Faculty Research Interests

2009-2010

ANATOMY & NEUROBIOLOGY

Mark B. Moss, Ph.D., Chairman
Research focus on the neurobiology of learning and memory in non-human primate models, particularly with respect to aging and age-related disease. Specific interests include (1) the interaction of the prefrontal cortices with the medial temporal lobe limbic system in cognition; (2) the separate and combined effects of age and hypertension on cognition and integrity of the blood-brain barrier in a non-human primate model of hypertensive cerebrovascular disease and (3) parallel studies in normal aged humans and patients with MCI and Alzheimer’s disease. Techniques include automated behavioral assessment, functional and structural MR imaging, and an array of immunocytochemical and related anatomical-morphological techniques.

Marlene Oscar Berman, Ph.D.
Research explores the neuropsychological sequelae of human brain damage. Since the early 1970s, her research has been supported by grants from the Medical Research Service of the VA, and from the US Department of Health and Human Services. Her recent publications are on the cognitive and emotional changes that result from chronic alcoholism, as well as on the behavioral consequences of brain damage in patients with other disorders of the central nervous system. Her work on brain asymmetries addresses questions concerning the different roles of the two cerebral hemispheres in processing, understanding, and responding to visual information having emotional and non-emotional content.

Gene J. Blatt, Ph.D.
Research interests are focused on the neurochemistry and neuropathology of autism, affecting the development of limbic, cortical and cerebellar systems. Specific focus is on major neurotransmitter systems including the GABAergic, glutamatergic and serotonergic systems. Techniques utilized in these projects include immunocytochemistry, histochemistry, in vitro on the slide ligand binding to receptors, computer assisted densitometric analysis, stereology, and in situ hybridization via collaborative studies.

Amy N. Brodeur, M.F.S.
The field of criminalistics, particularly as it relates to crime scene processing and the identification of unknown biological material in a forensic setting. Course Director/Instructor for 3 courses in the Biomedical Forensic Sciences. Program: Crime Scene Investigation, Forensic Biology, Forensic Biology Laboratory; Course Director for 2 courses: Advanced Topics in Crime Scene Investigation, Techniques in Firearms Investigation. Consultant for Boston Police Department Crime Laboratory.

Patsy B. Cipolloni, M.D.
The long-term interest is in the functional synaptic organization of the cerebral cortex. The current ongoing projects are the analyses of the organization of the frontoparietal opercular cortices in the primate; the synaptic organization of various classes of pyramidal projection neurons of the cat neocortex; the areal, laminar, cellular and subcellular distributions of four classes of muscarinic receptors in the cortex and the synaptic organization of physiologically characterized and intracellularly labeled neurons of the neocortex.
Robin Cotton, Ph.D.
Improving methods involved in DNA identification with particular attention to levels of detection and samples which are refractive to commonly used procedures. Specifically, development of improved PCR reaction conditions to eliminate loss “drop out” of genetic information present in the sample at very low concentrations.

Catherine A. Grgicak, Ph.D.
Our research interests include designing and conducting studies relevant to forensic DNA testing. Current research focuses on the statistical evaluation of stutter intensity and heterozygosity ratios in 15 STR loci used in forensic analysis and the effect on mixture deconvolution and interpretation. Other validation projects include comparative studies of DNA extraction methodologies and amplification reproducibility of profiles generated during traditional- and mini- STR forensic typing.
Additional research involves the use of Laser Microdissection for forensic DNA applications, and the evaluation of degraded DNA and its effect on amplification. Characterizing the various types of DNA degradation will allow us to determine which in vitro repair mechanism to employ in order to improve PCR efficiency. Other projects focus on optimizing differential extraction procedures, where sperm cell ‘pre-lysis’ is negated during the initial stages of extraction, and improving overall DNA recovery during extraction. We’ve also studied effective and accurate quantification of human DNA by using real-time PCR while concurrently developing an electrochemical biosensor for reliable and fast quantification of degraded and non-degraded DNA.

Adam Hall, M.S.
Mr. Hall's research goals involve the instrumental analysis of chemically relevant evidence samples with specific applications to the trace analysis of ignitable liquids and explosive residues. The use of unique ignitable liquids such as biodiesel and E85 in arson cases and the investigation of non-conventional energetic materials synthesized from readily available substances and employed in improvised explosive devices are of primary interest.

Todd Hoagland, Ph.D.
Research explores the neurobiology of learning and memory in a non-human primate model, particularly with respect to cerebrovascular hypertension, aging and age-related disease. Specific interests include (1) the separate and combined effects of age and hypertension on cognition and integrity of the blood-brain barrier in a non-human primate model of cerebrovascular hypertension; (2) the neurohumoral effectors of fluid volume regulation and their pathophysiological contributions to hypertension. Techniques include automated behavioral assessment, functional and structural MR imaging, and an array of immunocytochemical and related anatomical-morphological techniques. Dr. Hoagland is also interested in medical education pedagogy. Recently the lab has explored medical student professionalism, adult learning theory, and incorporation of radiological imaging into the medical gross anatomy course.

Richard F. Hoyt, Jr., Ph.D.
Research is focused on two different topics, the biology of pulmonary small-granule neuroendocrine cells and factors influencing the differentiation of macrophages, and is being investigated by physiological, cell- and molecular biological, and morphometric methods. Work on mechanisms regulating peptide secretion by the endocrine cells has shown that their response resemble those of the carotid bodies. Recently, attention also has been devoted to the effects of steroid sex hormones on vaginal tissue structure and (patho) physiology.

Robert Joseph, Ph.D.
Dr. Joseph conducts research on neurocognitive development in children with autism. The focus of his research is on brain maturational processes as they relate to cognitive and behavioral functioning, particularly in the domains of social perception (face and gaze processing) and attention (orienting and search). To study these questions, he and his colleagues use magnetic resonance brain imaging and computerized tests that measure behavioral reaction time, eye-movement behavior, and psychophysiological response to visual stimuli.
Thomas L. Kemper, M.D.
Major areas of research interest are: (1) The effect of nutritional deprivation on the anatomical development of the rodent brain, (2) the anatomical organization of aging changes in the human and monkey brain, and (3) the anatomical changes in the brain of infantile autism, Rett’s syndrome and other developmental disorders. The major techniques used are whole brain serial sectioning, cell counting with stereology, and immuno-cytochemistry.

Ron Killiany, Ph.D.
Dr. Killiany’s research has focused on exploring the relationship between brain structure and cognition. Studies have focused on identifying the morphological changes that take place in the brain during aging and disease processes in order to gain insights into the mechanisms behind the specific cognitive changes that characterize these processes. Initial studies focused on the determining specific structure/function relationships during development in the memory system of the non-human primate as a model for human development. More recent studies have focused on the processes of normal aging and cerebrovascular disease. In this work part of the focus has been on characterizing the cognitive changes taking place in non-human primate models. In addition, Magnetic Resonance Imaging (MRI) studies were added in order to assess volumetric changes in the brains of healthy elderly and cognitively impaired subjects. The focus of research continues to evolve to include functional techniques such as fMRI (functional magnetic resonance images), SPECT (single photon emission computerized tomography) and PET (Position Emission Tomography) scanning in order to study the brain in vivo. A primary focus of Dr. Killiany’s research most recently has been aimed at exploring the value of MRI in predicting which subjects will develop cognitive decline of Alzheimer’s disease and which will remain cognitively stable. Ongoing studies are also focused on identifying changes in the brain of gulf war veterans.

Dae-Shik Kim, Ph.D.
Dr. Kim has a variety of research interests including: a) mapping the development and plasticity of the columnar organization in the mammalian cortex; b) investigation of the “Fusiform Face Area (FFA)” in human visual system using high-field (3T) magnet; c) the use of "Diffusion Tensor Imaging technique" to label the axonal connectivity pattern in vivo and in conjunction with high-resolution functional images; and d) research on development and application of columnar-resolution fMRI methods, and their verification using single unit and optical imaging techniques. Dr. Kim’s expertise includes single and multiunit recording, computational modeling, optical imaging of intrinsic signals, high field magnetic resonance imaging (3T, 4.7T, 7T, and 9.4T). He is interested in teaching: a) systems neuroscience; b) neurophysiology; c) developmental neuroscience; d) principles of neuroimaging; and e) anatomical and neurophysiological foundations of brain imaging.

Jennifer I. Luebke, Ph.D.
The general focus of our research is normal aging and Alzheimer’s disease. We use whole-cell patch-clamp and intracellular filling techniques to examine the electrophysiological and morphological properties of identified neurons in in vitro slices of the monkey and mouse neocortex. Electrophysiological properties of interest include action potential firing patterns and the underlying ionic currents responsible for generating specific patterns, as well as glutamatergic and GABAergic synaptic response properties. With regard to morphological properties, we are interested in detailed dendritic architecture and dendritic spine morphology and distribution. Both morphological and electrophysiological data from single neurons are incorporated into computational models in collaboration with theoretical mathematicians at Mt. Sinai School of Medicine. In addition, we collaborate with other investigators at BUSM who utilize molecular biological (single cell PCR and microarray) and electronmicroscopic (ultrastructural analysis) techniques to examine cells from which we record. Overall goals include: 1) to examine the individual and network properties of neocortical pyramidal cells in the prefrontal cortex; 2) to determine the effects of normal aging on these properties in behaviorally characterized rhesus monkeys, and 3) to determine the
effects of amyloid deposition and tauopathy (hallmarks of Alzheimer’s disease) on these properties in transgenic mouse models of Alzheimer’s disease.

**Maryann MacNeil, M.A.**
Research interests focused on the physiology of sleep, specifically on the influence of drugs of abuse on the circadian system. The effects of cocaine on young and old zebrafish were analyzed to determine the immediate effects of drugs of abuse on circadian rhythms, as well as monitoring age dependent changes in the circadian process.

**Tara L. Moore, M.D.**
Dr. Moore is an Assistant Professor in the department of Anatomy and Neurobiology and Director of the graduate program in Forensic Anthropology. She teaches courses in anatomy, neurobiology and forensic anthropology. She is a co-investigator on research projects funded by the National Institutes of Health that investigate the effects of age and age-related disease on the brain and the Principal Investigator on a project developing a non-human primate model of stroke and recovery. She has recently completed training courses with the Federal Bureau of Investigation in Human Remains Recovery and Crime Scene Management and Evidence Collection.

**Deepak N. Pandya, M.D.**
Major research efforts are directed to study cerebral cortical architecture of human and monkey. Studies also have carried out cortical connectional in monkey using retro- and anterograde tracer techniques. These studies have provided underlying principals of cortical organization. These principals follow the dual origin of cerebral cortex. Current studies deals with comparative architectonics of parieto-temporal areas in human and monkey. Investigations also are being done on the detailed organization of white matter pathways of the cerebral cortex. Other research efforts are also focused on connections of prefrontal and preoccipital regions in monkey. Research is aimed to provide more refined understanding of cortical connections. This in turn can lead to better understanding of cortical disorders and provide framework for further studies using behavioral and physiological approaches.

**Monica A. Pessina, Ph.D.**
Dr. Pessina is pursuing research related to the return of motor function after cortical injury in a primate model. The current project includes developing test measures and evaluation methods to objectively assess primate hand function after cortical lesion. These data are correlated with electrophysiological findings and histological observations to determine the extent of cortical plasticity after acute injury. Dr. Pessina also continues clinical work in the area of upper extremity rehabilitation at Massachusetts General Hospital and her clinical research addresses functional outcomes after hand injury. In addition, in an effort to continually evaluate and improve the educational process, Dr. Pessina is investigating innovative teaching methods and their effectiveness with both medical and dental students.

**Alan Peters, Ph.D.**
Studies are being carried out on the cerebral hemispheres of the non-human primate central nervous system to assess the effects of normal aging on its neurons, neuroligial and systems of myelinated nerve fibers. These studies involve the use of electron and light microscopy, confocal microscopy, quantitative counting methods and immunocytochemistry. The qualitative and quantitative results obtained are carefully examined to determine if there are correlations between increasing age and the cognitive status of the animals, or both of these factors. The basic point of these studies is to try to ascertain which of the many structures affected by normal aging are critical in determining the cognitive status of animals, and if any factors are more critical than others.

**Daniela Plesa-Skwerer, Ph.D.**
Investigating social understanding (social-perception and social-cognition) in people with developmental disorders (in particular Williams syndrome and autism) using complementary methodologies, including computerized behavioral tests, eye tracking, psychophysiological measures, and standardized assessments of cognitive functioning.
Investigating social-emotional development and socio-communicative abilities and impairments in children with developmental disorders, using observational and experimental paradigms and standardized assessments of cognitive and communicative functioning.

Itamar Ronen, Ph.D.
Dr. Ronen’s main interest is in developing new magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) methods for applications in neurobiology. One particular interest is in developing MR-based methods that could provide structural information on specific compartments in neural tissue. Such methods could increase the specificity of MRI to temporal and/or spatial variations in, e.g., axonal diameter, degree of myelination or amount of interstitial space. Another interest is multi-modal MRI of age related effects on the monkey brain, where collection of data using several MR-based modalities and co-analysis of these data sheds light on aging of the brain, a process that is defined by changes in a multitude of physiological, neurochemical and neuroanatomical variables that can be detected by MR on the one hand, and have strong impact on behavior on the other.

Douglas L. Rosene, Ph.D.
My research interests focus on identifying the neurobiological basis of learning and memory and related higher cognitive functions in the normal brain and the basis of disruption of these processes in various neurodegenerative diseases and forms of neurological damage. To accomplish this, the laboratory employs multidisciplinary methods to investigate these issues in animal models. These methods include combinations of behavioral, neurohistochemical, neurophysiological, neuroanatomical, and neurosurgical techniques to study these cognitive functions. We use a non-human primate model of normal aging and of cerebrovascular disease as well as a model of cortical stroke and of other brain lesions. In addition, a rat model of prenatal malnutrition is studied to identify the basis of the effect of this prenatal insult on the brain. Following behavioral characterization using a large array of behavioral testing methods, specific methods for neurobiological analysis of the pertinent brain changes include MRI and PET scans, standard histology, quantitative neuroanatomy using modern stereological methods, immunocytochemistry, enzyme histochemistry, and on the slide receptor autoradiography. In addition we have collaborations adapting methods of statistical physics to assess spatial relationships of the microcolumnar structure of the cortex and utilize in vivo and in vitro neurophysiological methods to assess the function of individual neurons and to follow this up with single cell gene expression analyses. More recent efforts include the use of methods of statistical physics to model and characterize spatial relationships of neurons in the cortex, especially as they form microcolumns, and the correlated use of diffusion MRI to characterize spatial features of axon pathways and neurons in the cortex.

Richard J. Rushmore, Ph.D.
Dr. Rushmore studies the unique contributions of cerebral and subcortical brain regions to functional activity in connected brain structures, and the link between neural activity in discrete cortical regions and specific behaviors. His work focuses on the posterior parietal cortex and the neurobiology underlying the neurological syndrome of visuospatial neglect. He is also interested in the capacity of the brain to undergo adaptive or maladaptive change following damage or reversible deactivation of cerebral cortical areas.

Julie H. Sandell, Ph.D.
My lab is interested in how the structure of the retina changes in patients with inherited retinal degenerations such as retinitis pigmentosa (RP). RP causes photoreceptor degeneration and it is the most common genetic cause of blindness. We are part of a large research group based at the Boston VA, MIT, and the Massachusetts Eye and Ear Infirmary which is trying to develop an implantable retinal prosthesis to bypass the degenerated photoreceptors and use the surviving cells to send a signal to the brain and restore vision in RP patients. We also study retinas from animal models of RP, including pigs and rodents. These animals are used to test implantable devices, and to develop
novel biological therapies for RP, including retinal stem cell transplants and neurotrophin-eluting hydrogel coatings for prostheses.

Jean-Jacques R. Soghomonian, Ph.D.
The laboratory focuses on the functional anatomy of the basal ganglia in normal animals and in experimental models of Parkinson's disease. Another complementary focus is on the organization and regulation of GABA neurons. One current specific objective is to study the plasticity of GABA-mediated signaling in the basal ganglia and the basis of 1-DOPA-induced dyskinesias in rodent models of Parkinson's disease. The research involves behavioral analyzes of motor activity, measurements of gene expression by in situ hybridization histochemistry and computerized quantitative image analysis techniques, measurements of protein expression by immunohistochemistry and western blotting and measurements of small neurotransmitter molecules by in vivo microdialysis combined with HPLC.

Helen Tager-Flusberg, Ph.D.
The overall aims of my research programs address questions about the developmental and neurocognitive mechanisms associated with the core phenotypes that define different neurodevelopmental disorders with special interest in autism, specific language impairment (SLI), and Williams syndrome. The main goals of projects are: (1) To define the disorders themselves - i.e. to shed light on the nature of the deficits and spared capacities that are unique and specific to particular syndromes; (2) To identify cognitive and neuroimaging "markers" that will facilitate research on the underlying genetics and the neuropathology of the syndromes; (3) to identify the earliest risk signs for autism and SLI and the early developmental trajectories associated with these complex disorders.

Kevin Thomas, Ph.D.
I am interested in societal and behavioral dynamics. At the cognitive level this involves understanding how people's preferences are ascribed and how they make sense of the world around them. This can include such things as how individuals follow groups or institutions in their decision-making practices. To test these types of behaviors requires an understanding of how individuals respond to stimuli and how this stimulus is processed. This process, known as the cybernetic sequence elucidates step-by-step actions from the input of the stimuli through how belief systems are structured. Controlled experiments are a means to uncover how these various process actions occur, what their limits are, and how other external influences may affect these process actions. In real world applications of this research we are exploring how individuals respond under healthcare emergency management and crisis situations.

Louis Toth, Ph.D.
The general goal of my laboratory is to investigate the reasons for having functional segregation in the cerebral cortex, and learn how the brain uses its functional architecture to help small collections of neurons to solve computational problems. Model systems range from squirrel to human, and include optical imaging, single unit recording, psychophysics and MR techniques. Some current projects include: 1) examining the functional segregation of face and landscape processing in early visual areas, 2) delineating functional maps in parietal cortex using fMRI, 3) investigating the nature of extrastriate cortical regions in non-human mammals and their relation to visual processing and 4) investigating the contribution of oscillatory activity in basal ganglia to modifying cortical response in normal and Parkinson's disease patients.

Antoni Valero-Cabre, MD PhD
Our team is focused on the study of neural plasticity and reorganization occurring at network level in nervous system. We are interested in the study of the circuitry underlying brain functions, their changes after intensive training and its anatomical and functional adaptation following damage in animals and human subjects. We seek more effective approaches to manipulate "at will" cerebral function to eventually ameliorate the neurological sequels generated by focal brain damage in human patients. All our explorations are based on a detailed analysis of the brain networks allowing the emergence of normal brain processing or training-induced post injury compensations in motor, visual and and visuo-spatial functions. We assay several rehabilitation strategies
based on intensive practice and its combination with non-invasive brain stimulation methods, such as Transcranial Magnetic Stimulation (TMS) and Direct Current Stimulation (tDCS). We ultimately aim at extracting some general principles, which have proved also useful in other types of lesions, functions and localizations in animals and humans.

Deborah W. Vaughan, Ph.D.
Dr. Vaughan is not currently engaged in laboratory research; current interests focus on questions involving teaching and education, especially as related to medical education. Research expertise focused on the effects of advancing age on the nervous system, specifically motor systems. Studies examined the effects of age on the ability of motor neurons to regenerate axons following injury and involved light and electron microscopy, in both morphological, cytochemical and immunocytochemical analyses. Research interests and consultation continue in areas involving the histological aspects of biomedical studies.

Elizabeth R. Whitney, Ph.D.
Research interests are focused on the neuropathology of autism and its relationship to the timing of this developmental disorder. Using immunocytochemistry and standard histological staining techniques, the cerebellar organization as well as the relative density of several neuronal subpopulations in the autistic cerebellum are examined. The study of cerebral cortical organization, using immunohistochemistry, is also being pursued. Based on the known timing and sequence of CNS developmental events, our data has been useful in gaining greater insight into the timing of the pathology in the autistic brain.

Irina Zhdanova, Ph.D., Associate Professor
The research is focused on the role of the circadian system in sleep, aging and effects of drugs of abuse, as well as age-dependent changes in the circadian processes. Two animals models are used, the zebrafish and rhesus monkeys. The methodological approaches include assessment of locomotor activity (image analysis techniques), cognitive functions (performance tests and classic conditioning), polysomnography (in primates only), measurements of intracellular messengers in brain tissue, evaluation of gene expression using real-time RT-PCR, radioimmunoassay and ELISA techniques.

Charles L. Zucker, Ph.D.
The retina, which is part of the central nervous system, is an outstanding model to investigate fundamental aspects of nervous system function due to its accessibility and to the ability to precisely control its natural (visual) input. The primary focus of our laboratory is the microcircuitry and dendritic properties that enable particular retinal interneurons to encode directional and motion information. We have shown that individual dendrites of these ‘starburst amacrine cells’ express distinct combinations of channels, receptors and transporters within different functional compartments of these dendrites and also likely release their neurotransmitters GABA and acetylcholine via distinct mechanisms. Therefore, under the umbrella of our studies directed toward understanding visual system function, we are actively investigating new aspects of the functional toolbox available to neurons throughout the central nervous system and how these properties relate to normal and pathological neuronal function. Toward this end, we utilize a variety of intracellular filling, immunohistochemical, confocal and electron microscopy techniques as well as targeted synaptic silencing using neurotoxins.

Ann Zumwalt, Ph.D.
Research interests include various topics related to the neurobiology of education, including the neurobiological underpinnings of adult learning and changes in perception as individuals grow from naïve learners to experts. Dr. Zumwalt uses adult learning theory to examine teaching techniques and document their efficacy in improving students’ retention of knowledge in the long-term. Dr. Zumwalt is also interested in clinical anatomy projects that advance clinicians’ understanding of anatomy with the goal of improving procedures such as surgical approaches, radiation treatments and other clinical interventions.
BEHAVIORAL NEUROSCIENCE

Marlene Oscar Berman, Ph.D., Director
Dr. Berman’s research seeks to understand the full extent of neuropsychological deficits and intact skills in neurological populations, including alcoholics with and without clinical signs of Korsakoff’s syndrome (severe amnesia for events occurring since the onset of extensive brain damage). Sensitive experimental paradigms are employed to detect subtle differences in the behavior of alcoholics compared to (a) healthy nonalcoholic individuals, and (b) neurological patients who have incurred brain damage from other than alcohol-related etiologies. The most recent studies have included structural and functional MRI correlates of emotional changes in alcoholic subjects.

Martin L. Albert, M.D., Ph.D.
Studies of aphasia, dementia, and aging from the perspective of cognitive neuroscience and behavioral neurology, and studies of the cognitive neuroscience of delusions.

Stanford H. Auerbach, M.D.
Studies of Alzheimer’s disease and related disorders, as well as sleep disorders, circadian rhythm disorders and neurobehavioral sequence of traumatic brain injury.

Helen Barbas, Ph.D.
Research focuses on the organization of the prefrontal cortex in primates and its role in central executive functions. It involves the investigation of bidirectional pathways between prefrontal cortices and structures associated with sensory, cognitive, mnemonic and emotional processes. The experimental approach involves neural tracers to label pathways, combined with histochemical, immunocytochemical, and molecular approaches to characterize their neurochemistry and synaptology.

Domenic Ciraulo, M.D.
Dr. Ciraulo’s primary research interest is the development of medications to treat alcohol and drug dependence. Studies include clinical medication trials in alcohol, cocaine, and opioid dependence, some of which include individuals with comorbid persistent mental illness. Other studies use neuroimaging, human pharmacology laboratory methods, and animal models to screen potential therapeutic agents.

Subimal Datta, Ph.D.
The work in our lab is centered on identifying the functions of mammalian sleep as well as the mechanisms that regulate it. Specifically, the cellular and molecular mechanisms of sleep-dependent memory processing in the mammalian brain as well as the mechanisms of slow-wave sleep (SWS) and rapid eye movement (REM) sleep are major components of our on going research. We believe that the key to fully understanding sleep processes lies in multi-dimensional approaches to the questions at hand. We are fortunate to have facilities to utilize multiple levels of analysis ranging from cellular to behavioral. In the electrophysiology lab, we use simultaneous recordings of single cell activities and polygraphic signs of the sleep-wake cycle in freely moving rats. Behavioral evidence of learning and memory can be evaluated using the behavioral testing suites, while neuropharmacological techniques are used to identify receptors and intracellular signal transduction pathways in freely moving conditions. Neuroanatomical techniques are used to identify neurochemical phenotypes and input-output pathways of functionally identified neuronal populations that are involved in the regulation of sleep and memory processing. Our biochemical and molecular techniques further clarify sleep and memory processing mechanisms by identifying the expression of relevant genes and proteins. All of these methods of research, each contributing a different piece to the greater puzzle, help to expand the understanding of the underlying functions and mechanisms responsible for generating and regulating mammalian sleep. Following are some selected publications that highlight ongoing research goals and the significant techniques used in our research program.
Danny G. Kaloupek, Ph.D.  
Dr. Kaloupek is expert in the application of psychophysiological measurement in relation to anxiety disorders, with emphasis on PTSD. Dr. Kaloupek helps direct the local laboratory shared by National Center for PTSD investigators for trauma-related psychophysiological studies with adults. He is co-PI of a recent study that measured the hippocampus by means of magnetic resonance imaging, and examined this structural information about the brain in relation to measures of memory, autonomic and cortisol response, and electrophysiological information processing. His research interests also include the health-related impact of traumatic stress.

Terence M. Keane, Ph.D.  
My research program involves the development of assessment and treatment methods for post-traumatic stress disorder (PTSD). Recent studies emphasized the psychophysiological parameters associated with this disorder. We are interested in the interrelationship of stress, psychological disorders, and physical health; further we are investigating the health services utilization implications of violence and traumatic disorders. We are also interested in the relationship of trauma exposure, PTSD, and contraction of HIV. Populations of interest are combat war veterans, refugees, and civilian survivors of war.

Maxine H. Krengel, Ph.D.  
I am currently researching the neurocognitive and neuroradiologic impact of Gulf War I service. I am examining toxicant exposures and correlating exposures and psychological issues with cognitive symptoms, health symptoms and brain MRI findings. I have also begun to study the cognitive implications of blast injury and am evaluating (neurocognitively) active duty and recently discharged veterans of operation Iraqi Freedom and Operation Enduring Freedom. I am also continuing to study the long term effects of deep brain stimulation for Parkinson's Disease.

Jacqueline Liederman, Ph.D.  
Dr. Liederman is interested in the neural mechanisms underlying behavior and how these change in the context of development and/or disease. Her training is primarily in physiological psychology. Research Interests: (1) how the two hemispheres collaborate and compete during information processing and how that is affected by split-brain surgery, learning disability and developmental maturation; (2) why boys are two to five times more likely to have neurodevelopmental disorders than girls, including autism, dyslexia, learning disabilities, attention deficit disorder, etc. (our current research examines factors underlying this male vulnerability during the prenatal period); (3) attentional phenomena such as blindsight and change blindness, i.e. circumstances when awareness and perception are dissociated.  
Teaching Interests: Developmental Neuropsychology; Neuropsychology; Developmental Psychology; Physiological Psychology (with emphasis on the human brain); Cognitive Development; Infant Development; Cerebral Dominance; Dissociated States of Consciousness.

Patrick McNamara, Ph.D.  
Research focuses on three broad areas: 1) language and cognitive deficits in Parkinson's Disease, 2) sleep disorders and the function of sleep and dreams; and 3) neuropsychiatry. A more recent line of research has been the emerging field of the neuroscience correlates of religiousness. Our Lab (see website at http://www.bumc.bu.edu/len) has always welcomed students and interns interested in developing their research skills.

Lena Moskovich, M.D., Ph.D.  
Research focuses on: (1) From the theoretical point of view -- the cerebral functional asymmetry; (2) From the neurocognitive aspects -- (a) the functional role of subcortical structures, and (b) the neurochemical correlates of behavior; and (3) From clinical aspects -- different types of cerebrovascular disease and parkinsonism.
Margaret Naeser, Ph.D.
Dr. Naeser focuses on two areas of aphasia research. The first area, Neural Networks and Language Recovery in Aphasia from Stroke: fMRI Studies, is a research project funded by the Medical Research Service, Department of Veterans Affairs. The goal of this project is to utilize functional magnetic resonance imaging (fMRI) to investigate brain reorganization for language behavior in chronic stroke patients with aphasia, especially recovery of naming and propositional speech in nonfluent aphasia patients. The fMRI studies are performed at BUSM’s Center for Biomedical Imaging. The second area, Transcranial Magnetic Stimulation to Improve Speech, is a research project funded by the NIH. This project investigates whether repetitive transcranial magnetic brain stimulation (TMS) can be used to improve speech and naming in patients with chronic, nonfluent aphasia. The TMS treatments are performed at the Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, and Harvard Medical School. Half of the patients are studied in Philadelphia, at the Hospital of the University of Pennsylvania, Department of Neurology. The hypothesis is that 1 Hz TMS, when applied to the right pars triangularis (right Broca’s area homologue), will suppress overactivation there, as has been observed on fMRI studies with chronic, nonfluent aphasia patients. The TMS is predicted to modulate the bi-lateral neural network for naming in these patients, thus improving their naming and speech. Dr. Naeser has also published research with acupuncture and laser acupuncture to treat paralysis in stroke; and pain in carpal tunnel syndrome. There are no ongoing acupuncture research studies at this time.

Deepak N. Pandya, M.D.
Dr. Pandya’s current studies deal with comparative architectonics of parieto-temporal areas in human and monkey. He is also investigating the detailed organization of white matter pathways of the cerebral cortex both in human and monkey. Other research efforts are focused on cortico pontine connections of premotor and motor areas and cortical connections of extrastriate visual areas. Research is aimed to provide more refined understanding of cortical connections. This, in turn, can lead to better understanding of clinical disorders and provide framework for further studies using behavioral and physiological approaches.

Carole Palumbo, Ph.D.
Research interest has focused on using neuroimaging techniques to study language disorders. Specifically, Dr. Palumbo has used CT and SPECT scanning and structural and functional MRI to study the relationship of neuropathology and neurophysiology to severity and recovery of aphasia in stroke patients, and language in normal aging.

Katharine Putnam, Ph.D.
Dr. Putnam uses several behavioral and neuroimaging techniques to measure behavior and neural activity in a variety of psychiatric disorders. She is especially interested in brain mechanisms of emotion from the perspective of affective neuroscience. Dr. Putnam conducts her research at BUSM and at the Department of Veterans Affairs Healthcare System’s Jamaica Plain campus.

Larry J. Seidman, Ph.D.
Primary research interest is in neurobehavioral aspects of schizophrenia and attention deficit hyperactivity disorder (ADHD), including etiology, brain dysfunction, cognitive-neuropsychological processes, structural and functional brain imaging (MRI) and treatment responsiveness, including effects of medications on cognition. Studies integrate genetics, brain development and neuropsychological measures of attention, memory, olfaction and executive function in patients and their first degree relatives.

Robert A. Stern, Ph.D.
Primary areas of funded research include cognitive and emotional aspects of dementia, thyroid-brain relationships, driving and dementia, and cognition and HIV-associated brain dysfunction. He has published on various aspects of neuropsychological assessment and is the senior author of several widely used neuropsychological tests and instruments. Dr. Stern has received several NIH and other national and local grants, has published over 180 journal articles, chapters, and abstracts, and is a Fellow of both the American
Neuropsychiatric Association and the National Academy of Neuropsychology. He has served on several national grant review committees, and is an Associate Editor of the Journal of Neuropsychiatry and Clinical Neurosciences.

Chris Streeter, M.D.
Dr. Streeter’s research interests are in the area of alcohol and drug dependence. Research projects include the application of functional MRI neuroimaging techniques to the study of treatment alternatives for substance-abuse disorders. This is important for understanding the mechanisms of actions of drugs on the central nervous system, as well as for treating alcohol, cocaine, and opioid dependence.

Helen Tager-Flusberg, Ph.D.
One of the central questions that is addressed in Dr. Tager-Flusberg’s research concerns the essential characteristics of the cognitive/linguistic phenotype that define different neurodevelopmental disorders, with special interest in autism, SLI, and Williams syndrome. Currently working on these disorders with funding from NIH with the following specific goals:
1. To define the disorders - i.e. to shed light on the nature of the deficits and spared capacities that are unique and specific to particular syndromes
2. The role of characterizing the cognitive architecture of neurodevelopmental disorders in illuminating theoretical issues of normal development (e.g., dissociation between grammar and functional usage of language in autism)
3. To explore the relationship between cognitive function and neurobiological substrates in these disorders using both structural and functional MRI
4. To investigate the developmental origins of the unique phenotypic characteristics of children with these disorders, including studying infants at high risk using behavioral and electrophysiological methods.

Mieke Verfaellie, Ph.D.
Research aims to elucidate the cognitive and neural bases of various forms of memory and encompasses three broad approaches. A first approach is a cognitive, information processing, analysis of the memory deficits that amnesic patients experience. This work aims to examine patterns of spared and impaired memory function using a variety of experimental memory tasks in the laboratory. A better understanding of the memory processes that remain relatively preserved in the face of memory impairment, and the various ways in which reliance on such processes can be enhanced, is critical for the development of new rehabilitation and memory-training programs for memory disordered individuals.
A second approach is to investigate the neuroanatomical substrates of different memory systems and processes. This work relies on (1) comparison of the locus of lesion in patients with different behavioral presentations; (2) volumetric analyses to quantify the extent of lesion in the medial temporal lobes in amnesic patients; and (3) functional MRI studies of memory in normal individuals as well as patients with amnesia. These studies all contribute to a better understanding of the way in which different components of a memory-related neural network interact. Finally, Dr. Verfaellie also uses a clinical neuropsychological approach in her research. This work has been aimed at better understanding the heterogeneity of clinical presentations among patients. Most recently, this has led to a collaborative study with the departments of neurology and cardiology at BIDMC, in which we evaluate cognitive and functional recovery in patients with cardiac arrest. By combining behavioral and neuroanatomical probes, we hope to gain better information about the precise nature of deficit patterns and their evolution over time, hence allowing better prediction of outcome.

BIOCHEMISTRY

David A. Harris, M.D., Ph.D., Chairman.
My laboratory investigates the molecular and cellular mechanisms underlying human and animal prion diseases. These fatal neurodegenerative disorders are of great public health concern because of the global emergence of bovine spongiform encephalopathy (‘mad
Prion diseases share important similarities with a larger group of neurodegenerative disorders, including Alzheimer’s, Huntington’s and Parkinson’s diseases, that are due to protein misfolding and aggregation.

Our work has two broad objectives. First, we wish to understand how the cellular form of the prion protein (PrPC) is converted into the infectious form (PrPSc). Encompassed in this objective are efforts to elucidate the cellular localization and trafficking of both PrPC and PrPSc, the nature of their association with cell membranes, as well as the molecular features of the conversion process itself. Second, we want to understand how prions kill nerve cells. In particular, we seek to identify what molecular form(s) of PrP represent the proximate neurotoxic species, where these forms are localized in the nervous system, and what cellular pathways they activate that lead to pathology.

We utilize a range of experimental systems, from transgenic mice, to cultured mammalian cells, to yeast (S. cerevisiae). We employ a wide variety of techniques, including protein chemistry, immunofluorescence and GFP-based cell labeling, light and electron microscopy, DNA microarrays, mouse genetics, neuropathology, and animal bioassays.

Carmela Abraham, Ph.D.

Our laboratory studies the molecular mechanisms leading to normal brain aging and the pathological processes that culminate in Alzheimer’s disease. We utilize the rhesus monkey as a model for understanding changes that occur during non-pathological aging. With microarray analysis we identified genes that play crucial roles in brain dysfunction leading to cognitive decline. An example is Klotho, a cytoprotective, anti-aging protein involved in insulin signaling. We found that Klotho expression is considerably decreased in the aged brains of monkeys, rats, and mice. We are now working to comprehensively characterize the role of Klotho in normal aging and disease. Our projects are to identify Klotho receptors in the brain and define the signaling pathways by which Klotho exerts its protective effects. We are also studying Klotho’s transcriptional regulation and identifying compounds to therapeutically exploit these protective effects. Another line of investigation in our lab is to understand the biology of the amyloid precursor protein (APP), the parent protein of the amyloid beta peptide (Abeta), which accumulates in the brains of Alzheimer’s disease patients and causes irreversible neurodegeneration. Certain mutations in APP result in autosomal dominant, early onset familial Alzheimer’s disease due to the increased production of Abeta. Since APP homodimerization is believed to be involved in Abeta formation in the brain we are studying whether various mutations in APP affect its homodimerization. We are working to identify molecules capable of intervening in this process to reduce the levels of toxic Abeta peptide in the brain.

Lawreen Connors, Ph.D.

The systemic amyloid diseases are protein misfolding and deposition disorders. These pathologies feature the destabilization of one of several plasma proteins; the amyloidogenic protein adopts a non-native conformation that leads to aberrant self-association and aggregation. The aggregates form defined fibrillar structures which ultimately precipitate as amyloid deposits in the extracellular compartments of targeted tissues/organs. In addition to the mechanical disruption of tissue function by the deposited amyloid fibrils, pathological effects are thought to be related to the acute cellular toxicity of soluble prefibrillar amyloid aggregates. We are studying the amyloidogenic nature of transthyretin (TTR), normally a soluble protein present in plasma and cerebral spinal fluid. Both wild-type and variant forms of TTR can form amyloid deposits, but disease onset is delayed in what appears to be an age-dependent mechanism. Our investigations are aimed at identifying specific factors required to initiate the disease process; these factors likely include structural features that are both intrinsic and extrinsic to TTR. Specific areas of interest include the roles of amino acid alterations, post-translational modifications (glycosylation, sulfonation, cysteinylatation) and heteroassociations in TTR amyloid fibril formation. We have extensively characterized TTR proteins derived from clinical specimens and identified proteomic differences in
patient vs. age-matched control serum and tissue samples. TTR structural modifications and heteroassociations identified in the clinical samples are studied in vitro with recombinantly-generated proteins and several compounds, including diflunisal and α-tocopherol, are being investigated as potential inhibitors of TTR aggregation and fibril formation. Furthermore, since TTR-associated amyloid diseases often feature cardiomyopathy, we are also studying the effects of amyloidogenic forms of TTR on cultured primary cardiac cells.

Catherine E. Costello, Ph.D.

The objective of our research is to establish the detailed structures of biopolymers in order to understand their structure-activity relationships as they influence or reflect biological processes related to health, growth and development, and disease. Our particular focus for new method development is on the needs of glycobiology, since carbohydrates and their conjugates (glycoproteins, glycolipids, etc.) are involved in targeting and immune system recognition, nervous system growth and development, infection, parasite response, carcinogenesis, and other critical processes. The techniques for full structural characterization of these complex molecules are much less developed than are methods for linear biopolymers (proteins and oligonucleotides). Recent introduction of new mass spectral ionization methods and rapid progress in means for mass separation and detection now make it possible to perform structural studies on low picomole amounts of samples even when they are complex mixtures. In our research program we are refining and extending the tools of mass spectrometry and are applying them to studies of biopolymers undertaken with collaborators at BUSM and other institutions around and outside the US. Our laboratory is a Resource Center sponsored by the NIH National Center for Research Resources.

Stephen R. Farmer, Ph.D.

Obesity has now reached pandemic proportions, resulting in dramatic increases in the occurrence of its associated disorders including diabetes and cardiovascular disease. Understanding the processes and metabolic perturbations that contribute to the expansion of adipose depots accompanying obesity is critical for the development of appropriate therapeutics. Expansion of white adipose (WAT) tissue depots particularly the intra-abdominal depots contribute to insulin resistance and inflammation that lead to type 2 diabetes, whereas brown adipose (BAT) resists expansion because it oxidizes lipids and, consequently, it is associated with an healthier phenotype. Our studies are focused on identifying the mechanisms regulating the formation and function of white and brown adipocytes (fat cells) using a variety of experimental approaches including overexpression and knock down of specific nuclear factors that we consider to be likely regulators of these processes in cells in culture as well as in mice. At present our focus is on nuclear factors that modulate the activity of the two principal regulators of adipogenesis (fat cell differentiation) peroxisome proliferator-activated receptor gamma (PPARg) and CCAAT/enhancer binding proteins alpha, beta and delta (C/EBPs). We are particularly interested in identifying the factors regulating commitment of mesenchymal progenitors to the adipogenic lineage and are adopting a variety of approaches to achieve this goal, which includes gene profiling to discover novel regulators as well as investigating the role of selected candidate genes.

