



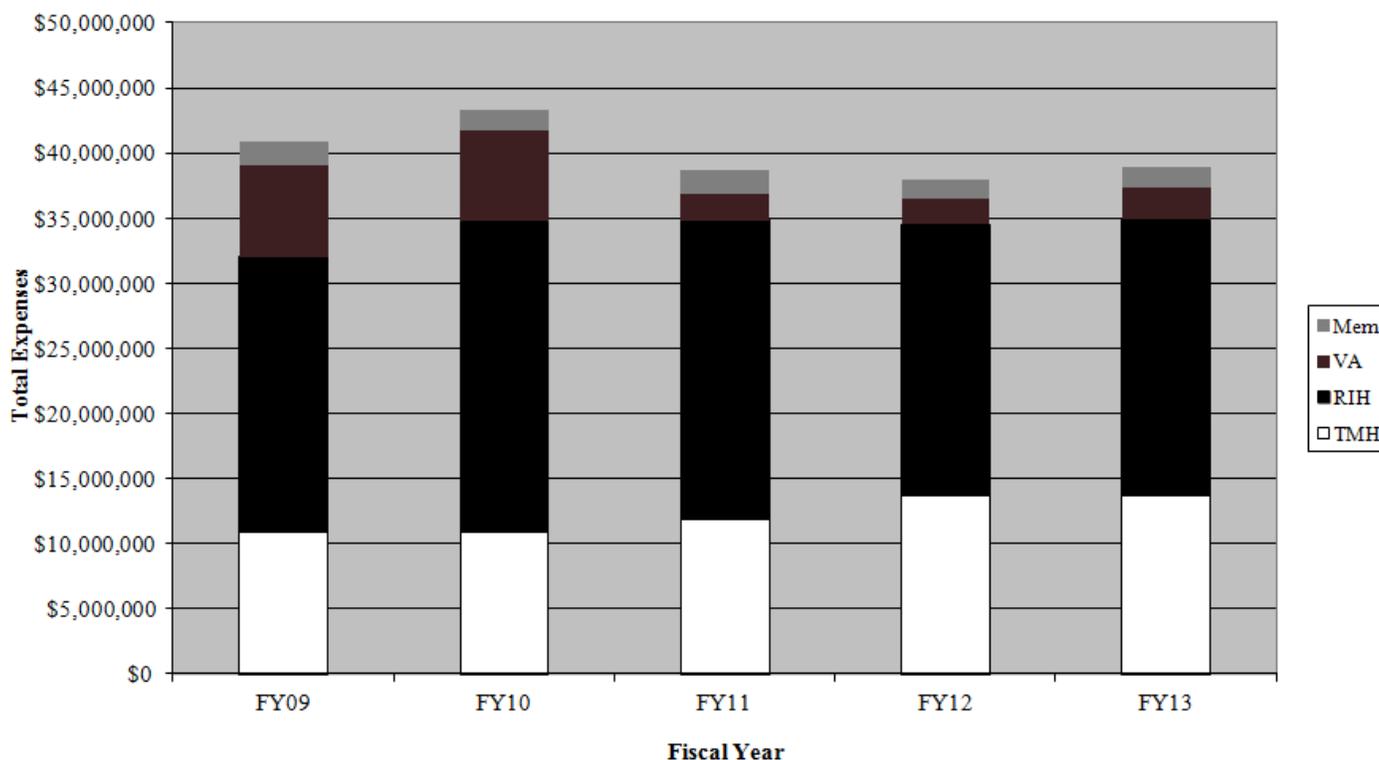
Research Overview Fall 2014

Brown University has long been regarded as a leader in all aspects of health care and teaching, including research. Despite significant reductions in federal funding for research over the past number of years, research funding at the affiliated hospitals within the Department of Medicine (Rhode Island Hospital, Memorial Hospital of Rhode Island, Veterans Administration-Providence and The Miriam Hospital) has remained steady with FY13 funding of \$39 million. Over 70% of current funding comes from federal programs such as NIH, HRSA, CDC, and DHHS.

Laboratories are highlighted by the creation of the 'Knowledge District' in Providence. This enterprise involves key research institutions including Brown University and Rhode Island Hospital. Major State of Rhode Island and City of Providence government officials are deeply involved in creating a central area focused on biomedical research. For Rhode Island Hospital, this includes a \$3 million laboratory construction of the Medical Oncology research program in the Coro facility, completed in 2012. Other programs in the Coro facility include the CardioVascular Research Center and the Genomics and Proteomics Center. The other major research facility for Lifespan in the Knowledge district is the Galletti Research Building, which houses the Liver Research Center, Diabetes and Endocrinology Research Center, and Infectious Disease laboratories.

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Research Growth FY09 - FY13



Continued from front page

In showing a commitment to research as an integral part of academic medicine, all three recently recruited Division Chiefs in the Department of Medicine have vibrant research programs: Dr. Angela Caliendo, Chief of General Internal Medicine; Dr. Eleftherios Mylonakis, Chief of Infectious Diseases; and Dr. Samuel Dudley, Chief of Cardiology.

Both basic and clinical research are well represented in the Department. For basic research, major strengths include the **Liver Research Center** (directed by Dr. Jack Wands), and **Medical Oncology and Stem Cell Research** (directed by Dr. Peter Quesenberry) and the **Cardiovascular Research Laboratory** (directed by Drs. Samuel Dudley and Gideon Koren). Academic aspects to research include NIH funded T-32 Training grants in Medical Oncology and Hematology, Cardiology/Pulmonary, Infectious Diseases, and Gastroenterology.

Clinical Research strengths include the Infectious Disease program under the direction of Drs. Timothy Flanigan and Charles Carpenter, which has a major program in both domestic and international HIV/AIDS (including an NIH funded **Center for AIDS Research** program and T-32 Training grant, Ryan White program funding, and Fogarty International program), **Research Section, General Internal Medicine**, under Dr. Peter Friedmann and the **Cardiology clinical research groups** under Drs. Paul Gordon, Peter Soukas, J. Dawn Abbott, James Arrighi and Barry Sharaf, (**Interventional Cardiology**).

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Cardiology

Samuel C. Dudley, Jr., M.D., Ph.D. Director of the Cardiovascular Institute at the Miriam, Newport, and Rhode Island Hospitals and the Chief of Cardiology at Rhode Island and the Miriam Hospitals. The research in Dudley laboratory spans from basic science targeting fundamental mechanisms underlying cardiovascular diseases to translational medicine aiming at advancing the diagnosis and treatment of sudden death and diastolic heart failure. Specific projects include exploring the mechanisms of the transcriptional and post-translational regulation of Na⁺ channel in heart failure, heart failure-mediated cardiac connexon regulation, the role of mitochondria in heart failure and arrhythmias, developing new blood tests for diastolic heart failure and sudden death, and developing new treatments for diabetes, diastolic heart failure, and sudden death. Work in the laboratory has resulted in >30 patents and one biotech company so far.

Clinical Cardiac Electrophysiology

Michael H. Kim, MD is a Professor of Medicine at the Warren Alpert School of Medicine of Brown University. His clinical and research interests focus on atrial fibrillation, catheter ablation, cardiovascular outcomes, quality of care, health economics, device based therapies, health care disparities, and arrhythmias in general. He is a national expert in atrial fibrillation disease management strategies and in cardiovascular outcomes with a perspective on arrhythmias. He serves as an editorial referee for numerous specialty journals and is on the editorial board of the Journal of the American College of Cardiology and the Journal of Cardiovascular Electrophysiology. Current research is focused on atrial fibrillation, specifically in regard to arrhythmia management (anticoagulation) with an eye towards cardiovascular outcomes. Other areas of active research involve health care disparities, antiarrhythmic drugs, and ICD outcomes.

Peem Lorvidhaya, M.D. is the principal (main and site) investigator of several clinical trials including a registry evaluating the ability of cardiac MR to identify patients with sarcoidosis having early cardiac involvement, a Phase 3 Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Effects of Once-Daily Oral Doses of 75 mg Azimilide Dihydrochloride on the Incidence of Cardiovascular Hospitalizations or Cardiovascular Death in Patients with an Implantable Cardioverter Defibrillator (SHIELD-

2), Left Ventricular Hypertrophy as Predictor of Sudden Cardiac Death and Implantable Cardioverter-Defibrillator Therapy, Validation of Electrocardiographic (ECG) Criteria for Left Ventricular Hypertrophy (LVH) by Cardiac Magnetic Resonance Imaging (CMR), SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial 10 Year Follow-Up, The Vest Prevention of Early Sudden Death Trial (VEST) PREDiction of ICD Therapies Study (PREDICTS), The Effect of Aging on the Conduction Properties of the Isthmus-Dependant Atrial Flutter Circuit, A Phase III, Active (Warfarin) Controlled, Randomized, Double-Blind, Parallel Arm Study to Evaluate Efficacy and Safety of Apixaban in Preventing Stroke and Systemic Embolism in Subjects with Nonvalvular Atrial Fibrillation, and the Block HF Study.

He also directs the complex devices and leads management program.

Basic Cardiovascular Research

Gideon Koren, M.D., Professor of Medicine, is interested in understanding the pathogenesis of cardiac arrhythmias through three main lines of investigation: 1) Genomic studies to elucidate the transcriptional program(s) that control the expression of membrane polypeptides involved in determining the duration of cardiac action potential and early and late afterdepolarizations, as well as the aging of the heart. As part of these studies Dr. Koren is interested in studying the differentiation and senescence of adult cardiac stem cells; 2) Investigation of the transcription, trafficking and localization of voltage-gated potassium channels in the cardiomyocytes and the effect of sex hormones on these processes; and 3) Creation of genetically modified animal models for studying sudden cardiac death. Specifically, Dr. Koren's laboratory is focusing on the molecular mechanisms underlying the turnover of HERG and KvLQT1 potassium channels in the heart and proteins that modulate this process. His group is characterizing the macromolecular complex (channelosome) that modulates the localization and function of several delayed rectifier potassium channels in the heart. In addition, his laboratory has analyzed and compared the phenotype of two novel transgenic rabbit models of long QT syndrome 1 and 2 (LQT1 and LQT2) using surface ECG; monitoring of alert, free-moving rabbits, programmed electrical stimulation (PES) of the right ventricle of anesthetized rabbits, and analyses of the biochemical and electrophysiological phenotype of rabbit cardiomyocytes derived from these hearts.

Bum-Rak Choi, Ph.D. at the Cardiovascular Research Center focuses on mechanisms underlying cardiac arrhythmias. His research is aimed at understanding the relation between calcium cycling and cardiac arrhythmias. Calcium plays an important role in controlling cardiac contraction and transcription of cardiac genes. Calcium also modulates the cardiac action potential, and under pathological conditions it contributes to unstable cardiac rhythm such as alternans and reentry. Dr. Choi uses a high spatio-temporal optical mapping system to record electrical activity and calcium cycling using fluorescent dyes at the organ level and engineered tissue level. The initiation of arrhythmia and reentry circuits can be identified to better understand the risk of arrhythmias and its mechanism. By mapping the initiation of arrhythmias, his lab investigates how abnormal calcium handling promotes conduction block and reentry formation in various pathological conditions such as heart failure, myocardial infarction, long QT syndrome using transgenic rabbit models, and myocardial infarction in aging heart. Combined with computer modeling studies using parallel GPUs or 3D engineered tissue culture from Dr. Mende's laboratory, he hopes to find molecular targets that can be safely modified to prevent rhythm disturbances and reduce the risk of sudden cardiac death in patients.

Ulrike Mende, M.D., F.A.H.A., Associate Professor of Medicine and Principal Investigator at the Cardiovascular Research Center, has a background in pharmacology and molecular cardiology and a particular research interest in the regulation of heart rate, contractile function and extracellular matrix production via G protein-mediated signaling pathways in the healthy and diseased heart. Signal transduction via heterotrimeric G proteins is one of the most important mechanisms of signal transfer across the cell membrane in virtually all cells, including cardiac cells. G proteins act as relay switches that link extracellular signals on the cell surface to changes in ion channel activity and second messenger pathways inside the cell, which in turn elicit changes in cellular function. Dr. Mende's research focuses on how perturbations in G proteins and their regulators in cardiac myocytes and fibroblasts contribute to the development of cardiac hypertrophy and fibrosis, heart failure and arrhythmias, with the long-term goal to identify potential new targets and strategies for pharmacological or genetic therapies. Her team conducts gain- and loss-of-function studies in primary heart cell cultures and genetically modified mouse models and uses molecular and biochemical assays to examine gene/

Cardiology (cont.)

protein expression as well as physiological techniques to assess heart cell and cardiac functions. Current projects in the Mende laboratory include investigations of (i) the regulation of G protein signaling in cardiac fibroblasts and their role in determining the cardiac remodeling response to hemodynamic stress, and (ii) the functional significance and mechanisms of communication between cardiac fibroblasts and myocytes under physiological and pathophysiological conditions. To that end, the Mende laboratory (in collaboration with other CVRC and Brown faculty) is developing novel 2D and 3D co-culture models that mimic key characteristics of cardiac tissue and allow for examination of myocyte-fibroblast communication under controlled experimental conditions.

