



2011

**WEILL CORNELL MEDICAL COLLEGE
RESEARCH HIGHLIGHTS**



Weill Cornell Medical College



WEILL CORNELL MEDICAL COLLEGE AND GRADUATE SCHOOL OF MEDICAL SCIENCES

Weill Cornell Medical College, the medical school of Cornell University, is among the top-ranked medical research centers in the country. Founded in 1898, the Medical College has been affiliated with what is now NewYork-Presbyterian Hospital since 1927. In addition to offering degrees in medicine, Weill Cornell also has PhD programs in seven broad programs of study in biomedical research at the Weill Cornell Graduate School of Medical Sciences, and the Tri-Institutional MD-PhD Program with neighboring Sloan-Kettering Institute and The Rockefeller University.

Since 1997, Dr. Antonio M. Gotto, Jr., has served as the Stephen and Suzanne Weiss Dean of Weill Cornell Medical College and Provost for Medical Affairs for Cornell University. A pioneering researcher in lipoproteins and apolipoproteins throughout his career, Dr. Gotto has played a leading role in several landmark clinical trials of statin drugs. Beginning in 2012, Dr. Gotto will become Co-Chairman of the Board of Overseers for the Medical College and Vice President of Cornell University. Dr. Gotto will be succeeded as Dean by Dr. Laurie H. Glimcher, one of the nation's leading physician-scientists and researchers, on January 1, 2012. Dr. Glimcher is the Irene Heinz Given Professor of Immunology at the Harvard School of Public Health, where she directs the Division of Biological Sciences program, and Professor of Medicine at Harvard Medical School, where she has headed one of the top immunology programs in the world.

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.

In its commitment to global health and education, Weill Cornell has a strong presence in places such as Qatar, Tanzania, Haiti, Brazil, Austria, and Turkey. Through the historic Weill Cornell Medical College in Qatar, the Medical College is the first in the U.S. to offer its medical degree overseas.

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.

ON THE COVER: Functional cellular and molecular biology assays coupled with high-resolution microscopy and live-cell imaging are used in the laboratory of Dr. Paraskevi Giannakakou to gain new information on the spatial and temporal regulation of microtubule-cytoskeleton dynamics and its effects on cancer-cell survival. (Cover image by Marisa Carbonaro, PhD, postdoctoral fellow in the Giannakakou laboratory)



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2011



The scientific enterprise at Weill Cornell Medical College has experienced dramatic growth over the past decade across the continuum of basic, translational, and clinical research. As part of the Medical College's strategic plan, and with the support of a \$1.3 billion capital campaign, the research faculty – numbering approximately 400 members – are making important contributions to further advancements in medicine. In New York City and in Doha, Qatar, Weill Cornell Medical College is flourishing on a number of research fronts. As you will read in this *2011 Research Highlights*, Weill Cornell has assembled an impressive community of scientists who are leading a wide range of research initiatives in their laboratories and through their clinical research. These initiatives have the potential to change the future of modern medicine, with programs supported by a research budget of more than \$200 million, including an impressive roster of National Institutes of Health RO1 grants and MERIT Awards. Some of the major grants received by Medical College scientists include nearly 500 RO1 grants in awards of up to \$5.5 million and nearly 30 MERIT Awards in amounts up to \$4.8 million. Following are a sampling of grants active in 2011-2012.

RO1 GRANTS

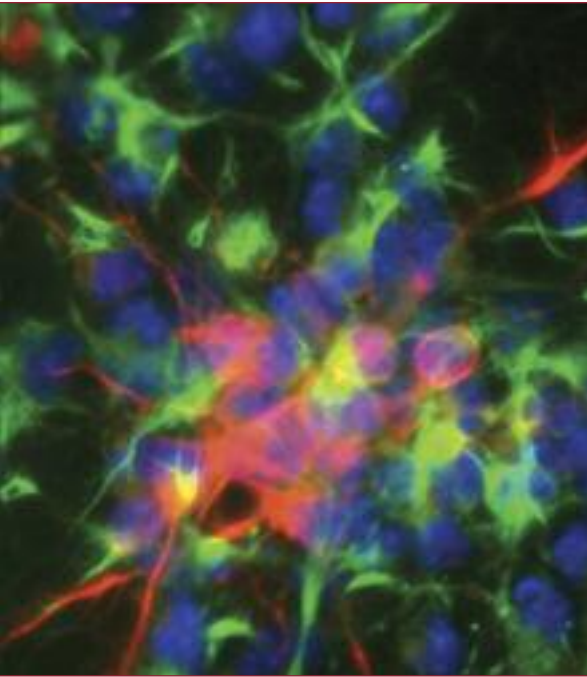
- Epigenome Interactions in Complex Neurogenetic Disorders: \$5.5 million (Transformative RO1)
- Biology of Lipoamide Dehydrogenase and 2-Hydroxy-3-Oxoadipate Synthase in Mtb: \$4.8 million
- Overlapping Airway Basal Cell Transcriptome Reprogramming in COPD and Lung Cancer: \$4.2 million
- Gene Therapy for Batten Disease: \$3.7 million
- A Collaborative System Approach to Diffusion of Evidence-Based Prevention: \$3.7 million
- RETINA: Reversed Polarity and Morphogenesis of RPE: \$3.4 million
- Molecular Basis of Protein Transport in Photoreceptor: \$3.4 million
- Hepcidin Therapy for Iron Overload and Hematologic Disorders: \$3.3 million
- Central Thalamic Deep Brain Stimulation: \$3.3 million
- Drug Targets in Mtb Gluconeogenesis, \$3.2 million.
- Biotin Synthesis and Biotin Ligation in Mtb: \$3.1 million
- Molecular Targeting of Diffuse Large B-cell Lymphoma: \$3 million

MERIT AWARDS

- Cell-Cell Interactions in Thrombosis: \$4.8 million
- Receptor-Mediated Endocytosis – Mechanism and Function: \$3.3 million
- Biomolecular Markers for Safe Minimization of Immunosuppression: \$2.1 million
- Neutralization of Primary HIV-1 Viruses: \$2.1 million
- Diabetic Vasculopathy and Mitochondrial eNOS: \$2.1 million

Additionally, the Medical College received an \$8 million grant from the National Center on Minority Health and Health Disparities to create the Comprehensive Center of Excellence in Disparities Research and Community Engagement, as well as a \$10 million grant from the National Institute of Mental Health to fund the Weill Cornell Institute of Geriatric Psychiatry.

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 \$40.9 million dollars to fund 92 projects. Stimulus funding is supporting work in AIDS, kidney disease, cancer, Parkinson's disease, with the single largest grant – \$1.9 million from the National Institute on Drug Abuse – funding the development of an adenovirus-based anti-cocaine vaccine.



Looking at two types of brain cells, neurons (red) and astrocytes (green), Weill Cornell scientists are revealing functions of micro RNAs in brain development and in motor neuron specification, which may provide new methods of stem cell-based therapies for neurodegeneration diseases and spinal cord injuries. (Courtesy of Dr. Tao Sun)

The biomedical research community at Weill Cornell Medical College is enriched by the contributions of specialized centers and institutes comprised of some of the world's most insightful and productive scientists. These programs address fundamental medical, psychological, and sociological issues confronting society today such as stem cell therapeutics, vascular biology, health challenges in underserved communities, and developmental psychobiology. Additional programs focus on aging, complementary medicine, hepatitis C, and computational biomedicine, to name a few.

Following are several important centers that exemplify the high level work that is being conducted in areas of great significance for the future of medicine.

Clinical and Translational Science Center

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 55 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 health care for the underserved.

Since its inception, the CTSC has supported over 100 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.

Ansary Stem Cell Institute

Stem cells, the primitive, unspecialized cells thought to have an unrivaled capacity to form all types of cells in the body, are the focus of the Ansary Stem Cell Institute at Weill Cornell Medical College, which 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.

Center for Vascular Biology

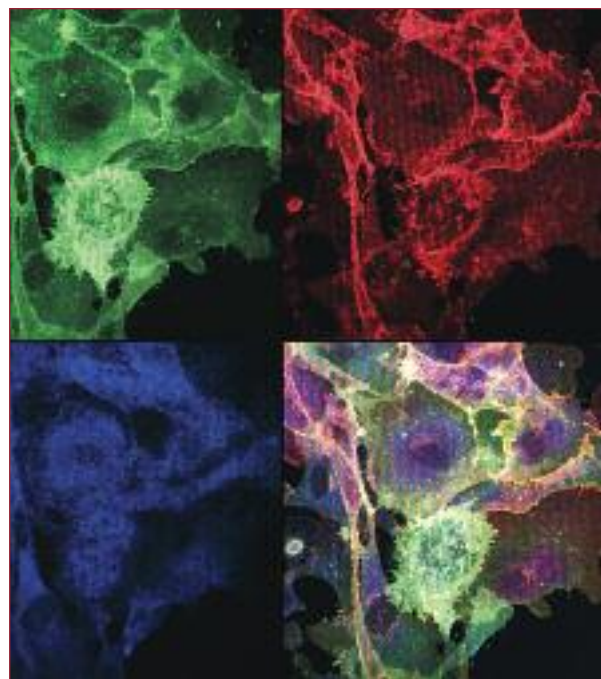
The Center for Vascular Biology, founded in 1995, is dedicated to biomedical research into vascular biology and disease. The vascular system permeates all organ systems; indeed, vascular health is essential for overall well-being of the organism. We have come to realize that abnormal changes in the vascular 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 the 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 in our knowledge base as well as therapeutic approaches, the vascular biology community provides a superb training environment in basic and translational research endeavors.

Comprehensive Center of Excellence in Disparities Research and Community Engagement

Cancer, diabetes, infant mortality, AIDS, and cardiovascular illnesses are among the most prevalent health care 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 health care 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. 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.

Sackler Institute for Developmental Psychobiology

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.



Endothelial cells that line the inner surfaces of blood vessels were grown in the laboratory and analyzed for the presence of the sphingosine 1-phosphate receptor and downstream signaling pathways by detecting specific molecules with labelled antibodies and visualization in a microscope that detect fluorescent signals. Different colors represent cellular localization and activity of specific molecules. This approach allows the detailed understanding of how blood vessel health is maintained by sphingosine 1-phosphate. This molecular mechanism is abnormal in many diseases, such as cancer and heart disease where blood vessels contribute to the disease process. (Courtesy of Dr. Timothy Hla)



Advanced digital micro-imaging captures clear and low-noise fluorescent, super high-resolution images enabling Weill Cornell scientists to achieve a highly accurate examination of microstructures.

OLYMPUS

Collaborations among scientists at Weill Cornell Medical College and their partnerships with academic medical centers and research institutes provide fertile ground for breakthrough discoveries and groundbreaking progress in science and medicine. The strength of these partnerships with the Medical College's parent institution, Cornell University in Ithaca, New York, and with some of the finest medical and research facilities in the world: NewYork-Presbyterian Hospital, Memorial Sloan-Kettering Cancer Center, The Rockefeller University, Hospital for Special Surgery, and The Methodist Hospital Research Institute in Houston, Texas, produces innovative research approaches, technologies, and more targeted therapies. Following are just a few of the collaborative programs that are making noteworthy contributions.

