### On the Cover:
Glutamate transporters are a major focus of study in the laboratory of Dr. Olga Boudker. In the central nervous system, glutamate transporters are responsible for the uptake of the neurotransmitter glutamate following rounds of synaptic signaling. Dysfunction of these transporters is implicated in numerous disorders such as neurodegenerative diseases, stroke, traumatic brain injury, epilepsy, and schizophrenia.

### WEILL CORNELL MEDICAL COLLEGE
Research Highlights

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MESSAGE FROM THE DEAN

Well into my first year as Dean, I continue to discover the greatness that is Weill Cornell Medical College. The scientific endeavors of our faculty span an amazing range of disciplines across the research continuum. Their work is further advanced through innovative collaborations and groundbreaking partnerships with institutions of note – from The Rockefeller University and Memorial Sloan-Kettering Cancer Center in our own neighborhood to Cornell University in Ithaca, The Methodist Hospital Research Institute in Texas, and as far away as our sister institution in Qatar, to name just a few.

In this report, we are pleased to highlight the work of nearly 60 outstanding, highly funded physicians and scientists, and their research laboratories, who are making exceptional contributions to science and medicine at every level. Some of these individuals are working at the molecular biological level, while others carry on investigations in experimental pre-clinical models and others through human clinical trials. The ultimate goal, of course, is to provide novel therapeutics and better ways to fight human disease. Critical to continuing to develop these new treatments is the ability of our clinicians, translational researchers, and basic scientists to meld ideas and share discoveries. This interdisciplinary model is the future of biomedicine.

Healthcare in this country is facing a watershed moment, and the challenges posed will require bold new ideas and a commitment to excellence. At Weill Cornell, a solid foundation is in place to further the institution as a world-class research enterprise. In 2014, we will open the Belfer Research Building that will usher in a new era in biomedical research. The building will double the Medical College’s available research space and is allowing us to actively recruit some several dozen top-tier, well-funded junior and senior physicians, physician-scientists, and PhD scientists who will become the next generation of clinical and research leaders. This effort has commenced with the recent appointment of Dr. Lewis Cantley, one of the world’s most preeminent scientists in translational research, who will direct our newly established Cancer Center.

Today, we have a unique opportunity available to very few American medical colleges: to bend the curve in clinical care, graduate education, and biomedical research. I am delighted to be here at this pivotal juncture in the history of Weill Cornell Medical College.

Laurie H. Glimcher, MD
Stephen and Suzanne Weiss Dean
Weill Cornell Medical College
Provost for Medical Affairs
Cornell University
This is an unprecedented time in biomedical research. From initiating breakthroughs in stem cell research to pioneering therapeutic applications of genomic and proteomic sciences to cultivating cutting-edge technology that is changing the way discoveries are made and analyzed, Weill Cornell Medical College is playing a considerable role in guiding the future of medicine.

In 2012, the Medical College received $49.6 million from the National Center for Advancing Translational Sciences of the National Institutes of Health to fund its Clinical and Translational Science Center. This Clinical and Translational Science Award is a five-year renewal of the largest Federal grant ever awarded to the Medical College by the NIH.

As the Medical College enters the final phase of its $1.3 billion Discoveries that Make a Difference campaign, its Research Leads to Cures initiative is focused on recruitment of distinguished scientists in a number of important fields of study. These individuals will join an impressive faculty whose efforts are currently supported by a research budget of more than $200 million, including an impressive roster of National Institutes of Health R01 grants and MERIT Awards. Some of the major grants received by Medical College scientists include over 250 R01 grants in awards of up to $5.4 million and 10 MERIT Awards in amounts up to $3.2 million. Following are a sampling of grants active in 2011-2012 (FY12).

**R01 GRANTS**
- Epigenome Interactions in Complex Neurogenetic Disorders: $5.4 million (Transformative R01)
- Biology of Lipoamide Dehydrogenase and 2-Hydroxy-3-Oxoadipate Synthase in Mtb: $4.4 million
- Overlapping Airway Basal Cell Transcriptome Reprogramming in COPD and Lung Cancer: $4.2 million
- Gene Therapy for Batten Disease: $3.7 million
- A Collaborative System Approach to Diffusion of Evidence-Based Prevention: $3.7 million
- Molecular Basis of Protein Transport in Photoreceptor: $3.2 million
- Central Thalamic Deep Brain Stimulation: $3.2 million
- Hepcidin Therapy for Iron Overload and Hematologic Disorders: $3.2 million
- Drug Targets in Mtb Gluconeogenesis: $3.1 million
- Biotin Synthesis and Biotin Ligation in Mtb: $3.1 million

**MERIT AWARDS**
- Receptor-Mediated Endocytosis – Mechanism and Function: $3.2 million
- Cell-Cell Interactions in Thrombosis: $2.5 million
- Biomolecular Markers for Safe Minimization of Immunosuppression: $2.1 million
- Sphingolipid Modulators of Vascular Growth and Homeostasis: $2.1 million
- Neutralization of Primary HIV-1 Viruses: $2.1 million
- Diabetic Vasculopathy and Mitochondrial eNOS: $2.1 million

**OTHER MAJOR GRANTS**
The National Institute of Neurological Disorders and Stroke awarded a $6.7 million grant to the Department of Neurology and Neuroscience to study proliferation, specification, and brain function, and a $4.9 million grant to the Department of Genetic Medicine to study gene therapy for metachromatic leukodystrophy. In addition, a $5.3 million grant was received by the Department of Genetic Medicine from the National Heart, Lung, and Blood Institute to study COPD metabolome, smoking oxidants, and aberrant ciliated cell function, and the National Institute of Child Health & Human Development awarded a $5.8 million grant to the Department of Neurology and Neuroscience to investigate risk genes and environmental interactions in neural tube defects.

**AMERICAN RECOVERY AND REINVESTMENT ACT**
Since the American Recovery and Reinvestment Act – also known as the economic stimulus package – was enacted in February 2009, Weill Cornell Medical College has received $48 million to fund 112 projects. Stimulus funding is supporting work in AIDS, kidney disease, cancer, Parkinson’s disease, with the single largest grant – $3.8 million from the National Institute on Drug Abuse – funding the development of an adenovirus-based anti-cocaine vaccine.
Major research is taking place throughout the biomedical community at Weill Cornell Medical College. Through the establishment of specialized centers and institutes, and collaborations among some of the world’s foremost and prolific scientists, great strides are being made in areas as diverse as bench-to-bedside research; psychological, sociological, and societal based studies; and innovations in computational biomedicine and healthcare informatics. Following are some of the many programs that demonstrate the influential work that is underway at Weill Cornell.

**Cancer Center**
Lewis C. Cantley, PhD
Director

The newly established Cancer Center at Weill Cornell Medical College and NewYork-Presbyterian Hospital marks a critical step in the transformation and acceleration of personalized translational medicine, research, and clinical care for cancer patients. The Center’s mission is to ensure that patients can have immediate access to emerging new therapies in a supportive and caring environment, while training future researchers and recruiting leaders in cancer research and clinical care.

The Cancer Center, which will be headquartered in the new Belfer Research Building, will provide research space, resources, and access to the latest state-of-the-art technologies for basic, clinical, and translational cancer research, as well as support for initiating and conducting novel clinical trials. A centralized cancer tumor tissue bank and patient database and system will enable the rapid evaluation of each patient’s cancer tumor for its genetic profile, associated gene expression, and mutations to accelerate the development of a personalized treatment plan or enrollment in clinical trials based on the individual’s genetic information.

As a collaborative, multidisciplinary research enterprise, the Cancer Center will organize Weill Cornell’s current efforts under a centralized structure, across faculty and departments. This will enable basic, translational, and clinical researchers to collaborate and efficiently convert conceptual breakthroughs into novel therapies and bridge the work of scientists and clinicians in the design and execution of investigator-initiated clinical trials. The Cancer Center will initially focus on colorectal, lung, melanoma, and hematopoietic cancers and expand to all cancers where there is a risk that standard of care will not lead to a cure, such as breast, prostate, pancreatic, endometrial, and ovarian cancers, and glioblastoma.

The Cancer Center’s researchers will conduct more detailed exploration of the molecular abnormalities in cancer cells and tumors to gain new insight into the underlying mechanisms of drug resistance or acquired resistance to therapies and test novel drug combination therapies to combat resistance. Also, identifying new biomarkers for resistance will help researchers more effectively triage patients into the specific therapies that will benefit them the most.

**Brain and Mind Research Institute**
Costantino Iadecola, MD
Director

In 2012, Weill Cornell Medical College and NewYork-Presbyterian Hospital came together to create the Brain and Mind Research Institute – a major initiative that will serve as the hub for neuroscience research and for training the next generation of basic, translational, and clinical scientists. With faculty from neuroscience,
neurology, psychiatry, psychobiology, neurosurgery, and radiology, the Institute will integrate expertise from multiple specialties to focus on:

- neurovascular conditions such as stroke, hypertension, and dementia
- neurodegenerative conditions such as Alzheimer’s, Parkinson’s, ALS, and aging
- neuroplasticity development, including learning, memory, brain malformations, pain, and addiction
- neuroimmunological conditions, such as multiple sclerosis
- mind and consciousness, including neurophysiology, coma, vegetative state, and minimally conscious state

The Institute provides a focal point for clinical and research faculty across the Medical College and the Hospital to pursue their areas of interest and expertise in neuroscience and related fields under one umbrella and facilitate the translation of discoveries into novel therapeutics for brain diseases. Neuroimaging modalities, including cell imaging, optogenetics, and functional brain imaging, will be used to identify biomarkers and advance novel diagnostics. The Institute builds on the groundbreaking interdisciplinary work of Weill Cornell faculty who conducted the first clinical trial of gene therapy for Parkinson’s disease and performed the world’s first successful use of deep brain stimulation to treat a minimally conscious brain-injured patient.

Clinical and Translational Science Center
Julianne Imperato-McGinley, MD
Director

In 2007, the National Institutes of Health awarded $49 million to Weill Cornell Medical College to establish the Clinical and Translational Science Center (CTSC) – one of 60 translational centers nationwide that brings together researchers and clinicians to advance community health. The multi-institutional consortium – Memorial Sloan-Kettering Cancer Center, Hospital for Special Surgery, Cornell University Cooperative Extension in New York City, Hunter College School of Nursing, Hunter College Center for the Study of Gene Structure and Function, NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and Weill Cornell Graduate School of Medical Sciences – is yielding new patient treatments, educating translational research scientists, and enhancing healthcare for the underserved.

Since its inception, the CTSC has supported over 140 pilot, planning, community engagement, and novel research and methodology projects in departments throughout the partner institutions. Projects include human and animal studies; basic, translational, and clinical research; community-based outcomes studies and registries; and novel uses for devices and technologies. The CTSC continues to serve as a source for essential resources, technological tools, and education programs, helping to accelerate the clinical application of basic science discoveries and creating an ideal multicenter clinical trials network. By providing an environment that allows optimal use of the Center’s considerable multi-institutional assets and diverse patient populations, research transitions seamlessly from bench to bedside to the community.

In 2012, the CTSC received renewed funding for an additional five years of the NIH’s Clinical and Translational Science Awards program. During the next funding period, the CTSC will build on the varied accomplishments achieved during the initial funding period, focusing on advancing translational science discoveries.
The renewed funding will also expand and enrich programs in drug discovery, education, and mentoring; increase research resources; and enhance healthcare to underserved communities of New York City.

Institute for Computational Biomedicine
Harel Weinstein, MSc, DSc
Director

The detailed understanding of complex interactions among genes and between proteins and other cell components that underlie normal and pathophysiological states of cells, tissues, and organs remains a significant challenge in biomedical sciences. The HRH Prince Alwaleed Bin Talal Bin Abdulaziz Alsaud Institute for Computational Biomedicine (ICB) is an academic and research unit presenting a novel approach to biomedicine that addresses that challenge. Its special perspective is mathematical modeling, large-scale computational simulation, and information management of genomes, proteomes, and complex physiological systems. The computational models of biological systems are created, using computer and informatics technology, from the analysis of the large amounts of data that are now available to scientists. The evolution of each biological system can thus be evaluated in space and time using simulation with powerful computational approaches. The results are tested in newly designed experiments based on the hypotheses generated from the computational models, and these are iteratively probed and refined in the lab.

Created less than a decade ago, the ICB enables physician-scientists to attack complex medical problems formerly beyond their reach by integrating genomic and cellular data with the larger issues of biomedicine. Scientists can pursue fundamental study and practical use of the basic, quantitative understanding of physiological function and disease in an integrative, multi-scale approach. The ICB has established the computational means for using the abundant genomic information to guide decisions for medical care and preventive medicine, placing it among the leaders in uncovering new capabilities of genomic tools, especially their ability to identify individual genetic variations that can guide medical care.

The ICB is home to the world’s highest-definition 3D virtual reality environment. Here, images of tissues and biological objects such as chromosomes and ion channels can be “entered” and explored, turned, expanded, and viewed layer by layer, bringing the scientists to the molecular and cellular level with exquisite clarity and precision.

Ansary Stem Cell Institute
Shahin Rafii, MD
Director

The Ansary Stem Cell Institute was established in 2004 with a $15 million grant from Shahla and Hushang Ansary. The Institute’s scientists are leaders in stem cell and developmental biology research. Their goal is to be able to use a patient’s own stem cells as treatment in a number of areas such as brain recovery following stroke, wound healing in diabetics, and heart muscle regeneration after a heart attack. In the seven years since its creation, the Ansary Institute has realized significant breakthroughs, including the discovery that endothelial cells have the potential to grow large amounts of adult stem cells, potentially offering therapeutic applications for organ regeneration and cancer cell inhibition. In addition, the Institute’s scientists have shown how endothelial cells influence the self-renewal of certain stem cells and...
have an “instructive role” in blood, liver, and lung regeneration. In the past year, the Ansary Stem Cell Institute has made progress on several projects.

**Generation of lineage-specific tissues from hESC and iPSC.** The group has demonstrated, for the first time, the potential for hESC-derived endothelium to generate hematopoietic derivatives.

**Repository for varied adult stem cells for scientific and therapeutic applications.** Ansary Stem Cell Institute scientists have established methods for providing unlimited sources of human embryonic, fetal, amniotic, and organ-specific adult stem cells to Tri-SCI researchers. Specifically, they have the capacity to generate GMP-grade validated stem cells and feeder support cells for scientists who envision translation of their studies to pre-clinical and clinical settings.

**Novel platform to generate tissue specific cell types via reprogramming of amniotic cells.** The Institute’s scientists have developed a novel approach for generating virtually unlimited quantities of engraftable, functional endothelium from amniotic cells that can be generated for a vast diversity of genotypes. Combining this with the increased potential for amniotic cells to generate endothelium and perhaps other lineage-specific specialized cell types, amniotic cells may provide an “off the shelf” resource for cell-based therapies.

**Center for Vascular Biology**

Timothy Hla, PhD  
*Director*

The Center for Vascular Biology, founded in 1995, is dedicated to biomedical research into vascular biology and disease. The vascular system permeates all organ systems; indeed, vascular health is essential for overall well-being of the organism. Physicians have come to realize that abnormal changes in the vascular system contribute critically to many serious diseases, including cancer, heart disease, stroke, and diabetes. Vascular biologists at Weill Cornell have been at the forefront of several aspects of vascular research, including the cell and molecular biology of endothelial cells, angiogenesis (also known as new blood vessel formation), and lipid mediators in vascular disease. The Center is also an intellectual home for scientists interested in vascular biology and disease from Weill Cornell and neighboring institutions. Cutting-edge research in the areas of regenerative biology, inflammatory vascular diseases, tumor microenvironment, lipid mediators, vascular cell biology, developmental biology and signaling, metabolomics, and hypertension are conducted. In addition to novel research discoveries that are making an impact on our knowledge base as well as on therapeutic approaches, the vascular biology community provides a superb training environment in basic and translational research endeavors.

**Sackler Institute for Developmental Psychobiology**

B.J. Casey, PhD  
*Director*

The Sackler Institute for Developmental Psychobiology – established more than two decades ago – focuses on human behavioral and brain development. It has garnered an international reputation for research and training using the techniques of brain imaging, human genetics, and behavioral methods in the domains of perceptual, cognitive, and emotional development. In addition, the Sackler Institute is rapidly establishing a high profile in genomic research, translating transgenic
mouse models to human behavior and disease. The Institute is using this approach to delineate the biological mechanisms underlying mental health and illness and to optimize both the type and timing of treatments and interventions for individuals with mental illness. Studies currently underway focus on risk factors related to anxiety, depression, and addiction and are moving the field toward preventive and personalized medicine for these disorders.

**Comprehensive Center of Excellence in Disparities Research and Community Engagement**

*Carla Boutin-Foster, MD*  
*Director*

Cardiovascular and cancer diseases are among the most prevalent healthcare challenges confronting the nation’s racial and ethnic minorities. Reducing the profound disparity in health status of these and other populations with limited resources and access to healthcare is the focus of the Comprehensive Center for Excellence in Health Disparities Research and Community Engagement (CEDREC) established in 2010. Created through an $8 million grant from the National Center on Minority Health and Health Disparities, a division of the National Institutes of Health, the Center is a consortium comprised of the Medical College, Hunter College School of Nursing, City University of New York, Lincoln Medical and Mental Health Center, and the Center for Healthful Behavior Change at New York University Langone Medical Center. CEDREC is conducting two randomized trials to improve blood pressure control and colon cancer screening, thereby improving health. With the understanding that nobody knows the problems in a community better than the people who live and work there, CEDREC developed a community engagement and outreach core to provide the infrastructure for improving the health of the community through sustained and expanded community partnerships.

**Center for Healthcare Informatics and Policy**

*Rainu Kaushal, MD, PhD*  
*Executive Director*

The new Center for Healthcare Informatics and Policy (CHiP) provides an exciting platform that will take technology and its role in the healthcare arena to a transformative level. Bringing together faculty with expertise that crosses multiple fields — informatics, clinical medicine, health services research, biostatistics, public health, healthcare policy, healthcare analytics, computer science, economics, and decision science — CHiP will foster the growth and effective use of technology, buttressing the healthcare industry for decades to come.

The Center’s experts will develop and evaluate innovations that improve healthcare, such as mobile devices, novel graphical interfaces, and natural language processing. Collaborative research through CHiP is focusing on a number of areas, including the effectiveness, cost-effectiveness, and comparative effectiveness of a variety of healthcare interventions. Researchers will measure the effects of health information technology on such outcomes as clinical quality and safety, economic value, technology adoption, consumer satisfaction, and provider experiences.

In addition, CHiP offers a two-year Fellowship in Healthcare Quality and Medical Informatics emphasizing research methods and a five-month, executive-format Health IT Certificate Program emphasizing pragmatic training to address the technical, legal, social, financial, and clinical environment surrounding implementation of electronic health records systems.
Collaborations among Weill Cornell Medical College faculty and their colleagues at other major institutions continue to provide extraordinary training for the physicians and scientists of tomorrow and unique opportunities for advancing medicine across the basic, translational, and clinical research arenas.

**Tri-Institutional MD-PhD Program**

Weill Cornell Medical College, The Rockefeller University, and the Sloan-Kettering Institute comprise an inter-institutional collaboration for joint MD/PhD training. These biomedical research and educational institutions, which are geographically adjacent to each other in New York City, are home to more than 35 members of the National Academy of Sciences. The program awards an MD degree from Weill Cornell Medical College and a PhD degree from either Weill Cornell Graduate School of Medical Sciences (formed by Weill Cornell Medical College and the Sloan-Kettering Institute), Gerstner Sloan-Kettering Graduate School, or The Rockefeller University. Now in its 40th year, the Tri-Institutional MD-PhD Program continues to draw on the unique resources available in the three institutions with a goal to educate tomorrow’s biomedical investigators. Each year over 500 students apply for an average of 14 positions per year, which are fully funded by the National Institutes of Health Medical Scientist Training Program. Students receive an advanced understanding of biomedical science and master state-of-the-art research skills in basic biological processes pertaining to human health and disease, working and training side-by-side with renowned investigators from around the world.

**Tri-Institutional Stem Cell Initiative**

The Tri-Institutional Stem Cell Initiative (Tri-SCI) is a major collaborative endeavor made possible by an initial $50 million gift in 2005 from The Starr Foundation, followed by a new $50 million gift awarded in 2012 to continue the work of this multi-campus program. Together, Weill Cornell Medical College, Memorial Sloan-Kettering Cancer Center, and The Rockefeller University are providing resources to support a broad portfolio of stem cell research, including funds for projects using both registered and non-registered human embryonic stem (hES) cell lines, and for work with human pluripotent stem (hPS) cells. As part of this initiative, support is also provided for three state-of-the-art core facilities to derive, maintain, and characterize human embryonic stem cells for the tri-institutional investigators. This includes the development of cell lines that model genetic diseases.

Recognizing the need to train the next generation of stem cell scientists, the Tri-SCI continues to sponsor the Tri-Institutional Starr Stem Cell Scholars Fellowship program and also provides support for lectures and seminars in the field that are of interest both to the scientific community and to the public.

Studies currently underway in laboratories on each of the three member campuses are generating new insights into basic stem cell biology and exploring the translational potential of stem cells in human disease, with a major focus on cancer, neurosciences, cardiovascular and angiogenesis, ophthalmology, and regenerative medicine and cell therapy. With more than 60 scientists involved in the Tri-SCI, breakthroughs have already begun to be realized.
Center on the Microenvironment and Metastasis
With funding of $13 million over five years from the National Cancer Institute, the Center on the Microenvironment and Metastasis at Cornell University (CMM), in partnership with Weill Cornell Medical College and the University at Buffalo, focuses on using nanobiotechnology and other related physical science approaches to advance research on cancer. The Center, one of 12 such Physical Sciences Oncology Centers across the country, deciphers the complexities of cancer using the insights and methods of physical sciences and engineering to further understand how cancer travels through the human body and how it acquires resistance to commonly used chemotherapy. Research advances are leading to new drug strategies to inhibit metastasis and tumor growth.

The CMM brings together a multidisciplinary team of 27 faculty and over 70 researchers from engineering, physics, biomedical sciences, and medicine in the pursuit of experimental and theoretical approaches to the major questions and barriers in the treatment of cancer. The CMM’s innovative in vitro and in vivo approaches and techniques promote our understanding of the tumor environment, yielding new pathways with which to intervene in the progression of cancer.

During the past year there were over 52 collaborations with the Center, with 30 researchers from 30 research centers. There has also been an increasing impact of the Center’s research through publications and presentations, with 19 peer-reviewed papers published, 15 manuscripts at press, accepted or submitted, and 30 papers presented at conferences.

Translational Research Institute on Pain in Later Life
Created in response to the millions of older adults experiencing persistent pain, the Translational Research Institute for Pain in Later Life (TRIPLL) seeks effective solutions to the problem of later-life pain, moving basic behavioral and social science and medical research findings more rapidly into programs, practices, and policies targeting older adults. A National Institute of Aging-funded Edward R. Roybal Center, TRIPLL is a collaboration among investigators at Weill Cornell Medical College, Cornell University College of Human Ecology, Columbia University’s Mailman School of Public Health, Hospital for Special Surgery, Visiting Nurse Service of New York, and the Council of Senior Centers and Services of New York City, Inc. TRIPLL focuses on:
1) building evidence-based pain prevention and reduction, and management practices, treatments, and interventions; 2) developing and translating research-based methods, tools, and strategies that facilitate successful translation of evidence into practice; and 3) developing and maintaining an effective infrastructure for conducting translational research on aging and pain in New York City.

Cornell Center for Behavior Intervention Development
With a $6 million grant from the National Heart, Lung, and Blood Institute, the Cornell Center for Behavior Intervention Development seeks to reduce obesity and obesity-related deaths in New York City’s African-American and Latino communities. The program is a joint endeavor of Weill Cornell Medical College, Cornell University, Lincoln Hospital in the Bronx, and Renaissance Health Systems in Manhattan in partnership with faith-based and community organizations. One of the Center’s studies, SCALE: Small Changes and Lasting Effects, takes an
interdisciplinary approach to lifestyle changes. Drawing on the expertise of psychologists, medical sociologists, nutritionists, and other experts working directly with community members in Harlem and the South Bronx, the initiative incorporates individually tailored programs that are more likely to be successful for participants. The study team is developing strategies aimed at reducing weight through small, sustained changes in eating behavior, coupled with sustained increases in physical activity.

**Cornell IMAGINE: Ithaca-Manhattan Graduate Initiative in Neuroscience**

This joint graduate training initiative combines the strengths of the psychology and cognitive science programs at Cornell University with the expertise of the neuroscience program at Weill Cornell Medical College. Cornell IMAGINE, based at Cornell University, specializes in basic analysis of perception, cognition, communication, and decision making, grounded in developmental and evolutionary perspectives, with a strong computational emphasis. The training facility is integrated by its focus on development, learning, and trajectories of behavioral change. The faculty are segmented into three interest clusters spanning both campuses. These include memory, attention and learning systems; communication systems focusing on language and emotional communication; and sensory and perceptual systems.

**Weill Cornell Medical College in Qatar**

Weill Cornell Medical College in Qatar (WCMC-Q) is a prominent example of a national investment in biomedical research and education, creating world-class facilities and research infrastructure. In accordance with the research priorities of Qatar and the Qatar Foundation, the WCMC-Q research program is well on its way to achieve three major objectives: 1) develop biomedical research capacity for the country; 2) develop sustainable human capacity; and 3) address pressing health needs in Qatar.

In the span of three years, the biomedical research program has grown to 28 active research labs that target multiple areas of biomedical research, providing significant breadth to tackle complex diseases such as diabetes. The idea is that complex multifactorial diseases will be dealt with in a multi-pronged approach at the molecular, cellular, biochemical, organismal, translational, and clinical levels. WCMC-Q researchers together with their research partners in Qatar, such as the clinicians at Hamad Medical Corporation (Qatar’s national health provider), have the expertise and the resources to make this happen.

The program’s success to date is evident in the faculty’s ability to garner significant extramural funding (totaling $50 million since the start of the program) and publish extensively in peer-reviewed journals (totaling 55 articles in 2010-11), several in high-impact journals such as *PNAS, Nature Biotechnology, Journal of Cell Biology, American Journal of Human Genetics,* and the *Journal of Biological Chemistry.* WCMC-Q faculty are also building a pipeline of patents with the goal of commercializing them in the future – ideally through Qatar Science & Technology Park – thus closing the research innovation circle and truly contributing toward building Qatar’s knowledge-based economy.

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The research effort at WCMC-Q remains in its early stages of development. However, a combination of factors has resulted in a productive research environment. At the national level, Qatar has invested significantly in research. This, coupled to well-equipped core labs at WCMC-Q and the unwavering commitment of its scientists to high quality research, is already producing internationally noted research and more is set to follow. Having established a strong administrative infrastructure and state-of-the-art core labs, WCMC-Q is now in a position to make an impact at the national and regional levels in the biomedical arena.

The Methodist Hospital Research Institute

Weill Cornell Medical College is affiliated with The Methodist Hospital Research Institute in Houston, Texas, actively collaborating on interdisciplinary research projects and training of the next generation of translational scientists. Laurie H. Glimcher, MD, the Stephen and Suzanne Weiss Dean of Weill Cornell Medical College, joined the Research Institute Board of Directors in 2012. The affiliation is also supported by former Weill Cornell Medical College Dean Antonio M. Gotto, Jr., MD, DPhil, serving as the head of the Research Institute Council of Deans, and Harold G. Craighead, PhD, of Cornell University serving as the Research Institute Dean of Physics.