Gaurav Choudhary, M.D. is a staff cardiologist at the Providence VA Medical Center. He is an investigator at the Vascular Research Laboratory at the Providence VAMC. The focus of his research is to evaluate the mechanisms underlying vascular dysfunction seen in pulmonary hypertension and cardiac dysfunction in the setting of lung diseases utilizing *in vitro*, *ex vivo* and *in vivo* approaches. He is currently funded by a VA MERIT award to investigate those areas in depth. He is also involved in clinical projects involving Echocardiography and Cardiac CT at the Providence VA.

Dimitry Terentyev, Ph.D., studies cellular and molecular aspects of cardiac excitation-contraction coupling, a mechanism underlying cardiac contractility. A major focus of his group is the study of processes that regulate intracellular calcium cycling under normal conditions and during cardiac disease. Abnormalities in calcium cycling are associated with dysregulation of cardiac rhythmic activity (arrhythmias) and depression of heart blood pumping function (heart failure). The aim of his group is to increase an understanding of basic mechanisms of heart failure and arrhythmias in order to contribute for the development of new strategies to treat these conditions.

Peng Zhang, M.D., M.S., Assistant Professor of Medicine, has a diverse background in medicine and cellular and molecular biology. He investigates cardiac remodeling in response to hemodynamic stress, with a particular focus on cardiac fibroblasts and their role and regulation in the normal and diseased heart. The long-term goal of his studies is to advance understanding of the signaling mechanisms that determine cardiac fibroblast function and may provide new opportunities for treatment and prevention of cardiac fibrosis, a major pathologic end-point of many forms of heart disease. Dr. Zhang utilizes both *in vitro* (primary cul-

ture of cardiac fibroblasts) and *in vivo* (reactive and reparative fibrosis) models along with gene manipulation approaches and analytical techniques (e.g., cellular and molecular assays, *in vivo* hemodynamic measurement). The current main focus of the research in Dr. Zhang's laboratory at the Cardiovascular Research Center is on the expression, regulation and role of microRNAs in regulating cardiac fibroblast function.

Weiyan Li, Ph.D., Instructor of Medicine, is interested in the biophysical properties and molecular mechanisms of ion channels and their involvement in the physiology and diseases of the heart. He uses patch clamp technique to study ion channels from acutely isolated or cultured cardiomyocytes, and heterologously transfected cells to understand their activation mechanism and contribution to cellular electrophysiology under normal and diseased conditions. With rich experience in biophysical studies of calcium-activated potassium channels, he is particularly interested in the cardiac function and mechanism of the small conductance calcium-activated potassium (SK) channel, which has been recently shown to play important roles in the cardiovascular system.

Karim Roder, Ph.D., Assistant Professor of Medicine (Research), research interests surround ubiquitination and the roles it plays in trafficking of membrane proteins. He is interested in the possible role of novel ubiquitin ligases in the rabbit heart regarding action potential duration (APD) and conduction velocity (CV). To address this, both *in vitro* and *in vivo* experimental approaches including proteomics, yeast two-hybrid system, the use of a novel 2D cardiomyocyte model, optical mapping and gene transfer are being used. The outcome of this study might lead to novel pathway(s) regulating APD or CV and identify novel genes that are linked to the QT interval. He is also interested in zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) to create knockout and knockin animals.

Interventional Cardiology

Paul Gordon, M.D., is an interventional cardiologist at The Miriam Hospital, and Director of the Miriam Hospital catheterization laboratory. Optimal duration of Dual anti-platelet treatment following coronary stenting. Investigation and management of clopidogrel resistance following stenting. Role of novel anticoagulants in the management of acute coronary syndromes. Investigating the effects of novel lipid lowering agents on angiographic and IVUS detected coronary atherosclerosis. Role of new

devices in treating CAD. Role of drug-eluting stents in large diameter coronary arteries. Role of Novel treatments to prevent contrast ATN. Stenting vs. CABG for the management of left main and multivessel CAD. Novel stents for acute STEMI and bioabsorbable stents for management of CAD. Stem Cell therapy for recovery of LV function after STEMI. Novel treatments for CHF from chronic LV systolic dysfunction – Parachute device to exclude LV apical aneurysm.

Barry Sharaf, M.D., is an interventional cardiologist at Rhode Island Hospital. He is the Site-Principle Investigator at Rhode Island Hospital of the NIH-NHLBI-sponsored FREEDOM Study investigating multi-vessel revascularization in patients with diabetes mellitus, and the NHLBI sponsored Women's Ischemia Syndrome Evaluation (WISE) study, investigating pathophysiologic mechanisms involved in women with suspicion of ischemic chest pain who are found to have normal coronary arteries. As Director of the Angiographic Core Laboratory, he is the Principle Investigator of the NHLBI sponsored Women's Ischemia Syndrome Evaluation (WISE) Study Angiographic Core Lab, which is performing a detailed quantitative and qualitative analysis on the coronary angiograms in this large cohort of women referred to the catheterization laboratory with suspicion of ischemia.

J. Dawn Abbott, M.D., is an interventional cardiologist at Rhode Island Hospital. Her research interests include percutaneous coronary intervention (PCI) and peripheral arterial disease. She has been the Site-Principle Investigator at Rhode Island Hospital for several NIH and industry funded studies. She has examined the importance of several factors such as stent selection (drug-eluting versus bare metal), gender, and antiplatelet therapy on outcomes in percutaneous intervention. She is the site P.I. on several currently enrolling and ongoing clinical research studies including the Renalguard trial assessing hydration strategies to prevent contrast induced nephropathy from cardiac catheterization, the RIVER-PCI trial investigating the role of ranexa in PCI patients with incomplete revascularization, and the PRESERVATION study a phase II trial examining a novel alginate post myocardial infarction to prevent ventricular remodeling and congestive heart failure.

Peter Soukas, M.D., is the director of Vascular Medicine and the Interventional Peripheral Vascular Labs in the Cardiovascular Divisions at the Miriam and Rhode Island Hospitals. In 2010, Dr. Soukas established the Brown Vascular & Endovascular Medicine Fellowship program, and serves as its director. Dr. Soukas' primary clinical research interest is carotid

artery stenting, and he was the leading New England enroller in the landmark NINDS-sponsored randomized CREST Trial. He has been a primary investigator for 17 different carotid artery stent trials, as well as a national proctor. He is currently a primary investigator for the Sapphire-WW, Freedom flow-reversal, CANOPY, Choice and SCAFFOLD carotid studies.

Another major interest has been in the role of embolic protection for renal artery stenosis, and was an investigator for the VIVA-Fortress trial, which utilized the FiberNet, a novel embolic protection device. His experience in embolic protected renal stenting was published in JVIR 2009.

Dr. Soukas has been a site primary investigator for over 50 trials over the past eight years in the field of interventional cardiovascular medicine. Current investigations also include the Bioflex iliac/SFA stent trial, the Open SFA trial, the EXCITE laser study for in-stent restenosis, the Tigris SFA RCT and the Lutonix BTK paclitaxel drug-eluting balloon trial for patients with critical limb ischemia. He will be the site principal investigator for the REDUCE HTN renal denervation trial for patients with refractory hypertension. Dr. Soukas performs pharmacomechanical thrombolysis for DVT and pulmonary embolus. He specializes in the endovascular treatment of chronic limb ischemia.

Noninvasive Cardiac Imaging

Siddique A. Abbasi, M.D., is a staff cardiologist and the Director of Cardiac MRI at the Providence VA Medical Center. His research focus is in the use of advanced cardiovascular imaging to investigate subclinical alterations in myocardial structure and function. He has a particular interest in the use of cardiac MRI to characterize the myocardium in individuals with obesity and diabetes, and also understanding the effects of weight loss on the heart. He is currently engaged in research looking at the effects of bariatric surgery on myocardial structure and function. Dr. Abbasi works closely with the Multi-Ethnic Study of Atherosclerosis investigators to study the epidemiology of cardiometabolic disease by investigating the role of insulin resistance, visceral adiposity, and weight loss on myocardial structure.

James A. Arrighi, M.D., is Director of Nuclear Cardiology at Rhode Island Hospital. Under his direction a number of research programs are in progress in the section of nuclear cardiology. These focus on

Cardiology (cont)

the use of myocardial perfusion imaging for cardiac risk stratification in special patient populations. Specific current projects include: 1) evaluation of the performance of stress testing in patients with lower risk patients with chest pain (chest pain unit population); 2) implementation and testing of strategies to reduce radiation exposure from nuclear cardiology studies; 3) investigating outcomes in patients with abnormal exercise ECG response and normal cardiac imaging. Finally, the Nuclear Cardiology Database Program will continue; this database can provide research opportunities for our residents and fellows. All patients undergoing perfusion imaging in the Nuclear Cardiology laboratory at RIH since 1995 have been entered into a database with extensive clinical and imaging fields, and trainees are often involved in projects that utilize this resource.

Michael Atalay, M.D., Ph.D., is Director of Cardiac MRI and CT at Rhode Island and The Miriam Hospitals. He holds a joint appointment in the Departments of Medicine and Diagnostic Imaging. Dr. Atalay has clinical and research interests in RV function assessment, cardiac amyloid, cardiac sarcoid, atrial septal defects, pulmonary embolism, and the modalities of MRI and CT. Specific active research includes (1) evaluating the potential utility of cardiac MRI (CMR) to identify patients with cardiac sarcoidosis, (2) validation of LVH by ECG using CMR as a gold standard, and (3) correlation of anatomic metrics with ASD shunt severity.

Athena Poppas, M.D., is Director of Cardiovascular Imaging at CVI. She is conducting studies focused on echocardiographic evaluation of heart disease in the elderly and women. She is a co-investigator of an NIH R01 research grant exploring the connection between neurocognitive changes, and cardiac and vascular dysfunction. She is a co-investigator on multicenter and investigator initiated projects in conjunction with the clinical electrophysiology, interventional and heart failure group. Echocardiographic predictors of recovery in peripartum cardiomyopathy patients, perioperative predictors of outcome of mitral and tricuspid valve repair, and 3D echocardiographic evaluation of the right ventricle. The echocardiography database is a resource for numerous residents and fellows.

Wen-Chih Wu, M.D., is on the faculty at the Providence VA Medical Center. He leads the nuclear stress testing section and the cardiovascular risk reduction clinic at the medical center. He conducts research in cardiovascular epidemiology and outcomes, and is currently the recipient of a VA Merit Review

Award to conduct a multi-center randomized controlled trial to study whether the use of clinical pharmacists in group medical visits in addition to usual care would be superior to usual care alone in cardiac risk reduction in patients with diabetes mellitus: "Group Intervention for DM Guideline Implementation". He is also funded through the VA Merit Review Award to implement the patient-centered medical home model in the inpatient floor to reduce rehospitalization in heart failure.

General Cardiology

George T. Charlton, M.D., I am completing an echo-based clinical project looking at the role of right ventricular function in severe aortic stenosis, trying to infer the pathophysiology of paradoxical low-flow aortic stenosis. I am also starting data analysis on a retrospective study looking at specific ECG findings that may predict an abnormal echocardiogram in patients who present with syncope. In the future, I plan to help consolidate our echocardiographic database and continue to perform observational clinical research.

Philip H. Stockwell, M.D., I am Principal Investigator for the RELAX-2 trial which is a randomized controlled trial investigating outcomes and potential mortality benefit of the drug Seralaxin in patients with decompensated heart failure. I am also investigating the role of BH4 in patients with diastolic heart failure in a small trial in cooperation with the VA.

Endocrinology, Diabetes and Metabolism

Harikrishna Bhatt, MD is investigating new therapeutic options for type 2 diabetics in clinical trials. His research also evaluates the efficacy of various outpatient insulin titration protocols and treatment strategies.

Vicky Cheng, MD is performing a retrospective record review of an evaluation of thyroid nodules.

Geetha Gopalakrishnan, MD coordinates the clinical trials program for the Division of Endocrinology. Her research has focused on women's health topics such as osteoporosis. She has directed studies on the effect of new pharmacological agents in the management of bone loss related to postmenopausal osteoporosis, hyperparathyroidism and cancer. She has collaborated with other investigators to determine the bone and body composition of certain disease states like HIV infection, breast cancer and anorexia. More

Endocrinology, Diabetes and Metabolism (cont)

recently, her research interest has broadened to include new treatments for diabetes.

Sarah Mayson, MD is conducting a retrospective evaluation of low versus high radioactive iodine dosing activities for thyroid remnant ablation in patients with follicular and hurthle cell carcinoma of the thyroid. Furthermore, she is compiling a comprehensive database of our institutional experience managing differentiated thyroid carcinomas.

