Clinical Research Training Faculty 2007-2008
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Introduction

Mount Sinai has maintained, since its inception, an outstanding reputation for innovative clinical investigation. Many groundbreaking contributions have been made by Mount Sinai physicians regarding the basic underpinnings and actions of various diseases (http://www.mssm.edu/theschool/history/reshistory.shtml). The increasing emphasis on rapidly translating basic science discovery to the development of new approaches to diagnose and treat disease requires the participation of physician-scientists who conduct clinical research, and close collaboration between basic scientists and clinical investigators.

Recognizing the need to provide the MSSM academic community with information about clinical/translational research interests and expertise of our faculty, a team representing leadership of the Graduate School of Biological Sciences, MD/PhD (MSTP) Program, Clinical Research Training Program (CRTP), and Doris Duke Program developed this resource. This Handbook provides contact information and summaries of the research interests of those MSSM faculty leading major clinical/translational research efforts.

We anticipate that this compendium will be used by pre- and postdoctoral students, fellows, house staff, and junior faculty who are seeking clinical research opportunities. Prospective MD, MD/PhD and PhD students are encouraged to use this book to explore such opportunities that would complement their basic research graduate programs. Please note that the descriptions are fully searchable on the World Wide Web at http://gsevals.mssm.edu/cr/

We encourage you to contact individual faculty members (contact information is provided) to learn more about their research programs. You may also contact the Graduate School Office for additional information.

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Box 1022
New York, NY 10029-6574
Clinical Research Disciplines: Translational research;

Specific Research Interest: Molecular genetics of cancers

Students: PhD: Erica Benson, Martina Kracikova
Postdoctoral Fellows: Gal Akiri, Pablo Lopez-Bergami, Cesar Munoz Fontella, Luca Grumolato, Zahid Khan, Risheng Ma, Salvador Macip, Alka Mahale, Sapna Vijayakumar, Xing Wang, Bo Zhao, Stefania Asciutti, Romi Biswas
Research Personnel: Scientists: Alka Mahale, Rui Fang Qiao -- Staff: Shen Yao, Hui Fang (Lisa) Qiao

Infrastructure Available: Guizhong Liu - Instructor

Summary of Research Studies:
The laboratory of Stuart A. Aaronson focuses on cancer gene discovery. Dr. Aaronson was one of the first investigators to apply insights concerning retroviral oncogenes to the identification of human cancer genes including, sis, ras, myc, erbB2, and to understanding of the involvement of altered growth factor signaling pathways in cancer. His current research includes investigations into the mechanisms by which tumor suppressor genes induce permanent growth arrest/senescence and the signaling pathways involved. He is examining the role of reactive oxygen species (ROS), which accumulate in response to p53 induction. He has also identified a novel p53 effector pathway involving sustained MAPK activation and identified growth factors and receptors, which are induced in a p53 dependent manner and contribute to activation of this signaling pathway. Finally, the lab is investigating other known and novel p53 response genes with respect to their involvement in cellular senescence.

Other projects include investigations of autocrine and paracrine acting growth factors PDGF, KGF, HGF, and Wnt ligands. In particular, the lab is investigating the mechanisms of activation of Wnt co-receptors, frizzled and LRP5/6, and the specific contributions of each receptor to canonical signaling through B-catenin upregulation. Another major goal is to elucidate transformation by up-regulated Wnt signaling and novel mechanisms activating this pathway in cancer cells. Finally, the laboratory is applying cDNA cloning technology and other functional genomic strategies to the discovery of novel targets for cancer intervention.


Aaronson, SA., Growth Factor and Receptor Tyrosine Kinases Science’s STKE , tr6 2005.


Maria Abreu, MD; Mount Sinai School of Medicine

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Clinical Research Disciplines: Patient-oriented research;

Specific Research Interest: Toll-like receptor signaling in the intestine, and inflammatory bowel disease.

Students: Arunan Vamadevan, Tyralee Goo
Postdoctoral Fellows: Masayuki Fukata, Suneeta Krishnareddy, Keith Breglio
Research Personnel: Anli Chen, Jason Cohen

Infrastructure Available: 1000 sq feet

Summary of Research Studies:
Emanating from my clinical interest in inflammatory bowel diseases, my laboratory explores several areas of basic and clinical research. Chronic idiopathic intestinal inflammation is characterized by aberrant bacterial reactivity and immune dysregulation resulting in damage to the intestinal lining. We wish to understand the paradox that the intestinal epithelium is usually not inflamed despite the presence of bacteria in the gut. To that end, we have focused on understanding the regulation of toll-like receptor (TLR) signaling in the intestine. TLRs are part of the innate immune response and activate pro-inflammatory signaling pathways in response to bacteria or bacterial products such as lipopolysaccharide (LPS). Our laboratory’s work has led the field in the characterization of the phenotype of the intestine with respect to bacterial product recognition. Our current work uses animal models of colitis to understand the role of TLRs in epithelial proliferation, repair, and bacterial homeostasis.

In the clinical realm, we have started a large IBD clinical phenotype and tissue repository. To date, we have the participation of over 400 patients or their family members. This repository will permit the identification of novel genes, biomarkers, and immunological pathways involved in IBD pathogenesis.

Location where the studies are carried out:
FPA


Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Kidney transplantation in highly sensitized patients, gene expression profiles of transplant kidney biopsies, immunosuppressive protocols in kidney transplant recipients

Research Personnel: Rosemarie Gagliardi, Clinical Research Director RMTI; Marjorie Small, Regulatory Compliance Manager

Infrastructure Available: The clinical research program includes a research director; regulatory manager; a senior nurse research coordinator and 10 research coordinators.

Summary of Research Studies:
See CV

Location where the studies are carried out:
FPA; Inpatient Hospital; GCRC; Laboratory

4- Akalin E, Dikman S, Murphy B, Bromberg JS, Hancock WW. Glomerular infiltration by CXCR3+ and ICOS+ activated T cells in chronic allograft nephropathy with transplant glomerulopathy. Am J Transplant 2003; 3:1116-1120
Specific Research Interest: Molecular basis of blood diseases

Summary of Research Studies:

The major emphasis of our laboratory is the study of the molecular basis of human blood diseases. There are two major model systems that we use for our studies. The first is the study of the molecular basis of human acute leukemia. More specifically, we study the role of a phosphoprotein p18 in the malignant phenotype of leukemic cells. We have cloned the human cDNA and chromosomal genes that encode this phosphoprotein. Our studies of the function of this gene suggest that it is involved in the control of the progression of cells through the G2-M phases of the cell cycle. p18 appears to be an important substrate for p34cdc2 kinase that is involved in cell cycle regulation. Our current studies aim at defining its exact role in the cell cycle and exploring its potential role in the process of differentiation of leukemic cells.

The second area of research that we are involved in is the study of the regulation of different members of the human globin gene family in health and in disease. We are particularly interested in the study of the normal regulation of the human alpha-globin gene. More recently, we have been able to extend our globin gene regulation studies to the field of globin gene therapy. We have developed a novel and very promising generation of retroviral vectors for gene therapy of disorders such as sickle cell disease and beta-thalassemia.


Juan Badimon, PhD; Mount Sinai School of Medicine
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Clinical Research Disciplines: Translational research; Behavioral medicine;

Specific Research Interest: Atherothrombosis, Lipids, Antithrombotics, Non-invasive imaging

Research Personnel: Randolph Hutter, Urooj M Zafar, Juan Viles, Brian Choi, Gemma Vilahur, Jose Rodriguez, Anthony Lopez, Stella Palencia, Karen Hiensch

Infrastructure Available: We use the shared facilities at MSSM

Summary of Research Studies:
The overall research interests of the Cardiovascular Biology Research Laboratory (Annenberg 24-30) are focused on a global approach to the prevention and treatment of atherothrombosis disease; one of the most recent lines of research is cell-based interventions for cardiac tissue regeneration. The laboratory is involved in translation research of the lipid and thrombotic processes affecting cardiovascular diseases. The lab has wide expertise in animal models of aterothrombosis (pigs, rabbits and mice). At the clinical level, Dr. Badimon’s lab is actively involved in the performance of Phase I and Phase IIa and b clinical trials to test new therapeutic interventions (antithrombotic and lipid-altering) for Cardiovascular Diseases.

Antithrombotic.
The group is actively involved in testing the antithrombotic activities of the newly developed antithrombotic agents. The most recent studies involved the study of direct thrombin inhibitors and specific inhibitors of the tissue factor pathway. Currently we are investigating the antithrombotic effects of a direct inhibitor of the coagulation Factor Xa.

Antiarteriosclerotic:
The lab has also been involved in clinical “proof-of concept” studies designed to establish the mechanisms of action of therapeutic interventions for the treatment of atherosclerosis. These studies combined the effects of the study drug not only at the systemic levels but also at the vascular levels by using the new non-invasive imaging modalities (MRI and MDCT). Statin, HDL-raiser and PPAR’s agonists are some of the studies carried out in the laboratory.

Location where the studies are carried out:
GCRC

Specific Research Interest: Molecular determinants of virulence of emerging viruses, including Ebola virus, Nipah virus and pandemic influenza virus

Students: PhD: St. Patrick Reid, Michael Ciancanelli, Charalampos Valmas, Kathilen Prins  
Postdoctoral Fellows: Patricia Aguilar, Lawrence Lenung, Osvaldo Martinez, Tshide Tsibane  
Research Personnel: Salman Chaudrey

Summary of Research Studies:
My interests lie in defining molecular determinants of virulence of emerging viruses. Two main avenues of research are being pursued.

1. The interferon (IFN) alpha/beta response is a major component of innate defense against virus infection. As a consequence, viruses have evolved ways to counteract this response. We are interested in defining the mechanisms by which emerging viruses block the IFN system. We have identified IFN-antagonists from a variety of viruses including Ebola virus, Nipah virus and Eastern equine encephalitis virus. The mechanisms by which these proteins function are diverse and a major focus of the lab. Two Ebola virus encoded IFN-antagonists identified by our group serve as useful examples. We have demonstrated that the Ebola virus protein VP35 functions to inhibit IFN-alpha/beta production by blocking the signaling pathways that activate interferon regulatory factor 3, a transcription factor which plays a central role in the induction of the IFN response. A second Ebola virus protein, VP24, acts by a separate mechanism and inhibits the JAK-STAT signaling pathways normally activated upon addition of IFN to cells. In this case, VP24 prevents the nuclear accumulation of activated STAT1 through an interaction between VP24 and the STAT1 nuclear localization signal receptor karyopherin alpha 1. We hypothesize that the combined functions of these two proteins contribute to the high virulence of Ebola virus. Studies on these and other IFN-antagonists also to seek to define how each protein contributes to viral pathogenesis and to determine whether these anti-IFN functions also affect host adaptive immune responses to infection.


Clinical Research Disciplines: Patient-oriented research; Health outcomes research;

Specific Research Interest: Interventions to reduce disparities and improve care of women with breast cancer. System, physician and patient factors affecting timeliness of needed urgent care.

Summary of Research Studies:
Dr. Bickell is a practicing primary care general internist in the Mount Sinai Division of General Medicine. She completed a primary care internal medicine residency at Montefiore Hospital and Medical Center in the Bronx, NY, a preventive medicine residency at the University of North Carolina at Chapel Hill where she received her M.P.H. in epidemiology, and a Robert Wood Johnson Clinical Scholars fellowship at University of North Carolina at Chapel Hill. In addition to academic appointments, Dr. Bickell served as a senior clinical research scientist at the NYS Department of Health in the Office of Quality Improvement.

Dr. Bickell's research focuses on the effect of patient characteristics including race, gender, insurance, experiences, attitudes and beliefs, on access to care and clinical outcomes, as well as the influence of physicians’ practice styles, attitudes, beliefs, and organizational characteristics on the quality and timeliness of care. Additional research interests include: assessing and improving the quality of care; reducing racial and ethnic disparities in care; community based participatory research; women’s health and gender-related issues; access to care for vulnerable populations; determinants and effects of continuity and coordination of care.

Dr. Bickell is the Principal Investigator of studies funded by the Agency for Healthcare Research and Quality and the National Cancer Institute to reduce racial disparities in and underuse of effective treatments for breast cancer using a physician-centered registry and tracking intervention, and a community-based patient-centered intervention. She is also involved in a regional American Cancer Society funded study to determine factors affecting vulnerable patients’ receipt of effective treatment for colorectal cancer.

Bickell N, Aufses AH, Chassin MR. Engaging Clinicians In a QI Strategy For Early-Stage Breast Cancer Treatment. QMHC 1998; 6:63-68.
Kenneth S. Boockvar, ;
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Dana H. Bovbjerg, PhD; University of Rochester School of Medicine and Dentistry

Associate Professor and Director, Biobehavioral Medicine Program, Department of Oncological Sciences

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Clinical Research Disciplines: Behavioral medicine;

Postdoctoral Fellows: Sara Higgins (PhD), Tiffany Edwards (PhD), Matthew Porter (PhD), Rachel Goldsmith (PhD), Catalina Lawsmin (PhD), Katarina Sussner (MPH)

Research Personnel: Brett Stoudt (MA), Nhan Truong (MA), Lukman Junaid (MS), Carol Pak (BA), Roy Kaluzhner (BA)

Summary of Research Studies:

My research focuses on biobehavioral processes in oncology. Broadly stated, the premise of the biobehavioral model of health and disease is that what people think and feel affects the state of their health and vice-versa. Effects are thought to be mediated by behavioral choices (e.g., smoking, cancer screening), as well as biological processes (e.g., endocrine and immune alterations), all of which are controlled by the central nervous system (CNS). According to this model, health, disease and response to treatment involve a complex interaction between pathological processes at the cellular (or molecular) level and outputs from the CNS. The CNS, in turn, is affected not only by factors in the external environment (e.g., stressors, social support), but also by factors in the internal environment (e.g., a developing cancer, chemotherapy agents), as well as by past experience (e.g., classically conditioned effects), response tendencies (e.g., personality), and heredity. Current programs of research in Biobehavioral Medicine, all based on this model, are exploring biobehavioral processes in healthy individuals at risk for cancer, individuals undergoing cancer treatment, and cancer survivors.


Wright CE, Valdimarsdottir HB, Erblich J, Bovbjerg DH. Poor sleep the night before an experimental stress task is associated with reduced cortisol reactivity in healthy women. Biological Psychology 2007; 74(3):319-27.
Andrea Branch, PhD; The Rockefeller University

Clinical Research Disciplines: Translational research;

Specific Research Interest: Molecular biology, pathogenesis, and treatment of the hepatitis C virus (HCV); development and application of novel bioinformatics tools for detecting cryptic genes and regulatory elements, with a special emphasis on infectious RNAs.

Students: PhD: Sarah Fishman, MD: Julio Gutierrez, PREP Scholar: Arielle Klepper
Postdoctoral Fellows: Cinzia Balestrieri
Research Personnel: Dr. Francis Eng, Dr. Jose Walewski

Summary of Research Studies:
Our group focuses on translational research on the hepatitis C virus. We work closely with clinical investigators to link our basic research to studies of human liver disease and its complications. We have used a combination of bioinformatics, classical methods of RNA biochemistry, and analysis of patient specimens to identify several novel genetic elements in HCV. Sarah Fishman (graduate student) is continuing to develop new bioinformatics tools and applying them to HCV sequence analysis. She and Cinzia Balestrieri (post doctoral associate) are using bioinformatics to design a prototypic cancer-causing HCV RNA sequence for testing in cell culture and animal models.

One of the new HCV genetic elements our bioinformatics tools revealed is an open alternate reading frame (ARF) whose products, ARFPs, are expressed during natural HCV infections. The ARF overlaps the viral nucleocapsid (core) gene. Dr. Francis Eng is using directed mutagenesis, transfection of tissue culture cells, and Western blot analysis to find the molecular switch that regulates expression of the core protein versus ARFPs. Dr. Jose Walewski is using indirect ELISAs to compare anti-ARFP antibody levels in patients with early versus late HCV liver disease. Dr. Joseph Odin is collaborating on FACS analysis and proliferation studies of T cell responses to ARFPs. Drs. Dawn Fishbein, Douglas Dieterich, Nancy Bach, Lewis Roberts (Mayo Clinic), and Kyong-Mi Chang (University of Pennsylvania) have clinical cohorts of patients with HIV, HIV/HCV co-infection, HCV, and other liver diseases and are collaborating by referring participants and/or providing banked specimens. Arielle Klepper (PREP student) is comparing anti-ARFP immune responses in HCV patients during acute and chronic phases of HCV infection and in patients undergoing interferon treatment. The immunology studies are being carried out to assess the potential of the ARFPs to be used as vaccine components.

Location where the studies are carried out:
East Building

Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: basic molecular and cellular transplantation immunobiology. Clinical interests: pediatric and adult liver, kidney, and pancreas transplantation.

Students: Levi Ledgerwood, Steven Esses
Postdoctoral Fellows: Yu Yang, Jordi Ochando, Nan Zhang, Ghirdari Lal, Helene Peche, Sheetal Ghelani
Research Personnel: Peter Boros, Minwei Mao, Dan Chen, Teresa Ku, YaoZhong Ding

Infrastructure Available: BASIC SCIENCE: complete array of equipment and facilities for cellular and molecular immunology including cell sorting, microvascular core, histology core, real time PCR, and confocal microscopy. CLINICAL RESEARCH: 10 full time research coordinators and research director, GCRC facilities. The clinical research program includes a research director, regulatory manager, a senior nurse research coordinator and 10 research coordinators.

Summary of Research Studies:
The process of the recognition of alloantigen, resulting in either graft rejection or tolerance to the graft, requires that T cells traffic to specific locations including the graft, secondary lymphoid organs, and other lymphoid tissue. Trafficking is controlled by the complex interaction of a variety of receptors and ligands including adhesion molecules and chemokines and their receptors. Recent studies in the laboratory show that proper trafficking is important for both rejection of, and tolerance to, allografts. Specific projects in the laboratory will investigate the cellular and molecular requirements for T cell trafficking during tolerance, and define novel molecules and pathways responsible for these important events. In particular, studies will focus on chemokine ligands and receptors, the novel molecule FTY720 that regulates sphingosine-1-phosphate receptor enzymatic pathways, and the interaction of antigen specific T cells and dendritic cells in the generation of suppressive regulatory CD4+CD25+Foxp3+ Treg.

While pancreatic endocrine islet transplantation is technically feasible, a number of hurdles remain, including the inability to purify and grow large quantities of islets or islet progenitors in order to transplant more individuals. The laboratory will investigate the use of embryonic stem cells or mature pancreatic progenitor cells as substrates for the identification and characterization of the stem cells and/or progenitor cells for pancreatic islets. A combination of cellular and molecular biology, gene trapping and flow cytometry will be used to purify and characterize these stem and progenitor cell populations to provide a high quality source of replenishable islets for transplantation and the cure of type I diabetes.

Location where the studies are carried out:
FPA; Inpatient Hospital; GCRC; Laboratory


Specific Research Interest: Protein expression and purification, enzymology, histology, animal models, protease involvement in arthritis and atherosclerosis

Summary of Research Studies:
Many human diseases are characterized by an excessive proteolytic degradation of proteins of the extracellular matrix (e.g., arthritides, osteoporosis, atherosclerosis, destructive lung diseases, cancer) or by an inappropriate proteolytic processing of proteins leading to autoimmune diseases and disorders caused by regulatory defects. Our laboratory is leading in the identification of novel therapeutic targets among intracellular lysosomal proteases and is focused on the role of these proteases in the pathogenesis of rheumatoid arthritis, atherosclerosis and certain forms of immune disorders. Our aim is to understand the role of lysosomal proteases in health and disease which may lead to new therapeutic approaches to treat these illnesses. To achieve our objective, we exploit an interdisciplinary approach which includes methods of molecular biology, enzymology, histology, animal models and a wide range of collaborations with clinical and biotech institutions.