The two institutions support joint collaboration of their researchers with reciprocity agreements for shared core technology facilities on the iLab platform, collaborative seed grant programs, and joint Institutional Review Board procedures to streamline clinical trials approvals. The Methodist Hospital Research Institute and Weill Cornell Medical College are also working together to create a de-identified clinical data repository as part of the National Center for Biomedical Computing i2B2 project to share data resources from The Methodist Hospital with the multi-institutional consortium of the Weill Cornell Medical College Clinical and Translational Science Center.

With this administrative and joint infrastructure support, The Methodist Hospital Research Institute and Weill Cornell Medical College joint research programs and centers are rapidly expanding, including:

- Development of a joint National Cancer Institute (NCI) designated comprehensive cancer center
- Networked NCI Physical Sciences in Oncology Centers, dedicated to understanding the physical principles of cancer development
- Joint program project grant applications
- Joint research projects:
  - Strategies to eliminate leukemia stem cells during remission, supported by the Leukemia & Lymphoma Society
  - Nanoparticle-mediated targeting of molecules for breast cancer treatment, supported by the New York State Department of Health
  - Development of live imaging techniques, miRNA-based therapeutics, and tumor-stroma cross-talk in primary and metastatic breast cancer, supported by the National Cancer Institute
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**SELECTED PUBLICATIONS**


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**Scott C. Blanchard, PhD**

**Associate Professor of Physiology and Biophysics**

Dr. Scott Blanchard and his team focus on the molecular mechanisms governing enzyme function and regulation for the purpose of developing therapeutic strategies for the treatment of human infection and disease. The studies undertaken employ an integrated battery of molecular, structural, biophysical, and chemical strategies, including the development and advancement of single-molecule imaging methods that yield unprecedented insight into the dynamic properties underlying the functions of biological machines. Single-molecule imaging enables the observations from the perspective of motion. Consequently, the dynamic properties of single molecules can be tracked over time and in response to stimuli to quantitatively reveal the structure-function relationship. Perhaps most critically, the single-molecule imaging approaches under development can be applied to investigations of many biological systems that have proven difficult or impossible to study using traditional methods.

The Blanchard lab has already developed the first single-molecule methods used to explore the structural and mechanistic determinants of aminoacyl-tRNA selection and substrate translocation on bacterial and mammalian ribosomes—reactions critical to determining the rate and fidelity of protein synthesis. Dr. Blanchard’s group was also the first to successfully extend such lines of investigation to integral membrane proteins involved in solute transport across lipid bilayers. This includes proteins such as the Na+–coupled neurotransmitter transporters, a family of proteins targeted by a broad array of mood-altering agents in humans. Pioneering technological efforts in the lab have also shown that single-molecule measurements can be used as a tool to streamline the determination of high-resolution structures of macromolecular complexes. This has led to the atomic resolution structures of functional configurations of the ribosome that have provided unprecedented insight into mechanisms of antibiotic actions blocking normal functions of the translation machinery.

To enable translational efforts centered on whole cells, the Blanchard lab has pursued a battery of investigations aimed at understanding the photophysical properties of the fluorescent compounds that are essential for whole-cell imaging. Technological developments on this front have played a key role in the publication of the first three-color, single-molecule fluorescence imaging studies of the bacterial ribosome and the continued advancement of new imaging and site-specific labeling modalities. By creating a new suite of organic fluorophores ("self-healing" dyes) spanning the visible spectrum, the lab ultimately plans to empower the examination of biological processes *in vivo* at the single-molecule scale using real-time super-resolution and multicolor fluorescence imaging.

Because it appears that physical and functional distinctions of the ribosome within the cancerous cell can be specifically targeted by small-molecule therapies, a key goal of the Blanchard lab is to address the misregulation of translation in the cancerous state and to understand how ribosomopathies alter the cellular proteome. The lab’s application of single-molecule imaging to dynamic processes of integral membrane protein function also has the potential to shed critical new insights on signaling processes at the membrane directly contributing to neurodegenerative disease. Correspondingly, the lab also plans to use single-molecule imaging to improve the search for new pharmacologic interventions that specifically regulate these critical information transfer processes.
John A. Boockvar, MD  
Associate Professor of Neurological Surgery

Dr. John Boockvar and his colleagues have focused on studies of brain tumor formation and brain tumor and stem cell survival, with a particular interest in improving how drugs are delivered to the brain and spinal cord. During the past five years, they have pursued research into better therapies for glioblastoma multiforme (GBM), a common primary brain tumor that has not responded well to currently available medical and surgical therapies.

In 2009, Dr. Boockvar, who directs Weill Cornell’s Brain Tumor and Stem Cell Research Laboratory and the Brain Tumor Research Group, and his neurological surgery colleagues performed the world’s first intra-arterial cerebral infusion of bevacizumab directly into a patient’s malignant brain tumor. The goal of the novel intra-arterial (IA) technique was to expose the tumor to higher doses of the drug therapy with less toxicity to the patient than administering the drug intravenously (IV). Because the blood-brain barrier prevents many IV-administered drugs from penetrating the blood vessel walls sufficiently, it is unclear if IV infusion enables current drugs to enter the brain. Since these agents are less toxic and their delivery leads to a higher tumor-drug concentration, this combination may provide a better outcome in patients with high-grade glioma.

Dr. Boockvar is now the principal investigator of several clinical trials using superselective intra-arterial infusion – a technique that can effectively increase the concentration of drug delivered to the brain while sparing the body of systemic side effects – for the delivery of novel therapeutics such as bevacizumab (Avastin®), temozolomide (Temodar®), or cetuximab. These Phase I clinical trials are testing the hypothesis that the drugs can be safely used by direct intracranial superselective intra-arterial infusion and ultimately enhance survival of patients with relapsed/refractory GBM. The trials will enable the researchers to determine the toxicity profiles and maximum tolerated doses and may alter the way the drugs are delivered to patients in the near future.

A Phase I/II trial of erlotinib (Tarceva®) is also underway for the treatment of relapsed/refractory GBM and anaplastic astrocytoma (AA). Erlotinib belongs to a class of drugs called epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and is approved for the treatment of non-small cell lung cancer. A percentage of malignant brain tumors, such as GBM and AA, express EGFR and therefore, by inhibiting this receptor, the researchers predict that they may be able to slow or arrest the growth of the tumor. Previous studies performed elsewhere indicate that erlotinib is safe to use in patients with brain tumors and may also have anti-tumor effects. The specific objective of this trial is to determine the rate of response and patient survival time to oral erlotinib in patients with and without the EGFRVIII and PTEN brain tumor mutation and to assess quality of life and survival.

In the laboratory, Dr. Boockvar and his team are investigating the link between brain tumor formation and adult human central nervous system stem cells. They seek to understand the differential sensitivity of patients with glioma to targeted therapeutics and whether tumor stem cells play a role in this response. By manipulating normal and tumor-derived stem cell signaling, Dr. Boockvar studies neural stem cell migration and invasion as this has relevance to glioma invasion and response to therapy.

SELECTED PUBLICATIONS


SELECTED PUBLICATIONS


Olga Boudker, PhD
Associate Professor of Physiology and Biophysics

Living cells are surrounded by lipid membranes, which are fundamental to their integrity. Membrane integrity is essential for compartmentalized life preventing an uncontrolled diffusion of proteins, metabolites, signaling molecules, and ions. The lipid bilayers of membranes represent formidable barriers for polar molecules, and cells have evolved an array of specialized proteins, transporters, and channels to assist their controlled trans-membrane passage.

Dr. Olga Boudker and her lab are interested in understanding the structure and mechanism of these proteins, focusing primarily on the gradients-driven transporters. These transporters are miniature molecular machines that are thought to undergo at least one critical conformational transition: from a state in which they are open to one side of the membrane, to a state in which they are open to the other side. During this transition, the substrate is sequestered from the aqueous solution on one side and released on the other. The Boudker lab’s central goal is to understand in structural detail the conformational states of the transporters and their dynamic properties.

The Boudker lab’s central goal is to understand in structural detail the conformational states of the transporters and their dynamic properties.

In the central nervous system, glutamate transporters are responsible for the uptake of the neurotransmitter glutamate following rounds of synaptic signaling. Rapid clearance of the transmitter is essential not only to allow for repeated rounds of neurotransmission, but also to prevent excessive stimulation of the glutamate receptors, which leads to cytotoxicity and neuronal death. Dysfunction of these transporters is implicated in numerous disorders such as neurodegenerative diseases, stroke, traumatic brain injury, epilepsy, and schizophrenia. Located in the plasma membranes of glial cells and neurons, the transporters couple uptake of a glutamate to the co-transport of three sodium ions and a proton and to the counter-transport of one potassium ion. The crystal structures of a bacterial homologue from Pyrococcus horikoshii, determined by Dr. Boudker and colleagues, revealed the transporter in a state in which the substrate-binding site is close to the extracellular solution, and in a state in which it is close to the cytoplasm. These structures showed that glutamate transporters function as miniature elevators with a central rigid scaffold and three cabins, which are loaded with the transported substrate and coupled ions and which traverse the thickness of the membrane.

Dr. Boudker and her colleagues have recently reported another structure of the transporter in which it was captured in an intermediate state. The intermediate state shows a cavity in the thinnest region of the transporter that is potentially accessible to extracellular and cytoplasmic solutions. This structure suggests a structural principle by which transport intermediates may mediate permeation of polar solutes other than the primary transporter substrates, such as chloride ions, a well-known property of the mammalian transporters of potential importance in modulating synaptic transmission.
Carla Boutin-Foster, MD
Associate Professor of Medicine
Associate Professor of Public Health

Dr. Carla Boutin-Foster is the Director and Principal Investigator of the Comprehensive Center of Excellence in Disparities Research and Community Engagement (CEDREC) at Weill Cornell. The mission of CEDREC is to improve minority health and eliminate health disparities by conducting innovative, cutting-edge transdisciplinary research; providing strong mentorship for junior investigators; and fostering community-academic partnerships that build community capacity for research. This year a new core was funded under CEDREC. The Environmental Health Disparities Core lends an environmental justice perspective to disparities research.

Dr. Boutin-Foster’s research focuses on addressing the psychosocial determinants of health disparities in cardiovascular disease and includes studies that focus on the association between cardiovascular disease and depressive symptoms, perceptions of stress, and social support. The common theme is to understand and intervene upon those factors that help to drive or motivate the adaptation and maintenance of healthy behaviors. Among Dr. Boutin-Foster’s most recently NIH-funded grants is TRIUMPH (Trial Using Motivational Interviewing and Positive Affect and Self-affirmation in Hypertension). This randomized, controlled trial is designed to improve blood pressure control in hypertensive black patients. Participants are recruited from medically underserved communities in the South Bronx and Harlem in New York City. The goal is to achieve improvements in medical adherence, reduce the rates of uncontrolled hypertension in African-Americans, and ultimately reduce the disproportionate rates of adverse hypertension-related events in African-Americans.

TRIUMPH applies three interrelated behavioral techniques to motivate health behavior change: positive affect induction, self-affirmation induction, and motivational interviewing. Trained research assistants deliver these techniques via telephone. Positive affect is a state of pleasurable engagement with the environment and reflects the extent to which a person feels enthusiastic, active, and alert. Positive affect may exert its impact on behavior by increasing the expectation that a specified health behavior change will result in a desirable outcome. Self-affirmation is a theory that describes the motivation to preserve a positive image and self-integrity when one’s self-identify is threatened. Self-affirmation can be induced through the active use of positive statements or memories about one’s accomplishments or successes to build self-confidence. This helps to build confidence in one’s ability to achieve a desirable health outcome. Motivational interviewing is a directive, patient-centered, counseling technique designed to motivate health behavior change. The goal is to facilitate patients to recognize and resolve the discrepancy between their present behavior and a desired future goal or outcome.

Dr. Boutin-Foster was recently appointed Assistant Dean for Faculty Diversity with a goal to develop a cadre of talented research faculty from diverse backgrounds who can contribute to biomedical research at Weill Cornell. She founded the annual Tri-Institutional SPARC Conference (Achieving Successful and Productive Academic Research Careers) in collaboration with The Rockefeller University and Memorial Sloan-Kettering Cancer Center to provide a forum for junior faculty all over New York City to enhance their knowledge of research, networking, and career development awards.

SELECTED PUBLICATIONS


Clinically significant depression affects a significant number of older adults. Consistent with the complex interaction of biological and psychosocial factors that contribute to depression, it is especially prevalent in older adults who are already vulnerable due to disability, medical illnesses, social isolation, and poverty. But despite evidence of effective pharmacological and psychosocial treatments, depression is commonly undetected, untreated, or poorly treated in these older adults.

The target of Dr. Martha Bruce’s research is this gap between research and “real world” practice. She focuses specifically on depression in older adults, working in partnership with primary care and other community-based settings, to develop and implement workable strategies to improve depression care and outcomes. Her interest in homebound older adults started with her analyses of epidemiologic data demonstrating that being homebound was both a powerful risk factor for depression, but also a significant barrier to receiving depression care in traditional outpatient settings. The premise of the research that followed was that organizations that provide other services to the homebound could also provide mental health services.

The science of mental health services delivery spans much of the translational research spectrum, beginning with epidemiology to describe the problem, intervention development, effectiveness trials, and then implementation trials. Dr. Bruce began by documenting that almost 15 percent of older patients of a typical home healthcare agency suffered from major depression. In most cases, depression was not identified and fewer than one in five received adequate treatment.

Dr. Bruce’s research builds on the premise that if we want the community practices to use evidence-based interventions, then we need to involve the community practices in intervention development and testing. With NIH funding, her group worked in partnership with three home healthcare agencies to adapt evidence-based interventions from primary care to fit the patients, practice, and organization of home healthcare. The purpose of improving an intervention’s fit is to increase its acceptability, feasibility, and sustainability in real world settings across the nation. Dr. Bruce’s group has used this approach successfully in home healthcare, aging services, and community-based primary care. They are completing an NIH-funded randomized trial of their Depression CAREPATH (Depression Care for Patients at Home) intervention in collaboration with eight home health agencies located in Florida, Arkansas, Michigan, Vermont, Philadelphia, and the Bronx.

From a public health perspective, improving real world practice requires not only effective and sustainable interventions, but also strategies to promote their uptake and use. Dr. Bruce’s current research focuses on implementation strategies that can be used in home healthcare and other sectors of care where the agencies are decentralized, resource poor, and widely dispersed. With NIH funding, the group has developed a web-based platform, including e-learning modules, to help agencies implement the Depression CAREPATH. This long-distance implementation strategy is being tested in a randomized trial of home health agencies spread across the nation, with the goal of improving depression care and outcomes of as many homebound older adults as possible.
Lewis C. Cantley, PhD
Director, Cancer Center

The research of Dr. Lewis Cantley, newly appointed Director of the Cancer Center of Weill Cornell Medical College and NewYork-Presbyterian Hospital, is focused on understanding the biochemical pathways that regulate normal mammalian cell growth and the defects that cause cell transformation. Dr. Cantley, whose early work was on the structure and mechanism of enzymes that transport small molecules across cell membranes, pioneered the application of fluorescence resonance energy transfer (FRET) for studying such processes.

In the mid 1980s, Dr. Cantley conducted research on biochemical mechanisms of cellular responses to hormones and growth factors that led to the discovery of the phosphoinositide 3-kinase (PI3K) signaling pathway. Dr. Cantley and his colleagues at Tufts University School of Medicine identified PI3K as an enzyme that co-purified with a variety of oncoproteins. Subsequent research from their laboratory and other laboratories showed that PI3K activation is critical for oncogene-mediated cell transformation, as well as for insulin-dependent stimulation of glucose uptake and metabolism, with the subsequent revelation that lipid products of PI3K directly activate the AKT/PKB protein kinase to provide a cell survival signal. This discovery, as well as subsequent discoveries from other laboratories that human cancers frequently have activating mutations in PI3K genes and/or inactivating mutations in the PTEN gene (encoding a phosphatase that degrades PI3K lipid products), stimulated pharmaceutical companies to develop PI3K pathway inhibitors for cancer therapy.

At Harvard Medical School, Dr. Cantley’s laboratory has been utilizing mouse models, genetically engineered with mutations in the PI3K pathway, to investigate opportunities for therapeutic intervention in diseases that result from defects in the PI3K pathway. Recent studies from this laboratory have revealed that growth factors, through activation of PI3K and other signaling pathways, cause major changes in cellular metabolism that are critical for the growth of cancer cells. Of particular interest, cancer cells invariably utilize an embryonic form of pyruvate kinase (PKM2) to channel glucose metabolites for optimal cell growth. Ongoing studies are defining how oncogene transformation of cells alters the flux of metabolites such as glucose and glutamine and how these changes enhance cell growth and cell survival.

In 2009, Dr. Cantley received one of only five grants from Stand Up 2 Cancer, a high-profile initiative created to bring new cancer treatments to patients in a faster time frame. The $15 million, three-year grant funded a team of researchers under Dr. Cantley’s leadership to investigate the role of PI3K in the development of breast, ovarian, and endometrial cancers.

Dr. Cantley has also pursued major research on the structural basis for specificity in protein/protein interactions in signal transduction cascades that control cell growth and survival. In particular, Dr. Cantley and his research team focused on the mechanism by which protein phosphorylation can control the assembly of signaling complexes. This technique was subsequently modified to determine optimal substrates for protein kinases. A novel oriented peptide library technique was developed to determine optimal phosphopeptides for binding to various protein domains. The identification of optimal peptides has facilitated the determination of the structure of protein-peptide complexes and explained how specificity in signaling is maintained. These studies led to a bioinformatics approach (Scansite) for predicting sites of protein phosphorylation and protein interaction from primary sequences.

Selected Publications


Dr. B.J. Casey, PhD

Sackler Professor of Developmental Psychobiology
Professor of Psychology in Psychiatry

Dr. B.J. Casey is a world leader in pediatric neuroimaging and its application to understanding typical and atypical human brain development. She uses brain imaging to uniquely examine transitions into and out of stages of development, especially the period of adolescence. Dr. Casey grounds this work in translational studies from rodent to human, developing models for several major developmental disorders with implications for targeted individualized treatment. The collaborative and highly interdisciplinary work in her laboratory broadly spans three key areas.

First, her seminal neuroimaging studies have moved the field of adolescent human brain development from simplistic notions of “aberrant” behavior in adolescents being attributed to delayed prefrontal cortical development to one that acknowledges an imbalance among regions within maturing frontolimbic circuitry during this developmental period. This imbalance leads to primitive limbic systems hijacking slower maturing, rational prefrontal systems in emotionally charged situations and resulting in less optimal actions and choices. These findings are relevant for understanding the inflection in substance abuse, affective disorders, and criminal behavior during adolescence that markedly differ from childhood or adulthood.

Dr. Casey’s studies have shown divergence in the typical progression of functional brain development in individuals with ADHD and those with anxiety disorders. These findings are important for understanding both pathways to these disorders and targeted treatments.

A second significant area of research by Dr. Casey has been in exploiting functional neuroimaging to develop biologically based theoretical models of normal and abnormal brain development. She establishes normative developmental trajectories of brain circuitry and then examines how children with clinical disorders either deviate or show a delay in the development of this circuitry. Her studies have shown divergence in the typical progression of functional brain development in individuals with ADHD and those with anxiety disorders. These findings are important for understanding both pathways to these disorders and targeted treatments.

A third area of research that reflects Dr. Casey’s most recent work is using human imaging and mouse genetics to identify the role of specific genes as a first step toward individualized and biologically targeted treatments of psychiatric disorders across development. In collaborative studies examining genetically altered mice and humans with allelic variance in neurotrophin and serotonin related genes, she is making new discoveries that could significantly change the way a clinician treats his or her patient. Her work is providing evidence for when during development an individual may be most responsive to cognitive behavioral therapies, and what type of therapy will be most effective for whom. This work is moving psychiatric practice into a new and exciting era of personalized and preventive medicine.
Mary E. Charlson, MD
William T. Foley Distinguished Professor of Medicine
Professor of Complementary and Integrative Medicine

Dr. Mary Charlson is an internationally recognized clinical epidemiologist and methodologist who leads a multidisciplinary research team conducting a broad array of clinical trials, outcomes research, and population-based studies designed to improve outcomes in patients with chronic illness. Among her many original contributions, she has developed new strategies for measuring the prognostic burden of chronic illness, including the widely used Charlson Comorbidity Index. Dr. Charlson has shown that patients with multiple chronic illnesses are driving a significant portion of healthcare costs, and how an adapted comorbidity index can predict the longitudinal costs of caring for patients with chronic disease. Dr. Charlson has also shown why disease management programs structurally cannot reduce costs of care because most of the costs are incurred by patients with multiple chronic diseases. She is currently working on strategies to manage such complex patients to improve outcomes and reduce costs.

Dr. Charlson’s research team has developed prognostic models for identifying patients with chronic disease at high risk of adverse events. Based on these models, they developed and evaluated innovative strategies for improving outcomes in randomized trials. Their research has resulted in significant improvement in outcomes in patients with coronary artery disease, hypertension, and asthma.

Recently, Dr. Charlson and her multidisciplinary team have tested a novel psycho-social intervention combining positive-afect and self-affirmation to help motivate behavior change in patients with chronic cardiovascular disease. This National Heart, Lung, and Blood Institute-sponsored consortium conducted three parallel studies, with a qualitative phase, pilot phase, and randomized trial phase. After completing extensive interviews and pilot studies to optimally tailor the intervention for application in ethnically and racially diverse populations, three parallel randomized trials were conducted that involved over 750 patients. Three papers published in the Archives of Internal Medicine detailed these first large, randomized trials, showing that people with chronic cardiovascular disease can use positive-afect and self-affirmation to help them make and sustain behavior change.

The combined findings of the consortium led Dr. Charlson and her team to develop an intervention to help motivate behavior change in overweight black and Latino adults, who have a disproportionate burden of health consequences from obesity. The project entitled, “SCALE: Small Changes and Lasting Effects,” an NHLBI-funded randomized controlled trial, is currently testing a small change approach to eating and physical activity behavior to produce 7 percent weight loss in black and Latino adults. Small changes include using smaller plates and drinking water rather than sweetened beverages. The multidisciplinary team involves faculty from both the Weill Cornell and Cornell University-Ithaca campuses. Dr. Charlson is also the Co-Principal Investigator on the NIMHD Weill Cornell Center of Excellence in Disparities Research and Community Engagement (CEDREC). The goal of this Center is to create an interdisciplinary academic and community research enterprise that will expand the capacity for conducting cutting-edge and trans-disciplinary research that will contribute to improving minority health and reducing health disparities in cardiovascular disease and cancer in Central Harlem and the South Bronx.

SELECTED PUBLICATIONS


SELECTED PUBLICATIONS


Selina Chen-Kiang, PhD
Professor of Pathology
Professor of Immunobiology and Microbial Pathogenesis

Dr. Selina Chen-Kiang has long studied cell cycle control of B cell immunity and cancer. Cancer is fundamentally a disease of uncontrolled cell division, due to the loss of orderly programmed gene expression and checkpoints that normally regulate the cell cycle. Cyclin-dependent kinases (CDKs) power progression through phases of the cell cycle. CDK4 and CDK6 in particular are required for entry and progression through the G1 phase. In many cancers, these two enzymes are over-expressed, ensuring continual growth. Targeting CDK4/CDK6 therefore represents a rational approach for cancer therapy.

Using PD 0332991, the only known selective and potent inhibitor of CDK4/CDK6 that is also reversible and orally bioavailable, Dr. Chen-Kiang and her colleagues have developed the first mechanism-based therapy to both inhibit tumor cell division and sensitize them to diverse, clinically relevant cytotoxic agents. They demonstrated that: 1) selective inhibition of CDK4/CDK6 leads to early G1 arrest; 2) upon release of the G1 block, a synchronized progression to S phase occurs; 3) prolonged G1 arrest (pG1) sensitizes tumor cells to cytotoxic killing, and 4) pG1 sensitization to cytotoxic killing is augmented in the subsequent S phase synchronization (pG1-S) when metabolic demands are heightened.

Dr. Chen-Kiang’s team was also the first to demonstrate that negative control of CDK4 and CDK6 by their physiologic inhibitor, p18INK4c, is required for homeostasis in B cell activation and for terminal differentiation to non-cycling plasma cells. They were also the first to show that CDK4 and CDK6 are dysregulated in the plasma cell cancer multiple myeloma (MM), as in the B cell cancer mantle cell lymphoma (MCL). Both are currently incurable diseases. On this basis, Dr. Chen-Kiang has implemented the novel CDK4/CDK6 combination therapy in treating MCL and MM, in collaboration with Drs. John Leonard and Ruben Niesvizky at Weill Cornell. In a Phase I single-agent study of PD 0332991 induction of pG1 in MCL, it was found to have encouraging clinical activity and an excellent toxicity profile. A Phase I/II clinical study in myeloma and a Phase Ib clinical study in MCL are in progress. In addition, this therapy will be tested in aggressive acute myeloid leukemia in the near future.

The next steps are to obtain a mechanistic understanding of cell cycle control of cell death and to discover novel molecular targets and genome-based biomarkers for therapy and patient stratification. Dr. Chen-Kiang hypothesizes that induction of pG1 sensitizes cancer cells to cytotoxic killing by restricting gene expression to those scheduled for early G1 but not other phases of the cell cycle, thereby forcing an imbalance in gene expression which is only incompletely restored after release of the G1 block. This hypothesis is being tested in primary tumor cells in serial biopsies obtained from clinical trials of MCL and MM in the context of the clinical response, by whole transcriptome sequencing in collaboration with Dr. Chris Mason at Weill Cornell. Complementing this approach, a sensitizing lethal suppression genome-scale pooled shRNA lentivirus screen is in progress to identify genes that are required to mediate cell cycle control of cytotoxic killing in collaboration with Dr. William Hahn at the Broad Institute. This integrated approach is deeply rooted in fundamental science and propelled by real time clinical application and the promise of advancing mechanism-based cell cycle therapy in cancer.
David J. Christini, PhD
Professor of Biomedical Engineering in Medicine
Professor of Physiology and Biophysics
Professor of Computational Biomedicine

The laboratory of Dr. David Christini studies cardiac electrophysiological dynamics using an integrated multiscale approach – from the subcellular level to the organ level. Dr. Christini’s group is primarily interested in illuminating the mechanisms underlying arrhythmia initiation and utilizing this knowledge to develop new arrhythmia therapies. Through the use of computational modeling and experimental approaches (primarily patch-clamping and calcium imaging of isolated cardiac myocytes), they have provided novel insights into the ionic factors that cause instabilities in the cardiac action potential and how these channel-level instabilities trigger cardiac arrhythmias in the whole heart. The lab’s work is primarily focused on three NIH R01 projects:

**Atrial fibrillation.** Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the developed world. Because AF has several variants, is multifactorial, and evolves over time, it is very difficult to study comprehensively in large-animal models. This is, in part, due to the inherent technical difficulties of imaging whole-atria electrophysiology in vivo. Predictive multiscale computational modeling has the potential to fill this research void. Dr. Christini and his colleagues are developing a multiscale modeling framework using data, including human MRI structural information and electrophysiological data, illuminating the impact of common ion-channel gene polymorphisms on drug-channel interactions. This is enabling the evaluation of potential pharmacological and device-based atrial fibrillation therapies.

**Cardiac alternans.** Cardiac alternans is characterized by a beat-to-beat alternation in membrane potential that is known to trigger cardiac reentry in experiments and has been correlated with risk for clinical arrhythmias. Studies have suggested that alternans may result from dynamical instabilities in either membrane voltage or calcium cycling. For many years, the membrane voltage mechanism was thought to explain the occurrence of alternans. More recently, evidence for the calcium mechanism has accumulated, pushing that theory to the forefront. In recent years, Dr. Christini’s lab has demonstrated that the two mechanisms are intertwined and play varying, but quantifiable, roles for different cardiac cell types. These findings have important implications for their ongoing investigations into device and drug therapy of repolarization-triggered arrhythmias.