Eduardo Nillni, PhD. Dr. Nillni is a recognized authority in the field of hypothalamic control of food intake and energy balance regulation. His early seminal work on the role of neuro-peptide hormones controlling food intake and energy dissipation provided the framework for many studies conducted today in other laboratories. Recently, his laboratory provided the first evidence that the deacetylase enzyme Sirt1 regulates food intake at the central level, and that endoplasmic reticulum stress in the hypothalamus induced by chronic obesity alters key hormones in the brain. He received several awards including a special recognition from the National Science Foundation and the Bruce Selya Award for Research Excellence. His work has been published in leading medical research journals, and he is a member of numerous advisory panels, editorial boards for academia and government.

Hilary Whitlatch, MD is conducting clinical research studies on biomarkers that correlate with risk of diabetes complications and on factors that influence the development of diabetic neuropathy. More recently, her research has expanded to evaluate factors that impact insulin resistance and to assess potential therapeutic options. One study being conducted involves cardiovascular outcomes evaluation of a new diabetic therapy.

Haiyan Xu, MD, PhD is investigating the mechanisms of obesity-related insulin resistance and type 2 diabetes. Her work is focused on the correlation of adipose inflammation and insulin resistance in obesity, novel factors in the regulation of adipose energy metabolism, and the mechanisms controlling hepatic gluconeogenesis. Dr. Xu's current projects include studies on the role of a novel AMPK related kinase in the development of adipose tissue inflammation and adipose energy homeostasis, and the effect of MAP kinase phosphatase 3 in obesity-related dysregulation of gluconeogenesis as well as hepatic lipogenesis. Dr. Xu was the recipient of the Lifespan 2010 Bruce Selya Award for Research Excellence.

Gastroenterology

Liver Research Center

Jack R. Wands, MD - Our research efforts involve the role of hepatitis B and C infection in the pathogenesis of hepatocellular carcinoma at the molecular level.

Suzanne de la Monte, MD, MPH is interested in the molecular mechanisms of programmed cell death as well as the role of aspartyl (asparaginyl)-beta-hydroxylase (AAH) in cell motility and invasiveness of tumor cells as well as neuronal cells.

Zoltan Derdak, M.D. Ph.D - My research interests involve insulin signaling in non-alcoholic steatohepatitis (NASH) and alcohol induced steatosis (ASH). I am interested in the role of p53 and its downstream effects on lipid metabolism and insulin resistance.

Miran Kim, PhD - Research interests are aimed on how to cross talk between IGF/IRS-1 and Wnt signaling pathway. To approach this aim, we use proteomic techniques to explore what kind of protein(s) are required to cross talk, how these proteins interact with each other. This research will provide to understand the molecular mechanism of hepatocarcinogenesis through Wnt signaling pathway.

Jisu Li, MD, PhD - Hepatitis B and C viruses are major causes of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. Our laboratory is interested in identifying hepatitis B virus receptors and co-factors.

Steven Moss, MD - Research interests are in the pathogenesis of gastrointestinal cancers in general and gastric cancer in particular. Since gastric cancer is the first malignancy related to a chronic bacterial infection, my laboratory examines the carcinogenic effects of *Helicobacter pylori* on gastric epithelial cells at cellular and molecular levels.

Shuping Tong, MD, PhD - Research interests involve investigations of hepadnaviral receptor proteins on hepatocytes. Using related duck hepatitis B virus (DHBV) as a model, we have identified p170, or duck carboxypeptidase D (DCPD), as a binding partner for viral pre-S envelope protein. Studies are in progress to define the contact site on the p170 for the pre-S1 region of DHBV.

Fusun Gundogan, M.D. - My research interests involve insulin and IGF signaling in the placenta with particular reference to fetal alcohol spectrum disorders. Our group is also interested in aspartyl (asparaginyl)- β -hydroxylase gene regulation during alcohol consumption in the placenta and neonate.

Gastroenterology (cont)

Clinical Research

Fadlo Habr, MD - Clinical interests are mainly in interventional Gastroenterology, mainly pancreatic-biliary endoscopy and photodynamic therapy. We'll be looking at the effects of PDT on end-stage cholangiocarcinoma. The Division of Gastroenterology at Brown Medical School is part of a multicenter national prospective study looking at the role of EUS in the evaluation of cystic lesions of the pancreas. Fluid from the pancreatic cyst will be aspirated under EUS-guidance and tested for specific genetic markers as well as for monoclonal antibodies.

Adam Harris, M.D. – My interest is in the pathogenesis and treatment of inflammatory bowel disease.

Amanda Pressman, M.D. – My focus is on womens' health in gastroenterology, and gastrointestinal motility with clinical and translational research.

Kittichai Promrat, MD – Interests are in the natural history and therapy of chronic liver diseases, in particular hepatitis B, C and nonalcoholic steatohepatitis (NASH). Research efforts involve the roles of insulin resistance and obesity in the pathogenesis of NASH. Another area of research interest is in identification of host immunogenetic factors that involve in clinical outcomes and treatment responses of viral hepatitis.

Harlan Rich, MD – Interests are in clinical Esophagology with an emphasis on gastroesophageal reflux disease and Barrett's esophagus, as well as general gastroenterology (including colorectal cancer screening, peptic ulcer disease, and irritable bowel syndrome). We are currently expanding the role of technology in clinical gastroenterology via the use of ambulatory telemetric pH and capsule endoscopy devices. Research includes creating a database on a large Barrett's surveillance population, studying the acute effect of esophageal acid perfusion on esophageal motility and LES function in humans, and studying genomic alterations in Barrett's epithelium.

Jeannette Smith, M.D. - I am interested in clinical and translational research on both toxin and viral-induced liver, as well as other GI diseases including the extraintestinal manifestations of inflammatory bowel disease, and colon cancer prevention.

Colleen Kelly, M.D. – My clinical research is focused on chronic *C. difficile* infection. I have developed a program of fecal transplantation wherein microbiota of the gut is analyzed before and after transplant; to date, results show that 95% of individuals undergoing

Gastroenterology (cont)

this experimental procedure have total eradication of the infection.

Silvia Degli-Esposti, M.D. – I have a major interest in hepatitis B and C infection during pregnancy including new treatment protocols aimed to reduce transmission of these two serious viral infections from the mother to the child at the time of delivery, or shortly thereafter. We also have a major program on the epidemiology of viral induced acute and chronic liver disease during pregnancy in the State of Rhode Island. Finally, I have an interest in designing training programs in gastrointestinal and liver disease(s) during gestation that compliment and extend GI Fellowship training in these areas which has served as a national model for the design of such a curriculum.

General Internal Medicine

Angela Caliendo, MD, PhD has extensive experience performing and developing molecular diagnostic tests for the detection and quantification of infectious diseases. She has experience in the design and execution of multi-center clinical studies, has Chaired working groups that have evaluated various CMV, HCV, and HBV viral load assays and her laboratory provides infrastructure and molecular testing for numerous multi-center clinical studies. She is also a member of the Aspergillus Technology Consortium, which was created to establish a repository of clinical specimens from subjects diagnosed with or at risk of *Aspergillus* infections and to test new diagnostic assays for *Aspergillus* infections. She has published over 100 peer-reviewed manuscripts covering various topics in clinical and diagnostic virology and microbiology.

Michele Cyr, MD served as co-principal investigator for the Women's Health Initiative. She also served as principal investigator examining the effects of exemestane on breast density in postmenopausal women and as principal investigator for a study of exemestane and breast cancer prevention in postmenopausal women. Both studies have been funded by the National Cancer Institute of Canada. She is working on collaborative research to identify successful strategies for faculty recruitment and development with faculty affairs deans from other institutions.

Mark Fagan, MD has published a number of articles related to medical education, including topics such as resident experiences with chronic pain patients, physician and trainee attitudes toward the

General Internal Medicine (cont)

physical examination, and factors influencing medical student career choice. Recently, Dr. Fagan received a grant from Lifespan Risk Management to support a project "Improving Chronic Pain Management in the Medical Primary Care Unit".

Carol Landau, Ph.D. is Co-Chair of Psychology and Psychiatry in Primary Care (PPPC) and has a joint appointment in the Department of Psychiatry and Human Behavior, where she serves on the Clinical Appointments Committee. Her articles address curricular development in residency training, narrative and reflective writing and professional development. She has received several grants from the Lifespan GME office, most recently for developing a primary care curriculum on refugee health. She has received awards for her work in women's health education, including the Clinician Educator Award from the North American Menopause Society. She also serves as an expert on women's health and behavior change for several websites including healthywoman.org and iVillage.com.

Kelly McGarry, MD has participated in several research projects in the area of prevention and treatment of osteoporosis. She has also written several peer-reviewed articles on this subject. She is a co-editor of the women's health textbook, *The 5-Minute Consult Clinical Companion to Women's Health*, by Lippincott Williams & Wilkins, the second publication was recently published. She and several colleagues recently contributed "Women's Health Topics" to Cecil's Essentials of Medicine, 9th Edition. Besides her interest in women's health, she also engages in medical education research. She and **Dr. Carol Landau** recently received two grants from the Lifespan GME Office to create educational curricula on professionalism & mindfulness for residents. Dr. McGarry served as the Education Director of the National Center of Excellence in Women's Health.

Mark Schleinitz, MD, MS has used decision analysis, cost-effectiveness analysis and meta-analysis to address a variety of clinical topics, including anti-platelet therapy for patients with vascular disease, breast cancer screening modalities and Medicaid policies for nursing homes. Currently, Dr. Schleinitz supervises the Quality Improvement and Continuity Clinic rotation for second-year residents. Each month residents analyze their clinic practice patterns compared to guideline recommendation and develop plans to improve their performance. He also

General Internal Medicine (cont)

serves as Director of Resident Research.

Rebekah Gardner, MD is interested in improving care transitions for patients across a variety of health care settings. Through her work at the state's Quality Improvement Organization, she helps to implement and then analyze the impact of interventions to reduce re-hospitalization rates. She also collaborates on statewide public reporting of physician use of health information technology.

DGIM Research Group

Christine Duffy, MD, MPH researches fertility changes associated with cancer in women; she received a K07 career award and ARRA supplement which funded the development and piloting of a decision aid to help women make fertility preservation decisions before breast cancer treatment. Dr Duffy also has a research interest in the primary care of cancer survivors.

Peter Friedmann, MD, MPH, Director, DGIM Research Unit, is nationally recognized for his health services and clinical research focusing on the organization, quality and implementation of treatment for substance use disorders. Dr. Friedmann is the lead investigator on a NIDA-funded investigation into the impact of the health reform on the substance abuse treatment system, and multisite study to implement overdose prevention and opioid dependence treatment into HIV practice settings. His studies examine implementation of evidence-based treatments for substance use disorders in medical, substance abuse treatment and correctional settings. He also directs the Center of Innovation on Long-Term Services and Supports for Veterans with Vulnerability at the Providence VA Medical Center. He has published over 120 peer-reviewed manuscripts in health services research and addiction medicine.

Susan Ramsey, PhD conducts research on co-occurring psychiatric, substance use, and medical conditions. She serves as principal investigator on two ongoing NIH-funded studies. The first study examines the impact of a brief alcohol intervention on diabetes treatment regimen adherence among individuals with type 2 diabetes who drink at at-risk levels. The goal of the second study is to develop and test a smoking cessation intervention tailored to patients with type 2 diabetes.

Geriatrics & Palliative Care

Richard W. Besdine, MD, the Division Director, has designed and managed research, healthcare delivery systems and educational programs on aging at three universities and in federal service. He is Professor of Medicine, Professor of Health Services Policy and Practice, Director of the Division of Geriatrics and Palliative Medicine, Director of the Center for Gerontology and Healthcare Research, and first Greer Professor of Geriatric Medicine. Research foci include quality of care (especially nursing homes), end-of-life care, pharmaco-epidemiology and health care disparities. Dr. Besdine also served as Interim Dean of Medicine and Biological Sciences at Brown Medical School (2002-2005). He oversees a \$7 M/year grant program in health services research and aging at the Center for Gerontology and Health Care Research – one of 11 research centers of the Brown University Program in Public Health, soon to become a school. Four faculty members from the Division of Geriatrics conduct their research in the Center. In 2006, a Reynolds Foundation 4-year grant of \$2 million was awarded to Brown, which enriched the Medical School mandatory curriculum with >80 hours of geriatrics content; Dr. Besdine was PI. Most of the Geriatrics Division faculty members participated in the project, and a new Reynolds project (\$1 M for specialist education in geriatrics was funded July 2013, to educate ~ 200 residents in multiple non-primary care specialties (ortho, surgery, emergency med, neurosurgery, psych). An award for a Center of Excellence in Geriatric Medicine and Training from the John A. Hartford Foundation supports career development for academic faculty in geriatrics. Three Division faculty members have received federal Geriatric Academic Career Awards in the past.

