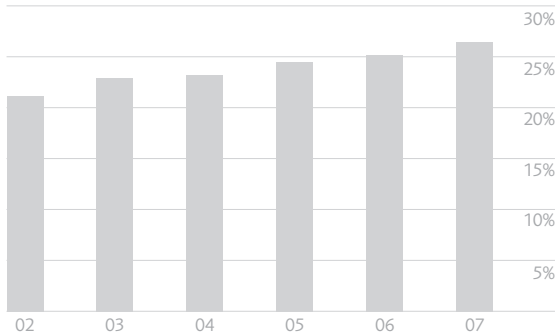
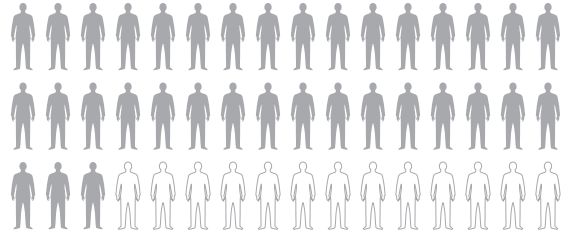
The unprecedented increase in prevalence of diabetes is certainly due in large part to the rising rates of obesity and limited physical activity of the US population.

26%

OBESITY RATE IN THE UNITED STATES, 2007

281,421,906

POPULATION OF THE UNITED STATES, 2000



OBESITY RATE IN THE UNITED STATES, 2007

8.0%

DIABETES RATE, 2007

of Obstetrics, Gynecology, and Reproductive Science as well as Pediatrics and the new Metabolism Institute are already under way.

Similarly, the use of advanced imaging technology can be of great value to epidemiologists, who are seeking to understand the course and progression of cardiovascular and renal disease in the community.

New research and clinical initiatives at the Cancer Institute also provide promising opportunities for a cancer epidemiology program. Moreover, preventive measures that involve nutrition, physical activity, and control of environmental exposures dovetail with strategies to reduce cardiovascular disease and diabetes.

The Potential of Genetic Epidemiology

Given the strength of Mount Sinai's genetics research faculty and the support of both the Department of Genetics and Genomic Sciences and The Charles R. Bronfman Institute for Personalized Medicine, there is meaningful opportunity to develop the genetic epidemiology of a variety of health problems and to combine these epidemiological findings with an understanding of normal genetic variation, gene expression patterns in health and disease, and genotype/phenotype correlations.

Combating Infectious Disease

The Disease Prevention and Public Health Institute is working closely with the Center for Investigating Viral Immunity and Antagonism (CIVIA), the internationally recognized infectious-diseases research faculty, which has particularly strong capabilities in virology. CIVIA operates a robust translational research program for evaluating host-pathogen response and will collaborate with the Institute to track and prevent epidemics and pandemics. Recent news about avian influenza, problems with effectively vaccinating against yearly flu outbreaks, and the possibility of terrorist attacks highlight the importance of epidemiology to virologists and microbiologists. The Institute recently recruited a leader to direct its infectious disease epidemiology efforts, and plans are under way to concentrate work in this key area.

Pioneering Psychiatric and Geriatric Studies

The Institute has also identified research opportunities in geriatric and psychiatric epidemiology. These two areas, which are underrepresented in the epidemiology literature, are being explored in collaboration with

The Institute is working closely with CIVIA, the internationally recognized infectious diseases research faculty, which has particularly strong capabilities in virology and can now collaborate with the Institute to track and prevent epidemics and pandemics.

CIVIA

Mount Sinai's internationally recognized Departments of Geriatrics and Adult Development and Psychiatry, with patient bases at both The Mount Sinai Hospital and the Bronx Veterans Administration Hospital. "There are very few places in the country pursuing psychiatric epidemiology. And there are even fewer places that are pursuing it in close collaboration with the more molecular, pharmacologic, and neuroimaging work. By bringing these endeavors together, Mount Sinai is in a pioneering position," says Dr. Savitz.

Training the Next Generation

In addition to its research program, the Institute will mentor future generations of health researchers in epidemiology and biostatistics and assist junior faculty in launching careers in clinical research. The Institute's expansion of and focus on translational, cross-disciplinary work provides opportunities for students earning a master's in public health and a master's of science, as well as students in the recently approved PhD Program in Clinical Research. The Institute also welcomes the participation of fellows and junior faculty throughout the school who are seeking involvement in clinical and epidemiologic research. In addition to introducing them to research opportunities, the Institute supplies administrative and logistical resources needed to foster successful research projects.

EXPERIMENTAL THERAPEUTICS INSTITUTE

Srinivas (Ravi) Iyengar, PhD

Interim Co-Director

Savio L.C. Woo, PhD

Interim Co-Director

Ming-Ming Zhou, PhD

Interim Co-Director

Putting
it all
together.

The Experimental Therapeutics Institute is a hub for the development of new drugs, devices, and intellectual property that result from Mount Sinai's basic and clinical research programs. Integrated research programs focus on small-molecule drug discovery, biological therapeutics, therapeutic vaccine development, target validation and side effects, and preclinical testing. Institute investigators conduct scientific and commercial assessments of promising research and technology, perform preclinical testing, and foster commercial relationships with pharmaceutical and medical device companies.

An Integrated Approach

“The Experimental Therapeutics Institute enables Mount Sinai to integrate the many facets of therapeutics research, including small-molecule drugs and gene- and cell-based therapeutics,” says Ravi Iyengar, PhD, Interim Co-Director, the Dorothy H. and Lewis Rosenstiel Professor and Chair of the Department of Pharmacology and Systems Therapeutics, and Professor of Oncological Sciences and of Psychiatry. “It also brings the emerging technologies in these fields to all Mount Sinai researchers to evaluate and develop their discoveries into therapeutics for complex diseases.”

Investigators work closely with many research programs, departments, and institutes at Mount Sinai, including The Charles R. Bronfman Institute for Personalized Medicine, The Black Family Stem Cell Institute, and the Cancer Institute. “Our work requires collaborative and multidisciplinary approaches,” says Ming-Ming Zhou, PhD, Interim Co-Director, the Dr. Harold and Golden Lampport Professorship in Physiology and Biophysics, Professor and Chair of Structural and Chemical Biology, and Professor of Oncological Sciences and of Pharmacology and Systems Therapeutics.

This program is developing small-molecule therapeutic agents against new disease targets identified by Mount Sinai investigators and creating technologies that will streamline the drug discovery process for small molecules.



The Small Molecule Drug Discovery (SMDD) Program

This program is developing small-molecule therapeutic agents against new disease targets identified by Mount Sinai investigators and creating technologies that will streamline the drug discovery process for small molecules. This work will allow researchers throughout Mount Sinai to apply cutting-edge technologies in chemical biology, cheminformatics, and medicinal chemistry.

The program has three specific goals:

- *Leverage the commercial potential of academic drug discovery through genome-wide target discovery and profiling.*
- *Accelerate lead optimization with focused chemical synthesis. This program, a rarity even among major biomedical research institutions, will use rational design and combinatorial or parallel synthesis strategies to optimize lead compounds efficiently.*
- *Enhance the intellectual property values of the most promising new therapeutic targets by generating toxicology profiles.*

Mount Sinai is well positioned to develop a new generation of therapeutic vaccines, based on the strength of its faculty in basic immunology and cancer biology, as well as its groundbreaking expertise in specific viral diseases, including the 1918 influenza virus.

Building on a Record of Discovery

Since the establishment of the Translational Chemical Biology Center (TCBC), Mount Sinai's small-molecule chemical screening facility, researchers have developed over thirty novel potential drug targets for which lead compounds have been obtained in very early stages of development.