Konstantin Kandror, Ph.D.

Adipocytes, skeletal myocytes and some neurons express a specific isoform of the glucose transporter protein, Glut4. Under basal conditions this transporter is localized in intracellular membrane vesicles which fuse with the plasma membrane upon insulin administration. Translocation of Glut4 plays a major role in post-prandial glucose clearance and, more generally, in glucose sensing and metabolic homeostasis in the body. For a number of years, my lab has been involved in the dissection of the "Glut4 pathway" in various insulin-sensitive cells. Another key physiological function of insulin is to inhibit lipolysis and to promote storage of triglycerides in fat tissue. Recently, we have discovered two novel pathways of regulation of lipolysis by insulin. One of these pathways is mediated by the insulin- and nutrient-sensitive mammalian Target of Rapamycin Complex 1, while the other is
mediated by transcriptional factor FoxO1. Currently, we are engaged in the dissection of both pathways at the molecular level.

Fat represents an important secretory tissue in the body. Unlike typical endocrine and exocrine cells, adipocytes produce and secrete several physiologically important proteins, such as leptin, adiponectin, lipoprotein lipase, etc. and switch the secretory process from one protein to another in response to changing metabolic conditions. We are exploring connections between food intake, obesity and secretion of adipokines in order to understand the central role of fat tissue in the orchestrating the overall response of the organism to changing metabolic conditions.

Kathrin Kirsch, Ph.D.

My laboratory is working on delineating molecular mechanisms that are important for tumor initiation and progression, with a specific focus on the expanding family of cytoplasmic adapter proteins. We are investigating the participation of p130Cas family proteins in growth regulation in cancers of the mammary gland. We have developed a transgenic animal model expressing a dominant-interfering p130Cas to investigate the role(s) of this molecule in normal mammary development and in breast cancer in vivo induced by aberrant expression of ErbB and Src family tyrosine kinases. Recently we have identified another adapter that associates with the SH3 domain of p130Cas, named CD2AP/CMS. We have found that CD2AP associates with the ubiquitin ligase c-Cbl in response to growth factors stimulation, and with F-actin. Moreover, we showed that CD2AP forms heterotypic complexes with its family member CIN85, and that both molecules bundle F-actin in vitro. Our current work with CD2AP is focused on its roles in growth factor signaling, cell adhesion and migration, and in growth factor-mediated remodeling of the actin cytoskeleton. In a collaborative effort with Dr. Sonenshein and Dr. Trackman, we are working on elucidating the mechanism of action of lysyl oxidase (LOX) on inhibition of Ras-mediated transformation. We have demonstrated that the propeptide region of LOX attenuates Ras- and Her-2/neu-dependent breast cancers in vitro and in xenograft models. Studies are in the progress to elucidate the mechanism of this inhibition. Long-term goals are to determine the potential for use the propeptide or derivatives in treatment of patients with Her-2/neu or Ras-mediated breast disease.

Matthew Layne, Ph.D.

Our long-term goals are to understand the transcriptional control of genes, which are upregulated in the vascular smooth muscle cells and fibroblasts in cardiovascular and pulmonary disease. We have identified a secreted protein, aortic carboxypeptidase-like protein (ACLP), which contains a collagen-binding discoidin and a catalytically inactive metallocarboxypeptidase domain. ACLP is expressed in vascular smooth muscle cells and is induced in the diseased blood vessel in vivo. We are defining the mechanisms by which ACLP regulates VSMC proliferation and function using in vitro assays and vascular disease models with transgenic and knockout mice. Additional projects in the lab are investigating the control of myofibroblast gene expression in pulmonary fibrosis. We are exploring the mechanisms of gene expression in de-differentiated VSMC and myofibroblasts and have identified novel transcription factor complexes that may coordinate the expression and subsequent deposition of extracellular matrix proteins in wounded VSMC and fibroblasts.

Cheng Lin, Ph.D.

Our research focuses on the development of mass spectrometry (MS) methods for the structural characterization of biomolecules. Specifically, we are interested in developing radical driven fragmentation methods that are amenable to the Fourier-transform ion cyclotron resonance mass spectrometry. One such method is the electron capture dissociation (ECD), which has several advantages over conventional slow heating methods. For instance, ECD retains labile side-chain modifications in proteins making it particularly suited for post-translational modification (PTM) analysis. ECD also produces extensive cross-ring cleavages in carbohydrates, which provides crucial information for studying complex glycan structure. Another tandem MS method that we are currently exploring is the vacuum ultraviolet photodissociation (VUV-PD). Unlike ECD, VUV-PD is applicable to singly charged precursor ions that are commonly produced by the matrix-
assisted laser desorption/ionization (MALDI). Our present research efforts also include the application of these methods to solve important biological problems, such as the protein deamidation, which plays an significant role in protein misfolding diseases and aging.

Zhijun Luo, Ph.D.
The overall research interest in my laboratory is to understand how protein phosphorylation regulates cell growth and metabolism, and how its alteration causes diseases such as cancer and metabolic disorders. Our ongoing research focuses on characterization of AMP-activated protein kinase and Raf kinase, both of which have been implicated in cancer and other disorders. AMPK serves as a fuel-sensing enzyme that is activated by binding of gamma subunit and phosphorylation of the catalytic 5' AMP to the subunit at Thr 172 by upstream kinases such as LKB1 and CaMKK. The activation of AMPK has been shown to improve metabolic syndrome and to be implicated in control of cancer cell growth. One of our research interests is to test the hypothesis that AMPK functions as a metabolic tumor suppressor. Using microarray and proteomic approaches, we have identified several target molecules regulated by AMPK and are currently evaluating their functional relationship with AMPK and biological relevance.

Raf kinases, consisting of three isoforms, Raf-1, B-Raf and A-Raf, act as immediate downstream effectors of Ras. They are implicated in tumorigenesis, inasmuch as activating mutations of the ras genes have been found in 20-30% of overall human cancers and activated mutants of B-Raf frequently reported in human cancers. Although the linear relationship of the Ras/Raf/MEK/Erk signaling pathway has been delineated, the mechanism of Raf activation still remains elusive. We have a long standing interest in characterizing phosphorylation of Raf for its activation, and identifying kinases responsible for these phosphorylation events and downstream targets in addition to MEK1/2.

Matthew Nugent, Ph.D.
The research in our laboratory is focused on how growth factors and the extracellular matrix interact to control mammalian cells. In particular, we are focused on how the large class of heparin-binding growth factors are regulated by heparin and heparan sulfate proteoglycans. We apply a combination of biochemical, molecular, biophysical, and computational approaches in conjunction with cell culture and animal studies to generate a systems biology view of growth factor regulation that incorporate the influence of multiple factors on one another. We apply this approach to studies aimed at understanding the details of growth factor-receptor recognition and activation, the regulation of angiogenesis, and the control of extracellular matrix turnover. The overriding theme to our research is to use quantitative methods to analyze complex biological processes in order to develop predictive models of living systems that can be used to probe basic mechanisms and to assist in the rational design of new therapies for human disease. Currently we are focusing on the involvement of these processes in cardiovascular disease and chronic obstructive pulmonary disease.

Paul Pilch, Ph.D.
The modern Western diet coupled with a sedentary lifestyle has led to an epidemic of obesity, a consequence of which is a dramatic rise in the incidence of type II diabetes mellitus, a malfunction in insulin-regulated metabolism. At the cellular level, type II diabetes is characterized by failure of insulin to act in liver, muscle and fat. We study aspects of insulin signaling and action in the latter two tissues. Insulin resistance in muscle (and fat) derives from the failure of insulin to activate the tissue-specific glucose transporter GLUT4. The activation mechanism for this process involves vesicle trafficking and protein targeting with regard to GLUT4 and the insulin receptor. We are characterizing the formation and protein content of GLUT4-containing vesicles; we are trying to identify the organelles through which they pass on their way to and from the cell surface and we are determining the communication mechanism(s) (signaling) from the insulin receptor to the GLUT4-containing vesicles. These studies involve both fat and muscle cells, and we are also studying the physiological role of cell surface (plasma
membrane) micro-domains called caveolae that are particularly abundant in these tissues. We have evidence for the hypothesis that caveolae (for little caves that are small invaginations of the plasma membrane into the cytosol) are involved in lipid trafficking. We continue to study other aspects of adipocyte and muscle cell biology to understand the interplay between glucose and fat metabolism as well as the interplay between adipocytes and muscle required for overall metabolic homeostasis. Indeed, we wish to uncover the mechanism(s) by exercise also regulates some of these same parameters independent of insulin. Understanding these pathways will help us to figure out how they are compromised in pathophysiological states such as diabetes.

Peter Polgar, Ph.D.

We are engaged in the study of mechanisms involved in the development of hypertension and the accompanying fibrosis in the heart and lung and the contributions of the angiotensin II, AT1, endothelin ETA and ETB, and prostanoid receptors to the process. We are attempting to determine the structure function relationships of these G-protein coupled receptors. These receptors are the targets of many drugs on the market today. Using mutagenesis we have been locating specific motifs or combinations of motifs in the receptors responsible for specific signals. We have also been able to block specific signals using cell permeable peptides mimicking specific receptor motifs. Knowledge of the tertiary structure of BKB2R and AT1R obtained from our mutagenesis experiments has provided important insight into understanding receptor function and for the design of transgenic mice. These transgenic mice are providing a unique tool to study the underlying signaling events of AngII in the aging process in a combined in vivo and in vitro environment and present as a unique model to study important signaling pathways involved in the progressive dysfunction of the cardiovascular system during aging. The laboratory is also differentiating human embryonic stem cells to eventually replace some of the cells damaged during hypertension and fibrosis which are critical to normal function of these organs.

Barbara Schreiber, Ph.D.

Research focuses on demonstrating the role of aortic smooth muscle cells in atherosclerosis. The development of the disease is clearly associated with elevated plasma cholesterol levels. Lipid laden “foam cells” derived from both smooth muscle cells as well as cells of the monocyte/macrophage lineage are prominent features of the atherosclerotic plaque. Nonetheless, there is a paucity of information regarding the direct effects of lipid accumulation on cell function. We have developed an in vitro model of cultured aortic smooth muscle cells isolated from neonatal rats and rabbits. The cells are treated with ßVLDL, a lipoprotein that accumulates in the plasma of rabbits fed a high cholesterol diet. Lipoprotein induced alterations in cell function are examined. An additional focus of the lab is on determining the role of serum amyloid A in smooth muscle cell lipid metabolism. Interestingly, this acute phase protein down regulates lipid biosynthesis, which may play a role in atherosclerosis. We are currently exploring the mechanism whereby this regulation is achieved. The lab relies on in vitro approaches (cell culture, immunohistochemistry and molecular biology) and an in vivo mouse model of restenosis/atherosclerosis.

Michael Sherman, Ph.D.

I. Research in my lab has focused on understanding the molecular mechanisms underlying the central role of the heat shock protein Hsp72 in cancer. In cancer cells Hsp72 is often expressed at very high levels, and its expression correlates with the aggressiveness of tumors. Recently we have found that Hsp72 regulates early stages of tumorigenesis. Indeed, Hsp72 can control signaling pathways initiated by major oncogenes, resulting in avoiding growth inhibition and facilitating cell proliferation and transformation. Our research addresses several questions:

1. How Hsp72 keeps the p53 pathway activated by PIK3CA oncogene under control?
2. How Hsp72 prevents cell senescence activated by Her2 oncogene.

II. In a distinct project we study a process of aggregation of abnormal polypeptides. When chaperone and protein degradation machineries fail to handle abnormal proteins, they
aggregate and cause cell toxicity, which may give rise to various neurological disorders. As the last line of defense, a special machinery has evolved that transports these toxic aggregates to a centrosome location via microtubules, which leads to relieve of toxicity. The resulting non-toxic single large aggregate is called aggresome. Previously we have established a yeast model to study aggregation and toxicity of the disease-causing polyptides with expanded polyglutamine domain. Now, using both yeast and mammalian systems, we are dissecting the pathway of aggresome formation. Our current research within this project uses genetics and biochemical approaches to addresses the following questions:

(1) What cellular components are involved in aggresome formation?
(2) What signaling pathways control aggresome formation?

Elizabeth Simons, Ph.D.

Our interest lies in the initial immune system’s response to a foreign entity by the phagocytic cells. Signal transduction and degranulation control in phagocytic cells and their precursors in response to chemotactic and phagocytic stimuli. We are currently concentrating on stimulation by organisms which evade the normal phagocytic killing processes and therefore remain vital (e.g. mycobacteria such as M. tuberculosis). The normal process is initiated by the cell membrane’s specific receptors and involves generation of cytoplasmic cation signals, leading to motion along a chemoattractant concentration gradient to the origin of the chemoattractant where different receptors are engaged, phagocytosis occurs, leading to fusion with organelles to form a phagolysosome whose contents include bactericidal agents such as reactive oxygen species, lytic enzymes and inhibitory factors. We believe that evasion by certain organisms occurs because the organism takes over control of the cells’ responses, either at the level of signaling, at the formation of the phagocytic vacuole, at its fusion with the internal organelles and/or in the environment of the phagolysosome itself. We’ve shown this to be true for certain fungi. The laboratory’s interests hence concern the kinetics of initial responses of a secretory cell to recognition, by its membrane receptors, of a specific stimulus. We are investigating the mechanism by which these signals are transmitted and result in the cells’ eventual functional degranulation. We differentiate between the chemotactic and phagocytic pathways, using fluorescent techniques to evaluate receptor identity, occupancy and ensuant response kinetics of individual cells, measured by flow cytometry. Kinetic measurements are performed, by fluorimetry, spectrophotometry and flow cytometry. Electrophoresis, chromatography, cellular cavitation and organellar separation, enzymology, microscopy, tissue culture, immunological techniques (ELISA and Western blotting) are all used.

Barbara Smith, Ph.D.

The primary goal in this laboratory is to establish a better understanding of the mechanisms involved in the control of collagen gene expression associated with tumor formation, inflammation, atherosclerosis, and fibrosis. Collagen is a family of connective tissue proteins that plays a critical role in remodeling after injury or during tumorigenesis and development. Our laboratory has been examining both activation and repression of collagen transcription using molecular biology approaches. We have demonstrated that collagen type I genes are methylated in the first exon in cancer cells and colon cancer. Collagen gene is silenced in certain tumors. A methylation sensitive DNA binding protein (RFX1) represses transcription by binding to the collagen gene transcription start site. This protein belongs to a family of proteins that can function as transcription activators or repressors. RFX1 interacts with a co-repressor complex containing histone deacetylase which could be involved with spreading of DNA methylation and silencing.

A RFX5 complex containing three other proteins (RFXANK/B, RFXAP, CIITA) are essential activators of major histocompatibility complex class II (MHC II) proteins that respond to interferon-gamma during inflammation and activate cells to become antigen producing cells. Interferon activates RFX5/CIITA synthesis and nuclear localization in human fibroblasts and smooth muscle cells. RFX5 proteins form a complex at the RFX site in collagen and recruits CIITA to repress collagen transcription through a
phosphorylation sensitive interaction with co-repressor complex. Thus, this family of proteins may be very important modulators of collagen expression during inflammation.

**Phillip Stone, Ph.D.**

Elastin is a highly crosslinked connective tissue protein with rubber-like tensile properties. As such it plays a key structural role in the blood vessels, lung and other organs. Under normal conditions elastin has a very slow rate of turnover. Proteolysis of elastin is associated with pathologic conditions; for example, pulmonary emphysema. Our research mission is to measure and understand pathologic elastin degradation and its failure to repair appropriately. We are currently working on understanding the signal transduction pathways that signal the upregulation of the repair mechanism. Another project is evaluating the delivery of recombinant human tropoelastin to loci in tissues requiring repair of elastin. We have shown that a portion of this tropoelastin becomes crosslinked into proteolytically damaged elastin. The laboratory is also involved in clinical studies involving elastin degradation. We have developed a novel assay for the measurement of specific elastin and collagen breakdown products that are cleared into the urine. Increased levels of these markers are found in a number of inflammatory conditions such as emphysema, cystic fibrosis, scleroderma, liver cirrhosis, inflammatory bowel diseases and provide a biochemical index of disease activity. We are currently partnering with a company in Cambridge to design and test elastase inhibitors for treatment of pulmonary emphysema.

**Karen Symes, Ph.D.**

Our major goal is to determine the molecular mechanisms that control cell movements using Xenopus embryos as a model system. We are identifying molecules that control normal cell movement in order to understand how mechanisms go awry and lead to aberrant cell movement in pathological conditions including certain birth defects and cancer metastasis. Using a wide range of techniques in developmental biology, molecular biology, and confocal microscopy, our current efforts are aimed at analyzing the role of platelet-derived growth factor in that process including its downstream signaling, interaction with the extracellular matrix and control of cytoskeleton reorganization.

A second area of research in the laboratory explores a problem central to both adults and embryos, the regulation of tissue homeostasis. In the adult, approximately one hundred thousand cells are produced every second by mitosis, and a similar number die by apoptosis. Alterations in this balance are thought to result in a variety of pathological conditions including cancer, as well as heart and neurodegenerative diseases. In the embryo, these processes play critical roles in coordinating the rate of development of different tissues and organs, and their disruption has severe consequences. Using Xenopus embryos as a model, we are exploring the mechanisms that initiate and execute apoptosis in the development of the notochord, a tissue that acts both as a as a primitive skeleton and as a signaling center that provides position and fate information for all three germ layers.

**Paul Toselli, M.D., Ph.D.**

Our research laboratory fosters the goals of the Biochemistry Department by assisting faculty and graduate students in the transmission electron microscopic and light microscopic analyses of in vitro, transgenic, and gene “knock-out” animal models for examining diseases such as atherosclerosis, breast cancer, and male infertility. We employ sensitive methods for detecting and localizing elastin mRNA and protein in plastic-embedded rat aortic smooth muscle cell cultures by in situ hybridization and immunogold antibody staining techniques. The cultured cells grow in multilayers, produce extracellular matrix elastin, and demonstrate a structural arrangement of cells and extracellular matrix similar to that observed in the medial layer of blood vessels. By using this in vitro model of vascular tissue, we hope to understand mammalian cell basic science, and then apply this knowledge for acquiring insight into disease processes that involve vascular smooth muscle cells and/or elastin.
Techniques used most often in the laboratory include transmission electron microscopy and light microscopy, electron and light microscopy immunocytochemistry and histochemistry, in situ hybridization and light microscopy autoradiography.

Vickery Trinkaus-Randall, Ph.D.

There are 3 ongoing areas of interest in our laboratory. 1: We are examining how epithelial wound repair occurs and are interested in the regulation of purinergic and EGF receptors. The purinergic receptors are also activated in a number of diseases including cystic fibrosis, alzheimers and dry eye. Our results suggest that specific purinergic receptors are important in cell migration and signaling to EGFR and phosphorylation of specific residues. Purinergic receptors are also involved in the development of tissue that is collagen rich and we are examining changes in expression with development and injury. These questions are addressed using a number of technologies including siRNA, site directed mutagenesis, mass spectrometry, confocal imaging (live cell imaging and evaluation of expression). 2: In the second project we are studying a disease called systemic amyloidosis, which is ultimately a disease resulting in misfolded proteins. The disease affects a number of organs (some are heart, liver, kidney and spleen) by deposition of fibrils. Our laboratory examines how cardiac fibroblasts respond to amyloid light chains and we also examine how the amyloid oligomers and fibrils form in the presence of sugar chains called glycosaminoglycans that are highly sulfated. We have shown that the cells secrete a more highly sulfated sugar chain (GAG) and hypothesize that the difference in the structure of the GAG chains ultimately alters fibril formation. Methods that are used include live cell confocal microscopy and trafficking, atomic force microscopy, and electron microscopy. 3: We are collaborating with faculty at two other facilities in Boston to produce 3-dimensional organ corneal constructs that are evaluated using a multidisciplinary approach including biochemical, morphological and engineering technologies

Zhi-Xiong Jim Xiao

My laboratory is interested in the function and regulation of tumor suppressor proteins p53 and the retinoblastoma protein (RB) in response to a variety of extracellular signals with an emphasis on breast cancer and lung cancer. We have demonstrated that genotoxic stresses induce specific p53 phosphorylation and protein conformation changes that lead to p53 activation, cell cycle checkpoint and apoptosis. Furthermore, we have identified interplay between the IGF survival signaling pathway and p53 regulatory pathway. Currently we have been working to investigate (1) genotoxic insults-mediated activation of p53 and p53 family members; (2) IGF-1/AKT signaling pathway in cell survival; (3) cell cycle regulation and function of oncoprotein MDM2; (4) role of retinoblastoma protein (RB) and E2F in lung cancer; (5) animal breast cancer model with focus on the mechanism of environmental carcinogen-induced mammary tumorogenesis, and (6) role and regulation of p53 family member p63 in human tumorogenesis.

Joseph Zaia

Glycosaminoglycans (GAGs) are linear oligosaccharides attached to proteoglycan core proteins in virtually every animal species and tissue. A large number of proteins bind GAGs including those involved in blood clotting, many growth factors, and several extracellular matrix proteins. Mutation in GAG biosynthetic genes leads to severe malformations, indicating the critical roles these carbohydrates play in development. Much of proteoglycan biological activity is mediated though protein-binding interactions. The group develops new bioanalytical methods to meet the emerging needs of biomedicine related to GAG function and is building a structural understanding of the roles of GAG during development, adult physiological processes and disease states. Dynamic regulation of GAG expression serves as a mechanism to elaborate the functions of the relatively limited number of proteoglycan gene products. This gives rise to the elaborate signaling feedback mechanisms required for higher animal physiological processes. The group aims to develop a mechanistic understanding of the roles of GAG expression related to human health. Specific projects include investigations into (1) heparan sulfate-growth factor interactions;
(2) heparan sulfate phenotypes in vascular disease processes;
(3) post-biosynthetic enzymatic and chemical modification to heparan sulfate structure and function;
(4) use of tandem mass spectrometry for structural analysis of GAGs. These projects focus on development and use of cutting edge mass spectrometric technology.

Joint Faculty
* Xingbin Ai, Research Assistant Professor (Assistant Professor of Medicine)
* Salomon Amar, Research Associate Professor (Professor of Periodontology & Oral Biology)
* David Atkinson, PhD, Research Professor (Professor of Biophysics)
* Clinton Baldwin, Research Assistant Professor (Professor of Pediatric Medicine)
* Peter Bergethon, MD, Associate Professor (Associate Professor of Anatomy & Neurobiology)
* John Bernardo, MD, Research Professor (Professor of Medicine)
* Jerome Brody, MD, Associate Professor (Professor of Medicine)
* David Center, MD, Research Professor (Professor of Pulmonary Medicine)
* Barbara Corkey, PhD, Professor (Professor of Medicine)
* Thomas Einhorn, Professor (Professor of Orthopedic Surgery)
* Douglas Faller, PhD, Research Professor (Professor of Medicine)
* Louis Gerstenfeld, Research Professor (Professor of Orthopedic Surgery)
* Ronald Goldstein, MD, Research Assistant Professor (Professor of Medicine)
* James Hamilton, PhD, Research Associate Professor (Professor of Physiology & Biophysics)
* Maria Kukuruzinska, Research Assistant Professor (Professor of Molecular and Cell Biology)
* Peter Morin, Research Assistant Professor (Assistant Professor of Neurology)
* Mary Jo Murnane, Research Associate Professor (Associate Professor of Pathology & Laboratory Medicine)
* Gwynneth D. Offner, PhD, Research Assistant Professor (Associate Professor of Gastroenterology)
* Frank Oppenheim, DMD, PhD, Associate Professor (Professor of Periodontology and Oral Biology)
* Hee-Young Park, PhD, Research Associate Professor (Research Associate Professor of Dermatology)
* Katya Ravid, PhD, Professor (Professor of Medicine)
* Miklos Sahin-Toth, Research Associate Professor (Professor of Molecular & Cell Biology)
* Jacqueline Sharon, Research Associate Professor (Professor of Pathology & Laboratory Science)
* G. Graham Shipley, PhD, Professor (Professor of Physiology & Biophysics)
* Donald Small, MD, Professor (Professor of Physiology & Biophysics)
* Remco A. Spanjaard, PhD, Research Assistant Professor (Associate Professor of Otolaryngology)
* Philip C. Trackman, PhD, Research Assistant Professor (Professor of Periodontology & Oral Biology)
* Abdulmaged Traish, Professor (Professor of Urology)
* Vassilis Zannis, Professor (Professor of Medicine)
* Yujun Zhang, Research Assistant Professor (Assistant Professor of Medicine)

BIOMEDICAL FORENSICS

Robin Cotton, Ph.D., Director
Improving methods involved in DNA identification with particular attention to levels of detection and samples which are refractive to commonly used procedures. Specifically, development of improved PCR reaction conditions to eliminate loss "drop out" of genetic information present in the sample at very low concentrations.

Amy N. Brodeur, M.F.S.
The field of criminalistics, particularly as it relates to crime scene processing and the identification of unknown biological material in a forensic setting. Course Director/Instructor for 3 courses in the Biomedical Forensic Sciences. Program: Crime
Scene Investigation, Forensic Biology, Forensic Biology Laboratory; Course Director for 2 courses: Advanced Topics in Crime Scene Investigation, Techniques in Firearms Investigation. Consultant for Boston Police Department Crime Laboratory.

Catherine A. Grgicak, Ph.D.
Our research interests include designing and conducting studies relevant to forensic DNA testing. Current research focuses on the statistical evaluation of stutter intensity and heterozygosity ratios in 15 STR loci used in forensic analysis and the effect on mixture deconvolution and interpretation. Other validation projects include comparative studies of DNA extraction methodologies and amplification reproducibility of profiles generated during traditional- and mini- STR forensic typing. Additional research involves the use of Laser Micro dissection for forensic DNA applications, and the evaluation of degraded DNA and its effect on amplification. Characterizing the various types of DNA degradation will allow us to determine which in vitro repair mechanism to employ in order to improve PCR efficiency. Other projects focus on optimizing differential extraction procedures, where sperm cell 'pre-lysis' is negated during the initial stages of extraction, and improving overall DNA recovery during extraction. We’ve also studied effective and accurate quantification of human DNA by using real-time PCR while concurrently developing an electrochemical biosensor for reliable and fast quantification of degraded and non-degraded DNA.

Adam Hall, M.S.
Mr. Hall's research goals involve the instrumental analysis of chemically relevant evidence samples with specific applications to the trace analysis of ignitable liquids and explosive residues. The use of unique ignitable liquids such as biodiesel and E85 in arson cases and the investigation of non-conventional energetic materials synthesized from readily available substances and employed in improvised explosive devices are of primary interest.

BIOIMAGING

Itamar Ronen, Ph.D., Co-Director
Dr. Ronen’s main interest is in developing new magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) methods for applications in neurobiology. One particular interest is in developing MR-based methods that could provide structural information on specific compartments in neural tissue. Such methods could increase the specificity of MRI to temporal and/or spatial variations in, e.g., axonal diameter, degree of myelination or amount of interstitial space. Another interest is multi-modal MRI of age related effects on the monkey brain, where collection of data using several MR-based modalities and co-analysis of these data sheds light on aging of the brain, a process that is defined by changes in a multitude of physiological, neurochemical and neuroanatomical variables that can be detected by MR on the one hand, and have strong impact on behavior on the other.

Hernán Jara, Ph.D., Co-Director
Research is focused in two complementary topics. First topic relates to the development of more informative (multi-spectral) quantitative MRI acquisition techniques for clinical as well as for research purposes. Second topic relates to the development of computer applications for extracting maximally and efficiently the information contained in such multi-spectral quantitative MRI data sets. This includes computer applications for extracting visual information as well as applications for quantifying the structures of biological systems from their images.

Dae-Shik Kim, Ph.D.
Dr. Kim has a variety of research interests including: a) mapping the development and plasticity of the columnar organization in the mammalian cortex; b) investigation of the "Fusiform Face Area (FFA)" in human visual system using high-field (3T) magnet; c) the use of "Diffusion Tensor Imaging technique" to label the axonal connectivity pattern in vivo and in conjunction with high-resolution functional images; and d) research on development and application of columnar-resolution fMRI methods, and their verification
using single unit and optical imaging techniques. Dr. Kim’s expertise includes single and multiunit recording, computational modeling, optical imaging of intrinsic signals, high field magnetic resonance imaging (3T, 4.7T, 7T, and 9.4T). He is interested in teaching: a) systems neuroscience; b) neurophysiology; c) developmental neuroscience; d) principles of neuroimaging; and e) anatomical and neurophysiological foundations of brain imaging.

BIOMEDICAL CRISIS MANAGEMENT

Kevin Thomas, Ph.D., Director

I am interested in societal and behavioral dynamics. At the cognitive level this involves understanding how people’s preferences are ascribed and how they make sense of the world around them. This can include such things as how individuals follow groups or institutions in their decision-making practices. To test these types of behaviors requires an understanding of how individuals respond to stimuli and how this stimulus is processed. This process, known as the cybernetic sequence elucidates step-by-step actions from the input of the stimuli through how belief systems are structured. Controlled experiments are a means to uncover how these various process actions occur, what their limits are, and how other external influences may affect these process actions. In real world applications of this research we are exploring how individuals respond under healthcare emergency management and crisis situations.

CELL AND MOLECULAR BIOLOGY

Vickery Trinkaus-Randall, Ph.D., Director

1: We are interested in the signals that cells utilize to migrate after injury or environmental changes including hypoxia. ATP is released at the site of tissue damage and rapidly activates purinergic receptors, which mediate cell communication and wound repair. Students are examining differences between EGF and nucleotide induced migration and recruitment of docking proteins to the EGFR. Previously we had shown that the activation of the purinergic receptors results in phosphorylation of a subset of tyrosine residues. Recently we have shown that two residues play an active role in the ability of a cell to migrate to a specific cue. Therefore the cells lose directionality and the ability to close a wound, but remain the ability to move. Our results provide evidence that while phosphorylation of EGFR may be critical for wound closure it can be achieved by either direct ligand stimulation or through other signaling pathways. When the latter occurs we hypothesize that recruitment of signaling molecules is modified. Purinergic receptors are also involved in the development of tissue that is rich in extracellular matrix and we are examining changes in collagen and proteoglycan expression with development. The P2X7 null mouse results in a lack of organization of the stromal matrix. Since the P2X7 receptor is a ligand gating channel and controls the flow of ions into the cell it was thought to play an important role in apoptosis and inflammation. However epithelial cells rarely apoptose and we found that while the cells demonstrate certain canonical P2X7 responses, others that are more typical of cell death such as blebbing and pore formation did not occur. We then demonstrated that the epithelial cells express C-terminal truncated P2X7 splice variants that respond to the agonist. These questions are addressed using a number of molecular and cell biological technologies including transfection, site directed mutagenesis, mass spectrometry, migration assays, confocal imaging (live cell imaging and evaluation of expression).

2: In the second project we are studying a disease called Primary (AL) amyloidosis. Amyloid deposition is hypothesized to play a role in many diseases including rheumatoid arthritis, diabetes, as well as the amyloidoses themselves. The amyloidoses exhibit deposition of insoluble fibrillar proteins in organs and tissues and AL amyloidosis results from a plasma cell dyscrasia. Glycosaminoglycans (GAGs) are one of the major extracellular matrix components and the in vivo relationship between GAGs and amyloid
deposits has been shown. Furthermore, the presence of MMPs has been shown to be correlated with the diseases. We have shown that when cells are exposed to AL/CL the LC is internalized and the cells secrete highly sulfated GAGs. We are currently asking if the sulfation of the GAGs plays a role in the formation of oligomers and fibrils. We are also asking what is the role of the core protein and MMPs on oligomer and fibril formation. Methods that are used include live cell confocal microscopy and trafficking, atomic force microscopy, and electron microscopy.

3: We are collaborating with faculty at two other facilities in Boston to produce 3-dimensional organ corneal constructs that are evaluated using a multidisciplinary approach including biochemical, morphological and engineering technologies.

Carlos Hirschberg, Ph.D.

The Role of Novel Regulation of Posttranslational Modifications in Development and Disease

Our laboratory is interested in studying the biogenesis, structure and function of lower and higher eukaryotes' cell surfaces and the extracellular matrix by using a combined biochemical, molecular biological and genetic approach. Our particular effort is focused on glycoproteins, glycolipids, and glycosaminoglycans. These play important roles in the regulation of cell growth, intercellular recognition, cell adhesion, and as receptors for hormones, toxins and growth factors.

A major research effort has centered around mechanisms of glycosylation, sulfation and phosphorylation of the above-named compounds. Specific questions which are being asked include the intracellular membrane topography of glycosylation, sulfation and phosphorylation reactions and how precursors are transported from their intracellular site of synthesis to the site(s) of glycosylation, sulfation and phosphorylation. We have characterized a number of transporters in the membrane of the rough endoplasmic reticulum and Golgi apparatus which transport precursors into the lumen of these organelles. These transporters are antiporters. We and others have described Chinese hamster ovary cells, yeast, protozoa, nematodes, insects and plants which are defective in transport of sugar nucleotides into the Golgi apparatus lumen. These mutants have a developmentally impaired phenotype and can cause a virulent wild type organism to become avirulent, demonstrating that the transporters are of physiologic relevance and may become drug targets. Recently the first diseases in such transporters were described: leukocyte adhesion deficiency II syndrome in humans and complex vertebral malformation in bovines. We have purified and cloned some of these transporters by using biochemical and molecular biological approaches, including genetic complementation. More recently, we are also studying the function of these transporters in C. elegans and are cloning and disrupting the genes of enzymes involved in the above posttranslational modifications, i.e., a Golgi GDPase from K. lactis, Candida albicans, and C. elegans. This approach should enable us to determine the functions of specific glycoproteins and glycosaminoglycans during development.

David E. Levin, Ph.D.

Stress signaling and cell wall biogenesis in fungi.

We use baker's yeast, Saccharomyces cerevisiae, as a model genetic organism in which to study the molecular mechanisms of stress signaling. The biomedical relevance of our work is centered on the identification of potential antifungal drug targets. One project concerns the dissection of the Cell Wall Integrity (CWI) signaling pathway, which detects and responds to cell wall stress during growth and morphogenesis. Because animal cells lack cell walls, this structure is an attractive target in fungal pathogens. Disruption of the fungal cell wall results in cell lysis. The CWI pathway uses a set of cell surface sensors that are connected to a small G-protein (Rho1), which activates signaling through a MAP kinase cascade. We have found in recent studies that the Mpk1 MAP kinase of the CWI pathway has a non-catalytic function in transcription initiation and elongation, in addition to its catalytic activity as a protein kinase. We are now working to understand this novel mechanism for transcriptional regulation. A second project exploits the need of fungal cells to maintain osmotic homeostasis through the regulation of intracellular glycerol
concentration. We have identified a pair of genes, named *GCA1* and *GCA2* (for Glycerol Channel Activators) whose function is to control the activity of the Fps1 glycerol channel, which acts as a plasma membrane vent that decreases turgor pressure by releasing glycerol from the cell. The fungal kingdom is replete with members of the Gca family of proteins, but they have not been found in metazoan organisms. For this reason, and because mutants in these genes undergo cell lysis as a result of excess turgor pressure, the Gca proteins may be suitable antifungal targets. Current studies are centered on understanding the biochemical function of Gca1/2 and their mode of regulation in response to osmotic stress. A third project concerns the regulation of glycosylphosphatidylinositol (GPI)-anchor production by the G-protein Ras. GPI-anchors are attached to proteins in the endoplasmic reticulum (ER) that are destined for the cell surface. This regulation is unusual because it involves Ras signaling at the ER, rather than at the plasma membrane, its well-studied site of action.

**Maria Kukuruzinska, Ph.D.**

*N-glycosylation regulates intercellular adhesion and cytoskeletal dynamics in development and cancer*

Work in my laboratory examines how the metabolic pathway protein N-glycosylation guides cell-cell adhesion and cytoskeletal dynamics in epithelial tissue development and cancer. Our studies with cultured cells in vitro have shown that N-glycosylation of E-cadherin, a major epithelial cell-cell adhesion receptor that forms adherens junctions (AJs), affects the recruitment of key regulatory components to AJs and their association with both the actin cytoskeleton and microtubules. Among the key regulators of N-glycosylation-dependent AJ stability is protein phosphatase 2A (PP2A), a stabilizer of AJs and an inhibitor of tight junctions (TJs). AJs that contain hypoglycosylated E-cadherin sequester PP2A from TJ components and form multi-protein scaffolds that contain dynein/dynactin complexes. This suggests that the functional significance of PP2A's recruitment to AJs with hypoglycosylated E-cadherin is to tether them to microtubules, most likely to promote the transport of polarity proteins to the apical membrane. Studies are underway to elucidate how changes in E-cadherin N-glycosylation status drive molecular reorganization of AJs and TJs as well as cytoskeletal dynamics and how these changes impact cellular signaling and function.

Another project investigates the roles of E-cadherin junctions and their N-glycosylation status in the mouse submandibular gland (SMG) development. These studies employ SMGs from different stages of embryonic development, as well as SMG organ cultures coupled with gene-specific inhibitory strategies including function-blocking antibodies, siRNAs and chemical inhibitors. We have shown that the differences in the organization of E-cadherin junctions define patterns of acinar and ductal cell fate already at the initial bud stage. Through the organization of different types of junctions, E-cadherin regulates proliferation of acinar and ductal progenitors, formation of new buds as well as rearrangements and survival of cells during tubulogenesis. Most recent studies have shown that E-cadherin collaborates with F-actin and myosin II in the planar cell polarity (PCP) pathway that drives the extension of the presumptive ducts during SMG morphogenesis. Our ongoing studies focus on how E-cadherin junctions are coupled to signaling pathways that drive duct formation during SMG development.

A related study examines how dysregulation of cellular N-glycosylation promotes the development and progression of oral squamous cell carcinoma (OSCC). OSCC is characterized by aberrantly high cellular N-glycosylation that correlates with excessive N-glycosylation of E-cadherin, unstable AJs and lack of TJs. Partial inhibition of cellular N-glycosylation in oral cancer cell lines with siRNA to the DPAGT1 gene, a key regulator of N-glycosylation, leads to reduced N-glycosylation of E-cadherin and stabilization of AJs and TJs. This drives the reversal of malignant cell morphology to the epithelial phenotype. Current studies examine E-cadherin scaffolds and downstream signaling events that lead to the loss of E-cadherin's tumor suppressive function in OSCC and other epithelial cancers.

**Phillips W. Robbins, Ph.D.**

*Glycosylation in higher and lower Eukaryotes*
The vast majority of eukaryotes (fungi, plants, animals, slime mold, and euglena) synthesize Asn-linked glycans (Alg) by means of a lipid-linked precursor dolichol-PP-GlcNAc2Man9Glc3. Knowledge of this pathway is important because defects in the glycosyltransferases (Alg1-Alg12 and others not yet identified), which make dolichol-PP-glycans, lead to numerous congenital disorders of glycosylation. In collaboration with John Samuelson and his group, we have used bioinformatic and experimental methods to characterize Alg glycosyltransferases and dolichol-PP-glycans of diverse protists, including many human pathogens, with the following major conclusions. First, it was demonstrated that common ancestry is a useful method of predicting the Alg glycosyltransferase inventory of each eukaryote. Second, in the vast majority of cases, this inventory accurately predicts the dolichol-PP-glycans observed. Third, Alg glycosyltransferases are missing in sets from each organism (e.g., all of the glycosyltransferases that add glucose and mannose are absent from Giardia and Plasmodium). Fourth, dolichol-PP-GlcNAc2Man5 (present in Entamoeba and Trichomonas) and dolichol-PP- and N-linked GlcNAc2 (present in Giardia) have not been identified previously in wild-type organisms. Finally, the present diversity of protist and fungal dolichol-PP-linked glycans appears to result from secondary loss of glycosyltransferases from a common ancestor that contained the complete set of Alg glycosyltransferases.

