

ACCELERATING SCIENCE—ADVANCING MEDICINE

Integrating Basic Science with Translational Medicine

Through our Master of Science, PhD, and combined MD/PhD programs, the Graduate School of Biological Sciences covers the entire translational continuum—from basic science discovery to population-based research on global health.

We view our curricula and programs as representing a translational continuum, rather than as separate entities, because it reinforces basic science as a critically important component of successful translation. Without basic science discovery, clinical innovation and therapeutic strategies would stagnate. In particular, we want our PhD students and MD/PhD students to formulate their research questions and design their studies in the most rigorous scientific fashion, yet have an eye toward relevance to disease and improvement of human health as an outcome of their efforts.

To that end, we have linked, conceptually and structurally, each of our eight multidisciplinary training areas (MTAs) with one of our 14 renowned science institutes. In addition, our newly established Institute for Genomics and Multiscale Biology, led by Eric E. Schadt, PhD, will provide the scientific expertise and focus to develop a new PhD track in genomics that will be firmly rooted in computational biology. Dr. Schadt recently joined Mount Sinai from Pacific Biosciences of California, Inc.

The connection between basic science and disease is also visible in several new curricular approaches. For example, first-year students in Pharmacology and Systems Biology will be taught pharmacology, physiology, and biochemistry within the context of organ systems and relevant diseases. We have also launched a new course for PhD students called “Translating Science.” In it, students interact extensively with clinicians to broaden their understanding of human disease, as well as representatives from industry and technology transfer. In addition, Neuroscience has added a core-sequence course titled “Advanced Topics in Clinical Neuroscience.” It introduces students to patients to complement didactic material on brain disorders. Our goal is to get future scientists thinking about diseases relevant to their area of basic science research early in their training.

Owing to our enhanced translational approach, I am pleased to report two success indicators: applications from the most promising science undergraduates have increased over 50 percent in the past two years, and many of our current



John H. Morrison, PhD, Dean of Basic Sciences and the Graduate School of Biological Sciences

students are lead authors on papers in top basic science journals. Much of their work, which is sampled on page 3, has clear translational implications.

Through this *Dean's Report*, I look forward to sharing this and more with you as we reimagine what is possible in science and in medicine.

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■ BEDSIDE TO BENCH

Two New Courses Help PhD Candidates Translate Science into Improved Patient Care

Graduate students at Mount Sinai are increasingly challenged to consider the real-world implications of their scientific work. This year, the Graduate School launched two new courses specifically designed to help students translate the results of their scientific research into clinical care.

In spring 2011, Eric J. Nestler, MD, PhD, Director, The Friedman Brain Institute, and Hongyan (Jenny) Zou, MD, Assistant Professor of Neurosurgery and Neuroscience, introduced “Advanced Topics in Clinical Neuroscience,” a course that covers clinical features of major neurologic and psychiatric disorders, including diagnostics, clinical pathology, course of illness, and treatment. The class will be offered each spring.

A key feature is that, each week, students meet patients with a disease of the nervous system. This gives PhD candidates a unique opportunity to learn more about the disorders they study in laboratory animals, and that, in turn, will improve the translational potential of their work.

“There are very few schools where future scientists are able to meet patients to discuss clinical issues with them and with one another,” Dr. Nestler says. “As clinical relevance becomes increasingly important, courses like this will make our students more competitive for research positions and grants.”

A second course, “Translating Science,” will launch in January 2012. Run by Ross L. Cagan, PhD, Associate Dean, Graduate School of Biological Sciences, and Miriam Merad, MD, PhD, Professor, Oncological Sciences and Medicine, the course distinguishes the difference between translational and basic research. It also focuses on the “business of disease,” featuring experts on many major disease areas and leaders from the pharmaceutical industry to discuss the drug-development process.