Monte Buchsbaum, MD; University of California, San Francisco

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Training Areas(s): NEU*
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Specific Research Interest: Brain imaging with positron emission tomography and magnetic resonance imaging

Students: PhD: Jason Schneiderman
Postdoctoral Fellows: Serge Mitelman, M.D., Eran Chemenski, M.D.
Research Personnel: Erin Hazlett, Ph.D. (Associate Professor), Samantha Lincoln, Randall Newmark, Adam Robson, Yulia Tojosjan

Summary of Research Studies:
The lab employs brain imaging techniques positron emission tomography, anatomical magnetic resonance imaging, diffusion tensor imaging, functional magnetic resonance imaging. We study primarily psychiatric patients and carry out cognitive neuroscience studies in patients and normal controls. We have four grants on schizophrenia, aggressive-impulsive personality disorder, alcoholism and autism. We scan patients on Wednesday or Friday and carry out computer image analysis of these scans. These involve warping the brain to standard coordinates and then carrying out pixel-by-pixel statistics. Students have had the opportunity to participate in administering neuropsychological tests, assist in scanning procedures, and trace anatomical structures on MRI for coregistration with functional images form PET.


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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Pathogenesis of asthma in the elderly; regulation of mucus cell metaplasia in asthma

Students: None
Postdoctoral Fellows: None
Research Personnel: None

Location where the studies are carried out:
GCRC
Specific Research Interest: Molecular and cellular basis of Alzheimer's disease, autism, and schizophrenia

Students: PhD: Yuki Kajiwara, MD/PhD: Christopher Plescia, James Young
Postdoctoral Fellows: Guiqing Cai, Sonia Franciosi
Research Personnel: Daniel English, Mihaela Gazdoiu, Michael Gertner, Jennifer Reichert, Rebecca Vitale

Summary of Research Studies:
Our laboratory uses methods of molecular genetics, molecular biology, and cell biology to understand the biological bases of the three neuropsychiatric disorders, Alzheimer's disease, autism, and schizophrenia.

In Alzheimer's disease, the biochemical and genetic studies carried out by many laboratories have implicated several key proteins (APP, presenilin, etc.) in the pathogenesis of the disease. In addition, with the discovery of these proteins, a new form of intercellular signaling, termed regulated intramembranous proteolysis (RIP) was identified. In our laboratory, we are using cell biological methods to understand the signal transduction cascades initiated by RIP and we are using functional methods to dissect the biological basis of the disorder. Our laboratory is a part of the Alzheimer Disease Research Center (ADRC) in the Department of Psychiatry (http://www.mssm.edu/psychiatry/adrc.shtml).

Although clearly a disorder that is primarily genetic, the genes for autism have yet to be identified. Our laboratory is carrying out linkage and association analyses in over 400 multiplex families to identify genes that underlie autism. A long-term, focused effort on chromosome 2 has identified several genes of profound interest, which are now being studied for function. Dr. Buxbaum is Director for Molecular Genetics for the Seaver Autism Research Center (http://www.mssm.edu/psychiatry/autism/seaver.shtml).

Microarray analysis, carried out in the unique brain bank maintained by the Department of Psychiatry at Mount Sinai, implicated genes involved in myelination and oligodendrocytes in schizophrenia. We have subsequently embarked on wide-scale analysis of such genes in the disorder, looking both at genetic parameters and at further expression studies. In the expression studies currently underway, we are examining the relationship between genotype and expression levels in human brain.


Specific Research Interest: TGF-ß/Smad signaling networks and transcriptomics/genomics; gene expression; genomics; proteomics; microarray; systems biology; nephrology; nephropathy; hypertension; diabetes mellitus; pathobiology

Students: MD/PhD: Kremena Star
Postdoctoral Fellows: T.K. Niranjan
Research Personnel: Sandra Merscher-Gomez, Wenjun Ju, Shaolin Shi

Summary of Research Studies:
My research interests are focused on early pathomechanisms in diabetic nephropathy and non-diabetic kidney diseases that cause kidney failure (end stage renal disease). Millions of Americans are affected with chronic diabetic and non-diabetic kidney diseases. When kidneys fail, the average life expectancy is just over two years and survival depends on costly and disabling dialysis or transplantation treatments.

We use state-of-the-art genomics and bioinformatics approaches to discover and characterize new molecular targets and pathways associated with apoptosis, transdifferentiation, and fibrogenesis in specialized renal cells exposed to diabetic and other stresses. TGF-ß / Smad signaling pathways and transcriptional targets are a major theme because TGF-ß is a key mediator of these processes.

Model systems in the laboratory include renal cell culture and mouse models of diabetic and non-diabetic progressive renal disease. Our lab has expertise in molecular and cellular biology, transgenic and knockout mouse models, ES cells and homologous recombination, microarray and quantitative real-time PCR, genotyping, bioinformatics and computational biology. A new translational genomic medicine program aims at identification and validation of molecular biomarkers that predict progressive kidney disease in humans.


Specific Research Interest: Molecular chaperones in cellular quality control and cancer. Protein kinase maturation and signaling networks. Systems biology approaches to chaperone function.

Students: Nadinath Nillegoda
Postdoctoral Fellows: Atin Mandal, Maria Theodoraki

Summary of Research Studies:
My lab studies the role of molecular chaperones in quality control. Two main projects are currently investigating: (1) how chaperones buffer the signaling capacity of the cell and (2) therapeutic approaches to chaperone inhibition control tumor growth.

In the first project we use yeast genetics to investigate how a kinase-specific chaperone called Cdc37 functions with Hsp90 to regulate kinase folding and activity. We have used proteomic approaches to determine the extent that these chaperones interact with yeast kinome. We found that these chaperones control kinase abundance in a general manner by affecting translation, and we are currently investigating the mechanism underlying this effect. We are also using systems biology approaches to understand gene networks controlled by Cdc37 to elucidate its role in buffering signaling systems.

The second project takes a more direct approach to cancer therapeutics by investigating how an Hsp90 inhibitor (geldanamycin and its derivatives) mediates rapid proteasome-dependent degradation of protein kinases. We are investigating how kinases are targeted for ubiquitination and degradation, and which chaperones function in this capacity. We are focusing on kinases that control tumor growth (Akt and Cdk4) and the role played by oncogenes in modulating the sensitivity of cancer cells to this drug.

Further studies are aimed toward integrating the systems biology derived from the yeast genetic approach with cancer therapeutics.

Hengjun Chao, MD; Peking Union Medical College
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Web Page: http://www.mssm.edu/labs/chaoh01/

Specific Research Interest: Gene therapy for hemophilia, Gene therapy for muscular dystrophy, Immune responses following AAV-based hemophilia gene transfer,

Postdoctoral Fellows: Ellen Cohn, Arpita Bharadwaj, Qifeng Zhou.
Research Personnel: Meagan Kelly, Dongsoo Kim

Summary of Research Studies:
1. To investigate mechanisms underlying host immunity and tolerance to FVIII and FIX following AAV-based gene transfer.
2. To develop spliceosome-mediated RNA trans-splicing mediated RNA repair for gene therapy of Duchene Muscular Dystrophy using AAV as the delivery vector.

Recent Publications:


Dennis Charney, MD; Pennsylvania State University

Dean of Academic and Scientific Affairs, Dean's Office
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Professor, Department of Pharmacology and Systems Therapeutics
Professor, Department of Neuroscience
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Clinical Research Disciplines: Translational research, Patient-oriented research;

Specific Research Interest: Psychobiology of Mood and Anxiety Disorders. Experimental Therapeutics. Psychobiology of Resilience to Extreme Stress

Infrastructure Available: Administrative, Biostatistics, Clinical Trials, Database Management

Summary of Research Studies:
The Mood and Anxiety Disorders

Location where the studies are carried out:
GCRC, Imaging Facilities, Research Clinics
Mark Chassin, MD; Harvard University, MA, USA

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Summary of Research Studies:

Mark R. Chassin, M.D., M.P.P., M.P.H., is the Edmond A. Guggenheim Professor of Health Policy and Chairman of the Department of Health Policy at Mount Sinai School of Medicine. He is also Executive Vice President for Excellence in Patient Care at The Mount Sinai Medical Center. Before coming to Mount Sinai, Dr. Chassin served as Commissioner of the New York State Department of Health. He is a board-certified internist and practiced emergency medicine for 12 years. He is a member of the Institute of Medicine of the National Academy of Sciences and co-chaired its National Roundtable on Health Care Quality.

In 2003, The Mount Sinai Medical Center launched a major new initiative, led by Dr. Chassin, to achieve unprecedented excellence in all aspects of patient care: safety, clinical outcomes, the experiences of patients and families, and the working environment of caregivers. This initiative is a combined effort of The Mount Sinai Hospital and Mount Sinai School of Medicine and aims to create models of world-class excellence in patient care that produce substantial, measurable, and sustainable gains in all of these vital dimensions of patient care.

In 2001, Dr. Chassin was recognized for his contributions to the fields of quality measurement and improvement with several honors. He was selected in the first group of honorees as a lifetime member of the National Associates of the National Academies, a new program of the National Academy of Sciences recognizing career contributions to the National Academies. He also received the Founders' Award of the American College of Medical Quality and the Ellwood Individual Award of the Foundation for Accountability.

Dr. Chassin’s research focuses on developing measures of the quality of health care, using those measures to improve quality, and understanding the relationship of quality measurement and improvement to health policy. The Department of Health Policy conducts a wide variety of health services and health policy research studies. Dr. Chassin received his undergraduate and medical degrees from Harvard University and a master’s degree in public policy from the Kennedy School of Government at Harvard. He received a master’s degree in public health from the University of California at Los Angeles.

Jia Chen, ScD; Massachusetts Institute of Technology

Associate Professor, Department of Community and Preventive Medicine
Associate Professor, Department of Pediatrics
Associate Professor, Department of Oncological Sciences

Training Areas(s): GGS*

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Specific Research Interest: Molecular and genetic epidemiology; genetic susceptibility; gene-environment interactions in human diseases

Students: PhD: Xinran Xu; Andreas Diplas
Postdoctoral Fellows: Anu Voho; Lambertini, Luca;
Research Personnel: Yvonne Lee

Summary of Research Studies:
Research of our laboratory focuses on genetic susceptibility of complex diseases such as cancer and developmental deficits, and the interactions of inherited susceptibility with nutritional and environmental factors in pathogenesis of these diseases. Such work is of great importance in identifying disease-causing exposure, clarifying disease etiology, and designing prevention strategies through dietary and lifestyle modifications. We are also expanding our research in trying to understand how inherited genetic variability may influence disease progression and host response to treatment.

Currently, our laboratory is conducting several large population studies. We are using multidisciplinary approach to study genetic as well as epigenetic contribution to breast cancer. Utilizing blood and tissue specimens collected from participants in several large on-going population studies, we are examining the associations of genetic variability in one-carbon metabolism and risk of breast cancer as well as disease prognosis. We are also investigating how one-carbon metabolism may influence epigenetic processes breast carcinogenesis. Another line of our research examines genetic contribution to the detrimental effects of pesticides exposure on reproductive health in pregnant women and neurodevelopment in the newborns.


Summary of Research Studies:

My human subject research is focused on the discovery of new biomarkers for diseases, particularly diseases that are currently not well served in terms of diagnostics. Current screening for diseases such as prostate and breast cancer involves blood testing and physical examinations. These initial screens do not provide highly accurate information for diagnosis, and, invasive tissue biopsies, which can cause great discomfort to patients as well as requiring hospital resources for the surgical procedure, are necessary in order to make accurate diagnoses.

I am developing minimally invasive techniques, using surrogate tissues for diagnoses of cancer, as well as for psychiatric and neurological disorders, for which there are currently no good biological diagnostic tools.

I am currently recruiting patient and healthy control subjects through collaborations with clinicians and scientists at Mount Sinai and New York University. These studies have been funded by the NCI, the NIMH and the NIA.
Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Human immunodeficiency diseases; mechanisms and treatments

Infrastructure Available: administrative, regulatory, biostatistical support, databases Laboratory/ technical/ nursing/ personnel support, and clinical trial management.

Summary of Research Studies:
In this laboratory, the area of investigation is human immunodeficiency diseases and immuno-reconstitution. This work has been supported by research grants from the Food and Drug Administration and the NIH, Division of Allergy Immunology and Transplantation, Child Health and Human Development and USIDNet. We are investigating B, T cell and dendritic cell immunity in a primary immunodeficiency disease, common variable immunodeficiency (CVID.) A recent theme is the investigation of B cell memory in this and other immune defects; CD27+B cells, and especially isotype switched B memory cells are deficient, which is related to lack of normal vaccine responses. How the development of B cell memory relies upon triggering of Toll like Receptors is under investigation, using methylated oligonucleotides containing CpG motifs. TLR9 function is abnormal in this immune defect a factor that leads to poor B cell proliferation, loss of cytokine production, lack of cell adhesion and defective B cell memory responses; plasmacytoid dendritic cells are also unable to respond normally to these or other TLR ligands. We are also particularly interested in the role of specific mutations in the TACI gene, either producing or influencing the CVID phenotype, and the role of related TNF family members in the abnormal immunity in B cell defects. Further studies using gene arrays in the investigation of human B cell defects are ongoing. While the phenotype of this disease is hypogammaglobulinemia, T cell and antigen processing defects result in anergy, defective co-stimulation, accelerated apoptosis and deficient cytokine production. We previously found that some of these T cell defects could be reversed by the administration of IL-2, allowing an opportunity to explore some of the mechanisms by which this cytokine activates and regulates human T cell immunity. Since T cell receptor co-stimulation is abnormal in CVID, a deficiency of intracellular signaling pathways could explain defective proliferation, anergy, cytokine deficiency, and premature apoptosis. We have investigated in what way the CD28 signaling other co-stimulatory pathways differ from normal T cells, analyzing early signaling events, membrane reorganization, up-regulation of Bcl-xL, and the effects of receptor triggering on transcription and stabilization of cytokine mRNA. In other studies we have found markedly deficient production of IL-12 by monocyte derived dendritic cells, a deficit that could further lead to anergy. We have also investigated ICOS gene and its ligand, in CVID subjects, since mutation of ICOS in humans can lead to the CVID phenotype.

Location where the studies are carried out:
5 East 98th street

Terry Davies, MD; University of Newcastle-upon-Tyne
Professor, Department of Medicine (Endocrinology, Diabetes & Bone Disease)
Professor, Graduate School of Biological Sciences
Professor, Center for Immunobiology
Professor, Department of Obstetrics, Gynecology and Reproductive Science

ProfessorTraining Areas(s): PSB*, IMM

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Clinical Research Disciplines: Translational research;

Specific Research Interest: Mechanisms in autoimmune disease with an emphasis on autoimmune thyroid disease

Postdoctoral Fellows: Marco Agote-Robertson PhD, Sayed Moshad PhD, Chris Michalek MD, PhD, Risheng Ma, PhD
Research Personnel: Rauf Latif PhD, Xiaoming Yin PhD, Zhong Yao

Infrastructure Available: All you need can be made available

Summary of Research Studies:
Autoimmune diseases of the thyroid- Murine models of human Graves' disease, Hashimoto's disease, and post-partum thyroiditis.

Research areas of emphasis include:
- Molecular characterization of TSH receptor post-translational processing including dimerization and cleavage;
- Development and characterization of monoclonal antibodies to the TSH receptor with thyroid stimulating activity.
- The role of fetal microchimerism in the susceptibility to autoimmune thyroid disease.
- The genetics of human autoimmune thyroid disease

The TSH receptor: This is the major autoantigen in Graves' hyperthyroidism and remains an elusive quarry ten years after it was cloned. Emphasis is placed on processing events involved with multimerization and intramolecular cleavage of the TSHR. We are also continuing to examine the role of the TSH receptor as a major autoantigen in Graves' hyperthyroidism, a uniquely human disease and the development of new mouse models for this disease which have confirmed its pivotal role.

Complex Genetics: The aim of this research is to detect the susceptibility genes for autoimmune thyroid disease using highly polymorphic microsatellite-based whole genome screening of informative families with Graves' disease and/or Hashimoto's disease. Our group is one of the few with experience in the analysis of families with these disorders and we have a large collection of well characterized families to study. Current area of emphasis is X CHROMOSOME INACTIVATION (xci) and how it regulates the autoimmune response.

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Robert Desnick, MD/PhD; Mount Sinai School of Medicine

Professor and Chairman, Department of Genetics and Genomic Sciences
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Clinical Research Disciplines: Translational research; Patient-oriented research; Health outcomes research; Molecular epidemiology;

Specific Research Interest: Human molecular genetics; genomics; gene therapy

Students: Visiting PhD: Luis Cunha
Postdoctoral Fellows: Sonia Clavero, Robert Dobrovolny, Smitha Gopakumar, Mert Sozen, Maikiko Yasuda
Infrastructure Available: Laboratory well-equipped to perform experiments, Department has DNA sequencing, proteomics (mass spectroscopy), tissue culture, and pathology cores.

Summary of Research Studies:
Molecular Genetics and Treatment of Lysosomal Storage Diseases; For the past two decades, studies of the lysosome and the pathogenesis and treatment of lysosomal storage diseases have been a major research theme of this laboratory. For example, in Fabry disease (alpha-galactosidase A [alpha-Gal A] deficiency), our group isolated the human alpha-Gal A gene, developed novel overexpression methods, and made knock-out mice with Fabry disease for preclinical studies of enzyme and gene therapy. These basic science studies provided the rationale for the clinical trials of enzyme therapy that proved effective in this disease. These studies culminated in approval of enzyme replacement for Fabry disease by the FDA in April 2003. Current studies are directed to: 1) develop novel therapeutic strategies to treat Fabry disease and other disorders due to protein misfolding by rescue of the misfolded protein, 2) develop gene replacement, and 3) identify and characterize mutations in the alpha-Gal A gene which cause Fabry disease. These represent opportunities for predoctoral/postdoctoral fellows to perform fundamental bench to bedside research.

Molecular Genetics of the Inherited Porphyrias: The inherited porphyrias are inborn errors of heme biosynthesis, each resulting from the deficient activity of a particular enzyme. Our laboratory has: 1) developed assays, 2) purified these enzymes, 3) isolated and characterized the cDNAs and genomic sequences encoding several enzymes, and 4) identified the molecular lesions causing the different porphyrias. Current efforts are focused at developing novel gene and stem cell therapies for the porphyrias using knockout/knock-in mice, generated in our laboratory.

Genomics, Pharmacogenetics/Pharmacogenomics, and Gene Discovery: Gene discovery efforts are directed to: 1) identify genes underlying various Mendelian and complex diseases using positional cloning and genome-wide association strategies, 2) identify genes by functional genomics, and 3) determine pharmacogenetic traits as a focus for studying human genetic variation. These studies have led to the discovery of the genes for several diseases and the opportunity to develop accurate diagnostic tests and new therapies. Studies are underway to identify variations in human genes involved in the metabolism of drugs that cause common and often life-threatening adverse responses. By identifying the key genetic variations using single nucleotide repeats (SNPs) in an individual's genome that alter a drug's activation, metabolism, transport, distribution and clearance, a person's pharmacogenetic profile can be determined, permitting personalized drug selection and dosage.

Location where the studies are carried out:
Basic research: Icahn Medical Institute (14th fl); Clinical studies: GCRC

6 - Scott et al.: CYP2C9, CYP2C19 and CYP2D6 allele frequencies in the Ashkenazi Jewish population. Pharmacogenetics, in press.
Clinical Research Disciplines: Translational research, Patient-oriented research;

Specific Research Interest: Molecular genetics of inherited metabolic disease and disease gene discovery

Students: PhD: Audrey Au, Andrew O'Shaughnessy PREP: Sarah Ann Anderson
Postdoctoral Fellows: Qiao Sun, Peter McGuire
Research Personnel: Alex Johnson, Albert Shen

Summary of Research Studies:
The focus of activity in the laboratory is the application of genomic approaches for the identification and characterization of genes that, when mutated, lead to inherited diseases in humans. Current projects focus on traits in which the disease phenotype suggest that identification of the disease gene will allow fundamental insights into more broadly relevant clinical conditions.