Recently, in collaboration with the Samuelson group we have also shown that the abundance of sequons (Asn-Xaa-Thr or Asn-Xaa-Ser), which are sites for N-glycosylation of secreted and membrane proteins, varies by more than a factor of four among phylogenetically diverse eukaryotes based upon a few variables. There is positive correlation between the density of sequons and the AT-richness of coding regions, although no causality can be inferred. In contrast, there appears to be Darwinian selection for sequons containing Thr, but not Ser, in organisms that have N-glycan-dependent QC of glycoprotein folding. Selection for sequons with Thr, which nearly doubles the sequon density in human secreted and membrane proteins, occurs by conditional selection, wherein the actual sequon density is greater than the sequon density calculated from the frequencies of Asn, Thr, and Pro. Conditional selection also appears to account for increasing sequon densities of the haemagglutinin of influenza viruses A/H3N2 and A/H1N1 over the past few decades of human infection. Very strong selection for sequons with both Thr and Ser in gp120 of HIV and related retroviruses results from conditional selection for sequons, amino acid composition bias, and increases in AT-richness. In summary, AT-content is an important predictor of sequon density, conditional selection for sequons with Thr occurs in phylogenetically diverse eukaryotes with N-glycan-dependent QC of glycoprotein folding, and multiple mechanisms may contribute to the very high density of sequons in viral envelope proteins.

Miklos Sahin-Toth, Ph.D.
The Role of Proteases in Pancreatitis.
Our laboratory studies how various proteases and their inhibitors in the pancreas contribute to the pathogenesis of pancreatitis. Pancreatitis is believed to occur due to inappropriate, intrapancreatic activation of digestive enzymes (e.g., trypsin, chymotrypsin, elastase), which are normally synthesized and stored in their inactive forms in the pancreas. Our long-term objectives are to understand the molecular mechanisms of human pancreatitis, using genetically determined pancreatitis (e.g., hereditary pancreatitis) as a biochemical model. The main focus of our research program is to provide biochemical evidence that genetic alterations in the three human trypsinogen isoforms (PRSS1, PRSS2 and PRSS3 genes) and the pancreatic secretory trypsin inhibitor (SPINK1 gene) can significantly influence the susceptibility for the development of pancreatitis. Thus, gain-of-function mutations in cationic trypsinogen can cause pancreatitis, while loss of function mutations in anionic trypsinogen can actually protect against pancreatitis. Loss of the inhibitory function of SPINK1 either due to mutations or to degradation by mesotrypsin can represent another risk factor for pancreatitis onset. The following specific projects are studied. (1) The role of human mesotrypsin in
pancreatitis. Mesotrypsin is a unique protease specialized for the degradation of trypsin inhibitors. Premature mesotrypsinogen activation might lower protective SPINK1 levels in the pancreas and contribute to the pathogenesis of pancreatitis. (2) Characterization of pancreatitis-associated cationic trypsinogen (PRSS1) mutants. Identification of novel mutation-dependent biochemical defects that lead to hereditary pancreatitis (3) Functional analysis of anionic trypsinogen (PRSS2) mutants that afford protection against pancreatitis. The concept that loss-of-function trypsinogen mutations can protect against pancreatitis provides independent evidence for the central role of trypsin in this disease. (4) Identification of the disease-causing biochemical defects in pancreatitis-associated SPINK1 mutants.

John Samuelson, M.D., Ph.D.
Biochemistry, cell biology, pathogenesis, and evolution of single cell parasites.

*The following faculty also participates in the Program in Cell and Molecular Biology. Please refer to their departmental listing.

Carmela R. Abraham, Ph.D., Biochemistry
Christopher Akey, Physiology and Biophysics
Kenneth Albrecht, Molecular Medicine, Genetics & Genomics
Karen N. Allen, Ph.D., Physiology and Biophysics
David Atkinson, Physiology and Biophysics
Jan K. Blusztajn, Ph.D., Pathology
Steven Bogen, M.D., Ph.D., Molecular Medicine
Berse Brygida Pathology and Laboratory Medicine
Esther Bullitt, Physiology and Biophysics
Wellington Cardoso, Pathology and Laboratory Medicine
Herbert Cohen, Ph.D., Molecular Medicine
Richard Cohen, Ph.D., Physiology & Biophysics
Barbara E. Corkey, Ph.D., Biochemistry
Ronald B. Corley, Ph.D., Microbiology
Carter Cornwall, Physiology and Biophysics
Catherine Costello, Ph.D., Biochemistry
Darrell Cotton, Molecular Medicine
Shoumita Dasgupta, Ph.D., Genetics & Genomics
Douglas Faller M.D., Ph.D., Pathology
Stephen Farmer, Ph.D., Biochemistry
Carl Franzblau, Ph.D., Biochemistry
J. Fernando Garcia-Diaz, Ph.D., Physiology and Biophysics
Caroline Genco, M.D., Microbiology and Molecular Medicine
Terrell T. Gibbs, Ph.D., Pharmacology
Suryaram Gummuluru, Ph.D., Microbiology
Hwai-Chen Guo, Ph.D., Physiology and Biophysics
Olga Gursky, Ph.D., Physiology and Biophysics
James A. Hamilton, Ph.D., Physiology and Biophysics
James Head, Ph.D., Physiology and Biophysics
Alan Herbert, Ph.D., Genetics and Genomics
Haya Herscovitz, Ph.D., Physiology & Biophysics
Konstantin Kandror, Ph.D., Biochemistry
Kathrin Kirsch, Ph.D., Biochemistry
Matthew Lane Ph.D., Biochemistry
William J. Lehman, Ph.D., Physiology and Biophysics
Adam Lerner, M.D., Pathology
Jennifer Luebke, Ph.D., Anatomy and Neurobiology
Zhijun Luo, Ph.D., Genetics and Genomics
C. James McKnight, Ph.D., Physiology and Biophysics
Landon Moore, Ph.D., Genetics and Genomics
Mary J. Murnane, Ph.D., Pathology and Laboratory Medicine
John Murphy, Ph.D., Molecular Medicine
Enrico Nasi, Ph.D., Physiology and Biophysics
Barbara Nikolaczyk, Ph.D., Molecular Medicine, Microbiology
Matthew Nugent, Ph.D., Biochemistry
Paul F. Pilch, Ph.D., Biochemistry
Nader Rahimi Ph.D., Biochemistry and
Katya Ravid, DSc/Ph.D., Biochemistry
Daniel Remick, Pathology and Laboratory Medicine
Ann Marshak-Rothstein, Ph.D., Microbiology
Douglas Rosene, Anatomy and Neurobiology
Carol Rosenberg, M.D., Pathology and Molecular Medicine
Sayon Roy
Neil B. Ruderman, M.D., Physiology and Biophysics
Shelley J. Russek, Ph.D., Pharmacology
Judith Saide, Ph.D., Physiology and Biophysics
Ivelisse Sanchez, Ph.D., Anatomy and Neurobiology
Julie Sandell, Ph.D., Anatomy and Neurobiology
Barbara Seaton, Ph.D., Physiology and Biophysics
Barbara Schreiber Ph.D., Biochemistry
David Seldin, M.D., Ph.D., Molecular Medicine
Jacqueline Sharon, Ph.D., Pathology and Laboratory Medicine
Michael Sherman, Ph.D., Biochemistry
David Sherr, Ph.D., Pathology and Laboratory Medicine
Graham Shipley, DSc/Ph.D., Physiology & Biophysics
Elizabeth R. Simons, Ph.D., Biochemistry
Barbara Slack, Ph.D., Pathology and Laboratory Medicine
Donald M. Small, M.D., Physiology and Biophysics
Barbara Smith, Ph.D., Biochemistry
Jean-Jacques Soghomonian, Ph.D., Anatomy and Neurobiology
Gail E. Sonenshein, Ph.D., Biochemistry
Karen Symes, Ph.D., Biochemistry
Guillermo Taccioli, Ph.D., Microbiology
Sambasivamoorthy Thiagalingham, Ph.D., Pathology and Laboratory Medicine
Philip C. Trackman, Ph.D., Periodontology and Oral Biology, Biochemistry
Gregory Tullis Ph.D., Molecular Medicine
Abdulmaged M. Traish, Ph.D., Biochemistry
Cyrus Vaziri, Ph.D., Pathology and Laboratory Medicine
Gregory Viglianti, Ph.D., Microbiology
Kenneth Walsh, Ph.D., Molecular Medicine
Zhi-Xiong Jim Xiao, Ph.D., Biochemistry
Bryan Yamamoto, Ph.D., Pharmacology
Qiang Yu Ph.D., Molecular Medicine
Joseph Zaia Ph.D., Biochemistry
Vassilis I. Zannis, Ph.D., Biochemistry
Irina Zhadanova M.D., Ph.D., Anatomy and Neurobiology
Raphael A Zoeller Ph.D., Physiology and Biophysics

CLINICAL INVESTIGATION

Susan Fish, Pharm.D., M.P.H., Director of M.A. in Clinical Investigation
Although she has a long history of research in the areas of clinical toxicology and emergency medicine, Dr. Fish has most recently focused on research ethics in general, and application of the federal regulations for waiver of informed consent in certain emergency research circumstances. In addition, issues relating to the design of clinical research and ethical implications of study designs are areas of expertise.

Carol A. Gloff, Ph.D.
Develop strategies for rapidly moving medical products through the preclinical and clinical trials process to marketing approval by the US Food and Drug Administration. (or more concisely, US regulatory affairs for medical products), international regulatory affairs for medical products, clinical and preclinical pharmacokinetics.

Chao-Yu Guo, Ph.D.
Conduct and analysis of various research projects at the Framingham Heart Study including general biostatistics, cross sectional and longitudinal studies, multivariate and survival analyses. Special interest is statistical genetics including linkage and/or association mapping and missing data studies.

Laurie A. Halloran, B.S.N., M.S.
Pharmaceutical business process improvement.

Lindsay McNair, M.D., M.P.H.
Clinical research ethics and research subject protection; ethical industry-sponsored drug development research; interactions between IRBs and the pharmaceutical industry.

Thomas J. Moore, M.D., Office of Clinical Research
Effect of foods on blood pressure and cardiac risk; Dietary Approaches to Stop Hypertension (DASH) diet; changing health behaviors via the internet.

FORENSIC ANTHROPOLOGY
Tara L. Moore, Ph.D., Director

Dr. Moore is an Assistant Professor in the department of Anatomy and Neurobiology and Director of the graduate program in Forensic Anthropology. She teaches courses in anatomy, neurobiology and forensic anthropology. She is a co-investigator on research projects funded by the National Institutes of Health that investigate the effects of age and age-related disease on the brain and the Principal Investigator on a project developing a non-human primate model of stroke and recovery. She has recently completed training courses with the Federal Bureau of Investigation in Human Remains Recovery and Crime Scene Management and Evidence Collection.

GENETIC COUNSELING

MaryAnn Whalen Campion, M.S., L.G.C., Program Director

Ms. Campion’s research interests are focused on prenatal genetic counseling, teratology, and ethics in genetics.

Maureen Flynn, M.S., L.G.C., M.P.H., Assistant Program Director

Ms. Flynn’s research interests are focused on clinical cancer genetics and public health genetics.

Jeff Milunsky, M.D., F.A.C.M.G., Medical Director

Dr. Jeff Milunsky’s research interests are focused on the genetic etiology of hearing impairment, the genetic etiology of mental retardation, and the genetic etiology of multiple congenital anomaly syndromes.

GENETICS AND GENOMICS

Kenn Albrecht, Ph.D.

Mammalian gonadal sex determination is a powerful system for studying organogenesis, cell fate determination, and the evolution of sex chromosomes and developmental regulatory mechanisms. Besides basic scientific interest, mammalian sex determination also is of biomedical interest. Approximately one in 1000 infants has a gonadal or genital anomaly. Furthermore, many of the known genes involved in sex determination also are implicated in pathological processes such as tumorigenesis and primary adrenal failure, and have essential roles in the normal development of organs other than the gonads. We use the mouse as a model system for studying mammalian sex determination and gonadal and adrenal organogenesis and employ genetic, molecular genetic, genomic, cell biological and embryological techniques. Currently, there are two main projects underway in the lab. In the first, we are investigating the molecular mechanisms of three mouse models of human sex reversal and adrenal dysmorphogenesis. In the second, we are identifying and characterizing new genes important for gonad development using genetic and genomic approaches such as microarray analysis of gene expression during organogenesis. Our long-term goal is to understand the molecular mechanisms of gonadal and adrenal organogenesis and their role in human disease.

Shoumita Dasgupta, Ph.D.

The popular press has called the twentieth century “The Century of the Gene.” During this time, genetics came forward as a central discipline in biology, first with the rediscovery of the work of Gregor Mendel at the turn of the century, later with the elucidation of the structure of DNA by Jim Watson and Francis Crick, and more recently with the development of recombinant DNA technologies by Paul Berg and Herb Boyer. These scientific events revolutionized the way we thought about biological problems. Mendel’s contributions led scientists to probe the genetic basis of inheritance while Watson and Crick helped to define the molecular nature of this inheritance. Berg and Boyer developed the tools that allowed scientists to manipulate these molecules of inheritance to more deeply understand their functions. Each of these events has had far-reaching consequences because of the explosion of scientific inquiry it both allowed and inspired. Currently, scientists of the twenty-first century are poised at the brink of another genetic revolution, this time triggered by the genome projects of organisms from
microbes to humans. With the availability of this data, it has become obvious that current computational tools alone are inadequate to fully mine this immense data set. Although the power of current genomic strategies is tremendous, they are not sufficient to determine gene function. Consequently, scientists are seeking to ascertain gene function using two main approaches. First, there is a great effort underway to create new technologies and computational tools to allow for large scale molecular analyses of complex systems. Secondly, these strategies are utilized alongside methods that take advantage of the powerful role of model organisms in helping to determine gene function, an important focus of the Genetics and Genomics department. This global perspective on the intricate networks that govern the machinery of life is causing a shift in the traditional paradigm of identifying the impact of individual genes on any given process. Instead, the revised concept that no gene acts in isolation is more easily explored with these new genomic and bioinformatics tools.

Mark S. Eller, Ph.D.
Our research focuses on the cellular responses to telomere disruption or critical shortening (uncapping). We have documented that DNA oligonucleotides homologous to the telomere 3' overhang (T-oligos) induce DNA damage responses similar to those from telomere disruption without actually altering the telomere structure. We hypothesize that exposure of this overhang is the critical feature of an uncapped telomere. Our research utilizes these T-oligos to study the mechanisms and outcomes of these telomere-mediated DNA damage responses in mammalian cells.

Lindsay A. Farrer, Ph.D.
Dr. Farrer’s research investigates genetic risk factors in familial neurodegenerative and other chronic diseases. In collaboration with other laboratories worldwide, his group has localized genes causing rare and common disorders including Alzheimer disease (AD), Wilson disease, Machado-Joseph disease, Waardenburg syndrome, hypertension, sensorineural deafness, and osteoarthritis. In collaboration with researchers at other institutions, Dr. Farrer is conducting a genome scan to search for genes conveying susceptibility to cocaine and opioid dependence among families with multiple affected members.

Alan Herbert, MB.ChB. Ph.D.
Dr. Herbert’s laboratory has just completed a whole genome scan of families from a community-based population that involved typing 100,000 single nucleotide polymorphisms per individual and identified a common variant that increases risk of obesity. The closest gene INSIG2 is involved in the regulation of fatty acid synthesis. Another variant affecting a gene in the same pathway, ACACA, is associated with leanness. Dr. Herbert is in the process of initiating a high-throughput screen of candidate drugs for these genes as targets, using a chemical library available through the Center for Methodologies and Library Development at Boston University. Analysis of other traits is also underway, potentially providing insight into pathways of addiction and genes that predict successful neurological aging.

Darrell M. Kotton, MD
Research interests are in the area of stem cell biology and gene therapy: 1) The role of bone marrow-derived stem cells in lung injury repair is evaluated in specified mouse models of lung injury. 2) Embryonic stem cell differentiation into lung epithelial cells: development of an ex vivo platform that models lung epithelial cell development from undifferentiated mouse embryonic stem cells. Regenerative medicine applications for healing the injured lung using lineage-directed embryonic stem cells are also studied. 3) Gene therapy of lung diseases using lentiviral vectors: lentiviral transduction of hematopoietic stem cells followed by transplantation, or intratracheal delivery of lentiviral vectors is used to overexpress or knockdown genes in mouse models of lung disease. More information is available at www.kottonlab.com.

Landon Moore, Ph.D.
Role of centromere three-dimensional structure in mitotic chromosome segregation: A prominent characteristic of human cancers and several genetic diseases, such as Fanconi anemia and Xeroderma pigmentosum, is chromosome instability. Centromere
structure is important in preventing chromosome instability by assembling sister kinetochores such that they face in opposite directions (a back-to-back orientation). This orientation occurs during G2/early prophase and is dependent on the selective removal of chromatid cohesion from the CENP-A chromatin (centromere resolution). The regulated removal of cohesion is essential for chromosome stability: yet this process, at present, is not well understood. Caenorhabditis elegans was selected as the model system because it is genetically tractable and because centromeric activity throughout the mitotic chromosomes (holocentric) allows mutations in centromere structure to be easily distinguished. Because the whole mitotic chromosome is analogous to a centromere, we used holocentric chromosome structure to screen for mutants that affect the three-dimensional structure of centromeres. From both a classical genetic and a genome-wide RNAi screen we obtained several chromosome instability (cin) mutants. These mutants are currently under investigation in the lab. Functional role for the catalytic domain of topoisomerase II in cohesin regulation: One of the mutants obtained from our screen, cin-4, is 89% identical to the catalytic domain of C. elegans topoisomerase II (top-2). Not surprisingly top-2 is required for chromosome structure as topoisomerase II is an enzyme that cleaves, manipulates, and rejoins DNA. Interestingly, cin-4, while a partial gene duplication of top-2, is required for a different function in organizing chromosome structure. We found that cin-4 is required for centromere resolution. In the absence of cin-4 function, cohesin is localized to sister kinetochores inhibiting their separation. The presence of cohesin alone is not sufficient to explain this inhibition. Removal of a cohesin dissociation pathway by WAPL-1 RNAi retains cohesin on mitotic chromosomes, but does not inhibit centromere resolution. These results together suggest that the catalytic domain of topoisomerase II interacts with cohesin in a different manner than the WAPL-1 pathway. Furthermore, this cin-4 mediated interaction has consequences for cohesion establishment and chromosome structure. Prior work has suggested a connection between topoisomerase II and cohesin, however the mechanism of this interaction is not understood. The presence of cin-4 in C. elegans as a duplication of the topoisomerase II catalytic domain with a specific role in cohesin regulation provides a unique opportunity to study the mechanism of topoisomerase II regulation of cohesin function. Role of HCP-1 and HCP-2 in cell cycle regulation in response to stress: In collaboration with the lab of Dr. Pamela Padilla, we found that the gene HCP-1 and HCP-2 interact with the spindle assembly checkpoint differently. HCP-1 is the likely ortholog of CENP-F in C. elegans and HCP-2 is 54% similar to HCP-1. Prior work demonstrated that HCP-1 and HCP-2 are synthetic lethal. We found that HCP-1 and HCP-2 have distinct phenotypes when each is separately removed via RNAi or genetic mutation suggesting that each gene performs other functions in addition to their common function. We are currently investigating the unique functions of both HCP-1 and HCP-2.

Daniel G. Remick, M.D.

The laboratory focuses on investigating the inflammatory response with particular emphasis on soluble mediators of inflammation, the cytokines. We are attempting to determine how the inflammatory response results in tissue/organ injury and death. To achieve this goal the laboratory uses a variety of methods ranging from whole animal models to isolated cells with reporter gene constructs. The primary theme which ties together all of the projects is the careful measurement of cytokines. Cytokines are peptide mediators of the inflammatory response which represent critical components. They have been successfully modulated to improve health in patients with severe diseases. One of the projects in the lab uses an animal model of sepsis. The primary push is to understand the immunopathology of sepsis, determine why organs fail and why mice die. Another project looks at how oxidants regulate chemokine expression. The third project examines the immunopathology of a novel model of murine asthma. For this model we immunize and challenge mice with a house dust extract which contains high levels of cockroach allergens. The ultimate focus of the lab is to understand the reaction to inflammation so that it may be modulated to improve health outcomes.
This lab investigates the molecular and genetic alterations that are important early in human breast carcinogenesis. Our overall goal is to identify the abnormalities characterizing early cancer development, even before the tissue is histologically fully malignant. We hypothesize that these genetic abnormalities are biologically meaningful and clinically relevant. In testing this hypothesis, we (and others) have shown that cancer-related abnormalities can be present in hyperplastic lesions and even in histologically normal epithelium. We study primary human tissues, and we ask questions and employ techniques suitable to that material, including laser capture microdissection, loss of heterozygosity and copy number alteration, mRNA and miRNA expression [measured by microarray and quantitative PCR], and immunohistochemistry. Since we attempt comprehensive genetic analyses of the data, the work is multidisciplinary, and collaborations with pathologists, geneticists, surgeons and bioinformaticians and biostatisticians are crucial. In addition, we have projects ongoing with organizations both inside and outside BUMC, including the Framingham Heart Study and the Nurses’ Health Study-Benign Breast Disease Substudy. Identifying and understanding the landscape of molecular and genetic abnormalities in premalignant and histologically normal tissue should generate novel markers of breast cancer risk, uncover mechanisms implicated early in tumorigenesis, and identify new targets for cancer prevention and treatment.

Avrum Spira, M.D.

Our laboratory research interests focus on applying high-throughput genomic and bioinformatics tools to the translational study of lung cancer and Chronic Obstructive Lung Disease (COPD). The primary research focus of our lab is to determine how cigarette smoking affects intra-thoracic (lobar bronchi) and extra-thoracic (mouth and nasal) airway epithelial cell gene expression and to use this information to develop a non-invasive genomic biomarker for lung cancer that can identify that subset of smokers who have, or are at risk for developing, lung cancer. Our lab has also begun to explore how this molecular “field of injury” in airway epithelium reflects information about the perturbation of specific oncogenic pathways within an individual, potentially allowing personalized genomic approaches to lung cancer chemoprophylaxis and therapy. This airway “field of injury” concept is also being extended to explore the molecular pathways that contribute to the pathogenesis of Chronic Obstructive Lung Disease, as well as identify non-invasive measures of the biological response to tobacco exposure that can be applied to large-scale population studies as part of the NIH/NIEHS Genes and Environment Initiative. Additionally, our lab is interested in understanding the underlying mechanisms of smoking-related disease risk and is seeking to identify microRNA alterations and DNA polymorphisms that are associated with the gene-expression changes characterizing the airway field of injury. Please see our website at www.pulmonomics.org for additional details.

Martin Steffen, M.D., Ph.D.

My lab works on developing the tools of systems biology for mammalian cells. Currently we are emphasizing the technique of mass spectrometry. Using mass spec, one can currently identify a few thousand proteins in a single experiment, as well as many important post-translational modifications (PTMs). Our guiding biological focus is cancer biology, and our interests are both at the level of basic research and clinical application. Specifically, we wish to characterize proteomic differences (identities, amounts, PTMs, splice forms) between normal and diseased tissue. We will also examine blood samples from donors with and without cancer as part of an effort to identify proteins that behave as early indicators of tumor development. An area of increasing interest is differentially phosphorylated peptides in lung cancer and normal tissue. In collaboration with Victoria Herrera and Nelson Ruiz-Opazo, we are investigating vascular integrity in hypertensive, hyperlipidemic, stroke-prone rats. The strains studied range in stroke susceptibility from zero to 100%, however the susceptibility is not simply proportional to either the degree of hypertension or hyperlipidemia, or a simple combination. Remarkably, the stroke phenotype can be completely eliminated by a simple nutritional intervention, a reduction of salt intake by 42%, but only if implemented
during gestational and early developmental periods. Proteomic profiles of brain microvessels of young rats reveal many molecular changes prior to the onset of any symptoms. These observed changes suggest possible pathogenic mechanisms for stroke susceptibility, and will allow us in the future to explore targeted preventive therapies. Our efforts in bioinformatics revolve around network identification, and protein function prediction. We have developed an algorithm for automated modeling of pathways in yeast, based only on two-hybrid protein interaction and microarray data. No prior knowledge of the pathway is needed. We now wish to extend this method to mouse and human. Protein function predictions are based on the integration of multiple “orthogonal” datasets and efficient capture of known annotation information.

Sam Thiagalingam, Ph.D.

Elucidation of the molecular basis of cancer metastasis and discovery of biomarkers for diagnosis, prognosis and therapy of cancer and psychiatric disorders. Our major research focus is on the use cancer genomics, employing primarily breast and colon cancers as model systems, to shed light on genomic instability, genetic and epigenetic aberrations and metastasis of cancer. We hope to elucidate the molecular basis of the multi-step cancer progression through these studies. Furthermore, we have also recently become interested in the role of epigenetics in the pathogenesis of major psychiatric disorders such as schizophrenia (SCZ) and bipolar disorder (BD). Our pioneering studies analysing the LOH frequencies of colon cancer showed that SMAD4 is the major target tumor suppressor gene localized to the minimally lost region on chromosome 18q. Subsequent studies have validated these observations in tumor analyses and from the comparative analysis of mouse models. As a follow up to these observations, based on our preliminary studies, we plan to test the hypothesis that the direct/indirect inactivation of Smad4 is a major switch allowing the conversion of benign tumors to the metastatic form during colon cancer progression. Except for the elucidation of an association between genetic alterations in the SMAD4 gene and gastrointestinal and pancreatic cancers, the nature and contributions of the other SMAD gene alterations in cancers is largely unknown. Therefore, we developed a novel technique known as Targeted Expressed Gene Display (TEGD) to survey various SMAD genes for differential expression. The loss of SMAD8 expression in multiple types of cancers, including 31% of both breast and colon cancers directly correlated with epigenetic silencing by DNA hypermethylation. We are in the process of investigating the temporal relationship between epigenetic inactivation of the SMAD8 gene and the stage(s) of breast cancer and are planning to determine the identities and roles of differentially regulated genes due to defective Smad8 signaling that mediate genesis and metastasis of breast cancer. We have also continued to maintain an interest in understanding the connection between genomic instability and cancer at the molecular level. It has been universally believed that defective spindle assembly checkpoint (SAC) causes aneuploidy. Interestingly, our studies uncovered a novel apoptotic checkpoint pathway regulated by the kinetochore proteins. We plan to continue these studies by performing a detailed analysis of the roles of individual kinetochore proteins in the maintenance of genomic stability. Our studies involving genetic and epigenetic analysis of lung cancer and the examination of the literature in the cancer field have enabled us to propose an academically simplified scheme to explain the complexity in cancer progression as a process that consists of a series of a cascade of interconnected functional sub-network modules of various alterations in a multi-modular molecular network (MMMN) encompassing multiple targets within each module. Our long-term goal is to contribute to the elucidation of the multi-modular molecular network (MMMN) cancer progression models as the road map to dissect the complexity inherent to cancer. Currently, we are in the process of using breast cancer as a prototype to perform proof of principle analyses to construct a MMMN cancer progression model. The fact that genetic makeup alone cannot explain the molecular basis of major psychiatric disorders such as SCZ and BD was instrumental for us to direct our attention to epigenetic alterations as the major cause of pathogenesis. Our studies showed that both hyper- as well as hypo-promoter DNA methylation changes of the genes RELN and MB-COMT respectively play...
critical roles in defining their altered functionality in major psychiatric disorders, SCZ and BD. Therefore, because of the possibility of gene-environment interactions mediated epigenetic modulation of gene function, we plan to extend these initial observations to establish a logical relationship between epigenetic DNA methylation changes and schizophrenia and bipolar disorder by analyzing candidate genes and a wide spectrum of genes.

Cyrus Vaziri, Ph.D.

Our broad long-term goal is to understand how mammalian cells maintain ordered control of DNA replication during normal passage through an unperturbed cell cycle, and in response to genotoxins (DNA-damaging agents). DNA synthesis is a fundamental process for normal growth and development. Accurate replication of DNA is crucial for maintenance of genomic stability. Many cancers display defects in regulation of DNA synthesis and it is important to understand the molecular basis for aberrant DNA replication in tumors. Moreover, since many chemotherapies specifically target cells in S-phase, a more detailed understanding of DNA replication could allow the rational design of novel cancer therapeutics. Our lab focuses on three main aspects of DNA replication control: I. The S-phase checkpoint, II. Trans-Lesion Synthesis (TLS) and III. Re-replication, as described below.

I. Molecular Basis of the S-phase Checkpoint: ‘Checkpoints’ are signal transduction pathways that respond to damaged DNA by exerting negative controls over cell cycle progression. The cell cycle delays triggered by checkpoints integrate DNA repair with cell cycle progression, thereby maintaining genomic stability. There is good evidence that cell cycle checkpoints are important tumor-suppressive mechanisms that protect against cancer. The protein kinase Chk1 mediates an S-phase checkpoint signaling pathway that inhibits the initiation step of DNA synthesis. A major goal of our laboratory is to identify Chk1 targets that mediate the S-phase checkpoint. Our analysis of known replication proteins has identified the essential DNA replication factor Cdc45 as a target of Chk1 signaling. Studies are underway to elucidate the mechanism(s) that mediate negative regulation of Cdc45 by Chk1.

II. Trans-Lesion Synthesis (TLS) DNA Polymerases and the S-phase Checkpoint: ‘Trans-Lesion Synthesis’ (TLS) polymerases synthesize DNA with low fidelity on undamaged DNA templates, yet replicate damaged DNA with relatively high accuracy. We have found that a specific TLS polymerase, DNA Polymerase kappa (Polκ), is recruited to sites of genotoxin-induced replication fork stalling. Polκ-mediated bypass of damaged DNA enables preserves the replication fork and allows continuation of DNA synthesis. It is likely that Polκ plays a role in preventing cancers induced by exposure to environmental genotoxins. We demonstrated recently that appropriate Polκ function requires an E3 ubiquitin ligase termed Rad18. The mechanisms that regulate Rad18 in response to DNA damage are unknown. We hypothesize that Rad18 is a direct or indirect target of Chk1 and that Rad18 regulation by Chk1 is a key step in TLS. Therefore, experiments are underway to determine the mechanisms by which Chk1 signaling regulates Rad18.

III. A Novel DNA ‘Re-replication Checkpoint’: To maintain genomic stability, it is important that each chromosome undergoes only a single round of DNA replication per cell cycle. Potentially, over-replication of the genome could lead to gene amplification, one of the hallmarks of cancer cells. We discovered a novel checkpoint mechanism that restricts DNA synthesis to ‘once-per-cell cycle’ in primary untransformed cells, but not in many cancer cell lines. Experiments are underway to identify the mechanism(s) that mediate the re-replication checkpoint and likely contribute to tumor suppression.

IMMUNOLOGY TRAINING PROGRAM

David M. Center, M.D.

Our laboratory studies the function of human CD4 and regulation of the cell cycle in T cells. Regarding the function of CD4, they laboratory discovered, cloned and characterized most of the biologic functions of Interleukin (IL-16). Since IL-16 utilizes CD4 as its receptor the discovery of IL-16 has led to a series of studies related to the
functions of CD4 itself that are independent of MHCII restricted accessory activity. Using functional and microarray analyses they are exploring the signal transduction pathways associated with CD4 activation by IL16 and the mechanisms of CD4's functions as a chemotactic factor and growth factor receptor. Most recently this work has led to the discovery that IL-16-CD4 interaction results in selective chemotaxis of CD4+CD25+ Regulatory T cells; and that IL-16 is sufficient to induce differentiation of CD4+CD25lo T cells to express FoxP3 and acquire regulatory T cell function. One major part of the laboratory looks at the role IL-16 plays in development of regulatory T cells using knock-out and over expressing mice and animal models of Th1 and Th2 driven inflammation, including a model of airway inflammation. The second focus of his laboratory relates to the study of a nuclear protein complex that targets histone deacetylases to specific transcription factors and represses transcription of a select family of genes involved in maintenance of T cell quiescence. The complex is regulated by T cell activation at the level of the scaffold protein as the enzymatically active components do not change with cell activation or during the cell cycle. Mutations and deletions in the scaffold protein, the precursor for IL-16 are common in T cell lymphomas and replacement of nuclear expression of the normal protein results in return to a normal cell cycle profile and loss of malignant characteristics. The current studies are exploring the mechanisms of regulation of Pro-IL-16 transcription itself as a regulatory element in T cell cycle and its role in the development of anergy. These studies include use of knock out and transgenic mice to study cell cycle related genes that lead to CD4+ T cell malignancies.

Ronald B. Corley, Ph.D.

My laboratory is interested in the relationship between innate and adaptive immunity, and how the two types of immune responses affect the other. A major interest has been the innate role of IgM antibodies, which have commonly been considered to be exclusively a part of the adaptive immune system. We have demonstrated an "adjuvant" role for IgM, and characterized some of the mechanisms by which IgM enhances adaptive immunity. Related to this, we have been investigating the effect injury has on adaptive humoral responses. Following several types of injury, the humoral immune system is often compromised, but the mechanisms are poorly understood. We are investigating parameters related to homing and longevity of memory B cells and plasma cells, functions of antibodies related to post-translational modifications and changes in the cytokine milieu that affects B cell function. Another interest of the laboratory, undertaken in collaboration with Ann Marshak-Rothstein and Greg Viglianti of this department, involves studies of the role that Toll-like receptors (TLRs) play in the activation of autoimmune B lymphocytes. We are interested in understanding how, and what intracellular compartment(s), ligands for intracellular TLRs, especially TLR9, intersect with these receptors in B cells, and the consequences of these interactions for the fate of the B cell and for B cell functions. Collaborative plans to initiate studies on innate and adaptive immune responses to filoviruses and candidate vaccines and therapeutics are underway with new faculty in the department.

William Cruikshank, Ph.D.

For many years my research has centered around the identification, biochemical characterization, cloning, and process of synthesis and secretion of Interleukin-16 (IL-16). Recently we have obtained data indicating that IL-16 may function in vivo primarily as an immunomodulator. Along those lines, my research is currently focused on the potential role of IL-16, as it relates to several different disease states. IL-16 has direct in vitro bioactivities; induction of CD4+ cell migration, induction of CD4+ lymphocyte cell cycle progression, and prevention of cellular apoptosis which are consistent with proinflammatory cytokines. As such IL-16 has been identified in association with the onset of several inflammatory conditions characterized by the infiltrate of CD4+ cells, such as asthma, sarcoidosis, multiple sclerosis, diabetes and Crohn's disease. During the next several years these studies will continue, with particular emphasis on animal models to establish the role of IL-16 in asthma, diabetes and rheumatoid arthritis. In addition to the induction of CD4+ cell migration, IL-16 also functions to induce cell cycle progression in peripheral CD4+ T cells. In vitro studies have demonstrated that IL-16 can function as
a competence growth factor, as stimulation induces expression of the IL-2 receptor and primes the cells for IL-2-induced proliferation. In T cell lines or transformed T cells IL-16 can function as a complete growth factor. Along those lines systemic levels of IL-16 have been reported to be elevated in individuals with T cell cancers such as Sezary and Mycosis fungoides. We are now also investigating the potential role of IL-16 to contribute to dysregulated T cell growth in these diseases.

Douglas V. Faller, Ph.D., M.D.

A major focus of our laboratory is the study of the basic molecular and cellular biology of virus- and oncogene-transformed cells and tumors. We are involved in determining the mechanisms by which viruses and their oncogenes cause tumors, through defining the ways in which oncogenes control host cell gene expression. A special interest of this laboratory involves viral regulation those cellular genes encoding proto-oncogenic molecules and cytokines. We are analyzing the molecular mechanisms by which oncogene-transformed cells become autonomous of growth factor requirements. This work involves the elucidation of growth-factor signal transduction pathways in normal and transformed mesenchymal and lymphoid cells, and study of the ways in which this signaling pathway is disrupted or circumvented in tumor cells. This work has resulted in new information regarding the transduction of growth factor signals by second messenger systems in both normal and transformed cells. My laboratory also studies the role of oncogenes in programmed cell death. A related area of his research is the interaction of retroviruses and the tumors they induce with cellular immune defense mechanisms. The means by which virus- or tumor-specific cytotoxic T lymphocytes, natural killer cells and monocytes recognize and destroy infected cells and tumors is under investigation, as are the molecular mechanisms by which tumors escape from immune surveillance. The mechanisms of aberrant control of Class I Major Histocompatibility Antigen gene expression in oncogene-transformed cells, virus-infected cells and naturally-occurring tumors are being determined. A new transactivation property of murine leukemia viruses has been elucidated, which controls the expression of genes in the host cell important to the leukemogenic process. My laboratory also has a translational research program which develops molecular cancer therapeutics derived from this basic research, and tests them in clinical trials.
Caroline A. Genco, Ph.D.

Dr. Genco's laboratory is interested in the characterization of bacterial virulence factors produced by the mucosal pathogens Neisseria gonorrhoeae, N. meningitidis, and Porphyromonas gingivalis, and the underlying molecular mechanisms by which these factors enable these organisms to cause disease. Dr. Genco’s laboratory is interested in how virulence genes are expressed in vivo and the role of iron in gene regulation in vivo. Iron starvation is used as a signal by many pathogens that they are in a host environment resulting in the expression of virulence factors that are transcriptionally regulated by iron through the ferric uptake regulator protein, Fur. Dr. Genco’s laboratory has defined the Fur-regulon in N. gonorrhoeae, N. meningitidis and in P. gingivalis and has established that Fur controls the expression of numerous genes that are required for the virulence of these organisms. Her laboratory as recently identified a novel mechanism for Fur-mediated regulation through small regulatory RNAs. Current studies are aimed at examining the regulation and expression of Fur-regulated genes in vitro, and in vivo directly in clinical specimens. Several different model systems are used to examine the interactions of bacteria with the host. These include animal models for gonococcal infection and P. gingivalis oral infection. Her laboratory also utilizes epithelial and endothelial cells to study the interactions of N. gonorrhoeae and P. gingivalis with host cells, which are permissive for these pathogens. Currently the laboratory is examining the interactions of N. gonorrhoeae with endocervical, ectocervical and vaginal cell lines. Using these cell lines they have demonstrated distinct proinflammatory responses in different compartments of the female lower genital tract. Furthermore she has also utilized these cells to demonstrate that infection with N. gonorrhoeae inhibits the apoptotic response of these cells. Thus N. gonorrhoeae may establish infection in women by inhibiting the apoptotic response to infection, thereby resisting killing from both the host cell and the innate immune response. Furthermore, prolonged survival of the host cell potentially allows the bacteria to successfully invade cervical tissue, eventually transcending to the upper genital tract. An exciting area of new work in Dr. Genco’s laboratory is examining the specific cellular and molecular mechanisms by which infectious agents contribute to chronic inflammation and specifically the role of the innate immune response in atherosclerosis. Dr. Genco has established that P. gingivalis accelerates atherosclerotic plaque accumulation and that is mediated by innate immune recognition to invasive bacterial infection. Her laboratory has established that P. gingivalis infection and inflammation in endothelial cells is mediated through fimbriae signaling through Toll-like receptors. Finally her laboratory has established that TLR2 plays a critical role in the atherosclerotic inflammatory response that is independent of dietary lipids. Current studies are focused on other chronic infections such as that caused by the respiratory pathogen Chlamydia pneumoniae. These studies employ in vitro model systems for platelet, endothelial cells, and macrophages. The common theme of these studies is to examine the role of infection and the innate immune response in early events associated with atherosclerosis in well-defined in vitro and in vivo systems.