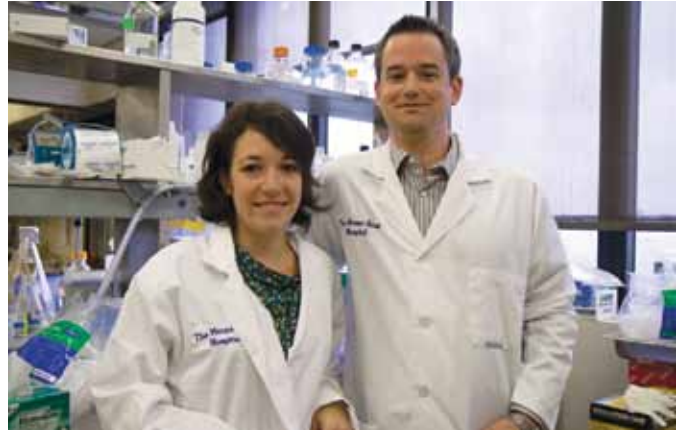
RESEARCH FRONTIERS

Marion Sourisseau, PhD, Receives 2011 Robin Chemers Neustein Award

In June, Marion Sourisseau, PhD, Postdoctoral Fellow in Microbiology, was selected from a pool of 30 applicants to receive the 2011 Robin Chemers Neustein Postdoctoral Fellowship Award.

The award carries a stipend of \$25,000 to help fund Dr. Sourisseau's research in the laboratory of Matthew J. Evans, PhD, Assistant Professor of Microbiology, into how the hepatitis C virus (HCV) recognizes and enters liver cells. This pathogen is the leading cause of liver cancer and the need for liver transplants in the Western hemisphere. Defining how HCV enters cells may uncover ways to keep the virus from entering, and that, in turn, would play a significant role in eliminating two major global health problems: cirrhosis and hepatocellular carcinoma. Dr. Sourisseau explains, "If we can uncover how virus particles interact with cellular factors to enable HCV entry, it might be possible to create inhibitors to disrupt this interaction." Dr. Sourisseau has already had promising results using antibodies to block the cellular factors that enable HCV cell entry.

Working with Dr. Evans, Dr. Sourisseau is striving to understand all the steps in the HCV life cycle.



Marion Sourisseau, PhD, and Matthew J. Evans, PhD

A native of France, Dr. Sourisseau received her PhD from the Pasteur Institute where she conducted research on HIV and Chikungunya virus. She specifically chose to come to Mount Sinai to work with Dr. Evans because of the related important research he has done with HCV.

NEW LEADERSHIP

Clinical Research Programs Combine Patient Care into Basic Research

The need for translational scientists is great and growing. Mount Sinai's longstanding PhD and MD/PhD programs are strategically designed with this need in mind, and recently we promoted two outstanding leaders and mentors to deepen and expand our array of translational training programs.



Yasmin L. Hurd, PhD

YASMIN L. HURD, PHD, has been named Director of the MD/PhD Program. Dr. Hurd is a renowned researcher and outstanding mentor who, as director of graduate students in clinical neuroscience at Sweden's Karolinska Institute, doubled the program's yearly student enrollment. During her five years at Mount Sinai, Dr. Hurd has been a true champion of translational research, working to integrate bench-to-bedside understanding into courses and training opportunities. As Director, she plans to build on this to organize the MD/PhD track in a way that allows students to start their careers faster. In addition to her role as Director, Dr. Hurd is Professor of Psychiatry, Pharmacology, and Systems Therapeutics and Neuroscience, Chair of the Diversity in Biomedical Research Committee (DBRC) at Mount Sinai, and Chief of the Center of Excellence in Mood and Motivation in the Friedman Brain Institute. Her translational research focuses on risk factors for addiction disorders, including genetics and developmental exposure to drugs of abuse using both human and experimental animal studies. Her work has been published in the *Journal of Neuroscience*, *Science*, *Proceedings of the National Academy of Science*, and *Biological Psychiatry*. Dr. Hurd is also active in several external organizations, including the Board of Scientific Counselors at the National Institute of Drug Abuse, National Institutes of Health (NIH) study sections, NIH Review Committees, and the MacArthur Foundation Neuroscience network. She is also a member of the American Society for Neuroscience, New York Academy of Sciences, and the College on Problems of Drug Dependence.