RESEARCH PROGRAMS

Tri-Institutional Stem Cell Initiative

The Tri-Institutional Stem Cell Initiative (Tri-SCI) is a major collaborative endeavor made possible by a \$50 million gift from The Starr Foundation. Together, Weill Cornell Medical College, Memorial Sloan-Kettering Cancer Center, and The Rockefeller University are providing resources to support research in stem cell biology, including funds for projects using non-registered human embryonic stem cell lines. As part of this initiative, support is 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.

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 Stem Cell Initiative, 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, 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 research centers across the country, is organized to decipher the complexities of cancer using methods derived from the physical sciences and engineering to further understand how cancer travels through the human body. Research pursued here may help identify new drug possibilities to inhibit metastasis and tumor growth.

Nationally, the 12 centers bring a cadre of theoretical physicists, mathematicians, chemists, and engineers to study the physical laws and principles of cancer; evolution and evolutionary theory of cancer; information coding, decoding, transfer and translation in cancer; and ways to deconvolute cancer's intricacies. The Center on the Microenvironment and Metastasis is focusing on three key projects:

- examining physio-chemical transducers and their role in tumor angiogenesis
- physical and chemical cues in tumor cell migration, and
- adhesion of tumor cells in the vascular microenvironment



Various stem cell and animal models, including zebrafish, are being used to understand how cell types, tissues, and organs form; why this process can fail during embryogenesis and throughout life; and how regenerative processes might be reemployed to treat debilitating diseases. (Courtesy of Dr. Todd Evans)



Benjamin M. Shykinds, PhD, Assistant Professor of Cell and Developmental Biology at Weill Cornell Medical College-Qatar (far right), and his research team are discovering that a seemingly random gene selection process determines a lot of what we smell; understanding it could reveal secrets about biological diversity and disease.

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, Memorial Sloan-Kettering Cancer Center, Visiting Nurse Service of New York, and the Council of Senior Centers and Services of New York City, Inc.

To improve the prevention and management of pain in later life, TRIPLL will:

- build evidence-based pain prevention, reduction, and management practices, treatments, and interventions
- develop and translate research-based methods, tools, and strategies that facilitate successful translation of evidence into practice
- develop and maintain 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. Stress, certain visual cues, even an individual's mood can all have a substantial impact on behavior and eating, according to Center findings, and affecting changes in these areas can lead to sustainable weight loss. The program is a joint endeavor of Weill Cornell Medical College, Cornell University, Lincoln Hospital in the Bronx, and Renaissance Health Systems in Manhattan. 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.

Weill Cornell Medical College in Qatar

The research program at Weill Cornell Medical College in Qatar plays a critical role in Qatar's significant biomedical research effort. In accordance with the research priorities of Qatar and the Qatar Foundation, the BMRP set out 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. Over the past two years the research program has made remarkable progress toward these objectives. Our continuing efforts to recruit high-caliber faculty members have resulted in 18 Faculty laboratories investigating broad areas of biomedical sciences, with a focus on basic, translational, and clinical studies aimed at improving the health of the Qatari population. Over the past year Weill Cornell-Qatar expanded its wet-bench research space to approximately 30,000 square feet to accommodate the program's impressive growth, which presently stands at ~100 researchers. In addition, a robust administrative infrastructure has been

established and seven centralized core support laboratories, including Bioinformatics Core; Cellular Imaging Core; Basic Core; Proteomics Core; iPS Stem Cells Core; and a Biostatistics Core to help clinical investigators with study design and analysis. With more than \$35 million in competitive research funding from the Qatar National Research Fund, and another \$15 million pending award, the research program is well on its way to becoming the leading biomedical research program in the region. Awarded grants support studies in diabetes, stem cell therapies, cancer, heart disease and other diseases of importance to Qatar and the region. Weill Cornell-Qatar is also working with the Qatar Foundation on the new Sidra Medical and Research Center.

The Methodist Hospital Research Institute

Weill Cornell Medical College is affiliated with The Methodist Hospital in Houston, Texas, collaborating in research initiatives with The Methodist Hospital Research Institute. The Institute shares similar research goals to Weill Cornell, emphasizing the development of treatments with ready applicability to human disease. One current collaboration with Weill Cornell's Department of Neurology and Neuroscience focuses on a three-year, \$1.5 million study entitled "Genes and Environment: Disease Gene and Folate Metabolic Pathway Interactions."

EDUCATIONAL AND TRAINING PROGRAMS

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.

Tri-Institutional MD-PhD Program

Weill Cornell Medical College, The Rockefeller University, and the Sloan-Kettering Institute for Cancer Research comprise an inter-institutional collaboration for joint MD/PhD training. These biomedical research and educational institutions, which are geographically adjacent to each other, 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 Memorial Sloan-Kettering Institute) or The Rockefeller University. Now in its 38th 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 approximately 410 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.



Among the 12 members of the 2011 entering class of the Tri-Institutional MD-PhD Program at their orientation meeting are (from left) Kevin O'Rourke from Middlebury College, Aryeh Zolin from Columbia College, and Michael Dreyfuss from Columbia University.



Ongoing upgrades of the Medical College's research facilities allow scientists to pursue bench work in contemporary laboratories.

George S. Alexopoulos, MD

Stephen P. Tobin and Dr. Arnold M. Cooper Professor in Consultation Liaison Psychiatry
Professor of Psychiatry

Dr. George Alexopoulos and his colleagues are pursuing a program of studies aiming to identify neurobiological abnormalities leading to depression in late life, with the explicit goal to develop targeted interventions. For this reason, among neurobiological abnormalities likely to characterize geriatric depression, their studies focus on those sustaining its symptoms.

Dr. Alexopoulos' group has been one of the first to identify the biological significance of cognitive impairment in late-life depression. They have shown that specific types of executive dysfunction are common in geriatric depression and increase the risk of non-response to classical antidepressants. In subsequent studies, they sought to identify structural and functional abnormalities underlying executive dysfunction and influencing response to antidepressants. Using diffusion tensor imaging, they showed that white matter microstructural abnormalities in frontolimbic areas are correlated with executive dysfunction and predict a low remission rate in patients with late-life depression treated with the serotonin antidepressant escitalopram. Microstructural abnormalities in frontolimbic areas were more common in depressed carriers of the serotonin transporter short allele (5HTTLPR) who also had a lower remission rate when treated with escitalopram than long allele homozygotes. These findings suggest that resistance to serotonin antidepressants in short allele (5HTTLPR) serotonin transporter carriers is, in part, mediated by frontolimbic white matter abnormalities. They have shown that carriers of the neurotrophin BDNFmet allele carriers were more likely to achieve remission than BDNFval/val homozygotes after treatment with escitalopram. However, this effect was not related to microstructural abnormalities conferring resistance to antidepressants.

Based on their earlier findings, Dr. Alexopoulos' group proposed that the brain metabolic changes mediating late-life depression may result from three interacting causes: aging (e.g., aging-related inflammatory responses) or disease (e.g., vascular-related factors); frontolimbic abnormalities serving as predisposing factors; and biological responses to chronic experience of stress. Using this model, they developed two experimental treatment strategies. The first strategy consists of biological interventions targeting aging-related factors contributing or predisposing to late-life depression. They used their findings to develop a neuroplasticity-based cognitive remediation intervention aimed to improve semantic strategy, the executive dysfunction shown to predict poor response to antidepressants. They are now testing this novel treatment in antidepressant resistant late-life depression. Another intervention, part of the same strategy, uses an anti-inflammatory antibiotic as an augmenting agent to classical antidepressants with the goal to reduce aging-related inflammatory responses sustaining late-life depression. The second strategy consists of psychosocial interventions targeting both the depressed elderly patient and the patient's "ecosystem." Their goal is to maximize the patient's behavioral competence and enable the patient's human environment to accommodate the remaining disability.

Dr. Alexopoulos and his colleagues are also pursuing an initiative consisting of intervention studies aiming to improve delivery of care for late-life depression in the community.



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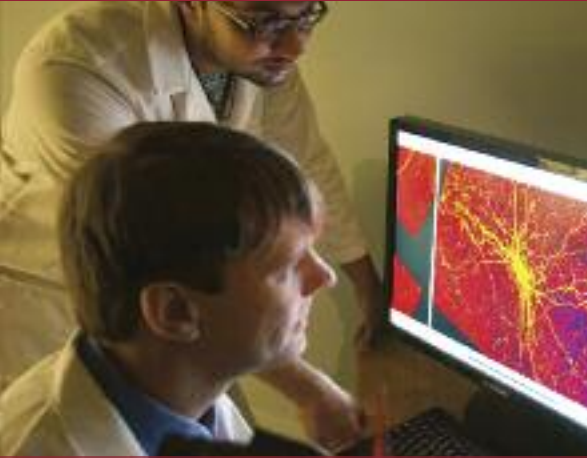
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Stewart A. Anderson, MD

Professor of Psychiatry

Professor of Psychiatry in Neuroscience

Dr. Stewart Anderson is a scientist-physician who spends 90 percent effort running a basic/translational neuroscience research laboratory, and 10 percent effort supervising the outpatient care for patients with schizophrenia. The focus of Dr. Anderson's laboratory concerns the molecular and cellular mechanisms that govern the development of the mammalian forebrain. The research lab uses mouse genetics, slice culture, and dissociated culture techniques, as well as mouse and human embryonic stem cells in transplantation experiments, to study the fate determination of interneurons of the cerebral cortex. Dr. Anderson and his colleagues are particularly interested in understanding the molecular underpinnings behind the fate determination and axon targeting of subclasses of GABAergic interneurons implicated in the neuropathology of schizophrenia. In addition, they are exploring the use of mouse and human pluripotent stem cell-derived interneurons in cell-based therapies for seizures, and as tools for the study of gene-gene and gene-environment interactions in brain diseases such as schizophrenia, autism, and epilepsy.

Embryonic origins of cortical interneuron subtypes. During development, interneurons of the cerebral cortex undergo a long migration from the base of the embryonic brain up into the developing cortex, where they eventually function to control the flow of information through the circuitry formed by excitatory projection neurons. To learn more about how functionally distinct subtypes of interneurons are generated, Dr. Anderson and his lab have conducted experiments in mouse embryos to determine where different types of interneurons come from and what genes are expressed in their cells of origin.

Specification of interneuron fate. Progress on interneuron origins permits more focused approaches to studying interneuron fate determination, which Dr. Anderson's group is conducting using genetically altered mice and transplantation studies.