**Real-time biological experiment control.** The ability to perturb biological systems has traditionally been limited to rigid pre-programmed protocols. In contrast, “real-time control” allows the researcher to dynamically probe a biological system with parameter perturbations that are calculated functions of instantaneous system measurements (e.g., the “dynamic clamp” paradigm), thereby providing the ability to address diverse unanswered questions that are not amenable to traditional approaches. Unfortunately, real-time control is not possible with standard computer operating systems and software. To circumvent these limitations, the Christini lab develops and releases a highly versatile real-time biological experimentation system known as Real-Time eXperiment Interface (RTXI; www.rtxi.org), helping to facilitate new experimental paradigms. RTXI, which is open source and free, is the leading tool of its type and has been adopted by many prominent neuroscience and cardiac electrophysiology laboratories.

**SELECTED PUBLICATIONS**


Dr. Ronald Crystal’s translational research program includes projects in genetic therapies, personalized medicine, and genomic studies. In addition to gene transfer technologies for gene therapy studies, Dr. Crystal’s laboratory utilizes microarray and high-throughput sequencing to characterize gene expression, single-nucleotide polymorphisms, and exome and whole genome sequences using clinical samples to identify candidate genes associated with complex diseases such as chronic obstructive pulmonary disease (COPD) and diabetes. The following examples of the lab’s work have generated international public interest.

**Personalized response to smoking.** Microarrays of human small airway epithelium from non-smokers, healthy smokers, and COPD smokers identified differentially expressed genes. Individualized responsiveness to smoking was quantified with an index score representing the percentage of smoking-responsive genes abnormally expressed. Smokers demonstrated personalized responses to smoking, though the transcriptome of healthy smokers with high index scores was indistinguishable from COPD smokers, suggesting the small airway transcriptome can classify individuals into smoking responsive subgroups in addition to using clinical criteria.

**Airway basal cell transcriptome.** The airway epithelium includes ciliated, secretory, columnar, and basal cells (BC). BC function as stem/progenitor cells in the airway. The transcriptome of purified, human airway BC was compared to the transcriptome of complete epithelium samples that contained all four cell types. A human BC signature was identified, providing novel insights into the biology of the human airway epithelium stem/progenitor cells.

**Vaccines for addiction.** Current strategies to help smokers quit have limited success due to the addictive properties of nicotine. Studies using an AAV gene transfer vector expressing a high affinity anti-nicotine monoclonal antibody were carried out. Single administration of this vector elicited persistent, high titers of an anti-nicotine antibody that inhibited the physiologic effects of nicotine. If this degree of efficacy translates to humans, this vector could be an effective preventative therapy for nicotine addiction.

**Genetic therapy for CNS disorders.** An AAV gene transfer vector was used to deliver bevacizumab, an anti-VEGF monoclonal antibody, to mouse eyes and single administration of this vector provided long-term suppression of neovascularization. Dr. Crystal also has an ongoing study in children with neuronal ceroid lipofuscinosis, a fatal childhood lysosomal storage disorder, using direct CNS infusion of a vector expressing the CLN2 gene. This trial involves a novel surgical/vector administration protocol that has received recognition in the neurosurgery field and by groups wishing to do similar work.

**Patterns of admixture in Qataris.** A genome-wide admixture study of Qatar was carried out in 156 individuals to develop a machine learning method that infers loci-specific genomic ancestry while simultaneously analyzing many possible ancestral populations. Simulations showed this method is more accurate than other popular admixture discovery tools, and is the first to efficiently scale for simultaneous analysis of 50-100 putative ancestral populations while being independent of prior demographic information.
Anna Di Gregorio, PhD
Associate Professor of Cell and Developmental Biology

The notochord is the axial structure that provides support to the developing body of all chordates, including humans, during embryogenesis. Notochord malformations cause severe human birth defects, including spina bifida and vertebral abnormalities. Yet, the genes controlling notochord formation and the molecular mechanisms that turn them on at the right time during embryonic development are still poorly characterized. To fill this gap in knowledge, the Di Gregorio lab is using an innovative approach, by elucidating the genetic blueprint of the notochord in one of the simplest chordates experimentally available: the ascidian *Ciona*, or “sea squirt.”

Why use a sea squirt to understand notochord formation? Among numerous experimental advantages, the sea squirt embryo develops a functional notochord within one day of fertilization, and notochord cells are easy to visualize; in vertebrates, instead, the notochord is gradually replaced by vertebrae and its remnants form the inner part of the intervertebral discs. Noticeably, these notochord remnants occasionally give rise to rare but often malignant tumors, called chordomas. Research in the Di Gregorio lab has shown that the notochord of *Ciona* expresses genes that are also expressed in the mouse notochord, and most likely in the notochord of human embryos as well.

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One of the genes that was conserved over half a billion years of chordate evolution is *brachyury* (a Greek word for “short tail”). In all chordates, mutations in this gene locus cause severe defects in notochord formation. However, unexpectedly, the *brachyury* locus has been found to be duplicated in patients suffering from familial chordoma. In other words, not having enough *brachyury* protein blocks notochord development, while having too much of this protein in notochord cells appears to facilitate tumor formation. Current projects in the Di Gregorio lab aim at determining the molecular basis of this unusual mechanism of action. The experimental approach is focused on the identification of regulatory DNAs that are bound by *brachyury*. A regulatory DNA is a region of a gene that does not encode for a protein, but rather is the repository of the information that dictates when and where the protein is going to be expressed during development. Regulatory DNAs therefore act as “switches” for gene expression; unlike protein-coding DNAs, they do not obey a particular genetic code and for this reason are difficult to identify, especially in complex genomes.

In *Ciona*, the Di Gregorio lab has assembled the first collection of notochord regulatory DNAs directly controlled by *brachyury*; these regulatory DNAs have been analyzed in detail and the minimal sequences necessary for their activity in the notochord have been identified. This work has led to the discovery of the different mechanisms employed by *brachyury* to activate gene expression in the notochord during different phases of its development. Their research has also begun to shed light on the development of this structure, its evolutionary origins, and the mechanisms that might be leading notochord remnants to give rise to tumors.
One of the research goals of Dr. Sabine Ehrt and her colleagues is to better understand the molecular basis for Mtb’s ability to resist host defense mechanisms.

Dr. Ehrt and colleagues have identified Mtb mutants that are hypersusceptible to such stress conditions and are also attenuated in the mouse model of TB. The identification and characterization of the molecular mechanisms underlying the loss of stress resistance and loss of virulence of these mutants will help to better understand the intracellular environment encountered by Mtb and shed light on the strategies the pathogen employs to resist host defense mechanisms.

Dr. Ehrt’s group is also interested in the metabolic environment Mtb faces within its host. Metabolic adaptation to the host niche is a defining feature of the pathogenicity of Mtb, yet Mtb’s central carbon metabolism and its metabolic adaptations to the intracellular environment of a host cell remain incompletely defined. They are investigating the metabolic pathways Mtb requires to establish and maintain chronic infections.

In collaboration with Dr. Dirk Schnappinger’s laboratory in the Department of Microbiology, Dr. Ehrt’s team has developed controlled expression systems that allow silencing of mycobacterial genes in vitro and in vivo. They apply these systems to create conditional knock-downs of mycobacterial genes that are important for growth and persistence within the host. These conditional knock-down mutants allow them to investigate if a mycobacterial gene is required at all or only at specific stages of an infection. They also are used for drug target evaluation and studies of essential mycobacterial genes.
Todd R. Evans, PhD  
Professor of Cell and Developmental Biology in Surgery

Research in the laboratory of Dr. Todd Evans is focused on the molecular regulation of organogenesis and regeneration. For this purpose, two model systems are used in a complementary manner. Embryonic stem cells (ESCs) are used to study pluripotency and the generation of progenitor cells and differentiated lineages in an in vitro setting, and the zebrafish animal model is used to study organ development and morphogenesis during embryogenesis.

The Evans laboratory was involved in the discovery and initial characterization of the family of GATA transcription factors. These six proteins play essential roles coordinating the development of many different organ systems. Research projects are ongoing to understand the upstream signals that control their activity and the downstream pathways that mediate their function. This has led to projects in hematopoietic, cardiovascular, liver, and lung development. For example, the group is studying the function of BMP signaling upstream of Gata2 for regulating hematopoeisis. With respect to the cardiovascular system, they have described functions for Gata4, Gata5, and Gata6 during embryogenesis and for homeostasis and regeneration of the adult cardiovascular system.

The Evans laboratory was involved in the discovery and initial characterization of the family of GATA transcription factors. In the past year, they used deep-sequencing of RNA from embryos or embryonic hearts depleted for specific GATA factors, and discovered new downstream target genes that regulate cardiac cell specification and heart morphogenesis. Remarkably, SNPs in one exciting new target gene have recently been associated with human heart disease based on GWAS studies, demonstrating how zebrafish work can be translated to modeling human disease. In recent collaborative work, the group also found that Gata4 is a key target for the cardiac regenerative program in an injured adult zebrafish heart.

In another strategy, the group is studying the directed differentiation of specific cell types through manipulation of GATA-dependent programs in mouse and human ESCs. These studies aim to develop cellular therapies for cardiac, liver, and lung diseases. They also employ mouse and human induced pluripotent stem cell (iPSC) technology, which is generating insight into how epigenetics can control regulatory networks with relevance to cancer stem cells. Other iPSC projects are focused on the aging process and human disease models. Chemical biology projects have been used to identify novel small molecules that can modulate key developmental pathways, including retinoid signaling. It is the overall goal of the group to control with exquisite specificity regenerative pathways in the model systems, and then translate these findings to treat organ-based disease. In addition to many strong collaborations with laboratories at Weill Cornell Medical College (S. Chen, Y. Houvras, T. Fahey, S. Rafii, T. Hla, M. Guzman, M. Ross, H. Stuhlmann, A. Melnick), they also pursue projects with investigators around the country (R. Levine and J. Coudhuri at Memorial Sloan-Kettering Cancer Center, G. Fishman at New York University, K. Poss at Duke University, B. Das at Kansas, and many others).

SELECTED PUBLICATIONS


Joseph J. Fins, MD, MACP
Chief, Division of Medical Ethics
The E. William Davis, Jr., MD Professor of Medical Ethics
Professor of Medicine, Professor of Public Health
Professor of Medicine in Psychiatry

As humanist and physician-scientist, Dr. Joseph J. Fins has eloquently affirmed society’s ethical obligation to patients with disorders of consciousness and our responsibility to pursue knowledge that will benefit this marginalized population.

At a time when academic life has become increasingly fragmented, Dr. Fins has engaged in translational work in medical ethics drawing upon the sciences and the humanities to appreciate, and respond to, the ethical implications of medical progress. In the 1990s, Dr. Fins developed clinical pragmatism, a method of moral problem solving to bridge the gap between ethical theory and clinical practice. This work, inspired by the American Pragmatic tradition, developed through his leadership of the Ethics Consultation Service at NewYork-Presbyterian/Weill Cornell. Clinical pragmatism was a novel formulation. Unlike the dominant bioethics paradigm of principlism, it did not emphasize principles and moral absolutes, but rather the importance of process, hypothesis generation, contingency, and particularistic inductive reasoning, much like the scientific method itself. Dr. Fins’s scholarship has brought pragmatism into mainstream bioethics, both here and abroad, with particular relevance to ethics case consultation, palliative care, and decision-making at life’s end.

With an ongoing commitment to interdisciplinarity, Dr. Fins’s more recent efforts have been in the nascent field of neuroethics. He has had a pioneering impact articulating a neuro-palliative ethic of care for patients with disorders of consciousness, brain conditions, such as the vegetative and minimally conscious states. Dr. Fins was the first ethicist to write on the use of neuromodulation in disorders of consciousness and the role of neuroimaging in understanding these conditions. Working with Weill Cornell neurologist and neuroscientist, Dr. Nicholas D. Schiff, Dr. Fins was a co-author of their 2007 Nature paper on the use of deep brain stimulation after severe traumatic brain injury. Dr. Fins laid out the ethical and regulatory framework for this landmark study and helped shape its scientific design. He articulated a highly original ethical formulation that made the study possible, invoking distributive justice claims for inclusion of subjects who could not provide informed consent because of decisional incapacity. Using sources in the history of medicine, he argued that the neglect of these patients was an unintended (and unrecognized) legacy of the right-to-die movement. By deconstructing the biases distorting the study’s risk-benefit analysis, he asserted that the minimally conscious were an ethically proportionate subject population for this hypothesis driven research.

Dr. Fins is currently completing a book entitled, Rights Come to Mind: Severe Brain Injury, Ethics & The Struggle for Consciousness, under contract with Cambridge University Press. His scholarship has been supported by a Health Policy Investigator Award from the Robert Wood Johnson Foundation, as well as funding from the Buder, Dana, and Katz Foundations. President of the American Society for Bioethics and Humanities, Dr. Fins is an elected Member of the Institute of Medicine of the National Academy of Sciences and a Fellow of the American Academy of Arts and Sciences.
Daniel W. Fitzgerald, MD
Associate Professor of Medicine

Dr. Daniel Fitzgerald conducts clinical and translational research in Haiti and Tanzania that aims to improve the survival and quality of life of people with AIDS in resource-poor settings. Research includes studies of antiretroviral therapy (ART) and of major complications of HIV infection, including tuberculosis, tropical diseases, and cervical cancer. The training of United States, Haitian, and Tanzanian physician-scientists is an integral part of his research activity.

Dr. Fitzgerald conducted clinical studies in Haiti to demonstrate that ART can be successfully administered in resource-limited settings. He evaluated outcomes of the first 1,000 AIDS patients treated with ART in Port-au-Prince, Haiti. Outcomes in Haiti were comparable to those achieved in the United States. This study provided critical evidence in support of international efforts to make ART available to AIDS patients worldwide. He conducted a randomized trial of early versus deferred ART for HIV-infected patients with a CD4 T cell count between 200 and 350 cells/mm³, which showed that early ART decreases mortality four-fold. This study prompted the World Health Organization to change international guidelines for the provision of ART and affected the care of millions of people globally.

Dr. Fitzgerald’s study prompted the World Health Organization to change international guidelines for the provision of ART and affected the care of millions of people globally.

Studies are being conducted in Haiti and Tanzania to improve the diagnosis and treatment of tuberculosis in HIV-infected people. Tuberculosis presents atypically in HIV-infected people, and the standard diagnostic tests often do not detect the disease. In collaboration with basic scientists from Weill Cornell in New York, studies are ongoing to find metabolites of the tuberculosis bacteria in the blood or urine that could be used as a new diagnostic biomarker. Studies are also ongoing looking at new drug therapies to treat tuberculosis.

Studies in Tanzania are exploring the interactions between the tropical parasite Schistosoma and HIV infection. In northern Tanzania near Lake Victoria, one-half of the population is infected with the parasite Schistosoma. Studies suggest that schistosomiasis may cause genital inflammation and thereby increase the risk of HIV infection. Further, once HIV infected, schistosomiasis may accelerate HIV disease progression.

Women with HIV are five times more likely to develop cervical cancer than other women, and cervical cancer is now the third leading cause of death in HIV-infected women in Haiti. In collaborations with bench-top scientists from Weill Cornell, Dr. Fitzgerald is examining the effects of HIV infection upon the metabolism of the inflammatory molecule Prostaglandin E₂, which is a known mediator in the development of certain cancers. This is an interesting molecule for study because safe and inexpensive drugs like aspirin block the synthesis of Prostaglandin E₂ and could potentially be studied as cancer prevention drugs for HIV-infected women at risk for cervical cancer.

SELECTED PUBLICATIONS


Dr. Paraskevi Giannakakou’s laboratory focuses on the cellular events that depend on the microtubule cytoskeleton, and on gaining a deeper understanding of the mechanism of action of clinically used microtubule targeting drugs (MTDs) in order to develop more effective and individualized therapies. Dr. Giannakakou’s laboratory uses functional cellular and molecular biology assays coupled with high-resolution microscopy and live-cell imaging to gain new information on the spatial and temporal regulation of microtubule-cytoskeleton dynamics and its effects on cancer-cell survival. The clinical success of taxanes, and other microtubule inhibitors, together with their broad spectrum of antitumor activity, argue that tubulin represents the single best target identified in clinical oncology. However, today, 15 years following the FDA approval of Taxol® for clinical oncology, there is still no understanding of the molecular basis of clinical response to Taxol treatment.

Dr. Giannakakou believes that important, heretofore unrecognized, determinant underlying taxane sensitivity is the involvement of the microtubule cytoskeleton in intracellular trafficking and signaling. As such, her laboratory has identified new roles for the microtubule cytoskeleton in the transport and activation of important cancer transcription factors such as the tumor suppressor p53, the hypoxia-inducible factor 1α, and most recently the androgen receptor in prostate cancer.

Dr. Giannakakou’s laboratory has previously shown that MTDs exert their antiangiogenic effects through significant down-regulation of HIF-1alpha protein levels and transcriptional activity. More recently, her laboratory has demonstrated that the androgen receptor, a major driver of prostate cancer that remains active even after androgen-deprivation therapy, traffics on microtubule tracks for its translocation from the cytoplasm to the nucleus where it activates target genes such as PSA. Her team has also showed that MTDs, by disrupting the microtubule cytoskeleton, sequester the androgen receptor within the cytoplasm, therefore inhibiting its subsequent transcriptional activation. These results provide a rationale for why the taxanes represent the sole class of chemotherapy agents that improves survival of metastatic prostate cancer patients. However, despite their clinical success, not every patient responds to MTD-based chemotherapy and the development of clinical drug resistance makes patients, previously sensitive to chemotherapy, insensitive. Thus, a better understanding of the molecular basis of clinical drug resistance to taxanes and other widely used MTDs is imperative in order to prolong patient survival.

One of the major impediments to understanding MTD drug resistance has been the lack of tumor tissue for molecular analyses. To overcome this, new technologies have been developed to capture and analyze circulating tumor cells (CTCs) from the peripheral blood of patients, which provides a readily accessible source of tumor material. Dr. Giannakakou is collaborating with Dr. Brian Kirby from the Department of Engineering at Cornell University and Drs. David Nanus and Linda Vahdat from the Division of Hematology/Oncology at Weill Cornell to develop microfluidic devices that specifically capture CTCs from metastatic prostate or breast cancer patients. The ultimate goal is to utilize these devices to capture and molecularly analyze tumor derived CTCs using a simple, non-invasive blood draw to determine the best treatment for each patient based on the molecular make-up of their tumor cells. Ultimately, Dr. Giannakakou seeks to identify new molecular targets that affect or are affected by microtubule dynamics and can be used to develop better targeted therapies.
The laboratory of Dr. Laurie Glimcher pursues a cross-disciplinary understanding of how cell biology affects the immune system. A major contributor to the field of immunology, Dr. Glimcher has focused most of her career on understanding how different subsets of immune cells develop and are regulated. She is known for her discovery of XBP-1, a transcription factor important in lipogenesis and in the endoplasmic reticulum (ER) stress and the unfolded protein response (UPR). One component of her lab’s studies is centered on the interplay of ER stress with immune function, with neurodegenerative diseases, and with cancer.

The complex regulatory pathways governing T helper (Th) lymphocyte responses are critical for both the development of protective immunity and for the pathophysiologic immune responses underlying autoimmune, infectious, and malignant diseases. Dr. Glimcher’s laboratory uses biochemical and genetic approaches to clarify the molecular pathways that regulate CD4 T helper cell development and activation. While at Harvard, she and her colleagues studied the transcriptional pathways that control this important immune checkpoint, defining the genetic bases of both interleukin-4 (IL-4) and interferon-gamma (IFN-γ) expression in T lymphocytes. They identified the proto-oncogene c-maf as the transcription factor responsible for T helper type 2-specific IL-4 expression. Subsequently, Dr. Glimcher’s lab discovered the first T helper 1-specific transcription factor, T-bet, and demonstrated that this single factor is a master-regulator of IFN-γ gene expression and the Th1 phenotype. Dr. Glimcher’s landmark paper in Cell on the T-bet transcription factor has been cited more than 1,100 times.

With the knowledge that T-bet controls Type 1 immunity in cells of both the adaptive and innate immune system, the Glimcher laboratory has been investigating the function of T-bet in dendritic cells in mucosal immunity and tumorigenesis with an emphasis on inflammatory bowel disease. The lab’s interest in lineage commitment in lymphocytes has expanded to the B cell with the discovery of XBP-1. The researchers have demonstrated a function of this factor in the generation of antibody-secreting plasma cells, in innate immunity to pathogens, in neurodegenerative disease, and in lipid disorders.

With evidence that a reciprocal relationship exists between cells of the immune and skeletal systems, Dr. Glimcher’s lab has begun bridging work in both fields with the goal of developing clinical therapeutics for diseases that share properties of inflammation and bone remodeling. Through large scale screens, Dr. Glimcher and her research team identified new proteins that control osteoblast and osteoclast commitment and activation in skeletal biology. In one recent study, they found that mice lacking the large zinc finger protein Schnurri-3 (Shn3) display increased bone mass, in part attributable to augmented osteoblastic cell formation. Further study elucidated that in addition to regulating bone formation, Shn3 indirectly controls bone resorption by osteoclasts in vivo. Although Shn3 plays no cell-intrinsic role in osteoclasts, Shn3-deficient animals show decreased serum markers of bone turnover. With significant implications for diseases of bone, including osteoporosis, osteoarthritis, and cancer metastasis to bone, their work in this area may provide a conceptual framework to therapeutically manipulate these responses in the settings of human disease.

Selected Publications

The laboratory of Dr. Lorraine Gudas is focused on developing cancer prevention strategies, cancer treatment therapies, and tissue regenerative therapies. Dr. Gudas and her group are involved in the discovery of new drugs that cause normal stem cells and cancer stem cells to change their molecular characteristics and differentiate, i.e., to become more mature, specialized cells. Cancer cells that have “stem-like” properties are generally more malignant and dangerous to the patient.

One nutrient/vitamin that they have shown to cause stem cell differentiation is the vitamin A metabolite, retinoic acid. Retinoids, which include both natural and synthetic derivatives of vitamin A (retinol), control many aspects of normal cell differentiation, and influence the process of carcinogenesis. While there are small amounts of retinoic acid in our bodies from the vitamin A in the foods we eat, larger, pharmacological doses of retinoic acid are used in treating some types of leukemia and in reducing the occurrence of other types of human cancer. Retinoic acid works by going into the cell, where it binds to a protein that changes the levels of mRNAs, and subsequently, the levels of proteins in the cell.

Dr. Gudas is very excited by recent experiments from her lab showing that retinoic acid also works by another mechanism. They have now shown that retinoic acid changes the levels of specific mRNAs and proteins in cells in part by changing the “epigenetic state” of the cell. This means that retinoic acid can cause alterations in proteins, called histones, which surround DNA on the chromosome. When the histones are altered by the addition of retinoic acid, many other proteins in the cell are then made in greater amounts, and the cell starts producing large amounts of the types of proteins characteristic of a more mature, specialized cell type rather than those of a stem cell. For instance, after retinoic acid addition, normal stem cells start making more proteins called keratins, and keratins are important for a type of differentiated cell, called an epithelial cell, to function properly in our bodies.

Dr. Gudas and her group are involved in the discovery of new drugs that cause normal stem cells and cancer stem cells to change their molecular characteristics.

The lab has shown that many types of human tumors (prostate cancer, kidney cancer, breast cancer, and others) don’t contain enough vitamin A and retinoic acid, even though the patient is eating enough of the vitamin in his or her diet. Their experiments suggest that during cancer development the cancer cells, by a variety of mechanisms they are studying, reduce their levels of vitamin A and retinoic acid so that they remain in a more “stem-like,” proliferating state. Their goal is to employ new drug combinations to overcome this block in cell differentiation, make the cancer stem cells become more “mature,” and thereby improve the survival of cancer patients.

They also are studying tissue regeneration after injury. Normal stem cells play an important role in making new cells and tissues after injury, and these stem cells also differentiate during the repair and regeneration of tissues. Their studies on the identification of novel combinations of nutrients and drugs that can enhance and improve regeneration should help both soldiers seriously wounded in battle and victims of accidents with severe tissue injury.
Atherosclerosis is an inflammatory disease characterized by the accretion of cholesterol-laden plaque in the artery wall. During the pathogenesis of atherosclerosis, alterations in eicosanoid biosynthesis and reactive oxygen species production occur by mechanisms that are not well understood. The delineation of these mechanisms is the focus of Dr. David Hajjar’s research.

Eicosanoids are a group of biologically active compounds derived from the cyclooxygenase (COX) and lipoxygenase catalytic pathways and include the commonly named prostaglandins. These eicosanoids play important physiological roles in the regulation of many processes. Nitric oxide (NO), produced in blood vessels by the nitric oxide synthases, is another critical mediator of both physiologic and pathophysiologic processes in the regulation of vascular tone and inflammation. Atherosclerotic lesions contain increased levels of inducible COX (COX-2) and nitric oxide synthase (iNOS). Recent developments show that both enzymes are bound, and the fate of eicosanoid synthesis is linked to NO and its higher oxides (NOx) derived from iNOS. The principal aim of Dr. Hajjar’s work is to define the mechanisms by which NO and prostaglandin synthetic pathways interact to alter eicosanoid biosynthesis, as well as the impact of these mediators on atherosclerosis and thrombosis. Over the years, Dr. Hajjar has defined the roles and mechanisms of these complex signaling interactions in order to gain an understanding of the pathophysiological processes in atherosclerosis using animal models and the consequences of pharmacological interventions.

The principal aim of Dr. Hajjar’s work is to define the mechanisms by which NO and prostaglandin synthetic pathways interact to alter eicosanoid biosynthesis.

In recent work, Dr. Hajjar showed that the enzyme prostaglandin H2 synthase (PGHS, also known as cyclooxygenase) regulates the production of eicosanoids that modulate physiologic processes in the vessel wall, contributing to atherosclerosis and thrombosis. He demonstrated that various forms of NOx can have different modulatory effects on the activity of PGHS-1, the predominant isozyme in platelets. These and other studies revealed that the active heme center of PGHS-1 regulates peroxynitrite-induced modification and loss of enzyme reactivity, indicating that heme may play a decisive role in catalyzing these processes in PGHS-1 when exposed to nitrative stress in an inflammatory setting. Collectively, these studies show for the first time that iNOS influences PGHS expression and its activity, which can contribute to modification of an important enzyme involved in inflammation during atherosclerosis. Since iNOS-derived species are required for robust atherosclerosis-associated peroxynitrite production in peripheral organs, these studies have contributed importantly to the understanding of the complex alterations in eicosanoid metabolism that occur during the pathogenesis of heart disease where inflammation occurs.

SELECTED PUBLICATIONS
Scientists in Dr. Katherine Hajjar’s laboratory identified the annexin A2 system as a novel key component of the fibrinolytic system. Expressed on endothelial cells, annexin A2 (A2) is a calcium-regulated, phospholipid-binding protein that forms a heterotetrameric complex with protein p11 (S100A10). The Hajjar lab discovered that the A2 complex binds two major components of the fibrinolytic system, plasminogen and tissue plasminogen activator, and accelerates the generation of plasmin at cell surfaces. Evidence is now emerging that the annexin A2 system contributes to fibrin homeostasis in human health and disease.