Current projects include:

**Tubulin-folding defects in human disease**
The genetic basis of HRD/AR-KCS has been determined to be mutation of TBCE, a tubulin-specific chaperone. The phenotype of affected humans includes mental retardation, ocular malformations, skeletal abnormalities, immune dysfunction and hypoparathyroidism from failure of parathyroid development. Biochemical characterization has confirmed that the disease pathophysiology is not caused by loss of tubulin folding function, suggesting a novel role for the protein. Interaction with a microtubule growth regulator, EB1 has been demonstrated, consistent with a role in organization of microtubules. Current work is focused on validating this proposed function and exploring the role of TBCE in maintaining microtubule stability, a potential common pathogenic pathway disturbed in several neurodegenerative disorders.

**Chemokine mutations in WHIM syndrome**
WHIM syndrome is a rare dominant immunodeficiency with hypogammaglobulinemia, neutropenia and predisposition to warts. All kindreds evaluated have been found to carry truncation mutations in the tail domain of the CXCR4 chemokine receptor. A transgenic mouse model of the disease will be established to allow detailed characterization of the hematologic defects, allowing a more complete understanding of the biology of the chemokine ligand in immune function. These insights may also provide information on the nature of the normal immune response to HPV infection.

**Genetic basis of lymphedema and choanal atresia**
We have ascertained a large multiplex pedigree with autosomal recessive inheritance of lymphedema and choanal atresia. Linkage studies have been successful in mapping the disease locus and positional cloning studies are ongoing. Basic molecular mechanisms of lymphangiogenesis have only recently been described, suggesting that identification of the gene involved in this phenotype will contribute significantly to our understanding of this important vascular system.

Clinical Research Disciplines: Patient-oriented research;

Specific Research Interest: New HCV and HBV drugs. Pharmokinetics of drugs in liver disease. HCV, HBV in HIV

Research Personnel: Alison Uriel, Juanita Jones

Infrastructure Available: Administrative support and clinical trial management

Summary of Research Studies:
HCV Treatment with polymerase inhibitor NM283, Protease inhibitor VX 497 and BMS protease inhibitor.
HBV treatment with new drugs
Pharmacokinetics of efavirenz in Childs B cirrhotics

Location where the studies are carried out:
GCRC 5 E 98th St


M. Rodriguez-Torres,1* F.J. Torriani,2 V. Soriano,3 M. J. Borucki,4 E. Lissen,5 M. Sulkowski,6 D. Dieterich,7 K. Wang,8 J.-M. Gries,8 P.G. Hoggard,9 D. Back,9 for the APRICOT Study Group Pharmacokinetics of Ribavirin & NRTIs in APRICOT Study Antimicrobial Agents and Chemotherapy, October 2005

Reichenberg, Abraham a; Gorman, Jack M a; Dieterich, Douglas T Interferon-Induced Depression and Cognitive Impairment in Hepatitic C Virus Patients: A 72 Week Prospective Study. AIDS Vol. 19, 2005


Specific Research Interest: Psychosocial Factors In Preventive Health And Cancer Treatment Related Adjustment Disorders

Research Personnel: Justin Mitchiner, Allyson Ross, Kim Freeman

Summary of Research Studies:

Dr. DuHamel and her colleagues are evaluating a pain communication skills intervention developed to improve patient-physician communication, which in turn is hypothesized to improve patients' pain management and quality of life.

With collaborators in the Departments of Gastroenterology, and Oncological Sciences, Dr. DuHamel is investigating the impact of educational materials designed for African Americans to increase their rates of endoscopic CRC screening.


With collaborators at multiple sites, Dr. DuHamel and her colleagues are evaluating a psychosocial intervention designed to improve long-term adjustment in survivors of traditional and mini/light bone marrow and stem cell transplantation (BMT/SCT).


Andrew Dunn, MD; New York University

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Clinical Research Disciplines: Patient-oriented research;

Specific Research Interest: Anticoagulation and Thrombosis; Outpatient Deep Vein Thrombosis Treatment; Mathematical Modelling of Warfarin Dose Adjustments

Summary of Research Studies:
Dr. Andrew Dunn graduated for New York University Medical School in 1992, and completed a residency in internal medicine at Mount Sinai Medical Center in 1995. Dr. Dunn remained at Mount Sinai as a member of the faculty in the Division of General Medicine, and is currently a Practice Chief in the General Medicine Clinic and Director of the Primary Care Anticoagulation Service. His primary area of clinical and research interest is anticoagulation and thrombosis. Dr. Dunn has developed and directs an innovative program to facilitate home treatment of deep vein thrombosis. He has given numerous lectures in this field, including a workshop at a National meeting of the Society of General Internal Medicine. In addition, he has presented his research at regional and national meetings, and published several articles on this topic. He is currently a principal investigator for randomized trials of a novel anticoagulant for the treatment of deep vein thrombosis and pulmonary embolism, as well as leading an investigation of the use of low-molecular-weight heparin for perioperative anticoagulation for patients on long-term warfarin.

Richard A. Embry, PhD; University of California, Berkeley, CA
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Summary of Research Studies:
Dr. Embry’s research interests focus on the evaluation of mental health and child welfare system reform efforts; development and dissemination of evidence-based practices with children; and interpersonal violence in the lives of people with physical disabilities.


Sukru Emre, MD; University of Istanbul in Turkey

Professor, Department of Surgery
Professor, Department of Pediatrics
Professor, RMTI (Transplantation Institute)

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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Hepatitis B pre and post transplant treatment; transplant immunosuppression protocols; steroid withdrawal protocols; immunosuppression free protocols;

Research Personnel: Rosemarie Gagliardi, Clinical Research Director RMTI; Marjorie Small, Regulatory Compliance Manager

Infrastructure Available: The clinical research program includes a research director; regulatory manager; clinical research supervisor; nurse research coordinators and 10 research coordinators.

Summary of Research Studies:
Dr. Emre earned his M.D. at the University of Istanbul in Turkey. He went on to complete his residency in Surgery and a subsequent fellowship in Hepatobiliary Surgery, both at the University of Istanbul. In 1988, he was appointed Associate Professor of Surgery at the University of Istanbul. In 1989, Dr. Emre came to U.S. to study transplant immunology and clinical Liver transplantation. He first did his research fellowship at SUNY Health Science Center and then joined the Liver Transplant team at Mount Sinai in 1990. Dr. Emre's major academic devotions have been solving complex clinical problems in both pediatric and adult liver transplantation and maximizing the availability of donor organs. He has a particular interest in the application of split-liver and living-related techniques, and in 1997 hosted a major national split-liver workshop. At the end of 1997, as a senior faculty member, Dr. Emre was appointed Director of Pediatric Liver Transplantation Program at the Recanati Miller Transplantation Institute.

Under Dr. Emre's leadership, the pediatric transplant program at Mount Sinai has become one of the nation's best, with a 95 percent one-year patient survival rate and a 2 percent five year patient survival rate. Dr. Emre also helped develop and structure Mount Sinai's Transplant Surgery Fellowship Program, one of the most sought-after training programs in the country. His many society memberships included the American College of Surgeons, American Society of Transplant Surgeons, The American Association for the Study of Liver Diseases, The International Liver Transplant Society, New York Transplantation Society, New York Surgical Society, United Network of Organ Sharing, American Hepato-Pancreato-Biliary Association, International Pediatric Transplant Association, the Publication Committee of Studies for Pediatric Liver Transplantation, and the UNOS Pediatric Transplantation Committee. He currently serves on the editorial boards for the Annals of Medical Sciences, Pediatric Transplantation, and Liver Transplantation. Dr. Emre is the author of over 140 publications and seven book chapters.

Location where the studies are carried out:
FPA; Inpatient Hospital; GCRC

Stephanie A. Engel, 

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Susan Essock, PhD; Mount Sinai School of Medicine

Professor and Director of the Division of Health Services Research, Department of Psychiatry

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Clinical Research Disciplines: Health outcomes research;

Specific Research Interest: Mental Health Services Research

Summary of Research Studies:
- Assertive Community Treatment for the Dually Diagnosed - The goal of this project is to extend the follow up period to 8-10 years in the Connecticut Dual Diagnosis Study, to yield critical information on the pattern, stability, prediction, timing and correlates of remissions of substance use disorder in the persons with SMI.
- Effectiveness of Switching Antipsychotic Medications - The goal of this project is to assess the relative effectiveness of staying on a current antipsychotic medication versus switching to a different one.
- Evaluation of Kids Oneida Phase III, Waiver and ICM Programs - The goal of this project is to evaluate the impact of the New York State Medicaid waiver for children’s services and to compare client-level outcomes under the Waiver program to those under Intensive Care Management programs.
- Meeting the Mental Health Needs of NYC Youth Living in Group Homes - The goal of this project is to develop and pilot test an evidence-informed practice model for youth with serious mental health needs who also present placement challenges within the New York City child welfare system.
- Developing Monitoring Tools to Improve Accountability for Quality - The goal of this project is to assist the New York City Department of Health and Mental Hygiene in evaluating the effectiveness of a re-focused Early Intervention program.
- Evaluation of Project Liberty in Response to the 9/11 Terrorist Attacks - The goal of this project was to assist the New York State Office of Mental Health in evaluating the impact and effectiveness of its response to the attacks on the World Trade Center.
- Cost-Effectiveness of a Consumer Advocacy Program - The major goal of this project was to evaluate the cost effectiveness of a consumer-operated advocacy training program.
- KIDS Oneida Phase II Evaluation and Evaluation of the Implementation of Brooklyn Housing Project - The goal of this project was to evaluate the impact of the New York State Medicaid waiver for children’s services and to evaluate the impact of changes in the provision of housing in Brooklyn for people with serious mental illnesses.

RECENT PUBLICATIONS:


Jackson CT, Covell NH, Frisman HK, Essock SM: Validity of self-reported drug use among people with co-occurring mental health and substance use disorder. Journal of Dual Diagnosis, 1: 49-63, 2005


Zahi Fayad, PhD; University of Pennsylvania

Professor, Department of Radiology
Professor, Department of Medicine (Cardiology)
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Specific Research Interest: Using imaging to study cardiovascular disease

Students: Claudia Calcagno (MD), Wei Chen (PhD), Anne Beilvert, Mark Lobatto, Eik Leupold, Kelly Myers, Anne Bystrup
Postdoctoral Fellows: Venkatesh Mani (PhD), Karen Saebo (PhD), David Cormode (PhD), Silvia Aguiar (MD), Esad Vucic (MD), Alessandra Barazza (PhD), Stephane Silvera (MD), Hamza El Aidi (MD), Rima Fayad (MPH), Katsumi Hayashi (MD)
Research Personnel: Daniel Samber, Yu Zhou, Linda Yang (MD), Frank Macaluso, Anna Oltarzewska, Lena Marra

Summary of Research Studies:
Fayad's current research is in the development and use of multimodality cardiovascular imaging including, magnetic resonance (MR), computed tomography (CT), and positron emission tomography (PET), and molecular imaging using nanotechnology to study cardiovascular disease.

His recent focus has been on the noninvasive assessment of atherosclerosis. He holds several patents in the field of imaging. Clinical and experimental observations have established the importance of atherosclerotic plaque composition, rather than size, in lesion vulnerability and subsequent thrombogenicity upon disruption. Dr. Fayad has developed several techniques for the in vivo assessment of atherosclerotic plaques and for the study of cardiovascular morphogenesis and function using innovative imaging method.

The work is currently focused on preclinical studies in animal models of cardiovascular disease and clinical human trials using a variety of molecular imaging techniques.


Ana Fernandez-Sesma, PhD; Mount Sinai School of Medicine of the City University of New York
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Specific Research Interest: I am interested in the antiviral immunity against human pathogens (influenza and dengue virus) using human systems

Students: Kester Haye and Hannah Phipps-Yonas (Shared with Dr. Thomas Moran)
Research Personnel: Dabeiba Bernal-Rubio

Summary of Research Studies:
In collaboration with Dr. Thomas Moran’s laboratory, our main interest is the interaction of different viruses with human dendritic cells (DCs), since DCs are the antigen presenting cells responsible for the initiation of antiviral immune responses (Th1).

One of our projects is to study the effect of viral antagonists on the maturation pattern of human DCs. By using quantitative real time PCR (qRT-PCR) and other techniques such as flow cytometry and multiplex ELISA, we can determine the changes in the maturational profile of humans DCs after infection with different viruses. We have used influenza viruses and recombinant NDV viruses in our system. Data generated from these studies contributed to the funding of the Center for Investigating Viral Immunity and Antagonism (CIVIA).

As an independent researcher, my main project has been to study the interaction of Dengue virus (DV) with dendritic cells and the initiation of immunity by this virus using human cells. We also want to analyze the effect of pre-existing immunity to DV in the initiation of immunity by human DCs. We have an ongoing collaboration with Dr. Jorge Muñoz at the Centers for Disease Control (CDC) in Puerto Rico for this project. Additionally, we are generating recombinant NDV expressing DV proteins in collaboration with Dr. Adolfo García-Sastre’s laboratory.


Daniel S. Fierer, MD; Yale University School of Medicine

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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: HIV persistence despite therapy; HIV infection of kidney and brain

Research Personnel: Jonathan Williams, M.D.
Paul Frenette, MD; Laval University

Irene and Dr. Arthur Fishberg Associate Professor, Department of Medicine (Clinical Immunology)
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**Specific Research Interest:** 1) Trafficking of hematopoietic stem cells (HSCs) and regulation of HSC niche 2) Mechanisms mediating vascular occlusion in sickle cell disease

**Students:** MD/PhD: Wei-ming Kao
**Postdoctoral Fellows:** Michela Battista, Ph.D., Jack Chang, Ph.D., Simon Mendez-Ferrer, Ph.D.
**Research Personnel:** Anna Peired, MS, Andres Hidalgo, Ph.D. (Research Associate), Patricia Shi, M.D. (Clinical Research Associate)

**Summary of Research Studies:**
Hematopoietic progenitor trafficking: The molecular mechanisms responsible for the trafficking of hematopoietic stem / progenitor cells (HSC / HPC) between the bone marrow and the blood compartments. HSC migration in and out of the BM is a critical process that underlies modern clinical stem cell transplantation. We are interested in the molecular mechanisms involved in these activities. We have recently described a role of the sympapthetic nervous system in regulating the attraction of stem cells to their niche. A major focus in the laboratory currently is to dissect the neural pathways that influence niche function using genetic and pharmacological gain- and loss-of-function approaches.

Adhesion mechanisms of sickle cell vaso-occlusion: A separate project in the lab concerns the role of adhesion molecules in the pathophysiology of sickle cell disease. Sickle cell disease originate from a single base mutation in the beta globin gene, leading to hemoglobin polymerization, cell sickling and vascular occlusions. We have showed using intravital microscopy of the cremaster muscle that sickle erythrocytes interacted with leukocytes adherent on the vessel wall and that these interactions lead to vascular obstructions. We have recently begun analyses using a novel digital multichannel fluorescence videomicroscopy system that allows us to dissect in real time the cellular and molecular components that participate in the vasoocclusion.


Hidalgo A, and Frenette PS. Enforced fucosylation of neonatal CD34+ cells induces selectin ligands that enhance the initial interactions with microvessels but not homing to bone marrow. Blood 2005 105(2):567-75.


Katayama Y, and Frenette PS. Galactocerebrosides are required postnatally for stromal-dependent bone marrow lymphopoiesis. Immunity 2003 18:789-800.
Scott Friedman, MD; Mount Sinai School of Medicine

Irene and Dr. Arthur M. Fishberg Professor, Department of Medicine (Liver Diseases)
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Clinical Research Disciplines: Translational research, Patient-oriented research;

Specific Research Interest: 1) Role of KLF6 tumor suppressor gene in cancer pathogenesis; 2) Molecular regulation of hepatic fibrosis; 3) Testing of novel antifibrotic therapies in preclinical models and human trials

Students: MD/PhD: Ursula Lang, Zhara Ghiassi-Nejad; Doris Duke Medical Student Research Fellow: Andrew Paris
Postdoctoral Fellows: Augusto Villanueva, M.D.; Pippa Newell M.D.; Mirko Tarrochi, M.D.; Beatriz Muniz, M.D.; Sara Tofannin, Ph.D.
Research Personnel: Johnny Loke, M.S. (Lab Manager); Feng Hong M.D.; Judit Peix; Jinsheng Guo M.D, PhD. (visiting scientist)

Infrastructure Available: Liver cell culture laboratory; Real time PCR; All standard Cell and Molecular Biology tools; Fibrosis morphometry; Clinical Research management team

Summary of Research Studies:
Role of KLF6 in Cell Growth and Human Cancer. We have cloned a novel Kruppel like factor, KLF6, from liver that is ubiquitously expressed, and mutated in a number of human cancers. Major KLF6-related research projects are:
- Identification of KLF6 transcriptional targets by array
- Role of KLF6 in liver development
- Inactivation of KLF6 in human cancers, esp. hepatocellular carcinoma
- Animal models of cancer with KLF6 dysregulation
- KLF6 Interacting proteins
- Animal models of KLF6 dysregulation (tissue specific KO; KLF6 +/- mice responses to injury and carcinogens)

Molecular Regulation of Hepatic Fibrosis. Our work explores the molecular mechanisms of wound healing and fibrosis in liver. We use a variety of animal and cell culture models to identify key inflammatory mediators and signaling molecules regulating the activation of hepatic stellate cells, the principle fibrogenic cells in liver. Additionally, we test candidate antifibrotic lead compounds to develop potential new therapies for patients with chronic fibrosing liver diseases.

Specific projects include:
- Testing of antifibrotic lead compounds in animal models
- Clinical trials of antifibrotic therapies in patients with chronic liver disease
- Exploration of mechanisms underlying risk-associated genes in hepatic fibrosis
- Role of KLF6 splicing in hepatic stellate cell activation

Location where the studies are carried out:
Icahn Medical Institute 1176

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Summary of Research Studies:
Valentin Fuster, MD, PhD, is the director of the Zena and Michael A. Wiener Cardiovascular Institute, the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, and the Richard Gorlin, MD/Heart Research Foundation Professor at Mount Sinai School of Medicine. Dr. Fuster earned a medical degree from Barcelona University in Spain. He completed an internship at Hospital Clinic in Barcelona and residency at the Mayo Clinic. Dr. Fuster is the recipient of three major ongoing National Institutes of Health grants. He has published more than 400 articles on the subjects of coronary artery disease, atherosclerosis and thrombosis, and he has become the lead editor of a major textbook on cardiology, The Heart (previously edited by Dr. J. Willis Hurst). He contributed first hand to the launching of the new Forum for Young Investigators of the American Heart Association (AHA).

Dr. Fuster is past president of the AHA and president-elect of the World Heart Federation. He is also former chairman of the Fellowship Training Directors Program of the American College of Cardiology (ACC). Dr. Fuster is a member of several other professional organizations, including the Institute of Medicine of the National Academy of Sciences and former member of the National Heart, Lung, and Blood Institute Advisory Council. Recently, he was named editor of the new Nature journal on cardiovascular medicine, Nature Clinical Practice Cardiovascular Medicine.

Dr. Fuster is a recipient of the Andreas Gruntzig Scientific Award of the European Society of Cardiology, the Lewis A. Conner Memorial Award for Scientific Accomplishments by the AHA, and the Distinguished Scientist Award from the ACC. Prince Felipe of Asturias awarded Dr. Fuster the 1996 Principe de Asturias Award of Science and Technology, the highest award given to Spanish-speaking scientists. Dr. Fuster received the James B. Herrick Achievement Award from the Council of Clinical Cardiology of the AHA and the Distinguished Service Award from the ACC. In April 2003, he received the Gold Heart Award, the AHA's highest award. Most recently, he was selected as a Distinguished Scientist of the AHA, one of the highest honors presented to only 15 scientists for their work in cardiovascular research over the last few years.
Janice Gabrilove, MD; The Mount Sinai School of Medicine

The James F. Holland Professor, Department of Medicine
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Clinical Research Disciplines: Patient-oriented research;

Specific Research Interest: Our research focuses on the development & conduct of scientifically based hypothesis-driven pilot experimental therapeutic strategies designed to exploit inherent biological features of specific malignant disorders.