Use of stem cells to study interneuron development. Dr. Anderson's research group is also directing mouse embryonic stem cells into interneuron progenitors using stem cells that they engineered to fluoresce green when they achieve an interneuron-committed fate. That fluorescence allows the cells to be isolated from the rest of the culture. They are using their new ability to derive interneurons from mouse and human stem cells to identify novel genes involved in the process, and then to search within this list for genes already associated with interneuron-related disease in humans (epilepsy, autism, schizophrenia, bipolar disorder). The Anderson lab is also generating putative inhibitory interneurons from human fibroblast-derived stem cells. This approach can be used for generating interneurons from patients with interneuron-related disease. This advance could be developed into an invaluable resource for studying the effects of known or suspected mutations in interneuron-related disease genes on human interneuron development.

Interneurons and epilepsy. Dr. Anderson is collaborating with Dr. Theodore Schwartz's lab in Neurosurgery to use interneuron progenitor transplants to treat cortical seizures in mice. They have found that interneuron progenitors transplanted into seizure foci in adult mice can mature, survive for months, and block seizure propagation. Studies are ongoing, as are efforts to generate modified interneurons from embryonic stem cells for use as a novel drug delivery system.

M. Flint Beal, MD

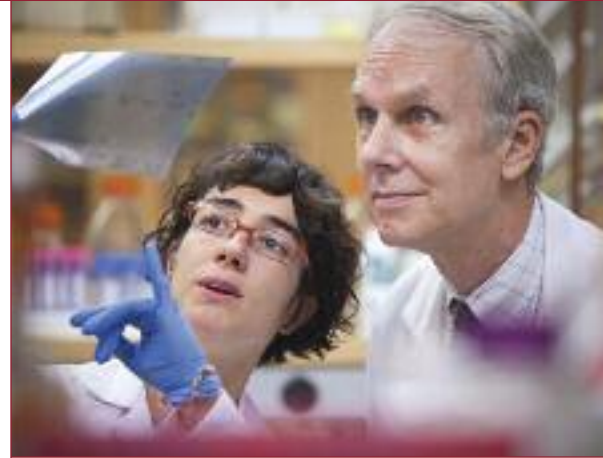
Anne Parrish Titzell Professor of Neurology
Professor of Neurology and Neuroscience

Led by Dr. Flint Beal, the Neurodegenerative Disorders Laboratory focuses on the pathogenesis of neurodegenerative diseases, with a particular interest in the role of metabolic dysfunction and oxidative damage. In the past several years, the research group focused on the role of PGC-1alpha, a critical transcriptional regulator of mitochondrial biogenesis and expression of antioxidant enzymes. They demonstrated that there is a deficit in expression of PGC-1alpha in Huntington's disease (HD) transgenic mice, as well as in the brain tissue, muscle tissue, and myoblasts from HD patients. This correlates with reduced numbers of mitochondria and increased mitochondrial fission in HD postmortem brain tissue. The lab successfully improved survival in HD transgenic mice using PPARgamma and pan-PPAR agonists to increase the expression of PGC-1alpha. The team is presently investigating the role of a deficiency of PGC-1alpha in the pathogenesis of Parkinson's disease (PD). They have showed that there is a deficiency of PGC-1alpha in transgenic mouse models of PD utilizing mutations in LRRK2, as well as in transgenic mice overexpressing alpha-synuclein mutations, which are associated with human PD.

Dr. Beal's group carried out preclinical studies of coenzyme Q10 demonstrating that they also exert additive neuroprotective effects in transgenic mouse models of PD and HD.

The lab has developed new transgenic mouse models of both LRRK2 induced PD and frontotemporal dementia caused by mutations in progranulin. Over the past few years, the researchers carried out a number of studies of the neuroprotective effects of triterpenoids, which activate the Nrf2/ARE pathway. This pathway stimulates the expression of a number of different antioxidant enzymes, protein chaperones, and glutathione synthesis, and also downregulates iNOS expression, COX expression, and other inflammatory cytokines. They demonstrated that administration of triterpenoids, or dimethyl fumarate, are effective in both the MPTP model of PD, and the 3-nitropropionic acid model of HD and that triterpenoids exert neuroprotective effects in transgenic mouse models of Alzheimer's disease (AD), reversing deficits in memory, oxidative damage, and amyloid plaque deposition. They also found that triterpenoids are effective in transgenic mouse models of HD and amyotrophic lateral sclerosis. This approach, therefore, appears to be very promising for development as a therapeutic intervention for neurodegenerative diseases.

Dr. Beal's group carried out preclinical studies of coenzyme Q10 and creatine, both of which have been shown to exert neuroprotective effects, demonstrating that they also exert additive neuroprotective effects in transgenic mouse models of PD and HD. This work led to Phase II and III clinical trials. They are also working on therapeutics for neurodegenerative diseases involving tauopathies, including frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, and AD. They found that inducers of autophagy, as well as agents that increase expression of PGC-1alpha, exert neuroprotective effects in animal models of tauopathy. The Beal lab has developed novel therapeutic interventions that exert neuroprotective effects and show efficacy in animal models. A number of these are undergoing further testing in advanced stage human clinical trials. The lab is also developing novel biomarkers for diagnosis and monitoring of disease progression.



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Scott C. Blanchard, PhD

Associate Professor of Physiology and Biophysics

Dr. Scott Blanchard joined the faculty of Weill Cornell Medical College in 2004, after completing graduate research in biophysics at Stanford University School of Medicine under the direction of Dr. Joseph Puglisi, an expert in the field of RNA research, and postdoctoral studies in applied physics at Stanford University, mentored by Dr. Steven Chu, recipient of the 1997 Nobel Prize in Physics and now the United States Secretary of Energy.

Since joining the faculty, Dr. Blanchard has contributed to numerous fields of graduate study as a member of the Departments of Biophysics and Biochemistry, the Tri-Institutional Program in Chemical Biology, as well as the Institute for Computational Biomedicine. In this time, his team, whose focus is to understand the molecular mechanisms governing enzyme function and regulation for the purpose of developing therapeutic strategies for the treatment of human infection and disease, has authored over 30 research publications, review articles, and patents. Two papers were recently highlighted in the *Faculty of 1000*.

Research in the Blanchard lab, supported by the National Institutes of Health, the National Science Foundation CAREER award, the Human Frontiers in Science Program, and the Irma T. Hirschl/Monique-Weill Caulier Trust, employs an integrated battery of molecular, structural, biophysical, and chemical strategies, including, and, in particular, the development and advancement of single-molecule imaging methods that enable insights into the dynamic properties of biological machines. The lab's major research contributions include the development of the first single-molecule methods used to investigate the bacterial ribosome, including the structural and mechanistic determinants of aminoacyl-tRNA selection and substrate translocation with respect to the ribosome – reactions critical to determining the rate and fidelity of protein synthesis. Aiding these advances, the Blanchard lab also achieved the first three-color, single-molecule fluorescence imaging of the bacterial ribosome.

The Blanchard lab's major research contributions include the development of the first single-molecule methods used to investigate the bacterial ribosome.

Traditionally, in order to understand how drugs affect enzymes, researchers have measured changes in the rate at which an enzyme generates product. The single-molecule approach provides the ability to observe enzyme function from the perspective of motion, and how such motions are influenced by the presence of substrates or drug compounds. Underscoring the lab's contributions to the advancement of single-molecule imaging methods, the Blanchard group also demonstrated novel strategies to improve the photophysical properties of organic fluorophores that are essential to this field of research. Leveraging the knowledge and technical infrastructure obtained through these endeavors, the group recently extended the practice of single-molecule imaging to the investigation of the dynamics of the neurotransmitter transporter family of membrane proteins, as well as the SAM-II riboswitch – distinct classes of molecules that also serve as important drug targets. With this foundation, research in the Blanchard lab is now aimed at next-generation experiments to further probe the molecular basis fidelity in these systems and expanding and improving the nature and efficacy of small-molecule therapies for the treatment of disease.

Gilbert J. Botvin, PhD

Professor of Psychology in Psychiatry

Professor of Psychology in Public Health

Dr. Gilbert Botvin's research focuses on understanding the causes and prevention of health risk behaviors, with a particular emphasis on adolescent tobacco, alcohol, and illicit drug use. His work has resulted in a number of seminal findings. He was among the first to demonstrate that adolescent cigarette smoking could be prevented with a classroom-based program; the first to demonstrate that smoking could be prevented using a novel approach designed to increase adolescent personal and social competence, pro-health norms, and skills for resisting peer and media pressures to engage in unhealthy behavior; and the first to discover that a single prevention approach could have an impact on multiple public health problems. Dr. Botvin's research shows that it is possible to cut cigarette smoking, binge drinking, and the use of marijuana and other illicit drugs by 50 percent or more.

One of the largest randomized trials conducted by Dr. Botvin and his research group examined prevention efforts among more than 5,000 students from 56 junior high schools in New York State. Students received the prevention program in the 7th grade, with additional prevention sessions in the 8th and 9th grades. At the end of the 9th grade, the prevention program significantly cut the rate of cigarette smoking, marijuana use, and immoderate alcohol use compared to untreated controls that did not receive the program. Long-term follow-up at the end of the 12th grade found significantly lower rates of heavy smoking and drinking, marijuana use, and poly-drug use among students who received the prevention program relative to controls. Two randomized trials showed that this prevention approach is also effective with inner-city minority youth and high-risk youth.

Dr. Botvin's most recent work focuses on strategies for moving effective approaches from research to practice. One randomized trial tests strategies for improving implementation fidelity by teachers and other prevention providers. Findings indicate that providing supplemental training and technical assistance that includes planning tools, just-in-time email reminders, and access to help via the Internet and telephone can significantly increase compliance. Since some barriers to implementation at the school or district level may require broader, systems-level changes, Dr. Botvin is currently leading a team of Weill Cornell Medical College and Cornell-Ithaca researchers in a second translational research study. This five-year study, which is funded by NIH's National Institute on Drug Abuse, is designed to identify and overcome a range of potential barriers to the widespread dissemination and use of effective school-based prevention programs. They are using a systems-focused method called "concept mapping" to develop and test an adaptive approach to system-level barriers.

In summary, research conducted by Dr. Botvin and his colleagues in the Division of Prevention and Health Behavior continues to provide important insights into the causes and prevention of adolescent health risk behaviors. Given the magnitude of the health problems associated with these behaviors, Dr. Botvin's prevention research has the potential for a considerable public health impact. For example, in the case of cigarette smoking alone, which causes over 430,000 deaths annually, just a 25 percent reduction in youth smoking offers the potential for saving over 100,000 lives per year.



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Carla Boutin-Foster, MD

Associate Professor of Medicine

Associate Professor of Public Health

Associate Professor of Complementary and Integrative Medicine

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 Center is funded by the National Institute on Minority Health and Health Disparities (NIHMD) of the NIH. 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 by fostering community-academic partnerships and building community capacity for 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, 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 can be induced by providing unexpected small gifts or compliments. One potential mechanism that positive affect may exert its impact on behavior is 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-identity 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.