Understanding the in vivo function of the A2 system is a major goal of the Hajjar lab. Their development of the A2-deficient mouse uncovered two important findings – first, the knockouts displayed the predicted accumulation of fibrin within blood vessels, and, second, the mice exhibited unexpected defects in new blood vessel formation (angiogenesis) – leading to the hypothesis that fibrinolysis and angiogenesis are functionally linked. This postulate has been strengthened by the observation that metabolic blockade of A2 function by the amino acid homocysteine leads to fibrin accumulation and defective angiogenesis. Evidence that A2 regulates hemostasis in humans derives from studies in patients with acute promyelocytic leukemia in which overexpression of A2 correlates with severe, sometimes life-threatening hemorrhage. Individuals with antiphospholipid syndrome, moreover, often have thrombosis in association with high-titer anti-A2 antibodies that inhibit A2 function or activate endothelial cells. High-titer anti-A2 antibodies have also been reported in a cohort of patients with cerebral vein thrombosis.

An appreciation for the role of the A2 system in human health and disease requires knowledge of its regulation at the molecular level. The Hajjar lab recently discovered that synthesis of A2 is regulated by ischemia through the action of the hypoxia-inducible factor-1 transcription factor, which binds directly to a hypoxia responsive element within the A2 gene promoter. This mechanism underlies ischemic retinal vascular disease in a mouse model that mimics retinopathy of prematurity and diabetic retinopathy. Further work has revealed that while endothelial cell A2 stabilizes protein p11 and prevents its proteasomal degradation, p11 supports the src kinase-stimulated, nonclassical secretion of A2 from the cytoplasm to the cell surface. In addition, recent collaborative studies have shown that the A2 system promotes tumor cell invasion in two brain tumor models of glioblastoma multiforme, and that annexin A2 may inhibit activation of the innate inflammatory system in a model of joint disease by maintaining the integrity of intracellular organelles known as lysosomes. Future studies will build upon these emerging pathways to develop strategies aimed at understanding and manipulating the A2 system in settings of human disease.
Hugh C. Hemmings, Jr., MD, PhD  
Professor of Anesthesiology  
Professor of Pharmacology

There are two principal areas of research in Dr. Hugh Hemmings’ laboratory: mechanisms of general anesthetic drugs and neuroprotective mechanisms in global cerebral ischemia. Dr. Hemmings’ lab has demonstrated neurotransmitter- and anesthetic agent-specific effects on neurotransmitter release that involve effects on presynaptic ion channels. The specific ion channels affected and the mechanisms of these effects are currently under investigation. Recent findings indicate that protein phosphatase-1 is activated in global cerebral ischemia. A combination of biochemical, genetic, and proteomic techniques are being employed to determine the biochemical mechanisms of this pathophysiological regulation and its potential as a therapeutic target for this devastating disease.

**Mechanisms of general anesthetic.** The pharmacology and toxicology of general anesthetics are remarkably incomplete for such a widely used and clinically important class of drugs. Despite their widespread clinical use, understanding of the molecular and cellular mechanisms of general anesthetic action in the central nervous system is insufficient to explain how any anesthetic produces amnesia, unconsciousness, or immobilization (with increasing doses), the cardinal clinical features of general anesthesia. Anesthetics have potent and specific effects on synaptic transmission, including both presynaptic actions on the release of neurotransmitters and postsynaptic actions on their receptors. Dr. Hemmings’ lab aims to understand the presynaptic mechanisms of anesthetic effects on neurotransmitter release, which is essential for developing anesthetics with improved side-effect profiles and for optimization of current anesthetic techniques in high-risk patients. Current focus is on the region- and transmitter-specific actions and Na+ channel blocking mechanisms of volatile anesthetics. Such studies are essential to understanding the balance between desirable and potentially toxic anesthetic effects on excitatory and inhibitory synaptic transmission.

**Neuroprotection and global cerebral ischemia.** Global cerebral ischemia due to cardiac arrest results in debilitating neurological impairment necessitating costly long-term healthcare. Yet there is currently no specific medical therapy. Global cerebral ischemia is associated with extensive cell death. These processes are tightly regulated by several mechanisms, including a critical role for protein phosphorylation. Protein phosphatase-1 is a serine/threonine protein phosphatase that has been implicated in the regulation of cell death. Dr. Hemmings and his colleagues have identified and purified a novel form of protein phosphatase-1 in mammalian brain that is activated in vivo in animal models of global cerebral ischemia. They hypothesize that this enzyme is a component of the signal transduction pathways that link global cerebral ischemia to cell death. They have purified and characterized this enzyme from control and ischemic pig brain following cardiac arrest with resuscitation and reperfusion, and are currently studying its regulation by reconstitution of the identified components in vitro.

These studies will elucidate physiological and pathophysiological mechanisms that regulate protein phosphatase-1 activity in the brain and define its role in the control of cell death in global cerebral ischemia. This approach is targeted to the development of rational mechanism-based therapies to attenuate ischemic brain cell death with a long-term goal of clinical translation.

**SELECTED PUBLICATIONS**


Barbara L. Hempstead, MD, PhD
O. Wayne Isom Professor of Medicine

The research in Dr. Barbara Hempstead’s laboratory focuses on the biology of growth factors, termed neurotrophins. Dr. Hempstead was a member of the team that identified signaling receptors for neurotrophins, the Trk receptor tyrosine kinase, and identified proneurotrophins as independent death-promoting ligands. Small polypeptides, neurotrophins were initially identified for their potent biological actions in promoting the survival and function of neurons. However, Dr. Hempstead’s laboratory identified unanticipated effects on the vasculature, particularly the blood vessels of the heart. One member of the neurotrophin family, brain derived neurotrophic factor or BDNF, is a required growth factor to permit the normal development of the heart vasculature, and is further induced following vascular injury. These results suggest that mechanisms to augment BDNF signaling may promote angiogenesis following tissue ischemia.

In a second major line of investigation, Dr. Hempstead’s laboratory identified precursor forms of the neurotrophins, or proneurotrophins, as independent ligands that induce cell death. Proneurotrophins are not normally present in healthy tissues, but are upregulated following tissue injury, where they mediate cell death or dysfunction utilizing a distinct receptor system. Proneurotrophins are induced following brain injury and epilepsy, and strategies to impair proneurotrophins provide neural protection. Ongoing work is evaluating strategies to block proneurotrophin effects in a variety of injury paradigms. Thus, the long-term goals of their research are to identify new therapeutic approaches to neurodegenerative diseases and cardiovascular diseases.

Dr. Hempstead was a member of the team that identified signaling receptors for neurotrophins and identified proneurotrophins as independent death-promoting ligands.

Previous research by Dr. Hempstead and her colleagues shed light on a neural growth factor called proBDNF, finding that it is present and potentially active during the perinatal period when the brain’s circuitry and memory-encoding regions are being refined. ProBDNF is the precursor form of mature BDNF, and both are active in the hippocampus and cortex – areas key to learning, memory, and higher thinking. Intriguingly, proBDNF and BDNF induce different actions; BDNF promotes the differentiation of new neurons and their constituent parts and proBDNF promotes the pruning of synapses. The results suggested that the nervous system plays an active role in both potentiating and dampening its own activity.

The researchers developed new techniques that enabled them to observe when and where proBDNF and mature BDNF were being made in a mouse model. They found that proBDNF is most highly expressed in the hippocampus during the postnatal period of the mouse at about days 3 to 21, when large numbers of axons and synapses are being formed. They also found that p75 receptors, a class of receptors that encode a “death domain” in which neurons are killed or pruned, are also active during this period. Extrapolating her findings from mouse to human, this finding provided new insight into how the brain is wired and how this wiring is refined – particularly during the developmental stages.
Timothy Hla, PhD
Professor of Pathology and Laboratory Medicine

Dr. Timothy Hla works on cells that line the vascular tree called endothelial cells. Two decades ago, while a postdoctoral trainee, Dr. Hla discovered a new receptor in activated endothelial cells. He later discovered that this molecule binds to a naturally occurring lipid molecule called sphingosine 1-phosphate (S1P). Since his discovery of the first S1P receptor, much work has been done and it is now known that five S1P receptors regulate vital functions in the body, such as blood vessel function and immunity.

Serendipitously, a drug with origins in traditional Chinese medicine was discovered to block the S1P receptor and reduce autoimmunity in the devastating disease of multiple sclerosis (MS). It is now known that abnormal immune cells that attack the nerve cells need S1P receptors to traffic into the central nervous system and by targeting the receptor, nerve cell loss is reduced and patients with MS experience a better outcome. Research in the Hla laboratory has played an important role in understanding how this new drug, fingolimod, works. As all drugs go, efficacy is coupled with side effects. Recent work from the Hla laboratory suggested that interference with S1P receptors on endothelial cells may account for side effects encountered by MS patients when taking this drug. These basic science efforts are stimulating the search for better S1P receptor drugs, which may have utility in a wide spectrum of autoimmune diseases, including psoriasis and rheumatoid arthritis.

Current research in the Hla laboratory is focused on better defining S1P-related mechanisms and developing new ways to prevent blood vessels from becoming inflamed and clot-prone.

Interestingly, S1P is carried by HDL, also referred to as the particle which carries the “good” cholesterol. In collaboration with scientists in Europe, the Hla laboratory discovered that an apolipoprotein M is the carrier of S1P in HDL. Since S1P in HDL is thought to be one of the mechanisms by which HDL protects people from heart disease and stroke, this work has tremendous potential to help people who are at high risk for cardiovascular problems. Current research is focused on better defining S1P-related mechanisms and developing new ways to prevent blood vessels from becoming inflamed and clot-prone. Since the damage of the endothelial cell is one of the most important events in heart disease and stroke, preservation of endothelial cell function using the S1P pathway is extremely promising.

S1P and its five receptors also regulate many other processes in the body, such as cell growth and migration. As such, it is important in cancer and angiogenesis. Using mouse and zebrafish models in collaboration with Dr. Todd Evans in the Department of Surgery, the Hla lab is examining how the S1P system regulates abnormal angiogenesis and cancer. The Hla laboratory has discovered that a simple molecule called S1P works in complex ways to regulate many essential bodily functions and that one can control complicated diseases if one understand the molecular details in depth. Since vascular health is essential for all organs, this work has far-reaching implications to prevent and control human diseases.

SELECTED PUBLICATIONS


Xin-Yun Huang, PhD  
Professor of Physiology and Biophysics

Research in the laboratory of Dr. Xin-Yun Huang is focused on several cellular signaling pathways, their physiological functions, and their applications in disease treatments. Cellular signaling and cell-cell communication allow the multitude of physiological processes in individual cells to proceed in a coordinated fashion to the benefit of the organism. Signaling molecules are often perturbed in diseases and are major targets for drug development.

One major research program is addressing the molecular signaling mechanism by which G protein-coupled receptors and G proteins control cell functions. Dr. Huang and his colleagues are deciphering their physiological functions in cell migration, angiogenesis, cardiovascular diseases, and tumor metastasis using a combination of approaches, including molecular, cellular, biochemical, genetic, structural, and systems biological tools, as well as animal models. G protein-coupled receptors are transmembrane proteins that act as key gatekeepers between external signals and cellular responses. G protein-coupled receptors are the best pharmaceutical drug targets so far. Currently Dr. Huang’s lab focuses on:

• the signaling mechanisms by which one of the G proteins, G13, controls the migration of endothelial cells induced by G protein-coupled receptors and by receptor tyrosine kinases
• the physiological function of this regulation in embryonic angiogenesis and adult angiogenesis
• its implication in tumor angiogenesis

In addition, the lab has been using biochemical and biophysical techniques to investigate the mechanism of activation of G proteins by G protein-coupled receptors.

The second major research program in Dr. Huang’s laboratory focuses on tumor metastasis. Despite the significant improvement in both diagnostic and therapeutic modalities for the treatment of cancer patients, metastasis remains the major cause of mortality, being responsible for ~90 percent of all cancer deaths. Metastasis is a multi-step process wherein a primary tumor spreads from its initial site to secondary tissues/organs. This metastatic process is selective for cells that succeed in cell migration/invasion, embolization, survival in the circulation, arrest in a distant capillary bed, and extravasation into and multiplication within the organ parenchyma. Failure at any of these steps could block the entire metastatic process. Since tumor spreading is responsible for the majority of deaths of cancer patients, development of therapeutic agents that inhibit tumor metastasis is essential for cancer treatment. Tumor cell migration and invasion are critical steps in the process of tumor metastasis. For cell migration to proceed, actin cytoskeleton must be reorganized by forming polymers and bundles to affect the dynamic changes of cell shapes. Individual actin filaments are flexible and elongation of individual filaments per se is insufficient for membrane protrusion which is necessary for cell migration. Bundling of actin filaments provides rigidity to actin filaments for protrusion against the compressive force from the plasma membrane. Recently we have identified fascin as a therapeutic target for blocking tumor cell migration, invasion, and metastasis. Elevated levels of fascin have been found in metastatic tumors and are correlated with clinically aggressive phenotypes, poor prognosis, and shorter survival. The current objective of Dr. Huang’s research program is to develop fascin inhibitors as therapeutics for treating and preventing tumor metastasis.

SELECTED PUBLICATIONS

Costantino Iadecola, MD
Director, Brain and Mind Research Institute
George C. Cotzias Distinguished Professor of Neurology and Neuroscience

Research in the Division of Neurobiology, under the direction of Dr. Costantino Iadecola, focuses on the brain dysfunction and damage that underlie two of the most devastating brain diseases: stroke and dementia. Stroke, sometimes called “brain attack,” is the second cause of death worldwide and the leading cause of brain damage. It is most often caused by a blockage of the blood vessels that supply the brain and leads to immediate paralysis, blindness, confusion, or language problems. Dementia, such as Alzheimer’s disease, strikes an increasing number of elderly individuals resulting in severe memory problems, disorientation, confusion, and inability to care for oneself. The ultimate goal of Dr. Iadecola’s research is to shed light on the causes of stroke and dementia, and to develop new therapies for these conditions. This research flows along several interconnected lines.

**Hypertension and the brain.** High blood pressure, or hypertension, is a major cause of stroke and dementia. Dr. Iadecola and his colleagues have discovered that cerebral blood vessels are uniquely susceptible to the deleterious effects of hypertension, and they are studying how such malfunction of blood vessels leads to stroke and Alzheimer’s disease. Sleep apnea and aging, conditions well known to cause stroke and dementia, also alter brain blood vessels in a similar fashion. They have identified several therapeutic targets that would help protect the brain and its vessels from the damaging effects of hypertension.

**Why does the brain die after stroke?** Dr. Iadecola’s lab group is investigating the cellular and molecular alterations in the brain caused by blockage of the blood supply. They found that stroke activates certain cells of the immune system and produces brain inflammation. Blocking the action of these cells improves the brain damage caused by the stroke. They are now looking at what triggers inflammation and finding ways to stop it to salvage the brain. On the other hand, they also discovered that a certain type of immune cells protect the brain after stroke. This is a new and exciting area of investigation that may lead to developing new cell therapies for stroke.

**Alzheimer’s disease and stroke.** Once considered mutually exclusive, these two highly prevalent brain diseases are now known to have much in common. The work of Dr. Iadecola and his lab group have revealed that Alzheimer’s disease damages blood vessels in a manner similar to hypertension and stroke. Improving the performance of the blood vessels of the brain also improves the brain alterations produced by Alzheimer’s disease. They have identified a “receptor” in brain vessels that binds chemicals accumulating in Alzheimer’s disease (amyloid-β) peptides resulting in their damage and are developing ways to block this receptor to protect the brain from the damaging effects of amyloid-β.

**Bright and dark sides of brain plasticity.** The remarkable ability to learn and adapt to a changing environment, known as neuroplasticity, is a defining characteristic of the brain. Neuroplasticity is mediated by subtle changes in the connections through which neurons communicate with each other and can protect the brain from the damage associated with stroke and dementia. However, neuroplasticity also has a dark side. Dr. Iadecola and his colleagues have discovered that the synaptic changes that underlie learning and memory are similar to those induced by hypertension, drug addiction, and sleep apnea. They are developing ways to harness the “good” side of neuroplasticity to protect the brain from the damaging effects of stroke and dementia.
The ability of cells to perform various functions and to respond to signaling molecules has long been thought to be a consequence of the diversity of the proteins encoded in the genome. However, it is now becoming clear that the cell also contains a vast number of different types of RNAs that contribute to numerous diverse cellular processes. Indeed, the transcriptome is no longer thought to solely comprise tRNA, rRNA, and mRNA, but now includes microRNAs, termini-associated RNAs, long intergenic noncoding RNAs, toxic RNAs, and many other intriguing types of noncoding RNAs. The complexity of the noncoding RNA population points to the existence of a parallel layer of cellular regulation beyond that provided by proteins. Furthermore, mutations that affect these RNAs are now being recognized as causes of various diseases. A major goal of the Jaffrey laboratory is to apply molecular and chemical biology approaches to develop novel tools and imaging approaches to uncover the roles of these noncoding RNAs and the mechanisms of RNA regulation in cells.

A major impediment to studying RNA pathways is the absence of simple methods to image RNA trafficking in living cells. To address this problem, the Jaffrey lab has developed a novel class of RNAs that mimic GFP in cells and enable simple and robust genetic encoding of fluorescently tagged RNAs. These RNAs bind fluorophores resembling the fluorophore in GFP. Upon binding the fluorophores, the RNAs “switch on” these otherwise nonfluorescent molecules, resulting in fluorescence specifically associated with the tagged RNA. The researchers developed a palette of RNA-fluorophore complexes that span the visible spectrum. The Jaffrey lab has also discovered that mRNA is subjected to a reversible modification akin to phosphorylation in proteins. This modification, N6-methyladenosine (m6A), occurs in nearly 8,000 mRNAs and is enriched near stop codons and at the ends of transcripts. Furthermore, this modification is regulated by signaling pathways and during embryologic development. The Jaffrey lab also showed that the fat mass and obesity-associated protein gene, FTO, a highly prevalent obesity risk gene in humans, encodes an m6A demethylase, implicating m6A as an important regulator of body mass in humans.
Rainu Kaushal, MD, MPH
Frances and John L. Loeb Professor of Medical informatics

The American healthcare system is struggling with high costs despite lower than expected quality and safety. Dr. Rainu Kaushal and her team see great promise in the potential of health information technology and other transformative healthcare delivery policies to improve the value of healthcare. They conduct rigorous research to quantify potential opportunities and actual effects of various novel technologies and policies and then translate these findings into data-driven improvements in healthcare.

In 2001, Dr. Kaushal published a landmark study in the Journal of the American Medical Association showing that rates of potentially harmful medication errors were three times higher in pediatric than adult inpatients. Dr. Kaushal then conducted a series of inpatient and ambulatory studies further characterizing the causes of medication errors for children and potential solutions, including new roles for clinical pharmacists, educational material for parents, and the use of electronic prescribing. For several years, Dr. Kaushal has translated her pediatric patient safety research directly into quality improvement efforts as the Director of Pediatric Quality and Patient Safety at the Komansky Center for Children’s Health at NewYork-Presbyterian Hospital.

In 2010, Dr. Kaushal published another landmark paper showing for the first time that electronic prescribing can improve patient safety in community-based outpatient practices. Dr. Kaushal demonstrated, in 2011, that different electronic systems can have different effects on patient safety, depending on how they are implemented, configured, and used. This is an important methodological contribution, as it shows that – just like drugs and devices – healthcare delivery interventions need to be tested and compared for their effectiveness.

Dr. Kaushal has contributed to the literature on the costs and financial returns of implementing health information technology systems. Her work on the costs of a national health information network and the return on investment for a computerized order entry system have been frequently cited. Another publication articulates which specific functions of electronic health records and health information exchange are likely to drive financial savings. Dr. Kaushal has also conducted research showing that community-based health information exchange, electronic health records, and the patient-centered medical home are associated with higher quality of care. Additional work, funded by the Agency for Healthcare Research and Quality, developed a method for measuring quality in small group practices. Journal of General Internal Medicine.

Dr. Kaushal leads several multidisciplinary teams of investigators. The Health Information Technology Evaluation Collaboration, an academic consortium of five universities, is funded by New York State to conduct community-based participatory research on the effects of health information technology. The Center for Healthcare Informatics and Policy brings together physicians, health services researchers, informaticists, economists, biostatisticians, and others across several departments at Weill Cornell Medical College to create knowledge, provide education, generate innovation, and provide service at the intersection of health information technology and healthcare policy. Dr. Kaushal’s work continues to be timely and highly relevant to the national discussions unfolding about innovations in healthcare delivery.

SELECTED PUBLICATIONS


The broad goal of Dr. Francis Lee’s research program is to improve the understanding of neuronal cell biology in order to enhance the focus of clinical studies related to neuropsychiatric disorders. Dr. Lee’s laboratory addresses basic cell biology questions of how a family of growth factors, neurotrophins, are sorted in and secreted from neurons. A common single-nucleotide polymorphism (SNP) in one of the neurotrophins, brain derived neurotrophic factor (BDNF), has been shown by Dr. Lee to lead to defective BDNF trafficking in neurons. In humans, this genetic alteration (BDNF Val66Met) has also been associated with alterations in brain anatomy and memory, but its relevance to clinical disorders is unclear. Using a novel “knock-in” mouse model of this BDNF SNP, he determined that this SNP may lead to increased forms of anxiety that are resistant to standard drug treatments. These findings suggest that this BDNF SNP may predict patients’ responses to drug treatment and could lead to diagnostic testing to guide the treatment of depression, replacing the current “trial-and-error” method.

This past year, in collaboration with Dr. B.J. Casey and Dr. John Walkup, Dr. Lee has been studying the impact of this polymorphism in both mice and humans on fear-based behaviors across development. In particular, his laboratory has identified a novel form of brain plasticity in fear learning during early adolescence that may prove informative for understanding endogenous mechanisms to suppress unwanted fear memories. By examining fear conditioning in mice, as they transitioned into and out of adolescence, Dr. Lee’s laboratory found that a suppression of contextual fear occurs during adolescence. Although contextual fear memories were not expressed during early adolescence, they could be retrieved and expressed as the mice transitioned out of adolescence.

Dr. Lee’s findings suggest that this BDNF SNP may predict patients’ responses to drug treatment and could lead to diagnostic testing to guide the treatment of depression.

Dr. Lee has also expanded his efforts to study additional mouse models of anxiety disorders. His laboratory, in collaboration with Dr. Shahin Rafii, has found that a novel BDNF co-receptor, Slitrk5, that contributes to increased anxiety and compulsive-like behaviors will expand the scope of his research efforts and allow for a detailed investigation of the molecular and cell biology pathways potentially underlying the pathogenesis of additional affective disorders such as obsessive compulsive disorders. By establishing these animal models of anxiety-related disorders, Dr. Lee will be able to investigate the fundamental relationship between the trafficking fates and in vivo functional responses of these critical proteins in the nervous system, and provide a novel research framework to study the pathophysiology of neuropsychiatric disorders. He has started a remarkable range of collaborations to test these ideas using animal models and clinical translational studies in humans.

In 2009, Dr. Lee received a Presidential Early Career Award for Scientists and Engineers (PECASE), the highest honor bestowed by the White House Office of Science and Technology Policy for outstanding scientists and engineers in the early part of their independent research careers.
John P. Leonard, MD
Associate Dean for Clinical Research
Richard T. Silver Distinguished Professor of Hematology and Medical Oncology
Professor of Medicine

When the drug, rituximab—a monoclonal antibody directed against the CD20 molecule commonly present on the surface of lymphoma cells—was starting to come into general use as the first of its kind for the treatment of lymphoma, Dr. John Leonard was drawn to the opportunity to work on these exciting new targeted treatment options to potentially improve outcomes for patients with lymphoma, while minimizing treatment-related toxicity to improve quality of life. When administered to patients, these molecules can specifically target tumor cells, while relatively sparing normal cells, and can kill them via both direct and indirect mechanisms, including activation of the immune system. In the past few years, this type of treatment has made a major impact on the lives of patients with lymphoma, causing tumor shrinkage, improvement in symptoms, and in some cases, improved survival.

Today, Dr. Leonard and his research team have established one of the leading centers in the world for monoclonal antibody-based therapies and other novel therapeutics for lymphoma. Much of this work has involved the development of radiolabeled and unlabeled monoclonal antibody-based therapies for lymphoma, and other immune-based strategies for the treatment of lymphoma and related hematologic malignancies. They conducted the first major clinical trial of epratuzumab, a monoclonal antibody against the CD22 molecule on lymphoma cells, and have led other trials exploring its role as lymphoma therapy, including the first trial of combination antibody therapy (epratuzumab and rituximab), which could allow patients to delay or avoid chemotherapy. This work has led to involvement in the development of other classes of targeted agents, including proteasome inhibitors, histone deacetylase inhibitors, other epigenetic therapeutics, cell cycle inhibitors, and immunomodulatory and various kinase inhibitors. Several of these compounds that the group has evaluated have subsequently been approved by the FDA.

Dr. Leonard is currently collaborating with Dr. Ari Melnick in the Department of Medicine, Hematology, and Medical Oncology and the Department of Pharmacology, and Dr. Selina Chen-Kiang, Department of Pathology and Laboratory Medicine, exploring important aspects of lymphoma biology and new treatments for diffuse large cell, follicular, and mantle cell lymphomas.

Other efforts by the group include assessment of intensive versus non-intensive treatment strategies in various settings, studies of the utility of various imaging approaches in lymphoma, and issues relating to survivorship concerns of lymphoma patients in remission. Dr. Leonard is Vice Chair of the Lymphoma Committee for the Alliance for Clinical Trials in Oncology (formerly Cancer and Leukemia Group B), a cooperative group of the National Cancer Institute that helps to develop new standards of care for cancer treatment. Additionally, he recently became the Chair of the Scientific Advisory Board of the Lymphoma Research Foundation and the Leukemia and Lymphoma Society, where he contributes to advancing the research agenda and patient services missions of these organizations.

Recently, Dr. Leonard was named Associate Dean for Clinical Research at Weill Cornell, where he is leading the effort to improve and expand high-impact clinical research that synergizes with the clinical, laboratory, and educational missions of the Medical College.

SELECTED PUBLICATIONS


Steven M. Lipkin, MD, PhD
Associate Professor of Genetic Medicine

Most cancers are curable when detected early, before they have spread. Identifying individuals who are at higher risk of developing cancer so that cancer surveillance can be optimized for them is an important goal. Most of the patients with hereditary breast, colon, hematologic, or multiple primary cancers do not have mutations in the known risk genes. The laboratory of Dr. Steven Lipkin is using an innovative tiered, resource-conscious strategy incorporating whole exome, full genome sequencing, and previously untapped computational resources to discover, prioritize, and rigorously validate new constitutional risk genes. Dr. Lipkin and his colleagues have identified several candidate genes that they are investigating further. Such an approach can help build a research paradigm for other as-yet-uncharacterized cancer syndromes, and will identify individuals who will benefit from increased cancer surveillance, early detection, and targeted cancer prevention.

The laboratory of Dr. Steven Lipkin is using an innovative tiered, resource-conscious strategy to discover, prioritize, and rigorously validate new constitutional risk genes.

A Weill Cornell principal investigator in the Starr Cancer Consortium, Dr. Lipkin has a particular interest in colorectal cancer. In one study, Dr. Lipkin and his team discovered why statins appear to protect against colorectal cancer development in some individuals taking statins, but not all. They found that about 44 percent of Caucasians taking statins likely are not protected against cancer as well as others because they have inherited a particular gene variant. In a subsequent study, they genotyped 40 candidate genes known to be important for synthesis and metabolism of cholesterol through a population case-control study of colorectal cancer in northern Israel. Included in the 40 genes were six SNPs, or DNA sequences, within the HMGCR gene, which produces a critical enzyme involved in the formation of cholesterol. They found one SNP within HMGCR that was associated with statin protection against colorectal cancer.