Students: PGY2 trainees, Elizabeth Comen and Andrew Epstein
Postdoctoral Fellows: Karin Adelson; Sanjay Sharma; Cathy Marcotrigiano
Research Personnel: Qian Zhuo; Udi Gelbshtein; NP

Infrastructure Available: Office of Clinical Trials in the Department of Medicine and in the Division of Hematology/Oncology, which provides financial, regulatory and real time data management as well as clinical research assistants and access to research nursing time. Clinical Trial Management System, to be launched by the Department of Medicine

Summary of Research Studies:
We are currently conducting clinical research studies in the following areas:
1) Overcoming transcriptional Repression in AML. In this instance, we are conducting studies to evaluate the role of histone deacetylase inhibitors alone and in combination with lineage specific maturation agents, in an effort to foster clonal extinction of leukemic cells, by forcing cells to mature and exit the proliferative self renewing compartment; 2) inhibition of autocrine and microenvironmentally presented growth factors which contribute to delays in programmed cell death characteristic of disorders such as CLL and myeloma; 3) strategies to foster erythroid reconstitution in anemia of chronic disease/cancer as well as in the setting of low risk myelodysplastic syndrome, by interfering with negative regulatory cytokines contributing to impaired erythroid development or accelerated apoptosis and ineffective erythropoiesis; 4) strategies to interfere with specific signaling cascades of critical importance in specific oncologic conditions.

Specific Research Interest: Molecular biology of RNA viruses

Students: PhD: Joseph Ashour, Mark A. Chua, Natalia Frias-Stäheli, Estanislao Nistal-Villán, Adam Vigil
Postdoctoral Fellows: Svetlana Bourmakina, Elena Camero, Luis Martínez-Sobrido, Alicia Solórzano, Masaki Mibayashi, Randy Albrecht
Research Personnel: Richard Cadagan

Summary of Research Studies:
Our laboratory has developed several techniques which allow the genetic manipulation of negative strand RNA virus genomes. We are currently using this methodology in two major research areas.

Generation of negative strand RNA virus vectors. RNA viruses are effective inducers of humoral and cellular immune responses. Therefore, attenuated RNA viruses may be used to express protective antigens of other pathogens for which no safe attenuated strains are available. We are involved in the construction of recombinant influenza and Newcastle disease viruses expressing a variety of B-cell and T-cell epitopes from different pathogens. These recombinant viruses are being used to elicit immune responses against their expressed antigens. Specifically, we are interested in the generation of influenza virus vectors expressing selected antigens from HIV-1, malaria parasites, and tumor cells as a means to induce protective or therapeutic immune responses against these pathogenic agents.

Studies on the molecular pathogenesis of RNA viruses. The functions of cis- and trans-acting elements in the replication cycle of influenza virus and the interactions of such viral components among themselves and with host components are being investigated. For this purpose, we are introducing specific mutations into the genome of the virus, and the phenotypic characteristics of the generated virus mutants are being analyzed. These studies are also focused on the generation of attenuated influenza viruses with potential use as live vaccines against influenza. In addition, we are investigating the ability of different RNA viruses, including influenza, respiratory syncytial, dengue and SARS viruses, to inhibit the induction of innate antiviral immune responses in their hosts.


Clinical Research Disciplines: Patient-oriented research; Molecular epidemiology;

Specific Research Interest: Gene discovery for human genetic diseases, particularly those with congenital heart defects

Students: PhD: Cheryl Tan
Postdoctoral Fellows: Bhaswati Pandit
Research Personnel: Kimihiko Oishi, Jiang Zhang, Huwen Ying, Benjamin Reinherz

Summary of Research Studies:
The Gelb research group is focused on disease gene discovery using positional cloning/candidacy techniques and characterization of the biological roles of such genes in disease pathogenesis. The focus of the laboratory currently is on those traits that are associated with heart malformations. In the past few years, we have identified disease genes for Char and Noonan syndromes. The former is TFAP2B, which encodes a transcription factor of the AP-2 family, and the latter is PTPN11, which include the protein tyrosine phosphatase SHP-2. We are studying the roles of these disease genes in normal developmental and homeostatic processes as well as in disease pathogenesis. We are actively studying additional human genetic traits, both simple and complex, to identify additional disease genes with a particular focus on traits with cardiovascular abnormalities. After recruiting families of adequate size inheriting disorders, we undertake genome-wide scans with polymorphic DNA markers to identify genetic loci through linkage analysis, and then identify disease genes from among known or predicted genes residing in disease loci. The latter relies heavily on bioinformatics, including several software packages that predict genes and protein function. Ongoing biologic studies include site-directed mutagenesis, expression of wild type and mutant proteins in vitro and in eukaryotic cell culture, immunolocalization of proteins, creation of transgenic mice, and phenotyping of mouse models. Through collaborative efforts, we are also studying disease genes in other model organisms such as Drosophila melanogaster.

Location where the studies are carried out:
FPA


Clinical Research Disciplines: Translational research,

Specific Research Interest: Gene therapy for prostate cancer

Postdoctoral Fellows: Jian Pu, Michael Ost, William Selleck, Steven Canfield, Waleed Hassen

Summary of Research Studies:
I am interested in developing gene therapy strategies for prostate cancer. The laboratory is uniquely situated within the Department of Gene and Cell Medicine to directly translate bench work to the clinic. At the present time the focus of ongoing efforts are directed through 3 main projects.

Immunomodulatory Gene Therapy. Published work had noted the ability of pro-drug activation gene therapy through the HSV-tk and ganciclovir system to induce an important but limited immune response via a Natural Killer response. To enhance this response, studies explored the ability of IL-12 to further enhance NK effects and provide the stimulus to invoke T cell responses. Alone this cytokine resulted in strong growth effects which when combined with HSV-tk+GCV resulted in local and systemic growth inhibition. In addition these individual gene therapy approaches influenced tumor cell expression of Fas and FasL to stimulate further killing within tumors. An adenovirus expressing IL-12 will be utilized in a Phase I clinical trial in men with radiorecurrent prostate cancer this year, while in the laboratory work is focusing on improved vectors for the delivery of IL-12.

Vesicular Stomatitis Virus. A critical problem with in situ gene therapy, especially for the treatment of cancer, is the low transduction efficiencies experienced with standard viral vectors and the need for vector spread within the confines of an injected tumor. Studies thus far have noted the ability of wild type VSV to preferentially and rapidly replicate and kill prostate cancer cells. Ongoing work is focusing on re-engineering the virus to express various fusogenic glycoproteins to enhance viral spread and/or surface binding ligands to more specifically target prostate cancer cells for systemic delivery.

Androgen Receptor Degradation. Prostate cancer growth is intimately associated with the Androgen receptor (AR) and as such is an important target of therapy through androgen ablation. However, in time cancer cells develop resistance to the inhibitory effects of androgen withdrawal, but continue to express A. Using a co-chaperone, CHIP, studies have shown the ability to functionally inactivate the AR, which in turn can control the growth of AR-expressing androgen sensitive and independent prostate cancers. Using a Tet-inducible virus studies are presently exploring the mechanism through which these phenotypes are inhibited. Furthermore, the ability of CHIP to inhibit the development of prostate cancer and the hormone refractory state will be explored in a transgenic mouse model.

Location where the studies are carried out:
FPA, GCRC


Summary of Research Studies:

Dr. Halm’s research focuses on developing measures of the quality of health care, using those measures to improve quality, and understanding the relationship of quality measurement and improvement to health policy. Specific clinical topics of interest include: community-acquired pneumonia, asthma, carotid endarterectomy, and hip fracture. His research focuses on measuring overuse, underuse and misuse in health care, practice guidelines, changing physician, patient and organizational behavior, evidence-based approaches to management of common medical conditions, cost-effective use of medications, and patient safety.

He is the Principal Investigator of a federally-funded Agency for Healthcare Research and Quality (AHRQ) study to develop and validate measures of stability on discharge and predictors of poor post-hospital outcomes in patients with pneumonia, asthma, and hip fracture. He is also the Principal Investigator of a Robert Wood Johnson Foundation grant, “Improving the Outcomes and Quality of Care in Pneumonia.” Both of these projects are an extension of his previous work developing and evaluating evidence-based prediction rules and practice guidelines to rationalize the admission, antibiotic switch, and discharge decision in pneumonia. In addition, Dr. Halm is the Principal Investigator of a prospective, inner city asthma cohort study funded by AHRQ and the United Hospital Fund study that seeks to identify patient, process of care, system, and provider factors that predict relapse, poor functioning, and high resource. Other major projects include being a co-investigator on a federally-funded study measuring and improving the outcomes of carotid endarterectomy in New York State (surgery to prevent stroke). He is also the Project Director of the Asthma in the Elderly core of a National Institute on Aging-funded Center for the Study of Health Beliefs and Behaviors grant between Mount Sinai and Rutgers University. This work will focus on understanding and improving asthma knowledge, beliefs, and self-management practices among older adults in East and Central Harlem.

Vahram Haroutunian, PhD; Kent State University

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Specific Research Interest: Neurobiology of Alzheimer’s disease and Schizophrenia

Students: PhD: Afia Akram

Summary of Research Studies:
My research interests center around the neurobiology, neurochemistry and neuropathology of Alzheimer’s disease (AD), neurodegenerative disorders and of schizophrenia. This interest includes, but is not limited to, those aspects of disease neurobiology that impact on dementia. Human postmortem brain specimens and animal model systems are used to explore these issues. In the past few years our focus in AD has been on the neurobiological markers that are most closely associated with the onset of dementia and cognitive deficits. More recently, this interest has been expanded to the study of cardiovascular risk factors that may also be risk factors for AD. We have been working to understand the antecedents to and sequence of neurobiological abnormalities that are most closely associated with dementia onset. To study the neurobiology of the progression of AD further, our current emphasis is on microarray (DNA chip) surveys of different postmortem human brain regions in patients at different stages of AD. Historically, our animal model studies have utilized rodent systems with lesions of those neurochemical systems known to be affected in AD. We have characterized the effects of these neurochemical system lesions on learning and memory and on the induction and secretion of molecules (beta-amyloid precursor protein) known to be involved in AD. We have then conducted psychopharmacological studies to identify therapeutic agents that may be used to treat the lesion-induced cognitive deficits.

In schizophrenia, my research focus has been on the neurobiological abnormalities that may be related to the disease and the mechanisms that are responsible for the disease that affects elderly schizophrenics. These studies have included neuropathological characterization of postmortem brain specimens from schizophrenics and the molecular, biochemical, and neurochemical abnormalities that may be associated with schizophrenia and its dementia. We have demonstrated that the cognitive deficits of schizophrenia are not due to Alzheimer’s-like neuropathology and have begun extensive multidisciplinary investigations of the role of the glutamate / GABA systems in schizophrenia and its dementia. Most recently, microarray studies is brain specimens from schizophrenics have pointed us to investigate myelin and glial function. These investigations are being pursued with large scale microarrays, laser capture microscopy approaches to the study of the molecular neurobiology of specific cell types and by more traditional neurobiological techniques. Among the assay systems used are: neurochemical assays, neuropeptide assays, enzyme activity studies, and histochemistry; animal model studies; real-time RT-PCR; and Western blotting.

Clinical Research Disciplines: Patient-oriented research; Health outcomes research;

Specific Research Interest: Neurocognition in psychosis; Functional deficits in schizophrenia

Infrastructure Available: Extensive patient samples and clinical databases

Summary of Research Studies:
Examination of the course of cognitive impairment in schizophrenia; Schizophrenia and aging; Cognitive and functional status in older patients with schizophrenia

Location where the studies are carried out:
Community Based


Paul L. Hebert, ;

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Specific Research Interest: Transplant immunology, complement, T cells

Summary of Research Studies:
The research performed in my laboratory focuses on understanding the cellular and molecular immunologic events involved in rejection and tolerance of allogeneic organ grafts in mouse models and in humans. Using mouse models we assess a) how and where alloreactive T cell recognize antigens found in transplanted donor tissues and b) which induced effector mechanisms are essential for inducing graft pathology. Recently published work from our group has also delineated a new link between innate and adaptive immunity by demonstrating that alternative pathway complement components influence the strength of all T cell immune responses, including those directed at allogeneic tissues. Lessons derived from the animal studies are being "translated" into humans. I direct an NIH U01 multicenter trial to assess the utility of noninvasive markers to predict outcome in organ transplant recipients. The study is designed to provide a rational scientific foundation for therapeutic decision-making aimed at maximizing graft survival and minimizing toxicity in organ graft recipients.

PS Heeger, NS Greenspan, S Kuhlenschmidt, C Dejelo, DE Hricik, JA Schulak, and M Tary-Lehmann. Pretransplant frequency of donor-specific, interferon gamma-producing lymphocytes is a manifestation of immunologic memory and correlates with the risk of post transplant kidney rejection episodes J Immunol, 163:2267-2275,1999
Anna Valujskikh, Qiwei Zhang, Peter S. Heeger. CD8 T cells specific for a donor-derived, self-restricted transplant antigen are nonpathogenic bystanders following vascularized heart transplantation in mice J Immunol 176:2190-2196, 2006
Betsy Herold, MD; University of Pennsylvania

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Clinical Research Disciplines: Translational research;

Specific Research Interest: Defining viral and cellular requirements for herpes virus invasion; developing topical microbicides to prevent sexual and vertical transmission of HSV and other sexually transmitted diseases

Students: Sarah Wilson
Postdoctoral Fellows: Rebecca Madan, Esra Fakioglu, Vikas Shende, Pedro Mesquita, Gail Shust
Research Personnel: Assistant Professors: Natalia Cheshenko, Ph.D, Veronica Mas Casullo, M.D., Research Assistants: Ehsan Fam, Esmeralda Guzman, Sarah Wilson

Summary of Research Studies:
Our lab focuses on understanding how HSV-1 and HSV-2 invade cells and using this knowledge to develop novel strategies to prevent establishment of viral infection. Major projects ongoing in the lab a student might be involved with include the following:

1. Entry of HSV into cells is mediated by fusion of the viral envelope with the cell plasma membrane. The cellular pathways important in this fusion step, which is pH independent, have not been defined. Recent work from our lab shows that fusion is associated with increases in intracellular calcium ion concentrations and activation of tyrosine phosphorylation pathways. A major focus of study is to define the calcium signaling and tyrosine phosphorylation pathways required for viral entry. This project also involves determining how the virus triggers these pathways and will require generation of deletion viruses to determine role of specific viral glycoproteins in activating these pathways.

2. Recent studies from our lab have shown that HSV infects primary epithelial cells more efficiently from the apical compared with basolateral surfaces. The restriction to entry at the basolateral surface is not explained by a reduction in binding activity, but may be due to sorting of the signaling pathways required for fusion or transport of the incoming viral capsid to the cell nucleus. This has important implications for understanding viral invasion and the cellular components required during invasion. Theses studies focus on understanding requirements for infection of polarized cells.

3. Understanding the pathway of viral entry should provide the rationale for developing compounds as topical microbicides to prevent sexual transmission of HSV, a major co-factor in HIV transmission. Moreover, because the pathways of invasion for both viruses share similarities, compounds that block HSV invasion also may block HIV entry. In collaborative studies, we have identified several candidate topical microbicides now in clinical trial. Further studies are ongoing to identify new compounds and to understand, at a molecular level, how these compounds inhibit viral entry or cell-cell transmission of virus. In addition these studies are being expanded using explants and murine models of genital and rectal herpes. As a corollary to this work, we are also exploring the intrinsic anti-viral activity of cervical secretions. In addition, the effects of candidate compounds on inflammatory cells, cytokines, and SLPI are being assessed in culture, in animal modes and in pilot human trials being conducted at the GCRC.

4. Several epidemiological studies implicate HSV as a major co-factor in HIV acquisition and transmission. This project tests the hypothesis that HSV infection modulates the mucosal environment to increase acquisition of replication of HIV. Specifically, the project examines the factors in cervicovaginal secretions that mediate innate protection against HSV infection, determine how the virus overcomes these host defenses, and how the change in the mucosal environment increases risk for HIV acquisition or transmission.

Location where the studies are carried out:

GCRC

Patrick R. Hof, MD; University of Geneva, Switzerland

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Clinical Research Disciplines: Translational research;

Specific Research Interest: Experimental neuropathology, neurodegenerative disorders, brain aging; Functional anatomy of the cerebral cortex, comparative neuroanatomy; Computer-assisted morphometry, stereology, microscopy; Magnetic resonance microscopy, functional brain imaging

Students: PhD: Afia Akram NEU; MD/PhD: Devorah Segal NEU
Postdoctoral Fellows: Dara Dickstein, PhD; Estelle van der Gucht, PhD
Research Personnel: Bridget Wicinski, Sandy Harry, Douglas Ehlenberger

Infrastructure Available: Histology, confocal and standard microscopy, electron microscopy
Computational resources, stereologic software, brain imaging software
Supercomputer

Summary of Research Studies:
Our research is directed towards the study of selective neuronal vulnerability in dementing illnesses using classical neuropathological as well as modern quantitative immunohistochemical methods. We intend to develop a quantitative, detailed and cohesive definition of neuronal susceptibility to degeneration in the cerebral cortex, by extending data on Alzheimer disease to other dementing disorders as well as animal models of age-related illnesses, and by defining the key neurochemical and morphological characteristics linked to relative vulnerability (or resistance to degeneration) of identified neuronal populations. The regional and laminar distribution in the cerebral cortex of specific neuronal populations is investigated in a variety of neurodegenerative disorders, and quantitatively compared to Alzheimer disease and control brains. In addition, a detailed study of brains from aged patients with no records of neurological and psychiatric disorders is performed in order to define further the limits of normal aging in the brain.

We also investigate transgenic mouse models, expressing the human tau gene or mutations in the amyloid precursor protein. We study spatial and temporal relationships between neuronal integrity and reflections of degeneration such as tangle formation, amyloid deposition and microvascular damage. We employ high field magnetic resonance microscopy, stereologic, and mathematical modeling approaches to develop an accurate quantitative appraisal of the vasculature density in a region- and layer-specific manner. Neuronal morphology is assessed in a quantitative manner using intracellular injection of hippocampal and neocortical neurons coupled with computerized reconstruction to assess the degree to which the accumulation of pathologic markers causes dendritic atrophy and spine loss in different subtypes of neocortical pyramidal cells. A recent project on myelination patterns in schizophrenia uses similar approaches.

Such correlations of quantitative anatomical analyses and clinical data will be valuable to determine the causes and mechanisms of dementia and aging-related pathologies of the central nervous system. Altogether our research efforts will provide a quantitative assessment, in dementia cases of different severity and in relevant animal models, of the relative contribution of age-related vascular alterations, neurotic pathology and amyloid deposition to the progressive demise of selectively vulnerable neuronal subsets subserving cortical circuits critical for memory and cognition. The characterization of such vulnerable neurons and circuits is fundamental to the design of therapeutic strategies aiming at their protection or rescue.

Finally we are investigating mammalian brain evolution with a focus on cetaceans and great apes. These studies have led us to identify specific neuronal types in parts of the cerebral cortex known to be involved in social awareness, judgement, and attention, that can be considered as markers of adaptive mechanisms and functions in response to particular ecological pressure.