In addition to her research, Dr. Boutin-Foster directs the training and mentorship of junior faculty and the development of pipeline programs for students from middle school to undergraduates, and is active in building strong community-academic partnerships with local community constituencies. The ultimate goal is to develop a sustainable research enterprise that links academia with community partners to address and develop solutions to the most pressing health disparities.

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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 puberty. 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 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 puberty.

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.



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Ethel Cesarman, MD, PhD

Professor of Pathology and Laboratory Medicine

Approximately one-third of AIDS-related lymphomas are associated with infection by gamma herpes viruses. Most commonly, Epstein-Barr virus (EBV) is found in the lymphoma cells. A small proportion of AIDS-related lymphomas (approximately 5 percent) contains the Kaposi's sarcoma herpesvirus (KSHV/HHV-8). Dr. Ethel Cesarman's laboratory has been involved in the molecular characterization of malignant lymphomas, with particular interest in immunodeficiency-associated non-Hodgkin's lymphomas, including those associated with AIDS. Dr. Cesarman was part of the team that discovered the KSHV, and she found that this virus is consistently present in a subset of non-Hodgkin's lymphomas, known as primary effusion lymphomas (PEL), which led to the recognition of these lymphomas as a distinct disease entity. Dr. Cesarman's laboratory has continued to make important contributions to understanding molecular mechanisms of KSHV pathogenesis, including the development of cell lines that are the most widely used substrate for serologic assays, development of novel cell culture and mouse models of viral oncogenesis, and the identification and characterization of viral oncogenes involved in the pathogenesis of KS and PEL (KSHV vGPCR and vFLIP). The lab has found that lymphoma cells containing KSHV, as well those associated with EBV infection, depend on the expression of selected viral proteins for their survival. This provides an exciting opportunity for targeting viral proteins in order to treat cancers with viral etiologies. Dr. Cesarman is currently principal investigator of two NIH R01 grants supporting this work:

Survival signals in AIDS lymphomas. Dr. Cesarman's broad hypothesis is that viral proteins provide survival signals, and that interference with these signals can be used as a pathogen-specific therapeutic approach for viral malignancies. The goal of her lab is to better understand EBV-associated lymphomas by performing a comprehensive analysis to dissect the viral signals that are critical for tumor cell survival in order to use a rational combinatorial approach for the treatment of AIDS lymphomas. This work will reveal which viral gene products are involved in EBV lymphomagenesis and will help select viral targets for selection of appropriate growth of lymphoma cells. The data will help elucidate how best to inhibit EBV to improve the treatment of AIDS patients with lymphoma.

Targeting vFlip for the treatment of KSHV-associated malignancies. Dr. Cesarman's research group postulates that inhibitors of vFLIP will be useful for the treatment of malignancies caused by infection with KSHV. To date, no virus-specific therapies exist that inhibit the non-replicating virus in the tumor cells. This is particularly important for the treatment of Kaposi sarcoma, which is the most common cancer in several countries in Africa, and only palliative treatments exist. Specific objectives of this grant are to characterize small molecule inhibitors of vFLIP already identified and identify improved next generation inhibitors of vFLIP; evaluate other vFLIP interactions and assess their relevance to vFLIP function and viral pathogenesis; and test the most promising inhibitors of vFLIP in animal models of KSHV vFLIP malignancy. They seek to develop inhibitors of vFLIP and test them in mouse models.

Ongoing projects include the pathologic and molecular characterization of AIDS-related lymphomas, understanding the mechanisms of action of viral oncoproteins, developing better mouse models of viral oncogenesis, and identifying inhibitors of viral oncoproteins.

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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, that is, with a high burden of comorbidity, are driving a significant portion of health care costs, and how an adapted comorbidity index can predict the longitudinal costs of caring for patients with chronic disease. Through the comorbidity index, 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. These cannot be addressed through programs that target a single disease. She is currently working on strategies to manage such complex patients with a high burden of comorbidity to improve outcomes and reduce costs.

Dr. Charlson's research team has developed prognostic models for identifying patients which 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.

Dr. Charlson's research team has developed prognostic models for identifying patients which chronic disease at high risk of adverse events.

Recently, Dr. Charlson and her multidisciplinary team have tested a novel psychosocial intervention combining positive-affect 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. The trials showed that simple scripted positive-affect/self-affirmation intervention could be readily used by patients to achieve meaningful sustained changes in behavior.

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. The multidisciplinary team involves faculty from both the Weill Cornell and Cornell University-Ithaca campuses. Dr. Charlson and her colleagues are continuing to develop and refine interventions targeted at social epidemics such as obesity, and the underlying biological and behavioral phenomena.



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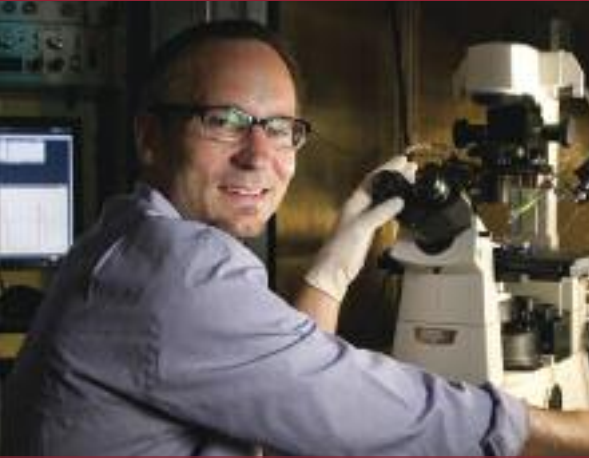
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David J. Christini, PhD

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 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 has developed a fast and 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, has been adopted by over 40 prominent neuroscience and cardiac electrophysiology laboratories.

Ronald G. Crystal, MD

Bruce Webster Professor of Internal Medicine

Professor of Medicine and Professor of Genetic Medicine

Dr. Ronald Crystal's translational research program includes projects in genetic therapies, personalized medicine, and genomic studies. In addition to technologies of gene transfer used in gene therapy studies, Dr. Crystal's laboratory utilizes microarray and RNA-sequencing technologies for genome-wide characterization of gene expression, single-nucleotide polymorphism, and exome and whole genome sequencing on clinical samples to identify candidate genes associated with complex diseases such as chronic obstructive pulmonary disease and diabetes. The following examples of the lab's work have generated international public interest.

Impact of smoking on the lung. Dr. Crystal and his colleagues demonstrated that the human small airway epithelium detects and responds to low levels of tobacco smoke with transcriptome modifications. This provided biologic correlates of epidemiologic studies linking low-level tobacco smoke exposure to lung health risk. The study identified genes most sensitive to tobacco smoke and defined thresholds at which the lung epithelium responds to low levels of tobacco smoke. In another study, the laboratory showed that plasma levels of endothelial microparticles (EMPs), small vesicles released from activated or apoptotic endothelial cells, are elevated in smokers with normal spirometry but reduced diffusing capacity of the lung. These findings are consistent with the concept that emphysema is associated, in part, with capillary endothelium apoptosis, suggesting that the early development of emphysema might be monitored with plasma EMP levels.

Gene therapy for CNS disorders. The impact of age of treatment by an adeno-associated virus serotype rh.10 (AAVrh.10) vector on ameliorating the symptoms of late infantile neuronal ceroid lipofuscinosis (LINCL), a fatal childhood lysosomal storage disorder affecting the CNS, was studied in the LINCL knockout mouse model. The study demonstrated benefit of neonatal treatment with three-fold increase in life expectancy with increased transgene expression throughout the brain and improved behavior compared to untreated controls. This suggests that neonatal treatment is advantageous and early detection and treatment is essential for effective genetic therapy for this type of disease. Dr. Crystal's laboratory has translated this technology to humans, with an ongoing study in children with LINCL using direct CNS infusion of our AAVrh.10 vector expressing the normal gene.

Vaccines for addiction. Based on the concept that anticocaine antibodies could prevent inhaled cocaine from reaching target receptors in the brain, Dr. Crystal's group hypothesized that an effective anticocaine vaccine could help reverse cocaine addiction. They developed an adenovirus-based anticocaine vaccine that evoked high-titer anti-cocaine antibodies in mice sufficient to completely reverse, on a persistent basis, the hyperlocomotor activity induced by intravenous administration of cocaine.

Genetic characterization of Qataris. With Dr. Andy Clark at Cornell University and colleagues at Weill Cornell Medical College-Qatar, Dr. Crystal's lab analyzed single nucleotide polymorphism genotype information from 168 Qataris to assay the genetic information for future studies. They demonstrated that the Qatari population has three primary affinity groups: Arab origin, descendants of Bedouin tribes; Iranian ("Persian") and other more eastern populations, including those of Central Asia; and Bantu-speaking Africans. The latter two groups show strong patterns of admixture and a continuous spread of genetic affinity from the Middle Eastern toward the Asian and African populations, respectively.



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Robin L. Davisson, PhD

Professor of Cell and Developmental Biology

Weill Cornell Medical College

Professor of Biomedical Sciences, College of Veterinary Medicine

Cornell University

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Despite a highly evolved set of regulatory systems, hypertension is a strikingly prevalent disorder in the developed world. Further understanding of the control of blood pressure is a critically important research priority. Working at the intersection of classic integrative physiology and molecular biology, Dr. Robin Davisson has made significant new insights into the molecular physiological determinants of hypertension and related end-organ pathologies. Much of Dr. Davisson's research effort has been focused on the molecular neurobiology of blood pressure regulation and neuro-cardiovascular diseases. The molecular substrates of the neural pathways involved in hypertension and heart failure have remained a mystery. Using sophisticated gene modification strategies that she pioneered for targeting specific circuits of the mouse brain, Dr. Davisson made the seminal discovery that neurons of the central nervous system utilize the free radical superoxide as a signaling molecule to modulate neuronal firing. She further showed that dysregulation in these so-called "redox" pathways in certain specific brain networks leads to several forms of chronic hypertension, as well as the excessive neural drive that follows a heart attack – setting the stage for new therapies for these devastating neuro-cardiovascular diseases.

In the course of this work, Dr. Davisson's team discovered a novel mouse model of pre-eclampsia, the leading cause of maternal death and a major contributor to perinatal morbidity/mortality worldwide. Two obstacles have hindered progress in understanding pre-eclampsia. First, in the clinical setting, research is limited to observations and interventions in mid-to-late pregnancy when maternal symptoms manifest – likely long after disease-causing events are set in motion. Second, the lack of a relevant animal model of pre-eclampsia has hampered basic research into disease mechanisms. Dr. Davisson's laboratory made a significant breakthrough in discovering a faithful animal model of pre-eclampsia, which has put them in a unique position to impact the field.