The protective association was significantly stronger among individuals with what they dubbed the “A” SNP allele, or variant, compared with people who had a “T” variant. The researchers concluded that carriers of the A allele express more of the full-length protein that binds statins, and are therefore more sensitive to statins and more likely to experience the colorectal cancer risk reduction associated with long-term use – especially if a person has two A alleles. Carriers of the T allele are less sensitive to statins because they are missing part of the protein that binds to statins. A protective effect against colorectal cancer development is largely absent from people who have two T alleles. A test for this genetic variant has been incorporated into the National Cancer Institute-sponsored P5 clinical trial, which is evaluating the role of statins and aspirin to reduce colorectal cancer risk.

Dr. Lipkin has recently begun focusing efforts on identifying new gene mutations that increase an individual’s risk of developing colon and breast cancers and leukemias so that people carrying these mutations can be targeted for early detection and cancer prevention. This new project was ranked in the top 1 percent of National Cancer Institute-sponsored new projects in mid-2012.
patients with cancer and metastatic disease. Education of bone marrow cells are hoped to significantly improve survival in therapeutic development in the metastatic process. Interventions to prevent these insights are integral steps towards identifying molecular and cellular targets for therapeutic development in the metastatic process. Interventions to prevent metastasis. In addition, an exosome protein signature could be used to identify tumor-derived exosomes and bone marrow cells in patients with widespread metastatic disease. Consistent with these findings, higher amounts of MET were found in circulating microparticles known as exosomes, which carry tumor information such as mRNAs, microRNAs, DNA, and proteins, as new factors in the crosstalk between tumor cells and cells in the tumor microenvironment. Tumor-derived exosomes circulate in the bloodstream and fuse with cells in distant organ sites, mediating vascular leakiness, inflammation, extracellular matrix remodeling, and the formation of metastatic niches that enhance metastatic burden and the number of sites metastatic lesion. These bone marrow cells express vascular endothelial receptor 1 (VEGFR1), as well as integrins that allow binding to fibronectin-produced sites. Together, these cells provide a platform of chemokines, growth factors, matrix-degrading enzymes, and adhesion molecules, accelerating assembly of the metastatic lesion.

Since this newly recognized field in cancer biology has been described by Dr. Lyden and colleagues, an intense research focus related to mechanisms at the pre-metastatic niche, and to the metastatic niche, have been ongoing. One component that remains particularly perplexing is the tissue-specific pattern of metastatic progression in cancer. Unraveling an explanation for preferential metastasis to specific organs known as organotropism has been challenging. To date, little is known about the tumor-derived secreted factors that mediate the formation of the pre-metastatic niche and hence organotropism of metastatic disease. Recently, Dr. Lyden and colleagues (H. Peinado et al) have identified tumor-secreted microparticles known as exosomes, which carry tumor information such as mRNAs, microRNAs, DNA, and proteins, as new factors in the crosstalk between tumor cells and cells in the tumor microenvironment. Tumor-derived exosomes circulate in the bloodstream and fuse with cells in distant organ sites, mediating vascular leakiness, inflammation, extracellular matrix remodeling, and the formation of pre-metastatic niches that enhance metastatic burden and the number of sites metastatic disease, explaining the organotropic specificity of cancer. Exosomes are also preferentially fused with bone marrow-derived cells, promoting their “education” to a pro-vascularogenic, pro-migratory, and pro-metastatic phenotype and enhancing their mobilization to pre-metastatic niche sites. Proteomic profiling revealed that highly metastatic melanoma exosomes expressed high levels of the MET oncoprotein as compared to non-metastatic exosomes. Moreover, exosomal transfer and delivery of an oncogenic cargo to bone marrow-derived cells resulted in the increase of MET-positive bone marrow-derived cells in melanoma models. Consistent with these findings, higher amounts of MET were found in circulating tumor-derived exosomes and bone marrow cells in patients with widespread metastasis. In addition, an exosome protein signature could be used to identify patients who are more likely to develop distant metastatic disease.

These insights are integral steps towards identifying molecular and cellular targets for therapeutic development in the metastatic process. Interventions to prevent or reduce the metastatic burden by targeting exosome production, transfer, and education of bone marrow cells are hoped to significantly improve survival in patients with cancer and metastatic disease.

David C. Lyden, PhD, MD
Stavros S. Niarchos Associate Professor in Pediatric Cardiology
Associate Professor in Pediatrics and Cell and Developmental Biology

Dr. David Lyden and colleagues have examined the earliest steps prior to influx of metastatic tumor cells in distant organs. They have defined the cellular and molecular events leading to the formation of the “pre-metastatic niche” that identifies the receptive microenvironment at designated sites prior to the influx of metastatic tumor cells in distant organs known as “metastatic niches” following tumor cell engraftment. They uncovered a crucial role for specific bone marrow-derived cells of myeloid lineage in priming distant tissues for tumor cell metastasis. Dr. Lyden showed that factors released by the primary tumor drive the recruitment of bone marrow-derived cells to fibronectin-enriched sites in the vicinity of the future metastatic niche. These bone marrow cells express vascular endothelial receptor 1 (VEGFR1), as well as integrins that allow binding to fibronectin-produced sites. Together, these cells provide a platform of chemokines, growth factors, matrix-degrading enzymes, and adhesion molecules, accelerating assembly of the metastatic lesion.

SELECTED PUBLICATIONS


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Ca\(^{2+}\) is a ubiquitous intracellular messenger that mediates various physiological processes including fertilization, muscle contraction, neurotransmitter release, and the regulation of gene expression. As such Ca\(^{2+}\) plays fundamental roles in regulating intracellular signaling. The specificity of the cellular response downstream of the intracellular Ca\(^{2+}\) signal is encoded in its spatial and temporal properties. Hence different cell types and even the same cell type during its development and differentiation handle Ca\(^{2+}\) signals differentially. However, the molecular mechanisms mediating the remodeling of the Ca\(^{2+}\) signaling machinery during cellular development remain poorly understood.

Dr. Khaled Machaca and his colleagues have made significant contributions to the understanding of the regulation of Ca\(^{2+}\) signaling pathways during cellular development and division using oocyte maturation as their preferred model system. Ca\(^{2+}\) is the universal signal for egg activation at fertilization and for mediating the critical egg to embryo transition. Ca\(^{2+}\) signals remodel during oocyte maturation to endow the egg with the capacity to activate at fertilization and transition to embryogenesis. The Machaca lab has shown over the year that this remodeling involves some of the key channels and transporters that underlie Ca\(^{2+}\) signaling. The plasma membrane Ca\(^{2+}\) ATPase is removed from the cell membrane into an intracellular vesicular pool and the IP3 receptor forms large patches in the context of the remodeling of the endoplasmic reticulum during meiosis. Furthermore, the predominant Ca\(^{2+}\) entry pathway in the oocyte, store-operated Ca\(^{2+}\) entry (SOCE), inactivates completely during oocyte maturation. SOCE inactivation has been shown by the Machaca lab to be due to modulation of the two molecules mediating SOCE, STIM1, and Orai1. STIM1 clustering is inhibited and Orai1 is internalized during oocyte maturation.

Dr. Khaled Machaca and his colleagues have made significant contributions to the understanding of the regulation of Ca\(^{2+}\) signaling pathways during cellular development and division using oocyte maturation as their preferred model system.

Because oocyte maturation is a contributing limiting factor in infertility treatments, this line of investigations has the potential to improve human infertility treatments. Furthermore, given the ubiquitous role that Ca\(^{2+}\) signals play in a variety of cellular signaling pathways, these studies are likely to have wide-ranging implications to a variety of human diseases, including hypertension. In fact, current studies in the Machaca lab focus on the regulation of the IP3 receptor in hypertension.

Dr. Machaca’s group is also interested in elucidating the signaling and cellular mechanisms regulating the arrest and resumption of the meiotic cell cycle during oocyte maturation. These studies have implicated a role for Zn\(^{2+}\) in resumption of the meiotic division at ovulation.
Research in Dr. Fred Maxfield’s laboratory uses sophisticated microscopy imaging to gain insight into basic processes in cell biology and to understand how these processes are associated with disease. Because many fundamental processes are similar in cells from various tissues, this approach leads Dr. Maxfield’s research into several different diseases, which might seem to be unrelated until one sees similarity in the underlying cellular mechanisms. One example is a process called endocytosis, which is used by cells to take in nutrients and also to remove unwanted materials from the extracellular environment. Normally, such materials are taken into a digestive organelle called the lysosome, where the ingested molecules are broken down and reutilized by the cell to make membranes and proteins. A well-characterized example is the uptake of lipoproteins by cells. This process evolved to deliver cholesterol that is obtained from the diet or made in the liver to be distributed to cells throughout the body, where the cholesterol is used as an essential component of cell membranes. The process leads to atherosclerosis and heart disease when there is excess cholesterol.

Recently, Dr. Maxfield’s group used careful high resolution microscopy imaging to see how specialized cells, called macrophages, interact with cholesterol deposits from lipoproteins similar to those found in the walls of blood vessels. Surprisingly, they found that rather than taking in the lipoproteins and digesting them inside the cells (as had been presumed for many years), the cells actually create a digestive organelle, a lysosomal synapse, outside the cell. This releases cholesterol outside the cells and may lead to abnormal deposition of cholesterol crystals, a hallmark of advanced atherosclerosis.

Several years ago, Dr. Maxfield became interested in the similarity between uptake of lipoproteins by macrophages and the interaction of macrophage-like cells in the brain, called microglia, with Alzheimer’s amyloid deposits. His laboratory showed that a cell-surface receptor, called a scavenger receptor, which had been shown to be involved in uptake of some lipoproteins by macrophages, was also able to lead to internalization of Alzheimer’s amyloid fibrils by microglia. Unexpectedly, the microglia were unable to digest the amyloid even though they delivered it to their lysosomes, the digestive organelle of the cell. In recent studies, Dr. Maxfield’s group showed that this was due to poor acidification of the lysosomes. They also recently identified the molecular mechanism for this weak acidification in microglia and indicated ways in which this might be corrected to allow for better clearance of amyloid deposits.

In some inherited disorders, the lysosomes fail to function properly because of a missing or defective protein. One such disorder is Niemann-Pick type C disease, which leads to cholesterol accumulation in lysosomes and is usually fatal before age 20. Dr. Maxfield’s laboratory carried out a microscopy-based screen for compounds that might ameliorate the cholesterol accumulation. A recent study showed that a class of drugs called HDAC inhibitors were very effective in cells from patients. Some of these drugs are FDA approved for other diseases, and Dr. Maxfield and his collaborators at the NIH and Notre Dame are arranging for clinical trials in Niemann-Pick type C disease.
Ari M. Melnick, MD
Associate Professor of Medicine

A majority of tumors are caused by mutations or inappropriate expression of master regulatory factors that can “reprogram” normal cells into cancerous tissue. Under the direction of Dr. Ari Melnick, researchers are developing ways to identify these master regulatory proteins and to dissect out their molecular mechanisms of action. By combining sophisticated gene mapping tools that can track the location of these factors throughout the genome, together with advanced structural biology and biochemistry methods, Dr. Melnick’s team has discovered how several of these cancer-causing factors work at the most basic level, by hijacking and taking control of thousands of different genes using a variety of biochemical mechanisms. These findings are leading directly to novel forms of treatments for patients with B-cell lymphomas, leukemias, and other tumors.

Dr. Melnick’s team discovered that a master regulatory protein, called BCL6, causes aberrant growth and survival of lymphoma cells through a specific “intermolecular bridge.” BCL6 mediates its cancer-causing actions by attaching to other proteins. Traditionally, protein-protein interactions have been viewed as being too difficult to block with small-molecule drugs. By observing the atomic scale structure of BCL6 attached to its partner proteins, Dr. Melnick and colleagues identified a critical "hot spot" that appeared to be amenable to designing a drug. Using this information, his lab generated a peptidomimetic drug, called RIBPI, that destroys this bridge, which restored lymphoma cells back to their normal programming. Dr. Melnick and his colleagues used structure-based advanced computational modeling to design small molecule inhibitor drugs that work similarly to RIBPI. The BCL6 inhibitors are highly effective in killing lymphoma cells and were non-toxic to normal tissues. They discovered that the molecular chaperone Hsp90 plays a central role in diffuse large B-cell lymphomas and that a newly developed inhibitor of Hsp90, called PUH71, has potent anti-lymphoma effects. Based on these data, the National Cancer Institute is supporting translation of PUH71 to clinical trials.

Dr. Melnick’s group discovered that the molecular chaperone Hsp90 plays a central role in diffuse large B-cell lymphomas and that a newly developed inhibitor of Hsp90 called PUH71 has potent anti-lymphoma effects.

In other research, Dr. Melnick and his colleagues recently established a technology platform for deciphering how genes are controlled in cancer cells. The technique combines biochemistry, mathematics, and computational biology to capture at a holistic level the molecular instructions that control cancer cells and can even decode those epigenetic instructions that control gene expression independently of DNA sequence. Using this approach in large cohorts of patients with acute myeloid leukemia (AML), they were able to show for the first time that profound disruption of epigenetic gene regulation is a universal feature of tumors, identified new biologically and clinically distinct forms of AML, discovered a common epigenetic signature that underlies almost all AML (thus showing that epigenetic lesions occur more frequently and universally than genetic lesions), and identified a predictive DNA methylation-based biomarker for patient survival that outperforms the traditional currently available biomarkers.
The laboratory of Dr. Anant Menon is interested in membrane biogenesis, a critical activity required for cell growth, differentiation, and maintenance. It is a particularly complex process in eukaryotic cells as these cells have a characteristically diverse set of membranes with unique compositional and functional identities. Dr. Menon and his colleagues consider a number of questions. How are the components of biological membranes synthesized? How are they inserted and assembled into a pre-existing membrane template? How are molecules transported across membranes and exchanged between different membrane-bound compartments? Their current focus is on the molecular mechanisms of intracellular lipid transport. Lipids are generally amphipathic—they have a polar head and a hydrophobic tail. These features pose a challenge: the polar headgroup makes it next to impossible for lipids to move spontaneously across cellular membranes on a reasonable timescale, whereas the apolar nature of the tail prevents fast lipid movement from one membrane to another, via the aqueous cytoplasm. Nevertheless, cell growth and homeostasis demand that lipids move rapidly across and between membranes in cells, and for this specialized machinery must exist. Dr. Menon’s research team is interested in identifying the molecular components of this machinery and understanding lipid transport mechanisms.

Cholesterol is an important constituent of biological membranes. Cells make cholesterol in the endoplasmic reticulum, a biosynthetically active intracellular compartment, or import it by receptor-mediated endocytosis of lipoproteins. Regardless of its source, cholesterol is mainly found in the plasma membrane where it represents 40 percent of the lipids. Cellular cholesterol levels are tightly controlled by acute responses as well as by transcriptional programming, both of which require sterol exchange between membranes. By analyzing sterol transport in baker’s yeast, the Menon lab discovered that it occurs largely by non-vesicular mechanisms requiring cytoplasmic transport proteins. The researchers recently developed methods to visualize sterol transport in living yeast cells, and they are now combining this technology with genetic and biochemical approaches to identify the enigmatic sterol carriers.

Lipid movement across membranes (lipid flip-flop) is required at many biological levels. For example, it is needed for protein N-glycosylation and the clearance of apoptotic cells; in bacteria, it is needed for cell wall assembly. Activity assays reveal that unique membrane-embedded transport proteins facilitate flip-flop whereas others act as lipid pumps. A number of lipid pumps have been identified, but facilitators of lipid flip-flop have eluded researchers for decades. Dr. Menon and his colleagues recently reported that the visual receptor rhodopsin facilitates phospholipid flip-flop at a rapid rate. This activity is important for clearance of by-products of the visual cycle whose accumulation contributes to the progression of macular degeneration. They are now analyzing how rhodopsin carries out this remarkable transport function. In collaboration with Dr. Alessio Accardi at Weill Cornell, they identified proteins that facilitate calcium ion-dependent lipid scrambling at the plasma membrane. This is a key event that enables activated platelets to facilitate coagulation at sites of blood vessel injury and signals macrophages to engulf cells undergoing programmed cell death. In a parallel effort with Dr. Johannes Graumann of Weill Cornell Medical College-Qatar, Dr. Menon’s lab is using quantitative proteomics to identify facilitators that flip lipids needed for protein N-glycosylation in the endoplasmic reticulum. Through these efforts the Menon laboratory hopes to reveal basic mechanisms of cell biology, as well as identify new targets for therapeutic intervention.
Teresa A. Milner, PhD
Professor of Neuroscience

Throughout the life cycle, estrogens and other gonadal steroids can influence many brain functions. In addition to regulating reproductive functions and homeostasis, estrogens can affect cognitive and emotional processes, as well as autonomic functions. Dr. Teresa Milner’s research focuses on delineating the mechanisms by which estrogens influence cognition, particularly those related to drug abuse and to cardiovascular functions during menopause.

Women are more susceptible to several aspects of drug addiction than men, including relapse following stressful events. The hippocampus is a brain region that is critically involved in learning relevant to drug abuse. Moreover, estrogens and opioid peptides, by binding to select receptors, can modulate learning processes in the hippocampus. Over the years, Dr. Milner’s research has localized both estrogen and opioid receptors in rodents using electron microscopic immunocytochemical methods to help elucidate the mechanisms by which estrogens and opioids interact to impact learning relevant to drug abuse. In particular, her lab has found that estrogen receptors (ERs) are not only found in nuclei where they can influence genomic events, but also are located in synapses where they can influence rapid communication between nerve cells.

Dr. Milner’s research has localized both estrogen and opioid receptors in rodents to help elucidate the mechanisms by which estrogens and opioids interact to impact learning relevant to drug abuse.

Dr. Milner also has demonstrated that the mu- and delta-opioid receptors (MOR and DORs, respectively) are present on select subtypes of hippocampal neurons where they can influence the balance of excitation and inhibition. Her most recent studies indicate that estrogens regulate endogenous hippocampal opioid peptides and MORs and DORs in a manner that could promote learning processes relevant to drug abuse and relapse after chronic stress.

After menopause, hypertension and stress reactivity increases in women. Dr. Milner’s research investigates the central mechanisms by which estrogens regulate blood pressure in rodents to help understand the development of hypertension and stress reactivity in menopause. Her research has shown that receptors for estrogens and other ovarian steroids have a regionally selective location relative to cardiovascular brain circuits.

Using combined neuroanatomical and physiological approaches, Dr. Milner’s lab has shown that estrogens, primarily via ER beta, regulate angiotensin-signaling in the rostral ventrolateral medulla, a brain region crucial for the regulation of blood pressure. Her most recent research utilizes a new “accelerated ovarian failure” model of menopause to study the mechanisms by which changes in estrogen levels during menopause influence cells in the hypothalamic paraventricular nucleus, a brain region critical for integrating and coordinating neurohumoral responses involved in blood pressure regulation. These studies have contributed importantly to understanding changes in the brain during menopause that contribute to the increased susceptibility to hypertension.

SELECTED PUBLICATIONS


John P. Moore, PhD  
Professor of Microbiology and Immunology

The laboratory of Dr. John Moore is focused on contributing to international efforts to prevent and treat HIV-1 infection. This virus has already infected and killed tens of millions of people, particularly in the developing world, and it continues to spread. While nowadays excellent drug therapies are available to treat infected people, provided they have access, prevention successes have been partial and patchy.

Dr. Moore’s laboratory has several different, but interrelated, basic science research programs that are based on understanding how the virus enters the cells it infects, and on finding ways to prevent that process from happening. Specific inhibitors of virus entry are now available, including licensed drugs. Working within a research consortium, Dr. Moore and his colleagues are studying how some of these inhibitors can be used to prevent virus transmission, not just treat it. More specifically, they are evaluating the protective potential of compounds that block access to the CCR5 receptor for HIV-1 on the surface of target cells. These inhibitors, alone and in combination with other types, are being tested in the rhesus macaque model of vaginal HIV-1 transmission. To help improve the chances that inhibitors like these would actually be used by women, they are studying ways to deliver them in a user-friendly, minimally inconvenient manner. One such approach is to formulate the inhibitors in plastic rings that can be inserted vaginally and left in place for up to a month, gradually releasing the active compound where it is needed. Another is to use silicone gel formulations similar to personal lubricants that can be applied only once a day. In a related study, scientists in the lab are testing whether this kind of approach to prevention can be combined with vaccination. Do two partially effective intervention approaches work better together than apart?

The laboratory of Dr. John Moore is focused on contributing to international efforts to prevent and treat HIV-1 infection.

Dr. Moore’s laboratory is also involved in vaccine-related research, particularly work on the viral envelope glycoproteins that are involved in virus entry. These proteins are the targets for antibodies that neutralize virus infection. In principle, this kind of antibody could protect people from HIV-1, if ways to induce them consistently by vaccination could be devised. To gain more information on how to do this, Dr. Moore and his researchers are working with colleagues elsewhere to obtain detailed structural information on the envelope glycoproteins in a trimeric configuration that mimics how they appear on the virus surface. They hope that this kind of information could help them and others design improved versions of the envelope glycoproteins for use as vaccine components. They are also testing how to make the envelope glycoproteins more immunogenic by studying how they interact with cells of the immune system and learning how to overcome limitations on how the body raises antibodies to them.

A third project involves understanding how HIV-1 becomes resistant to the inhibitors that prevent virus binding to the CCR5 receptor. Dr. Moore’s lab found that the resistant viruses still use CCR5, but do so differently. They now seek to obtain fundamental information on the way the virus interacts with CCR5, and how, by doing so, it enters cells both when the inhibitors are present and when they are not.

SELECTED PUBLICATIONS


Veazey RS, Ketas TJ, Dufour J, Moroney-Rasmussen T, Green LC, Klasse PJ, Moore JP. Protection of rhesus macaques from vaginal infection by vaginally delivered Maraviroc, an inhibitor of HIV-1 entry via the CCR5 co-receptor. *Journal of Infectious Diseases*. 2010 Sep 1;202(5):739-44.


Dr. Anne Moscona is widely recognized as one of the world’s leading experts in viral pathogenesis and treatment. The overall goal of Dr. Moscona’s research is to understand the steps in the entry of enveloped viruses into their target cells, as the first step in infection. The focus is on a group of paramyxoviruses that includes pediatric respiratory pathogens, as well as emerging lethal viruses. The fundamental aspects of this research have identified key roles of viral glycoproteins during the receptor binding and entry process, and most recently have elucidated some of the interactions between the two surface glycoproteins during the process of virus-induced membrane fusion.

Dr. Moscona identified critical roles of the viral receptor binding protein in activating the viral fusion/entry process during infection, proving that the binding protein actively triggers its partner fusion protein to mediate entry. She has identified essential contributions of the host tissue to pathogenesis, and the interplay between host and viral factors during viral entry and infection.

Dr. Moscona identified potential targets for entry inhibitors for pediatric respiratory viruses.

Dr. Moscona is also a prominent investigator in the field of emerging lethal pathogens, known for her work on the Nipah and Hendra viruses, paramyxoviruses that are causing outbreaks with recent evolution of human-to-human transmission. In addition to acute infection, these viruses may lead to late-onset disease or relapse of encephalitis years after initial infection, as well as persistent or delayed neurological sequelae. For these viruses she has elucidated entry mechanisms and identified new antiviral targets and is developing candidate therapeutics.

Dr. Moscona has tackled the problems of antiviral resistance, and based upon her fundamental studies of resistance mechanisms, has contributed to the discussion of antiviral development and resistance for influenza.

Current projects in Dr. Moscona’s group include basic studies on the mechanisms of virus-induced membrane fusion, centered on parainfluenza virus for the most fundamental research, with Nipah virus as a contrasting mechanism, along with some of the interactions between the two surface glycoproteins during the process of virus-induced membrane fusion. However, these novel antiviral approaches, in turn, have yielded valuable tools and reagents for study of basic mechanisms.

Dr. Moscona’s investigations into the human parainfluenza viruses are of critical importance because these respiratory viruses cause croup, bronchiolitis, and pneumonia, leading global causes of disease and death in infants and children under five years of age. In revealing specific mechanisms of the two viral surface proteins during entry, Dr. Moscona identified new potential targets for entry inhibitors for pediatric respiratory viruses.
Carl Nathan, MD
Chair, Microbiology and Immunology
R.A. Rees Pritchett Professor of Microbiology
Professor of Medicine
Professor of Microbiology and Immunology

In work spanning four decades, Dr. Carl Nathan established that lymphocyte products activate macrophages, that interferon-gamma is a major macrophage activating factor in mice and humans, and that mechanisms of macrophage antimicrobial activity include induction of the respiratory burst and inducible nitric oxide synthase (iNOS), which he and his colleagues purified, cloned, knocked out, and characterized biochemically and functionally.

Although iNOS helps the host control Mycobacterium tuberculosis, Mtb resists sterilization by host immunity. Non-replicating Mtb exhibits relative resistance to conventional anti-infectives, resulting in the need to treat tuberculosis longer than almost any other infectious disease and the emergence of hereditable drug resistance. One goal of Dr. Nathan’s lab is to identify new anti-infectives that aim to shorten the course of treatment and provide effective therapies against drug-susceptible and drug-resistant strains of TB. The biochemical basis of Mtb’s persistence is the present focus of Dr. Nathan’s laboratory. Genetic and chemical screens have identified enzymes that Mtb requires to survive during non-replicative persistence, including the proteasome, a serine protease that controls intrabacterial pH, and components of pyruvate dehydrogenase and nucleotide excision repair, along with inhibitors of each.

Under Dr. Nathan’s leadership, the faculty within the Department of Microbiology and Immunology pursue diverse projects, but share the concern of how genomes regulate themselves and each other. Their interest in genetic information spans the spectrum from how information can be extracted, understood, and applied at the genomic level to how gene products interact at the atomic level.

After graduation from Harvard College and Harvard Medical School, Dr. Nathan trained in internal medicine and oncology at Massachusetts General Hospital, the National Cancer Institute, and Yale before joining the faculty of The Rockefeller University from 1977 to 1986. Since 1986, Dr. Nathan has been at Weill Cornell Medical College, where he has served as Founding Director of the Tri-Institutional MD-PhD Program, Senior Associate Dean for Research, and Acting Dean. A member of the National Academy of Sciences, the Institute of Medicine of the National Academies, and a Fellow of the American Academy of Microbiology, Dr. Nathan serves as Associate Scientific Director of the Cancer Research Institute; on the scientific advisory boards of the American Asthma Foundation and the Rita Allen Foundation; as a member of the Board of Governors of the Tres Cantos Open Lab Foundation; and on the juries for the Paul Marks Prize at Memorial Sloan-Kettering Cancer Center and the Lurie Prize of the Foundation for NIH.

He recently stepped down from 10 years of service as a Trustee of Hospital for Special Surgery and Chair of the Board of Trustees’ Research Committee, and from the Scientific Advisory Committee of the Cambridge Institute for Medical Research at Cambridge University, United Kingdom. Since 1981, Dr. Nathan has served as an editor of the Journal of Experimental Medicine. In 2009, he received the Robert Koch Prize for his work on host defense against infection.

SELECTED PUBLICATIONS


**Steven M. Paul, MD**  
Professor of Neuroscience, Psychiatry and Pharmacology

The research laboratory of Dr. Steven Paul, who is also the Director of the Helen & Robert Appel Alzheimer’s Disease Research Institute, seeks to better define the underlying pathogenesis of Alzheimer’s disease (AD). How do the genes known to greatly influence the risk of developing the most common form of late-onset AD (and the proteins they encode) actually contribute to the subsequent molecular and cellular events leading to the neuropathological signatures of the disease, namely amyloid plaques and neurofibrillary tangles? The latter subsequently leads to the neurodegeneration that typifies the disease and ultimately the dementia and other signs and symptoms of AD.