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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Compulsive, impulsive, and anxiety disorders; autism

Postdoctoral Fellows: Latha Soorya, Ph.D., Jennifer Bartz, Ph.D., Heather Berlin, Ph.D., Ting Wang, Ph.D.
Research Personnel: Erica Swanson, Jade Rusoff, Kate Stamper, Bryann Baker, Suah Kim

Infrastructure Available: Seaver and New York Autism Center of Excellence; Compulsive, Impulsive, and Anxiety Disorders Program

Summary of Research Studies:
Seaver and New York Autism Center of Excellence Program: Efficacy of citalopram in autism; efficacy of divalproex sodium in autism; efficacy of levetiracetam in autism; efficacy of fluoxetine in autism; 5HT imaging in autism; neuroimaging studies; family genetic studies in autism.
Compulsive, Impulsive, and Anxiety Disorders Program: Fluoxetine in pediatric body dysmorphic disorder; psychopharmacology/psychotherapy study in body dysmorphic disorder; topiramate in the treatment of pathological gambling; binge eating disorder with obesity; topiramate augmentation in the treatment of obsessive-compulsive disorder; fMRI in obsessive-compulsive disorder.

Location where the studies are carried out:
Annenberg 22-66, GCRC

Clinical Research Disciplines: Translational research;


Summary of Research Studies:
The research group investigates the neurobiology underlying drug abuse and related psychiatric disorders. The work is focused on the systematic study of the human brain of drug abusers and subjects with psychiatric disorders in relation to opioid neuropeptide, cannabinoid and dopamine neuronal systems. Drug abuse and, e.g., major depression are associated with alterations of mood, cognition, and motivation, thus, an important goal is to identify and map specific genes in the mesocorticolimbic system, which regulate emotional function. Techniques such as in situ hybridization, RT-PCR, DNA microarray, western blot and in vitro autoradiography are used for the detailed analyses of genes, and respective protein products, in discrete mesocorticolimbic brain areas. Molecular, biochemical, and in vivo studies of the human brain are assessed in relation to individual genotype in order to identify neurobiological correlates of functional genetic polymorphisms linked to addiction and affective disorders. Epigenetic mechanisms, e.g., DNA methylation, are also evaluated in relation to the regulation of gene expression.

A significant area of investigation is related to assessing the impact of prenatal drug exposure on human fetal brain development that may enhance later risk for substance abuse and psychiatric disturbances. Collaborative efforts are underway for in vivo imaging of the developing mesocorticolimbic system to examine the neurobiological association between behavioral traits (e.g., inhibitory control deficit) that appear to increase risk for substance abuse disorders. ?As complement to studies of the human brain, animal models are used to examine in vivo neurotransmitter levels (e.g., dopamine as measured by the microdialysis technique) in discrete mesocorticolimbic brain areas during, e.g., drug self-administration behavior. The animal studies are designed to mimic the prenatal and adolescent drug exposure (particularly cannabis) seen in humans, and subsequent adult behaviors are linked to in vivo neurochemical fluctuations as well as molecular and biochemical events in the same subject.


Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Gastrointestinal cancer; colonic polyposis syndromes; inflammatory bowel disease;

Students: Matthew Diamond (MSTP); Christina Twyman (Johns Hopkins School of Medicine)

Research Personnel: Yan Zheng

Infrastructure Available: The basic research lab is located in the East Building. Clinical research coordinators assist with the conduct of clinical trials.

Summary of Research Studies:
Basic research studies focus on the role of trefoil factors in GI cancer biology. We are exploring how these proteins, which have very high sequence homology, confer very different functional properties to GI cancer cells and signal through distinct pathways. Clinical research studies are exploring risk factors for colon cancer in patients with inflammatory bowel disease, and conducting studies to test the efficacy of stool DNA testing for early detection of colon cancer in patients with, or without, IBD. Community outreach studies involve enhancing awareness and performance of colon cancer screening among minority populations.

Location where the studies are carried out:
FPA, GCRC, Community-based, Hospital

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Clinical Research Disciplines: Patient-oriented research;

Specific Research Interest: Development of topical microbicides to prevent transmission of HIV, innate mucosal immunity in the female genital tract, solid organ transplantation in HIV-infected recipients & end-organ complications of HIV infection.

Students: Sarju Patel

Infrastructure Available: biostatistical support & data base development through the GCRC, regulatory monitoring

Summary of Research Studies:
PI on the following NIH funded studies:
* PRO 2000 Gel Inhibits HIV and HSV Infection Following Vaginal Application: A Double Blind Placebo-Controlled Trial
* Effect of Repeated Applications of PRO 2000 Gel on Inflammatory Mediators in Cervicovaginal Secretions in Women at Low Risk for HIV-1 Infection – 14 Day Trial
* Cervicovaginal secretions convey innate resistance to genital herpes infection.
* Site Co-PI on an NIH funded multi-center trial to study the clinical, immunologic and pharmacologic consequences of kidney and liver transplantation in people with HIV infection
* PI on a GCRC study to determine the effects of HIV on bone mass in the elderly
Co-PI on a GCRC study to determine the prevalence, risk factors, and relevant markers for peripheral arterial disease in people with HIV infection

Location where the studies are carried out:
GCRC


Clinical Research Disciplines: Patient-oriented research;

Specific Research Interest: Autoimmune hepatitis before and after transplantation; Hepatitis B & C; NAFLD and Adherence to medical regimens

Location where the studies are carried out:
FPA

Lawrence Kleinman,

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Clinical Research Disciplines: Translational research;

Specific Research Interest: Molecular pathogenesis and therapy of HIV

Students: MD: Paul Rosenstiel
Postdoctoral Fellows: Xin Yan Liu, Mirella Salvatore, Natalia Teleshova
Research Personnel: Bouchera Zerhouni-Layachi

Infrastructure Available: approximately 1000 sq ft of bench area, p2-p3 culture facility; separate areas for laser capture dissection, microscopy and PCR amplification

Summary of Research Studies:
The primary focus of the work done in this laboratory is the molecular pathogenesis and therapy of Human Immunodeficiency Virus 1 (HIV-1) infection. Ongoing molecular pathogenesis studies include establishing the role of virus and host factors in determining disease progression in HIV-1 infection. Studies include the isolation and characterization of host factors that are part of an innate immune response to HIV. These include CD8+ cell-derived factors that have inhibitory effects against HIV-1 utilizing an established panel of herpesvirus saimiri (HVS)-transformed CD8+ cells in the laboratory, which have proven to provide a continuous source of supernatant with potent HIV-1 inhibitory activity. A second project is determining the anti-HIV activity of host defensins. The laboratory participates in a multi-investigator program project focused on determining the virologic, cellular and genetic determinants of HIV-associated nephropathy (HIVAN). This project utilizes primary clinical isolates and clinical biopsies to address the viral, cellular and genetic determinants of this entity. In collaboration with Paul Klotman's laboratory we have demonstrated that the renal epithelial cell is a unique target for infection in vivo and serves as a long-term viral reservoir. Ongoing studies focus on the mechanism of viral entry into this unique target as well as the role of genetic background in epithelial cell involvement.

The laboratory is a part of two multi-investigator program project grants focused on the development of topical microbicides with anti-HIV activity. The topical microbicides initiative studies the anti-HIV and anti-HSV potential of candidate agents that can be used to prevent the sexual transmission of these pathogens with a primary focus on mechanism and toxicity.

Location where the studies are carried out:
GCRC


Clinical Research Disciplines: Translational research; Patient-oriented research; Epidemiologic research;

Specific Research Interest: HIV pathogenesis; HIV associated nephropathy; renal diseases; podocan; sidekick

Students: Ryan Ashby
Postdoctoral Fellows: Li Huang, Guozhe Yang, Zhengzhe Li
Research Personnel: Research Faculty: Avelino Teixeira; Mentored Faculty: Lewis Kaufman, Michael Ross

Summary of Research Studies:
The major objectives in my laboratory are to understand the molecular basis of HIV associated nephropathy and to use this information in clinical practice. Our Program Project Grant, now in its 6th year supports research that addresses the genetic risk of Blacks to this disease, the role of the virus in producing the disease, the host responses to infection, and the signaling pathways that mediate disease.

Our laboratory is a blend of both basic and clinical research in molecular virology and AIDS pathogenesis. We developed the first small animal model of HIV associated nephropathy (HIVAN) using transgenic techniques. We were the first laboratory to demonstrate that HIV directly causes HIVAN, that HIV can be found in human renal epithelium, that the kidney is a reservoir for replicating virus and that the renal epithelium serves as a compartment distinct from peripheral blood.

Our current work focuses on viral pathogenesis and host responses to HIV infection. We demonstrated that the Nef gene of HIV is responsible for stimulating podocytes to proliferate and then identified the pathway that mediates this response. Current work is focused on the interactions between Vpr and Nef in HIVAN pathogenesis. In addition, we are exploring the mechanisms of HIV transmission between renal cells and the evolution of the virus in this compartment.

Using functional genomic strategies, we have identified host genes that respond to HIV-1 in kidney, many of which are novel candidates for renal pathogenesis in general. This work has identified a novel member of the small leucine rich repeat family that we have named Podocan whose expression is increased in the kidney of HIV infected patients and transgenic mice. Podocan has multiple important biological functions including regulation of bone and mineral metabolism as well as vascular responses to injury. We have also identified two other critical genes, FAT10, a gene that mediates apoptotic response to HIV infection and Sidekicks 1 and 2, genes that regulate homophilic cellular attachment.

Finally, our clinical work focuses on the epidemiology of the HIVAN epidemic, the factors associated with increased risk, and the role of co-infection in accelerating disease and increasing risk. Overall, this work is a blend of human studies, animal modeling, cell biology, and molecular virology intended to improve our understanding of both HIV pathogenesis as well as renal diseases in general.

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Summary of Research Studies:
Harold W. Koenigsberg, M.D., is Associate Professor of Psychiatry at Mount Sinai School of Medicine. He has had a longstanding research and clinical interest in borderline personality disorder (BPD), is coauthor of two books on the treatment of borderline personality disorder, and has published widely on the neurobiology, phenomenology and treatment of the disorder. He is currently studying the emotional instability characteristic of borderline personality disorder. To better understand the neurobiology of emotional instability, he is using functional magnetic resonance imaging (fMRI) methods to identify brain networks activated as borderline patients process emotional stimuli. He is also studying the role of second messenger systems in emotional instability in BPD. A principal area of his interest is in the interaction between the neurobiologic and psychosocial components of the personality disorders. In addition, Dr. Koenigsberg is principal investigator of an NIMH funded neuroimaging study of cognitive processing in schizotypal personality disorders and in schizophrenia.


Specific Research Interest: My research is in the area of environmental pediatrics. I focus on the impact of environmental toxins such as lead, mercury, pesticides and air pollution on the health and development of children.

Research Personnel: Maida Galvez (MD), Nathan Graber (MD), Leonardo Trasande (MD)

Summary of Research Studies:
For the next five years the unifying scientific theme of the Mount Sinai Children’s Environmental Health Center will be Endocrine Disrupting Chemicals in the Urban Built Environment. Research in the Center will focus on contemporary-use EDs - phthalates, alkyl phenols, especially bisphenol A, pesticides and phytoestrogens. These chemicals have become widely dispersed in the urban environment. Significant levels are found in the bodies of nearly all Americans, and levels of many are highest in children and in minorities. Yet relatively little is known either about urban children’s sources of exposure to the synthetic EDs or about the possible effects of these chemicals on children's health. By focusing on EDs, their sources, relationship to diet, physical activity, somatic growth, childhood obesity and neurobehavioral development in the urban environment, we hope to elucidate relationships that will guide evidence-based efforts to improve children's health.

Current fellows in Environmental Pediatrics have already gained unique training from CCHE in developing expert testimony for presentation before national, state and local policy makers, speaking at press conferences, and participating in health services research projects. Last year, with funding from the New York City Department of Health and Mental Hygiene, fellows developed guidelines for managing lead poisoning in pregnancy. Fellows are currently conducting an epidemiological analysis of the prevalence of diseases of environmental origin and of toxic environmental exposures confronting children in New York State through a project funded by the New York Community Trust.

An additional resource is a newly established Breast Cancer and the Environment Research Center, one of four such Centers across the United States. This new Center will study environmental exposures in childhood and adolescence that may predispose women to breast cancer. The new centers- University of Cincinnati; Fox Chase Cancer Center, Philadelphia, PA/Mount Sinai School of Medicine (MSSM); University of California, San Francisco; and Michigan State University, East Lansing- are funded jointly by the National Institute of Environmental Health Sciences and the National Cancer Institute, both agencies of the National Institutes of Health, at a total of $5 million a year over seven years, or $35 million. These Centers originated from the desire to seek new and innovative ways to identify environmental risk factors for breast cancer. The strength of these Centers is that all will work collaboratively towards the common goal of clarifying whether exposures to environmental agents affect early development of the breast and the subsequent risk of breast cancer. Investigators at Mount Sinai are conducting a five-year study in East Harlem to determine whether environmental exposures are associated with early puberty in girls. Early puberty is a risk factor for breast cancer, cardiovascular disease, and diabetes. Thus, uncovering risk factors for early puberty will also lead us closer to understanding the causes of these other diseases.

Clinical Research Disciplines: Translational research;

Specific Research Interest: The role of insulin and the insulin-like growth factors in pathological states including diabetes, growth, bone disorders and cancer.

Postdoctoral Fellows: Yingjie Wu, Ruslan Novosyadlyy, Radoslav Sadic, Danielle Lann.

Research Personnel: Hui Sun

Summary of Research Studies:
The laboratory of Derek LeRoith MD PhD focuses on understanding the insulin and insulin-like growth factors in disease states. His current research includes studies using animal models of Type 2 diabetes and understanding the pathophysiology of the disorder as well as response to various established and newly discovered therapies. Using these models the laboratory is studying the effects of hyperlipidemia on the progression of the disease as well as on the vascular complications. These studies involve both phenotyping the metabolic responses using in vivo techniques such as hyperglycemic-euglycemic clamps, as well as in vitro cell culture studies on inflammatory cells and adipocytokines that are involved in the vascular complications. In addition, this model is being used to study the effects of diabetes on bone, a common disorder.

Another set of studies involves the insulin-like growth factor system and its role in cancer. These involve both cell culture studies of the insulin-like growth factor-1 receptor signaling pathways that affect cell cycle proteins, ER stress, cell survival, migration and cell proliferation. The animal models include gene-deletion studies of the IGF system; both IGF-1 and the IGF-1 receptor and effects on breast and colon cancer and metastases. These and other on-going studies are expected to identify novel targets for cancer therapy.

Location where the studies are carried out:
Laboratory

Yakar S; Nunez NP; Pennisi P; Brodt P; Sun H; Fallavollita L; Zhao H; Scavo L; Novosyadlyy R; Kurshan N; Stannard B; East-Palmer J; Smith NCP; Perkins SN; Fuchs-Young R; Barrett JC; Hursting SD; LeRoith D.

Increased tumor growth in mice with diet-induced obesity: Impact of ovarian hormones.

ENDOCRINOLOGY 147 (12): 5826-5834 DEC 2006

Kim CH; Pennisi P; Zhao H; Yakar S; Kaufman JB; Iganaki K; Shiloach J; Scherer PE; Quon MJ; LeRoith D. MKR mice are resistant to the metabolic actions of both insulin and adiponectin: discordance between insulin resistance and adiponectin responsiveness.


Zhang, Y., Karas, M., Zhao, H., Yakar, S., LeRoith, D. 14-3-3 sigma mediation cell cycle progression is p53-independent in response to IGF-I receptor activation.


Wu, Y., Cui K., Miyoshi K., Hennighausen L., Green, J.E., Setser, J., LeRoith, D. and Yakar, S. Reduced circulating insulin-like growth factor I levels delay the onset of chemically and genetically induced mammary tumors.

Specific Research Interest: (1) Steroid hormone and growth factor regulation of prostate cell development and carcinogenesis. (2) Prostate cancer-bone interactions.

Students: MD, Michelle Wilson
Postdoctoral Fellows: To Be Appointed
Research Personnel: Senior Scientist: XinHua Liu, Ph.D., (Research Asst. Professor); Research Assistant/Laboratory Manager: Shen Yao, M.D.

Summary of Research Studies:
Our laboratory studies the mechanisms underlying the predilection of prostate cancer to metastasize to bone and to induce an osteoblastic reaction in bone. Specifically, we use in vitro co-culture models as well as in vivo models (growth of human prostate cancer cells in SCID mice) to determine the interactive roles of COX-2/PGE2, interleukin-6 (IL-6), steroid hormones, and the canonical Wnt signaling pathway in prostate cancer bone metastatic disease.

Another area of focus is the regulation of normal and abnormal prostate cell differentiation by steroid hormones. Specifically, we have determined that both estrogens and androgens regulate prostate epithelial cell differentiation utilizing human and rat epithelial cell cultures. Steroid hormones modulate the expression of the prostate tumor suppressor protein KLF6 and its dominant-negative splice variant (sv1-KLF6) thereby providing a possible mechanistic link to their effect on prostate cell proliferation and differentiation. Ongoing studies will attempt to isolate a prostate stem cell population in order to study the factors that lead to aberrant differentiation leading to cancer stem cells. We utilize both human and rat cells lines as well as human tissue for these studies.


Clinical Research Disciplines: Patient-oriented research; Epidemiologic research; Health outcomes research;

Specific Research Interest: antiphospholipid antibodies, telemedicine for stroke (telestroke), hemostatic markers, thrombolytic therapy, stroke clinical trials

Postdoctoral Fellows: Ramandeep Sahni, M.D.
Research Personnel: Fern Werner

Infrastructure Available: Office, clinical research space, computers, data bases

Summary of Research Studies:
- Developing telemedicine systems for acute stroke care and clinical trials
- Determining hemostatic factors that impact thrombolytic therapy-related hemorrhage, outcome and treatment response
- Determining the significance of novel antiphospholipid antibodies as a risk factor for recurrent stroke and thrombo-occlusive events
- Determining factors causing stroke from intracranial atherosclerosis

Location where the studies are carried out:
ER, Neurology Stroke Service inpatients and outpatients


Specific Research Interest: Mechanisms of allergic diseases, food allergy and allergic asthma, developing novel therapies for treating diseases

Students: PhD: Kamal Srivastava

Postdoctoral Fellows: Irena Kirman, MD, PhD; Yuming Chen, PhD; Helen Rovelas, MD; Jing Cao, PhD

Research Personnel: Instructor: Bolledula, Jayaprakasam, PhD; Teng Fei Zhang, PhD; Research coordinator: Srinivasulu Doddaga, PhD; Renguang Du, MB and Angie Yang

Summary of Research Studies:

1. Immunologic and genetic bases of allergic disorders: Our laboratory developed the first murine models of cow milk and peanut allergy. Interestingly, we found that, as appears to be the case in humans, induction of hypersensitivity or tolerance to food proteins in mice is influenced by genetic background. We have identified susceptible and tolerant food allergy strains. We are using this well established model system as a tool to dissect the immunoregulatory and genetic mechanisms underlying induction of oral tolerance or hypersensitivity using advanced immunologic and molecular techniques, and determining whether the findings in mice apply to humans. These projects are funded by NIH and other organizations.

2. Novel therapies for food allergy: We are developing several possible interventions for treating food allergy, including plasmid-DNA based immunotherapy; cytokine therapy (IL-12); engineered food allergen protein-based immunotherapy, ImmuSoy (soy product based on a Japanese traditional formulation technique), and herbal therapy (based on Traditional Chinese Medicine). Giving the efficacy and safety of herbal therapy (FAHF-2) on food allergy in animal studies, herbal therapy for food allergy is the first novel therapy to be employed in clinical trials (Phase I and II). We will also determine the immunotherapeutic mechanisms of FAHF-2, focusing on memory T cell, B cells and mast cells. These projects are funded by NIH and other organizations.

(Selected from 40 publications)


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Specific Research Interest: Cell biology, proteomics and genetics of hyperuricemia and progressive kidney disease

Postdoctoral Fellows: Victor Anbalagan
Research Personnel: Elizabeth Herman (MD), Mohammed Rafey (MD), Xianzhong Wu

Summary of Research Studies:
We are studying the etiology and predictors of progressive kidney disease which is now estimated to be a significant health problem for as many as 20 million people in the United States.