Julio Defillo-Draiby, MD, Assistant Professor of Medicine, came to us after a 2-year clinical and research fellowship in Geriatrics at Yale. He is leading the collaborative program with the Orthopedics Joint Replacement Center of Excellence at The Miriam Hospital. In this role, while co-managing vulnerable elderly patients, he teaches Orthopedics house staff to enhance their ability to prevent, recognize, and manage common geriatric problems arising in the hospital. Outcomes Data on of this new project reveal decreased length of stay, more home discharges and probably decreased rehospitalizations. A manuscript is being prepared. Dr. Defillo-Draiby also is the Geriatrician educator at the Miriam Hospital for nursing and rehabilitation. He also welcomes medical students in the Scholarly Concentration on Aging. Dr. Defillo-Draiby's clinical work also includes primary care and consultation in the Geriatrics Practice and post-acute and long-term nursing home care at Oakhill and Epoch.

David M. Dosa, MD, MPH, is a scientist and teacher Associate Professor of Medicine and of Health Services Policy and Practice; he maintains dual appointments in the Division of Geriatrics and Palliative Medicine

at Rhode Island Hospital and the Division of Primary Care at the Providence Veteran's Administration Medical Center. Dr. Dosa has conducted multiple funded projects on evaluating and improving quality of care in nursing homes. He has worked on grants to improve the identification of delirium, and has studied the effects of hurricane disasters on frail nursing home residents. He is actively involved in several projects currently related to emergency preparedness in nursing homes, including a National Institute on Aging RO1 award to evaluate the effects of disaster evacuation on frail elderly nursing home residents. He is also funded on a VA Career Development Award to identify inappropriate medication use in the nursing home.

Ana Tuya Fulton, MD, Assistant Professor of Medicine, is Chief of Medicine at Butler Hospital, the academic base for Psychiatry at Brown and the Care New England Director of Geriatric Medicine. Her interests include medical care of the psychiatric patient, with a particular focus on care of the geriatric patient. Areas of research and publication are improving and preventing unnecessary transitions of care, and care at the end of life, both with a focus on persons with advanced cognitive impairment. Dr. Fulton was assistant PI for the \$2M Reynolds Foundation grant to the Medical School for enriching medical student and resident education in geriatrics from 7/06-6/08. She has written curriculum content and exam questions for multiple courses. In addition, Dr. Fulton is the psychiatry lead for the Reynolds 2 foundation grant to enrich geriatrics content for specialty residencies. Dr. Fulton is a Hartford Foundation Change AGENTS awardee as of July 2014 with a project designed to create a system wide delivery system of care for older adults in the Care New England hospital system. To date, Dr. Fulton has over 25 peer-reviewed publications and has written several chapters for review textbooks.

Stefan Gravenstein, MD, MPH, Adjunct Professor of Medicine and of Health Services Policy and Practice at Brown University, is presently located at Case Western Reserve University as Professor of Medicine, Interim Chief of Geriatrics and Palliative Care, and Director, Center for Geriatrics and Palliative Care. His career-long research has been clinical and translational, using the model of influenza to study basic mechanisms of disease pathophysiology, especially cardiovascular events in older persons. He has had uninterrupted extramural support for his work since 1987. He remains engaged in multiple roles for the Division. Since 2007, his work has expanded to the study of care transitions with Healthcentric Advisors (Medicare's Quality Improvement Organization for

Geriatrics & Palliative Care (cont)

Rhode Island), and research collaborations with the Gerontology Center studying quality improvement in long-term care and impact of influenza and influenza vaccine effectiveness (Vincent Mor, Pedro Gonzalez and Aurora Pop-Vicas in Providence; Ed Davidson in Virginia). He also continues mentoring fellows and junior faculty at a distance (care transitions, co-management in geriatrics, influenza, antibiotic stewardship, hospital acquired conditions, quality improvement and influenza vaccines). Opportunities to participate in research and acquire research skills are available for areas involving care transitions, care quality, survey design and analysis, medication use, and health literacy.

Edward W Martin, MD, MPH, is Associate Professor of Medicine, Chief of the Section of Hospice and Palliative Medicine in the Division, and the Chief Medical Officer of Home and Hospice Care of Rhode Island. He is the program director of the Hospice and Palliative Medicine Fellowship. Dr Martin was previously the Medical Director at the Eleanor Slater Hospital, the state's long term medical and psychiatric hospital. He serves on the regulatory committee of the National Hospice and Palliative Care Organization. His research interest is hospice and palliative care, specifically in reducing barriers to accessing hospice. Dr. Martin is a preceptor for medical students, residents and fellows in hospice and palliative care in inpatient and home settings.

Lynn McNicoll, MD, Associate Professor of Medicine, received a 3-year federal Geriatric Academic Career Award (2007-10). She is Director of Education for the Division of Geriatrics and responsible for all educational activities out of the Division of Geriatrics. She is funded as Co-PI on the Reynolds Foundation Next Steps Grant educating 7 residency programs and 3 faculty programs, and is director of the Scholarly Concentration Program at Alpert Medical School and in particular the Scholarly Concentration on Aging. Dr. McNicoll conducts research and quality improvement projects involving care of hospitalized older persons. She has published >25 original peer-reviewed articles and >30 other publications. Working with Healthcentric Advisors of Rhode Island, she led the Statewide ICU Collaborative to improve care of all ICU patients for 8 years. She is Director of Quality Management and Outcomes for the Department of Medicine and has been spearheading projects on reducing unnecessary blood tests and improving communication with older persons.

Nadia Mujahid, MD, Assistant Professor of Medicine, leads the Geriatrics-Orthopedics Co-Management Program at RIH. She has developed and

is implementing a curriculum for orthopedic residents and nursing staff, supported by our Reynolds Foundation grant, designed to anticipate and prevent dangerous complications in elderly hip fracture and joint replacement patients; e.g., delirium, falls, medication errors, infection. She has developed pre- and post-operative management protocols to expedite the time to surgery; improve pain management; and reduce variability of care, thus reducing LOS, readmission rates and enhancing the overall patient experience. Data are being collected and analyzed with the assistance of Drs. Gravenstein and McNicoll. Several medical student research projects are underway to collect and analyze data on clinical outcomes. Resident project opportunities are considerable.

John B. Murphy, MD, is Professor of Medicine and of Family Medicine, and Executive Vice President for Physician Affairs for Lifespan. His academic interest is in education, specifically focused on teaching primary care physicians to care for older persons. Dr. Murphy is a Past President and Chairman of the Board of the American Geriatrics Society.

Aman Nanda, MD, Associate Professor of Medicine, is a teaching scholar. He is Program Director for the Geriatric Medicine Fellowship. His main interest is in teaching medical students, residents, and fellows in every domain of practice in geriatric medicine. He is a preceptor for medical students in the Scholarly Concentration in Aging, as well as in the nursing home experience during the medicine clerkship. His research interests include medical education, dizziness in older persons and quality of care in nursing homes.

Renee R. Shield, PhD, Clinical Professor of Health Services, Policy and Practice, is a cultural/medical anthropologist, who helped lead the mixed methods evaluation in the highly successful Donald R. Reynolds Foundation program of geriatrics integration in the Alpert Medical School curriculum (2006-2011). She is Program Director and Evaluator for our 2nd Reynolds grant, funded 7/13 for 4 years to educate residents and faculty in 8 specialties and subspecialties. She teaches a seminar course on the Design and Evaluation of Programmatic and Educational Interventions with geriatricians, conducts an educational session on transitions for internal medicine interns, and co-directs the Scholarly Concentration in Aging program in the medical school. Her research has focused on reform initiatives in health care, including reducing and improving transitions in sites of care among older adults, enhancing nursing home and end-of-life care, and improving primary care through patient-centered medical home and electronic health records. She also studies the role of physicians and medical directors in long term care institutions.

Mriganka Singh, MD, Assistant Professor of Medicine, is a geriatrician trained in the Brown fellowship program and recruited to the faculty July 2012. She

Geriatrics & Palliative Care (cont)

leads the Geriatrics-Trauma Surgery Co-management Program at RIH. She is developing and is implementing a curriculum for surgery residents and nursing staff designed to anticipate and prevent dangerous complications in elderly trauma patients, supported by our Reynolds Foundation grant; e.g., delirium, falls, medication errors, infections. Data are being collected and analyzed, using the Trauma Registry, with the assistance of Dr. McNicoll. Dr. Singh also provides primary care and consultation services in the Geriatrics Practice at East Avenue. She also manages post-acute and long term care residents at Tockwotton Nursing home.

Jensy Stafford, MD, is an Assistant Professor of Medicine with a secondary appointment in Family Medicine. She has been with Division of Geriatrics and Palliative Medicine since July 2012, after completing a clinical fellowship in Palliative Medicine at Massachusetts General Hospital and Dana Farber Cancer Institute. She is the Associate Fellowship Director for the Hospice and Palliative Medicine Fellowship and the course director for the Hospice and Palliative Medicine elective for medical students. She is an Associate Medical Director for Home and Hospice Care of RI. She works in the inpatient hospice setting and does inpatient Palliative Care consults at the Miriam Hospital.

Joan M. Teno, MD, MS., is Professor of Health Services Policy and Practice and of Medicine, and Associate Director of the Center for Gerontology and Health Care Research. She is a health services researcher, hospice associate medical director, and internist certified in Geriatrics and Hospice and Palliative Medicine. Dr. Teno has served on numerous advisory panels, including IOM, WHO, American Bar Association and NIH study section. As a scientist and clinician, Dr. Teno has devoted her career to measuring and improving quality of end-of-life care for vulnerable populations, especially those in NHs. Dr. Teno is the creator of the Family Evaluation of Hospice Care survey that is now used by 1700 hospices across the US. Dr. Teno is a current member of the Institute of Medicine committee that is studying end of life care in the USA. Dr. Teno current research is focus on the following topics: 1) hospice payment reform with a focus on examination of vulnerabilities of Medicare Hospice Benefit; 2) implementation of a national survey to examine the quality of hospice care for public reporting; 3) creation of indexes of potentially burdensome transitions at the end of life; and 4) further work to examine physician role in feeding tube decision making in persons with advance dementia.

Geriatrics & Palliative Care (cont)

Lidia Vognar, MD, was recruited in July 2013 to the Division of Geriatrics and Palliative Medicine and to the Division of Primary Care at the Providence VAMC, after a research-intensive 3-year geriatrics fellowship at Duke and the Durham VAMC. Academic appointment is pending. Her area of research is elder abuse; she has developed and disseminated a curriculum on elder abuse for physicians and medical students, as well as for other health professionals. She is eager to precept residents and students on projects related to elder abuse.

Hematology & Oncology

The Hematology/Oncology Division has a broad research portfolio including basic, translational and clinical research projects. Drs. Quesenberry and Dr Ramratnam each received large COBRE grants totaling over \$22 million for 5 years and renewal applications are either pending or in preparation. This supports fellow/junior faculty development. Dr Quesenberry was also awarded a T32 Hematology Training Grant (initiated August 1, 2012) and a Common Fund Grant with collaborators in Torino, Italy on the role of mesenchymal stem cell-derived vesicles in reversing renal and marrow injuries (initiated August 1, 2013).

COBRE Center for Stem Cell Biology

The Division of Hematology/Oncology houses the Center of Biomedical Research Excellence (COBRE) Center for Stem Cell Biology (CSCB) under the direction of Dr. Quesenberry. This center is supported by a National Center for Research Resources (NCRR) division of NIH (Grant P20 RR025179). The major goal of the project is to develop junior investigators in Rhode Island. This supports core laboratories, seminar speakers, and the work of junior investigators who have not previously been funded. The CSCB supports three research cores: 1) a Flow Cytometry Core under the direction of Mark Dooner that offers state of the art flow cytometry equipment and expert analysis, 2) a Molecular Core under the direction of Dr. Bharat Ramratnam that offers laboratory assays for the quantification and manipulation of nucleic acids, and 3) an administration core

The Administrative Core of the COBRE CSCB works closely with the COBRE CCRD (see below) to support the academic pursuits of junior investigators.

COBRE Center for Cancer Research Development

The Division of Hematology/Oncology also holds a grant from the NCCR (Grant P20 RR 17695) providing support for the COBRE Center for Cancer Research Development (CCRD). The mission of the CCRD is to foster the career development of promising junior faculty members interested in cancer research by providing mentoring from senior investigators and state-of-the-art technology. The CCRD supports two research cores: 1) a Proteomics Core under the direction of Dr. Arthur Salomon that offers state-of-the-art equipment such as a 2-D gel electrophoresis and mass spectrometry for the isolation, identification, and characterization of proteins, and 2) a Molecular Pathology Core under the direction of Dr. Murray Resnick that provides Center investigators with capabilities for assessing the expression of specific proteins at the RNA or protein level using in situ hybridization, tissue microarrays, laser capture microdissection, QPCR and sophisticated image analysis software.