Inflammation has a profound effect on the connective tissue, causing its resorption and limiting repair of damaged structures. I am interested in how cytokines induce cell death including the activation of transcription factors that globally affect pro-apoptotic gene expression. These studies involve the use of specific inhibitors of apoptosis and cytokines as well as mice with targeted genetic deletions to study their functional role in repair of injured connective tissue and bone. A pathology where this dysregulation may come into play is diabetes mellitus in which the production of mediators that regulate inflammation is altered. Diabetes-associated cytokine dysregulation may represent a common link in a number of diabetic complications including retinopathy and impaired wound healing. A limited ability to repair lost tissue may also represent a mechanism for greater net loss of bone and connective tissue associated with diabetes-enhanced periodontal disease and impaired fracture healing in diabetics. My laboratory is
investigating mechanisms through which these processes are negatively impacted by diabetes via altered transcription factor activity and cytokine dysregulation.

**Adam Lerner, M.D.**

PDE project: PDE4B, a cAMP phosphodiesterase (PDE), is up-regulated in murine thymocytes undergoing apoptosis following in vivo crosslinking of CD3 (EMBO 1996). Given that chronic lymphocytic leukemia cells (CLL) undergo apoptosis following treatment with the non-specific PDE inhibitor theophylline, we tested whether PDE4 might be the physiologic target of theophylline. Inhibition of PDE4 with rolipram reproducibly induces CLL apoptosis (Blood 1998) by a mitochondrial pathway involving BAD and PP2A (Blood 2003). Interestingly, PDE4 inhibitors also activate EPAC, a cAMP-activated Rap1 GDP exchange factor that is not expressed in any other circulating hematopoietic cell (Blood 2004). PDE4 inhibitors confer their most dramatic apoptotic effects in conjunction with glucocorticoids. PDE4 inhibitor-mediated PKA activation augments glucocorticoid-induced GRE transactivation in primary human B-CLL cells and inhibition of PKA blocks glucocorticoid-mediated apoptosis in CLL (Biochem Pharmacol 2005). PDE4 inhibitors augment levels of glucocorticoid receptor transcript and protein in CLL cells but not in normal hematopoietic cells (Clin Cancer Res 2007). See our recent review of this field in Biochem. J. 393, 21–41 (2006).

AND-34 project: I cloned AND-34 in the same study of anti-CD3-mediated thymocyte apoptosis described above (EMBO 1996). AND-34 has an SH2 domain as well as a domain with homology to the cdc25 domain of ras-family GDP-exchange factors (GEFs). We identified a tyrosine phosphorylated protein associated with AND-34 as p130Cas, a focal adhesion adapter protein (J. Immunol. 1999). Over-expression of either AND-34 or p130Cas leads to antiestrogen resistance in breast cancer cells. AND-34 binds to p130Cas through its GEF-like domain (JBC 2000). Despite its carboxy-terminal domain with homology to cdc25, AND-34's principal biochemical activity is that of indirectly activating the GTPases Rac and Cdc42 (Cancer Res. 2003). AND-34 is expressed in B cells but not T cells and alters their motility and adhesion (J Immunol 2003). AND-34 over-expression leads to Rac activation as a result of its ability to activate PI3K (JBC 2000). Despite its carboxy-terminal domain with homology to cdc25, AND-34's principal biochemical activity is that of indirectly activating the GTPases Rac and Cdc42 (Cancer Res. 2003). AND-34 is expressed in B cells but not T cells and alters their motility and adhesion (J Immunol 2003). AND-34 over-expression leads to Rac activation as a result of its ability to activate PI3K (JBC 2000). Among three highly related gene family members in humans, only AND-34 induces anti-estrogen resistance and cyclin D1 promoter activation, while all three can activate Rac and Cdc42 (J Cell Physiol 2007).

**Ann Marshak-Rothstein, Ph.D.**

My laboratory is primarily interested in factors regulating T and B lymphocyte activation, function, longevity, and apoptosis, especially in animal models of systemic autoimmune disease. We have found that those autoantigens or autoantigen complexes capable of co-engaging the B cell antigen receptor and a member of the Toll-like receptor family can efficiently activate autoreactive B cells. The main interest of the lab is to further characterize the autoantigens involved in this mode of activation scheme and to further delineate the unique functional properties of B cells stimulated by BCR/TLR coengagement. Other projects in the lab have focused on the lymphocyte abnormalities associated with the lpr and gld mutations, lesions that result in the failure to functionally express the Fas and Fas-ligand molecules, respectively. Specific ongoing projects include: (1) B cell stimulatory activity of defined dsDNA fragment immune complexes; (2) functional properties of autoreactive B cells activated by TLR/BCR co-engagement; (3) effects of TLR activation on BCR-mediated signaling cascades; (4) effects of TLR inhibitors on the development and progression of systemic autoimmune disease; (5) the role of Fas/FasL interactions on the in vivo persistence of tumor specific T cells; (6) pro-inflammatory and anti-inflammatory aspects of soluble and membrane-bound FasL; and (7) inducible models of systemic autoimmune disease.

**John R. Murphy, Ph.D.**

Our research is focused in four areas: structure and genetic analysis of the diphtheria toxin repressor (DtxR), molecular mechanisms of diphtheria toxin catalytic domain delivery into the eukaryotic cell cytosol, diphtheria toxin-based cytokine fusion proteins, and structure function analysis of interleukin 7. The regulation of diphtheria tox gene expression is controlled by DtxR, an iron-activated repressor which also controls the
expression of a constellation of iron-sensitive genes. The dtXR gene has been cloned and DtxR has been overexpressed in recombinant *Escherichia coli*. The X-ray crystal structure of both the apo- and metal ion activated forms of DtxR, and of the ternary complex between DtxR/Ni2+/tox operator DNA have been partially solved. We have developed a positive genetic selection system for the direct cloning of both dtXR alleles and DtxR target operator sequences. Using this system, we have isolated the first positive mutants of DtxR. Since DtxR and its homologues control the expression of virulence factors in many important Gram positive pathogens, the positive dominant mutants suggest that DtxR may be a target for the development of a new class of “antimicrobial” that would phenotypically convert pathogenic strains to their non-pathogenic counterparts. We are also focused on the structure/function analysis of the diphtheria toxin molecule. Diphtheria toxin contains at least three functional domains: ADP-ribosyltransferase, membrane translocation domain, and a eukaryotic cell receptor binding domain. Biochemical genetic analysis has shown that each domain must function in an ordered and sequential fashion for the toxin molecule to bind to its receptor on the surface of a sensitive eukaryotic cell, be internalized, and facilitate the delivery of the ADP-ribosyltransferase to the cytosol. To further probe the structural requirements for ADP-ribosyltransferase entry into the cytosol, we have designed a family of “new” toxins by receptor binding domain substitution. The first of these fusion toxins has been approved by the Food and Drug Administration for the treatment of cutaneous T cell lymphoma, and these fusion protein toxins are currently being used to probe the molecular mechanisms by which the catalytic domain of the toxin is delivered from the early endosome to the cytosol of target cells.

**Barbara S. Nikolajczyk, Ph.D.**

My lab is interested in understanding immune system gene regulation in the physiological context of chromatin. We are focusing on two types of genes. Our long-term interest in immunoglobulin genes focuses on regulation of both the heavy chain (μ) and light chain (κ) loci. Regions originally identified as transcriptional enhancers in these genes play key roles in activating Igμ and κ for recombination during B cell development. The Igμ intronic enhancer is activated in the earliest B cell precursors, while Igκ enhancers are gradually activated later in B cell development. The most likely candidates for activating both genes are sequence-specific DNA-binding transcription factors. Because an overlapping set of transcription factors activates both enhancers, it is unclear how temporal differences in Ig enhancer activation are established. Our goal is to tease out differences in chromatin accessibility and protein association of Igμ and κ enhancers towards understanding tissue-specific gene regulation. The second family of genes we are studying are the cytokine genes. Specifically, we have shown that the cytokine IL-1β is activated from a “poised promoter architecture” characterized by constitutively accessible chromatin and constitutive transcription factor association. We have further shown that IL-1β transcription is inducibly activated in monocytes using a mechanism unique among cytokines: cellular stimulation results in post-translational modification of a constitutively associated transcription factor, leading to recruitment of additional factors including RNA polymerase II. The net result is mRNA production. We are further defining mechanistic details of this pathway and are investigating how IL-1β is activated from a inaccessible gene structure in B cells. Finally, in more clinically relevant work, our newest studies suggest that diabetic patients, who most often succumb to inflammatory disease, may utilize fundamentally unique mechanisms to activate IL-1β production from hematopoietic cells. These studies may suggest targets for alleviating the over-production of pro-inflammatory cytokines generally associated with the devastating effects of chronic glucose dysregulation in patients.

**David C. Seldin, M.D., Ph.D.**

My laboratory has two major areas of research on the molecular basis of human disease. One is on kinase pathways in tumorigenesis: we study the regulatory serine-threonine kinase protein kinase CK2 (casein kinase II), a kinase that is upregulated in leukemic cells and other tumors. We have shown that overexpression of CK2 in transgenic mice
leads to tumors in tissues (lymph node, mammary gland) where it is mis-expressed, proving that CK2 has the potential to serve as an oncogene. Ongoing research in the laboratory is aimed at identifying the targets of CK2 in lymphomagenesis and breast cancer. Recent work suggests that the stability/proteosome susceptibility of critical transcription factors, including the myc oncoprotein, is regulated by CK2 phosphorylation. We have also linked CK2 activity to the Wnt pathway, a signaling pathway whose elements include the adenomatous polyposis coli gene product APC and beta-catenin; one or the other of these is mutated in many human cancers. CK2 stabilizes beta-catenin, augmenting its activity as a transcriptional co-factor for TCF and LEF, and promoting expression of myc and cyclin D1. To study the essential roles of CK2 in cells, we have knocked out the catalytic subunits individually be gene targeting, and shown that the alpha subunit is required for heart development, and the alpha' subunit is required for male germ cell development. The other major area of research in the laboratory are the systemic amyloidoses. These are a set of diseases of protein misfolding in which polymers of protein form fibrils that are deposited in tissues, leading to organ failure and death. Of particular interest is AL or primary amyloidosis, which is due to deposition of clonal immunoglobulin light chains. We are studying the sequence and structure of these light chains and developing animal models of disease, in the hopes of developing targeted small molecule or immunotherapies to complement or replace the role of chemotherapy in treatment of the disease.

Jacqueline Sharon, Ph.D.

The current research goals of the laboratory are to develop immunotherapies and elucidate the mechanisms of protective immunity against inhalational tularemia, an acute lethal infectious disease. Tularemia is caused by the gram-negative intracellular bacterium Francisella tularensis, which has been classified as a Category A Select Agent – a likely bioweapon. The high virulence of F. tularensis and the threat of engineered antibiotic resistant variants warrant the development of new therapies to combat this disease. We are developing antibody-based therapies for post-exposure treatment of tularemia and testing them in an inhalational mouse model of tularemia.

David H. Sherr, Ph.D.

The laboratory employs state-of-the-art cellular and molecular technologies to research three specific areas of basic and applied science: 1) mechanisms through which environmental chemicals suppress the immune system ( the “A” Apoptosis team ), 2) molecular signaling leading to environmental carcinogen-induced and spontaneous breast cancers ( the “B” Breast Cancer team, 3) development of vaccines for the treatment of cancer and primary amyloidosis ( the “C” Cancer/Amyloid Immunotherapy team ). The common element in these 3 disciplines is the involvement of an environmental chemical receptor, the aryl hydrocarbon receptor (AhR), in the suppression of the immune system and in maintaining tumor cell growth.

Gail E. Sonenshein, Ph.D.

Major interests of my laboratory center on the Rel/NF-kappaB family of transcription factors and on the c-myc oncogene, which play pivotal roles in the control of cell proliferation, apoptosis and neoplastic transformation. Research efforts are divided into two projects: 1) Rel/NF-kappaB family activity. This lab has made several key discoveries on the roles of the Rel family of transcription factors. Rel factors were shown to regulate c-Myc gene transcription, through two functional elements. Furthermore, Rel factors were found to protect various cancer cells from apoptosis, including B cell lymphomas and breast cancer cells. Studies are in progress to characterize the mechanism by which various agents affect Rel family activity, such as anti-Ig treatment, CD40L, and TGF-beta 1, and their roles in immune tolerance and cancer. 2) c-Myc function. The c-Myc protein is believed to function both as a transcriptional activator, as well as a repressor. Max protein has been shown to play a central role facilitating c-Myc binding to an E-box, promoting its ability to transactivate. A novel mechanism whereby c-Myc inhibits transcription of genes that contain an initiator (Inr) element has been discovered, and our recent data suggests Max is also involved in this repression. Experiments to further elucidate this mechanism are in progress.
Gregory A. Viglianti, Ph.D.
Worldwide, heterosexual transmission accounts for most HIV-1 infections. Clearly, controlling heterosexual transmission of HIV-1 would be a significant step toward eliminating this global epidemic. To achieve this goal, it will be important to delineate the cellular and molecular events that affect virus transmission. Although both inflammatory and ulcerative sexually transmitted infections (STIs) enhance sexual transmission of HIV-1, the underlying mechanisms leading to this enhancement have not been fully elucidated. Enhanced susceptibility to infection may be due to a number of factors, including the disruption of the integrity of the cervicovaginal epithelial barrier, recruitment of HIV-1 target cells such as Langerhans/dendritic cells (LC/DC), macrophages (MØ), and T lymphocytes to sites of inflammation, and direct activation of target cells by STIs. A common feature of STI pathogens is that they encode ligands for members of the Toll-like receptor (TLR) family of pattern recognition receptors and these ligand-activated TLRs can both activate HIV-1 target cells and induce local inflammatory responses. Ligand-activated nuclear receptors (NR), including peroxisome proliferator activated receptor (PPAR), liver X receptor (LXR), glucocorticoid receptor (GR), and estrogen receptors (ER) are potent inhibitors of TLR-induced inflammatory gene expression in MØ, LC/DC, and epithelial cells. In addition, retinoic acid receptor (RAR) and PPAR ligands have been shown to repress HIV-1 gene expression while estrogen has been shown to block vaginal transmission of SIVmac. A goal of our laboratory is to determine the role of TLR-signaling in augmenting HIV-1 infection of target cells that are found in the cervicovaginal mucosae. Our major, and long-term goal is to examine the potential role of ligand-activated NR as inhibitors of HIV-1 transmission. We hypothesize that ligand-activated NR act by: 1) directly repressing HIV-1 transcription, and 2) by limiting the TLR-induced inflammatory microenvironment that favors HIV-1 replication. We are currently focusing are efforts to 1) evaluate the impact of NR/TLR crosstalk on HIV-1 replication and inflammatory gene expression in primary LC, DC, and MØ, 2) examine the effects of NR/TLR crosstalk on HIV-1 infection of target cells and inflammation in vaginal and cervical tissue explants and in an organotypic model of the human vagina, and 3) determine the molecular mechanism(s) of TLR-modulated HIV-1 transcription and how it is regulated by NR signaling.

Lee M. Wetzler, M.D.
Dr. Wetzler’s laboratory investigates innate and adaptive immunity and microbial pathogenesis, especially in regards to vaccine development. One major aspect of this work centers on the pathogenic Neisseria, Neisseria gonorrhoeae and Neisseria meningitidis. He has found that the major outer membrane protein of these organisms, the Neisserial porin PorB, can work as an immune adjuvant due to it recognition by the pattern recognition receptor TOLL-like receptor (TLR) 2. He has found that antigen presenting cells, including B cells, dendritic cells and macrophages, are activated by PorB in a TLR2 , TLR1 and MyD88 dependent manner, inducting upregulation of class II MHC, costimulatory molecule CD86 and other markers of activation. Moreover, MAPK signaling events are required for the upregulation of the expression of these markers, as well as production of pro-inflammatory cytokines. Moreover, using an in vivo peritoneal mouse model of inflammation, we have shown that both PorB and intact N. meningitidis induce a significant cellular influx and pro-inflammatory cytokine production, which is also TLR2 dependent. However, we also found that mast cells are activated during this process, which may be in a TLR2 independent manner, along with a significant influx of eosinophils, indicative of induction of a TH2 type cellular response. Studies are continuing to investigate the mechanisms of these phenomena. We are also investigating the use of this TLR2 ligand, PorB, as a vaccine adjuvant using classic antigens like OVA and more relevant antigens like bacterial capsular polysaccharide. This work has also been extended to investigate the adjuvant activity and mechanism of immune stimulation of the B subunit of cholera toxin. We have found that CTB induces antigen presenting cell stimulation via the lipid raft ganglioside GM1 via induction of a cell-signaling program ending in NF-kB and CREB activation and gene transcription. This work is still on going. Finally, a new major thrust of the Wetzler lab is investigating
the immune response and natural history of Francisella tularensis pulmonary infection in mice and using this data to aid in developing vaccines towards this potential bio-terrorist agent. We have found that using PorB as an adjuvant and Francisella LPS as an atigue, we can enhance protection in these mice, which is likely due to induction of antibodies and improved immunity (potentially both innate and adaptive immunity. It appears that induction of IL-1beta may be more associated with survival bith during natural infection and after vaccination, while IL-6 and IL-17 may have the opposite effect, being more associated with death after pulmonary infection. Finally we have recently found that induction of bronchial associated lymphoid tissue (BALT) after vaccainion also appears to be associated with protection. These IBALT structures are long lasting and may be due to persistent antigen stimulation, which we are currently investigating.

MEDICAL NUTRITION SCIENCES

Susan K. Fried, Ph.D., Director

Adipocytes are highly specialized cells that store and release energy according to the needs of the organism. They are also now recognized as endocrine cells that synthesis and release hormones in proportion to energy storage and changes in nutritional status (e.g. obesity/overfeeding, fasting and refeeding). My research focuses on the mechanism regulating adipocyte metabolism and endocrine function. Because adipocytes from different regions of the body display distinct metabolic properties, a major goal of my laboratory is to understand the molecular mechanisms underlying regional differences in adipocyte metabolic and endocrine function. The long-term goal is to understand why obesity and an upper body fat distribution are associated with metabolic abnormalities such as type 2 diabetes and atherosclerosis, and why a lower body adipose tissue (femoral-gluteal) typical of women is actually protective. My lab’s recent work addresses the regulation of leptin, an adipocyte hormone that regulates metabolism and appetite and is centrally involved in the regulation of body weight. Our current studies focus on the regulation of leptin translation. We have demonstrated that elements within the 5-UTR of leptin stimulates, while the 3-UTR inhibits translation. The insulin stimulation of leptin mRNA translation requires both UTRs. Current studies are investigating the cis elements and trans acting factors that mediate the nutritional regulation of leptin mRNA translation. Another line of investigation is directed at understanding the molecular basis of sex and depot differences in adipocyte and adipose tissue function. Specifically, we are using microarrays to identify the primary targets of glucocorticoid in human adipose tissues in vivo and in vitro, and assessing the functional roles of these genes. We are also initiating studies of estrogen action in human adipose tissue.

Caroline M. Apovian, M.D., F.A.C.P., F.A.C.N.

Dr. Apovian’s ongoing research includes several areas of weight loss, weight maintenance, and the molecular effects of weight change. In conjunction with the Department of Cardiology, she is looking at weight loss and its effects on endothelial cell function, adipose cell metabolism and inflammation. Dr. Apovian is also researching the bariatric surgery population in the Nutrition and Weight Management Center. In collaboration with Beth Israel Deaconess Medical Center, she is studying quality of life before and after weight loss surgery. She is also looking at the effects of bariatric surgery on adipose tissue and the effects of a novel meal replacement program on body composition. Dr. Apovian’s research also includes novel pharmacotherapeutic antiobesity agents, such as leptin. She is currently completing a study designed to quantify the relative inflammatory burden and cytokine expression of adipose cells in human fat stores in obese participants after weight loss treatment with low-fat vs. low-carbohydrate diets.
**Shalender Bhasin, M.D.**

Male and female reproductive endocrinology, sexual dysfunction in men and women; testosterone deficiency and body composition; erectile dysfunction.

**Barbara Corkey, Ph.D.**

The main goal of work in the Corkey laboratory is to determine how fuels generate the signals to communicate among different organs in the body to modulate hormone and adipokine exocytosis, electrical activity, metabolism and gene expression. It involves assessment of the influence of metabolites and mitochondrial energy state on intracellular signal transduction in adipocytes, pancreatic β-cells, liver and human fibroblasts. Recent emphasis has been on ion handling, respiration, the signaling consequences of cellular energy state, the influence of fatty acids on protein kinases and the role of fatty acids and long acyl CoA on signal transduction. Unique resources of the laboratory include imaging, fluorescence and amperometric techniques to measure responsiveness of living cells to various treatments and stimuli. Work is done in collaboration with scientists at Boston University School of Medicine, the BioCurrents Laboratory of the Marine Biological Institute, the Karolinska Institute, the Universities of Chicago, Montreal and Pennsylvania, and the Hamner Institutes for Health Sciences.

**Stephen R. Farmer, Ph.D.**

The overall focus of my laboratory is to understand the molecular mechanisms controlling the formation and function of adipocytes with a focus on identifying the signaling pathways and transcription factors that regulate adipogenesis. Projects presently under investigation include the role of PPARgamma (peroxisome proliferator-activated receptor gamma) and the C/EBPs (CCAAT/enhancer binding proteins) in regulating the sequential expression of the adipogenic factors that control the differentiation of preadipocytes into adipocytes and expression of genes that control various adipocyte functions including insulin-dependent glucose uptake and production of adiponectin. We are also investigating the mechanisms by which the adipocyte responds to changes in energy balance by focusing on role of the NAD-dependent deacetylase, SIRT1, and the hypoxia-induced factor-1 alpha (HIF-1alpha) in regulating adipocyte gene expression.

**Wen Guo, Ph.D.**

Dr. Wen Guo belongs to the Muscle and Aging Unit (MAU) of the Endocrinology section of Department of Medicine. The goal of our work is to improve human health through modification of fat tissue metabolic performance. The current research interests focus on adipose tissue function, muscle – fat cross communication, and how these can be causally related to cardiovascular risk. On-going studies include (1) premature atherogenesis caused by HIV protease inhibitor and adipose tissue lipolysis, (2) resistance to diet-induced obesity and atherogenesis caused by induction of muscle hypertrophy using myostatin inhibitors, (3) myokine effects on fat cell development, (4) impaired IGF signaling by fatty acid during myogenic differentiation, and HIV-related atrophy and myostatin inhibitors. We address these issues using both cultured cell models and animal models. We routinely culture myoblasts and adipose cell lines and primary human bone marrow mesenchymal stem cells, primary mouse adipocyte and preadipocytes, muscle fibers and satellite cells. The animal models we use for atherogenesis include mouse models deficient in apoE or LDLr as well as both that are also knockout of myostatin. Myostatin deficient mice are exceptionally lean with double muscle and hence are an excellent model for studying muscle hypertrophy and metabolic disease. In some cases, especially for the HIV-related projects, we also use primates as the disease model through collaboration with New England Primate Research Center. The techniques used in our research include both classic and modern tools of biochemistry, molecular biology, animal physiology, micro-surgery, pathology, magnetic imaging, indirect calorimetry, and many others.

**James A. Hamilton, Ph.D.**

Dr. Hamilton’s laboratory is developing and applying novel physical approaches to study of obesity, metabolic syndrome, and cardiovascular disease. 13C NMR methods pioneered in his laboratory have been used to describe the interactions of fatty acids and drugs with binding sites on albumin, and new studies are currently correlating important
details predicted by NMR with recent x-ray crystal structure. New fluorescence approaches have been developed to characterize the diffusion of fatty acids into adipocytes and evaluate the effects of drugs and inhibitors on fatty acid uptake. A newer focus of research is the application of magnetic resonance imaging (MRI) to examine fat tissue and atherosclerosis. These studies extend from animal model systems (mouse and rabbit) to humans. The work emphasizes interactions of different disciplines on translation of basic biophysics to human disease aspects. Our study of subjects with metabolic syndrome and obesity explores the hypothesis that a unifying feature of metabolic syndrome is enhanced deposition of lipids throughout the body outside of the normal adipose stores. These inappropriate stores include hepatocellular triglyceride, perivascular and pericardial triglyceride. MR imaging will identify and quantify site-specific abnormalities in obese patients such as cardiac functions. In our animal studies of atherosclerosis, imaging of live mice allows us to follow diseases and therapies in a single animal over a long period of time. A rabbit model of the acute event of atherosclerosis, plaque rupture and thrombosis is being studied to develop MRI for prediction of unstable and high risk plaques. In humans with advanced carotid atherosclerosis who are undergoing endarterectomy, we will use MRI to determine evidence of inflammation and plaque vulnerability and perform in vivo and ex vivo to enhance the application of MRI to carotid plaque characterization.

Michael F. Holick, PhD, MD

and his team of researchers continue to be leaders in the field of vitamin D, osteoporosis, metabolic bone disease, psoriasis and hair research. Dr. Holick’s work explores the nature of vitamin D deficiency and concludes it to be one of the most commonly unrecognized medical conditions, a condition that leaves millions at risk of developing not only osteoporosis and fractures but also numerous serious and often fatal diseases, including several common cancers, autoimmune diseases, infectious diseases and heart disease. Because the skin is an important source of vitamin D, a human skin equivalent and a liposomal model have been developed to mimic the photoproduction of vitamin D in human skin. Using these models systems, researchers demonstrated that during exposure to solar simulated-sunlight, a unique membrane-associated mechanism stabilizes the previtamin D$_3$ in a cis,cis-conformation and results in its rapid conversion to vitamin D$_3$. It has now been demonstrated that human skin also produces several photoproducts including tachysterol and lumisterol, which may have important biologic functions in the skin. Research is underway to further evaluate this. They have initiated a program to evaluate the effect of vitamin D deficiency in advancing colon tumor growth.

Konstantin V. Kandror, Ph.D.

Diabetes mellitus represents one of the major health threats to modern civilization, and its worldwide prevalence is increasing at an alarming rate. In diabetes, insulin cannot stimulate glucose entry into the cell, as it does in normal individuals. As a result, extra glucose stays in the blood and causes multiple health problems. As insulin-regulated glucose transport is the major molecular defect in diabetes, it represents the main focus of our lab. Insulin activates glucose uptake by translocating glucose transporter isoform 4 (Glut4) from its intracellular vesicular storage pool to the plasma membrane. This process, along with exocytosis of synaptic vesicles in neurons, insulin-containing granules in the pancreas, water channel-containing vesicles in the kidney, etc., represents an example of a widely spread type of the biological regulation via regulated exocytosis. Impaired translocation of Glut4-containing vesicles in diabetes may have two explanations. First, the molecular defect may lie in the signal transduction pathway that connects the insulin receptor in the plasma membrane and intracellular Glut4-vesicles. Second, the cell biology (i.e. the protein composition, biogenesis, intracellular trafficking) of Glut4-vesicles may be impaired. Our lab pursues both these directions using the wide arsenal of modern techniques that include molecular biological methods, protein biochemistry, subcellular fractionation, microscopy and in vivo studies.

Elizabeth A. Krall Kaye, PhD, MPH

Dr. Kaye’s research interests focus on the link between systemic and oral diseases such as osteoporosis and periodontal disease. Other areas of interest include the interaction
of genetics and diet on risk of osteoporosis, osteoporosis in men, nutrition and oral health, and oral health consequences of smoking.

**Lynn L. Moore, D. Sc.**

Lynn L. Moore, D.Sc., Associate Professor of Medicine, directs the Framingham Children’s Study, which has shown how lifestyle factors starting early in life relate to the development of obesity during childhood and later cardiovascular risk. Much of Dr. Moore’s recent research has dealt with key analytic questions related to obesity and diabetes: the effect of obesity and diabetes, including gestational diabetes, on pregnancy outcome; effects of sustained and non-sustained weight loss on the risk of adult-onset diabetes, hypertension, and cardiovascular disease; effects of weight and weight gain on cancer risk (colon, breast, prostate, lung); the causes and consequences of obesity in childhood; and the effects of anemia on the risk of heart failure and cardiovascular disease.

**P. Kirstin Newby**

Dr. Newby is a nutritional epidemiologist whose research expertise is in the field of diet and obesity, and she has conducted studies on the dietary etiology of obesity among children, adolescents, and adults in the US and abroad. Her studies have used both traditional and novel approaches to measure diet, ranging from single nutrients, foods, and beverages to total diet quality and dietary patterns. Her research expertise is in the field of dietary patterns, which measures dietary intakes based on the way foods are actually consumed; she has conducted methodological research on the measurement, reproducibility, and validity of these methods and has also studied other epidemiological and statistical issues. Her work is recognized for using the dietary pattern approach to show associations with obesity, which is especially important since these food-based methods are more comprehensible by the public hence are better suited to inform dietary guidelines.

**Paul F. Pilch, Ph.D.**

Cell biology of fuel utilization in adipocytes and skeletal muscle. The modern Western diet coupled with a sedentary lifestyle has led to an epidemic of obesity, a consequence of which is a dramatic rise in the incidence of type II diabetes mellitus, a malfunction in insulin-regulated metabolism. At the cellular level, type II diabetes is characterized by failure of insulin to act in liver, muscle and fat. We study aspects of insulin signaling and action in the latter two tissues. Insulin resistance in muscle (and fat) derives from the failure of insulin to activate the tissue-specific glucose transporter GLUT4. The activation mechanism for this process involves vesicle trafficking and protein targeting with regard to GLUT4 and the insulin receptor. We are characterizing the formation and protein content of GLUT4-containing vesicles; we are trying to identify the organelles through which they pass on their way to and from the cell surface and we are determining the communication mechanism(s) (signaling) from the insulin receptor to the GLUT4-containing vesicles. These studies involve both fat and muscle cells, and we are also studying the physiological role of cell surface (plasma membrane) micro-domains called caveolae that are particularly abundant in these tissues. We have evidence for the hypothesis that caveolae (for little caves that are small invaginations of the plasma membrane into the cytosol) are involved in lipid trafficking. We continue to study other aspects of adipocyte and muscle cell biology to understand the interplay between glucose and fat metabolism as well as the interplay between adipocytes and muscle required for overall metabolic homeostasis. Indeed, we wish to uncover the mechanism(s) by exercise also regulates some of these same parameters independent of insulin. Understanding these pathways will help us to figure out how they are compromised in pathophysiological states such as diabetes.

**Vasan Ramachandran, M.D.**

Dr. Ramachandran is a senior investigator at The Framingham heart Study, which is a long-standing ongoing longitudinal epidemiological cohort study. Over the years, careful monitoring of the Framingham Study population has led to the identification of major CVD risk factors, as well as valuable information on the effects of these factors such as blood pressure, blood triglyceride and cholesterol levels, age, gender, and psychosocial issues.
Risk factors for other physiological conditions such as dementia have been and continue to be investigated. In addition, the relationships between physical traits and genetic patterns are being studied. For more about the Framingham Heart Study please go to: http://www.framinghamheartstudy.org/about/index.html

**Rahul Ray, PhD**

Dr. Ray’s research interests include the structural biology of the vitamin D and estrogen endocrine systems (structure of hormone receptors, structure-activity relationship studies); proteomic/combinatorial approaches to develop drugs for cancers of prostate and breast, and novel approaches to site-specific delivery of cancer drugs.

**Neil Ruderman, M.D., Ph.D.**

Dr. Ruderman’s research deals with the effects of insulin, exercise, and fuels on cellular metabolism, signal transduction, and most recently, gene expression. Its focus in the past 10 years has been on a malonyl CoA fuel sensing and signaling mechanism described by his laboratory and its regulation by AMPK. His group has proposed that dysregulation of this mechanism, leading to increases in fatty acid esterification and/or the generation of reactive O2 species, plays a causal role in the pathogenesis of many forms of insulin resistance in skeletal muscle and the early endothelial cell damage that antedates atherosclerosis in diabetes. Their research also examines the notion that activation of AMPK prevents this dysregulation and, perhaps independently, B-mediated gene expression). Some of the later events that it causes (e.g., NF investigators in his unit and their fellows work primarily with skeletal muscle (Saha), some with cultured vascular cells (Ido), and still others with adipocytes (Luo). Thus, from a conceptual perspective, mechanisms worked out in one system are often tested in others. The techniques employed by the Ruderman laboratory include reporter gene assays, adenoviral gene transfer (cultured vascular cells), immunofluorescence microscopy, protein separation, enzyme analysis, and metabolite determination by spectrophotometric and chromatographic methods. The models used include incubated tissues, cultured cells, intact rodents and, in some collaborative efforts, humans. Many program faculty are co-investigators and/or advisors in this work, as are individuals from other institutions. The latter include Drs. Marc Prentki, University of Montreal (malonyl CoA regulation); E.W. Kraegen, Garvan Institute, Australia (insulin resistance in rodents in vivo); Guenther Boden, Temple University (insulin resistance in humans); and David Carling, Hammersmith Hospital, U.K. (molecular biological approaches to study AMPK action in vascular cells).

**Orian S. Shirihai, M.D., Ph.D.**

Mitochondrial oxidative damage plays a key role in degeneration, aging and metabolic diseases. Our goal is to determine how damage is prevented or contained, how dysfunctional mitochondria are recognized and removed, and how mitochondrial networks participate in these processes. We study two disease models in which oxidative damage to mitochondria play a key role in the development of pathology. In diabetes, nutrient-induced oxidative damage has been shown to be a major mediator of endocrine dysfunction and β-cell loss. In bone marrow, oxidative damage induced by iron and hemeintermediates, leads to the development of sideroblastic anemia and myelodysplastic syndrome. By tagging and tracking individual mitochondria in intact β-cells we discovered the existence of a quality control mechanism that relies on both fusion and fission. Following mitochondrial fission some daughter units depolarize. These units display a lower likelihood for subsequent fusion and are apparent targets of autophagy. Moreover, this model predicts that the inhibition of mitochondrial dynamics (MtDy) by Gluco-lipo-toxicity (GLT) may have a cumulative effect and result in an increased portion of dysfunctional units over time. Such enrichment of dysfunctional mitochondria could explain the long lasting effect of GLT, a phenomenon that has been shown to impact animals’ prognosis many months after a high fat diet has been discontinued. More information can be obtained by going to his lab’s website: www.shirihai-lab.org
Keith Tornheim, Ph.D.
I previously studied spontaneous oscillatory behavior of glycolysis in muscle extracts. These oscillations involve the regulatory properties of the key control enzyme, phosphofructokinase, which was therefore the object of related kinetic studies. We are now testing the hypothesis that such oscillatory behavior of glycolysis and the ATP/ADP ratio underlies glucose-stimulated oscillations in intracellular free Ca2+ and insulin secretion in pancreatic islets. Such oscillations can increase the potency of insulin, and loss or derangement of these oscillations may contribute to the development of type 2 diabetes. Fuel metabolism and AMP-activated protein kinase in vascular tissue, muscle and other tissues. This research project, in collaboration with other members of the Diabetes and Metabolism Unit, in part concerns the metabolic changes that may be responsible for the frequently occurring vascular complications of diabetes.

Affiliated:
Nawfal W. Istdfan, M.D., Ph.D.
Nutrition and cancer; regulation of cell proliferation and the effects of polyunsaturated fatty acids on cancer; insulin resistance in obesity; mechanisms of cardiovascular disease in obesity.

Joanne Krasnoff, Ph.D.
My research interests include examining changes in body composition and physical function during aging and chronic illness (i.e. cardiovascular disease, rheumatoid arthritis, HIV, organ transplant, chronic kidney disease and cancer). The Laboratory of Exercise Physiology and Physical Performance is currently involved with several collaborative, ongoing NIH-funded and other projects: 1) Effect of testosterone replacement on body composition, muscle size, strength and function and physical performance; 2) Effects of Testosterone Replacement on Atherosclerosis Progression in Older Men with low Testosterone Levels; 3) Assessing the effect of Progressive Resistance Training in Patients with Class III Obesity. The purpose of this pilot study is to assess the feasibility of a 12-week supervised progressive resistance training program with Class III obese patients. We hypothesize that this intervention will increase muscle strength, function and physical performance, as well as improve insulin sensitivity.

Marie McDonnell, M.D.
Diabetes, nutrition, and immune function

MENTAL HEALTH COUNSELING AND BEHAVIORAL MEDICINE

Stephen Brady, Ph.D., Director
Dr. Brady’s principal areas of clinical, research and teaching interests include HIV/AIDS, serious mental disorders, trauma, and gay/lesbian identity formation. I have been the recipient of a NIMH Training Grants for HIV/AIDS Mental Health and recently the Co-Principal Investigator for a study examining HIV/AIDS, Trauma, Substance Abuse and Cost. I recently completed a 3 year NIH study “HIV Prevention with the Mentally Ill; Motivation-Skills with MHCBM faculty member Dr. Berger-Greenstein and other affiliated faculty” I have presented at numerous conferences and have numerous publications relevant to this area of interest. “I am currently the Chairman on the Council of Psychology and AIDS for the American Psychological Association”

Jori Berger-Greenstein, Ph.D.,
Dr. Berger-Greenstein’s clinical and research interests are in the areas of general behavioral medicine and health psychology, HIV/AIDS, trauma, and ethics. She recently concluded a three-year National Institute of Mental Health (NIMH)-funded study investigating the efficacy of HIV prevention interventions for people with serious and persistent mental illness, in collaboration with Dr. Stephen Brady, the MHCBM Program Director. She spent five years serving as a clinician in a federally-funded, multi-site intervention study designed to investigate the effect of a motivational interviewing intervention on adherence for people living with HIV/AIDS. She has published several articles on the topic of HIV/AIDS and presented at numerous professional conferences. Dr. Berger-Greenstein is also a behavioral health provider at the Boston Medical Center
Behavioral Health Clinic, where she provides clinical evaluations and psychotherapy for adult outpatients.

Jane O'Hern, Ph.D.
Has been a practicing psychologist of the past forty years, her academic training at Michigan State University and Boston University was followed by a career which included: teaching; administration including being the chairman of programs in counselor education and counseling psychology at Boston University; Peace Corps assessment; and a small private practice. In addition, Dr. O'Hern has worked in Europe and Asia. Her research interests are in interdisciplinary program development, and the measurement of counselor sensitivity. She has received numerous grants from the U.S. Departments of Education and Defense as well as from the National Institute of Mental Health.

Rachel J. Levy-Bell, Psy.D.
Dr. Levy-Bell has focused her career on teaching and furthering the clinical and professional development of therapists, psychiatrists, and medical students. She has worked intensively as a supervisor and advisor to a multiplicity of students in the clinical, academic, and research realms. Over the next several years she plans to expand her work in the field of psychology by increasingly spending more time as a clinician working in direct care with patients with medical and psychological disorders. Her clinical practice will include working with adult and geriatric populations.

Janice N. Furlong, M.S.W., LICSW
Dr. Furlong's scholarly and practice interests include collaborative therapy with multi-stressed families; narrative therapy; treatment of youth and adults living with trauma, depression, anxiety, and chemical dependency; and gender bias in assessment and treatment.

MICROBIOLOGY

Ronald B. Corley, Ph.D., Chairman
My laboratory is interested in the relationship between innate and adaptive immunity, and how components of the two discrete systems interact to generate long-lasting protective immune responses. Our research focuses on two major areas. The first area focuses on IgM antibodies as efficient bridges of innate and adaptive immunity. We are interested in the role of IgM antibodies as innate mediators that promote adaptive immune responses when complexed with cognate antigen. We have demonstrated an “adjuvant” role for IgM, and characterized some of the mechanisms by which IgM enhances adaptive immunity. Related to this, we have been investigating the effect traumatic injury has on adaptive humoral responses. Following several types of injury, the humoral immune system is often compromised, but the mechanisms are poorly understood. We have found that following such trauma, IgM fails to act as an adjuvant in priming immune responses, and we are focusing on changes in the uptake and processing of these complexes in splenic follicles as a major consequence leading to immune suppression. The second area of work in the laboratory focuses on the consequences of infection with highly pathogenic hemorrhagic fever viruses, such as filoviruses, on the innate and adaptive immune responses. Patients and animals infected with viruses including Ebola virus, for example, generally fail to make adaptive immune responses and succumb to infection. While this is often attributed to dysfunctional innate immune responses, the nature of the defects in immune responses to these viruses is poorly understood. We have begun studies to dissect the early immune responses to these viruses, understand how they affect the ability of infected animals to initiate adaptive immune responses, and identify the components of infection that lead to the cytokine storms that characterize infection with these viruses.