Dr. Paul’s research has helped shed light on genetic factors that dramatically increase risk for Alzheimer’s and actually cause the brain abnormalities that lead to the loss of neurons and the symptoms of the disease. The work of Dr. Paul and his laboratory team has focused on the most common genetic risk factors for late onset AD, the apolipoprotein E (apoE) alleles. ApoE4 carriers have a 3-15 fold greater risk for developing AD (heterozygotes and homozygotes respectively) and apoE2 is a known protective allele, reducing risk by approximately 50 percent. How do these two apoE alleles, which differ by only two codons/ amino acids, so dramatically alter the risk to develop AD?

Over the past 15 years, Dr. Paul’s laboratory, in collaboration with several other laboratories, has shown that apoE4 is a major determinant of brain-amyloid burden in vivo. Using a series of transgenic mouse models, the researchers have shown age-dependent and apoE isoform-dependent (E4>E3>E2) increases in brain amyloid burden that closely recapitulates what is observed in AD patients. More recent work in the Paul laboratory has shown that the brain levels of amyloid-β-peptides (Aβ), which form amyloid plaques, are greatly influenced by the apoE isoform expressed (E4>E3>E2) and that soluble brain levels of Aβ are already increased at a very early age and then continue to increase in an apoE isoform- and age-dependent manner.

The apoE isoform-dependent changes in brain Aβ levels are due to apoE isoform-dependent alterations in local Aβ metabolism and clearance (E4>E3>E2) and appear to involve differential metabolism of Aβ by microglia and astrocytes.

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In related work, Dr. Paul and his research team have shown that microglia and macrophages metabolize Aβ in an apoE isoform-dependent manner via a novel C-terminal peptidase among other proteases. Their data help to explain recent PET neuroimaging findings in elderly patients at high genetic risk for AD which show early apoE isoform-dependent accrual of Aβ in brain and the formation of amyloid plaques many years before the onset of AD. Finally, their most recent data suggest an important role of apoE4 in the formation of tau aggregates and neurofibrillary tangles, the other major neuropathological hallmark of AD. Their findings have both diagnostic and therapeutic implications and both are being actively pursued.

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**SELECTED PUBLICATIONS**


Gregory A. Petsko, DPhil  
Mahon Professor of Neurology and Neuroscience

For over 30 years Dr. Gregory Petsko and his colleague, Prof. Dagmar Ringe, have used protein crystallography, molecular biology, and genetics to probe the relationship between protein structure and function. Their research has been concerned with the three-dimensional structures and dynamics of proteins and their biochemical functions, with a particular focus on the structural basis for efficient enzymic catalysis; direct visualization of proteins in action by time-resolved protein crystallography; the evolution of new enzyme activities; and the biology of the quiescent state in eukaryotic cells.

During the past 10 years, Drs. Petsko and Ringe have pursued groundbreaking research not only on how proteins work, but how they are related to the causes of neurodegenerative diseases. They use the techniques of genetics, structural biology, and structure-guided drug discovery to identify, validate, and exploit novel targets for the treatment of age-related neurodegenerative disorders such as Alzheimer’s, Parkinson’s, and Lou Gehrig’s diseases.

During the past 10 years, Drs. Petsko and Ringe have pursued groundbreaking research not only on how proteins work, but how they are related to the causes of neurodegenerative diseases.

Alzheimer’s disease starts when a protein that should be folded up properly for normal brain functioning instead misfolds and then aggregates. Interestingly, diseases that affect other parts of the brain also show similar aggregates of misfolded proteins. This suggests that a therapeutic approach developed for Alzheimer’s might also be used to treat many neurological diseases. With this in mind, they have been collaborating with Dr. Scott Small of Columbia University on the development of drugs that will route the Alzheimer’s protein away from the subcellular compartments where misprocessing and aggregation begin. Two of their compounds have shown good results in neurons in cell culture, and are now being tested in mouse models of Alzheimer’s disease.

The pathological hallmark of Parkinson’s is the accumulation in nerve cells of dense clumps of another aggregated protein, called alpha-synuclein. Alpha-synuclein does not normally form such aggregates in healthy brain cells, so identifying the process that triggers its aggregation in the early stages of Parkinson’s disease may provide a therapeutic opportunity. Focusing on what might be nucleating the formation of the synuclein aggregates, they identified an enzyme that clipped synuclein, forming rapidly aggregating fragments, and showed that inhibiting it with a specific drug blocked the formation of the synuclein fragments, thereby preventing or delaying the formation of the aggregates that these fragments promote. Two such inhibitors are now being tested in several rodent models of Parkinson’s disease.

Finally, they have been developing a novel gene therapy for amyotrophic lateral sclerosis (Lou Gehrig’s disease or ALS). By overexpressing the human UPR1 gene, which codes for a protein that is involved in a cellular pathway called nonsense-mediated decay, they have succeeded in completely blocking the death of motor neurons in cell culture models of ALS. With the help of several collaborators, they have been able to engineer a virus to carry this gene into the spinal motor neurons, and are now testing the therapy on rat and mouse models of ALS to see if it can either retard or halt the progression of the disease.
Shahin Rafii, MD
Arthur B. Belfer Professor in Genetic Medicine
Professor of Medicine

A pioneer in the fields of vascular biology and stem cell research, Dr. Shahin Rafii has established novel preclinical models to target vascular cells for the treatment of stem cell-related disorders by paving the way to exploit the potential of pluripotent stem cells for therapeutic organ revascularization and cancer targeting. He has made the following seminal discoveries.

**Bone marrow-derived endothelial precursors are required for tumor angiogenesis.**
This discovery was hailed by the journal *Nature* as revolutionary for blood vessel formation. Dr. Rafii introduced the concept that tumors and regenerating organs rely on stem cells from the bone marrow to help build new blood vessels. Both tumor cells and injured tissue, such as that at the site of a heart attack, stroke, or organ transplant, can recruit stem cells from the bone marrow. He discovered mobilizing factors that activate the stem cells in bone marrow that form new blood vessels destroyed by chemotherapy or radiation.

**Adult testes can be turned into stem cells.** Dr. Rafii described how cells from the testes of adult male mice can be turned into stem cells, thereby opening the way to therapeutic use of spermatogonial stem cells (SSC) for regenerative medicine. He demonstrated that reprogrammed SSC could develop into working blood-vessel tissue, as well as contractile cardiac tissue and brain cells, and others. He isolated SSC and showed a conversion of SSC into multipotent stem cells, indicating the pluripotency of adult germline stem cells. Since the donor and recipient are identical, use of SSC for cell transplantation will allow establishment of individual cell-based therapy avoiding many of the ethical issues associated with embryonic stem cells.

**Signaling pathways and transcriptional networks promote endothelial differentiation.**
Dr. Rafii identified signaling pathways and transcriptional networks that promote and augment endothelial differentiation in human embryonic stem cell (hESC) culture, with more than 80 percent of the population differentiating to cardiovascular derivatives. He established a method for vascular differentiation from hESC to scale up the serum-free humanized feeder-based differentiation platform to test the ability of discreet vascular subpopulations to restore vascular perfusion in model left descending coronary artery ligation induced ischemia. This presents an unprecedented resource for pre-clinical study of cell-based therapies of cardiovascular disease.

**Organ specific blood vessels produce a specific set of growth factors that support expansion of organ specific progenitor cells and augment organ regeneration.**
Dr. Rafii identified the molecular and cellular pathways that allow expansion and engraftment of hepatocytes and augment liver regeneration, showing that after 70 percent partial hepatectomy, activation of liver sinusoidal endothelial cells (LSECs) by production of paracrine factors – defined as angiocrine factors – induce liver regeneration. He defined the phenotype of LSECs and has shown that LSECs are composed of a specialized vascular network that is in direct cellular contact with hepatocytes and sustains the regeneration of remaining lobes of the liver. Hepatocyte transplantation provides for a clinically plausible approach to improve liver function. Therefore, identification of the molecular and cellular pathways that allow expansion and long-term engraftment of hepatocyte or augment liver regeneration will have significant therapeutic impact.

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**SELECTED PUBLICATIONS**


M. Cary Reid, MD, PhD
Associate Professor of Medicine

The work of Dr. Cary Reid over the past decade has focused on the epidemiology and treatment of common pain disorders (e.g., back pain, osteoarthritis, neuropathic pain) in older adults. Dr. Reid’s research is informed by training in both geriatric medicine and clinical epidemiology. His work has involved elucidating risk factors for pain onset and adverse outcomes (e.g., disability) after development of various pain disorders.

Dr. Reid has conducted epidemiologic analyses focusing on the prevalence and strategies employed by older adults to self-manage pain, as well as outcomes associated with these strategies, to include activity restriction, exercise, use of relaxation techniques, and religiosity. His work has also involved developing, testing, and implementing various non-pharmacologic interventions for older adults with non-cancer pain disorders such as back pain and osteoarthritis. Examples include implementation and evaluation of specific exercise protocols, cognitive-behavioral interventions, as well as combined exercise and cognitive-behavioral programs for seniors with pain. Given established disparities in the management of pain as a function of race/ethnicity, much of this work has focused on the development and testing of pain programs in minority communities.

Dr. Reid has conducted epidemiologic analyses focusing on the prevalence and strategies employed by older adults to self-manage pain, as well as outcomes associated with these strategies.

Dr. Reid’s recent work has also been directed towards identifying research gaps in knowledge regarding the pharmacologic management of pain among older adults and examining the role of specific analgesic agents as treatment for diverse pain disorders. These gaps include uncertainties regarding the long-term safety and efficacy of commonly employed analgesic medications, lack of knowledge regarding factors that predict positive (or negative) treatment outcomes associated with specific analgesic medications, as well as limited knowledge regarding optimal approaches to prevent or minimize side effects, which increase as a function of age. His work also involves identifying strategies to extend the reach of evidence-based pain programs for use by older minority adults, particularly those living in underserved neighborhoods.

Dr. Reid serves as the Director of Cornell University’s Edward R. Roybal Center for Translational Research on Aging, an NIH-funded center that focuses on pain in later life. The goals of the Roybal Center include translating the findings of basic behavioral, medical, public health, and social science research into treatments, intervention programs, and policies that improve the health and well-being of older adults who suffer from or are at increased risk for pain; promoting translation of evidence-based practices, treatments, and interventions across diverse venues to improve management of pain; and developing and testing innovative methods, tools, and strategies that facilitate successful translation of evidence into practice. Dr. Reid also directs Weill Cornell’s Center of Excellence in Geriatric Medicine. This John A. Hartford sponsored grant seeks to train the next generation of leaders in geriatric medicine.

SELECTED PUBLICATIONS


Dr. Rodriguez-Boulan’s landmark papers in 1978 and 1980 that demonstrated the polarized budding of enveloped RNA viruses from cultured canine kidney cells (PNAS, 1978; Cell, 1980) introduced the MDCK model (in collaboration with Cereijido and Sabatini) which quickly became the paradigmatic model to study the generation and maintenance of epithelial cell polarity. Over 6,000 publications have used this model, as indicated by a recent PubMed search. Using a combination of various biochemical, molecular, structural, and live imaging approaches, his laboratory has contributed over 150 publications using this model that elucidate sorting signals, sorting compartments, and trafficking routes of apical and basolateral proteins, as well as various components of the polarized trafficking machinery of epithelial cells (e.g. clathrin and clathrin adaptors).

Dr. Rodriguez-Boulan has discovered a variety of mechanisms responsible for epithelial cell polarity using the MDCK model system that he co-introduced in 1978. His research also focuses on the interaction between the two major cells in the outer retina, the retinal pigment epithelium, and the retinal photoreceptors, which are essential for normal vision.

A second major focus of Dr. Rodriguez-Boulan’s laboratory is the interaction between the retinal pigment epithelium (RPE) and the photoreceptors, respectively, the first and second layers of the retina, which is key for normal vision. His laboratory has made major contributions in this area, including the discovery of a major RPE receptor (the integrin αvβ5) for phagocytosis of rod outer segments, a circadian process that occurs every day and is essential for retinal health. His group recently reported that the RPE belongs to a small group of epithelia (also including the liver and the kidney proximal tubule) that lacks the major basolateral sorting adaptor AP-1B and therefore expresses various basolateral proteins at the apical plasma membrane, with profound consequences for the physiology of the host epithelia. Finally, his group has discovered a group of small drugs (cyclodextrins) that efficiently remove lipofuscin from RPE. These drugs may turn out to be useful therapeutic agents for genetic and age-related retinal diseases that accumulate lipofuscin, such as Stargardt disease and age-related macular degeneration (AMD), a major cause of blindness among the senior population, for which there is no cure yet.
M. Elizabeth Ross, MD, PhD
Professor of Neurology and Neuroscience

The laboratory of Dr. Elizabeth Ross studies how genes direct brain construction, combining basic science and clinical genetic components in three major projects:

**Neural tube formation — spina bifida.** Neural tube defects (NTDs), principally spina bifida and anencephaly, affect one to two per 2,000 pregnancies or more worldwide. Using both animal models and human populations, Dr. Ross and her research team investigate the complex genetic and gene-environment interactions that predispose to NTDs. They showed that prenatal folic acid (FA) supplementation could prevent NTD in the Crooked tail (Cd) mouse strain in a manner that closely paralleled human clinical experience. They identified the Cd gene defect in the Lrp6 co-receptor that is required for Wnt signaling, a pathway essential for early brain development. Illuminating a previously unrecognized interaction between FA supplementation and Wnt signaling, they showed that both low and high FA levels attenuate responses to Wnt. This was the first demonstration that FA supplementation could have harmful effects on neural tube closure, depending on individual genetic background. They are leading a multicenter clinical effort to discover complex genetic and epigenetic traits causing NTDs, using genome-wide, massively parallel sequencing to identify human polymorphisms and DNA and chromatin methylation marks associated with increased NTD risk.

**Role of cell cycle regulation in patterning brain — microcephaly.** The many genetic and environmental factors leading to microcephaly (small brain) together affect 2 percent of the population worldwide. Most of these disorders arise from failure of cell division to generate sufficient neurons and glia during embryonic and early postnatal development. Studies by the Ross lab in neurogenesis were the first to recognize that the cell cycle protein, G1-phase active cyclin D2 (cD2), has an important role in brain formation. Loss of cD2 leads to microcephaly with selective interneuron deficits in both cerebellum and forebrain. This is due to the differential use of cD2 and cyclin D1 (cD1) in precursors of the subventricular zone (SVZ) vs. the ventricular zone (VZ), respectively, of developing forebrain. These interneuron deficits lead to behavioral abnormalities and seizures due to inhibitory GABA deficits. Their research showed that cD2 expression is critical for intermediate progenitor proliferation in the mouse SVZ and that cD2 is the predominant cyclin expressed in the human fetal SVZ at 19 gestational weeks, suggesting particular importance of cD2 for human brain development.

**Cytoskeletal regulation in motile neurons required for migration and synaptogenesis — autism spectrum disorders and epilepsy.** Dr. Ross’ laboratory discovered the unexpected role of a gene associated with lissencephaly (smooth brain), Lis1, in signal transduction through small GTPases to the actin-based cytoskeleton of motile neurons. Lis1 participates in the dynein protein motor complex component of intracellular transport, and many consider Lis1 synonymous with dynein function. However, their studies indicate Lis1 is also required for signalling that modulates actin rich structures like growth cones and filopodia. They investigate the ability of Lis1 to regulate plasticity of neural networks relevant to autism and epilepsy. They also seek additional neuronal migration genes through investigation of patients with brain malformations and their families.

**SELECTED PUBLICATIONS**


Mark A. Rubin, MD
Homer T. Hirst, III, Professor of Oncology in Pathology
Professor of Pathology and Laboratory Medicine
Professor of Pathology in Urology

Dr. Mark Rubin has made significant contributions to the field of prostate cancer research in the area of genomics and biomarker development, including the publication of the first expression profiling study in prostate cancer and the identification of important prostate cancer biomarkers (e.g., AMACR, Hepsin, EZH2, PIM1, and JAGGED1). In 2005, the team made a landmark discovery with the identification and characterization of recurrent ETS rearrangements in prostate cancer involving TMPRSS2-ERG and TMPRSS2-ETV1. This paradigm-shifting work demonstrated that over 50 percent of prostate cancers harbor recurrent gene fusions involving an androgen driven promoter, TMPRSS2, and an ETS family member transcription factor, and invigorated a new line of research trying to establish a molecular classification of prostate cancer similar to AML. These fusions are virtually 100 percent prostate cancer specific and are being developed into diagnostic and prognostic clinical tests to supplement PSA testing.

Extending this genomic work to other types of mutations, Drs. Rubin and Levi Garraway (Broad Institute of MIT and Harvard) conducted a first-in-class study demonstrating novel mutations involving the PI3K/PTEN/AKT pathway through inactivating mutations of MAGI2, a PTEN scaffolding protein. The Rubin lab has also demonstrated recurrent functionally active mutations occurring in around 10 percent of ETS rearrangement negative prostate cancers. Dr. Rubin continues to develop novel approaches for genomic discovery. His group was one of the first to use laser capture microdissection, tissue microarrays, oligonucleotide arrays, and Next Generation Sequencing technology for translational research. He has also been at the cutting edge of helping develop computational approaches to analyze emerging data from expression profiling and oligonucleotide arrays and Next Generation Sequencing. His collaborative role in team science was recognized by the inaugural AACR Team Science Award in 2007 for the discovery and characterization of recurrent gene fusions in prostate cancer.

In further research, Dr. Rubin and his colleagues are investigating chromatin conformation changes in diseases such as cancer and how oncogenic transcription factors, which bind to thousands of sites across the genome, influence gene regulation by globally altering the topology of chromatin. Using unbiased high-resolution mapping of intra- and interchromosome interactions upon overexpression of ERG, an oncogenic transcription factor frequently overexpressed in prostate cancer as a result of a gene fusion, they demonstrated that oncogenic transcription factor overexpression is associated with global, reproducible, and functionally coherent changes in chromatin organization. These results have broader implications, as genomic alterations in other cancer types frequently give rise to aberrant transcription factor expression.

In other recent work, the Rubin lab sequenced the exomes of 112 prostate tumor and normal tissue pairs to determine if recurrent somatic base-pair substitutions are less contributory in prostate tumorigenesis. Identifying new recurrent mutations in multiple genes, with SPOP the most frequently mutated gene, the researchers determined that prostate cancers with mutant SPOP lacked ETS family gene rearrangements and showed a distinct pattern of genomic alterations, and therefore, may define a new molecular subtype of prostate cancer.
Timothy A. Ryan, PhD
Professor of Biochemistry

Dr. Timothy Ryan’s laboratory studies the molecular basis of how neurons in the brain communicate. Neurons make use of two main forms of communication: an electrical signal that carries information within a given cell and chemical communication that carries information from one cell to another at specialized junctions called synapses. Diseases of the brain, such as neurodegenerative disorders or psychiatric disorders, are all thought to be manifest at synapses and lead to changes in the ability of brain cells to efficiently communicate. In the last decade, neuroscientists have tracked down many genetic associations between these diseases and synaptic function. The challenge is to understand how synapses work at a molecular level to devise a scheme to repair synaptic lesions. Dr. Ryan’s lab devises new methodologies that allow them to study living synapses at work in great detail by labeling individual protein molecules that form part of the synaptic machinery with a fluorescent molecule. This enables them to see what the function of that molecule is in a synapse as it does its work, which is to communicate with another neuron.

The Ryan lab focuses on two key aspects of synaptic function. Chemical message synapses used to communicate are stored in specialized compartments called synaptic vesicles that reside within the synapse. Each synapse only contains ~100 of these synaptic vesicles. When an electrical stimulus travels down a neuron to the synapse, it triggers one of the synaptic vesicles to release its content into the tiny space between neurons. Electrical signals, however, often arrive at a furious pace, often as high as 50 times per second.

The Ryan lab is dissecting how the efficiency of the process that causes vesicles to release their content is controlled. The lab recently discovered that a protein known to play an important role in pain sensitivity and the target of one of the most widely prescribed medications for neuropathic pain, Neurontin, is critical in controlling how many calcium channels are at synapses. Electrical signals, when they arrive at the nerve terminal, open a gate that allows calcium to flow into the synapse through calcium channels. This entry of calcium is the “trigger” that causes the chemical message to be sent. Dr. Ryan’s lab discovered that a protein called “alpha2delta” controls how many of these gates are present at synapses. This suggests that a mechanism by which Neurontin functions to limit pain is reducing the number of these gates. In another study they showed that in a certain type of dopamine neuron, a protein named calbindin controls how much calcium is available to trigger the sending of the message once calcium flows in. Dopamine, one type of chemical message that neurons can send, is especially important in controlling many behaviors.

Once a vesicle releases its chemical message, the entire vesicle must be remade locally and refilled with message. This process of vesicle recycling is of particular interest to Dr. Ryan’s lab. Studies have uncovered how this process is controlled and what gene products are critical. A certain portion of these vesicles are always held in reserve and did not seem to normally participate in the process of delivering the chemical message. Recently the lab showed that the reserve vesicles are held in check by a particular enzyme called CDK5. Blocking this enzyme allows synapses to make use of the full complement of synaptic vesicles. Through these approaches, Dr. Ryan and his research team hope to eventually be able to write repair manuals for synapses that don’t work properly.
Dr. Bruce Schackman is Chief of the Division of Health Policy in the Department of Public Health at Weill Cornell. His research includes cost and cost-effectiveness analyses conducted alongside clinical trials and cohort studies; simulation modeling of comparative effectiveness and cost-effectiveness outcomes; and implementation science. His current projects focus on economic evaluations of screening, prevention, and treatment for HIV and hepatitis C, and the cost-effectiveness and comparative effectiveness of opioid dependence treatment as it affects quality of life.

Dr. Schackman has an ongoing collaboration with the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) modeling group based at Massachusetts General Hospital in Boston. Working with this group, he has co-authored studies of the lifetime cost of HIV care in the United States, the cost-effectiveness of earlier treatment and expanded HIV screening, and the economic value of pharmacogenomics testing for HIV care. Results of these studies have been widely cited, including in the President’s National HIV/AIDS Strategy for the United States.

Dr. Schackman also collaborates with clinical trial teams as a member of the NIH-supported AIDS Clinical Trials Group and the National Institute on Drug Abuse Clinical Trials Network (CTN). With funding from the National Institute on Drug Abuse (NIDA) he recently led an economic sub-study of a CTN trial of on-site rapid HIV testing in drug treatment programs. Using cost and outcomes results from the CTN trial and the CEPAC model, he found that on-site rapid HIV testing met commonly accepted cost-effectiveness thresholds. His team also produced an HIV testing budgeting tool for drug abuse treatment programs and collaborated in describing implementation challenges. He is now using trial results and simulation modeling to evaluate the cost and cost-effectiveness of on-site rapid hepatitis C testing in drug treatment programs, in combination with rapid HIV testing and on its own.

In a recent study funded in part by the Robert Wood Johnson Foundation, Dr. Schackman and his colleagues found that treating opioid dependence with long-term outpatient buprenorphine-naloxone in primary care settings may be cost-effective, but that results are highly dependent on quality of life on and off treatment for which data are limited. To address this evidence gap, he has recently been funded by NIDA to develop with colleagues a set of “off the shelf” quality-of-life weights that can be used in future economic evaluations of new pharmacologic interventions to treat the growing problem of opioid dependence, particularly dependence resulting from misuse of prescription opioid drugs. Dr. Schackman and Ann B. Beeder, MD, Associate Professor of Public Health and Psychiatry, have begun a new collaborative research and training initiative called the Program in Addiction Treatment Effectiveness and Economics.

Dr. Schackman has a longstanding collaboration with the investigators at the Groupe Haitien d’Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) in Haiti and the Weill Cornell Center for Global Health, and he is actively involved in research training programs in support of Haiti’s national scale-up of HIV treatment. In conjunction with a GHESKIO randomized trial of earlier HIV treatment that led to the World Health Organization revising their HIV treatment guidelines, Dr. Schackman and colleagues found that earlier initiation of treatment is indeed cost-effective if toxicity monitoring tests that have low value in resource-limited settings are eliminated.
Nicholas D. Schiff, MD  
Professor of Neurology and Neuroscience  
Professor of Public Health

Dr. Nicholas Schiff directs an integrative translational research program with a primary focus on understanding the process of recovery of consciousness following brain injuries. This research program links basic systems and clinical neuroscience with the goal of developing novel neurophysiologic and neuroimaging diagnostics applied to human subjects and therapeutic strategies. Dr. Schiff and his research group have contributed several landmark advances, including the first demonstrations of brain structural alterations occurring in the setting of very late recovery from severe brain injury.

More recently, Dr. Schiff and his colleagues have taken insights into the neurophysiological mechanisms of arousal regulation and of deep brain electrical stimulation techniques to demonstrate evidence that long-lasting, severe cognitive disability may be influenced by electrical stimulation of the human central thalamus. Dr. Schiff received the 2007 Research Award for Innovation in Neuroscience from the Society for Neuroscience for this research. This work provides an important foundation for developing further understanding of both the mechanisms of recovery of consciousness and basic mechanisms underlying consciousness in the human brain.

Dr. Schiff and his colleagues demonstrated that long-lasting, severe cognitive disability may be influenced by electrical stimulation of the human central thalamus.

Dr. Schiff’s research involves close collaboration with investigators at the Citigroup Biomedical Imaging Center and with long-standing colleagues Drs. Keith Purpura and Jonathan Victor in the Systems Neuroscience group. In collaborative studies with Dr. Purpura, animal models of central thalamic deep brain stimulation are providing fundamental understanding of the circuit mechanisms underlying this novel therapeutic method and insight into the thalamocortical mechanisms underlying arousal regulation and conscious behavior. In collaboration with Dr. Victor, methods of advanced signal processing are being developed and applied to the study of human brain electrical signals obtained from normal subjects and patients recovering from severe brain injuries.

The clinical and scientific program is paralleled by collaborative studies directed by Dr. Joseph Fins in the Departments of Public Health, Medicine, and Psychiatry. Dr. Fins’ studies are aimed at the ethical and policy dimensions of this research field, which has a unique and strong impact on medical practice. Dr. Schiff and Dr. Fins co-direct the CASBI (Consortium for the Advanced Study of Brain Injury) program.

Dr. Schiff’s research program has a strong international reach through his leadership of a large consortium grant from the James S. McDonnell Foundation, which links his research team with groups at Cambridge University, University of Liege, Belgium, Harvard University, and Hebrew University, Israel. This international collective is focused on developing a large database to assess the specificity and sensitivity of novel diagnostic methods and to deepen clinical-pathologic correlations underlying recovery from severe brain injuries.
SELECTED PUBLICATIONS

Dirk Schnappinger, PhD
Associate Professor of Microbiology and Immunology

The number of new tuberculosis cases is still rising and reached almost 10 million in 2010. The extraordinary impact of this infectious disease on public health is in part due to drug-resistant strains of Mycobacterium tuberculosis, which in some cases have acquired resistance to four or more drugs. These extensively drug-resistant strains continue to emerge and spread. Success rates for treating drug-resistant tuberculosis are generally low and mortality can reach 100 percent for outbreaks in patients co-infected with HIV. New drugs are thus needed to limit the impact of tuberculosis on global health.

Significant progress has recently been made in the identification and characterization of new small molecule compounds that can kill M. tuberculosis. However, the attrition rate in drug discovery is high and it is unlikely that the number of current lead compounds is sufficient to solve the global health problems caused by tuberculosis. The paucity of validated targets and new lead compounds are therefore significant bottlenecks in the search for new drugs against tuberculosis.

Dr. Dirk Schnappinger and his colleagues have developed genetic approaches for the conditional inactivation of M. tuberculosis genes.