The Administrative Core of the CCRD has organized several events including a monthly seminar series, an annual Cancer Research Symposium and public awareness outreach events. The CCRD is located on the fourth floor of the Coro Center at One Hoppin Street. For more information go to CCRD's website:

www.rih-cobre-cares.org

Stem cell and vesicle research

Dr. Peter J. Quesenberry is the Principal Investigator on "Stem Cell Biology: New Directions in Clinical and Basic Research" and an R01 entitled, "Genetic Information Transfer to Hematopoietic Cells: Role of Microvesicles." The work in Dr. Quesenberry's lab focuses on basic studies on the phenotype of the hematopoietic stem cell, on how this phenotype may alter with cell cycle transit, and/or influences on injured tissue. There is a major emphasis on engraftment models and defining the basic nature of the stem cell along with microvesicle modulation of cell phenotype. The work is supported by state-of-the-art flow cytometry, fluorescent imaging, molecular genetics, and a small animal irradiator core. Recently he has begun studies on the capacity of mesenchymal stem cell derived vesicles to reverse murine marrow stem cell radiation damage and Tylenol liver damage.

Dr. Jason Aliotta has several ongoing projects to determine the ability of adult bone marrow-derived stem cells to participate in the production of lung cells

in various murine lung injury models. He was awarded a K08 (Dr. Quesenberry mentor) for this work and is focusing on the characterization of lung-derived microvesicles and their ability to induce marrow-derived stem cells to assume a lung cell phenotype. He is also working on animal models of alterations of pulmonary function and the capacity of marrow cells to alter pulmonary function. Most recently he has evolved a model of pulmonary hypertension in mice and is now studying whether mesenchymal stem cell derived vesicles can reverse pulmonary hypertension.

Dr. Devasis Chatterjee has previously received grant funding to pursue studies on second messenger signaling and inhibition of tumor growth in breast cancer. He has also been supported by the COBRE and is investigating the role of cell survival and apoptotic pathways in the regulation of patient clinical outcome and tumor growth in gastric cancer. His area of interest is on proteins that regulate signal transduction pathways during cancer progression in response to clinically relevant chemotherapeutic compounds or *Helicobacter pylori* infection. Most recently, he is studying the capacity of tissue derived vesicles to reverse the cancer phenotype (anchorage independent growth and chemoresistance) of rat and human prostate cancer.

Dr Laura Goldberg is pursuing the definition of the true marrow hematopoietic stem cell and its cell cycle status and differentiation potential. She has begun work on extracellular vesicle modulation of the marrow stem cell phenotype and circadian rhythms of extracellular vesicles.

Dr. Patrycja Dubielecka-Szczerba is a PhD working on approaches to reverse resistance to tyrosine kinase inhibitors in chronic myelocytic leukemia.

Dr Sicheng Wen is a new Research Fellow on the T32 Grant. He is studying the capacity of mesenchymal stem cell derived vesicles to reverse radiation damage to marrow.

Clinical Trials

Dr. Howard Safran is a national leader in gastrointestinal oncology. He is a member of the NCI/CTEP esophageal task force, the pancreatic cancer task force and the GI cancer steering committee. He is an author of over 75 publications. He is an editor for Up-To-Date-Online in GI oncology and has served in this role for over 5 years. He has been a journal reviewer for the New England Journal of Medicine, Lancet, The Jour-

Hematology & Oncology (cont)

nal of Clinical Oncology and Cancer. He is a Professor of Medicine at Brown University and the Medical Director of the Brown University Oncology Group (BrUOG) and The Lifespan Oncology Clinical Trials office.

In Dr. Safran's role as the medical oncology chair of the GI committee for the Radiation Therapy Oncology Group, he has been a highly effective national leader in clinical trial design, trial monitoring and data analyses. He is the Principal Investigator of the newly activated RTOG 1010, a Phase III study evaluating the addition of trastuzumab to trimodality therapy in HER2 expressing esophageal cancer. This national Phase III study was based on BrUOG Phase I/II studies. He also was among the principal leaders developing the Phase III cooperative group study, RTOG 0436, evaluating the addition of cetuximab to chemoradiation for esophageal cancer. Dr. Safran has played the lead role bringing together the RTOG, SWOG and the EORTC for the Phase III study RTOG 0848, which will ultimately answer the question of the role of adjuvant radiation in pancreatic cancer. Following CTEP approval, all three Phase III studies – RTOG 1010, RTOG 0848 and RTOG 0436 were rapidly activated due to Dr. Safran's experience and skill in writing protocols, problem solving and organization. Dr. Safran was also medical oncology principal investigator for RTOG 9704, the largest adjuvant pancreatic cancer study ever performed.

Dr. Safran receives research funding from the Radiation Therapy Oncology Group. He is also the principal investigator for the NIH BIQSFP grant to Rhode Island Hospital for determining HER2 expression by IHC and FISH in support of the national trial, RTOG 1010, for which he is principal investigator. Dr. Safran is also principal investigator of the recently submitted RIH response to RFP N01-CM-01018-83 entitled "Early Therapeutics Development with Phase II Emphasis."

Other members of the division currently serving as study chairs for investigator-initiated clinical trials conducted by BrUOG include Dr. Anthony Mega (prostate cancer), Dr. Humera Khurshid (lung cancer), and Dr. Ariel Birnbaum (head and neck cancer).

Translational Cancer Research

Dr. Peter Quesenberry along with **Dr. Devasis Chatterjee** have developed a program of translational research projects related to "Cancer Crosstalk: The Role of Microvesicles" evaluating the capacity of cancer cells to alter the phenotype of normal neoplastic cells by transfer of genetic information in cancer derived microvesicles. The research structure includes both basic

laboratory individuals and cancer clinicians working in the areas of prostate cancer, lung cancer, breast cancer and leukemia.

Immune Regulation and Acute Leukemia

Dr. Loren Fast is a cellular immunologist primarily studying the responses of T cells. One series of experiments examines the effects of pathogen reduction of blood products prior to transfusion on the function of the leukocytes in those blood products. This work is funded by CaridianBCT. Another series of experiments is trying use allogeneic responses to generate anti-cancer responses or alternatively to block those responses in order to prevent graft-versus-host disease. A third set of experiments is trying to understand the immune responses in individuals chronically infected with HCV and develop approaches to enhance their immune system to clear the virus. This work is funded by project funding from the TRIAD grant awarded by NIH to URI. The fourth series of experiments examines the role of granzymes in the immunosenescence that occurs with aging and inflammatory conditions such as sepsis and rheumatoid arthritis.

Dr. John Reagan is an Assistant Professor of Medicine who has been investigating cellular immune therapy protocol for refractory leukemia and lymphoma. This is a new FDA approved and accruing patients. The thinking is that host tolerance to cancer is reversed by stem cell rejection.

Breast Cancer Research

Dr. Mary Ann Fenton is actively involved in clinical research in breast cancer neoadjuvant trials. Also, Dr. Fenton serves as Chairman of the Data Safety Monitoring Board of the Brown University Oncology Group (BrUOG). She is first author on an article for the BrUOG Study group entitled, "Frequent pathologic complete responses in aggressive Stages II to III Breast Cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab" (Journal of Clinical Oncology, October 2009).

Prostate Cancer

Dr. Anthony Mega is pursuing different approaches to treatment of prostate cancer.

Colorectal Cancer

Dr. Kimberly Perez, a junior faculty member, interested in colorectal cancer.

Immunology & Infectious Diseases

The Division of Infectious Diseases provides comprehensive inpatient and outpatient infectious disease care at The Miriam and Rhode Island Hospitals, Memorial Hospital, Veterans Administration Medical Center, and Women and Infants Hospital. The mission of the Division is to provide state of the art care for all patients with any type of infectious disease, to teach and mentor medical students, house officers and fellows in the art and science of infectious diseases, and to pursue clinical and basic research that investigates the manifestations and treatment of infectious diseases. The Division Director is Eleftherios Mylonakis, MD, PhD, FIDSA.

The Division has a number of areas of expertise including Bacteriology, Global Health, HIV/AIDS, Infection Control, Virology and sepsis research. The Division is active in clinical, translational, and basic science research, and in FY2013 received close to 15 million dollars in external funding. The Division hosts a 2 year clinical fellowship in infectious diseases and an NIH funded T32 fellowship in clinical research on infections related to substance abuse.

Research Programs

Antimicrobial Drug Discovery

The rate of new antibiotic discovery is unlikely to meet the expected need for the foreseeable future. Groups in our Division are working to identify new classes of antimicrobials with antivirulence or immunomodulatory efficacy and evaluate toxicity/efficacy.

Center for Biodefense and Emerging Pathogens

Based at Memorial Hospital, the Center is an active program where we are testing and developing rapid diagnostic systems using microfluidic DNA and RNA detection systems.

Global Health

The Global Health Initiative (<http://brown.edu/initiatives/global-health>) is a multidisciplinary university-wide effort to reduce health inequalities among underserved populations locally and worldwide through education, research, service and development of partnerships. With current projects and programs in 33 countries - 28 of which are in developing countries - Brown is particularly well-positioned to expand and to accelerate these efforts through the Global Health Initiative. Under the guidance of Jack Elias, Dean of the Division of Biology and Medicine, Edward J. Wing, MD, former Dean, and Susan Cu-Uvin, MD, GHI Director, the Initiative encompasses

a wide range of practitioners and researchers across medicine, public health, biomedical research, social science, and engineering to provide sustainable solutions in partnership with communities and institutions in Africa, India, Southeast Asia, the Caribbean, and the Pacific.

The Brown AIDS International Training and Research Program (AITRP)

The Brown AITRP trains and mentors scientists in developing countries to address the AIDS epidemic primarily through advanced degree training, along with long term and short term training tracks in prevention research, biomedical and behavioral interventions. The program supports established research training programs at partner sites in India, Cambodia, the Philippines, Kenya and Ghana. The training program is directed by Susan Cu-Uvin, MD and is supported by mentoring faculty from multiple Brown departments and institutes. Other Brown collaboration sites include Ukraine, Haiti, and Rwanda.

HIV/AIDS

The Division has an in-depth focus in the area of HIV/AIDS. The NIH funded Lifespan/Tufts/Brown Center for AIDS Research (<http://192.138.176.29/cfar>), based at The Miriam Hospital supports laboratory and clinical HIV prevention and treatment research. The NIH Center grant strongly supports the primary thematic goal of the Lifespan/Tufts/Brown CFAR, which is to carry out translational research dealing with the treatment and prevention of HIV infection in hard-to-reach populations, both in New England and in several countries in the developing world.

The AIDS Clinical Trials Unit (ACTU) at The Miriam Hospital/Brown University has been an outstanding success. This is one of 60 units around the country, which is NIH funded to participate in multi-center HIV and AIDS treatment trials. The ACTG conducts clinical trials in HIV-infected adults to test novel therapeutic interventions focused on HIV-associated inflammation and resulting end-organ disease, tuberculosis, viral hepatitis and HIV cure.

Health Disparities, Advocacy and Policy

The Center for Prisoner Health and Human Rights (www.prisonerhealth.org) founded by Drs. Jody Rich and Scott Allen in 2005 and based in the Divi-

Immunology and Infectious Diseases (cont)

sion of Infectious Diseases, seeks to advance the health and human rights of criminal justice populations through research, education, and advocacy. The Center identifies, initiates, and supports projects that respond to the epidemic of incarceration and recidivism in the criminal justice system and the associated complex public health crisis.

Infection Prevention and Control

Over the last 2 decades, Dr. Leonard Mermel has investigated the epidemiology and pathogenesis of healthcare-associated infections. Original research published over the last year involves ongoing collaboration with Kerry LaPlante, PharmD studying antimicrobial lock therapy for prevention and management of catheter-related infections and Anubhav Tripathi, PhD studying novel diagnostic modalities for *C. difficile* infection, as well as work with other collaborators on various infection control topics.

Mycology

The major focus of our work in Mycology is the study of fungal pathogenesis. We use molecular biology and surrogate invertebrate hosts to identify novel antifungal compounds and study basic, evolutionarily conserved aspects of fungal virulence and host response.

Sepsis Research

Our laboratories have had a long term interest in translational research to develop novel immune based adjuvants for severe sepsis and septic shock. This work is ongoing on several platforms including in vitro tissue culture and whole blood assays for bacterial toxins and virulence factors, host cell-pathogen relationships with emphasis on cytokine and chemokine biology, biomarkers and endotoxin immunology.

Sexually Transmitted Diseases

The publically-funded HIV/STD Clinic at The Miriam Hospital provides accessible testing and prevention services to the community. Started in 2012, the clinic provides diagnostic capabilities for a wide range of sexually transmitted diseases (STDs). The Clinic is under the direction of Philip A. Chan, MD, and strives to provide important clinical services as well as cutting edge prevention interventions such as pre-exposure prophylaxis (PrEP) to prevent HIV infection. Ongoing surveillance and research also helps to better understand routes of transmission and epidemiology of different STDs.