Recent data suggest that elevated uric acid levels may cause hypertension, renal disease and cardiovascular disease in addition to gout. The mechanisms by which uric acid levels become elevated are poorly understood. We are studying the molecular mechanisms of urate transport, particularly the urate ion channel hUAT, and its role in hyperuricemia in AASK subjects and in subjects with severe gout.

Recent clinical proteomic studies in cancer subjects have shown that patterns of serum proteins can be strong predictors of normal or disease states. We are performing a proteomics project to determine whether patterns of serum proteins can predict progression and non-progression of renal disease in AASK subjects.

There appear to be genetic predispositions for hypertension and renal disease. To better understand this, we are evaluating a large multicenter clinical data set, the African American Study of Kidney Disease and Hypertension (AASK). Genetic and pharmacogenomic studies of AASK subjects are ongoing to try to understand the genetic basis for susceptibility to hypertension, progressive renal failure, and their sequelae such as cardiac hypertrophy, coronary artery disease, and atherosclerosis, as well as effectiveness of drug therapy.


Lawrence Liu, MD; University of the East Ramon Magsaysay Memorial Medical Center, Quezon City, Philippines

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Specific Research Interest: Dr. Liu’s areas of clinical interest include living donor liver transplantation, outcomes of liver transplantation, complications of cirrhosis, and chronic hepatitis B infection.


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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: The Mount Sinai Liver Cancer Program is conducting studies in clinical and translational research in hepatocellular carcinoma. As Director of Research of this program I am mentoring junior faculty and post-docs and fellows in the study of new treatments for the disease in the setting of phase II/III studies, and in the study of the pathogenesis of the disease, by using a tissue bank of more than 250 samples. We are conducting investigations assessing genetic alterations (by SNP arrays), gene expression profiles (by microarray analysis) and signal transduction pathways involved in the progression of the disease (with cell lines and animal models).

Postdoctoral Fellows: Eric Lemmer MD/PhD, Augusto Villanueva MD,
Research Personnel: Patricia Lopez ,MD (Faculty) Elisa Wurmach, PhD (Faculty). Cathy Burns (Research coordinator), Judit Peix, (Lab technician).

Infrastructure Available: The clinical studies are phase II/III studies conducted in FPA. The translational research is conducted in Scott Friedman's Lab (Division of Liver Diseases), Sam Waxman's Lab (Div Hem/Oncology) and the core of Personalized Medicine (Erwin Bottinger's Lab). We have collaborations with Dana-Farber Institute in Harvard (Matthew Meyersson's Lab), Hospital Clinic, University of Barcelona and National Cancer Institute, Milan.

Summary of Research Studies:
Clinical studies:
1. Randomized controlled trial assessing Sorafenib vs placebo in the treatment of advanced HCC
2. Randomized controlled trial comparing internal radiation with Y-90 vs best supportive care in the treatment of advanced HCC
3. Assessment of DCP as a marker for early diagnosis of HCC
4. Natural history of HCC with portal vein invasion

Translational studies
1. Integrative genomic analysis of HCC. Integrative analysis of gene expression profiles and somatic genetic alterations assessed by microarrays and SNP arrays
2. Molecular signature for the diagnosis of early HCC
3. Role of HH signaling pathway in HCC
4. Molecular targeting therapies in HCC. We are conducting studies in cell lines and animal models with new agents blocking EGFR pathway, Ras/MAPKK pathway and Akt pathway.

Location where the studies are carried out:
GCRC and FPA

Summary of Research Studies:

Retrospective review of patients with hepatocellular carcinoma and macroscopic vascular invasion.

Retrospective review of HCV treatment with Pegylated interferon and Ribavirin in cirrhotic patients.

Dr. Lopez's current clinical research focus on treatment of advanced hepatocellular carcinoma with novel signal transduction inhibitors and on the impact of liver transplantation in patients with hepatocellular carcinoma after the MELDS implementation.


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John Martignetti, MD/PhD; Mount Sinai School of Medicine

Associate Professor, Department of Genetics and Genomic Sciences
Associate Professor, Department of Pediatrics
Associate Professor, Department of Oncological Sciences

Training Areas(s): GGS*, MCBDS

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Specific Research Interest: Genomics, molecular biology, cancer genetics, gene discovery, hereditary cancers, cancer syndromes, tumor suppressor genes, linkage analysis

Students: PhD: Maria Ramirez, Becky Mosig, Analisa DiFeo // PREP: Joshua Jamison

Postdoctoral Fellows: Olga Camacho, Yolanda Fernandez, Berrin Ozturk

Research Personnel: Ian Parker, Esteban Terzo, Fei Huang

Summary of Research Studies:

Translational research projects in this laboratory are directed towards identifying genes and molecular mechanisms underlying a number of diverse human diseases including sporadic and hereditary forms of cancer. To achieve these aims, basic and advanced molecular biology/genomic methodologies are used and developed, including linkage analysis, positional gene cloning, high-throughput and large-scale DNA sequencing, mutation detection, genotyping, automated fluorescent loss-of-heterozygosity (LOH), and generation and analysis of knockout and transgenic mouse models. Current research projects range from studies pursuing gene discovery and characterization in prostate, ovarian, colorectal, skin and bone cancers to identification of and gene discovery in novel human obesity, arthritis, and bone dysplasia syndromes. In each project, extensive intra- and inter-university collaborations between clinicians and basic-science researchers define the multi-modality approach to defining the biologic basis of disease.


Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Liver diseases including acute liver failure; hepatitis B; hepatitis C; renal disease related to liver diseases; liver transplantation;

Postdoctoral Fellows: Alison Uriel MD
Research Personnel: Rosemarie Gagliardi, Clinical Research Director RMTI; Marjorie Small, Regulatory Compliance Manager

Infrastructure Available: Currently the Medical Director of Clinical Research in the division of Liver diseases.

Summary of Research Studies:
Long-Term Assess Of Treatment Outcomes with Entecavir And Lamivudine for Chronic Hep B infection;
A preliminary Asses. Of safety and antiviral activity of open-label Entecavir Plus Lamivudine Therapy in Subjects with Chronic Hep B who have Viremia on monotherapy in other Entecavir trial;
A Phase III Study of the Comparison of Entecavir to Lamivudine in Chronic Hep B subjects with incomplete response to current lamivudine therapy;
Multicenter, Open Label, Phase IV Study Evaluating the Efficacy and Safety of 16-week versus 24 week treatment with Pegasys® in combination with Copegus® in interferon-naïve Patient with chronic Hep C Genotype 2 or 3 virus infect;

Location where the studies are carried out:
FPA; Inpatient Hospital; GCRC


Lloyd F. Mayer, MD; Mount Sinai School of Medicine

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Clinical Research Disciplines: Translational research;

Specific Research Interest: Regulation of mucosal immune responses; antigen presentation by intestinal epithelial cells

Students: Keren Rabinowitz, Steven Esses
Postdoctoral Fellows: Stephanie Dahan, Dmitry Yanilin, Paul Arnaboldi, Jen Rockfeld, David Dunkin, Surabh Mehandru
Research Personnel: Research Assistant:, Jianyu Xu, Hong Xing Li

Infrastructure Available: Link to surgical pathology with access to 15-20 surgical resection specimens per week allowing for studies of human mucosal immunity.

Summary of Research Studies:

Our laboratory studies the regulation of mucosal immune responses in both human and murine systems. Specifically we focus on the role that intestinal epithelial cells play in this process. Intestinal epithelial cells express non-classical class I molecules that are involved in the activation of unique populations of regulatory T cells. They also express a tumor associated antigen, carcinoembryonic antigen, that, along with CD1d, activates a population of CD8+ Tregs called TrE cells. Current studies focus on the characterization of different Treg populations in the intestine as well as different CEA subfamily members and their ability to interact with distinct class Ib molecules. These studies have extended into the role of such cells in fetal/maternal interactions where activation of distinct Treg populations may occur restricted by other CEA subfamily members.

Other studies in murine systems look at the role of epithelial cell antigen presentation in vivo, by the induction of oral tolerance. Antigens are introduced in isolated intestinal loops and tolerance induction is assessed. Data show that tolerance can be induced in loops that contain organized lymphoid tissues (Peyer's patches) as well as those where there are no PPs (epithelial cells only). Current studies focus on defining differing mechanisms of tolerance induction in the two loops.

Finally, we are interested in translating these findings into human disease. We have developed models of abnormal antigen presentation in inflammatory bowel disease (Crohn's disease and ulcerative colitis). Epithelial cells derived from surgical specimens from these patients fail to activate TrE cells but rather activate inflammatory CD4+ T cells. Defects in class Ib and CEA expression appear to be responsible for this finding. Defining mechanisms involved in the failure to express these regulatory surface molecules is a current focus. This has been translated into in vivo assessments. We have also identified defects in oral tolerance in these patients. The mechanisms involved in the generation of oral tolerance in normal controls as well as the mechanisms involved in the defect in oral tolerance in IBD patients are also being studied.

Location where the studies are carried out:
EB 11-02

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Clinical Research Disciplines: Patient-oriented research;

Specific Research Interest: Studies are focused on the natural history and treatment of the lysosomal storage disorders.

Research Personnel: Judes Fleurimont, CRC; Sharmaine Lewis

Summary of Research Studies:
Our group has been delineating the natural history and disease manifestations in Niemann Pick disease Types A and B. These longitudinal studies have included annual evaluations on the GCRC to determine disease progression and to identify clinical endpoints for a clinical trial of enzyme replacement therapy that is expected to begin soon. In addition, we have been studying disease manifestations in carriers of this recessive disorder and have found that almost a third of carriers display some manifestations including low HDL-cholesterol and hyperlipidemia.

Location where the studies are carried out:
GCRC


Mary McKay, PhD; Mount Sinai School of Medicine

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Summary of Research Studies:
Dr. McKay directs a large program of research focused on identifying the mental health needs of urban children and their families. In addition, she and colleagues are testing numerous family and community-based strategies to meet the prevention and mental health needs of urban youth and families. Dr. McKay also has a Career Scientist Award that is meant to develop opportunities for parents to collaborate in the design, delivery and testing of mental health oriented programs.

Location where the studies are carried out:
community-based

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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: posture and gait; vestibular system; effects of spaceflight; Parkinson's disease (locomotor assessment)

Postdoctoral Fellows: Hamish MacDougall

Summary of Research Studies:
My laboratory is funded primarily by NASA and focuses on the effects of microgravity exposure on sensorimotor function. We are currently working on two main projects: 1) head-eye coordination during simulated shuttle landings in the shuttle training simulator at NASA Ames Research Center, using Galvanic vestibular stimulation (GVS - transmastoidal electrical stimulation of primary vestibular afferents via surface electrodes) to simulate the sensorimotor deficits engendered by exposure to microgravity; 2) ambulatory assessment of gait and freezing in Parkinson's disease.

Location where the studies are carried out:
Community-based, NASA Johnson Space Center, NASA Ames Research Center


Susan Morgello, MD; Duke University

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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: hiv/aids; neuropathology; clinicopathologic correlates

Research Personnel: Research Assistants: Jacinta Murray, Dr. Ruijin Shi, Dr. Desiree Byrd, Dr. Elizabeth Ryan, Dr. Monica Rivera-Mindt

Infrastructure Available: the manhattan hiv brain bank

Summary of Research Studies:
The laboratory utilizes molecular, immunohistochemical, and more traditional histochemical techniques to study nervous system complications in patients with Human Immunodeficiency Virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). A large clinical program of research focusing on the psychiatry, neuropsychology and neurology of advanced HIV infection provides the basis for translational research in the laboratory.

Recently the focus has included: pathogenesis of AIDS-related myelopathy and distal sensory polyneuropathy; racial/ethnic disparities in neuroAIDS disorders; and the elucidation of hepatitis C virus as a possible agent in the generation of HIV-related nervous system disorders. In addition, a wide variety of descriptive clinico-pathologic projects to delineate emerging HIV-related nervous system disorders are ongoing with house staff members in the departments of neurology and pathology.

Location where the studies are carried out:
GCRC, Annenberg 2


John Morrison, PhD; Johns Hopkins University School of Medicine

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Clinical Research Disciplines: Translational research;

Specific Research Interest: Neurobiology of aging, plasticity, and cortical organization. Steroid effects on cortical circuitry and function.

Students: PhD: Charles Park, Lauren Silbert, Athena Wang; MD/PhD: Deena Goldwater; MD: Melynda Barnes; Undergraduates and Summer Students: Spencer Lynch, Jessica Myers
Postdoctoral Fellows: Murat Yildirim, Rebecca Shanks
Research Personnel: Instructor: Jiandong Hao; Lab Manager: Bill Janssen; Research Assistants: Twethida Oung, and Daniel Christoffel

Summary of Research Studies:
The goals and interests of the Morrison laboratory reflect those of the larger enterprise that represents the Kastor Neurobiology of Aging Laboratories, those being the elucidation of the anatomic, physiologic and molecular changes in the aging brain, the mechanisms which drive those changes, and their behavioral consequences. This encompasses the study of age-related diseases in the brain such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), as well as age-related functional decline that occurs in the absence of frank disease. Along these lines, our research program includes several related components, with the three primary areas being the cellular and synaptic organization of cerebral cortex, selective vulnerability in neurodegenerative disorders, and glutamate receptor plasticity in the hippocampus as it relates to performance in general and age-related memory impairment in particular. These efforts involve cellular neuropathologic analyses of human brain, experimental and neuropathologic analyses of non-human primate cortex, and detailed neuropathologic analyses of genetically manipulated mice. For example, we have worked extensively on mouse transgenic model of ALS and AD, and have been able to delineate several principles of selective vulnerability in these models that have broad applicability to neurodegenerative disorders and aging. Virtually all of our microscopic analyses are quantitative in nature, employing several powerful software programs for computer-assisted quantitative analysis of neuronal attributes in both the healthy brain and under pathologic circumstances.

We are particularly interested in the cellular and molecular events underlying the functional decrements often seen in normal aging, such as age-related memory impairment. In contrast to AD, cell loss is not likely to be a significant contributor to functional decline in normal aging. We have revealed both structural and molecular aspects of plasticity that decline with aging. Shifts in expression and distribution of key molecules (e.g., NMDA receptors) and the structural attributes of synapses occur in aging, and in a manner that would have profound effects on synaptic transmission in key hippocampal and neocortical circuits. Much of our current work is aimed at the interface between endocrine senescence and neural aging. Circulating estrogen levels also profoundly affect NMDA receptor levels and synapse number in key hippocampal and neocortical circuits, suggesting a potential molecular substrate for the beneficial effects of estrogen replacement on cognitive function. We are currently pursuing the links between age-related decreases in estrogen levels (i.e., menopause), NMDA receptors, dendritic spines, and cortical circuits in behaviorally and hormonally characterized aged non-human primates. In addition, we are pursuing collaborative studies in behaviorally and electrophysiologically characterized rats that will allow us to draw direct links between molecular plasticity at the synapse and stress-induced alterations in performance. Many of these studies involve quantitative analysis of the molecular constituents and structural attributes of the synapse employing neuronal reconstruction and electron microscopic immunogold localization of specific AMPA and NMDA receptor subunit proteins, allowing for a level of spatial resolution combined with molecular specificity that is unprecedented with respect to analysis of the synapse.


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Antonia New, MD; Mount Sinai School of Medicine

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Clinical Research Disciplines: Translational research; Patient-oriented research; Behavioral medicine;

Specific Research Interest: Regional brain control of emotion, specifically anger and aggression. Additionally, exploring models of stress resistance and vulnerability using emotional probes with functional brain imaging.

Students: Larry Sprung, Amir Garakani, Hua Yan
Postdoctoral Fellows: Joseph Treibwasser (current)
Research Personnel: An interdisciplinary group of faculty, fellows, and research assistants. See Mood and Personality Disorder Web site.

Infrastructure Available: We have a large mood and personality program with resources to recruit and evaluate research subjects. We have resources to do psychophysiology studies, functional MRI, anatomical MRI and positron emission tomography.

Summary of Research Studies:
1) PET scans of anger in borderline personality disorder and controls to examine brain activation in the prefrontal cortex/amygdala circuit.
2) Startle eyeblink modulation and fMRI with emotional provocation in borderline personality disorder, schizotypal personality disorder and healthy controls to characterize emotion regulation.
3) fMRI studies during emotion provocation in women after sexual assault, contrasting those who are stress resilient and those with PTSD.
4) The effect of dialectical behavioral therapy on fMRI and psychophysiological measures in borderline personality disorder.
5) Propranolol treatment acutely after sexual trauma to prevent PTSD.

Location where the studies are carried out: GCRC, Neuroscience PET laboratory, Imaging Science Laboratory


Maria New, MD; University of Pennsylvania

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Clinical Research Disciplines: Translational research; Patient-oriented research; Molecular epidemiology;

Specific Research Interest: Fundamental definition of clinical syndromes resulting from errors in adrenal steroid production; molecular genetic basis for these disorders and introduction of innovative treatments including prenatal diagnosis and treatment and gene therapy of congenital adrenal hyperplasia; low renin hypertensive disorders of childhood; intersex disorders.

Students: Peter Vasquez, Alexey Dyachkov MD, Victoria Yuryeva MD
Postdoctoral Fellows: Frances Guevarra MD, Arlene Mercado MD, Lien Trinh MD
Research Personnel: Susan Baker PhD, Andrew Jacovina PhD, Berrin Longmire MD, Saroj Nimkarn MD, Karen Su MD, Robert Wilson PhD

Infrastructure Available: Extensive

Summary of Research Studies:
Dr. New’s work in steroid biochemistry combines the fundamental definition of clinical syndromes, identification of the molecular genetic basis for these disorders, and introduction of innovative treatments, several of which have had worldwide impact. The clinical and molecular genetic characterization and treatment of the various forms of congenital adrenal hyperplasia are a central pursuit. Dr. New identified aldosterone as the basis of salt wasting in classical CAH, established the diagnostic criteria used by pediatricians around the world, was the first to describe the milder nonclassical form of CAH, and with her team mapped and cloned the gene and identified mutations for classical and nonclassical CAH. Her team determined that the nonclassical form of 21-hydroxylase deficiency CAH is the most common autosomal recessive disorder known, with a frequency of 1 in 100 in the general population of New York City; it is more prevalent in certain ethnic groups, notably Ashkenazi Jews, and we continue to explore the prevalence and underdiagnosis of this disorder. Dr. New’s CAH patient population is one of the largest and most consistently and longitudinally studied in the world. Current projects include prenatal treatment of CAH, gene therapy of CAH, continued study of the relationship between genotype and phenotype in CAH, and the effects of androgens on gender identity. A second major line of research is the pathophysiology of adrenal hypertension. Early in her career Dr. New discovered a new mechanism of disease in a syndrome she called “apparent mineralocorticoid excess AME.” Her team subsequently mapped and cloned the gene for the enzyme in 11beta-hydroxysteroid dehydrogenase and discovered the mutations which cause the disease. Identification of the pathophysiology of AME opened a new field of receptor biology by demonstrating that the action of the steroid-receptor-ligand complex is regulated by an enzyme that alters the ligand: in normal people cortisol is converted by 11beta-HSD to cortisone, which cannot bind to the renal mineralocorticoid receptor. The receptor is therefore protected from being overwhelmed by cortisol in normal subjects. In contrast, in patients with AME, who lack the 11beta-HSD enzyme owing to a genetic mutation, cortisol binds to the mineralocorticoid receptor and causes fatal low-renin hypertension. Dr. New discovered that administration of spironolactone displaces cortisol from the receptor and safely and effectively treats this otherwise fatal hypertension. She is now studying a mild form of AME, which may shed light on mechanisms of hypertension that have applicability to hypertension of many pathophysiological origins. In addition, her team studies the effect on growth in children with CAH of a regimen of growth hormone combined with leuprolide. In December 1999, she reported the first cases (in two sisters) of partial resistance to all steroids (glucocorticoids, mineralocorticoids, and androgens), but not to thyroid hormones or to vitamin D; her team continue to investigate what may be the first global transcription factor defect in humans.