"Developing new therapeutics requires access to libraries of compounds and assays, because then, and only then, will our basic biomedical knowledge be translated into more useful treatments," says Savio L. C. Woo, Interim Co-Director of the Institute, Mount Sinai Professor in Gene Medicine, Professor and Chair of Gene and Cell Medicine, and Professor of Genetics and Genomic Sciences and of Oncological Sciences.

This transition is already taking place. Molecular targets have been identified, and drug discovery processes are being developed for cancer, HIV/AIDS, pain, osteoporosis, psychiatric disorders, peanut allergy, type II diabetes, obesity, inflammatory bowel disease, polycystic kidney disease, and heart failure.

The Biotherapeutics and Vaccine Program

Biotherapeutics Division

Biologics, as the name implies, are products that are synthesized biologically rather than chemically. Biotherapeutics include humanized monoclonal antibodies and other recombinant proteins, gene vectors, and cell transplants. Designed to be highly specific, biotherapeutics promise to replace many of the currently marketed, chemically synthesized drugs. Mount Sinai has proven expertise in the research and development of biotherapeutics, as well as experience in bringing these products to market. This division has three units: protein-based biotherapeutics, gene-based biotherapeutics, and cell-based biotherapeutics.

The Protein-Based Biotherapeutics Unit will build upon a successful tradition of product development at Mount Sinai. Fabryzyme, for example, is one of the unit's FDA-approved biotherapeutic enzymes. It has been commercialized by the Genzyme Corporation to treat children with Fabry's disease.

Mount Sinai researchers have also constructed a monoclonal antibody drug that inhibits platelet aggregation. Called Abciximab, it was developed into a biotherapeutic drug by Centocor, Inc., and has been successfully commercialized to prevent ischemic complications of percutaneous coronary infarctions and unstable angina.

The Gene-Based Biotherapeutics Unit will focus its efforts on gene transfer and stem cell research taking place throughout Mount Sinai. Currently, several research groups are developing gene therapeutics for genetic diseases as well as complex disorders, such as Alzheimer's disease, cardiovascular disorders, and cancer. Other investigators are testing immune-based gene therapy in patients with metastatic breast, colon, and prostate cancers, and others, still, are developing oncolytic microbial agents that replicate selectively in tumors but not in normal cells, taking this work from animal studies into patients with liver cancer. By providing practical expertise and core laboratory facilities, the Gene-Based Biotherapeutics Unit will help streamline the development of biotherapeutics.

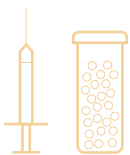
The Cell-Based Biotherapeutics Unit translates knowledge of stem cell biology into therapies for tissue regeneration. Mount Sinai researchers are working to develop treatments based on adult embryonic stem cells. Ultimately, when basic researchers know how to manipulate embryonic stem cells in a controlled and safe way, this rich source of therapeutic potential will be applied in the Cell-Based Biotherapeutics Unit. The Institute will work closely with The Black Family Stem Cell Institute on developing human embryonic stem cells as therapeutic substrates.

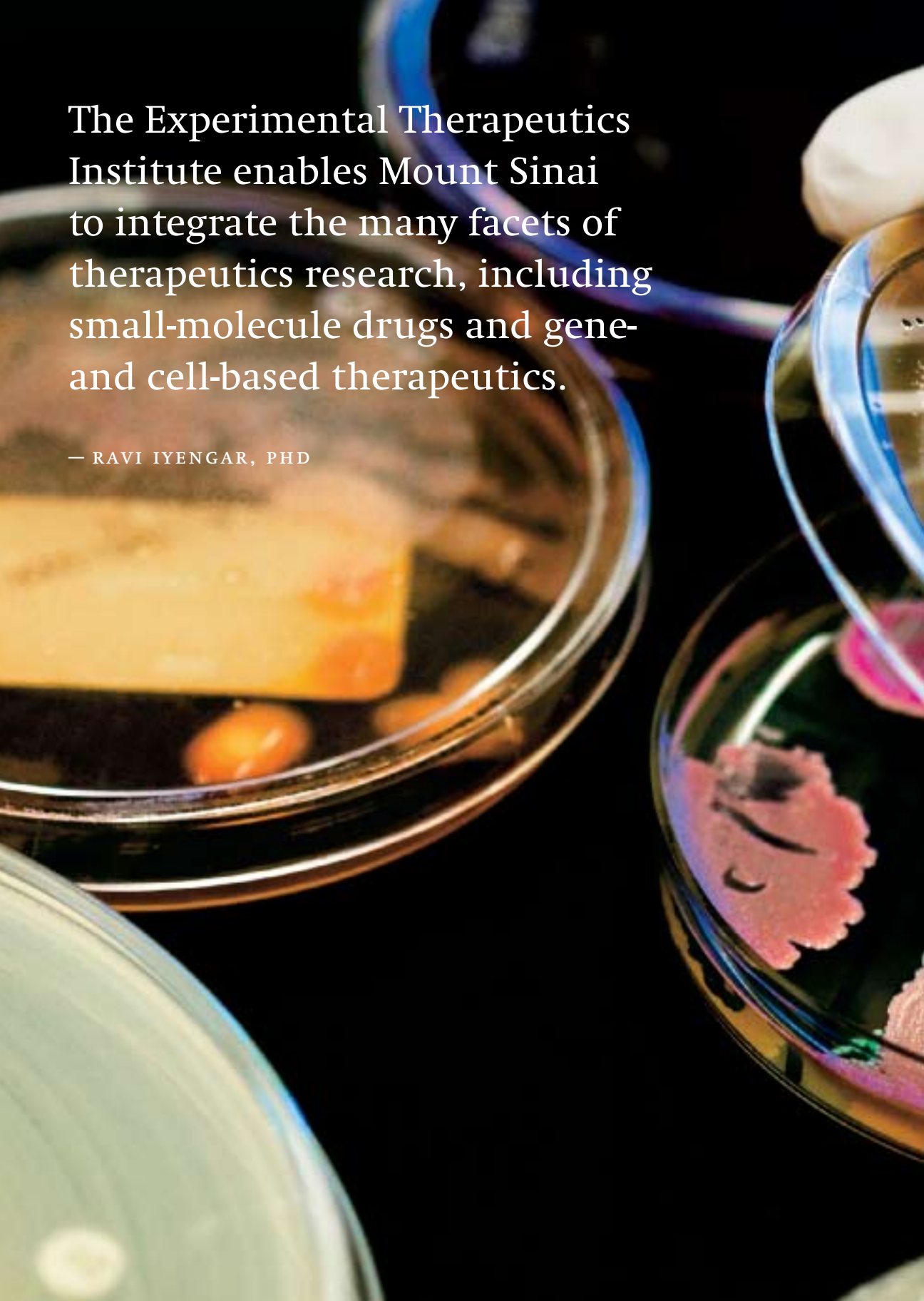
Therapeutic Vaccine Division

Mount Sinai is well positioned to develop a new generation of therapeutic vaccines, based on the strength of its faculty in basic immunology and cancer biology, as well as its groundbreaking expertise in specific viral diseases, including the 1918 influenza virus.

The Therapeutic Vaccines Division combines the strengths of Mount Sinai in the discovery, animal testing, and clinical testing of new generations of vaccines. Traditionally, vaccines have been developed to prevent transmission of infectious diseases or to elicit a beneficial immune response against infectious, inflammatory, and malignant processes, such as cancer.