Deborah J. Anderson, Ph.D.
My research program addresses immunologic aspects of human reproductive health, and has contributed to advances in understanding immunological mechanisms underlying male and female infertility, recurrent miscarriage, preeclampsia, gynecologic oncology and the sexual and vertical transmission of HIV-1. Our current research is focused on the
development of vaccines and topical microbicides for the control of sexually-transmitted pathogens including HIV-1. Towards this end, we are studying mechanisms of cell-associated HIV transmission and fundamental features of local immune defense functions at genital mucosal surfaces that affect HIV-1 pathogenesis and transmission.

Selwyn A. Broitman, Ph.D., FACG

Dr. Broitman’s current interest is in the recently evolving relationship of statin drugs as protection against colon tumors and possibly other tumors as well. Over a decade ago his lab called attention to a cohort of individuals who normally had lowered cholesterol levels but a high body mass index and a high incidence of colon cancer - which was later substantiated by the Framingham heart studies. This remarkable cohort of individuals which may have a genetic predisposition to colon cancer ultimately led to studies in which statins given to individuals to lower cholesterol levels appear to reduce the incidence of colon cancer - a seemingly opposite effect if the focus is on serum cholesterol levels. The lab further demonstrated LDL receptors on human and animal colon tumors, the inability of colon tumor cells to compensate for cholesterol overload as hepatocytes do and that isoprenes, cholesterol precursors essential for the post translation modification of certain cellular proteins, can be inhibited by d-limonene or its derivative perilyl alcohol. The studies initially implied that statins may inhibit the development of metastatic lesions to the liver. Ultimately a complex mechanism was evolved to illustrate that statins (Lovastatin in these studies) may inhibit the isoprenylation of the Ras gene among others. Mutations in the Ras gene are among a number of mutations which predispose to the development of colon and other cancers. Recent epidemiologic studies indicating individuals on statins to lower cholesterol have a decreased incidence of colon cancer have rekindled interest in this area. Dr. Broitman interests have included the impact of nutrition on disease states. He was a Co-author at the National Academy of Sciences of the first major inquiry on “Diet Nutrition and Cancer”, (National Academy Press 1982) and later World Health Organization Study Group on “Diet, Nutrition and Prevention of Non-Communicable Disease” 1988. Currently he is Administrative Director of the Julie Fund at BUMC which provides awards for nutritional research including genomics, metabolism, obesity, epidemiology and surgery. It has been effective in highlighting the need for intensive studies in those areas of nutrition that contribute to, or are directly causal for, over 60% of the deaths in the USA. The abysmal long-term success of diets of any type, and the questionable surgical procedures over the past 30 years have been good indicators how little is known about appetite regulation and metabolic efficiency. Hormonal mediators as leptin, ghrelin, insulin and the interplay of the neuroendocrine circuits and the gastrointestinal tract via the vagus are just coming within the sphere of knowledge. The trigger of leptin released from lipid in the gastrointestinal tract acting on receptors in the hypothalamus induces the interplay of pro-opiromelanocortin and amphetamine responsive neurons which stimulate appetite. Simultaneously, neuroprotein Y and Argouti responsive neurons, also activated simultaneously, by leptin suppresses appetite. Thus anabolic storage and catabolic utilization reverberates between these entities. In turn gratification, reward, and motivation from the limbic and paralimbic areas of the brain are activated by neurotransmitters releasing neuropeptides as dopamine and endorphins. The process is complex. Thus cutting calories, high or low protein sugar or fat diets are fine to get you to the prom in three months but don’t count on it in the long run. Nor is surgery the answer unless death of the patient is the alternative.

John H. Connor, Ph.D.

My laboratory is interested in how viruses interact with the cells they infect. We are currently focused on understanding virus interactions with the host protein synthesis machinery. Protein synthesis is a central issue in virus replication. Though viruses need to make new proteins to replicate, they do not carry their own protein synthesis machinery. Instead, they utilize the protein synthesis machinery of their host. We are building an understanding how viruses accomplish this hostile takeover. We work with a prototype negative strand RNA virus, vesicular stomatitis virus (VSV) that is currently being developed as a potential anti-cancer agent and as a vaccine vector. In cells that are infected with VSV, host protein synthesis is rapidly inhibited, but the host protein
synthesis machinery translates large amounts of viral protein. Using genetic, molecular biological, and rational mutagenesis approaches, we are investigating how VSV interacts with and dominates the host translation machinery. Our studies have shown an important role for multi-protein translation initiation complexes, and suggest that a cellular stress-response triggered by infection is advantageous to the virus and harmful to the host. We are currently determining the signal transduction pathways that are activated and inactivated by viral infection to define host factors that contribute to virus pathogenesis. Other projects ongoing in the laboratory include the study of viruses that have replication defects that poison even wild-type virus replication and investigating how viruses trigger and disarm kinase signaling cascades. We are collaboratively involved in designing novel vaccines against emerging infectious diseases, and identifying novel broad spectrum antiviral compounds.

Rachel Fearns, Ph.D.
The research in my lab focuses on respiratory syncytial virus (RSV), the major cause of pediatric respiratory disease. In addition to being an important pathogen in its own right, RSV is highly related to a number of other medically important viruses, including measles, mumps, rabies and Ebola viruses. These viruses all have a genome consisting of a single strand of RNA and share many aspects of gene expression and genome replication. The RNA genome is not recognized by cellular polymerases, and instead each virus has its own RNA dependent RNA polymerase to perform transcription and genome replication. The fact that this polymerase is distinct from cellular enzymes makes it a good target for antiviral drugs and so we wish to understand better it functions to aid the design of inhibitors. An intriguing feature of this polymerase is that it is able to perform two different RNA synthesis activities: transcription to produce capped and polyadenylated mRNAs and RNA replication to produce progeny genome RNAs. A major goal of our research is to understand the initial stages of these processes to determine how the polymerase is controlled between these different activities. This involves a molecular analysis of the structure of the polymerase and associated proteins using a combination of biochemical and genetics techniques. In addition, there is evidence that the intracellular environment and innate immune responses might alter polymerase activity, even causing cessation of virus RNA synthesis under certain circumstances. We are interested in determining how the cellular environment might affect different stages of virus RNA synthesis, and what impact that might have on the outcome of infection.

Susan H. Fisher, Ph.D.
The research in my laboratory focuses on global systems which regulate the expression of enzymes involved in nitrogen metabolism in response to nutrient availability in the sporulating Gram-positive soil bacterium Bacillus subtilis. Genes expressed at high levels during nitrogen-limited growth are controlled by two related proteins, TnrA and GlnR, that bind to similar DNA sequences under different nutritional conditions. Genetic studies indicate that the wild-type glutamine synthetase protein is required for the transduction of this signal to both the TnrA and GlnR proteins. We have shown that the feedback-inhibited form of glutamine synthetase inhibits TnrA DNA binding activity in vitro. This indicates that glutamine synthetase regulates TnrA by a protein-protein interaction which sequesters TnrA and inhibits DNA binding. The feedback-inhibited form of glutamine synthetase activates GlnR DNA binding by different mechanism. Glutamine synthetase acts as an assembly chaperone for the formation of GlnR dimers. We are using genetic techniques and biochemical approaches to characterize how glutamine synthetase interacts with TnrA and GlnR.

Thomas W. Geisbert, Ph.D.
Our laboratory focuses on the pathogenesis of emerging and re-emerging viruses that require Biosafety level 4 (BSL-4) containment and on the development of countermeasures against these viruses. Our work particularly emphasizes studies on viruses causing hemorrhagic fever (HF) including Ebola virus, Marburg virus, and Lassa virus. Efforts focus on: 1) developing, refining and characterizing animal models that accurately reproduce human viral HF infection; 2) identifying critical pathogenic processes of viral HF infections that could be exploited as targets for therapeutic
interventions. Particular emphasis is placed on determining the basis of coagulopathy and shock that characterize HF viral infections; and 3) measuring the therapeutic benefits of interrupting pathogenic processes that are important in the development of HF viral infection. Currently, there are no vaccines against Ebola, Marburg, or Lassa viruses approved for use in humans. Our laboratory focuses primarily on using recombinant vesicular stomatitis virus (rVSV) as a vaccine vector for viral HF. We have shown that rVSV-based HF viral vaccines can completely protect nonhuman primates against Ebola HF, Marburg HF, and Lassa fever. Specific interest areas include modifying rVSV vectors for optimal safety and immunogenicity, identifying antigens needed to develop a multiantigen vaccine that can protect against major groups of HF viruses, and determining the role of cellular and host immune responses in protection.

Caroline Attardo Genco, Ph.D.

Dr. Genco’s laboratory is interested in the characterization of specific bacterial virulence factors produced by the mucosal pathogens *Neisseria gonorrhoeae*, *N. meningitidis*, and *Porphyromonas gingivalis*, and the underlying molecular mechanisms by which these factors enable these organisms to cause disease. She is particularly interested in mechanisms utilized for colonization and in particular in the ability of environmental factors to modulate bacterial gene expression. Her laboratory has defined the mechanisms of iron transport in both *N. gonorrhoeae* and *P. gingivalis*, characterized several outer membrane receptors required for transport and utilization of iron. Dr. Genco’s laboratory is particularly interested in how virulence genes are expressed in vivo and the role of iron in gene regulation in vivo. Iron starvation is used as a signal by many pathogens that they are in a host environment resulting in the expression of virulence factors that are transcriptionally regulated by iron through the ferric uptake regulator protein, Fur. Dr. Genco’s laboratory has defined the Fur regulon in *N. gonorrhoeae*, *N. meningitidis* and in *P. gingivalis*. Her studies have established that the transcriptional regulatory protein Fur controls the expression of numerous genes that are required for the virulence of *N. meningitidis* and *N. gonorrhoeae*. Her laboratory as also recently identified a novel mechanism for Fur-mediated regulation through small regulatory RNAs. Current studies are aimed at examining the regulation and expression of Fur-regulated genes in vitro, and in vivo directly in clinical specimens. Several different model systems are used to examine the interactions of bacteria with the host. These include animal models for gonococcal infection and *P. gingivalis* oral infection. Her laboratory also utilizes epithelial and endothelial cells to study the interactions of *N. gonorrhoeae* and *P. gingivalis* with host cells, which are permissive for these pathogens. Currently the laboratory is examining the interactions of *N. gonorrhoeae* expressing GFP (green fluorescent protein) with endocervical, ectocervical and vaginal cell lines. Using these cell lines they have demonstrated distinct proinflammatory responses in different compartments of the female lower genital tract. Furthermore she has also utilized these cells to demonstrate that infection with *N. gonorrhoeae* inhibits the apoptotic response of these cells. Thus *N. gonorrhoeae* may establish infection in women by inhibiting the apoptotic response to infection, thereby resisting killing from both the host cell and the innate immune response. Furthermore, prolonged survival of the host cell potentially allows the bacteria to successfully invade cervical tissue, eventually transcending to the upper genital tract. Another area of interest in Dr. Genco’s laboratory is the development of vaccine candidates to prevent *P. gingivalis* induced periodontal disease. Using several different animal models her laboratory has demonstrated that the *P. gingivalis* cysteine proteases (gingipains), major virulence factors of this organism, function in a protective manner in animal models following *P. gingivalis* challenge. Finally, an exciting area of new work in Dr. Genco’s laboratory is examining the specific cellular and molecular mechanisms by which infectious agents contribute to chronic inflammation and specifically the role of the innate immune response in atherosclerosis. Dr. Genco has established that *P. gingivalis* accelerates atherosclerotic plaque accumulation and that is mediated by innate immune recognition to invasive bacterial infection. Her laboratory has established that *P. gingivalis* infection and inflammation in endothelial cells is mediated through fimbiae signaling through Toll-like receptors. Finally her laboratory has
established that TLR2 plays a critical role in the atherosclerotic inflammatory response that is independent of dietary lipids. Current studies are focused on other chronic infections such as that caused by the respiratory pathogen *Chlamydia pneumoniae* in well-defined models of atherosclerosis and defining the role of the innate immune response in accelerated atherosclerosis. These studies employ in vitro model systems for platelet, endothelial cells, and macrophages. The common theme of these studies is to examine the role of infection and the innate immune response in early events associated with atherosclerosis in well-defined in vitro and in vivo systems.

**Rahm Gummuluru, Ph.D.**

The research in my laboratory is broadly focused on the role of dendritic cells (DCs) in the initiation and propagation of HIV-1 replication and the mechanism of subversion of dendritic cell program by HIV-1. A thorough understanding of HIV–DC interactions is of paramount importance, especially since DCs are believed to be the first immune competent cells to encounter virus in the genital mucosa. Virus-infected DCs can facilitate a more efficient spread of virus to replication-permissive CD4+ T cells within the genital mucosa or in draining lymph nodes following migration of DCs to secondary lymph nodes. To this end, we are using genetic, immunological and biochemical approaches to identify the molecular mechanisms of HIV-DC interactions. HIV-1 trafficking within DCs also seems to bypass conventional endocytic organelles, i.e., endosomes and lysosomes. Virus localization within a novel non-lysosomal compartment not only has the potential to protect the invading HIV from being degraded, but also creates a latent reservoir of virus that could present a major challenge for eradication by antiretroviral therapy. Current studies in the laboratory utilizing molecular and cell biology techniques have implicated glycosphingolipids present in the virus particle membrane as key molecules necessary for capture of HIV-1 particles by DCs, and for virus trafficking to non-lysosomal vesicular compartments. Further studies are underway to identify the dendritic cell-specific receptor that captures HIV-1 particles in a glycosphingolipid dependent manner, as well as the nature of the glycosphingolipid-dependent HIV-1 intracellular trafficking pathway. These studies will aid in our understanding of the mechanism of HIV transmission to the naïve host and might lead to the identification of novel therapies that prevent transmission and initial establishment of HIV-1 infection.

**Andrew J. Henderson, Ph.D.**

Effective strategies for eradicating HIV infection will depend on purging virus from cellular reservoirs that harbor transcriptionally latent HIV provirus. How HIV latency is established and maintained is poorly understood since studies on HIV transcription repression have been hindered by the rarity and inaccessibility of latently infected cells. The primary focus of the Henderson lab is developing approaches to investigate how cellular signals regulate HIV transcription and replication. Current projects include examining signal transduction pathways that impact HIV replication, including repression of provirus transcription. We have characterized both positive and negative signaling pathways that impact multiple steps of the HIV replication cycle. In addition, we have gained a better understanding of how latent provirus is induced providing potential new therapeutic targets for HIV. These studies have provided a better understanding of the factors that limit HIV expression in different cell populations as well as general insights into mechanisms of tissue-specific gene expression.

**Robin Ingalls, M.D.**

The ability of innate immune system to sense invasion by a pathogenic organism and respond appropriately in order to control infection is paramount to survival. To that end, an array of receptors and binding proteins has evolved as part of the innate immune system to detect invading microorganisms. My laboratory is interested in Toll-like receptors and the intracellular signaling pathways that contribute to the innate recognition of Gram-negative bacteria, with a particular focus on mucosal immunity. We have a variety of *in vitro* and *in vivo* models in the laboratory to address the interaction of *Neisseria* and *Chlamydia* species with epithelial cells and macrophages. One major focus of the laboratory is exploring the role of TLR2 in host defense against *C. trachomatis*. Previous work in our laboratory established a role for TLR2 in cellular
responses to chlamydia species. In our recent _in vivo_ work we have observed that TLR2 plays a protective role in the lung but a detrimental role in the genital tract during infected mice with the mouse pathogen, _C. muridarum_. The goal of this project is to determine the specific cell types that are responsible for this difference. As part of this project, we are also trying to identify the specific ligands in chlamydia that are important for TLR2-dependent and independent cell activation, and characterize TLR2 signaling mutant strains of chlamydia that lack the cryptic plasmid. A second focus of the laboratory is exploring the role TLRs and NLRs in host defense against _N. gonorrhoeae_. Previous work in our laboratory established a role for TLR4 and TLR2 in cellular responses to _Neisseria_ species _in vitro_ and we have recently completed _in vitro_ studies that also demonstrate that gonorrhea can activate Nod receptors. Our ongoing _in vivo_ studies in TLR4 mutant mice demonstrate that TLR4 is important for early bacterial clearance and neutrophil function, and we plan to complete studies in TLR2 and Nod1/2 mutant mice when back breeding is complete. The third focus of the laboratory relates to the role of innate immunity on regulating acute and chronic inflammation associated with the respiratory pathogen _Chlamydomphila pneumoniae_. We are in the process of defining the specific receptors and ligands that are responsible for IL-1b activation during infection, and will investigate the role of IL-1b in _C. pneumoniae_-induced atherosclerosis.

**Mark S. Klempner, M.D.**

Dr. Klempner's research includes investigations into the basic molecular biology and pathogenic mechanisms of the Lyme disease spirochete, _Borrelia burgdorferi_, patient-based clinical research on prevention, diagnosis and treatment of Lyme disease and novel molecular methods for detecting, identifying and quantifying microorganisms. Using _in vitro_ and _in vivo_ models Dr. Klempner's laboratory has a longstanding interest in the molecular mechanisms of microbial invasion. His laboratory was the first to determine that the Lyme disease spirochete binds and utilizes host proteases in order to facilitate invasion. The laboratory is also studying the role of matrix metalloproteinases in the pathogenesis of Lyme disease. Dr. Klempner's patient based studies focus in several areas ranging from diagnostic tests to vaccine protection to post Lyme disease syndrome. He has studied novel diagnostic tests for Lyme disease which are based on conserved regions of a variable lipoprotein, participated in the evaluation of the highly effective recombinant OspA Lyme disease vaccine and has been a leader in clinical studies of patients with persisting symptoms following treatment for acute Lyme disease (so called post Lyme disease syndrome). Recent studies have focused on defining genetic susceptibility to infection with _Borrelia burgdorferi_ and possible relationships of HLA haplotypes with persisting symptoms. As part of an NIH and NSBRI/NASA funded initiative in collaboration with investigators at the Photonics Center and the Department of Physics his laboratory has begun the development of a novel method for rapid detection and identification of microbial species in environmental and biological specimens. Method involve microfluidic/PCR systems and _surface enhanced Raman spectroscopy_ (SERS) which is an optical technique that uses scatter from an incident visible or near infrared laser to generate detailed vibrational spectra. Dr. Klempner is also developing a research program focused on molecular mechanisms that facilitate the ability of arthropod vectors to support the development of pathogenic microorganisms that can be transmitted to humans. In October 2003, Dr. Klempner became the Principal Investigator of a grant from the National Institute of Allergy and Infectious Diseases to build one of two National Biocontainment Laboratories. Known as the National Emerging Infectious Diseases Laboratories (NEIDL), these laboratories will study emerging infectious diseases of global importance. Dr. Klempner serves as the Director of the NEIDL. The focus of research is on basic and translational studies leading to improved understanding of the pathogenesis of these agents, and development of diagnostics, therapeutics and vaccines for these infectious diseases.

**Ann Marshak-Rothstein, Ph.D.**

My laboratory is primarily interested in factors regulating T and B lymphocyte activation, function, longevity, and apoptosis, especially in animal models of systemic autoimmune disease. We have found that those autoantigens or autoantigen complexes capable of
co-engaging the B cell antigen receptor and a member of the Toll-like receptor family can efficiently activate autoreactive B cells. The main interest of the lab is to further characterize the autoantigens involved in this mode of activation scheme and to further delineate the unique functional properties of B cells stimulated by BCR/TLR coengagement. Other projects in the lab have focused on the lymphocyte abnormalities associated with the lpr and gld mutations, lesions that result in the failure to functionally express the Fas and Fas-ligand molecules, respectively. Specific ongoing projects include: (1) B cell stimulatory activity of defined dsDNA fragment immune complexes; (2) unique patterns of gene expression elicited by TLR/BCR co-engagement; (3) effects of TLR activation on BCR-mediated signaling cascades; (4) effects of TLR inhibitors on the development and progression of systemic autoimmune disease; (5) the role of Fas/FasL interactions on the in vivo persistence of tumor specific T cells; (6) pro-inflammatory and anti-inflammatory aspects of soluble and membrane-bound FasL; (7) therapeutic applications of forced FasL expression on tumor cells; (8) specific targeting of naturally formed FasL microvesicles to tumor populations; and (9) role of metalloproteinase cleavage on FasL function in vitro and in vivo.

Gustavo Mostoslavsky, M.D., Ph.D.

Embryonic Stem Cell Modeling of Intestinal Differentiation: Embryonic Stem Cells (ESC) are pluripotent undifferentiated cells capable of giving rise to cells from all three germ layers. This unique ability makes them ideal candidates to model early development allowing us to study the basic signaling mechanisms involved in stem cell fate determination. At the same time, manipulating ESC differentiation toward a specific developmental pathway holds a great promise for their use in regenerative medicine. One focus of our lab is differentiating mouse ESC into intestinal epithelial cells in order to understand the complex signaling pathways involved in intestinal commitment from endodermal progenitors and undifferentiated stem cells. iPS cells: Our lab has a major interest in the study of induced Pluripotent Stem cells or iPS cells and the development of tools for their generation and characterization. Recent pioneering work by the laboratory of Dr. Yamanaka showed that fibroblasts transduced with retroviral vectors expressing four transcription factors, Oct4, Klf4, Sox2 and cMyc can be reprogrammed to become pluripotent stem cells that appear almost indistinguishable from ESC. In contrast to ESC, iPS cells are genetically identical to the individual from whom they are derived, raising the prospect of utilizing iPS cells for autologous cell based therapies without risk of rejection. We have recently developed a single lentiviral vector, named pHAGE-STEMCCA, capable of generating iPS cells from post-natal fibroblasts with the highest efficiency reported to date. We aimed at using iPS cells in parallel to ESC for the study of intestinal lineage specification and their potential for regenerative medicine. Characterization and Isolation of Intestinal Stem Cells: The identification of Intestinal Stem Cells (ISCs) has long-eluded investigators. The recent discovery of LGR5 as a putative marker of ISCs has opened a window for their study and characterization. We use several methods, including gene marking and gene transfer technologies to study ISC biology and their potential use in cell and gene therapy. Hematopoietic Stem Cell Manipulation for the Study of Stem Cell Self-Renewal and Differentiation: Hematopoietic Stem Cells (HSCs) are the most thoroughly characterized stem cell population in the body and their study has resulted in well established methods for their isolation, purification and reliable assays of HSC function. During the last few years we have substantially improved our ability to genetically manipulate HSCs using viral vectors for gene transfer. Despite these efforts, few genes are known to play a role in the processes of stem cell self-renewal and differentiation. Understanding the molecular mechanisms that govern those unique functions are crucial for developing the promise that stem cells hold for developmental biology and regenerative medicine. In our lab, we use lentiviral viral gene transfer to study the role of several molecules in long-term HSC self-renewal and differentiation. Hematopoietic Stem Cell Manipulation for the Correction of Immunodeficiencies: Our longstanding interest in the immune system combined with our experience in manipulating HSCs have culminated in several studies whose goal is genetic correction of Severe Combined Immunodeficiency (SCID). It has recently become clear that many
SCID patients suffer from a spectrum of previously unrecognized hypomorphic mutations leading to partially impaired V(D)J rearrangement activity. The best example of this type of immunodeficiency is Omenn Syndrome (OS), which is caused in most cases by Rag hypomorphic mutations. While it is well established that the genetic defect in either of the RAG genes is the first determinant of the clinical presentation, the mechanism by which specific Rag mutations induce such diverse immunological phenotypic outcomes is still poorly understood. We have recently started a collaboration with a group at Harvard Medical School to use a variety of lentiviral vectors expressing Rag1 to study its role in immune dysregulation and to develop a new therapeutic approach for Rag1 related immunodeficiency based on lentiviral mediated gene therapy.

Elke Muhlberger, Ph.D.

Ebola and Marburg virus, the only members of the filovirus family, are causative agents of viral hemorrhagic fever. With mortality rates as high as 90%, these viruses represent some of the most deadly human pathogens. We are interested in identifying virus- and cell-specific factors that contribute to virulence and pathogenicity of these viruses. With regard to the virus-specific determinants, we are mainly interested in the filovirus replication machinery. Filoviruses belong to the group of nonsegmented negative-sense RNA viruses. The viral genome is replicated and transcribed by the virus-encoded RNA-dependent RNA polymerase complex. Our working hypothesis is based on the idea that high replication efficiency may be a prerequisite for high virulence. According to this hypothesis, viral infection should be controlled by the infected host if the replication efficiency is reduced. In order to compare the replication and transcription efficiency of filovirus species that differ in their pathogenicity, we have established minigenome systems for the highly pathogenic Ebola virus species Zaire, the less pathogenic Ebola virus species Reston as well as for Marburg virus. These systems are used for detailed investigation of cis-acting signals on the RNA genome and for structure-function analyses of the viral proteins involved in replication and transcription. Minigenome systems are useful tools to investigate the filoviral replication cycle under low biosafety level conditions. A second topic of our investigations involves filovirus-host interaction. As many other viruses, filoviruses have evolved various mechanisms to evade the early innate immune response. We are interested to identify cellular targets of filovirus antagonists. These studies include regulation of IFN-mediated pathways, regulation of apoptotic processes and regulation of proinflammatory responses in infected cells. Together, these investigations will provide a better understanding of how filoviruses evade or modulate cellular antiviral mechanisms and will help to develop antiviral countermeasures.

John R. Murphy, Ph.D.

Our research is focused in two areas: molecular mechanisms of diphtheria toxin catalytic domain delivery into the eukaryotic cell cytosol, and peptide activators of the diphtheria toxin repressor, DtxR. We have developed a positive genetic selection system for the direct cloning of both dtxR alleles and DtxR target operator sequences. Using this system, we have isolated positive dominant mutants of DtxR (e.g., DtxR(E175K)). Since DtxR and its homologues control the expression of virulence factors in many important Gram positive pathogens, the positive dominant mutants suggest that DtxR may be a target for the development of a new class of "antimicrobial" that would phenotypically convert pathogenic strains to their non-pathogenic counterparts. We have now isolated and partially characterized a family of peptide activators of wild type DtxR, and have shown that that these agents have the properties of cationic antimicrobial peptides (CAMPs). Diphtheria toxin contains at least three functional domains: ADP-ribosyltransferase, membrane translocation domain, and a eukaryotic cell receptor binding domain. Biochemical genetic analysis has shown that each domain must function in an ordered and sequential fashion for the toxin molecule to bind to its receptor on the surface of a sensitive eukaryotic cell, be internalized, and facilitate the delivery of the ADP-ribosyltransferase to the cytosol. To further probe the structural requirements for ADP-ribosyltransferase entry into the cytosol, we have designed a family of "new" toxins by receptor binding domain substitution. Using the fusion protein toxin DAB389IL-2, we
Barbara S. Nikolajczyk, Ph.D.
My lab is interested in understanding inflammation in type 2 diabetes patients. Inflammation is strongly implicated in the most dire complications of type 2 diabetes, including cardiovascular disease and stroke. We are focusing on two cell types that promote inflammation in these patients: monocytes and B cells. Monocytes are well known to produce significant amounts of pro-inflammatory cytokines. We are specifically interested in how IL-1 beta, a cytokine at the apex of multiple pro-inflammatory cascades, is hyper-expressed by monocytes from type 2 diabetics. We have defined a “poised promoter architecture” for the IL-1 beta locus in normal monocytes. This structure is characterized by a constitutively accessible promoter and constitutive transcription factor association. Current work is aimed at understanding how this structure is changed in patients to result in IL-1 beta hyper-production. Another series of analyses in monocytes will define the role the IL-1 beta processing complex known as the inflammasome plays in IL-1 beta hyper-production in diabetics. Although inflammasome dysregulation itself can lead to inflammatory disease, a role of the inflammasome in diabetes has not been appreciated. A second focus of the lab is to understand how B cells contribute to type 2 diabetes through production of pro-inflammatory cytokines. We have found B cells in type 2 diabetes patients are fundamentally altered such that they unexpectedly respond to pro-inflammatory stimuli. Ongoing analyses are characterizing these responses as well as the underlying molecular mechanisms driving them. These studies are aimed at identifying targets for alleviating the over-production of pro-inflammatory cytokines generally associated with the devastating complications of inflammation in type 2 diabetes patients.

Stephanie Oberhaus, Ph.D.
My current interests and expertise focus on medical, dental and graduate education. I am actively involved in curriculum development and revision, and in developing innovative learning and teaching tools using a variety of technologies. I also collaborate with students and faculty on a variety of educational projects. My past research efforts and continuing interests focus on understanding the nature and mechanisms of viral pathogenesis to control viral-induced cell death, i.e. to limit cell death in viral disease or to promote cell death in cancer. My laboratory used a mouse model system and a variety of cultured cell lines to study the nature and role of reovirus-induced apoptosis in viral-induced liver disease. Our studies focused on reovirus-induced cholestatic disease, which has been proposed as an experimental model for a rare and serious disease in infants called extrahepatic biliary atresia. Reovirus has also been shown to exhibit oncolytic properties, i.e. it infects and kills tumor cells, but not non-tumor cells in vivo. This virus is already being tested in clinical trials for the treatment of cancer. My laboratory conducted studies to determine the mechanism of reovirus-induced death in cancer cells and the viral and cellular factors involved in this process. Our data showed that treating breast cancer cells with reovirus in combination with low intensity ultrasound provided a synergistic killing effect. These results suggest that reovirus may be useful as a cancer therapeutic and that therapy may be “tailored” by treating certain types and stages of cancer with specific reovirus strains, perhaps in combination with other cancer therapeutic agents.

Ian R. Rifkin, M.D., Ph.D.
There are two main research aims in my laboratory. The first aim is to understand the pathogenesis of the systemic autoimmune disease systemic lupus erythematosus (SLE), with the ultimate goal of identifying new therapeutic targets. We mainly use mouse models and in-vitro systems for these studies, although we also work with human cells and patient material. Specific projects include: 1) Studying mechanisms and signaling pathways responsible for the activation of dendritic cells in SLE. This project is based on our original observation that dendritic cell activation by nucleic acid autoantigen-
containing immune complexes occurs through the dual engagement of an Fc receptor and a Toll-like receptor (TLR9 for DNA autoantigens and TLR7 for RNA autoantigens). Ongoing studies aim to characterize the precise nature of the stimulatory autoantigens in more detail, and to determine the overall contribution of TLR-mediated dendritic cell activation to SLE pathogenesis. 2) Determining the role of interferon regulatory factor 5 (IRF5) in lupus pathogenesis. IRF5 has recently been identified as a major susceptibility gene for SLE in humans and plays an important role in TLR signaling. We are using a combination of in vivo and in vitro approaches to evaluate the biological role of IRF5 in SLE. The second main aim of our research is to determine the mechanisms responsible for the premature atherosclerosis seen in SLE. Premature atherosclerosis is a major cause of morbidity and mortality in patients with SLE, although the lupus-specific risk factors responsible for this are poorly understood. In collaboration with Dr. Walsh in Molecular Cardiology, we have developed a novel mouse model of premature atherosclerosis and SLE, and are using this model to explore underlying pathogenic mechanisms and test new therapeutic approaches.

**John C. Samuelson, M.D., Ph.D.**

*Entamoeba histolytica*, *Giardia lamblia*, and *Trichomonas* are simple eukaryotes, which cause dysentery, diarrhea, and vaginitis, respectively. Our laboratory in collaboration with my colleague Phillips Robbins uses molecular biological methods to study the biochemistry, cell biology, pathogenesis, and evolution of these important human pathogens. One project attempts to determine the composition of the walls of *Entamoeba* and *Giardia* cysts, which are the infectious and diagnostic forms. The *Entamoeba* cyst wall is composed of chitin (a homopolymer of GlcNAc) and unique chitin-binding lectins that cross-link fibrils and make the wall impenetrable to small molecules. The *Giardia* cyst wall is composed of a unique homopolymer of GalNAc and lectins that bind the GalNAc homopolymer. Our studies focus on how the *Entamoeba* and *Giardia* cyst walls are made during encystation and how these walls are broken or degraded during excystation. A long term goal of these studies is to develop better diagnostic reagents for the *Entamoeba* and *Giardia* cysts and to determine whether cyst wall components may be vaccine candidates. A second project attempts to understand Asn-linked glycosylation in *Entamoeba*, *Giardia*, and *Trichomonas*, as well as in *Plasmodium*, *Cryptosporidium*, and *Toxoplasma*, which cause malaria, diarrhea, and opportunistic infections, respectively. In particular, we use bioinformatics to predict lipid-linked N-glycan precursors, as well as N-glycan-associated proteins involved in quality control in the ER lumen. We test our predictions using biochemical methods, which include determinations of carbohydrate structures and purification of glycoproteins by lectin columns. These studies suggest 1) the present diversity of N-glycans derives in part from secondary loss of genes encoding enzyme involved in N-glycan precursor synthesis, 2) protists with short N-glycans lack N-glycan-dependent quality control, and 3) there is Darwinian selection for sites of N-glycans in secreted proteins of diverse eukaryotes and viruses. Unique parasite sugars may be novel vaccine candidates or targets for antimicrobial lectins. A third project is concerned with how *Entamoeba*, *Giardia*, and *Trichomonas* adapt to the anaerobic environment in the intestinal lumen. We have identified an atrophic mitochondrion-derived organelle, which lacks enzymes of oxidative phosphorylation in *Entamoeba*. We have also identified numerous bacterium-like fermentation enzymes in these protists, which appear to have been obtained by lateral gene transfer (LGT). Although LGT is frequent between bacteria, it is unusual between bacteria and eukaryotes. Two of the bacterial genes acquired by LGT appear to be important for activating and inactivating metronidazole, the best drug against these organisms. The long term goal of these studies is to determine why *Entamoeba*, *Giardia*, and *Trichomonas* are susceptible to metronidazole and how these protists might become resistant to the drug.

**David C. Seldin, M.D., Ph.D.**

My research affiliations are with Hematology-Oncology, the Women’s Health Interdisciplinary Research Center, and the Amyloid Treatment & Research Program. Our laboratory work is focused upon the study of molecular pathways in cancer and blood
diseases, and the development of mouse models of disease. I also participate in clinical research studies of amyloidosis and stem cell transplant. Our cancer signaling studies stem from the observation that certain highly conserved regulatory serine-threonine kinases in cells are overexpressed in leukemias, lymphomas, and solid tumors. We have focused upon protein kinase CK2 (casein kinase II), which can act as an oncogene when overexpressed in transgenic mice. Targets of CK2 in cancer include c-myc, NFκB, and the Wnt pathway. In Wnt signaling, for example, CK2 phosphorylation stabilizes the transcriptional co-factor beta-catenin, augmenting TCF/LEF-dependent transcription, which turns on myc and cyclin D1 expression. In collaborative experiments, we have shown that CK2 and Wnt signaling play a role in breast cancer induced by environmental carcinogens. To understand the critical role of CK2 in development, we have used homologous recombination in ES cells to knock out the major catalytic subunit of CK2, the alpha subunit, which is embryonic lethal, and the minor alpha prime catalytic subunit, which causes male sterility. AL (primary) amyloidosis is a clonal plasma cell disease in which morbidity and mortality is due to the tissue deposition of misfolded, aggregated monoclonal immunoglobulin light chains (LC) fibrils. We are cloning and sequencing LCs from patients to identify the sequence determinants of fibril formation, assess their biophysical properties, and create transgenic models for use with new imaging technologies such as high field MRI, and for preclinical drug testing.

Gregory A. Viglianti, Ph.D.
Research in the Viglianti laboratory focuses on two main areas: 1) cofactors that influence the mucosal transmission of HIV-1; and 2) the role of endogenous nucleic acid autoantigens as mediators of systemic lupus erythematosus. 1) Mucosal immune responses of the lower female reproductive tract to sexually transmitted pathogenic microorganisms leads to an inflammatory response that enhances the heterosexual transmission of HIV-1. Inflammation is initiated largely by signaling through members of the Toll-like family of innate immune receptors (TLR) that are activated by pathogen-encoded ligands. This inflammatory response enhances HIV-1 transmission by inducing the recruitment of target immune cells such as Langerhans/dendritic cells (LC/DC), macrophages (MØ), and T lymphocytes to the mucosa and by direct activation of these cells. Recent findings have demonstrated that activation of certain nuclear receptors (NR), including peroxisome proliferator activated receptor (PPAR), liver X receptor (LXR), and glucocorticoid receptor (GR) potently inhibits TLR-induced inflammatory gene expression in MØ, LC/DC, and epithelial cells. Studies in our laboratory are directed toward evaluating: 1) the ability of ligand-activated NR to inhibit the mucosal transmission of HIV-1, in particular LC/DC-mediated trans-infection of T cells; and 2) the molecular mechanism(s) of how ligand-activated NR inhibit TLR-induced transcription of both HIV-1 and inflammatory cytokine genes. 2) Autoimmune diseases such as systemic lupus erythematosus (SLE) are characterized by the overproduction of antibodies, many of which recognize ribonucleoprotein and/or chromatin related autoantigens. A common feature of these autoantigens is that they include DNA or RNA. Our laboratory, in collaboration with Dr. Ann Marshak-Rothstein, is defining the protein and nucleic acid composition of these immunostimulatory autoantigens and determining whether different forms of apoptosis are capable of selectively releasing these autoantigens from cells, thereby making them accessible to autoreactive B cells.

Lee M. Wetzler, M.D.
Dr. Wetzler's laboratory investigates innate and adaptive immunity and microbial pathogenesis, especially in regards to vaccine development. One major aspect of this work centers on the pathogenic Neisseria, Neisseria gonorrhoeae and Neisseria meningitidis. He has found that the major outer membrane protein of these organisms, the Neisserial porin PorB, can work as an immune adjuvant due to its recognition by the pattern recognition receptor TOLL-like receptor (TLR) 2. He has found that antigen presenting cells, including B cells, dendritic cells and macrophages, are activated by PorB in a TLR2 , TLR1 and MyD88 dependent manner, inducting upregulation of class II MHC, costimulatory molecule CD86 and other markers of activation. Moreover, MAPK signaling events are required for the upregulation of the expression of these markers, as
well as production of pro-inflammatory cytokines. Moreover, using an in vivo peritoneal mouse model of inflammation, we have shown that both PorB and intact *N. meningitidis* induce a significant cellular influx and pro-inflammatory cytokine production, which is also TLR2 dependent. However, we also found that mast cells are activated during this process, which may be in a TLR2 independent manner, along with a significant influx of eosinophils, indicative of induction of a TH2 type cellular response. Studies are continuing to investigate the mechanisms of these phenomena. We are also investigating the use of this TLR2 ligand, PorB, as a vaccine adjuvant using classic antigens like OVA and more relevant antigens like bacterial capsular polysaccharide. This work has also been extended to investigate the adjuvant activity and mechanism of immune stimulation of the B subunit of cholera toxin. We have found that CTB induces antigen presenting cell stimulation via the lipid raft ganglioside GM1 via induction of a cell-signaling program ending in NF-kB and CREB activation and gene transcription. This work is still on going. Finally, a new major thrust of the Wetzler lab is investigating the immune response and natural history of Francisella tularensis pulmonary infection in mice and using this data to aid in developing vaccines towards this potential bio-terrorist agent. We have found that using PorB as an adjuvant and Francisella LPS as an antigen, we can enhance protection in these mice, which is likely due to induction of antibodies and improved immunity (potentially both innate and adaptive immunity. It appears that induction of IL-1beta may be more associated with survival both during natural infection and after vaccination, while IL-6 and IL-17 may have the opposite effect, being more associated with death after pulmonary infection. Finally we have recently found that induction of bronchial associated lymphoid tissue (BALT) after vaccination also appears to be associated with protection. These iBALT structures are long lasting and may be due to persistent antigen stimulation, which we are currently investigating.