The model, known as BPH/5, spontaneously develops the clinical sequelae of pre-eclampsia, including late-gestational hypertension and proteinuria during the last trimester of pregnancy (days 14-21), which, as in humans, resolve upon delivery. Late gestation in BPH/5 is further characterized by kidney lesions and blood vessel dysfunction, additional hallmarks of the disease. Careful studies have revealed that the maternal syndrome is preceded by severe defects in the placenta starting very early in pregnancy, underscoring the critical need for studies in animal models since investigations of early placentation in humans is not possible. Most recently they have shown that vascular endothelial growth factor (VEGF), a protein that is critical for new blood vessel formation and remodeling during pregnancy, is profoundly dysregulated during pregnancy in this mouse model. They went on to show that by using viral gene transfer to correct the VEGF abnormalities early in pregnancy, they could prevent much of the maternal and fetal abnormalities observed in these mice. The model offers unprecedented opportunities and numerous ongoing studies by Dr. Davisson and her collaborators aimed at gaining insights into the molecular pathogenesis, identification of potential biomarkers, and development of new treatments for this devastating disease.

Sabine Ehrt, PhD

Professor of Microbiology and Immunology

Approximately eight million people develop active TB each year, with two million dying from the disease. The cause of tuberculosis is *Mycobacterium tuberculosis* (*Mtb*), a slow-growing aerobic bacterium that divides every 16 to 20 hours. It is estimated that one-third of the world's population is chronically infected with *Mtb*. Most individuals respond to infection with *Mtb* by mounting a strong cellular immune response that prevents active disease but does not sterilize the infection. *Mtb* has developed strategies to persist within macrophages, its major host cells, even in the face of fully developed T-cell immunity. Thus, there is a fine balance between the host immune response that controls the infection and the pathogen's ability to evade and manipulate this response.

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. They generate and characterize *Mtb* mutants that are susceptible to stresses encountered by the bacterium during persistence within the host. In an infected host, *Mtb* primarily resides within the phagosomes of macrophages. One strategy the pathogen deploys to prevent its intracellular killing is to arrest phagosome maturation. However, after cytokine activation of the macrophage, the phagosome matures along the endosomal-lysosomal pathway. *Mtb* can persist within even mature phagosomes, indicating that the bacterium possesses resistance mechanisms against defenses of activated macrophages, such as low pH, reactive oxygen and nitrogen species, iron limitation, and others.

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.

The researchers have identified *Mtb* mutants that are hyper susceptible to such stress conditions. Some of these mutants 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 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 during pathogenesis 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.



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David Eliezer, PhD

Associate Professor of Biochemistry

Research in the laboratory of Dr. David Eliezer is focused on understanding the role in disease of protein-protein and protein-lipid interactions that are mediated by protein folding and/or misfolding transitions. A particular focus of the lab is to investigate proteins that are genetically linked to neurodegenerative diseases such as Parkinson's disease (PD), with a major project involving structural studies of the protein alpha-synuclein. This protein aggregates into amyloid fibrils that are found deposited as characteristic Lewy bodies in the brains of PD victims. Alpha-synuclein also influences synaptic vesicle fusion, the process by which neurons communicate with each other in the brain, and disruptions of this function could also play a role in PD. Because of the role of alpha-synuclein in vesicle fusion, Dr. Eliezer and his colleagues are studying other proteins involved in this process, such as complexin, a protein that may "staple" vesicles at the neuron surface until they are ready to release their contents. Dr. Eliezer's lab also works on several other Parkinson's proteins, with names such as DJ-1, PINK1, and LRRK2.

Recently suggested links between heart disease, diabetes, and Alzheimer's disease have led Dr. Eliezer's group to preliminary studies...of intracellular cholesterol transport proteins, including the START domain protein STARD4.

The Alzheimer's disease linked protein tau is also the subject of a major project in Dr. Eliezer's lab. Like synuclein, tau forms filamentous aggregates that are found deposited inside neurons in the form of neurofibrillary tangles. The lab's studies focus on the earliest events that underlie tau aggregation, as well as on the way that tau interacts with or binds to cellular species that modulate its behavior, such as anionic lipids and the surface of structural components of the cell such as microtubules.

Recently suggested links between heart disease, diabetes, and Alzheimer's disease have led Dr. Eliezer's group to preliminary studies of apolipoproteins, proteins that shuttle cholesterol outside the cells in the circulatory system, and of intracellular cholesterol transport proteins, including the START domain protein STARD4. STARD4 has been shown to increase intracellular cholesteryl ester formation and is controlled at the transcriptional level by sterol levels in cells. In collaboration with Dr. Frederick Maxfield, Chairman, Department of Biochemistry, they found that STARD4 is very efficient in transporting sterol between membranes *in vitro*. Cholesterol levels are increased in STARD4-silenced cells, while sterol transport to the endocytic recycling compartment and to the endoplasmic reticulum are enhanced upon STARD4 over-expression.

The Eliezer lab also has an interest in insulin-signaling responsive proteins such as IRAP, especially in light of increasing links between diabetes, neurodegeneration, and heart disease. Many of the proteins that they study share common and interesting properties, such as being intrinsically unstructured when isolated in dilute aqueous solutions, misfolding and forming highly ordered insoluble protein aggregates that become deposited in tissues, and binding to lipids, inducing dramatic folding transitions. The goal of Dr. Eliezer's group is to elucidate how the basic structural and biophysical properties of these proteins contribute to their role in disease.

Todd R. Evans, PhD

Professor of Cell and Developmental Biology in Surgery

Dr. Todd Evans was recruited to Weill Cornell Medical College in 2009 to help build a strong basic science program focused on stem cell and regenerative biology in the context of a strong clinical program, and to encourage translation of research discoveries and impact development of new cellular, genetic, and pharmacological therapies. Research in the Evans laboratory 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 progenitor cells in an *in vitro* setting, and the zebrafish animal model is used to study organ development and morphogenesis.

A central tenet of developmental biology is that understanding programs used to build organs can provide important insight into the genetic regulatory networks underlying human congenital and acquired diseases. 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, considering stem cell biology, lineage commitment, cell differentiation, and organ morphogenesis. For example, the group is studying the function of BMP signaling upstream of Gata2 for regulating hematopoiesis. With respect to the cardiovascular system, they have described functions for three related regulatory genes (Gata4, Gata5, and Gata6) during embryogenesis and in maintaining homeostasis of the adult cardiovascular system. This includes functions in cardiac-associated foregut endoderm (Gata4), coronary smooth muscle (Gata6), myocardial cell survival (Gata4), and heart tube morphogenesis (all three).

Embryonic stem cells (ESCs) are used to study progenitor cells in an *in vitro* setting, and the zebrafish animal model is used to study organ development and morphogenesis.

It might be possible to re-engage the key molecular pathways for regenerative purposes. For example, in recent collaborative work, the group found that Gata4 is a key target for the cardiac regenerative program in an injured adult zebrafish heart. For translation of molecular studies, the group developed expertise in human ESC models, to isolate, quantify, and study stem and progenitor cell fates, and for the directed differentiation of specific cell types through manipulation of GATA-dependent programs. They also developed strong expertise in mouse and human induced pluripotent stem cell (iPSC) technology, including robust protocols for generating iPSC lines from small human peripheral blood donations. Chemical biology projects have been used to identify small molecules that can modulate key developmental pathways.

These capabilities, coupled with strong collaborative clinical programs at Weill Cornell, have led to new exciting projects in the Evans laboratory that exploit stem cell biology to study aging, cancer, and asthma. It is the goal of the group to control with exquisite specificity regenerative pathways in the model systems, and then translate these findings to enhance organ function.



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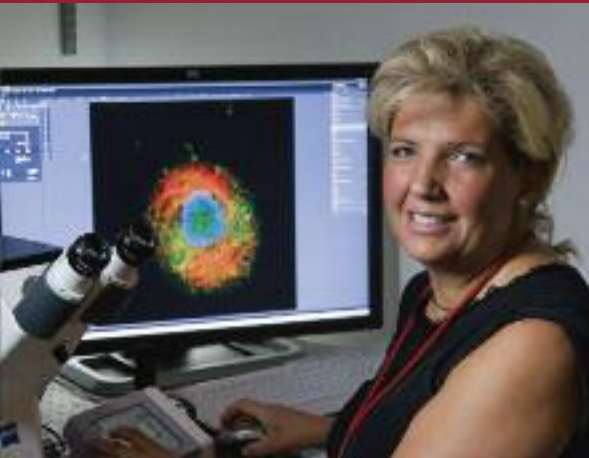
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Paraskevi Giannakakou, PhD

Associate Professor of Pharmacology in Medicine

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 Taxol's FDA approval 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 1 α , and most recently the androgen receptor in prostate cancer.

Dr. Giannakakou's laboratory has previously shown that MTDs exert their anti-angiogenic effects through significant down-regulation of HIF-1 α 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.

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Lorraine J. Gudas, PhD

Revlon Pharmaceutical Professor of Pharmacology and Toxicology
Professor of Pharmacology

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.

Experiments in the Gudas lab suggest that during cancer development the cancer cells reduce their levels of vitamin A and retinoic acid.

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.



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David P. Hajjar, PhD

Frank H.T. Rhodes Distinguished Professor of Cardiovascular Biology and Genetics
Professor of Biochemistry
Professor of Pathology and Laboratory Medicine

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.

Dr. Hajjar showed that the enzyme prostaglandin H2 synthase regulates the production of eicosanoids that modulate physiologic processes in the vessel wall, contributing to atherosclerosis and thrombosis.

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 nitritive 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 our understanding of the complex alterations in eicosanoid metabolism that occur during the pathogenesis of heart disease where inflammation occurs.

Katherine A. Hajjar, MD

Brine Family Professor of Cell and Developmental Biology
Professor of Pediatrics in Medicine

Hemostasis is the process by which bleeding is curtailed following blood vessel injury. It is initiated by an enzymatic cascade, which culminates in the activation of thrombin, the enzyme that converts soluble plasma fibrinogen into insoluble fibrin. The fibrinolytic system regulates hemostasis by activating the serine protease plasmin, which cleaves cross-linked fibrin to generate biologically active polypeptides. Scientists in Dr. Katherine Hajjar's laboratory identified the annexin A2 system as a 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.

The Hajjar lab discovered that the A2 complex binds two major components of the fibrinolytic system, plasminogen and tissue plasminogen activator.

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 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 also 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 for stimulating A2 expression underlies ischemic retinal vascular disease in a mouse model that mimics two human diseases, retinopathy of prematurity and diabetic retinopathy. Further work has revealed that while endothelial cell A2 stabilizes protein p11 and prevents proteasomal degradation, p11 supports the src kinase-stimulated, nonclassical secretion of A2 from the cytoplasm to the cell surface. In addition, the lab has uncovered a novel feedback mechanism whereby plasmin, generated by the A2 system, interacts with toll-like receptor-4 to activate intracellular protein kinase C (PKC). PKC subsequently disrupts the complex with p11 and restricts further translocation to the cell surface. Future studies will build upon these emerging pathways to develop strategies that target the A2 system in specific disease settings.



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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 health care. 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.

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 ischemic cardiovascular diseases.