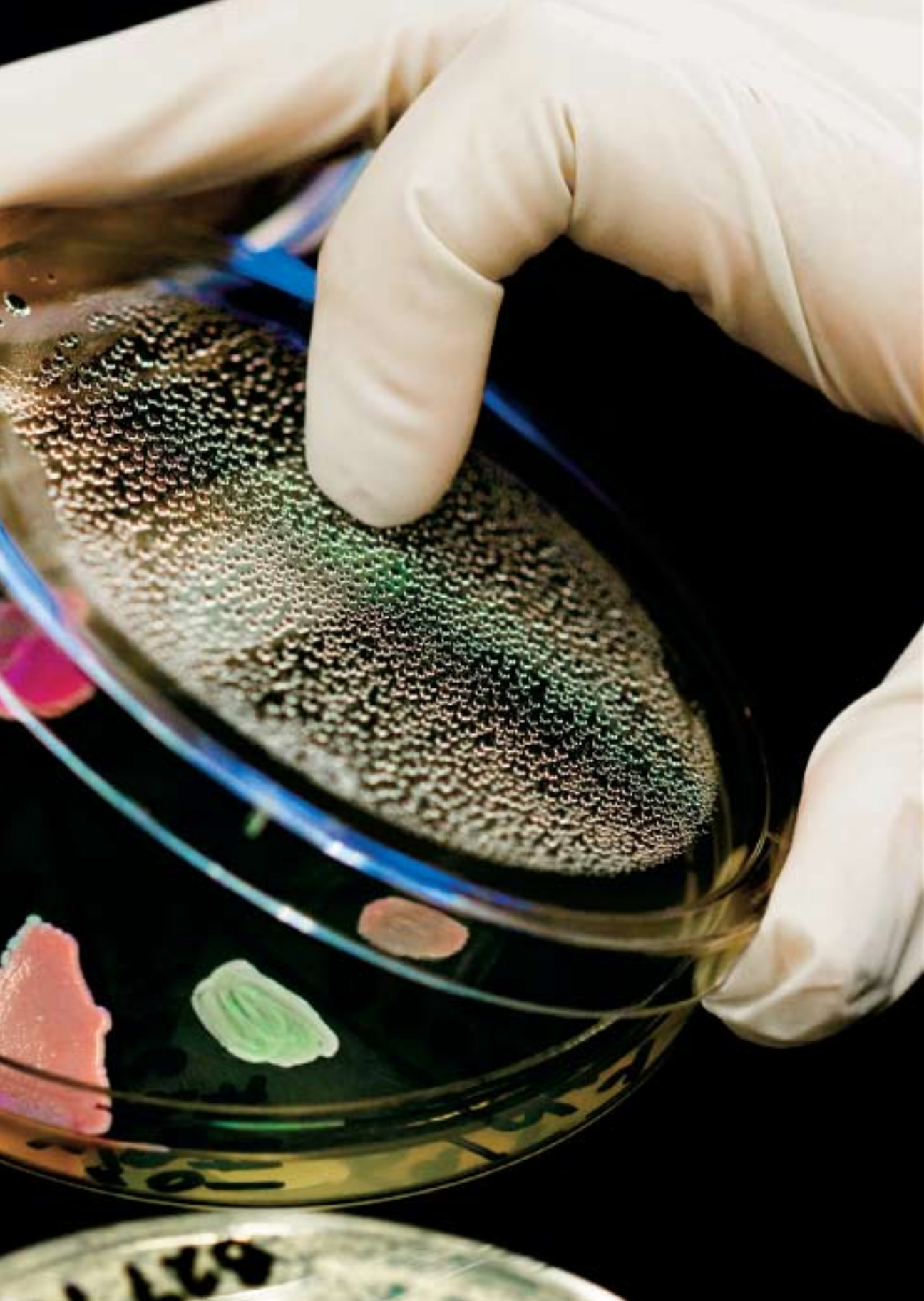
Today, researchers are focusing on therapeutic vaccines in chronic viral infections, including HIV, hepatitis C, antibiotic-resistant bacteria, and anthrax, to name a few.



A close-up photograph of several petri dishes containing cell cultures. The dishes are arranged in a cluster, with some showing pinkish-red cell colonies and others showing more diffuse, yellowish-orange growth. The lighting is dramatic, highlighting the textures of the cell cultures against a dark background.

The Experimental Therapeutics
Institute enables Mount Sinai
to integrate the many facets of
therapeutics research, including
small-molecule drugs and gene-
and cell-based therapeutics.

— RAVI IYENGAR, PHD



Today, researchers are focusing on therapeutic vaccines in chronic viral infections, including HIV, hepatitis C, antibiotic-resistant bacteria, and anthrax, to name a few. In addition, therapeutic vaccines could potentially treat other inflammatory diseases, including autoimmune diseases, severe allergic responses, and malignancies. Vaccines could also be useful for protection against bioterrorist attacks.

Target Validation and Side-Effects Program

The Target Validation and Side-Effects (TVSE) Program applies mathematical, statistical, and bioinformatics approaches to develop a systems-level understanding of how all classes of therapeutics (small molecules, proteins, gene, and cell medicines) work at the whole-organism level. This integrated systems pharmacology approach enables the Institute to analyze and predict both the beneficial and unwanted effects of a given compound. The program uses the emerging discipline of network sciences as a bridge between mathematical and statistical models and the more traditional applications of statistical analyses for predicting drug effects.

The TVSE Program will integrate its activities with those of The Charles R. Bronfman Institute for Personalized Medicine and the clinical informatics initiatives at The Mount Sinai Hospital. These collaborations will enable the Institute to develop computational models that can predict the effects of potential therapeutics on patients with different genotypes.

Current methods for testing drugs for FDA approval suffer the same major defect found in the drug discovery process: a failure to understand drug effects at the systems level. Drugs that work well at the cellular level may not work in animal models because pathway interactions and redundancies are not taken into account during the initial target-selection process. Additionally, genotype and physiological status contribute substantially to the reasons why some patients display these side effects but others do not. Developing appropriate network models can help identify functionally and temporally distal side effects and define which populations should and should not receive the therapy.

Mount Sinai researchers, who have already constructed detailed interaction models for neurons, are building such models for human dendritic cells and kidney cells (podocytes). A separate project has

The program uses the emerging discipline of network sciences as a bridge between mathematical and statistical models and the more traditional applications of statistical analyses for predicting drug effects.



constructed a network map of gene targets for FDA-approved drugs and the interactors of these gene targets. Merging these networks and then identifying patterns and potential proximal and distal relationships in the drug will be valuable in developing the new field of systems pharmacology and therapeutics.

The Network Sciences and Statistical Modeling Unit is developing models that can be used to predict therapeutic efficacy and side effects. The Numerical Simulation Unit focuses on developing methods that can predict quantitative indices of therapeutic potency and efficacy. The Bioinformatics Unit develops qualitative and quantitative databases for use in constructing and analyzing networks that will be customized for drug interactions in individual patients.

Preclinical Testing Program

The Preclinical Testing Program will serve as a central, institution-wide resource for preclinical testing. The program will provide expertise for toxicology and side-effect testing in cellular models in an integrated manner with the TVSE Program and The Charles R. Bronfman Institute for Personalized Medicine.

THE CHARLES R. BRONFMAN INSTITUTE FOR PERSONALIZED MEDICINE

Erwin P. Bottinger, MD

Director

Right
on
target.

The Charles R. Bronfman Institute for Personalized Medicine integrates genomic, molecular, and preventive medicine; biomedical informatics; biospecimen research; and genetic analysis to advance the understanding, treatment, and prevention of disease. Institute researchers are exploring how an individual's vulnerability to certain conditions and responsiveness to treatments are influenced by genetic information and environmental exposure. This new model of genome-informed customized health care promises to dramatically advance the clinical practice, delivery, and economics of health care.