Travel Clinic

The University Medicine Travel Clinic at the Miriam Hospital provides comprehensive travelers' health services, including routine and travel vaccines, malaria prevention, travelers' diarrhea prevention and management, general advice about keeping healthy during travel, and diagnosis and treatment of travel-related illness. Our travel team consists of medical assistants and Board Certified Infectious Disease Specialists.

Virology

Faculty are interested in several chronic viral infections. Basic studies in HIV are supported by the CFAR Laboratory of Retrovirology that provides viral load testing, CD4/CD8 T lymphocyte enumeration and drug resistance assays for all research studies. Active areas of research interest include the proteomic and nucleic acid determinants of HIV-1 acquisition and disease progression and the impact of drug and alcohol abuse on HIV infection.

Faculty

Nicole E. Alexander, MD, MPH, research interests include implementation of public health strategies, health care disparities, and access to care. Dr. Alexander's translational efforts informed removal of the written consent barrier to HIV testing among pregnant women, and then in all health care settings.

Curt G. Beckwith, MD, is the Program Director of the Infectious Diseases Fellowship at Brown University. Dr. Beckwith also conducts NIH-funded research related to HIV and viral hepatitis among at-risk populations, including persons involved with the criminal justice system and substance users. Research interests include novel testing approaches for HIV and viral hepatitis and development and implementation of interventions to improve adherence to HIV treatment and care.

Charles C. J. Carpenter, MD, directs the NIH-funded Lifespan/Tufts/Brown Center for AIDS Research and has served as Chair of the Antiretroviral Treatment Panel of the International AIDS Society-USA and co-authored their recommendations on antiretroviral treatment published annually in JAMA.

E. Jane Carter, MD, is an expert in both domestic and international TB control as well as direct TB

Immunology and Infectious Diseases (*cont*)

care. She is the current President of the International Union Against TB and Lung Disease. She is also the director of the Brown Kenya Exchange program, part of the AMPATH Consortium (a group of North American Universities in partnership with Moi University School of Medicine in Eldoret, Kenya working in collaboration with the Kenyan Ministry of Health to bring health access to all). Under the exchange, Brown students, residents and faculty work with peer partners on site both to provide care and to perform research.

Philip A. Chan, MD, MS, is director of the sexually transmitted diseases (STD) clinic at The Miriam Hospital Immunology Center. He performs research in HIV epidemiology as well as other STDs. Dr. Chan has expertise in HIV prevention including diagnosis and testing, as well as pre- and post-exposure prophylaxis (PrEP and PEP, respectively).

Cheston B. Cunha, MD, attending in adult infectious diseases at The Miriam Hospital and Rhode Island Hospital. He is an Assistant Professor of Medicine at Brown University Alpert School of Medicine. Dr. Cunha obtained his medical degree from the Pennsylvania State University College of Medicine in Hershey, Pennsylvania. He completed his residency in Internal Medicine at Brown University at the Rhode Island Hospital and Miriam Hospital. He also completed his fellowship in Infectious Disease at Brown University. Dr. Cunha's clinical and research interests include general infectious diseases, antimicrobial therapy, ancient plagues, fever of unknown origin (FUO), and zoonoses. He serves as associate editor of the book *Antibiotic Essentials*. Dr. Cunha is currently the Coordinator of the Rhode Island Hospital and Miriam Hospital Antimicrobial Stewardship Program.

Susan Cu-Uvin, MD, is the Principal Investigator of Brown/Tufts Fogarty AIDS Training Research Program, co-PI of an RO1 (HD072693) to assess the effect of reproductive hormones on HIV acquisition. Her other funded studies are in the areas of cervical cancer screening/prevention and treatment in Kenya, female mucosal immunology, and HIV microbicides. She is the Director of the Brown Global Health Initiative.

Erika M. D'Agata, MD, MPH, research focuses on the transmission dynamics of multidrug-resistant organisms in a variety of healthcare settings, including dialysis units and long-term care facilities. Her research focuses on characterizing and quantifying the most effective prevention strategies aimed at minimizing their spread, using both clinical epidemiological methods and mathematical modeling.

Staci A. Fischer, MD, is a nationally recognized ex-

pert on infections among solid organ transplant recipients and infections transmitted with organ and tissue donation. Studies are ongoing evaluating the risk of infection with new immunosuppressive medications, tracking donor-transmitted infections, and the effect of immunosuppression on chronic hepatitis C in renal transplant recipients.

Timothy P. Flanigan, MD, spearheaded the HIV Care Program at the Rhode Island Department of Corrections and has received NIH funding to develop improved treatments for HIV infection. In particular, he has initiated an innovative program of community based support to improve HIV treatment among marginalized communities. He also participates in international ID work in Ghana, Ukraine, India and Liberia.

Joseph I. Harwell, MD, primary focus has been in Asia, where he served as the Regional Clinical Officer for the CHAI country programs in Cambodia, China, Indonesia, Papua New Guinea, and Vietnam. These programs have had particular emphases on children and rural areas, where the economic, structural, and technical barriers to care and treatment are considerable.

Rami Kantor, MD, directs the Miriam Hospital HIV drug resistance laboratory. His research incorporates bioinformatics, molecular epidemiology, clinical and basic laboratory research. He is NIH-funded with research interests that include transmitted and acquired drug resistance in diverse HIV variants and settings; HIV transmission networks; treatment-failure monitoring in resource-limited settings; and laboratory infrastructure, assays and bioinformatics tools development and their implementation in resource-limited settings."

Bettina M. Knoll, MD, PhD, research interests are in clinical and translational research involving iatrogenically immunocompromised hosts, in particular patients undergoing chemotherapy treatment.

Erna Milunka Kojic, MD, research focuses on HPV infections among HIV-positive women and the development of squamous cell carcinomas in the genital tract. She is co-Founder of the 1st Menopause Clinic for HIV+ Women in the US based in the Miriam Immunology Center, a Brown University affiliate.

Awewura Kwara, MD, MPH, research focuses on HIV and TB coinfection and improved co-treatment

Immunology and Infectious Diseases (cont)

of the two infections in the same individual. The treatment of TB and HIV often require the co-administration of 7 or more different drugs. Individual differences in drug metabolism, drug-drug, as well as drug-gene interactions may lead to ineffective therapy due to low drug concentrations or toxicities due to high drug concentrations of some of the drugs.

Michelle A. Lally, MD, MSc, divides her time as an HIV Prevention researcher at The Miriam Hospital, and the Associate Chief of the Medical Service at the Providence VA. In both roles, she welcomes the opportunity to work with residents! Her research interests include the integration of biomedical and behavioral interventions to prevent HIV, and quality improvement efforts that focus on disease prevention.

Jerome M. Larkin, MD, research interests include home-based intravenous antibiotic therapy, tick related infections and HIV infection in children and adults. He has served as a Clinical Mentor in HIV education for health care workers with Clinton Health Access Initiative of the William Jefferson Clinton Foundation.

John R. Lonks, MD, research has explored the mechanism of pneumococcal resistance, particularly as it pertains to macrolide antibiotics. This program has characterized the clinical failure of therapy with macrolides among individuals with invasive pneumococcus treated with macrolide antibiotics.

Leonard A. Mermel, DO, ScM, is a former President of the Society for Healthcare Epidemiology of America and an internationally-recognized authority on hospital epidemiology and infection control. His research is focused on understanding the epidemiology, pathogenesis, and prevention of healthcare-associated infections, particularly intravascular catheter-related infections.

Maria D. Mileno, MD, research interests include the wellness and practices of travelers. She has written extensively on infectious disease topics related to travelers and tropical medicine as an Associate Editor of Travel Medicine Advisor and elsewhere. Recognized nationally and internationally, she is currently part of the Scientific Review Committee for the 2015 Conference of the International Society of Travel Medicine.

Brian Montague, DO, academic interests lie in global health education, implementation science related to comprehensive care delivery for HIV, viral hepatitis, and other significant coinfections.

Eleftherios Mylonakis, MD, PhD, is internationally

recognized for his research on the study of host and microbial factors of infection and the discovery of antimicrobial agents, or substances that kill or inhibit the growth of microorganisms such as bacteria or fungi. Dr. Mylonakis, who has edited five books on infectious diseases, is also the founding editor-in-chief of *Virulence*, an international, peer-reviewed journal that focuses on microbial infections and host-pathogen interactions.

Gerard Nau, MD, PhD, is a physician-scientist with interests in innate immunity and genetic predisposition to infections. His laboratory studies host-pathogen interactions and bacterial pathogenesis, and is internationally known for its work on tularemia. The main objective is to translate information from pre-clinical studies into new therapies to treat infectious diseases, especially those caused by antibiotic-resistant bacteria.

Bharat Ramratnam, MD, currently has an NIH funded project which is focused on a better understanding the role of reproductive hormones on HIV-1 transmission (R01HD072693) and determining whether substance abuse alters a cell's capacity to support viral replication (P01AA019072). A separate interest is in better defining the cellular components of atypical responses to HIV such as those observed among individuals who become infected but are able to autonomously control viral replication.

Aadia Rana, MD, primary research focus is evaluating and improving adherence to medical care and treatment among HIV-infected patients, a vital issue which impacts individual health as well as public health. She has several ongoing projects evaluating factors that impact adherence to HIV care and treatment among: patients at the Miriam Hospital Immunology clinic, postpartum HIV-infected women in Mississippi, and postpartum HIV-infected women in Ghana.

Louis B. Rice, MD, is an international authority on antimicrobial resistance in bacteria. His research interests include understanding the mechanisms of antibiotic resistance in bacteria; preventing hospital infections; and developing antibiotic usage strategies that will minimize the emergence and spread of antibiotic resistance.

Josiah D. Rich, MD, research focus is on the overlap between infectious diseases and illicit substance use and disadvantaged populations, especially prisoners and others involved with the criminal justice system. He is the Principal or Co-investigator on

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several research grants involving the treatment and prevention of HIV and other infectious diseases.

Karen T. Tashima, MD, directs the NIH funded HIV Clinical Trial Unit at The Miriam Hospital to investigate new therapies for HIV, hepatitis C and novel approaches to HIV infection and its associated inflammatory state. She developed a national study to evaluate whether a class of antiretroviral medications should be included in regimens for patients with drug resistant virus.

Lynn E. Taylor, MD, is an HIV and viral hepatitis specialist focusing on HIV and viral hepatitis coinfection. She developed and directs Miriam Hospital's HIV/Viral Hepatitis Coinfection Program, providing multidisciplinary care to HIV/hepatitis C virus (HCV) and HIV/hepatitis B coinfecting persons. Her research, policy and community work involves extending HCV care to persons with HIV and co-existing psychiatric and substance disorders, and improving HCV screening, diagnosis and treatment access.

Allan R. Tunkel, MD, PhD, MACP, is an internationally recognized expert in central nervous system infections and has authored or co-authored more than 235 publications (original articles, reviews, editorials, books and book chapters) in his fields of interest. He was the Editor of MKSAP16 Infectious Diseases, and is one of the Associate Editors of MKSAP17. Dr. Tunkel Chaired the Infectious Diseases Society of America (IDSA) Practice Guideline Committees which developed practice guidelines for Bacterial Meningitis and Encephalitis; he is currently Chair of the IDSA Practice Guidelines Committee which is developing guidelines on Healthcare-Associated Ventriculitis and Meningitis. He was recently appointed as Associate Dean for Medical Education at the Warren Alpert Medical School of Brown University.

Edward J. Wing, MD, was the former Chair of Medicine at Brown for 11 years and former Dean of Medicine and Biology at Brown for 5 years. He is currently Professor of Medicine at Brown in the Department of Medicine. He developed international health programs within the Department to improve both education and clinical research in the Dominican Republic, Haiti, Brazil and Kenya. These programs have developed innovative approaches to HIV diagnosis and treatment, but also seek to improve general medical care in both the inpatient and ambulatory settings.

Kidney Disease & Hypertension

Research in the Basic Sciences

Lance Dworkin, MD serves as Vice Chairman for Research, Academic Affairs and Ethics in the Department of Medicine, and as Director of the Division of Kidney Disease and Hypertension for both Rhode Island and the Miriam Hospitals. He is a lead investigator in an effort to identify the role of glycogen synthase kinase-3beta (GSK) in chronic renal injury. He directs studies examining the effects of GSK on the molecular mechanism(s) governing tubulointerstitial inflammation, matrix synthesis and degradation and in renal epithelial cells as they relate to renal fibrosis and scarring. The work incorporates studies in mice in which GSK has been deleted in kidney epithelial cells, in several animal models of chronic renal disease as well as cell culture work in renal tubular cells.