Location where the studies are carried out:
Clinic, GCRC
Yasuharu Okuda,

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Location(s)

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Laurie Ozelius, ;

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Specific Research Interest: Host-virus interactions; vaccines and antivirals; virulence factors of RNA viruses

Students: PhD: Gina Conenello, Carolin Guenzel, Heinrich Hoffmann; MD/PhD: Mila Ortigoza, Taia Wang
Postdoctoral Fellows: Qinshan Gao, Rong Hai, Sarah Kopecky-Bromberg, Anice Lowen, Samira Mubareka, Megan Shaw, John Steel, Kathryn Fraser, Silke Stertz and Mark Yondola
Research Personnel: Research Assistant: Christopher Narbus

Summary of Research Studies:
Our group is interested in fundamental questions concerning the genetic make-up and the biology of viruses. We use molecular biological techniques to understand how viruses replicate and how they interact with cells to cause disease in their hosts. Emphasis is on the study of RNA viruses, including influenza, paramyxovirus and corona (SARS) viruses.

There are three major research directions in our laboratory at the present time.
(1) By genetically changing influenza viruses via recombinant DNA techniques, we are studying viral genes and gene products. Using these reverse genetics techniques, we are trying to develop novel influenza virus vaccines and vaccine vectors.
(2) Another interest is the identification of novel targets for antivirals.
(3) We are identifying intracellular proteins that interact with viral proteins, and we are studying the biological function(s) of these cellular proteins. We are also studying the cellular mechanisms involved in the nucleo-cytoplasmic transport of influenza virus RNAs and the (intracellular) trafficking of viral components in general.

We are interested in training students and postdoctoral fellows who will become independent investigators in "molecular" studies of infectious viral diseases.


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Clinical Research Disciplines: Patient-oriented research; Health outcomes research;

Specific Research Interest: neuropathic pain; bone nociception; back pain; headache

Research Personnel: Dionne Bobb, Angela Sanchez

Infrastructure Available: research coordinators; data management; administrative and biostatistical support

Summary of Research Studies:
Dr. Pappagallo’s research has been funded by the National Institutes of Health, various foundations, and the pharmaceutical industry. In 2003, the National Institute of Neurological Disorders and Stroke (NINDS) awarded Dr Pappagallo with a $1.7 M grant to study intravenous pamidronate for chronic mechanical back pain. Dr Pappagallo’s research has also included studies of pain mechanisms and controlled trials of treatments for complex regional pain syndrome (also known as reflex sympathetic dystrophy), multiple-sclerosis-related neuropathic pain, post-herpetic neuralgia, and migraine headaches. Dr Pappagallo currently holds a total of five patents (two US and three European) for novel approaches to pain therapy. Some of his novel therapies concern long-lasting, non-opioid analgesic, vanilloid preparations that have been shown to reduce pain for weeks to months. Dr Pappagallo is particularly known for his work in establishing opioid responsiveness in the treatment of postherpetic neuralgia.


Giulio M. Pasinetti, MD/PhD; University of Milan

Professor, Department of Psychiatry, Department of Neuroscience, Department of Geriatrics and Adult Development

Training Areas(s): NEU*, IMM

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Specific Research Interest: Neuronal Degeneration in Alzheimer’s Disease and Model System

Students: Emi Ling, Roselle Vittorino, Lindsey Conley, Casey McDonald
Postdoctoral Fellows: Xianjuan Qian, PhD, Shrishailam Yemul, PhD, Wei Zhao, PhD; Bret Stetka, MD; Carmen Diaz, PhD
Research Personnel: Faculty: Lap Ho, PhD, Hanna Reding, PhD, Jun Wang, PhD.

Summary of Research Studies:
The primary research goals in Dr. Pasinetti’s lab is to investigate the biological processes which occur when, during aging, subjects with normal cognitive functions convert into the very earliest stages of Alzheimer’s disease (AD) and then to frank dementia. The long-term goal of Dr. Pasinetti lab is to improve the diagnosis of patients who are in the very earliest stages of Alzheimer’s disease (AD), and to identify early molecular neurobiological abnormalities so that effective pharmacological treatments to slow or halt disease progression can be developed. Toward this goal Dr. Pasinetti lab initiated a series of studies to characterize gene activities in the brain of early AD cases and animal model system of AD neuropathology, using high throughput cDNA and microarray approaches. Recent studies in Dr. Pasinetti lab found that the expression of genes involved in synaptic functions, cell cycle, and cytoskeleton/cell adhesion, may play an important role in the onset and possibly the clinical progression of Alzheimer’s disease dementia. More recently, Dr. Pasinetti’s lab using a combination of genomic-proteomic techniques is presently characterizing and purifying abnormal expressed gene products in the brain that may share similarities in respect with promotion of neurodegenerative disorders including amyotrophic lateral sclerosis and Parkinson’s disease among others. Based on the outcome of these studies, Dr Pasinetti’s lab is presently using newly developed transgenic mouse models of disease to test pre-clinically the potential therapeutic relevance of novel drug treatments.


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Clinical Research Disciplines: Translational research;

Specific Research Interest: Differentiation and migration of dendritic cells

Students: Emma (Lo) Kuan
Postdoctoral Fellows: Claudia Jakubzick, Chunfeng Qu, Julie Helft, Stephane Potteaux, Molly Ingersoll
Research Personnel: Theodore Kaplan, Farida Goubaeva

Summary of Research Studies:
My research laboratory carries out basic research on the differentiation and trafficking of monocytes and antigen-presenting dendritic cells. More recently, we have begun to study these cell types and their behavior in the context of atherosclerosis. One of the fascinating properties of dendritic cells is their special capacity to efficiently emigrate out of tissues to lymph nodes via lymphatic vessels. Some of our research is directed to the study of basic mechanisms that regulate dendritic cell development from monocytes and the migration of dendritic cells to lymph nodes. These two fundamental lines of study now significantly influence our approach to studying atherosclerosis. We have observed in multiple model systems that monocytes that become dendritic cells readily emigrate out of tissues, usually via lymphatic vessels, whereas macrophages typically remain resident in the tissues where they form. To prevent the ongoing accumulation of macrophages in tissues and to maintain homeostasis, we hypothesize that it is important that some monocytes that enter a particular tissue continuously differentiate into dendritic cells that in turn subsequently emigrate from that tissue. We have proposed that this homeostatic process breaks down in atherosclerosis, such that monocyte-derived dendritic cells fail to emigrate and consequently aberrantly accumulate within plaques, contributing to plaque progression. Conversely, we propose that restoring the emigration of these cells from plaques facilitates plaque regression. This proposal is based in part on evidence from a model system that permitted us to trace whether and under what conditions cells emigrate from lesions. We have recently developed new techniques to trace monocyte fate within atherosclerotic plaques that will allow us to focus further on the differentiation of plaque-infiltrating monocytes to dendritic cells and macrophages and to identify mechanisms that affect their emigration from lesions. For the foreseeable future, the laboratory will remain connected to the study of monocyte biology and dendritic cell migration in a normal, non-diseased setting, while increasingly mobilizing our efforts to address these topics in the context of atherosclerosis.


Specific Research Interest: Mechanisms of Neurodegeneration; Signal transduction; aexpression, processing, and function of APP and presenilins

Students: Mike Green

Postdoctoral Fellows: Claudia Litterst; Nikolas Arbez; Chaoyang Wang; Jindong Xu; Zen Kouchi; Gweltas Mauger

Summary of Research Studies:

Neurodegenerative disorders are characterized by a chronic, progressive, and selective loss of neurons in cognitive, sensory and motor systems. Alzheimer disease (AD) is the most common cause of dementia in the aged and results from severe neuronal loss and synaptic abnormalities. AD is characterized by the accumulation of amyloid plaques and neurofibrillary tangles. Most cases are classified as "sporadic" because they lack an obvious genetic etiology. A small percent of all cases segregates within families (FAD) suggesting a genetic etiology. The genetic defects of most FAD cases map on three genes: the amyloid precursor protein (APP) on chromosome 21 and presenilins 1 and 2 on chromosomes 14 and 1 respectively. PS-1 mutations are responsible for most FAD cases. Proteolytic processing of APP results in the production of Abeta peptides that aggregate to form the amyloid depositions. The mechanism by which APP and PS mutants promote neuronal cell death is not clear. There is evidence, however, that the FAD mutations interfere with the biological function of the proteins. In addition, many FAD mutants promote production of Abeta peptides, the precursor of the amyloid fibers.

To understand the consequences of the FAD mutations on neurodegeneration we study the genetics, molecular biology, and function of the wild type and mutant APP and PSs. Recently, we obtained evidence that PS1 is a component of the adherens junctions and regulates cell-cell adhesion and communication. PS1 concentrates at synaptic contacts and forms complexes with brain N-cadherin, an important component of synaptic structures. PS1 controls proteolytic processing of cadherins and production of peptides with signal transduction functions. For example, the PS1-dependent cleavage of N-cadherin is regulated by NMDA receptor activity and the resulting peptide promotes degradation of CBP thus regulating CREB/CBP-dependent gene expression. In addition, we showed recently that PS1 regulates the PI3K/Akt cell survival pathway. This is a new function of PS1 with potential applications in AD because this pathway plays central roles in neuronal survival (See Marambaud et al., 2003 and Baki et al., 2004 below). To answer our questions we use in vitro gene expression systems and transgenic mice expressing PS1 and APP mutants.


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Clinical Research Disciplines: Patient-oriented research; Health outcomes research;

Specific Research Interest: Adolescent Health (physical and mental), health disparities, mind body health, patient safety

Summary of Research Studies:
HPV among inner city adolescent girls; Disclosure of abuse among adolescents; Appropriateness of CEA; Health Care disparities among stroke patients; Patient Safety.

Location where the studies are carried out:
Adolescent Health Center
Clinical Research Disciplines: Translational research;

Specific Research Interest: Identification of genetic predictors of susceptibility for adverse responses to radiotherapy

Postdoctoral Fellows: Grace Fan (MD), Alice Ho (MD), Julian Moore (DO)
Research Personnel: David Atencio (PhD), Sheila Peters (BA)

Summary of Research Studies:
The development of adverse effects resulting from the radiotherapy of cancer limits the use of this treatment modality. The development of a test capable of predicting which patients would be most likely to develop adverse responses to radiotherapy, based upon the possession of specific genetic variants, would therefore be of value. In order to achieve this goal, Dr. Rosenstein has organized the Gene-PARE (Genetic Predictors of Adverse Radiotherapy Effects) project which represents a broad international effort through which radiation oncology departments are contributing to a continuously expanding biorepository maintained at Mount Sinai consisting of frozen lymphocytes and DNA isolated from cancer patients treated with radiotherapy. In conjunction with this biorepository, a database is maintained with detailed clinical information pertaining to diagnosis, treatment and outcome. The DNA samples are being screened using denaturing high performance chromatography (DHPLC) for variants in ATM, TGFB1, XRCC1, XRCC3, SOD2, hHR21, and potentially additional genes which control the biologic response to radiation. Evidence has been obtained through these studies that possession of variants in genes whose products play a role in radiation response is predictive for the development of adverse effects following radiotherapy. It is anticipated that the Gene-PARE project will yield information that will help radiation oncologists to use genetic data to individualize and optimize patient treatment.


Specific Research Interest: Dr. Sacks does clinical trials, meta-analyses, decision analyses and cost-effectiveness analyses on a wide variety of topics. Recently most have been in treatment of HIV and other infectious diseases, and in the use of complementary and alternative medicine.

Research Personnel: Deeaneele Pooran (MD/MPH student), Kaylan Babban (MD/MPH), Scott Ikeda (MD/MPH), Salina Lai (Stuyvesant High School)

Summary of Research Studies:
1) The design, conduct and analysis of clinical trials and natural history study (primary studies), to provide new data to directly answer clinical questions, and
2) Syntheses of existing data by meta-analysis, decision analysis and cost-effectiveness analysis, to provide guidance for urgent clinical problems for which primary data are not (or not yet) available. Dr. Sacks has recently become interested in complementary and alternative medicine (CAM) and is applying the principles of evidence-based medicine to determining which CAM remedies are actually effective.

Current projects
1) A clinical trial of the herb milk thistle for treatment of Hepatitis C infection.
3) A planning grant to investigate traditional Indian remedies (Siddha medicine) for HIV infection and its complications.
4) A cost-effectiveness analysis of probiotics to prevent antibiotic-associated diarrhea in hospitalized patients


Gersony DR, McLaughlin MA, Sacks HS, Fuster V, Gersony WM. Effect of beta blockr therapy on clinical outcome in patients with Mafran syndrome: Meta-analysis of data from 802 patients. Presented at American College of Cardiology, New Orleans, LA March, 1999 (abstract no. 1074-70)

Clinical Research Disciplines: Translational research;

Specific Research Interest: Immunopathogenic mechanisms of food allergic disorders and asthma; immunomodulatory therapies

Students: PhD: Kamal Srivastava
Postdoctoral Fellows: Jennifer Maloney, Rosalia Ayuso
Research Personnel: Alexander Grishin, PhD; Luda Bardina, MS; Galina Grishin, MS; Russell Castro, BS; Yesim Kucuk, MD

Summary of Research Studies:
Our laboratory is evaluating immunopathologic mechanisms of food allergic disorders. Specifically we are identifying allergenic proteins at a molecular and structural level, and investigating the interaction between IgE antibodies and allergenic proteins and the immune response at a cellular and molecular level. Studies utilize patient specimens and murine models in an attempt to elucidate underlying mechanisms. Allergenic proteins in egg, milk and peanut have been fully characterized and full-length cDNAs isolated and cloned. A number of therapeutic strategies are under investigation utilizing murine models of anaphylaxis and asthma including the use of "engineered" recombinant proteins, DNA vaccines, and CpG-conjugated proteins.

In addition, our laboratory is serving as the mechanistic center for the NIAID Inner City Asthma Consortium. The consortium is investigating the role of allergic sensitization in inner city children and its potential role in the increased morbidity and mortality found in this population. The overall goal is to determine whether the nature and quantity of environmental allergens within the inner city, especially cockroach, are unique in their ability to determine and drive the intensity of allergic inflammation in sensitized children residing in the inner city and thus the severity of their asthma.

The lab employs a variety of techniques to identify and purify proteins including SDS-PAGE, immunoblotting and HPLC. Recombinant proteins are generated from cDNA isolated from appropriate cDNA libraries. A variety of techniques are utilized to study both humoral and cellular responses of patient groups and controls. Characterization of cellular responses includes intracytoplasmic staining, mRNA generation, and characterization of cytokines secreted into cell supernatants. Similar studies are conducted in the murine models.

Location where the studies are carried out:
GCRC

Lisa Satlin, MD; Columbia University

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Clinical Research Disciplines: Translational research;

Specific Research Interest: Mechanoregulation of epithelial ion channels and transporters in kidney in health and disease; ontogeny of renal ion channels

Students: Phillip Mitchell, Ellen Antoine
Postdoctoral Fellows: Sevgi Gurkan
Research Personnel: Wen Liu, Yuan Wei, Beth Zavilowitz

Summary of Research Studies:

The focus of our lab is directed at defining the mechanisms leading to the acquisition, maintenance and regulation of transepithelial transport in the renal cortical collecting duct (CCD), the nephron segment responsible in the adult for the final renal regulation of potassium (K) and sodium (Na) homeostasis. In the CCD, urinary Na diffuses into principal cells through apical Na channels (ENaCs) and is extruded at the basolateral membrane in exchange for uptake of K by the Na-K pump. Cell K passively diffuses out of the cell down a favorable electrochemical gradient into the luminal fluid through apical K-selective (SK or ROMK) channels. Recent evidence from our laboratory indicates that high rates of tubular fluid flow (laminar shear) activate apical BK channels in a Ca2+-dependent manner. Using a combination of molecular, electrophysiologic, and functional techniques, we are exploring following major areas of investigation.

Mechanoregulation of epithelial ion transport: An increase in urinary flow rate (shear stress) in the collecting duct leads to an increase in intracellular Ca2+ concentration ([Ca2+]i), which in turn activates BK channels residing at the apical membrane. This leads to the well-described K loss associated with high urinary flow rates, as follows diuretic administration. The apical cilium present in principal cells in the collecting duct has been proposed to be a flow sensor. Using functional fluorescence dyes and digital ratio imaging applied to collecting ducts microperfused in vitro in their native geometry, we have begun to explore the molecular mechanisms underlying the mechanoinduced [Ca2+]i response. In collaboration with the Biomechanical Engineering Department at CCNY, we are using mathematical models to understand how fluid shear and hydrodynamic forces at the apical surface (including cilia and microvilli/microplicae) of the cells residing in this nephron segment are transduced into biochemical signals.

Developmental regulation of ion channels in the distal nephron: Kidneys of growing subjects efficiently retain urinary K and Na. In contrast to the high rates of net K secretion observed in CCDs isolated from adult animals, segments from neonatal animals show no K transport and a paucity of conducting apical K channels. Yet, the same neonatal segments possess functional ENaC channels and absorb Na at a rate half that measured in the adult. Studies are underway to discern whether the appearance of conducting SK, BK, and ENaC channels is regulated by transcription, translation, and/or post-translational processing. The role of epigenetic factors (diet and hormones, including aldosterone and angiotensin II) and signaling molecules in the regulation of gene and protein expression, channel activity, and tubular transport in the differentiating CCD are being explored.

Epithelial transport in polycystic kidney disease (PKD): Autosomal recessive PKD (ARPKD), a disease associated with a high morbidity, is characterized by the progressive dilatation of collecting ducts and early onset of hypertension. We have sought to identify whether alterations in expression and regulation of epithelial transport pathways contribute to disease progression. We reported that cystlining cells are capable of avid Na absorption early in the course of the disease. Studies are ongoing to examine the molecular basis for this observation using kidney cell lines derived from ARPKD and age-matched normal kidneys and mouse models of PKD.

Clinical Research Disciplines: Epidemiologic research;

Specific Research Interest: Perinatal epidemiology, environmental epidemiology, epidemiologic methods

Summary of Research Studies:
1) Ethnicity and pregnancy outcome and New York City
2) Epidemiology of gestational diabetes

Location where the studies are carried out:
Community, Obstetrics Clinic


Alison Schecter, MD; SUNY Health Science Center

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Clinical Research Disciplines: Translational research;

Specific Research Interest: In vitro and in vivo of chemokine receptor biology as it relates to the cardiovascular system. Women's cardiovascular health and prevention

Students: Perry Altman, Tom Larocca, Yokiko Asai
Postdoctoral Fellows: Martina Schwarzkopf, Sima Tarzami,
Research Personnel: Shihong Zhang,

Summary of Research Studies:
Research in Dr. Schecter's laboratory is focuses on the role of chemokine receptors (receptors that mediate inflammation and cellular recruitment) in the cardiovascular system. We focus on in vitro and in vivo studies of endothelial, smooth muscle and myocardial cells. Current work focuses on:

1. The role of the chemokine receptors, CCR5, CXCR4, CCR3 and CCR8 in SMC. Studies are ongoing to determine the function of these receptors on SMC, their role in atherosclerosis and arterial injury using a murine injury model. Because the CXCR4 knockout is embryonic lethal, we are using a conditionally expressed CXCR4 knockout animals (in collaboration with Dan Littman, NYU) to understand the role of this receptor in the vasculature. We are currently measuring endothelial function(s) in response to chemokines as well as myocardial contractility.