Strategic Goals

“Mount Sinai has a history of innovative breakthroughs, and the next generation of clinical breakthroughs will come from the field of personalized medicine,” says Erwin P. Bottinger, MD, Director of the Institute and the Irene and Dr. Arthur M. Fishberg Professor of Medicine (Nephrology) and Professor of Pharmacology and Systems Therapeutics. “This is happening already. We are taking what we discover in the lab, from understanding who might be at risk for diabetic nephropathy to predicting which patients with hepatitis C will develop liver scarring, to meet the needs of our patients.”

Personalized medicine will also produce economic benefits: more tailored treatments can reduce hospitalizations, decrease morbidity and mortality, and reduce the costs of unnecessary diagnostics and treatments.

The Institute is dedicated to three objectives:

- *Provide clinical and translational investigators with greater and easier access to high-quality, standardized biospecimen collections, linked with full clinical information.*
- *Provide an academic research home and technology support for discovering clinically important genotype-phenotype associations through interdisciplinary, translational genomics programs.*
- *Facilitate clinical development of gene-based diagnostics and risk-assessment algorithms, and evaluate their impact on health care delivery at the patient and population levels.*

These initiatives will produce greater accuracy in diagnosing and preventing disease; interventions to treat disease at the earliest stages; drug development targeted to specific genetic variations; and customized treatments that will eliminate traditional trial-and-error methods.

Mount Sinai's Potential for World-Class Leadership

The infrastructure needed to build a world-class personalized medicine institute already exists at Mount Sinai. “Mount Sinai has the technology, both in the laboratory and in the statistical analysis, to study the predisposing genes for common diseases, such as Crohn’s disease,” says Robert J. Desnick, PhD, MD, Professor and Chair of the Department of Genetics and Genomic Sciences, and Professor of Gene and Cell Medicine,

A BURGEONING
MEDICAL
BIOINFORMATICS
BACKBONE WILL

CONNECT

RESEARCH LABS TO
PATIENT RECORDS
SEAMLESSLY AND
ANONYMOUSLY.

Linking of

**BIOBANK
PROCEDURES**

and

**CLINICAL
LABORATORY
SYSTEMS**

**THE INTEGRATION OF THE MEDICAL SCHOOL
AND HOSPITAL UNDER ONE ADMINISTRATION
ENABLES THE INSTITUTE TO TAKE ADVANTAGE
OF VAST AND DIVERSE RESOURCES.**

COMMUNITY
OUTREACH
PROGRAMS CAN
BOTH SERVE
OUTPATIENT
POPULATIONS

and

ATTRACT
SUBJECTS FOR
CLINICAL
STUDIES.

818

**FACULTY ARE MEMBERS
OF THE FACULTY
PRACTICE ASSOCIATES**

Pediatrics, Oncological Sciences, and of Obstetrics, Gynecology, and Reproductive Science.

In addition to drawing upon the expertise of leaders in basic research and technologies, such as imaging and medical bioinformatics, Institute faculty can also collaborate with a large staff of internationally renowned clinical investigators and clinicians who are conducting interdisciplinary research with well-established, NIH-funded patient databases.

Furthermore, the integration of the School of Medicine and the Hospital under one administration enables the Institute to take advantage of vast and diverse resources, including 818 faculty clinical practices on location, the linking of biobank procedures and clinical laboratory systems, a burgeoning biomedical informatics backbone that will connect research labs to patient records seamlessly and anonymously, and community outreach programs that can both serve outpatient populations and attract subjects for clinical studies.

Clinical Programs

Institute programs help Mount Sinai researchers define genetic risk, molecular pathogenesis, and the molecular diagnosis of common, complex diseases in unique patient populations, and they focus on four main categories: clinical and translational genomics, biomedical informatics, biobanking and biorepositories, and core technologies and services.

The clinical and translational genomic programs will support interdisciplinary, interdepartmental research groups where scientists, health care providers, educators, statistical geneticists, and policy experts work together in strategic and disease-focused areas: autoimmune, fibrotic, and inflammatory disorders; neuropsychiatric and neurodegenerative disorders; metabolic disorders; cancer; and asthma and hypersensitivity disorders. Institute investigators have initiated new studies exploring how gene-based, risk-assessment algorithms can be integrated into conventional clinical tools and communicated effectively at the patient and community levels.

Biomedical Informatics is a new academic program led by Peter L. Elkin, MD, Vice President of Biomedical and Translational Informatics for The Mount Sinai Hospital, and Vice Chair of Biomedical and Translational Informatics in the Department of Medicine; and Director of the Center for Biomedical Informatics. Dr. Elkin is a national and international leader in biomedical informatics. The program will

integrate the wealth of biological data collected in Mount Sinai's genomics and proteomics laboratories with phenotypic data stored in the Hospital's clinical information systems. Mount Sinai investigators will have access to genotypic, proteomic, and microarray shared core platforms data; they can then tie these data to standardized, controlled phenotypes categorized in the clinical information systems.

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The Institute's Biobank, directed by Marie Teil, MD, Director of Operations and Assistant Professor of Medicine (Nephrology) and of Medical Education, provides secured access to high-quality DNA/plasma samples collected through routine blood sampling from donors and patients. With the help of Mount Sinai's Internal Medicine Associates and Faculty Practice Associates, large numbers of patients are being recruited, with a goal of 20,000 donors annually. With the appropriate approvals, the samples can be linked with the corresponding medical records of the volunteers. These data will ultimately enhance genetic, pharmacogenetic, and even genetic epidemiological research. Eventually, the Biobank will extend its scope to enable standardized biobanking across all departments, centers, and institutes at Mount Sinai.

The Institute's Core Technologies and Services department has two main components. The Genomics Core Laboratory provides a range of genomics, proteomics, and automation support to collaborating investigators. The IT Core Lab provides collaborative services in database design and management (such as LIMS systems), software development, and programming script development.

Areas of Research

The Charles R. Bronfman Institute for Personalized Medicine has chosen six areas of research where it could achieve world-class leadership: immune disorders and autoimmunity, chronic kidney disease, chronic liver disease, allergic and hypersensitivity disorders, child health and developmental disorders, and neurodegenerative disorders.

In addition to having expertise in studying genotype-phenotype associations and gene-environment interactions in these areas, the Institute has access to a large and diverse patient population.

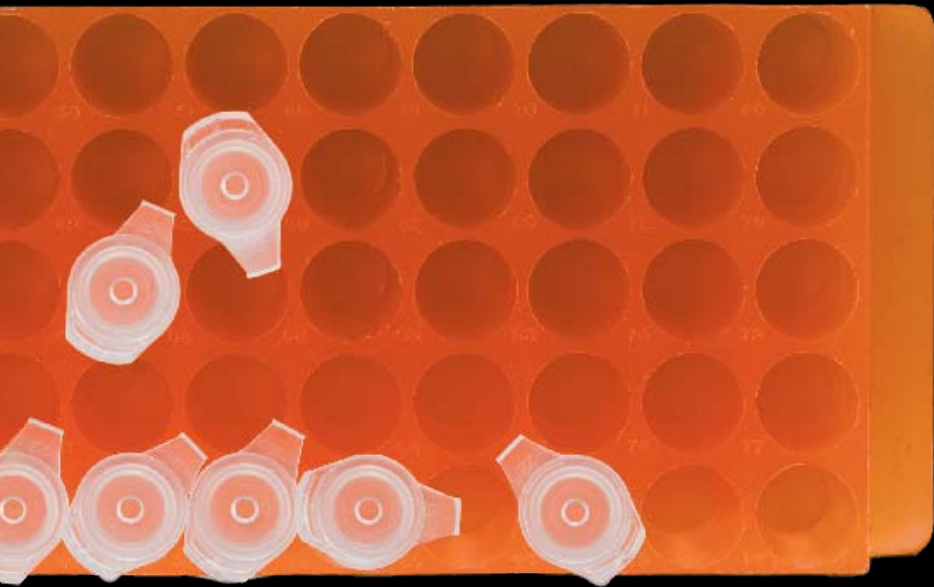
Immune Disorders and Autoimmunity

Mount Sinai already operates internationally recognized programs in the study of immune and autoimmune disorders, including the Multiple Sclerosis Center, the Inflammatory Bowel Disease Center, the Sarcoidosis

We are taking what we discover
in the lab, from understanding
who might be at risk for diabetic
nephropathy to predicting
which patients with hepatitis C
will develop liver scarring, to
meet the needs of our patients.