Ross L. Cagan, PhD

ROSS L. CAGAN, PHD, has been appointed Associate Dean of the Graduate School. Dr. Cagan is a world-class molecular biologist who uses fly models to study and understand human disease principles. He is also a dedicated mentor who, as Professor at Washington University in St. Louis, developed a vibrant research program focusing on the mechanisms and molecules involved in cell patterning. His work has important implications for cancer and diabetes treatments, and is highly compatible with Mount Sinai's translational approach to research and clinical care. Dr. Cagan is a co-founder of Medros Inc., a biotechnology company focused on cancer and diabetes therapeutics. Since joining Mount Sinai in 2007, he has proven to be a compassionate and effective mentor both within his laboratory and at the programmatic and departmental levels. In his role as Associate Director, Dr. Cagan plans to strengthen interdisciplinary ties across sections and expand translational programs that prepare students for non-traditional, non-academic jobs. He is also a Professor of Developmental and Regenerative Biology, Oncological Sciences, and Ophthalmology. His work has been published in *Nature*, the *Journal of Cell Biology*, *Developmental Cell*, *PLoS Computational Biology*, *Molecular Cell Biology*, and other elite journals. He received the Dean's Award for Excellence in Translational Science in 2009 and is a member of the Dean's Leadership Board and the Basic Science Advisory Council.

■ YOUNG PIONEERS

Mount Sinai's Graduate School of Biological Sciences is a magnet for visionary scientists, truly compassionate mentors, and the most promising students in the biomedical sciences. These factors result in significant research success, as demonstrated by this outstanding collection of student-led research papers.



YEN-SIN ANG

Wdr5 Mediates Self-Renewal and Reprogramming via the Embryonic Stem Cell Core Transcriptional Network
Cell, April 15, 2011 (vol. 145, issue 2, pp. 183-197)

Embryonic stem (ES) cell transcriptional and chromatin-modifying networks are critical for pluripotency.

My work demonstrates that WD repeat domain 5, a core member of the mammalian Trithorax complex, mediates functional cooperation between the transcriptional and epigenetic controls of self-renewal and somatic cell reprogramming. This work presents important implications for the understanding of pluripotency and use of ES cells in regenerative medicine.

Mentor: Ihor R. Lemischka, PhD, Director, The Black Family Cell Institute



SETH BERGER

Systems Pharmacology of Arrhythmias
Science Signaling 2010 April 20; 3(118):ra30. PMID: 20407125

Long-QT syndromes are associated with cardiac arrhythmias, which can be congenital when associated with genetic mutations or acquired as a drug side effect.

Protein-protein interaction network analysis demonstrated significant overlap between the targets of QT-interval prolonging drugs and the region of the human interactome surrounding the long-QT syndrome disease genes. Integrating clinical data from the FDA's Adverse Events Reporting System database validated the approach and provides systems-level understanding of medication adverse events. *Mentor: Ravi Iyengar, PhD, Director, Experimental Therapeutics Institute, and Professor and Chair, Pharmacology and Systems Therapeutics*



JOY CHEN

Design of embedded chimeric peptide nucleic acids that efficiently enter and accurately reactivate gene expression in vivo
PNAS September 28, 2010 vol. 107 no. 39 16846-16851

Existing treatments to reactivate fetal globin are not equally effective for all patients with hemoglobinopathies. We developed a chimeric peptide nucleic acid (PNA) that effectively enters the cell, binds to the fetal globin promoter, and reactivates this transcript in transgenic mouse cells and human peripheral blood cells. Our final molecule contains a promoter-binding PNA sequence within two amino acid motifs: one for cell/ nuclear entry, and another for target transactivation. *Mentor: James J. Bieker, PhD, Professor, Developmental and Regenerative Biology*



MICHAEL GREEN

Generation of anterior foregut endoderm from human embryonic and induced pluripotent stem cells
Nat Biotechnol. 2011 Mar;29(3):267-72. PMID: 21358635

Pluripotent stem cells hold great potential as a source for cellular replacement therapy. A remaining challenge is the development of protocols that guide embryonic stem cells into the particular cell type of interest. In this article, we describe a quantitative protocol to pattern pluripotent stem cells into anterior foregut endoderm, which gives rise to the lung, thymus, parathyroid, and thyroid. *Mentor: Hans-Willem Snoeck, MD/PhD, Associate Professor, Oncology and Medicine (Infectious Disease)*



AVNISH KAPOOR

The histone variant macroH2A suppresses melanoma progression through regulation of CDK8
Nature. 2010 December 23; 468(7327):1105-1109