Dr. Dirk Schnappinger and his colleagues have developed genetic approaches for the conditional inactivation of M. tuberculosis genes. In one of these approaches, the native promoter of a gene of interest is replaced with a synthetic “tet promoter” that contains binding sites for a tetracycline repressor, TetR. TetRs are bacterial transcription factors that can prevent binding of RNA polymerase and silence a promoter.

By codon variation and site directed mutagenesis, they adapted two forms of TetR for use in mycobacteria, which can silence tet promoters either in the presence or absence of a tetracycline. These two types of TetRs allow the construction of mutants in which a single mycobacterial gene is specifically silenced by the addition (TetOFF) or removal (TetON) of a tetracycline. More recently, they also developed a complementary approach in which tetracycline-inducible proteolytic degradation is employed to conditionally inactivate a target protein.

As tetracyclines can penetrate eukaryotic cells and tissue, as well as bacterial cells, either of these approaches can be used to inactivate an M. tuberculosis gene or gene product not only in vitro but also during mouse infections. In ongoing work, the researchers are applying these new genetic approaches to further elucidate how M. tuberculosis adapts to the hostile and changing environments it encounters during an infection, to rank potential drug targets according to their suitability for the development of new drugs, to study the mechanism of action of new drug candidate molecules, and to characterize essential genes of unknown function.
Heidi Stuhlmann, PhD
Harvey Klein Professor of Biomedical Sciences
Professor of Cell and Developmental Biology
Professor of Cell and Developmental Biology in Pediatrics

Development of a functional circulatory system in the vertebrate embryo is crucial for delivery of nutrients and oxygen to the embryo. Defects in the development of blood vessels result in death before birth or in congenital cardiovascular abnormalities. Vascular development involves two basic processes: vasculogenesis and angiogenesis. In vasculogenesis, blood vessels form de novo from endothelial progenitors. In angiogenesis, new blood vessels form from preexisting ones by proliferation and sprouting, differentiation, migration, extracellular matrix formation, and pericyte recruitment. Central to these processes are the endothelial cells that form a continuous layer lining the blood vessels.

In the adult, endothelial cells become quiescent but can respond to angiogenic signals to form new vessels. During physiological angiogenesis in the adult organism, such as wound healing and during pregnancy, endothelial cells are stimulated to form new vessels, a process termed neo-angiogenesis. Similarly, during pathological processes such as ischemia, myocardial infarct, repair of injured tissue, and tumor growth, endothelial cells become activated to sprout, migrate, and undergo remodeling. Thus, endothelial cells constitute a dynamic system that changes in response to environmental stimuli. Research in Dr. Heidi Stuhlmann’s laboratory focuses on understanding the molecular mechanisms that orchestrate these processes, using the mouse as a model system.

In a genetic screen for early developmental genes, Dr. Stuhlmann and her colleagues identified two novel genes that play important roles in vascular development and homeostasis. One of these, vascular endothelial zinc finger 1 (VEZF1), encodes an endothelial transcription factor that plays essential, dosage-dependent roles in vascular system development. Unexpectedly, they found that heterozygous embryos display lymphatic vessel abnormalities that are reminiscent of the human congenital malformation syndrome, nuchal edema. They are collaborating with Maternal-Fetal Medicine to investigate if human fetuses with nuchal edemas carry mutations in the VEZF1 gene, or show dysregulation of VEZF1 expression. Another exciting finding is that VEZF1 is involved in the epigenetic regulation of gene expression through the DNA methyltransferase DNMT3b.

A second gene identified in their screen, EGF-like domain 7 (EGFL7), is an early embryonic marker for endothelial cells and their progenitors. EGFL7 is a unique angiogenic factor: It is secreted specifically by endothelial cells, acts as a chemoattractant, and binds to the extracellular matrix. Importantly, Dr. Stuhlmann’s lab showed that EGFL7 interacts with and antagonizes endothelial Notch, a key vascular signaling pathway component. Ongoing studies indicate that EGFL7 expression is induced by hypoxia and vascular endothelial growth factor, VEGF, and that it plays an important role in physiological angiogenesis during pregnancy, in the bone marrow vascular niche, and in pathological angiogenesis in response to hypoxia and vascular injury. In collaboration with Dr. Robin Davisson’s group they are also investigating its role during placental development and placentopathies such as preeclampsia, a pregnancy-specific disease that is defined by sudden onset of hypertension and proteinuria in the last trimester.

SELECTED PUBLICATIONS


SELECTED PUBLICATIONS


Tao Sun, PhD

*Associate Professor of Cell and Developmental Biology*

The human brain is organized into distinct functional regions controlling complex behaviors. Accurate structural formation and precise function of the central nervous system rely on the production of multipotent and self-renewing neural stem cells (or progenitors) and the interconnection of specific cell types derived from them during development. Gene mutations and environmental factors can alter gene regulation during the development of the central nervous system and result in neurological disorders.

The research in Dr. Tao Sun’s laboratory seeks to reveal gene regulation mechanisms in normal and disease conditions. The goals are to address three broad and essential questions:

- What is the genetic regulation of brain asymmetry and handedness?
- How do neural stem cells self-renew and then differentiate into distinct cell types to establish complex brain anatomy and function?
- What are the molecular mechanisms regulating normal neural development and under human neurological disease conditions?

In Dr. Sun’s lab, researchers are using mouse genetic tools, mouse behavioral tests, neural stem cell cultures, and various molecular and cell biology approaches. They are investigating how gene alterations and mutations at developmental stages can affect behaviors in the adult using mouse models; how coding genes and non-coding RNAs such as microRNAs control neural development; and how they may be associated with neurological disorders.

The Sun lab has investigated microRNA functions in the developing central nervous system and found that microRNAs are important to control brain size.

Using a genetic screening approach, the lab has identified asymmetrically expressed genes in human fetal brains. Dr. Sun and his research team are now examining their functions in brain asymmetry and functional laterality using mouse models. The Sun lab has investigated microRNA functions in the developing central nervous system and found that microRNAs are important to control brain size. Ablation of microRNA function in developing brains can cause neurodegeneration defects. They have identified a group of microRNAs that play a role in promoting proliferation of neural stem cells in embryonic and adult brains. They have also discovered that a microRNA miR-9 is essential for motor neuron development in the spinal cord and axonal projections to target muscles.

Dr. Sun’s research has revealed a novel mechanism of gene regulation that is mediated by non-coding RNAs in neural development. Because of the technical advance of microRNA in vitro synthesis and delivery, microRNAs have become a promising means for gene therapies. Thus, the research of Dr. Sun’s lab of revealing functions of microRNAs in brain development and in motor neuron specification may provide new methods of stem cell based therapies for neurodegeneration diseases and spinal cord injuries.
Manikkam Suthanthiran, MB, BS
Stanton Griffis Distinguished Professor of Medicine
Professor of Medicine in Surgery and Professor of Biochemistry

The Founding Chairman of the Department of Transplantation Medicine and Chief of Nephrology and Hypertension at NewYork-Presbyterian/Weill Cornell, Dr. Manikkam Suthanthiran pursues research in transplantation immunology and molecular biology to improve outcomes following organ transplantation.

**Molecular Medicine.** Dr. Suthanthiran’s laboratory has pioneered the development of noninvasive gene-based assays to ascertain kidney transplant status, which had previously required an invasive kidney biopsy procedure. The original study, first conducted at Weill Cornell, led to an NIH-sponsored multicenter Cooperative Clinical Trial in Transplantation comprised of 500 subjects from major transplant centers in the United States. Results of the molecular studies of transplant recipients were presented at the plenary sessions of the 2011 American Transplant Congress Annual Meeting and the 2011 International Transplantation Society Meeting. Based on the bench-to-bedside approach, this study has led to state-of-the-art, individualized care (personalized medicine) of kidney transplant recipients. Recently, Dr. Suthanthiran and his research team have determined the expression profiles of small RNAs are considered as master regulators of immunity in kidney transplants.

**Human Pancreatic Islet Cell Transplantation.** The first successful human islet cell transplantation in the tri-state area for the treatment of Type 1 diabetes mellitus was carried out at Weill Cornell by an interdisciplinary team led by Dr. Suthanthiran. His laboratory established a human islet cell isolation facility and successfully transplanted Type 1 diabetic recipients. In a bedside-to-bench approach, the laboratory has developed approaches to meet the twin challenges of limited islet supply and their tendency toward early loss of function and successful transplantation without any immunosuppressive drugs.

**Transplantation without Immunosuppressive Therapy.** The ultimate goal in organ transplantation is transplant tolerance, that is, transplantation of organs without any drug therapy. Dr. Suthanthiran’s laboratory contributed to the first ever report on tolerance of mismatched kidney transplants, which was published in the *New England Journal of Medicine*. The ability to transplant a human organ without drug therapy is of exceptional significance. In recognition of their contribution, NewYork-Presbyterian/Weill Cornell was selected by the Immune Tolerance Network, NIH, to conduct the innovative transplant tolerance trials. Recently, Dr. Suthanthiran and his colleagues identified a molecular signature in the urine of patients who are tolerant of kidney transplants. Their research findings were published in 2010 in a premier journal, *The Journal of Clinical Investigation*.

**Personalized Medicine.** In 2009, Dr. Suthanthiran and his team initiated the first ever study of immunosuppressive drug, tacrolimus, under the guidance of urinary cell gene expression patterns. This NIH-sponsored molecular monitoring study was also recognized by the awarding of the NIH MERIT Award in 2009 to Dr. Suthanthiran.

**Outstanding Clinical Outcomes.** The advances made in the laboratory have been translated to make organ transplants safer, offer personalized therapy, and move from a reactive treatment strategy to a preventive and predictive approach. This is reflected in part by kidney transplant patient and graft survival rates at Weill Cornell being significantly higher than expected survival rates.

**SELECTED PUBLICATIONS**


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Jonathan D. Victor, MD, PhD
Fred Plum Professor of Neurology
Professor of Neurology and Neuroscience

Dr. Jonathan Victor’s research combines mathematical, computational, and experimental approaches to address fundamental problems in basic and clinical systems neuroscience. His laboratory’s basic research focuses on the design principles of sensory processing, both in the sensory periphery and in the brain, and how these design principles are implemented in neural circuits. Using the visual system as a model, the research seeks to determine the aspects of sensory information that are represented in the brain, the features of the activity of individual neurons and neural populations that support these representations, and realistic models for how these representations are transformed. Experimental approaches include psychophysical studies in man and multineuronal recordings in the primate brain.

The psychophysical studies have delineated a specific set of computations that characterize the statistics of the sensory input, and have shown that these computations are closely matched to the informative aspects of our visual environment. The neurophysiological studies have shown that these computations take place in primary visual cortex, arising from feedback interactions between cortical layers and dynamic reconfiguration of local networks by the incoming visual stimulus.

Basic research in Dr. Victor’s laboratory focuses on the design principles of sensory processing, both in the sensory periphery and in the brain, and how they are implemented in neural circuits.

Neurophysiological and psychophysical studies are complemented by theoretical work. One aspect of this work is the development of mathematical techniques to bridge the gap between traditional systems-identification methods (such as the “white noise” approach), and methods based on ethologically relevant stimuli, such as natural scenes. A second aspect is the development of strategies to analyze neural coding by individual neurons and neural populations, with a particular focus on information-theoretic tools. Dr. Victor is applying these techniques to the visual system and, in collaboration with Dr. Patricia Di Lorenzo of SUNY Binghamton, to the gustatory system.

Clinically oriented work is directed at understanding thalamocortical dynamics, and the role that alterations in these dynamics may play in the pathogenesis and/or symptomatology of neurologic diseases, including epilepsy and chronic brain injury. In collaboration with Dr. Nicholas Schiff and colleagues at Weill Cornell, Dr. Victor’s laboratory is analyzing EEG, functional imaging, and anatomical imaging in brain injury patients to probe these dynamics and their relationship to spontaneous and induced fluctuations in cognitive ability and behavior. A central aspect of the work is the development of mathematical models of thalamocortical interactions. These modeling studies support the notion that thalamic interactions may control cortical functional connectivity, and also inspire novel approaches to the analysis of the EEG. It is anticipated that both the investigational methods developed and the insights gained will generalize to other conditions, such as autism and Alzheimer’s disease, in which rapid fluctuations in level of function are a prominent feature.
Yi Wang, PhD
Faculty Distinguished Professor in Radiology
Professor of Biomedical Engineering

Dr. Yi Wang’s research interest is to develop magnetic resonance imaging (MRI) methods using mathematics, physics, electronic engineering, and computer science tools, and to work with clinicians and scientists to apply these developed imaging methods to improve basic scientific understanding, diagnose disease more accurately, and treat patients better.

Recently, Dr. Wang’s group has introduced a fundamentally new concept to MRI: quantitative susceptibility mapping (QSM) by inverting the magnetic field to define the local magnetization source for tissue characterization. So far, MRI practice primarily utilizes information from magnitude images and mostly discards phase images. Phase image allows detection of the local magnetic field. The inversion from magnetic field to magnetization source (tissue magnetic susceptibility in MRI) would generate a new contrast mechanism that may be a valuable addition to the traditional contrast mechanisms. Dr. Wang and his colleagues have developed effective conditioning and regularization approaches for an accurate and robust solution to this inverse problem. This novel QSM magnetic source MRI approach may for the first time provide an accurate and practical solution to the fundamental problem of contrast agent quantification in molecular MRI and contrast enhanced MRI, as well as quantification of endogenous contrast agents, including iron and calcium depositions and deoxyhemoglobin that are fundamental for investigating organ functions.

Dr. Wang is working with neurological clinicians to develop research projects on clinical applications of QSM. Potential clinical applications include mapping iron deposition in neurodegenerative diseases, including Parkinson’s and Alzheimer’s diseases, evaluating and measuring blood products in cerebral microhemorrhage and hemorrhagic stroke, evaluating hypoxia in ischemic stroke and tumor, and investigating myelin of unique negative susceptibility. Dr. Wang will work with neuroscientists, neurologists, and neuroradiologists to develop and apply QSM techniques.

Dr. Wang is also interested in working with scientists and clinicians to investigate other important QSM applications, including:

**Mapping bone mineralization in vivo.** While traditional water-based tissue contrasts in MRI cannot detect calcium, QSM allows mapping of calcium components due to their unique negative magnetic susceptibilities and may enable a powerful in vivo assessment of bone vulnerability.

**Mapping iron depositions in liver and heart.** While MRI is very sensitive to iron depositions, absolute iron quantification has not been possible so far. QSM can overcome this problem, enabling absolute iron quantification for accurate diagnosis and effective treatment of diseases involving iron overloading.

**Quantification of contrast agents in routine contrast enhanced MRI and in molecular MRI.** Currently, in vivo estimation of gadolinium concentration [Gd] in contrast-enhanced MRI is based on the assumption that [Gd] is linearly proportional to MRI intensity, which breaks down when [Gd] is high, such as in tumor imaging. This results in poor specificity in cancer diagnosis. QSM can overcome these limitations in contrast-enhanced MRI, which is promising for resolving pseudoresponse and pseudoprogression in cancer MRI.

**SELECTED PUBLICATIONS**


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Harel Weinstein, MSc, DSc
Chairman, Department of Physiology and Biophysics
Maxwell M. Upson Professor of Physiology and Biophysics

Dr. Harel Weinstein’s laboratory is devoted to studies of complex molecular systems in the cell, and of their function in mechanisms of cell-to-cell communication in physiological systems under normal conditions and in disease. The studies aim to gain quantitative insight into the gene and protein structure of molecular machines that carry out processes of a cell’s life and communication, such as receptors and transporters, the minute but powerful molecular machines responsible for neuronal signaling, and the regulation/deregulation of cell growth. Their malfunction or misdirection underlies a wide spectrum of disease, from neurological dysfunctions to drug abuse, and from cancer to diabetes. The studies in the Weinstein lab aim to uncover how disease sets in, how it evolves, and how to design therapies.

The lab’s work on receptors for the neurotransmitters serotonin and dopamine, and the proteins that transport them, illustrates how such studies have pioneered a quantitative understanding of molecular processes in key aspects of neurotransmission and cell signaling. Documented in the scientific literature over the last two years, these studies employed the strategy established in Dr. Weinstein’s lab of combining computational and experimental methodologies. The quantitative models used in the computational studies are based on mathematical modeling, molecular biophysics, and bioinformatics and engineering approaches in systems biology. Information and data are obtained from collaborative experiments in laboratories studying molecular structure and dynamics, and cell and organ physiology.

Combining these advanced tools, Dr. Weinstein’s lab was able to track for the first time how, and why, the transporter molecules change their shape to enable various substances to travel across the cell membrane and regulate transmission of the brain’s messages, and the manner in which drugs such as antidepressants, modify these actions. This was done with computational simulations using rules based on fundamental laws of physics, in computational “what if” studies able to interpret the observations from experiments in the lab, as well as from patients, at unprecedented atomic detail to produce structure-based information about mechanisms. These studies enabled the first detailed description of the molecular sites of action of antidepressant drugs, which are the transporters that normally remove neurotransmitters from the synapse.

The research led Dr. Weinstein and his collaborators to recognize for the first time in the computer simulations the manner in which the movements of the transporter proteins determine the binding and permeation of the transported molecule in the normal state of neuronal transmission. The new findings help explain not only how known antidepressant medications, such as Prozac and Zoloft (the selective serotonin reuptake inhibitors – SSRIs), produce their effects, but also highlight the way in which stimulants like cocaine and amphetamine act in altering the normal exchange process between cells in a variety of excited states. The new level of understanding of the key molecular mechanisms in neuronal signaling in the brain should also prove useful in the development of more targeted medication therapies for anxiety, depression, schizophrenia, and substance abuse.
Pengbo Zhou, PhD
Professor of Pathology and Laboratory Medicine

The focus of Dr. Pengbo Zhou’s laboratory is to understand the molecular mechanisms by which ubiquitin-dependent proteolysis operates under physiological and pathological conditions. Using a combination of biochemical, cell, and molecular biological and mouse genetic approaches, Dr. Zhou has carried out studies in many aspects of biology and regulation of the cullin ubiquitin ligases, including:

• initial discovery of the auto-ubiquitination mechanism by which cullin 1 (Cul1) dynamically assembles with distinct substrate receptors for targeting a wide range of substrates

• engineering of Cul1-based ubiquitin ligase for the development of the “protein knockout” technology that directs destruction of cellular proteins at will

• discovery of the cullin 4a (Cul4a) ubiquitin ligase in governing DNA repair/DNA damage checkpoint response and genomic integrity, normal and malignant hematopoiesis, spermatogenesis, and tumorigenesis

Aberrantly high levels of Cul4a were detected in a wide spectrum of tumor types, including breast cancer, liver cancer, squamous cell carcinomas, medulloblastomas, and methotheliomas. However, the role of Cul4a in tumor development has remained largely elusive. During the past 11 years, Dr. Zhou’s lab has focused its efforts on interrogating the physiological and pathological functions of the Cul4a ubiquitin ligase. The hope is that by understanding the mechanistic basis underlying Cul4a-dependent protein ubiquitination and destruction, they will determine how misregulation of these pathways contributes to tumorigenesis and harness this knowledge to design effective therapeutic strategies.

Dr. Zhou’s lab group is one of the first groups to initiate studies on Cul4a. Their initial investigations led to the discovery of Cul4a binding to DDB1 and DDB2, and the identification of DDB2, as well as the HOX homeodomain transcription factors as the first substrates of Cul4a-mediated ubiquitination. The lab generated conditional Cul4a knockout mice and revealed that Cul4a concurrently suppresses nucleotide excision repair and the DNA damage checkpoint pathways. Strikingly, the skin-specific Cul4a knockout mice are hyper-resistant to UV-induced skin carcinogenesis. Recently, the lab also generated the conditional Cul4b knockout mice and revealed an essential role of this second Cul4 family member in extraembryonic tissue development during mouse embryogenesis. Dr. Zhou’s lab also initiated collaborative studies that revealed the X-ray co-crystal structure of the Cul4a-DDB1 E3 ligase complex, generated conditional DDB1 knockout mice, and identified a novel function of the tumor suppressor Merlin in antagonizing tumorigenesis. It is noteworthy that Dr. Zhou’s recent NIH R01 grant application on delineating the tumorigenic role of Cul4a ubiquitin ligase received a priority score of 1 percent, the highest score that an NIH study section gives to exceptional applications.

Another direction of Dr. Zhou’s investigation involves further development and optimization of the protein knockout technology. To achieve maximal and rapid removal of target proteins, Dr. Zhou’s lab recently integrated the RNAi technology into the protein knockout system to simultaneously block synthesis and accelerate degradation of target proteins. These studies demonstrated dramatically improved efficacy of the kinetics in depleting stable cellular proteins, therefore significantly improved the ability to dissect cellular protein functions. This double knockdown system is a novel method that is particularly relevant for proteins that are not responsive to RNAi-mediated knockdown and for analyses that require the most rapid and thorough target protein ablation possible.
Recognizing the need to provide its faculty with the tools to conduct state-of-the-art research, Weill Cornell Medical College has developed 20 core facilities— from biomedical imaging to X-ray crystallography—all managed by scientific experts. They provide centralized access to equipment used by faculty in all departments, help to reduce duplication of resources, and allow the Medical College to remain at the forefront of biomedical research. Following are a few examples of the Medical College’s core facilities.

**Belfer Gene Therapy Core Facility**

The Belfer Gene Therapy Core Facility, a fully equipped core facility devoted exclusively to developing and assessing gene transfer vectors, provides the infrastructure to carry out basic, translational, and clinical research utilizing gene transfer. The Vector Core functions as a resource to investigators to provide centralized expert services and training in the design, creation, and production of gene transfer vectors, and to provide a characterized repository of gene transfer vectors and related reagents for use by investigators. The primary resource of the Vector Core is the expertise to efficiently design, construct, and produce gene transfer vectors, including adenovirus (Ad), adeno-associated virus (AAV), lentivirus, retrovirus vectors, as well as non-viral or plasmid vectors. Its analytical resources include quantitative PCR, 2 HPLCs, plate readers, a luminometer, a flow cytometer, automated liquid handling devices, equipment for rodent behavior analysis, and a database of the available vectors and plasmids that includes extensive sequence and restriction mapping data. The Good Manufacturing Practice Core facility occupies approximately 2,400 square feet devoted exclusively to production of gene transfer vectors and gene modified cells for human therapeutic trials.

**Citigroup Biomedical Imaging Center**

The Citigroup Biomedical Imaging Center at Weill Cornell Medical College is a state-of-the-art 15,000-square-foot research facility dedicated to the development of cutting-edge imaging technologies applied to a wide range of human diseases. Major equipment includes two 3.0 Tesla magnetic resonance imaging and spectroscopy systems, combined positron emission tomography/computed tomography, as well as comprehensive pre-clinical imaging instrumentation, including a 7.0 Tesla magnetic resonance imaging system and a newly installed combined positron emission tomography/computed tomography system. Fluorescence and luminescence imaging are also available. The Center also houses a 19 MeV dual beam cyclotron and complete radiochemistry facilities for the production of radiotracers.

The Citigroup Biomedical Imaging Center is staffed with physicists, radiochemists, engineers, technologists, and administrative personnel devoted to the development of novel imaging techniques that are available to investigators from across the University, as well as institutional partners including Memorial Sloan-Kettering Cancer Center, The Rockefeller University, Hospital for Special Surgery, and Hunter College.

**Computational Genomics Core Facility**

The Computational Genomics Core Facility provides access to state-of-the-art desktop bioinformatics software and computational tools for the analysis and management of gene expression data. The facility also offers consulting services in various areas of bioinformatics and computational biology and facilitates access to the larger infrastructure of the Institute for Computational Biomedicine.
Services provided by the Computational Genomics Core Facility include:

**Analysis of gene expression data.** The core provides users with commercial gene expression analysis programs and general data mining and statistical tools.

**Storage and organization of expression data.** The core provides and maintains GeNet, a web-based microarray data repository that facilitates sharing of microarray data. GeNet is seamlessly integrated with GeneSpring and helps individual labs store, archive, and search microarray data.

**Discovery through bioinformatics.** Gene expression profiles often highlight genes of unknown function. The core offers popular bioinformatics desktop tools, such as Vector NTI, Lasergene, Sequencher, Artemis, and ClustalX, to support a variety of sequence analysis tasks.

**Resources for advanced projects, collaboration, and training.** The Institute for Computational Biomedicine broadens the capabilities of the Computational Genomics Core Facility by offering an advanced bioinformatics infrastructure, expertise in bioinformatics, and computational biology methods and tools.

**Nuclear Magnetic Resonance**

The NMR core provides access to NMR instrumentation for the investigation of biological molecules. The facility consists of Varian 600 MHz and Bruker 500 MHz NMR spectrometers equipped for multidimensional heteronuclear NMR experiments. The 500 MHz NMR is primarily used for basic 1D and 2D NMR applications employed for characterization of synthetic products, chemical analysis, and determination of ligand binding. The 600 MHz NMR is utilized for solution studies of protein structure and motional dynamics. The core facility provides project consultation, training in NMR operation, and assistance in setting up NMR experiments.

Faculty associated with the core have expertise in protein NMR applications aimed at investigating biologically relevant proteins with disordered structure. There is a growing recognition that unfolded states of proteins play significant roles in important life processes and pathologies associated with protein folding, binding, signaling, and amyloid diseases. NMR spectroscopy is uniquely suited to examine changes in the conformation, structure, and mobility of proteins in solution using conditions closely approximating the biological environment.

**Epigenomics Facility**

The Epigenomics Facility of the Cornell University Life Sciences Core Laboratories Center and Weill Cornell Medical College provides an array of epigenomics research resources and services to the university community and to outside investigators. This inter-campus facility, with resources and services located at both Cornell University and Weill Cornell Medical College, offers DNA methylation sequencing and microarrays using novel methods developed by the core, protein-nucleic acid association (ChIP-Seq) analysis, RNA-seq, exon capture sequencing, and Sequenom Epityping. The core also provides complete data analysis services, including primary and secondary data interpretation, and hosts several data visualization tools for customers to view and compare and contrast their data with local and public datasets. The goal of the Epigenomics Facility is to meet the increasing need of investigators for rapid and accurate epigenomics project design, sample preparation, data generation, and data analysis of both targeted regions and genome-scale studies of DNA methylation, histone modification, and transcriptional programming.
The new Belfer Research Building will be environmentally friendly, energy efficient, and aesthetically pleasing, with a glass façade that reduces energy consumption and bathes interior areas with natural sunlight.

“Coupled with the brilliant scientists already on staff and with additional ones being recruited, the building is certain to house discoveries that will benefit my family, New Yorkers, and all mankind.”

— Robert A. Belfer

With the planned opening of the Belfer Research Building in 2014 and the 2010 opening of the Gertrude and Louis Feil Family Research Building, Weill Cornell Medical College has been developing an enviable research environment that will enable faculty to continue a rich history of scientific achievements.

The Gertrude and Louis Feil Family Research Building, which was made possible by a $30 million gift from the Louis Feil Charitable Lead Annuity Trust, is a seven-story state-of-the-art research facility that is home to Weill Cornell’s Division of Neurobiology and the Clinical and Translational Science Center. The Division occupies 70,000 square feet, providing optimal space for investigations into stroke, Alzheimer’s disease, and the factors that lead to both. Here some 40 scientists study similar topics but have varied areas of expertise. Communication among them is facilitated by the research building’s open design. A glass wall marks an inner perimeter, within which laboratories run almost the entire length of the building. In the lower level, the Clinical and Translational Science Center – a multi-institutional partnership that promotes translational research and multidisciplinary collaboration from bench to bedside and to the community – is also the hub of investigator-initiated clinical and translational research at Weill Cornell.