— ERWIN P. BOTTINGER, MD





Registry, the Asthma Study Group, the Glomerular Disease Study Group, the Allergy Program, and the Center for Emerging Pathogens. The Institute will provide a translational framework and offer an interdisciplinary focus to these groups.

Metabolic Disorders, Diabetes, and Kidney Disease

Mount Sinai is deeply involved in studying gene variants among African Americans with both hypertension and kidney disease. Furthermore, it is conducting genotyping studies to determine why some patients with chronic kidney disease deteriorate more quickly than others. The Institute will initiate an interdisciplinary clinical genomics cluster to create standards, share data, build a biobank, and conduct research that would show how genetic variants relate to the broad range of chronic kidney diseases.

Chronic Liver Disease

The Institute will provide the perspective and tools of personalized medicine in three areas where Mount Sinai has achieved international leadership: hepatitis C, hepatic fibrosis and cirrhosis with chronic liver disease, and liver cancer. The Institute plans to systematically phenotype patient populations with these diseases, build the Biobank's resources in order to conduct relevant genomic research in partnership with industry, and develop personalized assessments of patients to create more customized care plans for patients.

Allergic and Hypersensitivity Disorders

Food allergies, atopic dermatitis, allergic rhinitis, and asthma are all found among a so-called atopic phenotype. Mount Sinai has excellent research and clinical programs in all of these areas, and the Institute will further support these efforts by providing additional expertise in pharmacogenomics and molecular genetics.

“Personalized medicine will allow us to identify factors in individuals and treat them more precisely,” says Hugh A. Sampson, MD, Dean for Translational Biomedical Sciences, Chief of the Division of Allergy and Immunology in the Department of Pediatrics, and Professor of Pediatrics. “Eighty percent of children outgrow their egg or milk allergy, but with peanut allergy, only about 20 percent outgrow it. We want to look at

Mount Sinai already operates internationally recognized programs in the study of immune and autoimmune disorders, including the Multiple Sclerosis Center, the Inflammatory Bowel Disease Center, the Sarcoidosis Registry, the Asthma Study Group, the Glomerular Disease Study Group, the Allergy Program, and the Center for Emerging Pathogens.

which genes are turned on during certain reactions and identify patterns so we know who will outgrow the allergy.”

Child Health and Developmental Disorders

Through the Center for Children’s Health and the Environment and Pediatric Environmental Health Specialty Unit, Mount Sinai helps thousands of families focus on preventable risk factors that are threatening their children’s health at the genetic and environmental levels. The Institute plans to integrate these programs into a clinical genomics program.

Neurodegenerative and Neuropsychiatric Disorders

Mount Sinai programs in the area of neurodegeneration are world class. Since 1984, pioneering research has come from the Alzheimer’s Disease Research Center. The Robert and John M. Bendheim Parkinson’s Disease Center has been a magnet for collaboration in studying Parkinson’s disease. The Institute will enhance these ongoing translational efforts and use the new tools of clinical genomics to investigate the roots of both diseases.

Mount Sinai’s neuropsychiatric program integrates genomic research and clinical phenotyping expertise across a full spectrum of mental health disorders through the Seaver and New York Autism Center, the Laboratory of Neuropathology, and the Conte Center for Neuroscience of Mental Disorders. This program will also include the Obsessive and Compulsive Disorders Program and the Mood and Anxiety Disorders Program. These centers and programs have extensive NIH funding and are engaged in genotype-phenotype association discovery research and standardization of clinical phenotypes and definitions.

THE BLACK FAMILY STEM CELL INSTITUTE

Ihor R. Lemischka, PhD

Director

Core
questions.

Core
answers.

The Black Family Stem Cell Institute is Mount Sinai's hub for both basic and disease-oriented research on embryonic and adult stem cells. The therapeutic use of stem cells is one of the most promising areas of medicine for the decades ahead, and Mount Sinai is a pioneer in stem cell research. At the Institute, researchers are exploring such fundamental questions as: What makes a stem cell a stem cell? Why does one stem cell grow into a nerve cell and another into a muscle cell? How are cell fate decisions made? Is there a way to manipulate these decisions that would benefit patients? The new knowledge that will result from this research holds the promise of diagnostic and therapeutic breakthroughs.

Deciphering Basic Mechanisms

Progress in understanding the implications of stem cell research has been swift. Recent studies have shown that it is possible to reprogram adult skin cells into cells that are very similar to embryonic stem cells. Once stem cells can be grown and differentiated in a controlled way to replace degenerated cells and repair tissues, medical science may then be able to diagnose and cure many intractable diseases at their earliest stages, such as type 1 diabetes, Parkinson's disease, various cardiovascular diseases, liver disease, and cancers.

Much work must be done, however, before researchers are able to decipher and manipulate the mechanisms that establish different organ systems in the embryo, and then maintain them in adults.

Institute researchers are examining why stem cells function in types of niches, microenvironments, and pockets of activity. Investigators are also working to crack the code in stem cell communication by determining how stem cells signal to one another and to other cells.

“When we transplant a single stem cell from one mouse into another, that single stem cell is capable of finding its way to the right microenvironment, establishing itself, and initiating communication and growth,” says Ihor R. Lemischka, PhD, Director of the Institute and the Lillian and Henry M. Stratton Professorial Chair of Gene and Cell Medicine. “How does it know to do that? That’s what we want to decode.”

To advance this work, Mount Sinai is recruiting approximately twenty new faculty, about half of whom will be basic researchers and the other half more clinically oriented. As the field of stem cell research is relatively new, many of the major contributors are in the early phases of their careers. Consequently, recruitment efforts will focus on young researchers who will work closely with existing faculty.

Notably, the Institute’s culture is one that encourages interdisciplinary inquiry and analysis, and reinforces the value of collaboration between basic and applied researchers as an ultimate benefit to patients. Basic and applied researchers are recruited simultaneously to ensure that creative interactions flourish from the moment a project is conceived.

Ideally, about half of the Institute’s projects will involve embryonic stem cells and reprogrammed cells. The other half will involve adult

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stem cells, as both types of cells are critical to our understanding of disease and the development of cures. The Institute anticipates a wide range of collaborative interactions to focus on particular diseases. For example, collaborations to generate reprogrammed stem cells from a range of diseases resulting from inborn errors are already established and under way, enabling investigators to develop disease models that in turn may provide insights that lead to improved diagnostic and therapeutic possibilities.

Building on Current Stem Cell Work at Mount Sinai

New recruits will join a series of important, ongoing stem cell investigations at Mount Sinai as well as initiate new projects. For example, researchers studying how implants of stem cells grow when injected into live animals will collaborate with researchers from the Cardiovascular Research Institute and the Translational and Molecular Imaging Institute, who are learning how to phototag stem cells so that they can be monitored in these animals.