Dr. Hempstead's laboratory identified precursor forms of the neurotrophins, or proneurotrophins, as independent ligands that induce cell death.

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 encourage different actions; BDNF promotes the differentiation of new neurons and their constituent parts and proBDNF the pruning of synapses. The results suggested that the nervous system plays an active role in both potentiating and dampening its own activity as necessary.

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.



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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.

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.

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.

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Xin-Yun Huang, PhD

Professor of Physiology and Biophysics

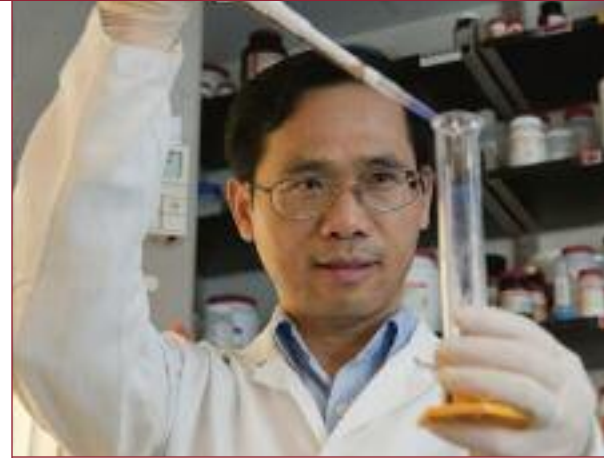
Research in the laboratory of Dr. Xin-Yun Huang is focused on several cellular signaling pathways, their physiological functions, and their applications in disease treatments. Cellular signaling and cell-cell communication allow the multitude of physiological processes in individual cells to proceed 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

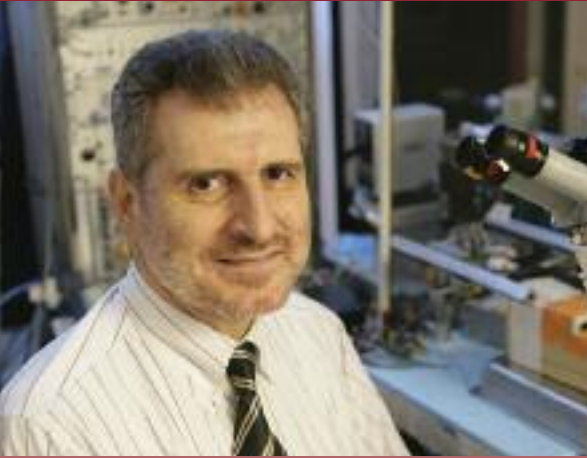
In addition, the lab has been using biochemical and biophysical techniques to investigate the mechanism of activation of G proteins by G protein-coupled receptors.

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.



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Costantino Iadecola, MD

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.

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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, a condition that has recently been recognized as a cause of stroke and dementia, also alters 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 the cells of the immune system and produces brain inflammation. Blocking such inflammation 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. Their findings suggest that modulation of the immune system is a new and powerful way to reduce stroke damage.

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.

Samie R. Jaffrey, MD, PhD

Associate Professor of Pharmacology

An important feature of neurons is that ribosomes are enriched at the tips of axons, where proteins are synthesized that allow axons to elongate and navigate towards its targets during embryogenesis. This process of “local translation” appears to be critical for brain development since mutations in proteins that traffic mRNA to axons or which influence translation of axonally localized transcripts cause mental retardation, autism, and other neurodevelopmental disorders. A major goal of Dr. Samie Jaffrey and his laboratory is to identify the pathways that regulate local translation in axons, and to identify the proteins that are synthesized within axons that are necessary for axon guidance and circuit formation. By generating cDNA libraries of axonal mRNA, they have identified a network of local translation events that mediate axonal responses to axon guidance cues. Intriguingly, many of the axonally enriched transcripts that Dr. Jaffrey and his colleagues identified are also selectively localized to the leading edge of migrating cells or to cellular protrusions, suggesting a functionally conserved mechanism for local translation in different forms of cellular motility.

Studies by Dr. Jaffrey’s lab have demonstrated the existence of local translation networks that orchestrate axon growth and guidance in brain development.

Their studies of axonal mRNAs have also revealed unexpected mechanisms of neuronal signaling. For example, they found that axonal transcripts include mRNAs encoding transcription factors. Under certain circumstances, signaling at the tip of axons leads to synthesis of transcription factors, which are subsequently transported to the cell body where they regulate gene expression pathways required for neuronal survival and axon guidance. These studies have demonstrated the existence of local translation networks that orchestrate axon growth and guidance in brain development.

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 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.

An RNA-fluorophore complex resembling enhanced GFP, termed Spinach, emits a green fluorescence comparable in brightness to fluorescent proteins. Spinach is markedly resistant to photobleaching, and Spinach-fusion RNAs can be imaged in living cells. These RNA mimics of GFP provide an approach to genetically encode fluorescent RNAs. Using Spinach, Dr. Jaffrey and his team have tagged small non-coding RNAs to study their localization in response to cellular signaling. Furthermore, they are currently using Spinach, as well as newer red and orange fluorescent RNA-fluorophore tags that they have developed, Carrot and Radish, to simultaneously image mRNAs and noncoding RNAs in living neurons. These genetically encoded fluorescent RNAs open the door to fundamentally new approaches to explore RNA biology in cells.



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Michael G. Kaplitt, MD, PhD

Associate Professor of Neurological Surgery

Dr. Michael Kaplitt directs the Laboratory of Molecular Neurosurgery and serves as Vice Chairman for Research in the Department of Neurological Surgery. Dr. Kaplitt's lab focuses on the use of gene therapy to treat neurological disorders. As a student in Weill Cornell's Tri-Institutional MD-PhD Program, Dr. Kaplitt helped to develop the field of gene transfer in the brain and nervous system, and he has continued that work for the past 20 years.

The Kaplitt lab is currently concentrating on using gene therapy to better understand and treat disorders, including Parkinson's disease (PD), Huntington's disease, depression, and drug addiction. One approach led to the first human trial of gene therapy for Parkinson's disease, with the groundbreaking procedures performed by Dr. Kaplitt at Weill Cornell in 2003. This was recently followed by the first successful randomized, double-blind clinical trial of gene therapy for any neurological disease, which confirmed the original results when compared with a group of patients receiving sham surgery. In the Phase II study, the experimental group received an infusion of the genetic material directly into their subthalamic nucleus, a key brain region involved in motor function. Patients who received the gene therapy showed a significant reduction in the motor symptoms of PD, including tremor, rigidity, and difficulty initiating movement compared with patients who underwent sham surgery. Dr. Kaplitt's lab continues to use similar techniques to understand how the loss of dopamine in Parkinson's disease influences brain function and how this can be reversed.

In collaboration with Nobel Laureate Dr. Paul Greengard at The Rockefeller University, the Kaplitt lab recently reported that restoring normal production of a gene product called p11 in a brain region called the nucleus accumbens can reverse depression-like symptoms in mice.

More recently, the lab has focused upon gene therapy for psychiatric disorders. In collaboration with Nobel Laureate Dr. Paul Greengard at The Rockefeller University, the lab recently reported that restoring normal production of a gene product called p11 in a brain region called the nucleus accumbens (which is a center for reward and satisfaction) can reverse depression-like symptoms in mice, while samples of nucleus accumbens tissue from depressed humans showed defective production of p11. This suggests that gene therapy to restore normal p11 in this area could be a novel treatment for human depression, and a current collaboration with the National Institute of Mental Health is testing this treatment in non-human primates in order to support a potential application for an initial human study.

Finally, since this same brain region is known to be central to addictive behaviors, Dr. Kaplitt's lab has been testing the role of p11 in this disorder and has found that p11 gene therapy can also block cocaine addiction in mice. The history of translating earlier basic research into successful human clinical trials raises the real possibility that ongoing research in the lab may result in new genetic therapies for a variety of neurological and psychiatric diseases.

Francis S. Lee, MD, PhD

Professor of Psychiatry

Professor of Pharmacology

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.

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.

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.



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John P. Leonard, MD

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 in 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 of lymphoma. Much of this work has involved the development of radiolabeled and unlabeled monoclonal antibody-based therapies for lymphoma, and vaccine 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, 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 and his research team conducted the first major clinical trial of epratuzumab, a monoclonal antibody against the CD22 molecule on lymphoma cells.

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 serves in leadership roles of boards 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.

Frederick R. Maxfield, PhD

Vladimir Horowitz and Wanda Toscanini Horowitz

Distinguished Professor of Neuroscience

Professor of Biochemistry

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.



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Timothy E. McGraw, PhD

Professor of Biochemistry

A primary activity of insulin is to regulate the flux of glucose into adipose and muscle. This process is defective in insulin-resistant conditions, such as Type 2 diabetes and metabolic syndrome. Insulin regulates glucose transport by controlling the amount of the GLUT4 glucose transporter in the plasma membrane (PM). GLUT4 is sequestered in specialized intracellular storage compartments and insulin reversibly increases glucose transport by inducing the translocation of intracellular GLUT4 to the cell surface. Hence, to understand how insulin controls the flux of glucose into cells and how this process is defective in insulin-resistance, it is necessary to understand how insulin controls the trafficking of vesicles that shuttle GLUT4 between intracellular storage compartments and the PM.

Over the past 15 years, Dr. Timothy McGraw's lab has been devoted to understanding GLUT4 trafficking. Initial contributions were to establish quantitative microscopy assays to characterize the behavior of GLUT4, the results of which have contributed to a detailed understanding of the GLUT4 trafficking itinerary. In recent efforts, Dr. McGraw's lab has used siRNA gene silencing and quantitative analysis of GLUT4 trafficking to address molecular aspects of the process, including identifying the proteins that transmit information from the insulin receptor to the GLUT4 transport vesicles. In collaboration with the Lienhard group (Dartmouth University), Dr. McGraw and his research team have shown that Rab10, a small GTPase, has an important role in insulin control of GLUT4. Their data support a model in which insulin, via activation of the protein kinase Akt2, activates Rab10. Active Rab10 promotes the efficient engagement of GLUT4 vesicles with the PM. Insulin, via a Rab10-independent mechanism, also accelerates fusion of the PM engaged vesicles. The data demonstrate that about half of the insulin-stimulated increase of GLUT4 in the PM is a result of the Rab10 stimulation of vesicle engagement, with the rest of the insulin effect on GLUT4 by Rab10-independent mechanisms. In addition, they have also contributed to the understanding of signal transduction. Specifically, the lab has established spatial control of signaling complexes as a key aspect of insulin signaling to GLUT4 by demonstrating that Akt2 isoform selectivity in the control of GLUT4 is determined by the specific localization of active Akt2 near sites of GLUT4 docking to the PM.