Glen B. Zamansky, Ph.D.

Research has concentrated on keratinocyte cell biology and cellular responses to ultraviolet radiation. Studies include: (1) the dynamic nature of the cytoskeleton of human epidermal keratinocytes; (2) the mechanisms by which UV radiation damages components of the cytoskeleton; (3) the relationship between DNA repair deficiencies and sunlight induced pathogenesis in the autoimmune disease systemic lupus erythematosus. These projects are currently inactive.

MOLECULAR MEDICINE

Carmela R. Abraham, Ph.D.

Our laboratory studies the mechanisms of normal brain aging and the etiology of Alzheimer's disease (AD). The 40-42 amino acid amyloid beta peptide (Aβ) is the major component of plaques that accumulate in the brains of AD patients. There is ample evidence that Aβ causes irreversible neurodegeneration. Therefore, the formation and clearance of Aβ are major therapeutic targets for the treatment of AD. Aβ is a proteolytic fragment of the amyloid precursor protein (APP), a ubiquitously expressed and conserved protein with unknown function. We are studying the physiologic function of APP and its role in the brain and particularly, in AD. Aβ accumulates in the AD brain likely as a result of aberrant clearance. In another project, we study a novel protease involved in the degradation of Aβ. Studying the proteases that degrade this peptide is crucial for understanding the etiology of the disease and for the design of therapeutic compounds aimed at decreasing the Aβ load in the brain. We also investigate normal human brain aging and use the rhesus monkey as a model. Rhesus monkeys develop cognitive impairment as they age. To our surprise, we could not detect cortical neuronal loss, but extensive changes were observed in the white matter volume and myelin, the insulating layer that surrounds nerve fibers and facilitates communication. We attribute these age-related changes to neuroinflammation. Specifically, we are interested in the expression of gene products that could contribute to the destruction of myelin. The myelin abnormalities may contribute to the cognitive deficits that are seen with normal aging. A gene we are currently focusing on is Klotho, an anti-aging gene that when deleted in mice leads to a
premature aging phenotype and when overexpressed results in a 30% lifespan extension and resistance to oxidative stress. We are studying the role of Klotho in myelin formation and repair. To prove our hypotheses we use biochemical and molecular techniques, including microarray analyses, light, fluorescent and confocal microscopy, cell culture and animal models.

Kenn Albrecht, Ph.D.

Mammalian gonadal sex determination is a powerful system for studying organogenesis, cell fate determination, and the evolution of sex chromosomes and developmental regulatory mechanisms. Besides basic scientific interest, mammalian sex determination also is of biomedical interest. Approximately one in 1000 infants has a gonadal or genital anomaly. Furthermore, many of the known genes involved in sex determination also are implicated in pathological processes such as tumorigenesis and primary adrenal failure, and have essential roles in the normal development of organs other than the gonads. We use the mouse as a model system for studying mammalian sex determination and gonadal and adrenal organogenesis and employ genetic, molecular genetic, genomic, cell biological and embryological techniques. Currently, there are two main projects underway in the lab. In the first, we are investigating the molecular mechanisms of three mouse models of human sex reversal and adrenal dysmorphogenesis. In the second, we are identifying and characterizing new genes important for gonad development using genetic and genomic approaches such as microarray analysis of gene expression during organogenesis. Our long-term goal is to understand the molecular mechanisms of gonadal and adrenal organogenesis and their role in human disease.

Deborah Anderson, Ph.D.

Sexually transmitted infections (STIs) are epidemic in the United States and worldwide, and have far reaching health, social and economic consequences. Each year more than twenty million men and women in the United States acquire an STI; the World Health Organization estimates the global annual incidence of curable STIs (excluding HIV-1 and other viral STIs) to be 333 million. Some STIs, such as those transmitted by the Human Immunodeficiency Virus Type 1 and high-risk human papilloma virus strains, can cause severe morbidity often leading to death. Others adversely affect fertility and neonatal health. Our current research is focused on the development of vaccines and topical microbicides for the control of sexually-transmitted pathogens including HIV-1. Towards this end, we are studying mechanisms of cell-associated HIV transmission and fundamental features of local immune defense functions at genital mucosal surfaces that affect HIV-1 pathogenesis and transmission.

Steven Bogen, M.D., Ph.D.

Dr. Bogen’s research group focuses on applied (translational) projects in the area of cancer detection and diagnosis, with an emphasis on new technology development. The group is currently working with a new platform discovery technology called Epitope-Mediated Antigen Prediction (E-MAP). We developed a method to identify the antigen to which a patient’s serum antibody binds without any other clues as to the antigen’s identity. The method uses a peptide combinatorial library to test billions of different peptide combinations, to find the best fit to the antibody’s binding site. The sequence is then matched to peptide sequences in the protein database. This method provides important clues to the etiology of diseases of unknown origin, without requiring any pre-existing suspicion or clinical clues. The method was published in Molecular and Cellular Proteomics, February 2008. The group first applied this technology to the analysis of paraproteins from patients with multiple myeloma. Those findings were published in Blood, January 2008. E-MAP is expected to create new discovery insights and diagnostic opportunities in B-lymphoproliferative disorders, autoimmunity, certain granulomatous diseases of unknown origin, and infectious diseases.

Steven C. Borkan, M.D.

The Renal Research laboratory focuses on the pathogenesis of renal epithelial cell death in acute, ischemic renal failure. Ischemia is a common cause of human kidney injury and despite the advent of renal replacement therapy (dialysis), causes significant morbidity and death in nearly 50% of patients. There is presently no treatment for ischemia-induced
renal injury partly due to a lack of insight into the mechanisms of cell death caused by ischemia. In this form of injury, the proximal tubule epithelial cell is major target of injury. Although early studies emphasized the role of cell necrosis in causing acute tubular injury (ATN), recent studies including our own emphasize the role of apoptosis in causing organ failure. We have extensively investigated the role of endogenous heat stress proteins (HSPs) in mediating cytoprotection by antagonizing apoptosis. We have concentrated on the anti-apoptotic functions of Hsp127 and Hsp70 - the major inducible stress proteins. These studies have identified key kinases that mediate cell death, regulate members of the BCL2 family and contribute to sublethal injury of the cell architecture (cytoskeleton and cell contact sites). Our future studies will include discovery of the role of mitochondrial dynamics (fission and fusion) in renal cell injury, the role of hexokinase, a the rate limiting step in glycolysis in antagonizing Bax-mediated mitochondrial membrane injury and will identify key co-factors (e.g., nucleophosmin) that mediate attack by Bax, a major pro-apoptotic BCL2 protein. It is our hope that improved understanding of the mechanism of renal cell injury will ultimately provide new strategies for preventing and treating human acute renal failure.

Jerome Brody, M.D.

Our laboratory is involved in clinical and basic studies of lung cancer, the #1 cause of cancer death in this country. Over 160,000 people die of lung cancer each year in this country and 2 million die worldwide. While cigarette smoking is the major cause of lung cancer, only 10-20% of heavy smokers actually develop lung cancer; presently 50% of lung cancers now occur in former smokers. There are no effective ways of diagnosing lung cancer at an early stage before it has spread, and, as a result, 5 year survival is ~15%, virtually unchanged for the past 3 decades. We have 2 general projects that attempt to define individual susceptibility to the carcinogenic effects of tobacco smoke and explore fundamental genomic issues relating to lung cancer biology. Our ultimate goals are to identify “at risk” smokers and former smokers, to develop new lung cancer early diagnostic tools, and to apply modern molecular and bioinformatic approaches to understanding the varied biology of human lung cancer. Early diagnosis of lung cancer and of susceptibility to the carcinogenic effects of cigarette smoke. This project explores the potential of gene expression profiles of airway epithelial cells obtained from a bronchoscopy from intrathoracic airways or from buccal mucosa in the extrathoracic airways to identify smokers who are at risk for developing, or who already have, lung cancer. We are defining the normal airway transcriptome (all genes transcribed in airway epithelial cells obtained from both intra- and extra-thoracic airways) and how that transcriptome is altered by smoking or by cancer. The tools we use include gene expression profiling, bioinformatics, and computer programming. Parallel studies correlate patterns of airway gene expression with serum and airway, thus linking the airway and serum proteome to lung cancer. New approaches to understanding lung cancer biology This project will use lung cancer cell lines and cells from resected human lung cancers to produce lung cancer in mice. Our goal is to link tumor gene expression profiles to the biologic behavior of lung tumors, defining genetic signatures that link to tumor growth rate, metastatic potential, and prognosis. By transfecting cells with a fluorescent marker we will be able to follow the course of tumor dissemination in living mice and by adding various inducible genes to the cells we will explore the potential of altering the progress of the cancers. The tools we use include molecular biology and construction of transflectable vectors into cells, bioinformatics in mice, and biochemistry to examine the mechanisms by which mutant genes can affect tumor growth.

Wellington V. Cardoso, MD, PhD

Our research is focused on the mechanisms that regulate the development of the respiratory system in the mammalian embryo. This process initiates early in organogenesis with the establishment of respiratory cell fate in the foregut endoderm and formation of the lung and tracheal primordia. The lung then develops into a tree-like system of epithelial tubules intertwined with vascular structures, which ultimately gives rise to the airways and alveoli. We are investigating how respiratory progenitor cells are initially specified in the foregut and how they generate a wide diversity of cell types.
characteristic of the mature lung. We use functional mouse genetic approaches, organ and cell culture, genome wide screen, in situ hybridization and other strategies to study the role of specific pathways in the developmental programs of the lung. This research provides insights into basic mechanisms of lung development and stem cell/progenitor cell biology. These studies also have an impact on our understanding of the pathogenesis of conditions such as lung immaturity and pulmonary hypoplasia, and mechanisms of repair in the adult lung. Ongoing research projects (see also: http://www.bumc.bu.edu/Dept/Content.aspx?DepartmentID=63&PageID=13266):
- Retinoic acid signaling in lung development:
- Fgf10 regulation of lung progenitor cell expansion and bud formation
- Fgf-heparan sulfate interactions in lung epithelial morphogenesis:
- Notch signaling in lung cell fate:

David Center, M.D.

Dr. Center is Boston University’s Associate Provost for Translational Research and the Director of the Clinical and Translational Research Institute funded by the NIH. As a result he directs Boston University’s efforts to facilitate translational research in all venues and leads a major effort in identifying new areas of development. His own laboratory is interested in two major themes which revolve around roles for Interleukin-16, co-discovered with Bill Cruikshank in 1982. The first theme relates to the functions of IL-16 as a immunomodulatory cytokine. Over the past several years, in collaboration with Bill Cruikshank, he has studied the role of IL-16 in recruitment and development of Regulatory T cells and demonstrated that it plays a key role in tolerance to airborne allergens. Utilizing transgenic knockout and overexpressing mice his laboratory is involved in demonstrating the patterns of CD4+ T cell trafficking through lymph nodes and lung parenchymal in normal and immunologically challenged lungs and identifying potential therapeutic implications of altering recruitment patterns of Regulatory T cells. The second major emphasis of his laboratory relates to the functional properties of the precursor protein for IL-16, Pro-IL-16 as a tumor suppressor gene. In these studies, along with Yujun Zhang he has shown that Interleukin-16 is synthesized as a precursor which is present in cytoplasm and nucleus of resting T cells. It contains a phosphorylation regulated nuclear localization motif and binds a nuclear chaperone hsc70 which is essential for transport to the nucleus where its presence induces arrest of the cell cycle at G0/G1. It inhibits the cell cycle by acting as a scaffolding protein that assembles a histone deacetylase complex targeted via binding to GA-BP to the Skp2 promoter using intermolecular PDZ binding motifs. Skp2 is an essential member of the ubiquitin ligase protein degradation pathway responsive for degrading the cell cycle cyclin dependent kinase inhibitor p27. In the presence of pro-IL-16, the complex inhibits Skp2 transcription, which in turn decreases p27 degradation resulting in rises in p27 levels and arrest of the cell cycle in G1. Current studies are directed at identifying mutations in Pro-IL-16 that predispose to T cell malignancies and determining its role is permissive exit from G1 in normal T cell activation and proliferation following antigen stimulation.

Links:
- Boston University Pulmonary Center: Immunology Group
- Boston University Asthma Clinical Center
- Boston University Allergy Clinical Center
- Boston University CTSI

Selected Publications:
3. Zhang, Y, Tuzova, M., Xiao, Z-XJ., Hanson, SK, Xie, H, Kornfeld, H, Cruikshank, WW, Center, DM. 2007 Pro-Interleukin-16 is a scaffold protein which targets Histone Deacetylase 3 to Transcription Factor GABP in the Skp2 Core Promoter. 2008 J. Immunol. 180:402-408.
Herbert T. Cohen, M.D.

Dr. Cohen's laboratory is addressing the molecular basis of renal cancer, renal cystic disease and renal development and offers special expertise in gene expression mechanisms, signal transduction, protein-protein interactions, transcription factors, and renal epithelial cell biology. The laboratory has identified the first member of new protein family, the Jade family of proteins, on the basis of its interaction with the von Hippel-Lindau tumor suppressor pVHL. pVHL protein is a key component of the cellular oxygen-sensing system. VHL is also the major renal cancer gene in adults. Jade-1 is a novel, growth suppressive plant homeodomain transcription factor that is the first protein found to be stabilized by pVHL. Jade-1 is also a ubiquitin ligase and key component of histone acetylation complexes. Interestingly, Jade-1 is stabilized by VHL protein in a manner that correlates with risk of renal manifestations in von Hippel-Lindau disease, which includes a cystic renal disease phenotype. A wider role for Jade-1 in renal cyst formation was therefore sought. Jade-1 is regulated by the product of the major gene for autosomal dominant polycystic kidney disease (ADPKD), polycystin-1, in a manner that is also disease relevant and physiologic. Importantly, Jade-1 serves as a critical ubiquitin ligase for the oncoprotein beta-catenin, which also plays critical roles in renal cancer, renal cyst formation and renal development. In part by controlling transcription and beta-catenin ubiquitination, Jade-1 and related family members are likely to be particularly important in many contexts.

Techniques:
Cancer biology and epithelial cell biology approaches, advanced molecular biology approaches, protein-protein interactions, yeast 2-hybrid screening, protein ubiquitination assays, protein-DNA interactions, transcription assays, gene expression mechanisms including microarrays, confocal microscopy, transgenic and knockout mice.

Richard A. Cohen, M.D.

The research interests of the Vascular Biology Unit center around the biology and pathophysiology of nitric oxide (NO) in the setting of vascular disease. Areas of study are currently focused on novel signaling mechanisms that rely on ion channels and transporters. These include the regulation of intracellular calcium via NO-dependent inhibition of store-operated calcium influx by its ability to stimulate calcium uptake by sarcoplasmic/endoplasmic reticulum calcium ATPase. Levels of NO and its actions in diseased blood vessels are regulated by oxidants that both destroy NO and introduce post translational modifications of its protein targets. Thus, the calcium ATPase target of NO is inactivated by oxidants in diseased arteries. Levels of oxidants are increased in diseased arteries by endogenous enzymes. In hypertension, superoxide anion production by vascular NADPH oxidase is upregulated, and in diabetes, endothelial nitric oxide synthase becomes partially uncoupled, producing superoxide anion in addition to NO. NO and superoxide react to form peroxynitrite, a potent oxidant. Presence of this oxidant in vascular tissue is evidenced by tyrosine nitration of proteins, including the calcium ATPase and prostacyclin synthase. Inactivation of the latter enzyme leads to vasoconstrictor prostanoids responsible for adhesion molecule expression and apoptosis of endothelial cells. Inhibiting NADPH oxidase, over expression of superoxide dismutase, and antioxidants to prevent oxidative changes in vascular proteins all represent therapeutic interventions being investigated.

Wilson Colucci, M.D.

Dr. Colucci’s laboratory is studying the mechanisms that mediate myocardial remodeling and failure. A major focus is to understand the roles of reactive oxygen species in mediating myocyte phenotype via their effects on cell growth, gene expression and apoptosis. Recently, they have demonstrated that oxidative stress, mechanical deformation and catecholamines can induce both hypertrophic growth and apoptosis in cardiac myocytes. Parallel studies are being performed in vitro and in vivo using cultured cardiac myocytes and genetically-modified mice, respectively in order to determine the relationship between the molecular/cellular events involved in cardiac remodeling and
alterations in physiological function that can be assessed at the single myocyte and whole heart level in transgenic and knock-out mice.

**Barbara Corkey, Ph.D.**

The main goal of work in the Corkey laboratory is to determine how fuels generate the signals to communicate among different organs in the body to modulate hormone and adipokine exocytosis, electrical activity, metabolism and gene expression. It involves assessment of the influence of metabolites and mitochondrial energy state on intracellular signal transduction in adipocytes, pancreatic β-cells, liver and human fibroblasts. Recent emphasis has been on ion handling, respiration, the signaling consequences of cellular energy state, the influence of fatty acids on protein kinases and the role of fatty acids and long acyl CoA on signal transduction. Unique resources of the laboratory include imaging, fluorescence and amperometric techniques to measure responsiveness of living cells to various treatments and stimuli. Work is done in collaboration with scientists at Boston University School of Medicine, the BioCurrents Laboratory of the Marine Biological Institute, the Karolinska Institute, the Universities of Chicago, Montreal and Pennsylvania, and the Hamner Institutes for Health Sciences.

**Catherine Costello, Ph.D.**

Biopolymer structural studies based on development and application of mass spectral methods. The objective of our research is to establish the detailed structures of biopolymers in order to understand their structure-activity relationships as they influence or reflect biological processes related to health, growth and development, and disease. Our particular focus for new method development is on the needs of glycobiology, since carbohydrates and their conjugates (glycoproteins, glycolipids, etc.) are involved in targeting and immune system recognition, nervous system growth and development, infection, parasite response, carcinogenesis, and other critical processes. The techniques for full structural characterization of these complex molecules are much less developed than are methods for linear biopolymers (proteins and oligonucleotides). Our protein studies include determinations of post-translational modifications related to oxidative stress in cardiovascular disease and investigations of protein misfolding disorders. Recent introduction of new mass spectral ionization methods and rapid progress in means for mass separation and detection now make it possible to perform structural studies on low picomole amounts of samples even when they are complex mixtures. In our research program we are refining and extending the tools of mass spectrometry and are applying them to collaborative studies undertaken with colleagues at BUSM and other institutions around and outside the US. Our laboratory includes a Resource Center sponsored by the NIH National Center for Research Resources and the NIH National Heart, Lung and Blood Institute-supported Cardiovascular Proteomics Center.

**William Cruikshank, Ph.D.**

Current research in the lab addresses the physical as well as functional interaction between CD4 and its natural ligand, interleukin-16. The studies are designed to investigate this relationship at several different levels. The first is to identify the mechanism by which IL-16 associates with CD4. This includes identification of binding, and bioactive, sites for both IL-16 and CD4. The interaction between IL-16 and CD4 appears to differ in Th1 versus Th2 cells, and therefore a focus of these studies is to delineate this difference. A second set of studies addresses intracellular signaling resulting from IL-16 stimulation of CD4+ T cells. This involves identifying and differentiating pathways involved in the induction of migration versus the effect of IL-16 on cell cycle progression. In addition, studies have indicated that IL-16 stimulation induces receptor cross-desensitization of several of the chemokine receptors. The relationship between CD4 signaling and chemokine signaling is also under investigation. The final set of studies address the in vivo role of IL-16 in the pathogenesis of inflammation. The generation and use of IL-16 transgenic and IL-16 knockout mice have clearly indicated that IL-16 functions to modulate inflammation in a model of allergic asthma. The elevated presence of IL-16 in the lung results in less airway reactivity and less inflammation. A similar finding is seen in a mouse model of rheumatoid arthritis. The mechanism for this effect resides in the ability of IL-16, by virtue of it’s binding to CD4, to
disrupt CD4 dimerization and subsequent contribution to T cell activation. The current hypothesis is that generation of IL-16 at sites of inflammation is a response mechanism that serves to limit the inflammatory response.

**Gerald V. Denis, Ph.D.**

All of the work in our lab is focused on the study of a novel transcriptional co-activator, the double bromodomain protein Brd2. This protein is related to the basal transcription factor TAF250; Brd2 binds to acetylated histones through its bromodomains, then recruits transcription factors and co-activators/co-repressors to chromatin. Through its association with the SWI/SNF complex, Brd2 helps remodel chromatin to regulate the transcription activity of many genes. This highly conserved and ubiquitous protein is essential for life; knockout of the gene is lethal in all organisms tested so far (mice, Drosophila, yeast). We have found that, in mammals, two key targets of Brd2 are the cyclin A locus, which controls cell cycle progression through S phase, and gene targets of the PPAR transcription factor, which controls adipogenic transcription. Brd2 is a positive regulator of cyclin A but a negative regulator of adipogenesis. In transgenic mice that constitutively express Brd2 in B cells, cyclin A is upregulated and the cell cycle is destabilized, leading to an aggressive non-Hodgkin’s lymphoma, which in humans is one of the major contributors to cancer death. We are developing new molecular profiling and therapeutic approaches to treat this malignancy. On the other hand, whole-animal knockdown of Brd2 in mice causes extreme, morbid obesity; dramatically illustrating a role for Brd2 in energy homeostasis. The unexpected role of Brd2 in energy metabolism has profound significance for human health: demographic projections warn of an enormous, worldwide increase in morbidity and mortality associated with obesity. The incidence of individuals with diabetes is expected to reach 366,000,000 by 2030; and these cases will be accompanied by numerous health complications. Much of the incidence Type 2 diabetes will be directly related to obesity. We are investigating human populations to understand Brd2’s involvement in obesity as well as hematologic cancers, and we are actively exploring Brd2 mechanisms of transcriptional control in collaboration with BUSM experts in diabetes and cancer.

**Isabel Dominquez, Ph.D.**

The canonical Wnt pathway is essential for proliferation and cell fate determination in adult tissues and during embryonic development. Our long-term goal is to characterize the mechanism of Wnt signaling and understand the role of the Wnt pathway in development and cancer. We are focusing our studies on the function, regulation and mechanism of action of two components of the Wnt pathway: the serine-threonine kinases CK2 and GSK3beta. To understand the role of these kinases in embryonic development, we utilize two model organisms: the frog Xenopus laevis and the mouse. In Xenopus laevis, we have implicated CK2 and GSK3beta in regulating maternal dorsal fate determination. Currently, we aim to determine how these two kinases are regulated endogenously during early frog Xenopus laevis development. In the mouse, through the study of CK2alpha ablated embryos, we have implicated CK2 in regulating cellular differentiation and morphogenesis of the heart. We are pursuing biochemical, molecular and genetic approaches to determine the downstream targets of CK2 during heart development. Concomitantly, we are using Xenopus and cell culture to understand the molecular mechanism of action of CK2 and GSK3beta in Wnt signaling. Understanding how the Wnt pathway is normally activated is a prerequisite to understand its dysregulation displayed in cancers. Utilizing Xenopus embryos, we have shown that CK2 is sufficient and necessary for canonical Wnt signaling. Ongoing studies focus in determining the mechanism of regulation of Wnt signaling by CK2, and in the development and testing of novel CK2 inhibitors in vivo in Xenopus and in vitro in breast and colon tumor cell lines.

**Thomas A. Einhorn, M.D.**

Research focus on the molecular mechanisms of skeletal repair. Specific areas of investigation include an understanding of the molecular genetics of fracture healing, cartilage repair, and bone regeneration. Studies are performed in vitro and in vivo. Both normal and genetically manipulated animal models are utilized including knockout,
conditional knockout, novel binary systems, and siRNA knockdown protocols. The roles of peptide signaling molecules, pro-inflammatory cytokines, pharmaceuticals and angiogenic agents on bone and cartilage repair and regeneration are investigated.

Douglas V. Faller, M.D., Ph.D.

A major focus of Dr. Faller’s laboratory is the study of the basic molecular and cellular biology of virus- and oncogene-transformed cells and tumors. He determines the mechanisms by which retroviruses and their oncogenes cause tumors, by defining the ways in which oncogenes control host cell gene expression. A special interest of his laboratory involves viral regulation those cellular genes encoding proto-oncogenic molecules and cytokines. Dr. Faller analyzes the molecular mechanisms by which oncogene-transformed cells become autonomous of growth factor requirements. This work involves the elucidation of growth-factor signal transduction pathways and cell cycle control in normal and transformed mesenchymal and lymphoid cells, and study of the ways in which this signaling pathway and cell cycle checkpoints are disrupted or circumvented in tumor cells. This work has resulted in new information regarding the transduction of growth factor signals by second messenger systems in both normal and transformed cells. His laboratory also studies the role of oncogenes in programmed cell death, and how this can be exploited for therapeutic intent. A related area of his research is the interaction of retroviruses and the tumors they induce with cellular immune defense mechanisms. The means by which virus- or tumor-specific cytotoxic T lymphocytes, natural killer cells and monocytes recognize and destroy infected cells and tumors is under investigation, as are the molecular mechanisms by which tumors escape from immune surveillance. The mechanisms of aberrant control of Class I Major Histocompatibility Antigen gene expression in oncogene-transformed cells, retrovirus-infected cells and naturally-occurring tumors are being determined. A new transactivation property of murine leukemia viruses has been elucidated, which controls the expression of genes in the host cell important to the leukemogenic process. His laboratory also has a translational research program which develops molecular cancer therapeutics derived from his basic research, and tests them in clinical trials.

Lindsay Farrer, Ph.D.

Dr. Farrer is Chief of the Genetics Program and a Professor of Medicine, Neurology, Genetics & Genomics, Epidemiology, and Biostatistics at Boston University Schools of Medicine and Public Health. He has served as the dissertation advisor or primary mentor for many pre-doctoral and postdoctoral trainees who have embarked on successful research careers. His laboratory is focused on identifying the genetic basis of several complex diseases and developing genetic mapping methods for locating modifiers for disorders whose primary defects are already known, but account for only a small portion of the phenotypic variation. Such modifier genes will probably be more amenable than the primary structural genes to strategies for delaying or modulating expression. Working together with other BU researchers, his lab is leading efforts to identify genes for hypertension and severe asthma, and genes influencing severity and expression of sickle cell anemia. In collaboration with researchers at other academic institutions, they are conducting genome scans to uncover genes conveying susceptibility to substance dependence and macular degeneration. In 2005, they identified a functional genetic variant in the complement factor H gene which accounts for approximately 50% of the attributable risk for macular degeneration, the leading cause of progressive vision loss and blindness in the elderly. Dr. Farrer’s major research focus is Alzheimer disease (AD). He directs the MIRAGE Project, a multi center study of AD funded since 1991 by the National Institute on Aging which has a long term goal of identifying genetic and environmental risk factors for AD. This study was the first to demonstrate that genetic factors have a major role in the development of AD. His team has also shown that the ε4 variant of apolipoprotein E (APOE), the strongest AD risk factor identified thus far, is more weakly associated with disease in men and persons older than 75 years. The aim of the currently funded project is to compare variations in genes related to vascular functioning with disease risk and pre-clinical changes evident on MRI scan of the brain in 1000 White and African American AD families. In 2007, Dr.
Farrer co-directed an international study which demonstrated in that neuronal sortilin-related receptor SORL1 is genetically and functionally associated with AD. Currently, his lab is conducting genome wide association studies for AD in Caucasian and African American families in the MIRAGE Study and in an inbred Israeli Arab community with an extraordinarily high prevalence of the disorder.

Lisa Ganley-Leal, Ph.D.

Human schistosomiasis, caused by three main species of tissue invasive parasitic trematodes, currently affects over 207 million individuals and remains a significant cause of morbidity in developing countries. Vaccine development for this disease has been hampered by a poor understanding of the mechanisms involved in protective immunity in humans. A relatively consistent finding in field-based studies is a correlation between high serum concentrations of parasite-specific IgE and resistance to reinfection following curative chemotherapy. However, the role(s) of putatively protective IgE remains elusive. In collaboration with the Centers for Disease Control and Prevention and the Kenyan Medical Research Institute, the correlates of immunity to schistosomiasis in an occupationally hyper-exposed group of Kenyan laborers are being investigated. Our preliminary data suggests that increased expression of the IL-4-induced IgE receptor found on B cells, CD23 (FcεRII), is strongly associated with a history of resistance against *S. mansoni* in the occupationally-exposed population. We are currently dissecting the role of CD23/IgE complexes in eliciting protective immunity to schistosomes by correlating field-based clinical studies with our *in vitro* model system to further vaccinology efforts for this disease.

Another focus of my laboratory involves the beneficial relationship between parasitic worms and the human immune system. While some parasitic worms induce significant pathology, such as schistosomes, others have co-evolved with humans and appear to immunomodulate the immune system in a favorable manner. Thus, the "hygiene hypothesis" is based on the premise that lack of exposure to helminths predisposes certain individuals to immune-mediated disease, such as inflammatory bowel disease (IBD). In collaboration with Dr. Francis Farraye and Dr. Barbara Nikolajczyk, we have found that B cells from patients with IBD are chronically activated and that parasitic helminths demonstrate the unique ability to downregulate this inflammatory response. This portion of my research therefore focuses on defining the host-parasite interaction between inflammatory B cells and worms with the ultimate goal of developing naturally-derived anti-inflammatories to treat patients with IBD and other chronic inflammatory diseases, such as diabetes.

Caroline Attardo Genco, Ph.D.

Dr. Genco's laboratory is interested in the characterization of specific bacterial virulence factors produced by the mucosal pathogens *Neisseria gonorrhoeae*, *N. meningitidis*, and *Porphyromonas gingivalis*, and the underlying molecular mechanisms by which these factors enable these organisms to cause disease. She is particularly interested in mechanisms utilized for colonization and in particular in the ability of environmental factors to modulate bacterial gene expression. Her laboratory has defined the mechanisms of iron transport in both *N. gonorrhoeae* and *P. gingivalis*, characterized several outer membrane receptors required for transport and utilization of iron. Dr. Genco's laboratory is particularly interested in how virulence genes are expressed *in vivo* and the role of iron in gene regulation *in vivo*. Iron starvation is used as a signal by many pathogens that they are in a host environment resulting in the expression of virulence factors that are transcriptionally regulated by iron through the ferric uptake regulator protein, Fur. Dr. Genco's laboratory has defined the Fur-regulon in *N. gonorrhoeae*, *N. meningitidis* and in *P. gingivalis*. Her studies have established that the transcriptional regulatory protein Fur controls the expression of numerous genes that are required for the virulence of *N. meningitidis* and *N. gonorrhoeae*. Her laboratory as also recently identified a novel mechanism for Fur-mediated regulation through small regulatory RNAs. Current studies are aimed at examining the regulation and expression of Fur-regulated genes *in vitro*, and *in vivo* directly in clinical specimens. Several different model systems are used to examine the interactions of bacteria with the host. These include animal
models for gonococcal infection and *P. gingivalis* oral infection. Her laboratory also utilizes epithelial and endothelial cells to study the interactions of *N. gonorrhoeae* and *P. gingivalis* with host cells, which are permissive for these pathogens. Currently the laboratory is examining the interactions of *N. gonorrhoeae* expressing GFP (green fluorescent protein) with endocervical, ectocervical and vaginal cell lines. Using these cell lines they have demonstrated distinct proinflammatory responses in different compartments of the female lower genital tract. Furthermore she has also utilized these cells to demonstrate that infection with *N. gonorrhoeae* inhibits the apoptotic response of these cells. Thus *N. gonorrhoeae* may establish infection in women by inhibiting the apoptotic response to infection, thereby resisting killing from both the host cell and the innate immune response. Furthermore, prolonged survival of the host cell potentially allows the bacteria to successfully invade cervical tissue, eventually transcending to the upper genital tract. Another area of interest in Dr. Genco’s laboratory is the development of vaccine candidates to prevent *P. gingivalis* induced periodontal disease. Using several different animal models her laboratory has demonstrated that the *P. gingivalis* cysteine proteases (gingipains), major virulence factors of this organism, function in a protective manner in animal models following *P. gingivalis* challenge. Finally, an exciting area of new work in Dr. Genco’s laboratory is examining the specific cellular and molecular mechanisms by which infectious agents contribute to chronic inflammation and specifically the role of the innate immune response in atherosclerosis. Dr. Genco has established that *P. gingivalis* accelerates atherosclerotic plaque accumulation and that is mediated by innate immune recognition to invasive bacterial infection. Her laboratory has established that *P. gingivalis* infection and inflammation in endothelial cells is mediated through fimbriae signaling through Toll-like receptors. Finally her laboratory has established that TLR2 plays a critical role in the atherosclerotic inflammatory response that is independent of dietary lipids. Current studies are focused on other chronic infections such as that caused by the respiratory pathogen *Chlamydia pneumoniae* in well-defined models of atherosclerosis and defining the role of the innate immune bacteria with the host. These include animal models for gonococcal infection and *P. gingivalis* oral infection. Her laboratory also utilizes epithelial and endothelial cells to study the interactions of *N. gonorrhoeae* and *P. gingivalis* with host cells, which are permissive for these pathogens. Currently the laboratory is examining the interactions of *N. gonorrhoeae* expressing GFP (green fluorescent protein) with endocervical, ectocervical and vaginal cell lines. Using these cell lines they have demonstrated distinct proinflammatory responses in different compartments of the female lower genital tract. Furthermore she has also utilized these cells to demonstrate that infection with *N. gonorrhoeae* inhibits the apoptotic response of these cells. Thus *N. gonorrhoeae* may establish infection in women by inhibiting the apoptotic response to infection, thereby resisting killing from both the host cell and the innate immune response. Furthermore, prolonged survival of the host cell potentially allows the bacteria to successfully invade cervical tissue, eventually transcending to the upper genital tract. Another area of interest in Dr. Genco’s laboratory is the development of vaccine candidates to prevent *P. gingivalis* induced periodontal disease. Using several different animal models her laboratory has demonstrated that the *P. gingivalis* cysteine proteases (gingipains), major virulence factors of this organism, function in a protective manner in animal models following *P. gingivalis* challenge. Finally, an exciting area of new work in Dr. Genco’s laboratory is examining the specific cellular and molecular mechanisms by which infectious agents contribute to chronic inflammation and specifically the role of the innate immune response in atherosclerosis. Dr. Genco has established that *P. gingivalis* accelerates atherosclerotic plaque accumulation and that is mediated by innate immune recognition to invasive bacterial infection. Her laboratory has established that *P. gingivalis* infection and inflammation in endothelial cells is mediated through fimbriae signaling through Toll-like receptors. Finally her laboratory has established that TLR2 plays a critical role in the atherosclerotic inflammatory response that is independent of dietary lipids. Current studies are focused on other chronic infections such as that caused by the respiratory pathogen *Chlamydia pneumoniae* in well-defined models of
atherosclerosis and defining the role of the innate immune response in accelerated atherosclerosis. These studies employ in vitro model systems for platelet, endothelial cells, and macrophages. The common theme of these studies is to examine the role of infection and the innate immune response in early events associated with atherosclerosis in well-defined in vitro and in vivo systems.

**Louis C. Gerstenfeld, PhD**

All of our studies focus on bone repair after trauma or surgical treatment. All of our ongoing research is translational and has adapted human surgical techniques to small animal models to address our research goals. We use a combination of state of the art assessments tools to examine fracture and bone repair in vivo including micro-computer assisted tomography (CT) biomechanical testing for strength and material property and novel tools of three dimensional tissue reconstruction of sequential histological specimens. We use cell based models of primary cultures isolated from the bone marrow and fracture callus and several skeletal cells lines to compliment our animal studies. We use all forms of state of the art molecular analysis both in vivo and in vitro including transgenic animal models, retroviral knock down strategies and various approaches of mRNA expression analysis from RT-PCR to large scale transcriptional profiling.

1) We have numerous ongoing projects covering a diverse set of pre-clinical trials of biological compounds, small molecule pharmaceuticals and cell based therapies that are directed at enhancing fracture healing. Our pre-clinical trials of compounds and drugs involve studies of Bone Morphogenetic Protein (BMPs), VEGF and PTH as therapeutics for improvements in bone healing. We also use cell based stem cell therapies to promote healing. 2) Our basic research studies in fracture healing focus on three project areas. One set of projects examines the role of the innate immune system as a primary initiator in bone regeneration after injury and have primarily focused on the role of tumor necrosis factor (TNF) and Fas mediated cell apoptosis. A second project area is focused on the VEGF signaling during fracture healing. Our final set of projects focuses on the role of inherited genetics in bone and variations in stem cell populations that give rise to repair tissues during fracture healing. This project makes use of inbred strains of mice that have definable variations in bone quality as defined by variation in geometric characteristics and material property intrinsic to mineral and matrix properties. This projects specifically examines how genetic variations effect fracture healing.

**Frank C. Gibson III, Ph.D.**

Dr. Gibson’s primary research interests focus into the mechanisms underlying microbial pathogenesis and gaining better insight into both host-specific and pathogen-specific activities/structures affecting diseases of the oral cavity. The principal organism studied in the Gibson lab is the anaerobic pathogen *Porphyromonas gingivalis*. Ongoing research interests in the Gibson lab include defining the properties of the capsular polysaccharide of *P. gingivalis* that influence disease caused by this organism. Dr. Gibson is interested in the defining the impact of chronic infections such as periodontal disease on the progression of systemic diseases including atherosclerotic cardiovascular disease. In addition, the Gibson lab has initiated studies to identify the influence of aging on the host inflammatory response directed at *P. gingivalis*. Genetic techniques, molecular approaches, as well as cell and animal modeling are routinely employed in the Gibson lab to better characterize novel host-pathogen interactions.

**Jianlin Gong, M.D.**

Dr. Gong’s research work is focused on the development of dendritic cell (DC)-based tumor vaccine. One of the DC-based tumor vaccine pioneered by her group is through the use of fusion between DC and tumor cells. The fusion of DC with tumor cells represents in many ways an ideal approach to deliver, process, and subsequently present tumor antigens to the immune system. DC-tumor fusion vaccine is effective in the elimination of established pulmonary metastases in the animals. Coculture of cancer-patient-derived T cells with the fusion vaccine induces CTL against autologous tumor cells. These studies have culminated in a phase I clinical trial of DC-AML fusion vaccine for patients with acute myelogenous leukemia (AML) in BMC organized by her and Dr. Adam Lerner in the division of Hematology/Oncology. In studying the molecular basis of
DC-tumor fusion vaccine, her laboratory has identified that the tumor-antigen peptides chaperoned by heat shock protein may be the therapeutic component of DC-tumor fusion cells. This finding could potentially be the basis for a vaccine for clinical use. Her laboratory has several transgenic murine models, including a mouse (MMT) with expression of polyomavirus middle T oncogene and development of spontaneous mammary carcinomas. This murine model mimics breast cancer development in humans and thus is highly relevant to the study of human breast cancer. MMT mice are being crossed with mice deficient in telomerase, the biologic clock that controls cell division, to determine the role of telomerase in the tumorigenesis of breast cancer.

**Robert Green, M.D., M.P.H.**

Dr. Green is the Associate Director of Boston University's Alzheimer's Disease Clinical and Research Program, and is the Clinical Director of the NIA-funded Alzheimer's Disease Center. Dr. Green's research interests are in early and preclinical detection, treatment and prevention of Alzheimer's disease. His current research studies have both a clinical and genetic focus. Dr. Green is Principal Investigator and Director of the REVEAL Study (Risk Evaluation and Education for Alzheimer's disease) a multi-center project funded by the National Human Genome Research Institute and the National Institute on Aging to develop genetic risk assessment strategies for individuals at risk for Alzheimer's disease. Dr. Green also serves as a consultant on the NIH-funded Cache County Memory and Aging Study and is the Boston site director of the NIH-funded ADAPT Study (Alzheimer's Disease Anti-Inflammatory Prevention Trial), one of the first large-scale intervention trials to prevent the development of Alzheimer's disease in at-risk family members. Dr. Green is the author of over 120 publications, serves on a number of advisory, editorial and grant review boards, and is immediate past President of the Society for Behavioral and Cognitive Neurology. He has been voted one of America's "Best Doctors" by his peers.