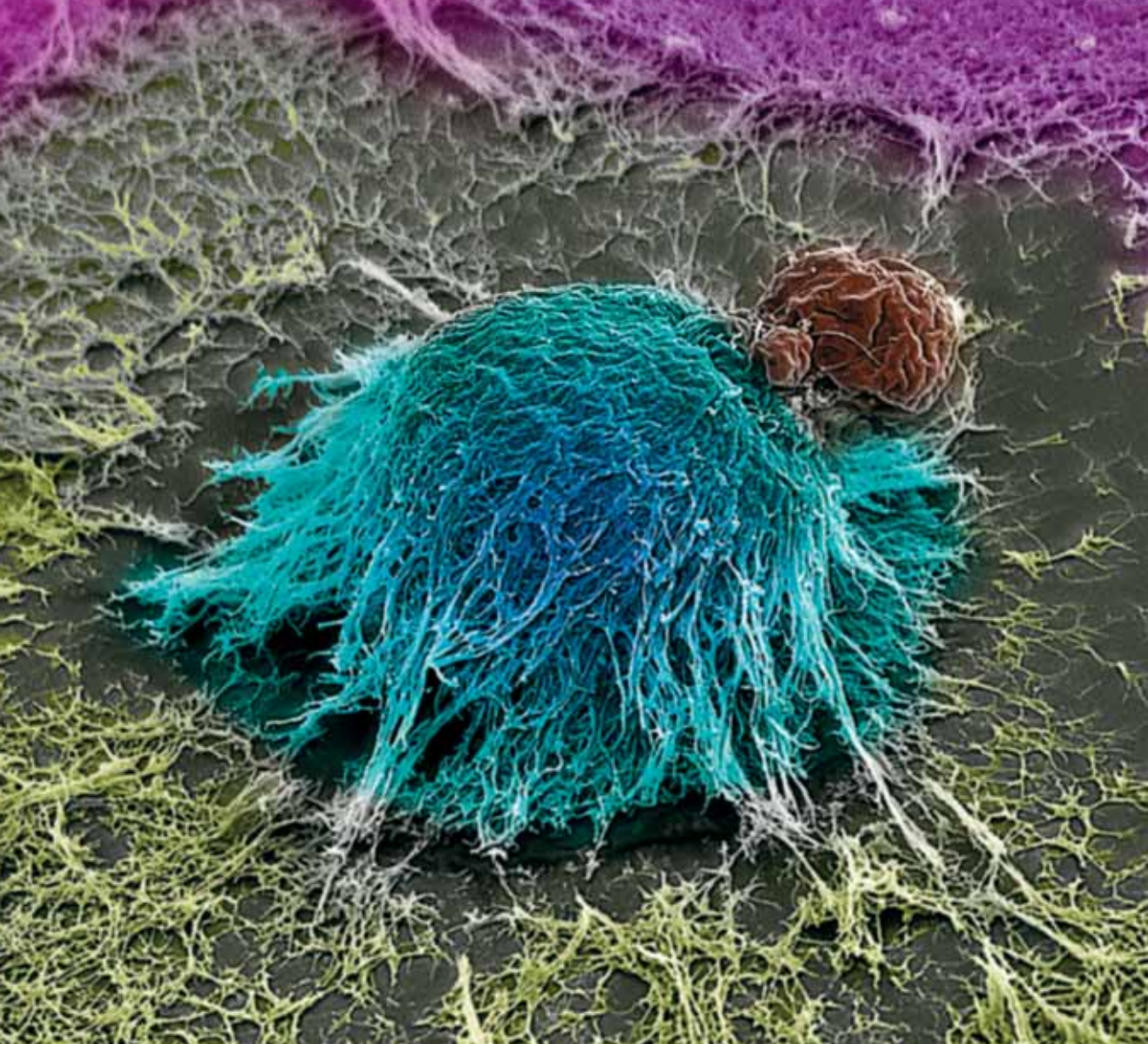
New stem cell faculty are joining with other researchers currently studying how to treat astrocytoma, a type of brain tumor. Drawing on the observation that certain types of stem cells, when injected into animals, will migrate to and remain in astrocytomas, these researchers are devising ways to make these astrocytoma-seeking stem cells into killer cells that destroy the tumors.

The arrival of Steven J. Burakoff, MD, Director of the Cancer Institute and Professor of Medicine (Hematology and Oncology) and Oncological Sciences, to lead the Cancer Institute is driving other collaborations that explore the potential role that stem cells may play in the origins of many cancers.

New recruits will play a pivotal role in research studies that use stem cell transplantation to treat certain cancers of the blood. The ultimate goal is to introduce hematopoietic cells, including stem cells, into the body after destroying the majority of cancer cells with chemotherapy. The new cells would replenish the body's red and white cell counts, and some immune cells would then destroy any remaining cancer cells.

Michael Rendl, MD, Assistant Professor of Developmental and Regenerative Biology, recently recruited from Rockefeller University, studies how stem cells in the skin are regulated. His studies could offer

Institute researchers are examining why stem cells function in types of niches, microenvironments, and pockets of activity. Investigators are also working to break the code in stem cell communication by determining how stem cells signal to one another and to other cells.



When we transplant a single stem cell from one mouse into another, that single stem cell is capable of finding its way to the right microenvironment, establishing itself, and initiating communication and growth. How does it know to do that? That's what we want to decode.

— IHOR R. LEMISCHKA, PHD

insight into the origins, diagnoses, and treatments of skin diseases such as melanoma cancers.

The liver transplantation group, which treats people with fibrotic livers, is eager to develop liver stem cell therapy. This therapy has the potential to supplant the use of donor livers, greatly relieving the liver transplant service, which depends upon unpredictable supplies of donor organs to treat a need that is expected to increase with the increasing incidence of hepatitis C.

Adult stem cells, which reside in many types of mature tissues, including intestine, skin, nervous system, and bone marrow, can replace the specialized cells of their resident tissue type. Therefore, adult stem cells from a patient can be harvested and treated with therapeutic genes or drugs in the laboratory, allowed to replicate, and transplanted back into the patient's damaged organ without a concern about immune-based rejection. By contrast, traditional organ transplantation from an unrelated donor is subject to rejection by the new host.

New Approaches to Stem Cell Research

In addition to relying on established approaches in experimenting with stem cells, The Black Family Stem Cell Institute plans to explore some very promising avenues using newly available research tools and quantitative approaches.

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Working closely with the laboratories of Ravi Iyengar, PhD, Interim Co-Director of the Experimental Therapeutics Institute, and Avi Ma'yaan, PhD, Assistant Professor of Pharmacology and Systems Therapeutics, computational tools will be developed to model and understand the mechanisms by which stem cells control their differentiation decisions.

Institute researchers will also investigate the potential of synthetic biology, a new field that aims to construct novel artificial biological circuitry in cells to regulate genes and intracellular pathways. By engineering cells in this way, drugs can be developed that activate these circuits in stem cells precisely, sparking them to differentiate into the desired specialized cells, such as lung, liver, or heart. This approach combines recent studies in areas as diverse as gene expression, cellular biology, and electrical engineering.

Pioneering Therapeutics

At the Experimental Therapeutics Institute, a cell-based biotherapeutics unit is working to translate knowledge of stem cell biology into therapies for tissue regeneration in patients. Initially, Mount Sinai researchers will develop treatments based on adult stem cells. Ultimately, when basic researchers are able to manipulate embryonic stem cells in a controlled and safe way, this rich source of therapeutic potential will also be put to use. Furthermore, the close collaboration between the Experimental Therapeutics Institute and The Black Family Stem Cell Institute will accelerate the ability to use human embryonic stem cells as therapeutic substrates.

TRANSLATIONAL
AND MOLECULAR
IMAGING INSTITUTE

Zahi A. Fayad, PhD
Interim Director

Picture
the
future.