The McGraw lab has investigated changes in the control of GLUT4 trafficking in insulin-resistance. Vesicle engagement and fusion have different sensitivities to insulin and they are differentially affected by the development of insulin-resistance. These results demonstrated unexpected complexities in the insulin-resistant state, and they establish that treatment of insulin resistance requires targeting of multiple pathways downstream of the insulin receptor. Provocatively, they observed in insulin-resistant adipocytes that control of GLUT4 is defective but not insulin regulation of the FOXO1 transcription factor, which has a role in control of fat metabolism. This phenomenon of uncoupled insulin action is known to occur in the liver, and their finding of this state in adipocytes suggests it might be a general phenomenon of insulin target tissues contributing to insulin resistance's pathophysiology.

In an expansion of his research program, Dr. McGraw is collaborating with Dr. Nasser Altorki to study the role of fibroblasts in lung tumorigenesis. They hypothesize that fibroblasts within the tumor environment provide specific metabolic and hormonal support for the cancer cells. By discovering how cancer-associated fibroblasts support tumorigenesis, they will reveal novel targets for the treatments of lung tumors.

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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.

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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.

Anne Moscona, MD

Professor of Pediatrics

Professor of Microbiology and Immunology

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. These fundamental findings have led, in the last five years, to the design of novel antiviral strategies that target each of the steps in entry. The novel antiviral approaches, in turn, have yielded valuable tools and reagents for study of basic mechanisms.

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.

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.

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 applications of the findings to preventing infection by parainfluenza virus, Nipah virus, and other pediatric respiratory pathogens (respiratory syncytial virus, measles virus, influenza) and emerging lethal viruses.



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Carl Nathan, MD

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 heritable 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.

Dr. Carl Nathan established that mechanisms of macrophage antimicrobial activity include induction of the respiratory burst and inducible nitric oxide synthase.

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; a Trustee of Hospital for Special Surgery and Chair of the Board of Trustees' Research Committee; on the scientific advisory boards of the American Asthma Foundation, the Rita Allen Foundation, and the Cambridge Institute for Medical Research; and a member of the Board of Governors of the Tres Cantos Open Lab Foundation. 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.

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 (A β), which form amyloid plaques, are greatly influenced by the apoE isoform expressed (E4>E3>E2) and that soluble brain levels of A β 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 A β levels are due to apoE isoform dependent-alterations in local A β metabolism and clearance (E4>E3>E2) and appear to involve differential metabolism of A β by microglia and astrocytes.

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.

In related work, Dr. Paul and his research team have shown that microglia and macrophages metabolize A β 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 A β 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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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 a 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.

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's recent work has also been directed towards identifying research gaps in knowledge regarding the pharmacologic management of pain among older adults.

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. With respect to specific classes of analgesic medication, Dr. Reid's work has included a meta-analysis that examined the effects of opioid therapy on both osteoarthritis-related pain and neuropathic pain. This study found that opioids are moderately effective for pain and improvement in physical function, but have no impact on quality of life.

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.



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M. Elizabeth Ross, MD, PhD

Professor of Neurology and Neuroscience

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

Neural tube formation – spina bifida. Neural tube defects (NTDs), principally spina bifida and anencephaly, affect 1 to 2 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 demonstrated that both low and high FA levels attenuate the response to Wnt stimulus. This was the first demonstration that FA supplementation could have harmful effects on neural tube closure, depending on individual genetic background. They are now leading a multicenter clinical effort to discover complex genetic and epigenetic traits causing NTDs, using deep resequencing to identify human polymorphisms, DNA, and chromatin 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 post-natal development. Studies by Dr. Ross and her research group 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 cerebellar hypoplasia and 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 are investigating the ability of Lis1 to regulate plasticity of neural networks relevant to autism and epilepsy. Additional neuronal migration genes are being sought through genetic investigation of patients with brain malformations and their families.

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. He has had a long-term collaboration with Dr. Arul M. Chinnaiyan (University of Michigan) with over 80 joint publications. Highlights from this work include 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. These findings have been validated worldwide and invigorated a new line of research trying to establish a molecular classification of prostate cancer similar to AML. The discovery has important translational implications; these fusions are virtually 100 percent prostate cancer specific and are now being developed into diagnostic and prognostic clinical tests to supplement PSA testing. The next steps for Dr. Rubin's laboratory are to develop a comprehensive molecular classification of prostate cancer using Next Generation Sequencing paired with novel computational tools. His group recently reported six novel Non-ETS prostate cancer gene fusions.

The researchers discovered that genomic rearrangements are significantly more common in prostate cancer as compared to other common cancers.

Extending this genomic work to other types of mutations, Drs. Rubin and Levi Garraway (Broad Institute of MIT and Harvard) have just reported on the Whole Genome Sequencing of seven high risk prostate cancers. This research discovered that genomic rearrangements are significantly more common in prostate cancer as compared to other common cancers and that the rearrangements are not random events, but rather driven by "transcription hubs" that appear different based on ETS rearrangement status. This first-in-class study demonstrates 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 will continue to develop novel approaches for genomic discovery. His group was one of the first to use laser capture microdissection, tissue microarrays, oligonucleotide arrays, and now 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.



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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. The human brain consists of ~10 billion neurons, each making up to ~10,000 synaptic contacts with other cells.

The efficiency of communication at synapses is thought to be the key substrate that the brain modifies when one stores information (i.e. learns something), learns a task, or makes specific associations between events in life. At the same time, diseases of the brain, such as neurodegenerative disorders like Alzheimer's and Parkinson's disease, or psychiatric disorders such as schizophrenia and bipolar disorder, 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 successfully tracked down many genetic associations between these devastating diseases and synaptic function. The challenge is to understand how synapses work well enough to devise a scheme to repair synaptic lesions. This will require understanding at a molecular level how synapses work. 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. To visualize these molecules, Dr. Ryan's lab uses sophisticated microscopes and specialized ultra-sensitive cameras to peer into the workings of rat and mouse brain neurons.

One of the key aspects of synaptic function that the Ryan lab has focused on regards the fact that the 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 it arrives at the synapse and this electrical stimulus 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.

Once a vesicle releases its chemical message, the entire vesicle must be remade locally and refilled with message. This process, termed vesicle recycling, is one of the areas of particular interest of Dr. Ryan's lab. Their studies in recent years have uncovered how this process is controlled and what gene products are critical. It has also been known for a long time that 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.

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.

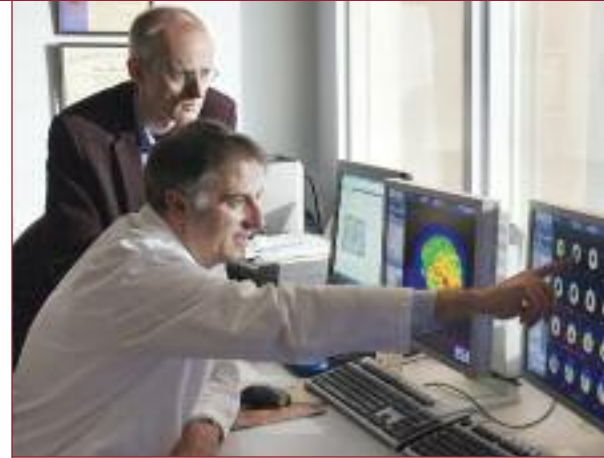
More recently, Dr. Schiff and his colleagues have taken insights into the neurophysiological mechanisms of arousal regulation and of deep brain electrical stimulation techniques to demonstrate evidence that long-lasting, severe cognitive disability may be influenced by electrical stimulation of the human 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.



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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.

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.

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.

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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. Dr. Stuhlmann and her research team have recently developed intravital imaging tools to visualize neovascularization in the living mouse. Specifically, they have developed a platform that uses viral nanoparticles for the multivalent display of fluorescent dyes. They hope that their studies will ultimately lead to advances in the diagnosis and treatment of dysfunctional endothelium, to allow repair of damaged vessels, and to restrict the blood supply in tumors.

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. 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.



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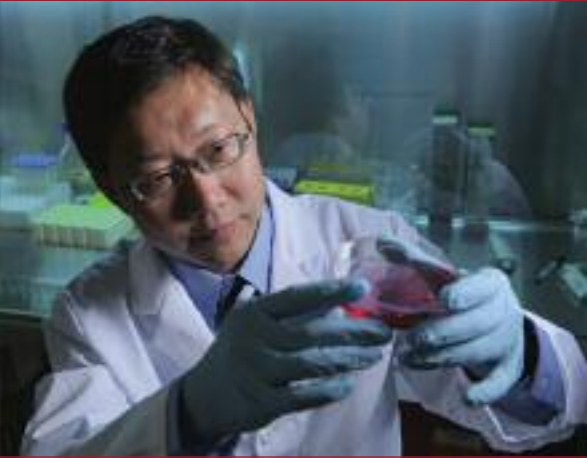
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Tao Sun, PhD

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, MD, 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 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.

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 NIH as one of three centers in the country (along with Harvard Medical School and University of Pennsylvania) 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.



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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 multineuronal recordings in the primate brain and psychophysical studies in man.

Their neurophysiological studies have shown that local cortical populations form functional networks that are dynamically reconfigured by the incoming visual stimulus. The psychophysical studies have delineated the specific set of computations to characterize the statistics of the sensory input, and that these computations are closely matched to the informative aspects of our visual environment.

Their neurophysiological studies have shown that local cortical populations form functional networks that are dynamically reconfigured by the incoming visual stimulus.

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.

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Harel Weinstein, DSc

Maxwell M. Upson Professor of Physiology and Biophysics
Professor of Physiology and Biophysics

Dr. Harel Weinstein's laboratory is devoted to studies in molecular and computational biophysics that address complex systems in physiology, and to the development and application of bioinformatics and engineering approaches to systems biology. The research examines, analyzes, and describes the function of cell components (membranes, proteins, DNA) with rigorous quantitative methods of computational biophysics, and integrates the knowledge into rigorous mathematical models of their mechanisms. The work addresses structural and dynamic mechanisms in fundamental biological processes such as signal transduction, neuronal signaling, and regulation of cell growth mechanisms, as well as the expression of these processes in the physiological functions of tissues and organs.

The quantitative models are based on experimental data from the laboratory, and use fundamental laws of physics and tools of mathematics and computer science to interpret the data in a manner unprecedented in its atomic detail and dynamic information about the mechanisms. The mathematical models are then used to simulate computationally the complex mechanisms by which cell components determine the state and fate of cells in disease and to develop new hypotheses that are tested experimentally. The new data is used to improve the models and the understanding they produce from simulations. The biomedical end points for these studies are neurotransmission in health and disease, drug abuse mechanisms, and cancer. As an example, the combination of computational and experimental methodology established in Dr. Weinstein's lab has enabled the first description of the molecular targets and actions of antidepressant drugs. The targets are proteins embedded in the cell membrane, whose function is to remove neurotransmitters from the synapse in a process essential for the proper function of neural transmission in the brain. The research on this class of cellular proteins, known as transporters, led Dr. Weinstein and his collaborators to the discovery of the structure-determined properties of these molecules that are targeted by the antidepressant drugs.