2. HIV is associated with vasculopathy and accelerated atherosclerosis. CCR5 and CXCR4 are the biologically relevant HIV co-receptors. We have demonstrated (in collaboration with Mary Klotman) that HIV can signal and infect human SMC. Studies are ongoing to determine the mechanism(s) of activation and infection of SMC by HIV in vitro and in vivo. We are using transgenic mice that express HIV, (courtesy of Paul Klotman), to determine the effect(s) of HIV on arterial injury and in the development of atherosclerosis. Of particular interest is the identification of genes that are affected by viral exposure using gene chip technology.

3. HIV and Cardiovascular Disease. We are currently beginning clinical studies to image and characterize atherosclerotic plaque in patients with and without HIV. These studies are in collaboration with Dr. Fayad, director of cardiovascular imaging, MSSM Dept of Infectious Diseases and Albert Einstein School of Medicine.

4. Chemokine Receptors on the Myocardium: We are currently measuring individual cardiac myocyte contractility, calcium mobilization and signaling pathways. In vivo studies include the hemodynamic assessment (pressure volume loops) of mouse and rat cardiac function as well as MRI assessment of cardiac function in murine models of myocardial infarction and ischemic/reperfusion.

Location where the studies are carried out:
GCRC

Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Solid Organ Transplantation in HIV patients; treatment of hepatitis C (HCV); hepatorenal syndrome type 1; hyponatremia; acute liver failure; treatment of hepatitis B (HBV); liver transplant immunosuppression; hepatocellular carcinoma; Intestinal transplantation.

Research Personnel: Rosemarie Gagliardi, Clinical Research Director; Marjorie Small, Regulatory Compliance Manager

Infrastructure Available: CLINICAL RESEARCH:
The clinical research program includes a research director; regulatory manager; a senior nurse research coordinator and 10 research coordinators.

Summary of Research Studies:
* Solid Organ Transplantation in HIV patients-Multi Site Study
* Pilot study on the efficacy and tolerability of daily consensus interferon (Intergen® (interferon alfacon-1) plus ribavirin in the treatment of hepatitis C (HCV) in patients with cirrhosis
* A double blind, placebo controlled, randomized phase III study of intravenous terlipressin in patients with hepatorenal syndrome type 1.
* A prospective, randomized, multicenter, open-label, comparative safety and efficacy study of prophylactically administered pegylated interferon alfa-2a (Pegasys®) plus ribavirin vs. no prophylaxis following liver transplantation for hepatitis C
* SR121463B in cirrhotic ascites treatment with hyponatremia: A placebo-controlled, dose-comparison study

Location where the studies are carried out:
FPA; Inpatient Hospital; GCRC; Laboratory


Clinical Research Disciplines: Translational research;

Specific Research Interest: The role of the innate immune response in transplantation

Summary of Research Studies:
The role of donor-derived chemokines in islet transplantation
The interplay between graft-specific physiologic responses to early injury and the innate host immune response is studied. This is especially relevant in clinical islet transplantation when relatively few islets are transplanted or when donor or isolation factors up-regulate cytokine expression. Our preliminary data demonstrate that islets have the capacity to behave in a similar manner to cells of the immune system, recruiting leukocytes from the blood stream. The hypothesis is that islet-derived mediators directly or indirectly affect islet engraftment, function and viability, and serve to further amplify the adaptive immune response. The goals are to characterize the innate immune response to specific stimuli in islet transplantation and to identify therapeutic strategies to improve islet transplant engraftment and survival.


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Clinical Research Disciplines: Translational research;

Specific Research Interest: The biology and treatment of lysosomal storage disorders; the role of lipid hydrolases in cell signaling

Students: MD/PhD: Eric Smith, PhD: Nataly Shtraizent
Postdoctoral Fellows: Raj Dhami, Efrat Eliyahu, Iwan Jones
Research Personnel: Research Faculty: Xingxuan He, Calogera Simonaro; Research Assistant: Yi Ge, Zhenxian Xu

Infrastructure Available: 1000 square feet of wet lab space, shared research space and access to departmental core laboratories

Summary of Research Studies:
Our laboratory studies the biology of lysosomal enzymes, genes and diseases. Our long-term goal is to utilize the basic knowledge gained from this research to develop and implement novel therapies for human patients who suffer from lysosomal storage disorders. Our research integrates molecular genetic, biochemical and cell biological techniques to accomplish these studies. A particular emphasis of the laboratory is the development and characterization of animal models for human lysosomal disorders, and the utilization of these animal models to evaluate novel therapeutic approaches. Among these approaches are stem cell transplantation, gene therapy, and enzyme replacement. We are also very interested in the mechanisms underlying genetic regulation of lysosomal proteins and the role these proteins play in cell growth and development. Towards this latter goal, we are studying the role of two enzymes, acid sphingomyelinase and acid ceramidase, in sphingolipid-mediated signal transduction, and evaluating how these enzymes can be used in cancer therapy to enhance tumor cell death.


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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Surgical Oncology, hepatocellular carcinoma (HCC); Liver Transplantation; Hepatitis C; Hepatitis B; living liver donor transplantation; acute cellular rejection; use of immunosuppression;

Research Personnel: Rosemarie Gagliardi, Clinical Research Director; Marjorie Small, Regulatory Compliance Manager; Mark Siegal, Research Coordinator

Infrastructure Available: CLINICAL RESEARCH:
The clinical research program includes a research director, regulatory manager, a senior nurse research coordinator and 10 research coordinators.

Summary of Research Studies:
* Systematic Integration of Patient-Oriented Research into the Clinical Pathway for Hepatocellular Carcinoma.
* An Evaluation of Chronic Thalidomide Administration in Patients Undergoing Chemoembolization for Unresectable Hepatocellular Cancer, supported through "Phase I Studies of Anticancer Drugs and Gene Therapy.
* Thalidomide for Unresectable Hepatocellular Cancer with Optional Interferon a2a Upon Disease Progression, supported through "Phase I Studies of Anticancer Drugs and Gene Therapy.
* Clinical, Immunologic and Pharmacologic Consequences of Solid Organ Transplantation in People with HIV Infection.
* Validation of Serum Markers for the Early Detection of Hepatocellular Carcinoma.
* A Phase 3 Randomized, Double-Blind, Controlled, Comparative Efficacy and Safety Study of Topical Recombinant Human Thrombin (rhThrombin) and Thrombin-JMI (Bovine Thrombin) in Surgical Hemostasis.

Location where the studies are carried out:
FPA; Inpatient Hospital; GCRC; Laboratory


Clinical Research Disciplines: Patient-oriented research; Behavioral medicine;

Specific Research Interest: Posttraumatic stress and adherence to treatment recommendations in medically-ill patients.

Research Personnel: Rachel A Annunziato, Ph.D.

Summary of Research Studies:
Two cohorts of patients are involved: children who had a transplant and adults who had a myocardial infarction. The transplant and MI are potentially emotionally traumatic events. The group studies the interaction between psychiatric morbidity, medical morbidity, adherence to medication regimens, and medical as well as psychiatric outcomes.


Scott Sicherer, MD; MSSM

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Clinical Research Disciplines: Patient-oriented research; Epidemiologic research; Health outcomes research;

Specific Research Interest: Food allergy

Summary of Research Studies:
Studies regarding epidemiology and clinical aspects of allergic diseases caused by specific foods such as peanuts, tree nuts and milk, the natural history of food allergy, atopic dermatitis, gastrointestinal manifestations of food allergies, epidemiology of food allergy, and psychosocial issues associated with food allergies.

Location where the studies are carried out:
GCRC, Community, FPA

Larry Siever,

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Jeremy Silverman, PhD; New York University

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Clinical Research Disciplines: Patient-oriented research; Epidemiologic research; Behavioral medicine; Molecular epidemiology;

Specific Research Interest: My group is especially focused on characterizing phenotypes and endophenotypes in schizophrenia, dementia, successful aging, and autism for use in molecular genetic studies.

Location where the studies are carried out:
Suite 1B Aron Hall; the broader NY Metro Region; Puerto Rico; Costa Rica


Clinical Research Disciplines: Health outcomes research;

Specific Research Interest: Perioperative outcomes for elderly patients

Research Personnel: see website

Infrastructure Available: Organize clinical trials office
Clinical Research Disciplines: Patient-oriented research; Epidemiologic research;

Specific Research Interest: Neurological complications of AIDS Botulinum toxin in spasticity

Postdoctoral Fellows: Adam Didio, MD
Research Personnel: Susama Verma (MD), Katia Cicurel (MD), Mary-Catherine George, Elena Micsa, Edwin Nunez

Summary of Research Studies:
The Mount Sinai-Neuro-AIDS Program is committed to the development of safe and effective treatments for the nervous system complications of HIV infection and extending the basic understanding of the mechanisms responsible for these disorders. The center carries out its mission through basic research, state of the art clinical care, experimental therapeutics and educational and outreach programs designed to reach the patient, health care provider and lay community.
The Mount Sinai Neuro-AIDS Program has conducted and published a wide range of clinical research studies, addressing HIV dementia, opportunistic brain infections and neoplasms, myelopathy (spinal cord disorder), peripheral neuropathies and myopathy (muscle disease). Our collaborators have performed seminal neurophysiologic, neuropsychological, and neuropathological investigations in these diseases. The Infectious Diseases group has particular strength in molecular biological techniques to investigate characteristics of the HIV virus within the central nervous system.
The Mount Sinai-Neuro-AIDS Program has been recognized as a leader in educational activities concerning all aspects of HIV disease. The program provides frequent lecture series, visiting fellowships, meetings, and resource materials. We have an active community outreach program covering a large inner city population, which has been highly successful in increasing AIDS awareness and care in these underserved regions.
Our group is also researching the clinical use of botulinum toxin injections for the treatment of spasticity. Spasticity is disabling muscle stiffness that occurs after injuries to the central nervous system, such as stroke or spinal cord injury.

Location where the studies are carried out:
Annenberg 2, GCRC


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Mary Solanto-Gardner, PhD; Mount Sinai School of Medicine

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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Dr Solanto's research interests are related to the etiology, diagnosis and treatment of AD/HD in adults and children. She has lectured and published articles on such topics as neuropsychological functioning in children and adults with ADHD, time-action and dose-response effects of methylphenidate (ritalin) on behavior and psychophysiology, effects of stimulant medications on cognitive and behavioral functioning, neurobiological mechanisms of action of stimulants, effects of reinforcement (reward) in children with ADHD, differentiating Combined and Predominantly Inattentive subtypes of ADHD, diagnosis of ADHD in adults, psychosocial interventions for adults with ADHD, effects of sugar in ADHD, and cross-cultural differences in ADHD.

Postdoctoral Fellows: Katherine Mitchell, Psy.D.
Research Personnel: David Marks, Ph.D.

Summary of Research Studies:
Dr. Solanto recently received an NIMH funded grant to investigate the efficacy of a 12-week cognitive behavioral group treatment for adults with AD/HD. The treatment targets metacognitive deficits in skills related to time management, organization, and planning. She is also Co-Investigator of two additional NIMH projects. One is examining dopamine function in adults with AD/HD, while the other is a PET study to measure and predict response in adults to Atomoxetine and Methylphenidate.

Location where the studies are carried out:
Mount Sinai School of Medicine, 19 East 98th St, Suite 5D, New York, New York 10029


Solanto MV. The Predominantly Inattentive Subtype of Attention-Deficit/HyperactivityDisorder. CNS Spectrums 2000; 5:45-51.
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Specific Research Interest: Biostatistical methodology; clinical trials

**Summary of Research Studies:**
I am developing statistical methods useful in the surveillance of bioterrorism. This is a continuation of my long-standing interest in detecting clustering. I had previously focused on clustering of disease in time, with particular emphasis on the scan statistic, the maximum number of events in a sliding time window. I hope, with the aid of doctoral students or other researchers, to also apply this methodology to search for homologies in molecular sequence data.

A second area of interest is to develop statistical methods in the context of genetics, particularly in collaboration with Dr. Wetmur's lab. A case control study of breast cancer in different ethnic groups had motivated the development of a new procedure to evaluate possible gene environment interactions when the genetic data is in the format of haplotypes composed of several biallelic loci. Current work concerns quantifying the loss of imputing haplotypes instead of getting them directly, and methods to be used when pooling DNA data from several individuals.

I also help develop statistical methods to design studies, and to analyze and explore the resulting data. Recent work in methodology for analyzing data deals with constructing confidence intervals for differences in proportions, and on analyzing trials in which survival is the outcome and in which there is a transient effect of treatment.


Summary of Research Studies:

For many years, I have studied defective differentiation which results in the development of hematologic malignancies. We were the first to demonstrate that all trans retinoic acid and arsenic trioxide targets the degradation of the leukemogeneic protein that causes acute promyelocytic leukemia (APL) and induces myeloid differentiation. These drugs have now been approved by the FDA and used throughout the world to treat this disease. We continue work in this field related to targeting leukemogenic proteins in other forms of leukemia and myelodysplastic syndromes. The present clinical studies related to this include the use of arsenic trioxide in the treatment of refractory low grade lymphoma. Preclinical studies are in progress utilizing arsenic trioxide in the treatment of AML1-EVI induced leukemia and myelodysplastic syndrome. We have also studied combination cytotoxic differentiation therapy and have demonstrated that combining fluoropyrimidines with interferon alpha, cyclooxygenase inhibitors and histone deacetylase inhibitors synergize to induce apoptosis in seven different colon carcinoma cell lines. A protocol is in progress based on this research to treat advanced and refractory colon carcinoma. We continue to develop novel and highly potent differentiation inducers. In collaboration with the National Cancer Institute, we screened 400 possible compounds and identified a novel compound called dithiophenes which induce differentiation in leukemia cells at nM concentration and apoptosis in many forms of cancer at slightly more concentration. The mechanism of action for these activities are under study. The development of dithiophenes from compound to a pharmaceutical agent to treat cancer is in progress.


James Wetmur, PhD; California Institute of Technology

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Clinical Research Disciplines: Molecular epidemiology;

Specific Research Interest: Molecular epidemiology; technology development for genomics and proteomics

Postdoctoral Fellows: Brian Hu, Anu Voho
Research Personnel: Madhu Kumar, Arnaud Ganee, Audrey Pendleton

Summary of Research Studies:
Some of our work involves molecular epidemiology. For example, one of our studies is a project using the birth cohort in the Mount Sinai Children’s Environmental Health Center, where we have examined human variation in activation and detoxification [e.g. paraoxonase-1 [PON1]] of organophosphates. We have found that not only do neonates have four-fold lower levels of paraoxonase than adults, but that those levels vary more widely with common promoter polymorphisms in neonates than in adults. Thus certain neonates have up to 10-fold less protection than adults. Low maternal PON1 together with maternal exposure to the organophosphate chlorpyrifos produced a significant effect on birth measurements.

There are five common polymorphisms in human PON1, three of which affect enzymatic activity. We have developed a single-molecule based molecular haplotyping system. The method involves duplex PCR across the heterozygous polymorphic sites on single template molecules isolated by an oil-water emulsion. By using jumping PCR in the emulsion to link the two PCR products, capping and allele-specific PCR readouts, we have determined PON1 haplotypes for the cohort study described above.

We will be applying our experience in molecular epidemiology to study allelic imbalance in human dendritic and T-cells challenged with various viruses in the Technology Development Component (TDC) of the Center for Investigating Viral Immunity and Antagonism. These studies should complement the transcriptome approach in the TDC and should lead to the discovery of new human variation evident only in the context of viral challenge. Such variation may be important in identification of susceptible individuals and in the development of vaccines. In addition, we have developed a multiplex single cell assay to quantitify transcripts that has allowed us to observe cell-to-cell and chromosome-to-chromosome variation in virus-infected human myeloid dendritic cells.

We are applying our experience with emulsion technology for the selection of bacterial clones expressing mutant thermostable DNA polymerases and accessory proteins. In the past we have studied mismatch repair proteins, assembled the complete downstream in vitro recombination system from Thermotoga maritima and have investigated the properties of Methanococcus jannaschii flap endonuclease (FEN-1).

Location where the studies are carried out:
Annenberg 16-30


Clinical Research Disciplines: Patient-oriented research; Epidemiologic research;

Specific Research Interest: Asthma, lung cancer, tuberculosis, clinical epidemiology and health outcomes research

Location where the studies are carried out:
Community-based


Wisnivesky J, Leventhal H, Halm E. A Prospective Study of Predictors of Asthma-Related Health Care Utilization and Quality of Life among Inner City Asthmatics. JACI, 2005; 116:636-42


Specific Research Interest: Measurement of environmental exposures, including diet and lifestyle factors and individual susceptibility, and their relationship to cancer risk, to reproductive dysfunction and to developmental disorders.

Summary of Research Studies:
Research has addressed ethnic variability in exposures and how these differences may be related to disease risk. In addition, her group is investigating environmental and genetic risks for early puberty, research that is intended to elucidate risk for breast cancer and other chronic diseases. She directs two research cohorts of children followed since before birth, to examine risks associated with prenatal exposures, including women who were exposed to chemicals and traumatic events at the World Trade Center on 9/11/2001; they and their children are now in the third year of followup. She and her colleagues recently received a 7-year grant from NIEHS to investigate environmental and genetic risks for early puberty, research that is intended to elucidate breast cancer risk.


Savio Woo, PhD; University of Washington

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Clinical Research Disciplines: Translational research; Patient-oriented research;

Specific Research Interest: Gene Therapy for Cancer and Inherited Diseases

Postdoctoral Fellows: Li Chen1, Li Chen2, Zhiyu Li, Lan Wu, Sun Tao
Research Personnel: Marcia, Meseck, Tian-Qui Huang, Sonal Habaran,

Summary of Research Studies:
Gene Therapy is an emerging biomedical discipline that will find applications in the treatment of a wide variety of diseases. A number of recombinant gene transfer vector systems have been developed in the past few years to achieve persistent gene transfer and expression in various animal models of disease. Phenylketonuria (PKU) is a metabolic disorder that predisposes affected children to development of severe and irreversible mental retardation, and is secondary to a deficiency of the hepatic enzyme phenylalanine hydroxylase (Pah). The recombinant adeno-associated virus has been shown to express therapeutic levels of transgene products in animals for an extended duration of time, and PKU mice treated with a recombinant adeno-associated virus (serotype-9) expressing murine Pah were cured of their metabolic deficiency. Another exciting novel strategy to deliver therapeutic genes into mammalian cells is to take advantage of a bacterial phage integrase system, which catalyzes a recombination reaction between a specific region in the phage genome and a homologous sequence in the genome of the bacterial host that resulted in the integration of phage genome into that of the bacterial host. A handful of pseudo-homologous sites are present in mouse and human cell genomes that are recognizable by the bacterial phage integrase, and plasmids containing the phage attachment site can be inserted into the mammalian genomes in a site-specific and unidirectional manner. Using this integration system, the mouse Pah gene was delivered to the liver of PKU mice that resulted in the long-term correction of their deficient phenotype. The cures achieved in these laboratory animal models of disease will support the development of clinical translational trials to treat patients with PKU as well as a variety of genetic disorders by gene therapy.

Most recently, it was discovered that many RNA viruses have the natural tendency to efficiently replicate selectively in tumor cells due to their attenuated responses to type I interferons. Of these, the Vesicular stomatitis Virus (VSV) is a particularly attractive oncolytic agent as its replication cycle in tumor cells is only 8-10 hours, which will permit extensive viral replication in tumors prior to the onset of anti-viral immune responses in the host. The virus has been proven effective in causing massive tumor destruction in laboratory animals bearing multi-focal Hepatocellular Carcinoma (HCC) and metastatic Colorectal Carcinoma (CRC) in their livers. The treatment also led to significant survival prolongation and a research grant from the National Cancer Institute was received recently to launch a clinical translational trial in patients with advanced liver cancer at Mount Sinai. Thus, gene therapy is rapidly developing into a novel biomedical discipline that can be productively applied in the treatment of both genetic and acquired disorders in humans, and it represents a fundamental form of molecular medicine that will have a major impact on health and healthcare for decades to come.


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