The Translational and Molecular Imaging Institute is advancing the science of imaging, from the development of new visualization technology to improved contrast agents. Once confined to clinical radiology and basic cell biology, biomedical imaging now enables in vivo detection of structures and events in biologic systems, ranging from individual macromolecules to whole organisms. Imaging tools can even facilitate studies of gene expression at the subcellular level, helping scientists unveil the secrets of all living systems. Institute researchers collaborate with investigators throughout The Mount Sinai Medical Center to increase the potential for making a major discovery.

Vision and Resources

Biomedical imaging in the twenty-first century offers unparalleled opportunities to transform clinical medicine. Today, the latest technologies are able to reveal biochemical alterations in metabolic pathways in response to therapy; localize brain activation during cognitive, motor, or sensory tasks; and track multiple cell types in real time as the cells migrate throughout the body.

The Translational and Molecular Imaging Institute will serve as a research catalyst for a new generation of translational and molecular imaging methodologies. Imaging modalities, including magnetic resonance imaging (MRI), nuclear, X-ray-based, and optical techniques, will be applied in both preclinical basic science and clinical research settings to improve diagnostic accuracy, to increase the understanding of pathophysiology and metabolism, and to measure therapeutic efficacy, such as measuring a cancerous growth to test whether a new drug has effectively shrunk a tumor. The Institute will also support and integrate advances in imaging physics, engineering, nanomedicine and nanochemistry, and image analysis.

Researchers and clinicians from all the Institutes will have greater and more comprehensive access to complex imaging equipment, including MRI and magnetic resonance spectroscopy (MRS), X-ray computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), and emerging modalities like bioluminescent and fluorescent imaging of intact organisms.

“We will be among the first in the world to combine an MRI and a PET in a single machine. This will provide high-spatial and high-contrast imaging with MRI and metabolic information from PET, which will lead to earlier detection of disease and also more targeted treatments,” says Zahi A. Fayad, PhD, Interim Director of the Translational and Molecular Imaging Institute and Professor of Radiology and Medicine (Cardiology). “By combining MRI and PET, we can further probe disease mechanisms. For example, with Alzheimer’s disease, an MRI gives us anatomical information about the brain, and the PET measures blood flow activity. This helps us track plaque development and pinpoint plaque formation, and it will ultimately lead to earlier detection, earlier diagnosis, and better treatments.”

Collaborative Opportunities

Radiology

The Institute facilitates the direct involvement of attending radiology physicians, residents, and clinical and basic researchers, which results in more coordinated and improved patient care. Imaging specialists have long worked with Mount Sinai's psychiatrists and cardiologists to diagnose and treat patients. The Institute will expand on this by allowing for interdisciplinary teams to use neuroimaging and structural and functional MRI and MRS techniques in order to develop diagnostic methods and treatments for patients with cardiovascular disease and brain disorders. Alzheimer's disease, mood disorders, and atherosclerosis are particularly promising targets for radiology.

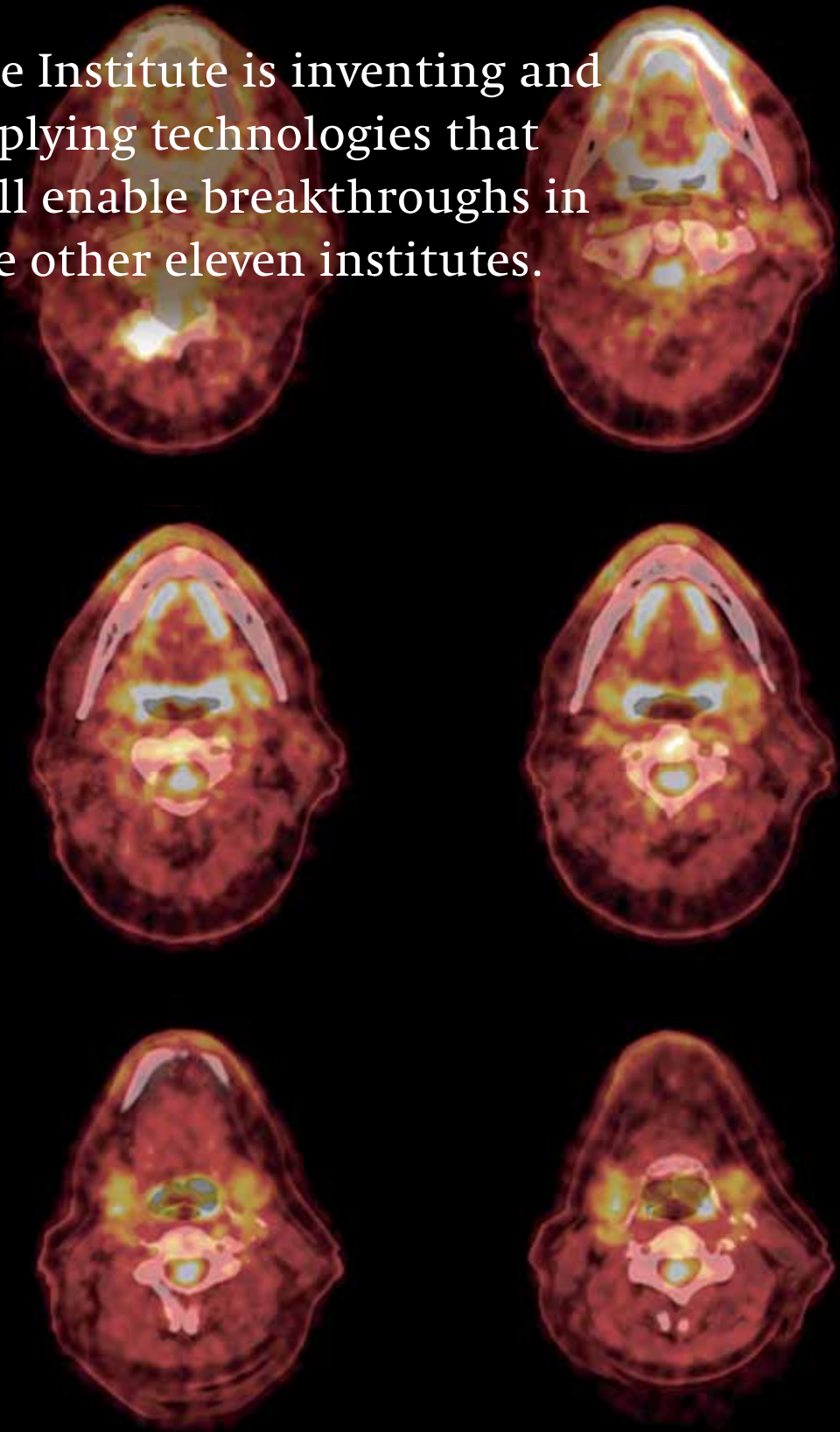
The Institute is also emphasizing chemical probes and nanomedicine, new technologies that can improve the sensitivity of detecting imaging-specific molecular events in vivo by one or two orders of magnitude as well as introducing new nanoparticles for improved drug delivery.