With powerful computational simulations, the Weinstein lab identified the movements of the transporter proteins that are related to the binding and permeation of the transported molecule. This showed for the first time how, and why, the transporters change their shape to enable various substances to travel across the cell membrane. This is essential in order to regulate transmission of the brain's messages by substances released across the synaptic gap from one neuron to another. The research demonstrated how the process starts with the binding of the transported substance at two different sites in the transporter, and how this induces structural changes that are propagated from the side of the molecule facing the outside of the cell to the other (far) side to cause the transporter to release its contents into the cell. Because widely used medications for depression modulate this transport process by binding to the transporters, the new findings help explain not only how antidepressants, such as Prozac and Zoloft, which are 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. This new understanding of a key molecular mechanism 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.



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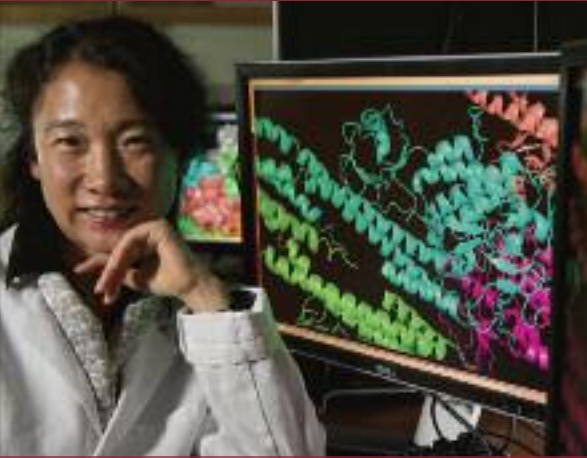
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Hao Wu, BM, PhD

Professor of Biochemistry

As physicist Erwin Schrödinger attempted to do in *What Is Life? The Physical Aspect of the Living Cell*, the laboratory of Dr. Hao Wu aims to elucidate the physical principles by which cells take a receptor activation signal and transform it to appropriate cellular responses. Through visualization of the signaling complexes at a molecular level, analysis of the biophysics of the interactions, and translation of *in vitro* observations to cellular insights, Dr. Wu's lab strives to understand the properties that the physical interactions confer to the signaling systems on a cellular level. These studies have broad impact on understanding and treating human disease conditions, such as malignancy and autoimmunity, in which cell signaling goes awry.

The lab's model system has been on immune receptors in the tumor necrosis factor (TNF) receptor (TNFR) superfamily and the Toll-like receptor (TLR) superfamily. These receptors induce cell survival, growth, differentiation, and death, and are of fundamental importance to mammalian biology. One fascinating aspect of these receptors is their extreme functional dichotomy, with some receptors connecting to cell survival responses while others mediating the opposing effects of cell death. In addition, these receptors do not contain enzymatic activities in their cytoplasmic tails; in contrast, they use separate adapter proteins, ubiquitin ligases, kinases, and caspases to build and amplify the signaling outcomes. The recent work of Dr. Wu and her research group illustrated an elegant common principle that both TNFRs and TLRs use for assembly of signaling complexes. This involves formation of helical towers of death domain proteins to generate and propagate receptor activation signals to induce the appropriate cellular responses. These oligomeric signaling complexes provide a platform for caspase and kinase dimerization and activation. Inhibition of formation of these signaling complexes would have been possible to modulate the signaling and diseases in immunity.

The recent work of Dr. Wu and her research group illustrated an elegant common principle that both TNFRs and TLRs use for assembly of signaling complexes.

One most important downstream effect of TNFR and TLR signaling is activation of the central kinase complex in NF- κ B signaling (IKK). Dr. Wu's lab team has determined the highly sought-after structure of IKK β in complex with a small molecule inhibitor, which revealed the mechanism of IKK kinase activity and substrate specificity. They showed that IKK activation likely involves a high order oligomerization by the upstream protein TRAF6. In one line of insight, their work revealed that the functional dichotomy in the opposing signaling of cell survival and cell death is due to recruitment of different molecules within a molecular "toolset," which are assembled together based on their intrinsic physical properties under different cellular contexts. A major surprise in this recruitment is the assembly of high order oligomers. The intrinsic cooperativity in the formation of these complexes would dictate an all-or-none "digital" response in signal transduction. This point echoes Schrödinger's statement that the laws of physics are statistical throughout and therefore only approximate. Their precision is based on the large number of atoms intervening, and in the case of signaling, the large number of molecules in the same signaling complex, leading to the cooperative, digital behavior.

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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 10 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 recently 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. 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.



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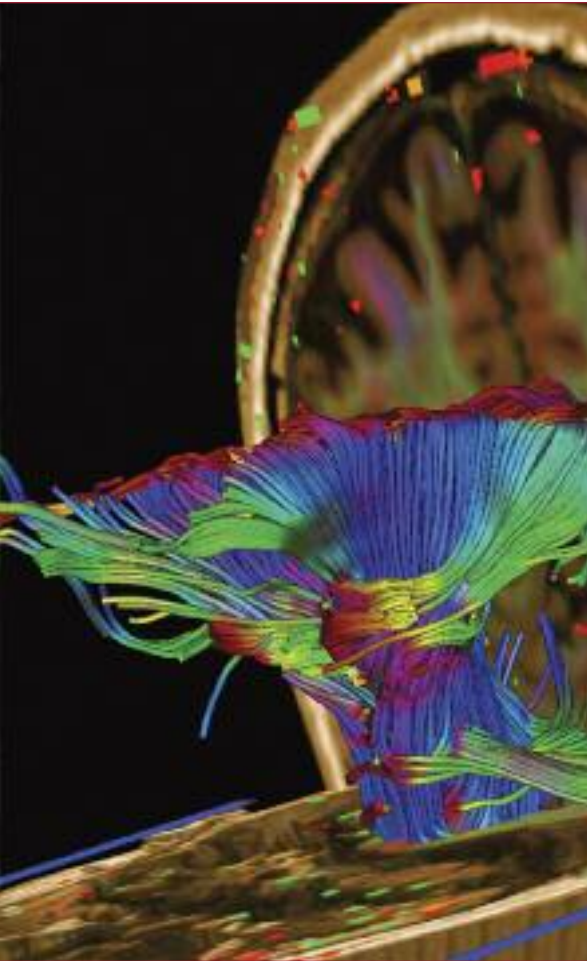
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Magnetic resonance image (MRI) fusion of anatomical and functional properties of the human brain. Color-coded white matter tractography visualizes neuronal fiber morphology, and a functional MRI overlay shows activation of the left motor cortex in response to a task, which in this case involves the subject thinking about playing a game of racquetball. (Courtesy of the Citigroup Biomedical Imaging Center)

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. Its analytical resources include quantitative PCR, 2 HPLCs, plate readers, automated liquid handling devices, and phosphor-/fluoro-imager, as well as a database of the available vectors and plasmids with extensive sequence and restriction mapping data. The facility of the Good Manufacturing Practice Core 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 and support of cutting edge imaging technologies applied to a wide range of human diseases. Major equipment includes 3.0 Tesla magnetic resonance imaging and spectroscopy systems, combined positron emission tomography/computed tomography, and comprehensive pre-clinical imaging instrumentation, including a 7.0 Tesla magnetic resonance imaging system and positron emission tomography. In addition, the Center houses a 19 MeV dual beam cyclotron.

The Center is staffed with physicists, radiochemists, technologists, and administrative personnel devoted to the development of new imaging techniques in support of scientific investigators from across the Medical College, as well as institutional partners including Memorial Sloan-Kettering Cancer Center and The Rockefeller University. Supported classes of imaging techniques include functional, anatomical, and spectroscopic magnetic resonance, and a fully equipped radiochemistry laboratory adjacent to the cyclotron for synthesis of radiotracers.

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.

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.

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, determination of ligand binding and characterizing conformation. 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 has 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.



State-of-the-art technology tools and systems, such as high resolution NMR spectroscopy, is used by Weill Cornell scientists to study a wide range of diseases in patients, from neurological and psychiatric disorders to cancer and vascular disease.

A decade ago, Weill Cornell Medical College celebrated the opening of its Whitney Pavilion Research Laboratories, which at the time increased laboratory research space by 26 percent. The laboratories were home to three major centers of advanced research in structural biology, neuroscience, and genetic medicine. In the 11 years since, the Medical College's research enterprise has continued to expand at an impressive pace with the ongoing recruitment of world-class faculty and the renovation of laboratories for clinical departments throughout the campus. Today, the Medical College's research environment is undergoing another transformation with the opening in 2010 of the Gertrude and Louis Feil Family Research Building and the planned completion of construction on the new Medical Research Building in December 2014.



Gertrude and Louis Feil Family Research Building

Gertrude and Louis Feil Family Research Building

The Gertrude and Louis Feil Family Research Building, made possible by a \$30 million gift from the Louis Feil Charitable Lead Annuity Trust as part of the Medical College's *Discoveries that Make a Difference* campaign, serves as a blueprint for 21st century science. The seven-story state-of-the-art research building is home to Weill Cornell's Division of Neurobiology and the multi-institutional Clinical and Translational Science Center. For the Division of Neurobiology, the 70,000-square-foot facility provides optimal space for investigations into stroke, Alzheimer's disease, and the factors that lead to both. The Division of Neurobiology comprises about 40 scientists who study similar topics but have varied areas of expertise, making efficient communication essential – and its space is designed to facilitate it. A glass wall marks an inner perimeter, within which laboratories run almost the entire length of the building. Downstairs, 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.



Rendering of the new Medical Research Building

Medical Research Building

When Weill Cornell Medical College debuts its new Medical Research Building in December 2014, its additional research capabilities will be extraordinary. The centerpiece of the Medical College's \$1.3 billion *Discoveries that Make a Difference* campaign, the 18-story, 480,000-square-foot building, located on East 69th Street between York and First Avenues, will more than double the Medical College's existing research space. The Medical Research Building will allow for the initial recruitment of 30 additional tenure-track faculty and become the hub for significantly expanded bench-to-bedside, health-focused research initiatives in cancer; children's health; diabetes, metabolic disorders, and obesity; global health and infectious diseases; heart health; neurodegenerative, neuropsychiatric diseases, and aging; and stem cell, developmental biology, reproductive and regenerative medicine, among others. Each of these areas will have their own dedicated floor, with some – such as cancer and cardiovascular disease – occupying two floors connected by an open staircase. The building's unique open floor plan will maximize collaboration among the Medical College's scientists and physician-scientists and feature adaptable spaces with workbenches that can shift as scientists move around and priorities change. Core facilities on each floor will provide centralized shared access to state-of-the-art technology, including high-throughput cell screening, genomics, and imaging technology, for use by faculty across all research areas. One floor will be dedicated to intercampus collaborations, providing a home for Ithaca-based researchers working with Weill Cornell scientists.

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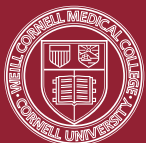
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