Shougang Zhuang, MD serves as the director of the Renal Diseases and Hypertension Division's laboratory research program. He is interested in the mechanisms of acute kidney injury and renal regeneration after injury, and in developing therapeutic agents that promote renal recovery after acute kidney injury (AKI) and that attenuate progression of renal fibrosis. His current projects are focused on determining the intracellular signaling events critical for renal epithelial cell dedifferentiation and development of renal fibrosis after injury, as well as defining the role of suramin in stimulating renal epithelial cell regeneration and inhibiting renal fibrosis following acute and chronic kidney injury. Dr. Zhuang has recruited two post-doctoral fellows to work with him on these projects and is also providing opportunities for residents, fellows and students to gain experience in basic research.

Rujun Gong, MD, PhD, is an independent Principal Investigator and Medical Research Scientist interested in the pathogenesis and novel therapies of glomerulopathies. His ongoing study is deciphering the molecular mechanisms accounting for podocytopathy, a disease of podocytes that drives the development and progression of proteinuria, glomerulosclerosis and loss of kidney function. In particular, Dr. Gong is examining the role of cytoskeleton disorganization and mitochondria dysfunction in mediating the podocyte injury. This project has been funded by the NIH RO1 grant. In close collaboration with Dr. Reg Gohh, Dr. Gong is conducting a clinical translational research to identify and then antagonize the circulating permeability factor in patients with focal segmental glomerulosclerosis, a prototype of podocytopathies. Together with Dr.

Kidney Disease & Hypertension (cont)

Lance Dworkin, Dr. Gong is also investigating the therapeutic intervention of renal interstitial inflammation and fibrosis. In collaboration with Drs. Andrew Brem and David Morris, Dr. Gong is examining the role of aldosterone in the progression of glomerular injury and renal fibrogenesis. Moreover, another translational research work by Dr. Gong recently unraveled a novel renoprotective activity of adrenocorticotropin, a pituitary hormone that was widely used half century ago for the treatment of lipoid nephrosis. This line of research could lead to a new therapy for refractory glomerulopathies. In addition to research and teaching, Dr. Gong has been responsible for the Jinling Hospital-Brown joint nephrology fellowship program and is in charge of a successful and exemplary Sister Renal Center Program between the renal division at Brown Medical School and the Research Institute of Nephrology at the Jinling Hospital in Nanjing, China. This Sister Renal Center Program was recently awarded the prestigious ISN Schrier Award at the World Congress of Nephrology in 2011. The well-established and successful translational renal research program directed by Dr. Gong has also become a problem based learning platform for the bench research work of medical students, residents and nephrology fellows.

Clinical Research in Kidney Diseases, Kidney Transplantation, and Hypertension

Lance Dworkin, MD is also the study chair and senior leader for the CORAL study, a large multicenter clinical trial funded by the NHLBI that is comparing angioplasty and stenting plus optimal medical therapy to medical therapy alone for the treatment of atherosclerotic renal artery stenosis. This study has enrolled approximately 900 patients at over 100 centers across the United States and internationally in Canada, Australia, New Zealand, Brazil, and Argentina. He also conducts clinical research in patients with hypertension from other causes, diabetes mellitus with renal manifestations, acute kidney injury, and in various types of chronic glomerular and kidney disease. Another interest is in communication between patients with chronic kidney disease and their physicians regarding treatment outcomes, which is being studied in collaboration with investigators from the School of Public Health. Another interest is in correlations between sleep apnea, hypertension and cardiovascular risk in patients with moderate to advanced chronic kidney disease.

Douglas Shemin, MD Dr. Shemin is the medical director of the dialysis program at Rhode Island Hospital, and his primary clinical and research interests

are renal replacement therapy and end stage kidney disease. His current research projects include novel treatments for diabetic nephropathy, infection in end stage renal disease, and the effect of dialysis time on outcomes in end stage kidney disease.

Reginald Gohh, MD is the Medical Director of Kidney Transplantation at Rhode Island Hospital and Brown University. He is participating in a number of studies evaluating the efficacy of various immunosuppressive agents in promoting successful long-term renal allograft function. This includes novel immunosuppressive agents such as FTY-720. Dr. Gohh also has a sub-contract from the NIH to evaluate the efficacy of IVIG in desensitizing highly sensitized patients awaiting renal transplantation, and he is involved in investigating the role of preemptive therapeutic plasma exchange in preventing recurrent focal and segmental glomerulosclerosis (FSGS) in kidney transplant recipients, and the pharmacokinetics of mycophenolate mofetil in diabetic kidney transplant recipients.

Andrew J. Cohen, MD has several clinical research interests. He is currently an investigator in an NIH-sponsored study of a cohort of the impact of Hurricane Katrina on a cohort of dialysis patients who suffered displacement following the storm. He is also currently engaged in the study of the efficacy of a structured, protocolized clinic for chronic kidney disease, administered by a nurse practitioner.

Susie L. Hu, MD is interested in the impact of chronic kidney disease on cardiovascular disease outcomes. She has validated a novel method of measuring kidney function with intravenous contrast dye during angiographic imaging among patient undergoing cardiac catheterization. This method of glomerular filtration rate measurement is also being validated among transplant donors as an alternative method of kidney function assessment. Her research interests also include anemia in acute kidney injury and its impact on outcomes; and uric acid levels and mortality risk among peritoneal dialysis patients.

John O'Bell, MD is involved in clinical investigation on the progression of diabetic kidney disease. Dr. Bayliss is involved in a clinical evaluation examining the role of transplant immunosuppression in subjects who reject renal transplants and return to dialysis.

George Bayliss, MD, is involved in a clinical evaluation examining the role of transplant immu-

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nosuppression in subjects who return to dialysis after failure of the transplant kidney. He is in charge of the home hemodialysis program at the outpatient Dialysis Unit of Rhode Island Hospital.

Terri Montague, MD is interested in nephrology in global health. She is currently involved in research projects looking at the impact that genetics may play in HIVAN and other chronic kidney diseases in sub-Saharan African. Her research interests also include looking at the incidence of Vitamin D deficiency in African populations.

Mohammed Faizan, MD is a pediatric nephrologist interested in hypertension in children, including the utility of ambulatory blood pressure monitoring in diagnosing and treating hypertension in children. He is also interested in novel treatments for nephrotic syndrome in children.

Maroun Azar, MD is board certified in both nephrology and geriatrics. He is interested in the role of palliative care in elderly patients with chronic kidney disease. Another interest is in outcomes in geriatric patients with end stage renal disease. These questions are being examined in collaboration with Dr. Dworkin, and with a group of investigators from the School of Public Health.

Pulmonary, Sleep Disorders & Critical Care

The Division of Pulmonary, Critical Care, and Sleep Medicine of the Warren Alpert Medical School at Brown University is strongly committed to the academic mission of the Department of Medicine. Each faculty member, whether full-time basic science, clinical research or clinical practice oriented, is encouraged to pursue independent research efforts. The success of these efforts is measured by the fact that, over the past 2 years, there are over 30 publications in the peer-review literature by division faculty. The strong point in the current research in is the diversity of these efforts. Research in our division encompasses a diverse mix of basic science biology, clinical studies, therapeutic trials, health services and ethics research. In fact, the division is committed to encouraging a broad array of such research. The funding of research in our division also comes from a wide area of sources, including traditional NIH, professional society, independent foundation, hospital-based, and industry funding. The Pulmonary/Critical Care Fellows have participated in many of the research projects listed below and have been lead authors are several publica-

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tions in peer-reviewed journals as a result of their research efforts.

Specific topics (discussed in more detail below) include:

Sepsis (mechanisms and treatment)

Knowledge translation

Acute lung injury

Pulmonary Vascular Disease (mechanisms and treatment)

Sleep disordered breathing associated with behavior disorders and treatments

Systemic vascular co-morbidities of COPD

Tuberculosis in rural Africa

End-of-life care in the ICU

Ethical and Practical aspects of rationing medical care

Role of Stem Cells in lung injury repair

I Sepsis Therapeutics and knowledge translation

Knowledge Transfer and the development of Performance Metrics

Mitchell Levy MD (Division Chief) is conducting work on performance improvement techniques, and has been working with The Surviving Sepsis Campaign to improve the survival of sepsis through a process of developing management guidelines, establishing a minimum global standard of care, and then producing an implementation model that facilitates the translation of the guidelines into a change in bedside practice. The Surviving Sepsis Campaign guidelines were developed and published first in 2004 and then revised and published in 2008 and 2012. He has conducted several trials, testing the impact of "sepsis bundles" and a multiple-faceted intervention in facilitating knowledge transfer. In partnership with the Institute for Healthcare Improvement (IHI), two sepsis bundles were developed in 2004, and a multi-faceted performance improvement project (Phase 3) was launched in North American, Europe, Asia and Latin America, the results of which were co-published in *Critical Care Medicine* and *Intensive Care Medicine* in January, 2010. Currently, there

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are over 30,000 patients in the sepsis database and a manuscript has been submitted, reporting the results of this next phase. Through funding from a Moore Foundation grant, a new initiative, early identification and management of Sepsis on the medical floors” will begin in early 2014

Knowledge transfer projects now include the introduction of a procalcitonin-guided antibiotic de-escalation as a component of antibiotic stewardship, in Rhode Island Hospital.

Predictive Models and Severity Scoring In Severe Sepsis

Mitchell Levy MD (Division Chief) is examining large data sets of severely septic patients to determine the viability of a disease-specific scoring system (Sepsis Severity Score) for assessing risk-adjusted mortality in patients with severe sepsis. Using recursive partitioning and regression analysis, statistical correlations with these features are being identified. The aim is to generate a predictive model incorporating these factors to identify mortality risk. The results of these efforts, in collaboration with Stan Lemeshow, the dean of Ohio State University School of Biostatistics, are in press in *Critical Care Medicine*.

Measurement in Critical Care Improvement

Several faculty members (**Mitchell Levy MD** and **Andrew Levinson, MD**) are participating in the management of a Rhode Island statewide collaboration for knowledge transfer and quality improvement in sepsis and end-of-life care in the ICU.

II Mechanisms and Biology of Lung Diseases

Pulmonary Endothelial Cell Injury

The **Vascular Research Laboratory** at the Providence VA Medical Center is comprised of several investigators who conduct basic and clinical research that explores mechanisms of acute lung injury, pulmonary hypertension, and RV dysfunction. Faculty are **Drs. Gaurav Choudhary, Elizabeth Harrington, Matthew Jankowich, James Klinger, Qing Lu, and Sharon Rounds**. PI's plus technical staff, graduate students, and post-doctoral fellows are examining the effect of cigarette smoke, adenosine, natriuretic peptide, and protein kinase C on pulmonary microvascular endothelial barrier function. Experiments in intact animals examine the effect of modulating these pathways on animal models of acute lung injury.

These studies are funded by the National Institutes of Health National Heart Lung And Blood Institute, the American Heart Association, and the Dept of Veterans Affairs.

The Vascular Research Laboratory is the site of the **CardioPulmonary Vascular Biology Center for Biomedical Research Excellence**. This multi-investigator Center provides funding for junior investigators studying basic mechanisms of vascular disease, with an emphasis on endothelial cell injury.

Gaurav Choudhary, MD Associate Professor of Medicine and Staff Cardiologist at the Providence VA Medical Center, is funded to study the development of pulmonary arterial hypertension and right ventricular failure in animal models of PAH. He also is investigating the role of ion channels in cultured endothelial cells and the effects of hypoxia on ion channel function.

Elizabeth Harrington, PhD Associate Professor of Medicine, studies the effects of reactive oxygen species on microvascular endothelial cells from heart and lung circulations. She is also investigating the role of a signaling enzyme, Protein Kinase C delta, as a protective agent that blunts microvascular injury in models of acute lung injury. She uses cell biology and physiologic approaches with cultured microvascular pulmonary endothelial cells and animal models of acute lung injury.

Qing Lu, DVM, PhD Associate Professor of Medicine, studies the role of cigarette smoke and adenosine signaling in development of lung vascular injury in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), emphysema and pulmonary arterial hypertension using a combination of studies of cultured cell system and animal models of these diseases.

Sharon Rounds, MD Professor of Medicine and of Pathology and Laboratory Medicine, and Chief of Medical Service, Providence VA Medical Center, studies the effects of altered post-translational processing of small GTPases on endothelial cell apoptosis and lung microvascular permeability. She is also interested in the effects and molecular mechanisms of cigarette smoke-induced acute and chronic lung injury. Both cultured lung vascular endothelial cells and small animals (mice and rats) exposed to lipopolysaccharide and/or cigarette smoke are used in her studies.

Stem Cell Biology in Acute lung injury

Pulmonary, Sleep Disorders & Critical Care (cont)

Jason Aliotta, MD Assistant Professor of Medicine, is studying the role of circulating and lung-derived extracellular vesicles in the pathogenesis of pulmonary vascular disease. Specifically, he is focusing on extracellular vesicles isolated from mice with monocrotaline-induced pulmonary hypertension and their ability to induce pulmonary hypertensive changes when infused into healthy mice. More recently, he has demonstrated that extracellular vesicles isolated from mesenchymal stem cells can reverse the pulmonary hypertensive changes induced by monocrotaline injury.