On November 9, 2011, Weill Cornell Medical College dedicated the Belfer Research Building, a pioneering facility that will double the amount of dedicated research space at Weill Cornell, allowing for the initial recruitment of 30 additional tenure-track faculty. A ceremony was held to recognize the generosity of the building’s many donors, including a $100 million gift from Renée and Robert Belfer, for whom the building is named.

When it opens in 2014, the 480,000-square-foot facility will rise 18 stories and have 13 floors of research laboratories targeting some of the most daunting health challenges, including cancer, cardiovascular disease, children’s health, neurodegenerative diseases, infectious diseases, and global health issues. The building will include such features as an indoor terrace, an airy two-story lobby, and an innovative double-paned glass curtain wall. The proximity of the new research building to the Weill Greenberg Center, the Medical College’s award-winning ambulatory care building, will further enhance communication between investigative researchers and practicing clinicians.

Designed by Ennead Architects, the Belfer Research Building has a unique open floor plan to maximize collaboration among the Medical College’s scientists and physician-scientists, and feature adaptable spaces that can accommodate changing priorities. Core facilities on each floor will provide centralized shared access to advanced technology, including high-throughput cell screening, genomics, and imaging technology, for use by faculty across all research areas. Space also will be dedicated to intercampus collaborations, offering a home for Ithaca-based researchers working with Weill Cornell scientists. In addition, an array of sophisticated lab equipment will be made available to partnering medical and academic institutions in the community.
Located on 69th Street between York and First Avenues, the Belfer Research Building will be diagonally situated across from the Weill Greenberg Center. With their similar design elements, the Belfer Research Building and the Weill Greenberg Center are thematically connected.
Weill Cornell Medical College research faculty are regularly cited for their professional achievements and elected as members to the nation’s preeminent scientific and biomedical organizations and professional societies. Among those so honored in 2011 and 2012 are:

**American Academy of Arts and Sciences**
- Fellow
  - Joseph J. Fins, MD, MACP
    - Chief, Division of Medical Ethics
  - E. William Davis, MD, Jr. Professor of Medical Ethics

**American Association for Cancer Research**
- Recipient, 2011 Prevent Cancer Foundation Award for Excellence in Cancer Prevention Research
  - Andrew J. Dannenberg, MD
  - Henry R. Erle, MD — Roberts Family Professor of Medicine

**American Association of Genitourinary Surgeons**
- Recipient, Barringer Medal
  - Peter N. Schlegel, MD
    - Chairman, Department of Urology
  - James J. Colt Professor of Urology

**American College of Cardiology**
- President
  - William A. Zogbhi, MD
    - Professor of Medicine

**American College of Physicians, New York Chapter**
- Recipient, Laureat Award
  - Joseph J. Fins, MD, MACP
    - Chief, Division of Medical Ethics
  - E. William Davis, MD, Jr. Professor of Medical Ethics

**American Heart Association**
- Champions of Heart & Stroke
  - O. Wayne Isom, MD
    - Chairman, Department of Cardiothoracic Surgery
    - Terry Allen Kramer Professor of Cardiothoracic Surgery
  - Richard C. Pasternak, MD
    - Clinical Professor of Medicine
  - Philip E. Stieg, PhD, MD
    - Chairman, Department of Neurological Surgery
    - Professor of Neurological Surgery

**American Hospital Association**
- Member, Board of Trustees, Health Research and Educational Trust, and Member, Committee on Research
  - Lawrence P. Casalino, MD, PhD
    - Chief, Division of Outcomes and Effectiveness Research
    - Livingston Farrand Associate Professor of Public Health

**American Urological Association**
- Recipient, Gold Cytoscope Award
  - Ashutosh K. Tewari, MD
    - Director, Lefrak Center for Robotic Surgery
    - Ronald P. Lynch Professor of Urologic Oncology
    - Professor of Urology and Public Health

**Association of Professors of Medicine**
- Recipient, Robert H. Williams, MD, Distinguished Professor Award
  - Andrew I. Schafer, MD
    - Chairman, Department of Medicine
    - E. Hugh Luckey Distinguished Professor of Medicine

**Biophysical Society**
- Recipient, Distinguished Service Award
  - Olaf S. Andersen, MD
    - Director, Tri-Institutional MD-PhD Program
    - Professor of Physiology and Biophysics

**HIV Congress**
- Recipient, Lifetime Achievement Award for Invaluable Contributions in the Field of HIV Medicine
  - Roy M. Gulick, MD
    - Chief, Division of Infectious Diseases
    - Professor of Medicine

**International Cytokine Society**
- Recipient, Honorary Lifetime Membership
  - Laurie H. Glimcher, MD
    - Stephen and Suzanne Weiss Dean, Weill Cornell Medical College
    - Professor of Medicine

**New York Academy of Medicine**
- Recipient, Academy Plaque for Exceptional Service
  - Anne Moore, MD
    - Medical Director, Weill Cornell Breast Center
    - Professor of Clinical Medicine

**New York Surgical Society**
- President
  - Fabrizio Michelassi, MD
    - Chairman, Department of Surgery
    - Lewis Atterbury Stimson Professor of Surgery

**Northeastern Group on Educational Affairs**
- Chair Elect
  - Carol F. Capello, PhD
    - Associate Director, Office of Curriculum and Educational Development
    - Associate Professor of Geriatric Education in Medicine

**Robert J. and Claire Pasarow Foundation**
- Recipient, 24th Annual Robert J. and Claire Pasarow Foundation Award
  - Antonio M. Gotto, Jr., MD, DPhil
    - Dean Emeritus and Co-Chairman, Board of Overseers, Weill Cornell Medical College

**U.S. Department of Health and Human Services**
- Senior Advisor, Office of the Assistant Secretary for Planning and Evaluation
  - William B. Borden, MD
    - Nanette Laitman Clinical Scholar in Public Health/Prevention — Women’s Health
    - Assistant Professor of Public Health
Their studies of neurons (left) and astrocytes are enabling Weill Cornell researchers to advance the understanding of brain development and further the potential of stem cell based therapies for neurodegenerative diseases. (Courtesy of Dr. Tao Sun)
Curtis L. Cole, MD
Andrew J. Collins, MD
Joseph P. Comunale, Jr., MD
Peter H. Connolly, MD
Joseph T. Cooke, MD
Amy E. Crane, MBA, MD
Carl V. Crawford, MD
Ronald G. Crystal, MD
Susanna Cunningham-Rundles, PhD

D
Darshana M. Dadhania, MD
Gregory F. Dakin, MD
Donald J. D’Amico, MD
Andrew J. Dannenberg, MD
Marilena D’Aurelio, PhD
Scott G. David, MD
Jessica G. Davis, MD
Owen K. Davis, MD
Robin L. Davisson, PhD
Ype de Jong, PhD, MD
Inmaculada de Melo-Martin, PhD
Ruba S. Deeb, PhD
Kir W. Deitsch, PhD
Tessa M.L. del Carmen, MD
Joseph J. Del Pizzo, MD
Christal G. Delagrammatikas, PhD
Anna-Maria Demetriades, BM, BCh, MA, PhD
Byron P. Demopoulos, MD
Maria T. DeSancho, MD, MSc
Richard B. Devereux, MD
Randi R. Diamond, MD
JoAnn Difede, PhD
Anna Di Gregorio, PhD
Annarita Di Lorenzo, PhD
Ruchuang Ding, BM, MS
Bisen Ding, MS, PhD
Hong Ding, PhD
Marc J. Dinkin, MD
Jennifer DiPace, MD
Leonard DiRe, MD
Jeremy Dittman, PhD, MD
Gary S. Dorfman, MD
Jennifer A. Downs, MD
Joan H. Drosopoulos, MS, PhD
Michele B. Drotman, MD
Lewis M. Drusin, MD, MPH
Yi-Chieh N. Du, PhD
Niels Dua, MS, MD
Marc J. Dubin, PhD, MD
Joachim W. DudenhAUSEN, MD
Jonathan P. Dyke, PhD

E
Soumitra R. Eachempati, MD
Matthew R. Ebben, PhD
Sabine Ehrt, PhD
Carolyn S. Eisen, MD
Brian Eiss, MD
Olivier Elemento, PhD
Rony T. Elias, MD
David Eliezer, PhD
Lora H. Ellenson, MD
Eric H. Elowitz, MD
Rebecca Elstrom, MD
Zuhal Ergonul, MD
Orli R. Etingin, MD
Todd R. Evans, PhD

F
Thomas J. Fahey III, MD
Erik S. Falck-Pedersen, PhD
Domenick J. Falcone, PhD
Giuseppe Faraco, MD, PhD
Brenna M. Farmer, MD
Dmitriy N. Feldman, MD
Eric J. Feldman, MD
Diane Felsen, PhD
Jose L. Fernandez, MD
Stephen J. Ferrando, MD
Edgar Figueroa, MD, MPH
Matthew E. Fink, MD
Madelon L. Finkel, PhD
Emily S. Finkelstein, MD
Joseph J. Fins, MD, MACP
Daniel W. Fitzgerald, MD
Peter Fleischut, MD
Neal E. Flomenbaum, MD
Conor P. Foley, PhD
Alyson N. Fox, MD
Maura D. Frank, MD
William W. Frayer, MD
Joel M. Friedman, DDS
Oren A. Friedman, MD
Gustavo F. Frindt, BSc, MD
Christine L. Frissora, MD
Kai-Ming G. Fu, MD, PhD
Hibiki K. Fujita, PhD
Michele Fuortes, MD, PhD
Richard R. Furman, MD

G
Christopher L.F. Gade, MD
James J. Gallagher, MD
Maya Gambarin-Gelwan, MD
Shanmugam Ganesan, MB, BS
Fran A. Ganz-Lord, MD
Dingcheng Gao, MS, PhD
Daniel Gardner, PhD
Kelly A. Garrett, MD
Francine E. Garrett-Bakelman, MD, PhD
Susan A. Gauthier, DO
Shari E. Gelber, MD
Joy M. Gelbman, MD
Mehmet R. Genc, MD, PhD
Fuqiang Geng, MM, PhD
Paul Gerardi, MD
Linda M. Gerber, PhD
Usama Gergis, MB, ChB
Hassan Ghomravi, PhD
Paraskevi Giannakakou, PhD
Patricia-Jane V. Giardina, MD
Sarah Giardina, PhD
Leonard N. Girardi, MD
Alicia E. Gittleman, MD
Michael J. Glass, PhD
Charles E. Glatt, MD, PhD
Marshall J. Glesby, MD, PhD
Laurie H. Glimcher, MD
Yves P. Gobin, MD
Benjamin S. Gold, MA, PhD
Dan E. Goldschlag, MD
Stanley J. Goldsmith, MD
Peter A. Goldstein, MD
Marc Goldstein, MD
Linnie M. Golightly, MD
Eva Gonzalez, MS, PhD
Gerry E. Goodrich, JD, MPH
John T. Gossey, MD, MS, MPH
Antonio M. Gotto, Jr., DPhil, MD
Bernice Grafstein, PhD
Richard D. Granstein, MD
Johannes Graumann, MS, PhD
Diego Gravotta, PhD
Jeffrey P. Greenfield, MD, PhD
Bruce M. Greenwald, MD
Kenneth W. Griffin, PhD
Elizabeth A. Grill, PsyD
Steven S. Gross, PhD
Amos Grunebaum, MD
Victor H. Guaiquil, MS, PhD
Brain imaging with positron emission tomography (PET) reveal normal cerebral metabolism during an awake state (left) versus low cerebral metabolism during a minimally conscious or vegetative state. (Courtesy of Dr. Nicholas D. Schiff)
Rachel Koshi, MB, BS, MS, PhD
Barry E. Kosofsky, MD, PhD
Paresh J. Kothari, MS, PhD
Arzu Kovankilikaya, MD
Ihhami Kovankilikaya, MD
Geri E. Kreitzer, PhD
Ana C. Krieger, MD, MPH
Karl H. Krieger, MD
Trine Krogh-Madsen, MSc, PhD
Ziad Kronfol, MD
Nicole Kucine, MD
William I. Kuhel, MD
Juhi Kumar, MD
Sonal Kumar, MD, MPH
David J. Kutler, MD
Charles O. Kwon, MD

L
Douglas R. Labar, PhD, MD
Mark S. Lachs, MD
Moncef Ladjimi, MSc, PhD
Yulia Landa, MS, PsyD
Harry M. Lander, PhD
Diane A. Lane, PhD
Joseph M. Lane, MD
Maureen E. Lane, PhD
Jennifer A. Langsdoft, MD
Richard I. Lappin, PhD, MD
Vassilios Latoussakis, MD
Norman A. Latov, MD, PhD
Jeffrey C. Laurence, MD
Francis S.Y. Lee, MD, PhD
Jennifer I. Lee, MD
Paul C. Lee, MD
Richard Lee, MBA, MD
Sang W. Lee, MD
Dana Leifer, MD
Gary J. Lelli, Jr., MD

M
Hongtao Ma, PhD
Xiaojing Ma, PhD
Yinghua Ma, PhD
Yuliang Ma, MS, PhD
Khaled Machaca, PhD
David C. Madoff, MD
Jordi Magrane, PhD
Ziyad Mahfoud, MS, PhD
Joel A. Malek, MS, PhD
Jaideep Malhotra, MD
Sameer Malhotra, MD
Charles Maltz, PhD, MD
Ravinder Mamtani, MB, BS, MD
Giovanni Manfredi, MD, PhD

Halinder S. Mangat, MB, BS
Samuel J. Mann, PhD
Aaron J. Marcus, MD
Patricia Marino, PhD
Tomer M. Mark, MD
Steven M. Markowitz, MD
Kristen M. Marks, MD
Peter Martin, MD
Johanna Martinez, MD
Christopher E. Mason, PhD
Bassem Masri, MD
Usha Mathur-Wagh, MB, BS, MPH
Frederick R. Maxfield, PhD
Sebastian A. Mayer, MD
Nayef Mazloum, PhD
Madhu Mazumdar, MS, MA, PhD
Kate E. McCann, MD
Patricia McDonald, DSW
Timothy E. McGraw, PhD
Ferenc Mechler, MSc, PhD
Carlos Medina, MD
Sonal S. Mehta, MD
Ari M. Melnick, MD
Andrew J. Meltzer, MD
Ellen C. Meltzer, MD, MSc
Kevin Mennitt, MD
Anant K. Menon, PhD
Sabiha Merchant, MB, BS
Samuel T. Merrick, MD
Nasrin Mesaeli, MSc, PhD
David B. Messinger, MD
Barnett S. Meyers, MD
Jason G. Mezey, PhD
Fabrizio Michelassi, MD
Shari R. Midoneck, MD
Raffaele Milizia, MD
Carlyle H. Miller, MD
David H. Miller, MD
Teresa A. Milner, PhD
Jeffrey W. Milson, MD
Robert J. Min, MD
Robert M. Minutello, MD
Ajay Mirani, MD
Vivek Mittal, PhD
Nurru L. Miligliche, MD, PhD
Vikash K. Modi, MD
Joseph J. Montano, MD
Anne Moore, MD
John P. Moore, PhD
Silvia D. Moore, PhD
Anne Moscona, MD
Paul D. Mozley, MD
Estomih Mtui, MD
Oliver J. Muenseter, MD
Sushmita Mukherjee, PhD
Mary R. Mulcare, MD
Paul Mullin, MD
Henry W. Murray, MD
Matthew Murrell, MD, PhD
Thomas Murry, PhD
Sergey Musatov, PhD
Alvin I. Mushlin, MD, ScM
Thangamani Muthukumar, MD
Monn M. Myat, PhD

N
Ralph L. Nachman, MD
Nady E. Nady-Mohamed, MB, ChB
S. Hani Najafi-Shoushtari, PhD
Govind Nandakumar, MD
David M. Nanus, MD
Syed Naqi, PhD
Carl Nathan, MD
Babak Navi, MD
Nancy M. Nealon, MD
Joshua P. Needleman, MD
Thanh D. Nguyen, MS, PhD
Yutaka Nibu, PhD
Ruben Nieszvizky, MD
Crina M. Nimigean, PhD
Sheila Nirenberg, PhD
Marcelo M. Nociari, MS, PhD
Dattatreyudu Nori, MD, MB, BChB
Bakr M. Nour, MD

O
Mallay Occhiogrosso, MD
Allyson J. Ocean, MD
Oksana Ocheretina, MS, PhD
Michael W. O’Dell, MD
Ji-eun Oh, MSc, PhD
Michiko Okamoto, MS, PhD
Peter M. Okin, MD
Sonja K. Olsen, MD
Matthew T. O’Neill, MD
Joseph R. Osborne, MD, PhD
James A. Osorio, MD
S. Nina Osorio, MD
David M. Otterburn, MD
Karin-Elizabeth M. Ouchida, MD
Darius A. Paduch, MD, PhD
Ji-Hye Paik, PhD
Gianpiero D. Palermo, MD, PhD
Lawrence G. Palmer, PhD
Ankur Pandya, MPH, PhD
Susan C. Pannullo, MD
Juliann M. Paolicchi, MD
Jean W. Pape, MD
Bhupesh Parashar, MB, BS
Laibaik Park, PhD
Athos Patsalides, MD, MPH
Steven M. Paul, PhD
Subroto Paul, MD
Roger N. Pearse, PhD, MD
Robert N. Peck, MD
Mark S. Pecker, MD
Eduardo M. Perelstein, MD, MPH
Francheska Perepletchikova, PhD
Jeffrey M.Perlman, MB, ChB
Jai S. Perumal, MD
Janey C. Peterson, EdD
Gregory A. Petsko, DPhil
Erica G. Phillips-Caesar, MD
Virginia M. Pickel, MS, PhD
Shari Platt, MD
Margaret M. Polaneczky, MD
Elizabeth Poole-Di Salvo, MD
Alfons Pompl, MD
Steven Pon, MD
Elisabetta C. Popa, MD
Dix P. Poppas, MD
Matteo Porotto, PhD
Jeffrey L. Port, MD
Mukesh Prasad, MD
Matthew J. Press, MD
Martin R. Prince, MD, PhD
R.A. Rees Pritchett, MD
Alexander Proekt, PhD, MD
Jane M. Prokop, MD
Kane O. Pryor, MB, BS
Bradley B. Pua, MD
Keith P. Purpura, PhD

P
Lidong Qin, PhD
Pounah K. Rabbany, PhD
Nathan M. Radcliffe, MD
Mayed M. Radi, MB, ChB
Shahin Rafii, MD
Barrie L. Raik, MD
Roheen Raithatha, MD
Ashish Raj, MS, PhD
Anjali M. Rajadhyaksha, PhD
Praveen B. Raju, MD, PhD
Kapil K. Rajwani, MD
Bharathi Raman, MD
Mayra Ramirez, MA
Sharda D. Ramsaroop, MD
Rama B. Rao, MD
Patrick J. Raue, PhD
Lisa D. Ravdin, MS, PhD
Akkamma Ravi, MB, BS, MD
M. Cary Reid, MD, PhD
William R. Reisacher, MD
Norman R. Relkin, MD, PhD
Joseph G. Rezza, MD
Hanna Rennert, PhD
Kyu Y. Rhee, MD, PhD
David S. Rickman, PhD
Arleen B. Rifkind, MD
Ellen K. Ritchie, MD
Stefano Rivella, PhD
Gail J. Roboz, MD
Scott A. Rodeo, MD
Enrique J. Rodriguez-Boulan, MD
Pablo Rodriguez del Pozo, MD, JD, PhD
Mary J. Roman, MD
Mark I. Rosenblatt, MD, PhD
Isadore Rosenfeld, MD, CM
Axel J. Rosengart, MD, PhD
Zev Rosenwaks, MD
Gail S. Ross, PhD
M. Elizabeth Ross, MD, PhD
Lisa Roth, MD
Neeta S. Roy, MS, PhD
S. Robert Rozbruch, MD
Jia Ruan, PhD, MD
Elayna O. Rubens, MD
Mark A. Rubin, MD
Francesco Rubino, MD
Joseph T. Ruggiero, MD
Andrew Ryan, PhD, MA
Timothy A. Ryan, PhD
Jae-Wook Ryou, MA, PhD
Isoflurane – a member of the modern family of halogenated ether anesthetics currently in widespread clinical use – is the subject of research at Weill Cornell, with a particular focus on its molecular properties and effect on neurotransmitters. (Courtesy of Dr. Hugh C. Hemmings, Jr.)

S
Arash Salemi, MD
Christine M. Salvatore, MD, MS
Mirella Salvatore, MD
Abraham Sanders, MD
Vladislav M. Sandler, MS, PhD
Pina C. Sanelli, MD
Santosh K. Sangari, MB, BS
Michael J. Satlin, MD
Anthony A. Sauve, PhD
Peter M.C. Savard, MD
John J. Savarese, MD
Andrea Sboner, MS, PhD
Joseph M. Scandura, MD, PhD
Bruce R. Schackman, PhD
Robert A. Schaefer, MD
Andrew I. Schafer, MD
Glenn L. Schattman, MD
Ronald J. Scheff, MD
Ellen J. Scherl, MD
Douglas S. Scherr, MD
Nicholas D. Schiff, MD
Marc Schiffman, MD
Peter N. Schlegel, MD
William S. Schley, MD
Anita M. Schmid-Frey, MSc, PhD
Dirk Schnappinger, PhD
Bryan J. Schneider, MD
Darren B. Schneider, MD
Felice H. Schnoll-Sussman, MD
Aaron P. Schulman, MD
Brian D. Schwartz, MD
Theodore H. Schwartz, MD
Beate Schwer, PhD
Thomas P. Sculco, MD
Marco Seandel, MD, PhD
Art Sedrakyan, MD, PhD
Samuel H. Selesnick, MD
Hector Peinado Selgas, PhD
Licia Selleri, MD, PhD
Sam Senturia, MD
Nitin K. Sethi, MB, BS
Manish A. Shah, MD
Shahrokh Shariat, MD
Aarti V. Sharma, MB, BS
Renat Shaykhiev, MD, PhD
Menachem M. Shemtov, MD
Haifa Shen, MD, PhD
Wen H. Shen, MS, PhD
Sujit Sheth, MD
Lei Shi, PhD
George Shih, MD
Jungho Shin, MD
Tsiporah B. Shore, MD
Jian Shou, MD
Parul Shukla, MD
Emily K. Shuman, MD
Dikoma C. Shungu, PhD
Benjamin M. Shykind, PhD
Lawrence J. Siegel, MD, MPH
Eugenia L. Siegler, MD
Randi B. Silver, PhD
Richard T. Silver, MD
Mary Simmerling, PhD
Rache M. Simmons, MD
Harjot K. Singh, MD
Harsimran S. Singh, MSc, MD
Naina Sinha, MD
Kimberly C. Sippel, MD
Jo Anne Sirey, PhD
Akhilesh K. Sista, MD
Lucy Skrabanek, PhD
Nikolaos Skubas, MD, DSc
Ralph L. Slepicka, MD
Rachel Smerd, MD
Duane M. Smith, MD
Kendall A. Smith, MD
Michael J. Smith, MD
Rosemary Soave, MD
Irina Sobol, MD
Robyn Sockolow, MD
Kristina Sole, MD
Lilja B. Solnes, MD, MBA
Aliza Solomon, DO
Gail E. Solomon, MD
Dolan Sondhi, PhD
Christian Song, MD
Toyouko Sonoda, MD
Mark M. Souweidane, MD
Steven D. Spandorfer, MD
Jason A. Spector, MD
Jeremy Sperling, MD
Arthur J. Spielman, PhD
Nitsana A. Spigland, MD
Pascal Spincemaille, PhD
Anatoly Starkov, PhD
Natalia N. Starkova, MS, PhD
Christopher E. Starr, ScB, MD
Michelle Staudt, PhD
Peter A.D. Steel, MB, BS, MA
Joel Stein, MD
Carolyn R. Steinberg, MD
Charles R. Steinberg, MD
Michael E. Stern, MD
Michael G. Stewart, MD
Philip E. Stieg, PhD, MD
Brendon M. Stiles, MD
Anne Stone, MD
Kingsley Storer, MB, BS, PhD
Carol L. Storey-Johnson, MD
Dean J. Straff, MD
Gladyw S. Strain, PhD
Heidi Stuhlmann, PhD
Christopher V. Sturiano, MA, PhD
Kotha Subbaramaiah, MSc, PhD
Lucian Sulica, MD
Ali A. Sultan, MD, PhD
Grace Sun, MD
Tao Sun, PhD
Ching-Hwa Sung, PhD
Manikkam Suthanthiran, MB, BS
Rajesh V. Swaminathan, MD
Alexander J. Swistel, MD
Paul Szabo, PhD
Hazel H. Szeto, MD, PhD
Massimiliano Szulc, PhD, MS

T
Jeremie A.R. Tabrizi, MD, PhD
Scott T. Tagawa, MD
Andrew H. Talal, MD
Adam D. Talenfeld, MD
Mia Talmor, MD
Xiao-Han Tang, PhD
Weill Cornell scientists employ state-of-the-art transmission electron microscopes in their research enabling them to explore intricate biological systems in three dimensions.
### SENIOR ADMINISTRATION

Laurie H. Glimcher, MD  
*Stephen and Suzanne Weiss Dean*  
Weill Cornell Medical College  
Provost for Medical Affairs  
Cornell University  
David P. Hajjar, PhD  
*Dean*  
Weill Cornell Graduate School of Medical Sciences  
Javaid I. Sheikh, MD  
*Dean*  
Weill Cornell Medical College in Qatar

### DEPARTMENT CHAIRS

#### Anesthesiology
- John J. Savarese, MD  
  *Professor of Anesthesiology*

#### Biochemistry
- Frederick R. Maxfield, PhD  
  *Vladimir Horowitz and Wanda Toscanini Horowitz Distinguished Professor of Neuroscience*

#### Brain and Mind Research Institute
- Costantino Iadecola, MD  
  *George C. Cotzias Distinguished Professor of Neurology and Neuroscience*

#### Cancer Center
- Lewis C. Cantley, PhD

#### Cardiothoracic Surgery
- O. Wayne Isom, MD  
  *Terry Allen Kramer Professor of Cardiothoracic Surgery*

#### Cell and Developmental Biology
- Katherine A. Hajjar, MD  
  *Brine Family Professor of Cell and Developmental Biology*

#### Dermatology
- Richard D. Granstein, MD  
  *George W. Hambrick, Jr. Professor of Dermatology*

#### Genetic Medicine
- Ronald G. Crystal, MD  
  *Bruce Webster Professor of Internal Medicine*

#### Medicine
- Andrew I. Schafer, MD  
  *E. Hugh Luckey Distinguished Professor of Medicine*

#### Microbiology and Immunology
- Carl F. Nathan, MD  
  *R.A. Rees Pritchett Professor of Microbiology*

#### Neurological Surgery
- Philip E. Stieg, PhD, MD  
  *Professor of Neurological Surgery*

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Weill Cornell Medical College is divided into 24 basic science and clinical departments. Physicians and scientists are engaged in cutting-edge research from bench to bedside, aimed at unlocking mysteries of the human body in health and sickness and toward developing new treatments and prevention strategies. Weill Cornell is the birthplace of many medical advances — including the development of the Pap test for cervical cancer, the synthesis of penicillin, the first successful embryo-biopsy pregnancy and birth in the U.S., the first clinical trial of gene therapy for Parkinson’s disease, and most recently, the world’s first successful use of deep brain stimulation to treat a minimally conscious brain-injured patient.

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In addition to its affiliation with NewYork-Presbyterian Hospital, Weill Cornell Medical College and Graduate School of Medical Sciences maintain major affiliations with Memorial Sloan-Kettering Cancer Center, The Rockefeller University, Hospital for Special Surgery, as well as with the metropolitan-area institutions that constitute the NewYork-Presbyterian Healthcare System. The Medical College is also affiliated with The Methodist Hospital in Houston, Texas.