**James A. Hamilton, Ph.D.**

Dr. Hamilton's laboratory is developing and applying novel physical approaches to study of obesity, metabolic syndrome, and cardiovascular disease. 13C NMR methods pioneered in his laboratory have been used to describe the interactions of fatty acids and drugs with binding sites on albumin, and new studies are currently correlating important details predicted by NMR with recent x-ray crystal structure. His laboratory has determined the complete solution structure of several intracellular fatty acid binding proteins (FABP) by multidimensional NMR and is studying the molecular details of ligand binding to FABP. New fluorescence approaches have been developed to characterize the diffusion of fatty acids into adipocytes and evaluate the effects of drugs and inhibitors on fatty acid uptake.

A newer focus of research is the application of magnetic resonance imaging (MRI) to examine fat tissue and atherosclerosis. These studies extend from animal model systems (mouse and rabbit) to humans. The work emphasizes interactions of different disciplines on translation of basic biophysics to human disease aspects. Our study of subjects with metabolic syndrome and obesity explores the hypothesis that a unifying feature of metabolic syndrome is enhanced deposition of lipids throughout the body outside of the normal adipose stores. These inappropriate stores include hepatocellular triglyceride, perivascular and pericardial triglyceride. MR imaging will identify and quantify site-specific abnormalities in obese patients such as cardiac functions.

In our animal studies of atherosclerosis, imaging of live mice allows us to follow diseases and therapies in a single animal over a long period of time. A rabbit model of the acute event of atherosclerosis, plaque rupture and thrombosis is being studied to develop MRI for prediction of unstable and high risk plaques. In humans with advanced carotid atherosclerosis who are undergoing endarterectomy, we will use MRI to determine evidence of inflammation and plaque vulnerability and perform in vivo and ex vivo to enhance the application of MRI to carotid plaque characterization.
Andrew J. Henderson, Ph.D.

Effective strategies for eradicating HIV infection will depend on purging virus from cellular reservoirs that harbor transcriptionally latent HIV provirus. How HIV latency is established and maintained is poorly understood since studies on HIV transcription repression have been hindered by the rarity and inaccessibility of latently infected cells. The primary focus of the Henderson lab is developing approaches to investigate how cellular signals regulate HIV transcription and replication. Current projects include examining signal transduction pathways that impact HIV replication, including repression of provirus transcription. We have characterized both positive and negative signaling pathways that impact multiple steps of the HIV replication cycle. In addition, we have gained insights into how latent provirus is induced providing potential new therapeutic targets for HIV. These studies have provided a better understanding of the factors that limit HIV expression in different cell populations.

Victoria Herrera, M.D.

Our research work focuses on the molecular genetic basis of hypertension and its target organ complications such as increased susceptibility to coronary artery disease and stroke with particular attention to gender-specific issues and fetal basis of these susceptibilities. Work also focuses on the investigation of the role of the dual endothelin-1/angiotensin II receptor (Dear) on cardiac and vascular network development. The investigation of molecular mechanisms underlying hypertension-coronary artery disease interaction involves a) the dissection of pathways involved in vulnerable plaque development and destabilization using an integrated approach spanning histopathology, transcription profiling, biomarker identification and in vivo pathway testing using transgenic rat models, and b) identification of genetic modifiers of hyperlipidemia relevant to gender and genetic background differences through total genome search for putative quantitative trait loci in F2 intercross hybrids. The investigation of the molecular mechanisms underlying hypertension-stroke interaction and dissection of gender-specific issues and fetal basis of adult-onset hemorrhagic stroke involves a) modeling in transgenic rats addressing both gender-specific issues and fetal basis mechanisms, b) investigation of disease course changes in cellular and molecular events in the neurovascular unit, and c) investigation of mechanism-based biomarkers predictive of risk or onset of hemorrhagic stroke. The investigation of the role of a unique dual-ligand receptor, Dear, in cardiac and vascular development involves tissue-specific gene targeting experiments in mouse models as well as development of in vitro experimental systems, based on initial observations identifying Dear as a key player in cardiac and vascular network formation.

Michael F. Holick, M.D., Ph.D.

Our research focuses on how sunlight provides humans with their vitamin D requirement and explores the multitude of roles that vitamin D has for health. Dr. Holick’s laboratory has several mouse models that evaluate the importance of vitamin D nutrition as a chemopreventive agent for human prostate and colorectal cancers. His laboratory is evaluating several novel vitamin D analogues that have the potential for treating colorectal and prostate cancer. Investigations into the mechanism of action as to how vitamin D regulates genes responsible for cellular and proliferation have provided insights into the importance of vitamin D for cancer prevention. A study is underway to evaluate the effect of giving a pharmacologic dose of vitamin D to men with prostate cancer to determine what its impact is on their prostatic specific antigen (PSA) levels as well as quality of life. In addition, a group of men with prostate cancer will be receiving ultraviolet irradiation to determine whether the skin’s production of vitamin D and its photoproducts have any additional benefit for controlling the rise in PSA level and improving quality of life. Studies are underway to better understand how exposure to sunlight affects both human cultured keratinocytes and melanoma cells in culture. The goal is to determine which genes are being regulated by ultraviolet irradiation and how this affects the proliferation and differentiation of the skin cells. Dr. Holick’s laboratory has been investigating the role of parathyroid hormone related peptide (PTHrP) in skin and hair proliferation and differentiation. Studies have shown that PTHrP receptor agonists inhibit
skin cell proliferation and induce terminal differentiation and have been effective in treating psoriasis. PTHrP receptor antagonists enhance epidermal and hair follicle keratinocyte proliferation resulting in stimulating in both skin and hair growth. A study is underway to evaluate the potential clinical application for the use of a PTHrP receptor antagonist for mitigating alopecia in women undergoing chemotherapy for breast cancer.

Robin Ingalls

Over the last decade, a new appreciation for the innate immune system has emerged in the immunology field. The innate immune system is the first line of defense against invading pathogens, and is required to optimize the more specialized adaptive immune response. Our laboratory is interested in understanding the innate immune recognition of pathogenic bacteria at mucosal surfaces. The mucosal surface, once described by the late Charles Janeway as the frontier of the immune system, is a complex biosystem providing physical, chemical and cellular defenses against pathogens while tolerating a host of commensal bacteria. One of the main projects of the laboratory is to understand the role of innate immune receptors, adaptor proteins and soluble mediators in driving responses to the sexually transmitted bacterial pathogens, *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. In particular we are interested in understanding mucosal immune response in the upper and lower female reproductive tract, as these infections disproportionately impact on women, leading to the complications of tubal infertility, ectopic pregnancy, and chronic pelvic pain. We have established *in vitro* and *in vivo* (mouse) models to study both the protective immune response as well as the complications associated with infection. In addition to our long-standing studies on sexually transmitted infections, we have recently started a project to compare the mucosal immune response in the respiratory tract with that of the genital tract, using the mouse pathogen *C. muridarum* and the human pathogen *C. pneumoniae*. Finally, related to the *C. pneumoniae* respiratory studies, we have also started to investigate the role of innate immunity in mediating the chronic inflammatory plaque formation associated with *C. pneumoniae* infection.

Mark Klempner, M.D.

Dr. Klempner's research includes investigations into the basic molecular biology and pathogenetic mechanisms of the Lyme disease spirochete, *Borrelia burgdorferi*, patient-based clinical research on prevention, diagnosis and treatment of Lyme disease and novel molecular methods for detecting, identifying and quantitating microorganisms. Dr. Klempner began his research in the area of host defenses against infection with particular emphasis on the biology of human neutrophils. After basic studies on pathways of signal transduction for secretion and the respiratory burst in neutrophils, as well as clinical studies on the intracellular penetration of antibiotics into these cells, Dr Klempner's research into Lyme disease naturally began with investigations of host defenses against this spirochete. His laboratory has studied how borrelia are killed by human neutrophils, how pathogenic strains resist neutrophil bacteriocidal activity, neutrophil chemotactic factors in synovial fluid of patients with arthritis due to Lyme disease, the ability of borrelia to penetrate and persist in human fibroblasts, and the acquisition of host proteases by borrelia which lead to tissue destruction and invasiveness of Borrelia burgdorferi. Recently his laboratory has cloned and characterized the oligopeptide transport (permease) system in borrelia and is currently investigating how borrelia adapts its nutrient capture to the particular environments that the bacteria encounters (e.g. tick, mouse, human). Using *in vitro* and *in vivo* models Dr. Klempner's laboratory is also studying the role of matrix metalloproteinases (which are made in response to Borrelia exposure) in the pathogenesis of Lyme disease. Methods employed in these studies include the generation of knockout mice deficient in matrix metalloproteinase and proteinase activators (e.g. plasminogen). Dr. Klempner's patient based studies focus in two general areas: vaccine protection and post-treatment chronic Lyme disease. In the vaccine studies Dr. Klempner participated in the human efficacy studies of the Osp A vaccine and was the principal investigator in studies of the consistency of manufacture of the vaccine. He is currently investigating the basis for loss of vaccine efficacy in the elderly (immune senescence) using the OspA lipoprotein
vaccine as a model system. With regard to the clinical studies on patients with post-treatment chronic Lyme disease the Klempner research team is studying, in a double blinded placebo controlled trial, whether intensive antibiotics are beneficial to these patients, whether evidence for persistence of the spirochete can be found in these patient, whether chronic Lyme disease symptoms are due to co-infections with other tick borne pathogens, the utility of novel diagnostic tests in these patients, and the development of a predictive model for patients who might benefit from treatment. His team has recently published the results of the treatment trial which determined that 90 days of antibiotics were not better than placebo and that evidence of persisting borrelial infection could not be found in these patients. The Klempner team also described the presence of a novel 130 kd matrix metalloproteinase in the CSF of some patients with post treatment chronic Lyme disease and the absence of sCD14 in these patients' serum (unlike patients with untreated chronic Lyme disease symptoms). A separate area of research in the Klempner lab is focused on the development of a novel system to detect and identify microorganisms that uses phage display libraries and microsensors. As part of an NSBRI/NASA funded initiative his laboratory has begun the development of "fingerprinting" phage display libraries which can detect, identify, quantify and discriminate bacterial and fungal species in environmental and biological specimens. Arrays of phage displayed peptides and antibody fragments are applied in a microarray to the surface of a microsensor to demonstrate the microarray microbial fingerprint response to selected bacterial and fungal species using optical readout and electronic MEMS resonator arrays. These response patterns are then used for the development of algorithms from the microarray response for the real time identification and discrimination of microbial species.

Darrell Kotton

The remarkable capacity of stem cell populations (such as adult hematopoietic stem cells and embryonic stem cells) to indefinitely self-renew or differentiate into multiple lineages has generated considerable excitement in the scientific and lay communities alike. Although stem cells hold enormous promise for the field of regenerative medicine, our approach is based on the long-term goal of understanding how stem cells recapitulate normal developmental milestones as they self-renew and differentiate. Because appropriate recovery of the lung epithelium after injury involves reactivation of early developmental pathways, understanding how embryonic stem cells differentiate and develop into lung epithelial lineages is likely to reveal how the lung recovers from injury and disease. For our studies we employ a murine embryonic stem cell line engineered to express three knock-in reporter molecules (Brachyury-GFP, Foxa2-hCD4, and Titf1-hCD8). Sequential expression of these reporters indicates the sequential differentiation of ES cells through a primitive streak-like stage into multipotent endodermal precursors followed by early lung epithelial progenitors. Thus, this novel tool should allow us to precisely quantify and purify cells progressing through early stages of endoderm and lung development. Currently we are able to efficiently derive multipotent definitive endoderm in 66% of cultured ES cells after activin A stimulation. These endodermal precursors may be purified by flow cytometry and possess the capacity to undergo further lineage specification into early liver, pancreas, and lung epithelial precursor phenotypes. In contrast to undifferentiated ES cells, which form teratomas in mice if transplanted, our purified endodermal precursors derived from ES cells may be transplanted under mouse kidney capsules where they do not result in teratomas but rather form organized luminal structures with a highly organized epithelium. We are currently focused on the derivation of Titf1+ lung epithelial progenitors from ES cells using a combination of growth factors (e.g. Activin A and FGFs) designed to mimic early in vivo development. Our plan is to test the in vitro and in vivo developmental potential of our ES cell-derived putative lung epithelial progenitors in a variety of ex vivo assays as well as in mouse models of lung injury. We believe the ES cell system provides an ideal platform to model the early developmental steps involved in lineage specification and differentiation of the lung epithelium from multipotent endoderm. Little is known about the mechanisms that control these early developmental cell fate decisions. We propose approaches designed to
evaluate candidate mechanisms controlling lineage specification of lung epithelium from multipotent endodermal precursors. These approaches are designed to test mechanisms for which there is support in the literature as well as in our preliminary data. For example, focused gene expression data obtained by analyzing ES cell-derived endoderm as well as microarrays prepared from the primordial lung field of developing embryos suggest that the transcription factor GATA6, the canonical wnt signaling pathway, and chromatin remodeling proteins (Brm, Brg1, and Suz12) all play important roles in specifying lung lineage in the developing endoderm

Robert Lafyatis, M.D.
The research of Dr. Lafyatis centers on understanding the pathogenesis of systemic sclerosis (also know as scleroderma). Scleroderma is a systemic autoimmune disease that leads to fibrosis of skin and internal organs and to vascular complication including pulmonary hypertension. The Boston University rheumatology section has a large clinical interest in scleroderma with the largest patient population in the New England area. The clinical program carries out multiple early and later phase clinical trials, providing many opportunities for patient related, translational studies. Closely coordinated with these studies and utilizing this patient population, Dr. Lafyatis is investigating biomarkers of disease activity thorough immunohistochemical studies of marker genes and microarray analyses of skin biopsies in collaboration with Dr. Michael Whitfield at Dartmouth Medical Center. These studies are designed to define biomarkers of disease activity and progression in patients with scleroderma. Dr. Lafyatis also directs the laboratory effort investigating scleroderma in collaboration with several investigators in the section and other investigators in the immunology program, the pulmonary center and the biochemistry department. We have a long-standing interest in fibrosis. Dr. Lafyatis and co-investigator Dr. Raphael Lemaire have particularly studied the tight skin (Tsk) mouse model of dermal fibrosis, and over the last several years made several critical observations. Mice with this phenotype develop tight skin caused by a mutation in the fibrillin gene. We have linked the phenotype in these mice closely to this mutation by showing that several proteins known to interact with fibrillin, microfibril associated protein-2 and fibulin-2, are increased in the hypodermis of these mice and may stimulate other matrix proteins. More recently we have found that two genes involved in intercellular signaling, the Nov (CCN3) and Wnt2 genes, are highly upregulated in these animals and we are currently investigating the roles of these regulators in mediating the effect of fibrillin on Tsk and scleroderma skin fibrosis. In addition, Dr. Lafyatis has been studying autoimmunity in scleroderma sparked by clinical/translational observations they made recently, showing that interferon-regulated genes are upregulated in white blood cells from scleroderma patients, as they are in several other diseases, including systemic lupus erythematosus. These continuing investigations have been greatly aided by a close collaboration with Dr. Jean van Seventer in the Boston University School of Public Health. We are currently investigating the roles of innate immunity and, in particular, toll-like receptor-mediated regulation of interferons in scleroderma by nucleic acid-containing immune complexes. This work is in collaboration with Dr. York (Rheumatology section), Dr. Ann Marshak-Rothstein (Microbiology Department) and Dr. Ian Rifkin (Nephrology Section) at the Boston University Medical Center. The goal is to extend observations made in systemic lupus erythematosus to scleroderma, regarding the association of autoantibodies to nucleic acids as potential activators of innate immunity to the pathogenesis of scleroderma vasculopathy and fibrosis.

Adam Lerner, M.D.
My laboratory studies two topics: cyclic nucleotide-mediated apoptosis in lymphoid malignancies and the role of a novel family of focal-adhesion-associated proteins in breast cancer anti-estrogen resistance. With regards to the first topic, we have shown that PDE4 cyclic nucleotide phosphodiesterase inhibitors inhibitors selectively induce apoptosis in chronic lymphocytic leukemia (CLL) cells. Such PDE4 inhibitors are already in clinical trials as antiinflammatory medications for asthma and COPD. We are interested in determining the mechanism by which such drugs kill CLL cells and the best way to take advantage of this activity in clinical trials in CLL. We are also studying EPAC,
cAMP-activated Rap1 GDP exchange factor that is activated in CLL cells following treatment with PDE4 inhibitors. Remarkably, CLL cells are the only circulating hematopoietic cells that appear to express functional levels of EPAC. As EPAC activation is anti-apoptotic when it occurs in the absence of concomitant PKA activation, we are interested in whether EPAC may be a novel therapeutic target in CLL. A second area of interest is AND-34, a novel p130Cas-associated protein that activates Rac and Cdc42 in breast cancer cell lines and in B lymphocytes. Over-expression of AND-34 or p130Cas induces anti-estrogen resistance in human breast cancer cell lines and, at least for AND-34, this appears to occur in a Rac-dependent fashion. We are examining the mechanism by which AND-34 activates Rac and what "upstream" signaling pathways initiate such AND-34-mediated Rac activation in breast cancer cells.

**Jining Lu**

miRNA are small regulatory RNAs that modulate gene expression by translational suppression and degradation of its target mRNAs. miRNAs play an essential role in development and diseases, such as cancer, cardiac hypertrophy and fibrosis. We are interested in the roles of miRNAs in lung development and diseases.

Roles of miRNAs in Shh or Tgfb signaling pathways in early lung development. Both Shh (sonic hedgehog) and Tgfb pathways play critical roles in lung development, however, little is known about the roles of miRNAs in these pathways. Our strategy is to profile miRNA expression in early lung explants in which Shh or Tgfb pathway activities are selectively inhibited. Then, we will study the function of miRNAs whose expression levels are influenced by Shh or Tgfb activity using in vitro or in vivo approaches.

The function of Tnrc6 gene family members in mouse lung development. This gene family encodes three members of the trinucleotide repeat containing 6 proteins, including Tnrc6a (GW182), Tnrc6b and Tnrc6c. These proteins associate with RNAs and Argonaute proteins in a cytoplasmic body called GW-body or P-body. In vitro assay has revealed their important roles in RNAi and miRNA induced gene silencing. Our objectives are to understand their roles in lung development in vivo using genetic approaches.

miR-129 in cell cycle regulation. It has been reported that miR-129 expression is downregulated in tumor cell lines or primary tumors derived from neural or gastric or colorectal tissue, however its role in cell proliferation is unknown. We have found that over-expression of miR-129 arrests the growth of multiple tumor cell lines originated from different organs. Currently we are studying the mechanism of miR-129-mediated cell growth arrest. We are also interested in the role of miR-129 in lung development and in homeostasis of adult lung in vivo.

miRNA in lung fibrosis. We will profile laser-captured samples from IPF or normal subjects to identify miRNAs that are significantly altered in some specific features of the IPF, such as fibrotic foci. We will study their roles in fibrosis using in vitro or in vivo approaches. We are also interested in the function of miRNAs downstream of Tgfb pathway in lung fibrosis, such as the role of miR-29 in this disease process.

**Weining Lu**

The primary research interests in my laboratory focus in the kidney development and the molecular basis of congenital anomalies of the kidney and urinary tract (CAKUT). CAKUT is a family of diseases with a diverse anatomical spectrum, including kidney anomalies (e.g. renal dysplasia, duplex kidneys, renal cystic diseases, hydronephrosis), and ureteric anomalies (e.g. vesicoureteral reflux, megaureter, ureterovesical or ureteropelvic junction obstruction). As many as 2% of human fetuses have renal and urological anomalies which is the primary cause of kidney failure in young children. These patients may present later in life with reflux or obstructive nephropathy, a condition that manifests with low nephron numbers, secondary focal and segmental glomerulosclerosis (FSGS), proteinuria, and hypertension. My research program has adopted combined human and mouse molecular genetics approaches to identify a
number of different developmental genes (e.g. ROBO2, NFIA) to the study of kidney development and CAKUT. The first human molecular genetics approach is to study individuals with CAKUT and apparent chromosomal defects, with the aim of using chromosomal translocations as signposts to identify these critical genes (reverse genetics). Thereafter, molecular identification and analysis of candidate genes as well as mutation studies in affected individuals with a familial pattern of CAKUT will be carried out (forward genetics). The second approach is to study temporal and spatial expression patterns of candidate genes in human and mouse. Meanwhile, we will generate and study knockout and transgenic mouse models of candidate genes to elucidate more fully their role in kidney and urinary tract development. Once these candidate genes (e.g. ROBO2, NFIA) have been identified, we will take a multidisciplinary approach to gain further mechanistic insights in vivo and in vitro on the role of these genes in normal and abnormal developmental processes of the kidney and urinary tract, and on the pathogenesis of CAKUT. This multidisciplinary approach includes the application of human and mouse molecular genetics, developmental biology, renal physiology, molecular biology, and biochemistry. The ultimate goal is to provide new knowledge of disease mechanisms underlying developmental antecedents of CAKUT and to identify potential therapeutic interventions.

Zhijun Luo, Ph.D.

Protein phosphorylation is an important regulatory process that controls almost all cellular programs including cell proliferation, differentiation, survival, apoptosis and metabolism. It is a process in which kinases catalyze the transfer of phosphate from ATP to target proteins at tyrosine, serine or threonine residues, thereby regulating their functions. Mutations of responsible kinases and their activators have been frequently found to associate with unrestrained growth of cancer cells. Thus, our overall research interest is to understand how protein phosphorylation regulates cell metabolism and growth and how its alteration causes functional abnormalities such as malignancy and the metabolic syndrome. Specifically, our current research projects include the following: (1) regulation and function of Raf kinase, an important effector of Ras and an upstream kinase of Erk and (2) regulation of cell metabolism in cancer cells by AMPK.

Monty Montano, Ph.D.

The Montano laboratory is broadly interested in host-pathogen genomics, muscle stem cell biology and aging research. The role of immune factors in determining muscle growth versus muscle atrophy is relevant to many disease states such as HIV associated wasting, muscular dystrophy and aging associated sarcopenia. My laboratory is currently engaged in an NIH funded study to investigate immuno-myogenic interactions in the context of muscle stem cell proliferation, lineage commitment and differentiation. Experimental systems include muscle stem cell isolation and monocyte co-culture using human and rodent cells. Experimental methods include flow cytometry, multiplex protein profiling, microarray analysis, retrovirology and cell and molecular biology. We are also using the model organism C.elegans in aging research of candidate longevity genes.

John Murphy, Ph.D.

The Biomolecular Medicine Unit: Research in the Unit of Biomolecular Medicine in the laboratory of Dr. John R. Murphy has continued to focus on the development of diphtheria toxin-based fusion protein toxins as experimental probes for cellular biochemistry, the genetic and structural analysis of the diphtheria toxin repressor (DtxR), and metal ion homeostasis and gene regulation in Bacillus anthracis. Studies on the molecular mechanism by which the catalytic domain of DAB389IL-2, a diphtheria toxin-based interleukin-2 receptor targeted fusion protein toxin, is specifically translocated from the lumen of early endosomes to the cytosol of target eukaryotic cells has clearly demonstrated that a cytosolic translocation factor complex is required for toxin entry (atts et al., J. Cell Biology, 2003; 160: 1139-1150). These studies have demonstrated that translocation of the toxin catalytic domain is dependent upon this complex of factors which include Hsp90 and thioredoxin reductase. Current studies are focused on the transmembrane domain of the fusion protein toxin and the characterization of a putative 12 amino acid “entry motif” required for membrane translocation. Additional studies in
the laboratory are focused on the molecular mechanism(s) and structural basis by which the diphtheria toxin repressor (DtxR) undergoes a transition metal ion-dependent transition from the inactive apo-form to the metal ion-bound active form of the repressor. These studies has shown that the src homology 3-like domain of the diphtheria toxin repressor, DtxR, modulates repressor activity through interactions with the ancillary metal ion binding site (Love et al., J. Bacteriol, 2003; 185:2251-2258). Since DtxR has provided the paradigm for the understanding of metal ion control of virulence gene expression in pathogenic gram positive bacteria, these studies have been recently extended to the molecular analysis of AntR, the DtxR homolog found in B. anthracis. The structural gene encoding AntR has been cloned, and the repressor has been expressed and purified from recombinant E. coli. AntR structure function is currently being analyzed by molecular genetic and biophysical methods.

Richard H. Myers, Ph.D.

Research interest is focused upon the application of genetic research methods for the investigation of adult onset diseases with complex etiology (Parkinson's disease, coronary heart disease, Alzheimer's disease, osteoarthritis, osteoporosis etc.). He has a long-standing interest in Huntington's disease and has participated in a wide range of research investigations for this disease. He was a member of the New England Huntington's Disease "Center Without Walls" since its inception in 1980. His HD studies may best be characterized as 'Neurobiological Studies' in that they include studies into the mechanisms disease expression, including complex genetic modifier studies and a series of neuropathological studies of effects of disease expression in the brain. He has been involved in a number of studies in positional cloning. From 1980 to 1993, he participated in the cloning of the gene for Huntington's disease. He then initiated the genome scan project in the Framingham Study, and initiated an NIH funded project for a genome scan in Parkinson's disease. Since 1993 he have participated in genetic linkage studies for hypertension (the HyperGEN study, one of the NHLBI Family Blood Pressure Program Project studies), and the genome scan in the NHLBI Family Heart Study.

Caryn L. Navarro

Molecular motor activity is important for the execution of many biological processes such as cell division, organelle positioning, intracellular transport, vesicle sorting and intracellular pathogen targeting. The dynein motor complex, which travels along the microtubule network carrying cargos of various sorts in a minus end directed fashion, plays a major role in all of these processes. The importance of this complex is seen in the dramatic phenotypes exhibited by most organisms when members of the dynein complex are mutated. For example, loss of function of the dynein associated protein Lissencephaly 1 (Lis-1), leads to neurodegenerative disease due to a lack of neuronal migration. Lis-1 is important for RNA localization, cell division and nuclear migration in the Drosophila ovary, as well as neuronal migration in the mammalian nervous system. Therefore, an understanding of how this complex recognizes its cargos, how directionality of movement arises and what cellular processes regulate complex movement will provide insight into the nature of diseases such as cancer and neurodegeneration. My research uses the Drosophila to understand the mechanisms of dynein directed molecular transport and how intracellular transport is affected by mutations in piRNA (piwi-interacting) pathway components. Drosophila provides a good model system to address these questions since directional transport is important for the establishment of oocyte fate and polarity as well as epithelial cell polarity and neuroblast fate, and many of the genes important for this process are conserved between Drosophila and higher eukaryotes. Furthermore, these processes can be visualized in vivo, and the well-established genetics of Drosophila makes this system easy to manipulate.

Barbara S. Nikolajczyk, Ph.D.

My lab is interested in understanding inflammation in type 2 diabetes and inflammatory bowel disease patients. Inflammation is strongly implicated in the most dire complications of type 2 diabetes, including cardiovascular disease and stroke. We are focusing on two cell types that promote inflammation in these patients: monocytes and B cells. Monocytes are well known to produce significant amounts of pro-inflammatory
cytokines. We are specifically interested in how IL-1 beta, a cytokine at the apex of multiple pro-inflammatory cascades, is hyper-expressed by monocytes from type 2 diabetics. We have defined a “poised promoter architecture” for the IL-1 beta locus in normal monocytes. This structure is characterized by a constitutively accessible promoter and constitutive transcription factor association. Current work is aimed at understanding how this structure is changed in patients to result in IL-1 beta hyper-production. A second focus of the lab is to understand how B cells contribute to type 2 diabetes and inflammatory bowel disease through production of pro-inflammatory cytokines. We have found B cells in type 2 diabetes patients are fundamentally altered such that they unexpectedly respond to inflammatory stimuli. Ongoing analyses are characterizing these responses as well as the underlying molecular mechanisms driving them. These studies are aimed at identifying targets for alleviating the over-production of pro-inflammatory cytokines generally associated with the devastating complications of systemic inflammatory diseases.

Gwynneth Offner, Ph.D.

Dr. Offner’s laboratory has had a long-standing interest in the structure, function and regulation of epithelial mucins. During the past decade, cloning studies on epithelial mucins have identified at least twenty distinct mucin genes, which can be divided into two groups: membrane-associated and secreted gel-forming mucins. Recent studies in her laboratory have focused on the former, specifically on MUC1. MUC1 is overexpressed in many cancers, including breast, colon, pancreatic and lung. Using RNA interference, her laboratory has shown that suppression of MUC1 gene expression leads to changes in cell phenotype and a decrease in the metastatic potential of cells. MUC1 is also expressed in normal cells, where it functions in epithelial cell protection. Dr. Offner’s hypothesis is that membrane bound mucins interact with secreted mucins to enhance the epithelial protective barrier. She has identified specific domains in the secreted mucin MUC5B which interact with a domain at the amino-terminal end of MUC1. Currently, she and her colleagues are investigating the binding of other proteins to the mucin scaffold, which could modulate mucin function in different cell and tissue types. The integrity of the mucin scaffold may have particular relevance to the pathogenesis of inflammatory bowel disease and this is a current focus in the laboratory.

Caroline Panhuysen, M.D., Ph.D.

Dr. Panhuysen’s research interests focus on the genetic epidemiologic analyses of complex traits. The use of these analytical methods such as analysis of familial correlations, segregation analysis, and linkage analysis, are designed to unravel evidence for the genetic basis of the disease with the purpose to get a better understanding of the etiology of the disease. Dr. Panhuysen has been actively involved in a genetic epidemiological study of a cohort of Dutch asthma families for the past 10 years. She is currently involved in genetic studies on Inflammatory Bowel Disease, Substance dependencies, Uterine Leiomyomata (fibroids) and Age-related Macular Degeneration (AMD).

Paul F. Pilch, Ph.D.

The modern Western diet coupled with a sedentary lifestyle has led to an epidemic of obesity, a consequence of which is a dramatic rise in the incidence of type II diabetes, a malfunction in insulin-regulated metabolism. The objective of my research is to describe the biochemical and cell biological details of the signaling pathway between the insulin receptor and its intracellular targets, principally the tissue-specific glucose transporter GLUT4. We study the following specific areas. We wish to determine how insulin regulates vesicular trafficking and protein targeting with regard to GLUT4 and the insulin receptor. We are characterizing the protein content of GLUT4-containing vesicles and we are trying to identify the organelles through which they pass on their way to and from the cell surface and to determine their characteristic components. The signal transduction pathway(s) components specific to insulin signaling remain incompletely described, and we are trying to fill in gaps in this process. The regulation of glucose uptake by insulin is tissue specific, and therefore, we study gene expression in muscle and fat relevant to this process. As part of this, we have examined signaling pathways leading to muscle
differentiation and the expression and regulation of the muscle specific mitochondrial uncoupling protein, UCP-3. The expression of this protein, and insulin independent regulation of Glut4 by exercise, is mediated by AMP-dependent protein kinase whose substrates we are seeking to identify. Finally, we also study the functions of caveolae, invaginations of the plasma membrane that are particularly abundant in adipocytes and in muscle that may function in these tissues in aspects of signal transduction and/or nutrient uptake.

Maria I. Ramirez, Ph.D.

The main focus of my research is the differentiation of lung epithelial cells during mammalian development. We study two developmental events at the molecular level: the initial determination and specification of the endoderm to become lung epithelium and the differentiation of alveolar type I cells to form the air-blood barrier perinatally. Molecular mechanisms that initiate lung formation from the embryonic foregut: Using extremely sensitive methods for dissection of small tissues and analysis of gene expression, we have identified new and known genes expressed during differentiation of endoderm cells into lung epithelial cells. Chromatin remodeling and DNA methylation genes significantly change their expression level coincident with the formation of the lung primordium. Based on these findings and the importance of chromatin modifications in the regulation of cell fate decisions in other developing systems, we are evaluating whether chromatin modifications and DNA methylation participate in initiation of lung development by establishing patterns of gene expression in the embryonic foregut, inducing lung cell fates. Lung alveolar type I cell morphogenesis: The extensive distal lung gas-exchange surface that supports respiration at birth forms in the last 2-3 days of gestation in mice. This process requires differentiation of epithelial type I and type II cells, vascular remodeling and thinning of the mesenchyme. During lung development, progenitor cuboidal epithelial cells remodel their apical and basolateral plasma membranes and cytoskeleton resulting in cell flattening, thinning and spreading. These processes, to which we refer collectively as cell flattening, are a hallmark of type I cell differentiation and are required for alveolar sac enlargement perinatally, and for repairing the lung epithelium after injury in the adult. We are studying epithelial type I cell flattening during development using models of normal and altered lung epithelial morphogenesis, focusing in the membrane enlargement and cytoskeleton reorganization that take place to increase the surface area covered by epithelial type I cells 25-100 fold during type I cell morphogenesis.

Katya Ravid, Ph.D.

The mechanisms that regulate lineage commitment and the subsequent steps of cellular maturation of bone marrow stem cells are poorly understood. In the platelet lineage, the early committed cells undergo a unique cell cycle leading to the formation of polyploid cells prior to fragmenting into platelets. Our goal is to study the genetic and signaling factors that control lineage commitment and the regulation of the cell cycle during this process. Studies focus on cell cycle regulation and its impact on the regulation of transcription of lineage specific genes, including in vascular smooth muscle cells. The systems used include: primary bone marrow cultures and cell lines as well as transgenic and knock out mice.

Ian Rifkin, M.D., Ph.D.

The overall goal of my research is to better understand basic mechanisms involved in the pathogenesis of systemic autoimmune disease in general and systemic lupus erythematosus (SLE) in particular. There are two main projects in the laboratory, both involving the use of murine models of lupus. The first project focuses on the identification and cloning of autoreactive T cells, testing the pathogenicity of the cloned T cells in-vivo, and studying their in vivo regulation and activation. The second project focuses on i)the role of autoantigen itself (DNA/protein or RNA/protein complexes) in activating the innate and adaptive immune responses characteristic of SLE through engagement of Toll-like receptors in dendritic cells and autoreactive B cells and ii) the development of strategies to inhibit this activation in vivo with a view to identifying novel therapeutic targets in
autoimmunity. In addition to the murine studies, collaborations have been established to test whether similar pathogenic pathways are important in human SLE.

Carol L Rosenberg MD
This lab investigates the molecular and genetic alterations that are important early in human breast carcinogenesis. Our overall goal is to identify the abnormalities characterizing early cancer development, even before the tissue is histologically fully malignant. We hypothesize that these genetic abnormalities are biologically meaningful and clinically relevant. In testing this hypothesis, we (and others) have shown that cancer-related abnormalities can be present in hyperplastic lesions and even in histologically normal epithelium. We study primary human tissues, and we ask questions and employ techniques suitable to that material, including laser capture microdissection, loss of heterozygosity and copy number alteration, mRNA and miRNA expression [measured by microarray and quantitative PCR], and immunohistochemistry. Since we attempt comprehensive genetic analyses of the data, the work is multidisciplinary, and collaborations with pathologists, geneticists, surgeons and bioinformaticians and biostatisticians are crucial. In addition, we have projects ongoing with organizations both inside and outside BUMC, including the Framingham Heart Study and the Nurses’ Health Study-Benign Breast Disease Substudy. Identifying and understanding the landscape of molecular and genetic abnormalities in premalignant and histologically normal tissue should generate novel markers of breast cancer risk, uncover mechanisms implicated early in cancer initiation and progression, and identify new targets for cancer prevention and treatment. This work has been supported by funds from the NCI, the Department of Defense, the LaPann Fund and the Susan G Komen, Mary Kay Ash and Avon Foundations.

Sayon Roy
We are working on projects related to the pathogenesis of diabetic microangiopathy, in particular, vascular complications in diabetic retinopathy and diabetic nephropathy. One of the projects involves applying a novel gene therapeutic strategy to normalize altered gene expression in the retinal capillary cells with the goal of preventing characteristic lesions of diabetic retinopathy. A second project, aims at understanding the role of gap junction intercellular communication in the development of retinal vascular lesions associated with cell death in early diabetic retinopathy. In this project we are investigating whether high glucose alters the expression of endothelial specific connexins (Cx37, Cx40, Cx43), and connexin phosphorylation. A third project attempts to unravel the mechanism(s) underlying blood retinal barrier breakdown in diabetic retinopathy. Because tight junction serves as the permeability barrier we are currently investigating whether the synthesis of occludin and ZO-1, and other endothelial tight junction proteins are altered by high glucose condition in vitro and in retinal capillaries of diabetic rats. A fourth project attempts to identify a biochemical link between the pathogenesis of diabetic retinopathy and diabetic nephropathy in terms of altered ultrastructure and function of the retinal and glomerular capillaries from the perspective of high glucose-induced overexpression of extracellular matrix proteins.

Neil Ruderman, M.D., Ph.D.
Dr. Ruderman’s research deals with the effects of insulin, exercise, and fuels on cellular metabolism, signal transduction, and most recently, gene expression. Its focus in the past 10 years has been on a malonyl CoA fuel sensing and signaling mechanism described by his laboratory and its regulation by AMPK. His group has proposed that dysregulation of this mechanism, leading to increases in fatty acid esterification and/or the generation of reactive O2 species, plays a causal role in the pathogenesis of many forms of insulin resistance in skeletal muscle and the early endothelial cell damage that antedates atherosclerosis in diabetes. Their research also examines the notion that activation of AMPK prevents this dysregulation and, perhaps independently, later events that it causes (e.g., NFκB-mediated gene expression). Some of the investigators in his unit and their fellows work primarily with skeletal muscle (Saha), some with cultured vascular cells (Ido), and still others with adipocytes (Luo). Thus, from a conceptual perspective, mechanisms worked out in one system are often tested in others. The techniques employed by the Ruderman laboratory include reporter gene assays,
adenoviral gene transfer (cultured vascular cells), immunofluorescence microscopy, protein separation, enzyme analysis, and metabolite determination by spectrophotometric and chromatographic methods. The models used include incubated tissues, cultured cells, intact rodents and, in some collaborative efforts, humans. Many program faculty are co-investigators and/or advisors in this work, as are individuals from other institutions. The latter include Drs. Marc Prentki, University of Montreal (malonyl CoA regulation); E.W. Kraegen, Garvan Institute, Australia (insulin resistance in rodents in vivo); Guenther Boden, Temple University (insulin resistance in humans); and David Carling, Hammersmith Hospital, U.K. (molecular biological approaches to study AMPK action in vascular cells).

Joshua D. Safer, MD
Diseases of cutaneous proliferation and differentiation are poorly treated. Among the elderly, chronic wounds cost $8-12 billion dollars annually in medical costs and more in to lost productivity. Current wound healing agents are expensive and have been associated with increased scarring. In addition, hyperproliferative skin diseases like psoriasis afflict 1% of the human population and result in further financial toll.

Although skin is the largest organ in the body, the role of thyroid hormone metabolism in epidermal proliferation has not been investigated with rigor. In the thyroid research unit we endeavor to establish mechanistic pathways integral to thyroid hormone action on adult skin. The research attempts to provide possible therapeutic targets for enhancing or suppressing the proliferative response of skin in such diverse conditions as psoriasis, burn injury, and wound healing. The laboratory has been developing a research program to demonstrate that local manipulation of thyroid hormone economy would prove a novel and cost-effective strategy for the treatment of cutaneous pathology.

The active thyroid hormone, $T_3$, is necessary for both growth and differentiation of skin cells. Previously we have found that epidermal proliferation is diminished in hypothyroid mice, that topical $T_3$ can stimulate epidermal proliferation and that topical $T_3$ can accelerate wound healing. The major circulating pro-hormone, $T_4$ is converted to $T_3$ by intracellular thyroid hormone deiodinases. Part of the research done in the lab relates to establishing thyroid hormone deiodinase expression and activity in order to highlight the potential to target the deiodinases in order to treat skin disease.