III Pulmonary Hypertension

The Pulmonary Hypertension Center

The Pulmonary Hypertension Center at Rhode Island Hospital has the largest population of PH patients in the Southern New England and the premier resource for PH patients between New Haven, Conn (Yale) and Boston. **James Klinger, MD**, Medical Director of the Pulmonary Hypertension Center at Rhode Island Hospital conducts basic science and clinical research on pulmonary vascular diseases, including pulmonary arterial hypertension, deep venous thrombosis and pulmonary embolism. **Dr. Klinger** is chair of the Pulmonary Vascular Disease Network of the American College of Chest Physicians, chair of the Pulmonary Circulation Assembly Program committee of the American Thoracic Society and a member of the Scientific Liason Committee of the Pulmonary Hypertension Association. He is also an associate editor for "Lung" and is a nationally known speaker in the area of pulmonary hypertension.

Dr Klinger's basic science projects focus on the role of the natriuretic peptide/cGMP/PKG pathway in modulating pulmonary hypertensive responses, pulmonary vascular endothelial permeability and maladaptive right ventricular hypertrophic responses. His lab examines the signal transduction pathway of cyclic nucleotides and their downstream protein kinases and their roles in pulmonary endothelial and smooth muscle cell hyperplasia. In particular, his work has focused on the role of the natriuretic peptides and their receptors. Dr. Klinger's work also examines the role of bone marrow progenitor cells and stems cells in pulmonary vascular remodeling and repair. His work is supported by the National Institutes of Health, National Heart, Lung and Blood Institute.

Dr. Klinger is also the principal site investigator for numerous industry sponsored multi-center clinical trials that explore new treatments and new combinations of treatments for pulmonary arterial hyperten-

sion. He also serves on the adjudication and steering committees of several multi-national industry sponsored clinical trials

Corey Ventetuolo, MD, MS is the Associate Director of the Pulmonary Hypertension Center and Direct of the Adult Extracorporeal Life Support Program at Rhode Island Hospital. She is studying the impact of the menstrual cycle and the hormonal milieu on markers of angiogenesis and pulmonary vascular and right ventricular function in pre- and post-menopausal women with pulmonary arterial hypertension, respectively, and the relationship between genetic variation in sex hormone pathways and right ventricular function in the Multi-Ethnic Study of Atherosclerosis-Right Ventricle Study. Her work is funded by the National Institutes of Health and the American Heart Association. Additional interests include the study of novel surrogate endpoints and factors which determine treatment response in cardiopulmonary disease as well as the development of robust clinical research in the area of adult extracorporeal life support.

Airway & Interstitial Disorders

Kevin M. Dushay, MD conducts research on disorders of the airways and interstitial lung disease, including asthma, COPD and pulmonary fibrosis. Currently, he is a site investigator for a Boehringer-Ingelheim Phase III trial of a new drug for IPF, and a Hoffman-LaRoche Phase III trial of Lebrikizumab, an anti-IL13 drug, for IPF. He also participates as a co- or sub-investigator on a number of other trials conducted in the Division.

Douglas Martin MD, is conducting a multicenter international research project on markers of disease progression in COPD (ECLIPSE study).

IV Chronic Obstructive Pulmonary Disease

Pulmonary Rehabilitation and Health Outcomes

Linda Nici, MD Clinical Professor of Medicine and Chief of Pulmonary/Critical Care at the Providence VA Medical Center, is nationally recognized for her work in pulmonary rehabilitation and patient education. Her funded research is focused on the effects of patient education on outcomes of chronic obstructive pulmonary disease.

Chronic Obstructive Pulmonary Disease and Co-Morbidities

Matthew Jankowich, MD Assistant Professor of

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Medicine, is funded by the Department of Medicine to study the effects of treatment of cardiovascular risk factors on systemic vascular compliance and LV function in patients with COPD, and is also studying the clinical syndrome of Combined Pulmonary Fibrosis and Emphysema.

Effects of Steroids on Severe Community Acquired Pneumonia

Matthew Jankowich, MD Assistant Professor of Medicine, is funded by the VA to study the effects of steroid therapy on preventing long-term sequelae of severe community acquired pneumonia.

Effects of Vasodilators on Pulmonary Hypertension Associated with COPD

Sharon Rounds, MD Professor of Medicine, **Gaurav Choudhary, MD** Associate Professor of Medicine, and **Matthew Jankowich, MD** Assistant Professor of Medicine, are funded by a multicenter VA Clinical Research Merit Review for a double blind, placebo-controlled study of the effects of Tadalafil on pulmonary hypertension associated with COPD.

V Global Health

Tuberculosis

E. Jane Carter, MD, Divisions of Infectious Disease, and Pulmonary and Critical Care Medicine, has focused her Tuberculosis research at her collaboration site Moi University School of Medicine and Moi Teaching and Research Hospital in Eldoret, Kenya also site of the Brown Kenya Exchange Program.

Dr. Carter is the PI of TB Reach- Active Case Finding in western Kenya Funded by the World Health Organization. This grant involves 4 aims: active case finding by lay community health workers, expansion of rapid TB culture diagnosis for TB, feasibility of GenXpert in active case finding in peripheral health centers and TB screening packages for children exposed to TB in households. Dr. Carter is also funded by WHO to conduct the study entitled Lot Quality Assurance Survey for TB Drug Resistance in western Kenya. Additionally she is funded under an MOU with the International Union Against TB and Lung Disease (Paris, France) to perform operational research training and projects; the first of these projects have focused on TB and Diabetes interaction in low income countries, TB and pregnancy and the effect of health systems integration on TB HIV outcomes.

Household Air Pollution (HAP)

Dr. Carter is the pulmonary PI of the NHLBI Cardiopulmonary Center of Excellence in Clinical Research awarded to Moi University School of Medicine and Moi Teaching and Referral Hospital in Eldoret, Kenya. Under this award, Dr. Carter is involved in projects looking at the relationship of household air pollution and isolated right heart failure in women, the effects of biomass exposure on low birth weight, and stove interventions to reduce HAP in western Kenya, Bangladesh, Peru and Nepal. An additional initiative of the COE is to evaluate the prevalence of obstructive lung disease in western Kenya.

Pulmonary Training in the Developing World

Dr. Carter is the coPI of the East African Pulmonary Training Grant from the World Lung Foundation and the Swiss Lung Foundation to establish a pulmonary training program at the University of Addis Abba, Ethiopia.

VI Sleep Medicine

Sleep and Mood Regulation

Dr. Katherine Sharkey is the PI on a K23 Career Development Award from the National Institutes of Mental Health that examines the impact of sleep and circadian rhythm disruption and serotonin and clock gene polymorphisms on perinatal mood regulation in women with a history of mood disorder. Her collaborators on this study include **Mary Carskadon, PhD**, **Teri Pearlstein, MD**, **John McGeary, PhD**, and **Valerie Knopik, PhD**. **Dr. Sharkey** also collaborates with PI **Mary A. Carskadon, PhD** on a study examining effects of sleep loss and genetics on depressed mood at the transition from high school to college.

Chronotherapy for Perinatal Mood Disorders

Dr. Sharkey is piloting a novel intervention "Integrated Chronotherapy" for depression and anxiety in pregnancy and the postpartum period. Funded by the Depressive and Bipolar Disorder Alternative Treatment Foundation and the Seleni Institute, these randomized clinical trials aim to determine whether chronotherapy (consisting of bright light therapy, sleep phase advance, and sleep restriction) can improve symptoms of depression and anxiety in the perinatal period better than usual care alone. **Drs. Teri Pearlstein, Carmen Monzon**, and **Ellen Flynn** are collaborators on this project.

Pilot Study of Phenotypic and Genotypic Pre-

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dictors of Treatment Success and Recovery from Obstructive Sleep Apnea Syndrome

The aims of this pilot study are to begin to define unique OSA phenotypes that have different symptom and treatment trajectories and to investigate whether specific biomarkers or neurocognitive performance profiles can distinguish these subgroups. In addition, sex differences will be examined. **Dr. Sharkey** leads this study and **Drs. Richard Millman, Ghada Bourjeily, and Teri Pearlstein** are co-investigators.

Cardiovascular Risk in Chronic Kidney Disease

The aims of this study is to determine whether obstructive sleep apnea and chemoreceptor functioning are instrumental in leading to cardiovascular morbidity and mortality in patients with Stage 3 -4 chronic renal disease. **Dr Richard Millman** is a co-investigator along with Drs Katherine Richman and Lance Dworkin from the Renal division **VII Health Services Research and Ethics**

Health Care Rationing In Critical Care Medicine

Nicholas Ward MD in 2008 published the first study of the scope and effect of healthcare rationing in critical care medicine in the US. Dr Ward's work on rationing of critical care in the US is now focusing on Physician staffing shortages in ICUs and he is chairman of the Society of Critical Care Medicine's Taskforce on ICU staffing that recently published both a study and national guidelines on this issue. As a member of the American Thoracic Society's Ethics Committee, he is now working on a statement regarding the role of stewardship in allocating critical care resources.

End-of-Life issues in the critically ill

Mitchell Levy MD (Division Chief) is continuing his work in end-of-life care. Over the past several years, he has published numerous manuscripts in the field, including one on the visiting hours in the MICU, as well as several opinion pieces, describing the barriers to adequate end-of-life decision making. Dr. Levy has completed a state-wide initiative on communication bundles in the ICU (with a research fellow as lead author) the results of which are being published (in press) in *Critical Care Medicine*.

Rheumatology

Edward V. Lally, MD has research interests in the area of scleroderma, osteoarthritis and rheumatoid arthritis. Dr. Lally is the Principal Investigator at Brown for the Scleroderma Clinical Trials Consortium (SCTC), an international multi-center therapeutics organization conducting clinical trials in scleroderma. Dr. Lally is also the Chairman of the Web/Publications Committee of the SCTC. Dr. Lally has completed a trial in scleroderma lung disease with Dasatinib, a tyrosine kinase inhibitor. This was a phase II trial in patients with scleroderma and interstitial lung disease, and part of a multi-center collaborative trial. Furthermore, he collaborates with Dr. James Klinger from the Division of Pulmonary Medicine in the evaluation and treatment of patients with pulmonary hypertension in the setting of connective tissue diseases. Dr. Lally is currently the Northeast Region representative to the Research Strategic Committee of the National Arthritis Foundation (AF). This committee sets research policy and funding levels for the AF.

Anthony Reginato, Ph.D., MD, clinical research interests have been in the area of early-rheumatoid arthritis, osteoarthritis, crystal-induced arthritis, and the application of musculoskeletal ultrasound in the diagnosis, treatment of rheumatic diseases. He has ongoing projects evaluating early arthritis with musculoskeletal ultrasound (MSUS), utilizing MSUS to evaluate the presence of crystals in asymptomatic hyperuricemic patients, patients with psoriatic arthritis, and early rheumatoid arthritis (RA) and acute monoarticular crystal-flare. He established the combined Dermatology-Rheumatology Outpatient Clinic (DROC) at the Providence VAMC to provide better access and care to our veterans with dermatological-rheumatological disease. Also in collaborations with Dr. Abrar Qureshi, recently established the Skin and Musculoskeletal (SAM) Center at lifespan, Rhode Island Hospital. Dr. Reginato is involved through the Pan-American League against Rheumatism (PANLAR) osteoarthritis (OA) study group in evaluating epidemiology of OA in Latin-America, and through the MSUS study group in the development of ultrasound guidelines for the study of rheumatic diseases.

Dr Reginato basic research interest has been in the area of bone development, osteoarthritis, crystal-induced arthritis, and more recently scleroderma. He is collaborating on the Granzyme B study with Dr. Lally and Dr. Fast to evaluate the levels of granzyme levels in patients with early-RA and the

Rheumatology (*cont*)

role of natural-killer (NK) cells in acute monoarticular gout flares. He is also interested in evaluating the role of endothelial-mesenchymal transformation (EmT) in scleroderma using animal models of skin and pulmonary fibrosis. Dr Reginato also has an interest in cartilage calcification and osteoarthritis and performing both genetic studies in families with Milwaukee shoulder and using animal models to evaluate the role of innate immunity in the development of cartilage calcification and osteoarthritis. Dr. Reginato has been awarded one of the project grants for the COBRE projects that is in collaboration with the Department of Orthopedic Surgery. Dr. Reginato has received five year funding for this project to investigate articular cartilage calcification in osteoarthritis. He has several collaborative projects with other investigators of the Department of Orthopaedic, evaluating the chondroprotective role of colchicine (Colcrys) in animal models of osteoarthritis in collaboration with Dr. Lei Wei and evaluating the mineralization and meniscal hypertrophy after anterior cruciate ligament (ACL) injury and evaluating the role of PTPase Shp2, an ubiquitous “dephosphorylation” enzyme, in bone formation with Dr. Wei Yang.

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