Increasing evidence demonstrates that tumor progression entails chromatin-mediated changes, but the role of histone variants in cancer initiation and progression remains unclear. We report that the histone variant macroH2A suppresses tumor progression of malignant melanoma. The tumor-promoting function of macroH2A loss is mediated, at least in part, through direct transcriptional up-regulation of CDK8. Taken together, our results demonstrate that macroH2A is a critical component of chromatin that suppresses the development of malignant melanoma. *Mentor: Emily Bernstein, PhD, Assistant Professor, Oncological Sciences, Dermatology*



JASMINE PEREZ

Influenza A virus-generated small RNAs regulate the switch from transcription to replication.
Proc Natl Acad Sci USA. 2010 Jun 22; 107(25):11525-30

Recent advances in small RNA biology have changed the shape of scientific research for several fields of vbiology, including influenza A virus (IAV) research. Here we describe the identification and characterization of IAV-derived small RNAs (svRNAs) that regulate IAV life cycle by controlling the switch from transcription to replication (Perez, et al., *PNAS* 107 (2010)). As svRNAs are produced by multiple strains of IAV, they provide a novel target for broad-spectrum antiviral therapies. *Mentor: Benjamin TenOever, PhD, Associate Professor, Microbiology*



TIMOTHY D. SILVERSTEIN

Structural basis for the suppression of skin cancers by DNA polymerase η
Nature. 2010 Jun 24; 465(7301):1039-43

DNA polymerase η (Pol η) is unique among eukaryotic polymerases in its ability for error-free replication through ultraviolet-induced T-T dimers, and its inactivation causes the variant form of the skin cancer-prone syndrome, xeroderma pigmentosum. We determined the crystal structures of Pol η in complex with a T-T dimer and undamaged DNA. These structures reveal features of Pol η that are crucial in suppressing the mutagenic consequences of sun exposure, thereby reducing the incidence of skin cancers in humans. *Mentor: Anel K. Aggarwal, PhD, Professor, Structural and Chemical Biology, and Oncological Sciences*



TAIA T. WANG

Vaccination with a synthetic peptide from the influenza virus hemagglutinin provides protection against distinct viral subtypes
PNAS November 2, 2010 vol. 107 no. 44 18979-18984

Influenza viruses are characterized by the ability to remodel surface proteins that are targets of adaptive immunity; this quality dictates the frequent production of novel vaccine formulations that reflect currently circulating virus strains. We have generated a novel peptide-based vaccine that protects mice against structurally divergent influenza viruses. Such a vaccine could be used as a single measure to diminish the impact of disease caused by both seasonal and pandemic influenza virus strains. *Mentor: Peter Palese, PhD, Professor and Chair, Microbiology, and Medicine (Infectious Diseases)*



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

THE BLACK FAMILY STEM CELL INSTITUTE

Director: Ihor R. Lemischka, PhD

THE CHARLES R. BRONFMAN INSTITUTE FOR PERSONALIZED MEDICINE

Director: Erwin P. Bottinger, MD

CHILD HEALTH AND DEVELOPMENT INSTITUTE

Director: Bruce D. Gelb, MD

CONDUITS: THE INSTITUTES FOR TRANSLATIONAL SCIENCES

Director: Hugh A. Sampson, MD

DISEASE PREVENTION AND PUBLIC HEALTH INSTITUTE

Director: Paolo Boffetta, MD, MPH

EXPERIMENTAL THERAPEUTICS INSTITUTE

Director: Srinivas Iyengar, PhD

THE FRIEDMAN BRAIN INSTITUTE

Director: Eric J. Nestler, MD, PhD

GLOBAL HEALTH AND EMERGING PATHOGENS INSTITUTE

Director: Adolfo García-Sastre, PhD

IMMUNOLOGY INSTITUTE

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

INSTITUTE FOR GENOMICS AND MULTISCALE BIOLOGY

Director: Eric E. Schadt, PhD

METABOLISM INSTITUTE

Director: Yaron Tomer, MD

THE RECANATI/MILLER TRANSPLANTATION INSTITUTE

Director: Sander S. Florman, MD

THE TISCH CANCER INSTITUTE

Director: Steven J. Burakoff, MD

TRANSLATIONAL AND MOLECULAR IMAGING INSTITUTE

Director: Zahi A. Fayad, PhD

THE ZENA AND MICHAEL A. WIENER CARDIOVASCULAR INSTITUTE

Director: Valentin Fuster, MD, PhD