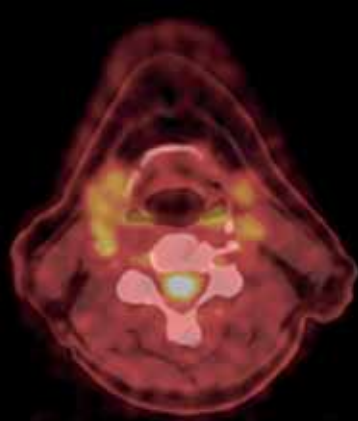
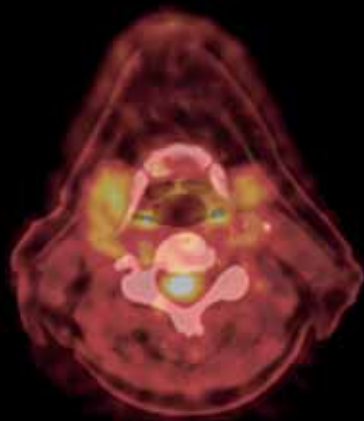
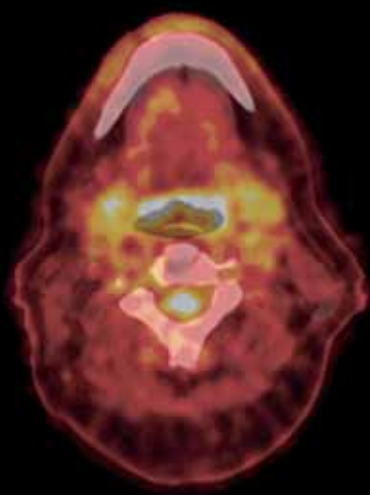
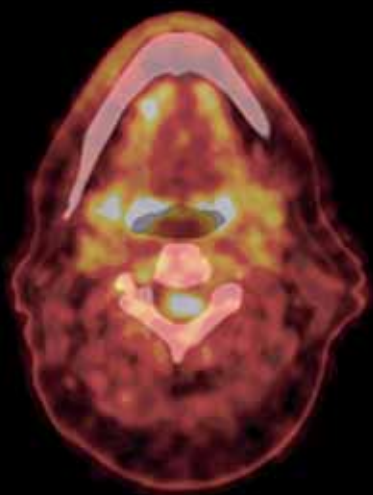
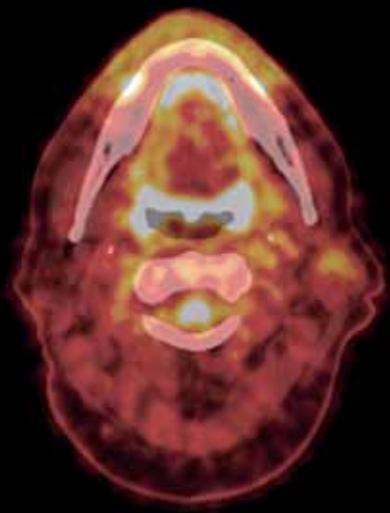
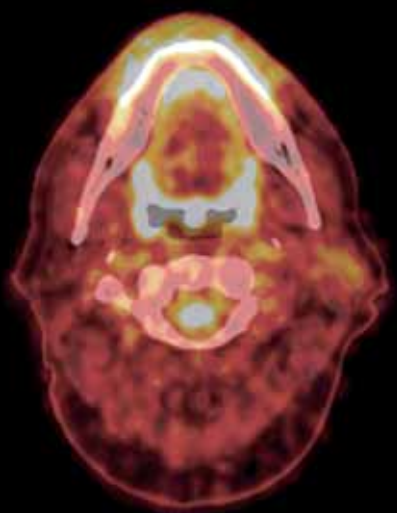
Neuroscience

Imaging advances are playing an increasingly important role in neuroscience research. Functional MRI offers a noninvasive look into the workings of the brain, the areas that are connected, and how those regions communicate. New methods in nerve fiber assessment allow white matter tracking to show disruptions or changes during disease progression. Together, imaging experts and neuroscientists can identify brain activity differences between Alzheimer's patients and healthy individuals, which will help identify patients at risk.

Another example of collaboration is the new interdisciplinary project on autism, which is using imaging techniques to find better ways to individualize and improve treatment strategies. The project, which combines basic science with clinical research, builds on the idea that in the autistic brain, neural circuitry involving the hormone oxytocin and its cell surface receptor differs from that in non-autistic brains. To measure neural circuitry changes, psychiatry faculty members are using MRI to test the effects of oxytocin in patients with autism. At the same time, in the laboratory, imaging specialists from the Institute are developing an MRI-based ligand to visualize the density and distribution of

The Institute is inventing and applying technologies that will enable breakthroughs in the other eleven institutes.





oxytocin receptors in a rodent model. The efficacy of this ligand may allow clinicians to screen their patients for more personalized treatment strategies.

Cardiovascular Studies

Mount Sinai pioneered the use of MRI to detect hidden plaque buildup within the arterial wall in a noninvasive way. Building on that work, collaborative research is now combining cardiovascular MRI with other technologies to noninvasively investigate both the lumen and the vessel wall.

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MRI

Other projects also illustrate how the Institute is helping to change the way cardiovascular research is conducted. Researchers are applying lipid-based nanoparticles to develop new ways to predict, prevent, and treat cardiovascular disease. For example, lipid-based molecular complexes, made with the primary protein component of HDL, can be rendered visible by MRI, CT, PET, and optical imaging when tagged with material such as gadolinium ions, iron-oxides particles, copper 64 nuclide, and near-infrared probes. These molecules can then be further modified with small peptides or antibodies for targeting specific tissues, cells, and proteins. In pilot studies, Institute researchers localized HDL nanoparticles, specifically in the atherosclerotic vessel walls of living animals and in inflamed high-risk plaques. They found that HDL-like nanoparticles may be effective for imaging atherosclerotic plaques and are also more practical, safer, and less costly than other, more complex contrast agents.

In another project, researchers associated with the Institute are using noninvasive imaging tests based on MRI, CT, and fluorodeoxyglucose (a glucose analog) PET to compare atherosclerosis regression in patients receiving statins and other novel cardiovascular drugs. These technologies create windows through which clinical researchers can monitor the effects of various drugs and dosages on plaque behavior in different vessels throughout the body.

Cancer Detection and Therapy

The long-term goal for the Institute and cancer therapy is the development of image-agent tagged chemotherapies whose dosage or composition can be altered based on real-time measurements of tumor response. Treatments will target both the cellular and molecular levels.

Because the Institute has extensive imaging technologies for use in both preclinical and clinical studies with cancer patients, it expects to streamline the process of moving from target and compound identification to individualized treatment of patients. In the near future, bioluminescent and fluorescent imaging may help find reporter genes that can reveal gene activity at the earliest phases of transition from hyperplasia to neoplasia.

Genetics

Based on Mount Sinai's success in using microMR for cardiovascular and neurological studies, the Institute will develop MR technology opportunities for in vivo studies that visualize reporter gene expression in space and time.

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Opening new avenues in small-animal research, some projects will employ nuclear imaging techniques like PET and SPECT or bioluminescence and fluorescence to create genetic reporter probes. Projects over the next few years may modify and find novel uses for microPET, microSPECT, microCT, and micro-ultrasound (US) for expanding the application of reporter gene technology. The next generation of reporter probes will help researchers understand when and where genes are expressed and how patterns of expression interact at the cellular level. This technology might also be applied to assess many aspects of phenotypic differentiation in animal models of disease, including morphologic and metabolic differences.

Metabolic Diseases

The Institute envisions projects that apply new ways to detect cardiovascular, renal, and cerebrovascular disease that will refine detection of metabolic diseases at all stages. There are opportunities to use imaging to noninvasively assess insulin-resistant patients and find out how they differ from healthy individuals. Imaging can also be used to examine how various diet and exercise programs return patients to their normal metabolisms, while radio- and MR-labeled compounds can noninvasively map out metabolic pathways.

SENIOR ADMINISTRATION

KENNETH L. DAVIS, MD
President and
Chief Executive Officer,
The Mount Sinai Medical Center

DENNIS S. CHARNEY, MD
Dean, Mount Sinai School
of Medicine,
Executive Vice President
for Academic Affairs,
The Mount Sinai Medical Center

DONALD T. SCANLON
Chief Financial Officer
Executive Vice President,
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