Current projects in the lab include the following: 1. Immunohistochemistry to demonstrate the tissue locations of the thyroid hormone deiodinases in a murine model. 2. Western protein analysis and rtPCR analysis of cultured cells for protein and gene expression 3. Cultured cells to quantify deiodinase activity in the cells found to express the protein and RNA.

In addition, projects in the lab include making use of a murine model where thyroid hormone, thyroid hormone analogs, and thyroid hormone antagonists can be topically applied to murine epidermis. Biopsies of the epidermis are taken and subject to investigation. The investigation includes immunohistochemistry, rtPCR, and BrdU incorporation into RNA. We supplement the in vivo experiments with a combined culture model in which a cell type can be evaluated after exposure to another cell type.

David Salant, M.D.
The focus of Dr. Salant's laboratory is on the immune basis of glomerular diseases with particular regard to the humoral mechanisms of glomerular cell injury in order to elucidate the mechanisms by which antibodies alter the function and morphology of glomerular visceral epithelial cells (podocytes). Experimental models of immunological glomerular diseases resembling those seen in man are used to obtain a fundamental understanding of the immunopathogenetic mechanisms of injury. Specific interests include: The structural biology of the podocyte and alterations that lead to the development of proteinuria. The effects of antibody- and complement-mediated podocyte injury on the podocyte cytoskeleton and slit-diaphragm protein complex. The role of complement regulatory proteins in limiting complement-mediated podocyte injury. The role of the notch family of signaling receptors in glomerular development and response to injury. Identification of the target antigen/s in human membranous nephropathy.
Jennifer J. Schlezinger

Humans receive significant ambient daily exposures to multiple environmental contaminants, including aromatic hydrocarbons (by-products of combustion), phthalate esters (plasticizers used in manufacturing PVC) and organotins (antifouling agents). These types of contaminants induce a suicide program (i.e. apoptosis) in developing B lymphocytes within the bone marrow. We want to know how synthetic chemicals override the naturally occurring cellular processes to induce death. We investigate multiple processes in the cell that may be altered by these chemicals, particularly how chemicals interact with receptors such as the aryl hydrocarbon receptor (AhR) and the peroxisome proliferator activated receptors (PPAR). Our newest research is focused on how activation of PPARγ in the bone marrow may alter the bone marrow microenvironment, potentially adversely effecting lymphopoiesis. Further, as real-world exposures, such as those at Superfund sites, typically involve complex chemical mixtures, we want to investigate how chemicals within the mixtures may interact to enhance deleterious effects. Understanding these pathways is important because loss of B lymphocytes could potentially impair the ability to mount an immune response to infections. On the other side of the coin, our understanding of death pathways and mixture interactions potentially may be put to use in the development of new chemotherapeutics.

Faina Schwartz, Ph.D.

I am interested in molecular genetics of complex disorders. Presently, several approaches are being pursued in search of genes and genomes involved in hypertension - an age-related disorder afflicting a large proportion of the adult US population. One project, funded by the National Institute on Aging, is designed to assess the role of the mitochondrial genome in hypertension (HTN). Over the past few years, we developed a novel method for the detection of mitochondrial involvement in complex disorders and applied it to the hypertension data set from 350 Caucasian and 98 African American pedigrees ascertained through the HTN clinics at Boston Medical Center and collaborating clinical sites. Remarkably, we found the fraction of families potentially due to mtDNA mutations to be ~55% (95% CI, 45%-65%). Sequence analysis of the entire mitochondrial genome in 10 African American and 10 Caucasian hypertensive probands from families with suspected mitochondrial involvement lead to the identification of several novel, as well as previously reported, mutations with a likely pathogenic effect. Presently, we seek to confirm our findings in an independent cohort, the Framingham Heart Study (FHS) participants, and to further assess the role of mtDNA variants in BP homeostasis. Our strategy combines epidemiologic and molecular genetic approaches and, to the best of our knowledge, is the first comprehensive study of the role of mitochondrial genes in hypertension and associated BP phenotypes conducted to-date. The major strengths of the study, that include the wealth of clinical and genetic data available for FHS subjects and the ability to perform longitudinal association analyses; the large number of DNA samples available through the BU SCOR program and the FHS resource that provide good power to detect association with common and rare mtDNA variants; the availability of two independent study samples for result confirmation; and the team of experienced collaborators with complementary areas of expertise, are bound to enhance our present understanding of the genetic determinants of blood pressure homeostasis. Another ongoing project, conducted in collaboration with Dr. Haralambos Gavras, is aimed at genome-wide gene expression profiling of organs in experimental animal models of hypertension using the method of Serial Analysis of Gene Expression (SAGE). We used the SAGE method to analyze the global transcriptional changes in the kidney, heart, and brain of mice that developed hypertension in response to chronic Angiotensin II administration, and identified several novel targets of Angiotensin II regulation. We plan to extend the methods established in our laboratory to the study of other complex phenotypes, such as longevity and a spectrum of aging-associated disorders.

John H Schwartz, M.D.

Renal epithelial cells are highly polarized. This polarization is required to perform biochemical work (transport) and to maintain the integrity of the epithelial tubular
membrane. I have interest in two different aspects of the polarity phenomena. The first deals with the molecular basis for the targeting and fusion of vesicles that are involved in the shuttling of aquaporin-2 and H+-ATPase to and from the apical membrane of renal collecting duct cells. We have demonstrated that the same subset of proteins involved in polarized exocytosis in neurons, SNARE proteins, are involved in the targeting in renal epithelial cells. We are currently identifying the signal cascade that regulates the activation of these SNAREs. The second area of interest deals with the effect of ischemia on the maintenance of junctional complexes in renal epithelial cells. Ischemia disrupts these complexes and induces a loss in the functional polarity of tubular epithelial cells. We have begun to identify the sequence of regulatory changes that induces the loss of ZA and the intermediate effect of the liberation of catenins from the ZA.

Expertise: Renal Physiology; acid-base homeostasis; ion transport; epithelial cell biology; ischemic renal disease

David C. Seldin, M.D., Ph.D.

My laboratory has two major areas of research on the molecular basis of human disease. One is on kinase pathways in tumorigenesis: we study the regulatory serine-threonine kinase protein kinase CK2 (casein kinase II), a kinase that is upregulated in leukemic cells and other tumors. We have shown that overexpression of CK2 in transgenic mice leads to tumors in tissues (lymph node, mammary gland) where it is mis-expressed, proving that CK2 has the potential to serve as an oncogene. Ongoing research in the laboratory is aimed at identifying the targets of CK2 in lymphomagenesis and breast cancer. Recent work suggests that the stability/proteosome susceptibility of critical transcription factors, including the myc oncoprotein, is regulated by CK2 phosphorylation. We have also linked CK2 activity to the Wnt pathway, a signaling pathway whose elements include the adenomatous polyposis coli gene product APC and beta-catenin; one or the other of these is mutated in many human cancers. CK2 stabilizes beta-catenin, augmenting its activity as a transcriptional co-factor for TCF and LEF, and promoting expression of myc and cyclin D1. To study the essential roles of CK2 in cells, we have knocked out the catalytic subunits individually be gene targeting, and shown that the alpha subunit is required for heart development, and the alpha' subunit is required for male germ cell development. The other major area of research in the laboratory are the systemic amyloidoses. These are a set of diseases of protein misfolding in which polymers of protein form fibrils that are deposited in tissues, leading to organ failure and death. Of particular interest is AL or primary amyloidosis, which is due to deposition of clonal immunoglobulin light chains. We are studying the sequence and structure of these light chains and developing animal models of disease, in the hopes of developing targeted small molecule or immunotherapies to complement or replace the role of chemotherapy in treatment of the disease.

Jacqueline Sharon, Ph.D.

The current research goals of the laboratory are to develop immunotherapies and elucidate the mechanisms of protective immunity against inhalational tularemia, an acute lethal infectious disease. Tularemia is caused by the gram-negative intracellular bacterium Francisella tularensis, which has been classified as a Category A Select Agent – a likely bioweapon. The high virulence of F. tularensis and the threat of engineered antibiotic resistant variants warrant the development of new therapies to combat this disease. We are developing antibody-based therapies for post-exposure treatment of tularemia and testing them in an inhalational mouse model of tularemia.

Paul Skolnik, M.D.

Dr. Skolnik is Professor of Medicine at the Boston University School of Medicine. He is the Director of the Center for HIV/AIDS Care and Research (CHACR) at Boston University Medical Center. Dr. Skolnik has a substantial record of serving as mentor for successful basic and clinical research trainees on NIH-funded T32 training grants and K08 awards. His current basic research interests include HIV-related innate immune responses in the lung, and modeling of cytokine and chemokine networks in the lung. Patient-derived samples are used in these studies whenever possible to most closely
mirror the in vivo situation. He also has expertise in clinical HIV/AIDS research design and methodology, and is site PI for the AIDS Clinical Trials Group (ACTG) at Boston University Medical Center. Dr. Skolnik has carried out many clinical trials of investigational new immunotherapeutic and antiretroviral drug therapies for HIV infection, and especially studies the immunologic effects of these anti-HIV therapies.

Gail Sonenshein, Ph.D.
The major research goals of my laboratory are to elucidate the mechanisms of activation and roles of the NF-kappaB (NF-kB) transcription factor family in breast cancer and other malignancies. Our laboratory showed that NF-kB factors are aberrantly activated in breast cancer, promote survival, growth and transformed phenotype of the cancer cells. Several oncogenes that have been implicated in breast cancer, including Her-2/neu and Ras, induce NF-kB. A major effort in the lab is to identify the signaling pathways and kinases mediating aberrant activation of NF-kB, including a new transcriptional pathway termed de novo RelB synthesis. We have prepared animal models to study the roles of the NF-kB, including the NF-kB c-Rel subunit, in breast cancer and mammary gland development. Using an MMTV-c-Rel mouse model, we showed that the NF-kB c-Rel subunit, which is activated in ~85% of human breast cancers, can play a causal role in mammary tumorigenesis. We have more recently shown that bitransgenic MMTV-c-RelxCK2 mice develop highly invasive mammary tumors, and implicated the aryl hydrocarbon receptor and master regulator Slug in this phenotype. We have also elucidated a new mechanism for the late onset of the tumors that appear in the MMTV-c-Rel, which involves activation of PKCtheta and release of repression of c-Rel by estrogen receptor signaling. Studies are in progress to further identify the roles of NF-kB in neoplastic transformation induced by environmental carcinogens, and of a new kinase IKKi implicated in invasive breast disease, and the anti-carcinogenic effects of the green tea polyphenol EGCG. We have also identified an inhibitor of activation of NF-kB by Her-2/neu and Ras in breast cancer: the pro-peptide domain of the enzyme lysyl oxidase (LOX-PP). More recently, LOX-PP has been found to inhibit pancreatic and lung cancers. Studies to test the efficacy of these inhibitors in vivo and to elucidate their mechanisms of action are in progress. The overall goals are to aid in the development of improved treatment modalities for cancer.

Martin Steinberg, M.D.
A single beta-globin gene mutation causes sickle cell anemia. Nevertheless, the exceptional phenotypic variability of this disease suggests that other genes could modulate its phenotype. We have discovered that polymorphisms in some genes were associated with discrete subphenotypes of sickle cell anemia, stroke for example, and with disease severity estimated by a more comprehensive analysis of laboratory data and clinical subphenotypes. In some of our studies we have learned that networks of interacting gene polymorphisms or SNPs and laboratory variables can predict the likelihood of stroke in sickle cell anemia with great accuracy, and also foretell the likelihood of near-term death. In genome-wide association studies of about 2,000 sickle cell anemia patients and 1500 centenarians, we hypothesize that independent studies of these groups will provide extensive information about disease predisposition. Using novel analytical methods we hope to facilitate a model of age-associated disease predisposition that transcends population origin effects and thus, represents the key genetic factors affecting disease predisposition that are inherent to all humans. With contemporary association analysis and novel bioinformatics we will compare associations with clinical features of sickle cell anemia including blood pressure, survival, stroke, osteonecrosis, priapism, leg ulcers and an integrated measure of disease severity that reflects pathophysiological elements of this disease. In centenarian subjects, using centenarian offspring vs. controls, we are studying genetic associations with clinical features including physical function, disease prevalence and age at onset of age-related conditions including hypertension, stroke, cardiovascular disease and dementia. We will use novel advanced network modeling techniques to suggest genes and pathways that play crucial roles in aging-related disease, such as stroke and hypertension.
We are studying gene expression in mononuclear cells and blood outgrowth endothelial
cells from patients with sickle cell pulmonary hypertension and controls in studies founded on our observations that inflammation and genes of the TGF-beta/BMP pathway seem to be associated with several disease subphenotypes. Finally, we are examining whether the serum proteome and oxidatively modified proteins in plasma are associated with sickle pulmonary hypertension.

Progressing from genome-based studies, through gene expression, to the serum proteome, these integrated genomic studies will further illuminate our understanding of the pathophysiology and genetic modulation of sickle cell disease, and bring us closer to our ultimate goal of discovering new therapeutic targets.

Sam Thiagalingam, Ph.D.

Research focuses on the use cancer genomics and molecular biology, employing primarily breast and colon cancers as model systems. We hope to contribute to the elucidation of the multi-modular molecular network (MMMN) cancer progression models as the road map to dissect the complexity inherent to cancer through these studies. Our approach to achieve this overall goal is to undertake research under the following topics: (i) The Smad signaling connection to colon cancer metastasis; (ii) The Smad signaling connection to breast cancer metastasis/bone metastasis; (iii) Development of therapeutic approaches to breast cancer by targeting TGF-beta signaling events; and (iv) hBub1 is a suppressor of p53 mediated cell death. Recently, we have also become interested in the role of epigenetics in the pathogenesis of major psychiatric disorders such as schizophrenia (SCZ) and bipolar disorder (BD). Because of the overwhelming evidence for the role of environmental factors in the presentation of the major psychiatric disorders, we hope to decipher a direct correlation between the altered epigenome and SCZ and BD. Our pioneering studies analysing the LOH frequencies of colon cancer showed that SMAD4 is the major target tumor suppressor gene localized to the minimally lost region on chromosome18q. As a follow up of these studies, we are working to unravel the molecular basis of SMAD4 inactivation in advanced metastatic colon cancer. Furthermore, overactivation of the signaling cascade mediated by increased levels of TGF-beta has been implicated in high incidence of breast cancer metastases. We have devised an inter-disciplinary research strategy to test the inhibitors of TGF-beta signaling as potential therapeutic agents for advanced breast cancer. We have also continued to maintain an interest in understanding the connection between genomic instability and cancer at the molecular level. Our genetic and epigenetic studies of lung cancer and the examination of the literature have enabled us to propose an academically simplified scheme to explain the complexity in cancer progression as a process that consists of various alterations in a multi-modular molecular network (MMMN) defined by a cascade of modular events encompassing multiple targets within each module. We are in the process of developing strategies to validate the MMMN model for breast cancer with the hope of paving the way for developing similar models for other cancers as well as the other complex diseases. Furthermore, in a series of preliminary studies on post-mortem brain samples, by investigating DNA methylation and polymorphisms of COMT and RELN in bipolar disorder and schizophrenia, we demonstrated that differential epigenetic modification of these genes play a significant role in the pathogenesis. We plan to extend these preliminary observations to establish a logical relationship between epigenetic changes and schizophrenia and bipolar disorder by analyzing candidate genes and a wide spectrum of genes.

Gregory Viglianti, Ph.D.

Worldwide, heterosexual transmission accounts for most HIV-1 infections. Clearly, controlling heterosexual transmission of HIV-1 would be a significant step toward eliminating this global epidemic. To achieve this goal, it will be important to delineate the cellular and molecular events that affect virus transmission. Although both inflammatory and ulcerative sexually transmitted infections (STIs) enhance sexual transmission of HIV-1, the underlying mechanisms leading to this enhancement have not been fully elucidated. Enhanced susceptibility to infection may be due to a number of factors, including the disruption of the integrity of the cervicovaginal epithelial barrier, recruitment of HIV-1 target cells such as Langerhans/dendritic cells (LC/DC), macrophages (MØ),
and T lymphocytes to sites of inflammation, and direct activation of target cells by STIs. A common feature of STI pathogens is that they encode ligands for members of the Toll-like receptor (TLR) family of pattern recognition receptors and these ligand-activated TLRs can both activate HIV-1 target cells and induce local inflammatory responses. Ligand-activated nuclear receptors (NR), including peroxisome proliferator activated receptor (PPAR), liver X receptor (LXR), glucocorticoid receptor (GR), and estrogen receptors (ER) are potent inhibitors of TLR-induced inflammatory gene expression in MØ, LC/DC, and epithelial cells. In addition, retinoic acid receptor (RAR) and PPAR ligands have been shown to repress HIV-1 gene expression while estrogen has been shown to block vaginal transmission of SIVmac. A goal of our laboratory is to determine the role of TLR-signaling in augmenting HIV-1 infection of target cells that are found in the cervicovaginal mucosae. Our major, and long-term goal is to examine the potential role of ligand-activated NR as inhibitors of HIV-1 transmission. We hypothesize that ligand-activated NR act by: 1) directly repressing HIV-1 transcription, and 2) by limiting the TLR-induced inflammatory microenvironment that favors HIV-1 replication. We are currently focusing are efforts to 1) evaluate the impact of NR/TLR crosstalk on HIV-1 replication and inflammatory gene expression in primary LC, DC, and MØ, 2) examine the effects of NR/TLR crosstalk on HIV-1 infection of target cells and inflammation in vaginal and cervical tissue explants and in an organotypic model of the human vagina, and 3) determine the molecular mechanism(s) of TLR-modulated HIV-1 transcription and how it is regulated by NR signaling.

Kenneth Walsh, Ph.D.

Research in the Walsh laboratory is focused in three areas. The major project investigates the signaling- and transcriptional-regulatory mechanisms that control both normal and pathological tissue growth in the cardiovascular system. Many of these studies involve analyses of the PI3-kinase/Akt/GSK/Forkhead signaling axis. This pathway is of critical importance in the regulation of organ growth and body size. Signaling through this pathway controls cellular enlargement (hypertrophy), cell death (apoptosis), and blood vessel recruitment and growth (angiogenesis). We have shown that the PI3-kinase/Akt/GSK/Forkhead signaling axis regulates multiple steps critical in angiogenesis including endothelial cell apoptosis, differentiation, nitric oxide production and migration. We have also shown that some of these signaling steps are important for cardiac hypertrophy during normal postnatal development, and that they regulate myocyte survival in models of heart disease. The second project investigates the role of the immune system in vascular disease. These studies focus on the Fas/Fas ligand system. Fas is a death receptor that mainly functions to downregulate inflammatory reaction. Aberrations in Fas-mediated apoptosis can contribute to a variety of vascular disorders including atherosclerosis. Current research employs transgenic mouse models to assess the interrelationships between vascular and autoimmune diseases. The third project explores the molecular mechanisms by which amyloid proteins are toxic to cells. The insoluble aggregates of the amyloid proteins Aβ40 and Aβ42 are the predominant components of the inclusion bodies and plaques characteristic of the vessels and neuronal tissues of the Alzheimer’s diseased brain. Cerebral amyloid angiopathy, a disease that affects the brain in half of elderly individuals, is also characterized by amyloid deposition in blood vessels. Our experiments are attempting to elucidate how amyloid proteins induce apoptosis and design strategies to ameliorate the toxicity of amyloid aggregates once they are formed in vascular smooth muscle cells.

H. Christian Weber, M.D.

The major thrust of Dr. Weber’s laboratory focuses on cell and molecular biological studies of mammalian bombesin receptors in human cancer and obesity. This family of G protein-coupled receptors comprises the gastrin-releasing peptide receptor (GRP-R), the neuromedin B receptor (NMB-R), and the orphan bombesin receptor subtype-3 (BRS-3). The human GRP-R is found ectopically expressed in human cancers of the colon, stomach, and prostate thereby mediating potent mitogenic properties through ligand specific receptor activation. Our research is directed towards the understanding of molecular mechanisms of aberrant GRP-R expression in epithelial cells and intracellular
signaling pathways relevant in GRP-R dependent cell proliferation. Furthermore, it has now been clearly established that GRP-R and BRS-3 play a significant role in the regulation of feeding behavior, obesity, and glucose homeostasis. Consequently, laboratory investigations are aimed at the elucidation of ligand-activated intracellular signaling events and molecular mechanisms by which bombesin receptors regulate energy homestasis.

Lee Wetzler, M.D., Ph.D.

Dr. Wetzler’s laboratory investigates innate and adaptive immunity and microbial pathogenesis, especially in regards to vaccine development. One major aspect of this work centers on the pathogenic Neisseria, *Neisseria gonorrhoeae* and *Neisseria meningitidis*. He has found that the major outer membrane protein of these organisms, the Neisserial porin PorB, can work as an immune adjuvant due to it recognition by the pattern recognition receptor TOLL-like receptor (TLR) 2. He has found that antigen presenting cells, including B cells, dendritic cells and macrophages, are activated by PorB in a TLR2, TLR1 and MyD88 dependent manner, inducting upregulation of class II MHC, costimulatory molecule CD86 and other markers of activation. Moreover, MAPK signaling events are required for the upregulation of the expression of these markers, as well as production of pro-inflammatory cytokines. Moreover, using an *in vivo* peritoneal mouse model of inflammation, we have shown that both PorB and intact *N. meningitidis* induce a significant cellular influx and pro-inflammatory cytokine production, which is also TLR2 dependent. However, we also found that mast cells are activated during this process, which may be in a TLR2 independent manner, along with a significant influx of eosinophils, indicative of induction of a TH2 type cellular response. Studies are continuing to investigate the mechanisms of these phenomena.

We are also investigating the use of this TLR2 ligand, PorB, as a vaccine adjuvant using classic antigens like OVA and more relevant antigens like bacterial capsular polysaccharide. This work has also been extended to investigate the adjuvant activity and mechanism of immune stimulation of the B subunit of cholera toxin. We have found that CTB induces antigen presenting cell stimulation via the lipid raft ganglioside GM1 via induction of a cell-signaling program ending in NF-kB and CREB activation and gene transcription. This work is still on going.

Finally, a new major thrust of the Wetzler lab is investigating the immune response and natural history of Francisella tularensis pulmonary infection in mice and using this data to aid in developing vaccines towards this potential bio-terrorist agent. We have found that using PorB as an adjuvant and Francisella LPS as an atigne, we can enhance protection in these mice, which is likely due to induction of antibodies and improved immunity (potentially both innate and adaptive immunity). It appears that induction of IL-1beta may be more associated with survival bith during natural infection and after vaccination, while IL-6 and IL-17 may have the opposite effect, being more associated with death after pulmonary infection. Finally we have recently found that induction of bronchial associated lymphoid tissue (BALT) after vaccinatin also appears to be associated with protection. These iBALT structures are long lasting and may be due to persistent antigen stimulation, which we are currently investigating.

Benjamin Wolozin

Our laboratory investigates the pathophysiology of neurodegenerative diseases. The research on Parkinson Disease pathophysiology of genetic factors implicated in Parkinson’s disease, including LRRK2, α-synuclein, parkin, DJ-1 and, LRRK2. We hypothesize that genetic mutations linked to Parkinson's disease converge onto two main cellular pathways, mitochondrial function or management of misfolded proteins. We perform the studies using genetically modified cells (e.g., primary neuronal cultures or cell lines) or genetically modified animals (principally *C. elegans*, but also mouse or human tissue from carriers), and apply the tools of molecular biology, immunochemistry and biochemistry. We have recently demonstrated that LRRK2 binds to MKK6, a kinase that lies upstream of p38 and regulates the stress response. Our studies in mammalian cells demonstrate that LRRK2 regulates membrane localization of MKK6, as well as of small GTPases, such as rac1. Using *C. elegans* lines expressing human LRRK2 (WT or
mutant) we demonstrated that LRRK2 modulates the stress response. Knockdown of the C. elegans homologues of MKK6 or p38 blocks the effects of LRRK2 in C. elegans, demonstrating the requirement of MKK6 for the actions of LRRK2. We have recently begun to examine the pathophysiology of Amyotrophic Lateral Sclerosis. This work focuses on a protein, TDP-43, that was recently shown to be the predominant protein that accumulates during the course of the disease. Our work in cell culture demonstrates that TDP-43 aggregates in response to stress, and suggests that TDP-43 functions in the stress granule pathway. Finally, our work on Alzheimer disease focuses on the interaction between the proteins that produce β-amyloid (amyloid precursor protein, presenilins and BACE) and the genes that regulate cholesterol metabolism. Our current work focuses on the mechanism by cholesterol regulates production of β-amyloid and processing of its precursor protein, APP, with a particular focus is on oxysterol binding proteins, which are regulated by oxysterols, the major cholesterol catabolite in the brain. A second line of research in my lab uses epidemiological approaches to identify promising drug candidates for therapy of Alzheimer's disease. We are using large databases to analyze the effect of every FDA approved medication on the incidence of Alzheimer disease, and then studying the relevant medications in the laboratory to determine the putative mechanism through which the medications might exhibit their protection.

**Michael Wolfe, M.D.**

The major interest in Dr. Wolfe's laboratory has always revolved around the physiological and pathological significance of gastrointestinal regulatory peptides. His lab has been conducting investigation aimed at determining the molecular mechanisms and intracellular pathways involved in mediating the trophic effects of gastrin in colorectal cancer and other malignancies of the gastrointestinal tract. These studies have indicated that gastrin exerts its effects, at least in part, through induction of the cytoplasmic protein, β-catenin and its downstream oncogenes and trophic factors, such as cyclooxygenase-2, cyclin D1, and PCNA. He and members of his lab have most recently reported that gastrin is a potent inhibitor of the tumor suppressor PPARγ. They are also examining the relationship between gastrin and cyclooxygenase-2 (COX-2) and are using both cell lines in culture and novel animal models to determine the specific role of gastrin in gastrointestinal carcinogenesis. Other current research interests include the physiological and pathological significance of glucose-dependent insulinotropic polypeptide (GIP). In addition to its acid inhibitory effects in the stomach, which was Dr. Wolfe’s original area of interest, GIP is a potent stimulant of insulin release by pancreatic islet β-cells when administered in physiological doses. His laboratory has successfully synthesized a GIP-specific receptor antagonist and is using it to determine the precise role of GIP both physiologically and under pathological conditions. Presently, the lab is investigating the role of GIP in lipid homeostasis using isolated and perfused adipocytes, differentiated 3T3-L1 cells, and various animal models. Members of his lab are also performing studies to examine the intracellular pathways by which GIP exerts its properties and the relationship of GIP to insulin in the fat cell. Finally, he and his collaborators have initiated studies using transgenic mice and other methods aimed at determining the developmental factors and pathways involved in the differentiation of intestinal stem cells and precursors into mature GIP-producing K-cells.

**Vassilis Zannis, Ph.D.**

Dr. Zannis' research focuses in two directions. The first direction is the structure and function of apolipoproteins A-I and apolipoprotein E and their role in the pathogenesis in cardiovascular disease. In addition, we are investigating the role of apoE in Alzheimer's disease. For these studies we have developed methodologies for high level of expression of variant apolipoprotein forms and their purification from the culture medium. The variant apoA-I forms are analyzed for their ability to bind to lipids an lipoproteins to bind to the scavenger receptor B1 (SR-B1) and to activate LCAT. The variant apoE forms are analyzed for their ability to bind to amyloid peptide &lsquo;&lsquo;A&lsquo;&lsquo; and to apoE receptors present in the brain (VLDL receptor E receptor II). The second direction is the role of the apoCIII enhancer on the transcriptional regulation of the human apoA-I CIII
gene cluster. In particular we are focusing on the role of hormone nuclear receptors which bind to proximal and distal sites as well as the role of the SP1 which binds to the apoCIII enhancer on these genes using transgenic animals and antisense methodologies.

Zhi-Xiong “Jim” Xiao, Ph.D.

Inactivation of the tumor suppressor proteins p53 and retinoblastoma protein (Rb) plays a key role in cancer development. We are interested in signaling cascade that regulates p53 and Rb in response to a variety of cell stress signals, particularly in breast, lung and liver cancers. We have discovered that DNA damages induce p53 phosphorylation and protein conformation changes that lead to p53 activation, cell cycle checkpoint and apoptosis. Additionally, we identified an interplay between the IGF signaling and the p53 pathway with regard to cell survival and cellular senescence. We also demonstrated that the E3 ubiquitin ligase MDM2 interacts with Rb and promoted Rb protein degradation. Currently, we are studying (1) the growth factor signaling (IGF1, AKT, mTOR and GSK3b) in regulation of p53 and Rb pathways during cell proliferation, apoptosis, muscle/neuronal cell differentiation, cellular senescence and aging; (2) regulation of proteasome-mediated degradation of Rb and p53; (3) function of p53-related p63 in epithelial stem cell biology and cancer metastasis.

Mengwei Zang, M.D., Ph.D.
The main goal of Dr. Zang’s laboratory is to investigate the physiological regulation of novel signaling molecules important in energy homeostasis and their impact in diabetes and cardiovascular complications. Better understanding of these molecular mechanisms will provide a great opportunity for the development of novel therapeutic strategies for metabolic syndrome and cardiovascular disease. A major focus is to determine how protein kinases or signal transduction pathways modulate glucose and lipid metabolism in hepatocytes by their effects on phosphorylation, protein-protein interactions and gene expression, and their implication for pathological dysregulation in insulin resistance and diabetes. Recent studies focus on the role of key energy sensors, such as AMP protein kinase (AMPK) and the NAD-dependent deacetylase (SIRT1), in the regulation of cell metabolism and diabetes. These studies have demonstrated that AMPK is required for metformin, one of the most widely prescribed type 2 diabetes drugs in the world, to prevent hepatocyte lipid accumulation caused by high glucose. Importantly, she has identified AMPK activation as a molecular mechanism for the beneficial effects of nature products, such as polyphenols including resveratrol, present in red wine, on hepatic lipid accumulation, hyperlipidemia and atherogenesis in type 1 and type 2 diabetic LDL receptor deficient mice. She and her colleagues have also defined SIRT1 as an upstream effector responsible for activating the LKB1/AMPK signaling pathway that explains the ability of polyphenols to inhibit high glucose-induced hepatocyte lipid accumulation. Our findings point to SIRT1 and AMPK as sharing a common pathway and functional consequence, providing major therapeutic targets for the treatment of diabetes. Parallel studies are being performed using in vitro cultured cell models and in vivo genetically-modified mice, to dissect the relationship between the cell signaling and alteration in cell metabolism that can be assessed from molecular and cellular levels that are integrated in diabetic mouse models. Current research is attempting to elucidate how these critical signaling pathways influence disease states, including fatty liver, dyslipidemia, and atherosclerosis in obesity, insulin resistance and type 2 diabetes. The ultimate goal is to provide new insight into the mechanism of insulin resistance and diabetes and to identify potential therapeutic interventions.

ORAL BIOLOGY

Frank Oppenheim, DMD, Ph.D, Director
Research of this laboratory focuses on studies pertaining to the structure and function of salivary proteins and their role in host defense mechanisms. Specific salivary proteins such as the proline-rich proteins and histatins constitute families of polymorphic proteins evolved by gene duplication, mRNA splicing and posttranslational proteolysis. These
proteins exhibit unique characteristics and unusual degrees of sequence homologies. They participate in basic molecular processes of mineral homeostasis and the innate immune defense. Physico-chemical approaches are used to determine their affinities to and repair of the hydroxyapatite crystal lattice. Oral biofilms are being characterized using quantitative proteomics and the determination of the phosphoproteome of oral proteins and peptide sources. The characterization of the salivary histatins protein family revealed that these proteins exert direct and indirect anti-microbial activities. His laboratory has made major progress in understanding the mechanism by which histatins, a unique family of salivary antimicrobial proteins, kill C. albicans, a pathogenic yeast, that occurs frequently in immunocompromised patients including those afflicted with AIDS. Structural analyses in conjunction with peptide biomimetics and recombinant expression methods resulted in the identification of functional domains within these proteins amenable to clinical and therapeutic exploitation. A major goal is to identify the mechanisms of action using both quantitative proteomics of cellular fractions and panels of yeast deletion and over expression mutants in conjunction with growth inhibition and cell killing assays. Emphasis on these processes is aimed at understanding the basic physiology of soft and hard tissue protection in the oral environment. Another line of research is devoted to use state-of-the-art analytical and proteomics approaches to characterize salivary constituents and to employ this information for the diagnosis of both oral and systemic diseases. Our latest efforts comprise studies which explore the use of salivary analyses for medical diagnostics using optical microfiber arrays.

**Salomon Amar, DMD, Ph.D.**

Dr. Salomon Amar’s research focuses on the molecular aspects of inflammatory processes and wound healing. At the molecular level Dr. Amar has identified a new transcription factor LITAF believed to control TNF gene expression. He has generated LITAF-deficient animals, which his laboratory is using to further characterize LITAF functions. These animals exhibit a phenotype consistent with in vitro observations, i.e., LPS immunity and reduced TNF-induced mortality. Dr. Amar’s research has also found that LITAF is partnering with a novel transcription factor that he cloned and sequenced named STAT6B. Together LITAF and STAT6B form a complex that enhances the LPS response TNF mediated. Other cytokines than TNF have now been shown to be regulated by LITAF-STAT6B complex. Recently, using cDNA array technologies, Dr. Amar identified an apoptosis pathway molecule SFRP1 preferentially activated by inflammatory cells and fibroblasts. Blocking SFRP1 in and experimental model of periodontal bone loss substantially reduced loss of alveolar bone otherwise occurring in the absence of this blocker. This finding provides the first evidence that modulation of apoptosis can be beneficial for the prevention and treatment of periodontal diseases. Dr. Amar’s group has recently demonstrated that infection with Porphyromonas gingivalis (P.g.), one of the important pathogens associated with human periodontal disease, activates the acute phase response (SAP) and enhances atheroma lesion formation in ApoE (+/-) mice. Furthermore animals treated under the same condition but lacking genetically IL-1 receptor were immune to P.g. and high fat diet (HFD), strongly advocating for the potential use of IL-1 blockers in the prevention and treatment of atherosclerosis. Finally Doxycyclines, an antibiotic routinely used to treat P.g. infection, was found to reduce substantially P.g. and of HFD-induced atherosclerosis. To substantiate these findings Dr. Amar has undertaken a human case-control study to determine the role of periodontal disease in endothelial dysfunction and systemic inflammation. A strong association between severe periodontal disease and endothelial dysfunction in otherwise healthy human subjects was observed. Periodontal disease and endothelial dysfunction were also associated with higher plasma levels of the acute phase reactant C-reactive protein (CRP). That study supports the hypothesis that severe periodontal disease leads to a state of systemic inflammation that impairs endothelial function. Using a bioinformatics platform, Dr. Amar’s group has recently generated large genomic and proteomics databases useful to map signal transduction pathways when an immune cell senses a microorganism. It is expected that this database platform will be made available to the scientific community in the very near future.
Robert Gyurko, DDS, Ph.D.
Research in Dr. Gyurko’s laboratory focuses on diabetes-induced tissue damage. While insulin prolongs the life of diabetic patients, long-term complications of diabetes result in severe damage in multiple organs, including the eye, kidneys, blood vessels and the periodontium. Leukocyte defects have been described in diabetes, but the molecular pathways by which hyperglycemia impacts leukocyte function are not well characterized. We have introduced a novel mechanism by which a molecular byproduct of energy metabolism, superoxide initiates premature aging and cell damage in leukocytes as well as in fibroblasts, leading to long-term tissue damage. A second experimental topic being investigated in the Gyurko laboratory is the actions of novel inflammation-resolving molecules on bone metabolism. Resolution of inflammation is a crucial step in healing of infected or damaged tissues, and a new class of molecules called resolvins is a key to this process. We have recently found evidence that resolvins not only help in inflammation resolution, but also inhibit bone resorption. We currently characterize the molecular mechanism of the actions of resolvins on osteoclasts and osteoblasts. If both inflammation-resolving and bone-sparing actions of resolvins are confirmed, that would make resolvins attractive drug candidates against inflammatory bone diseases such as periodontal disease, rheumatoid arthritis and osteoporosis.

Hatice Hasturk, DDS, M.S., Ph.D.
Dr. Hasturk’s main research interests are as follows:
Inflammatory Mechanisms of Novel Anti-inflammatory Products (in vitro and in vivo Animal Models) in periodontal inflammation and cardiovascular disease. Dr. Hasturk has considerable amount of experience and authored numerous articles in identifying the inflammatory mechanisms and resolution pathways involved in periodontal disease as well as identifying new pro-resolving molecules (i.e., lipoxins and resolvins) and other fatty acid compounds in the resolution of periodontal inflammation using experimental periodontitis model in rabbits. She has been carried out series of studies since 2003 using this established experimental periodontitis model demonstrating the actions of these novel molecules in prevention and treatment of periodontitis in vivo. Clinical Translational Research in the Treatment of Periodontitis and Systemic Diseases (Localized Aggressive Periodontitis, Diabetes, Cardiovascular Diseases): Dr. Hasturk has been working in clinical research by studying the inflammatory mechanisms of different types of periodontal disease and has published number of studies. She has recently received a K23 Patient oriented award from the National Institute of Dentocraniofacial Research (NIDCR). The goal of this study is to build on existing research projects in the area of periodontal health determinants and systemic disease and quality of life outcomes, with a special focus on the study of clinical interventional study of the relationship of periodontal diseases and diabetes and especially the impact of periodontal treatment on the control of the diabetic complications. Clinical Randomized Trials in the Prevention and Treatment of Periodontal Inflammation. Dr. Hasturk has been collaborating with a group of investigators at BUMC and in other institutions (i.e., Forsyth Institute, University at Buffalo, etc.) to test the new products and/or techniques and the defining the underlying mechanisms in the treatment of periodontal inflammation.

Eva Helmerhorst, M.S., Ph.D.
Dr. Helmerhorst’s research interests focus on oral microbial enzymatic activities. Proteolytic enzymes participate in a variety of pathological conditions pertinent to the oral cavity, including oral cancer and periodontal disease. Dr. Helmerhorst’s studies are geared towards characterizing the mammalian and microbial proteases that are present and active in oral fluid, and to define their proteinaceous targets using mass spectrometric approaches. The goal is to establish the role of saliva-associated proteolytic enzymes in oral health and disease.

Alpdogan Kantarci, DDS, M.S., Ph.D.
Dr. Kantarci’s main research interests are as follows: Inflammation and resolution of inflammatory pathways in periodontal disease and diabetes. Dr. Kantarci has authored numerous papers about the role of monocytes/macrophages and neutrophilic granulocytes and their signaling transduction
during the inflammatory disease processes. His work has recently focused on how the inflammation-induced environmental changes could impact the phagocyte response in disease and how these processes could be resolved by the use of novel resolution phase agonists (e.g. Resolvins).

**Mechanism of gingival fibrosis.** In collaboration with Dr. Philip Trackman, Dr. Kantarci has been working on the role of connective tissue growth factor and the mechanism of fibrotic changes in gingival tissues as a side effect of various medications.

**Biological mechanism of corticotomy-facilitated orthodontic tooth movement.** Dr. Kantarci has been leading a series of studies on the osteoblast and osteoclast activity in alveolar bone in response to orthodontic tooth movement with or without various methods to enhance the speed of the movement and the bone turnover.

**Cataldo W. Leone, DMD., D.M.Sc.**

Dr. Leone serves as the Associate Dean for Academic Affairs and currently has limited research activity. Previous research at BUGSDM has involved collaborative investigations of salivary protein structure and function (with Dr. Frank Oppenheim), and diabetes-mediated alterations in host inflammatory responses (with Dr. Dana Graves). Dr. Leone is Chair of the Oral Biology Ph.D. Qualifying Examination Committee and continues to serve on dissertation committees. He is also the immediate past director of an NIH/NIDCR grant that supported the short-term research training of minority and women dental students from five schools.

**Erdjan Salih, B.S., Ph.D.**

Dr. Salih’s research interests encompass studies in general biological/biomedical fields related to application of advanced protein chemistry and state-of-the-art mass spectrometric (MS) approaches. Studies are ongoing in qualitative/quantitative proteomics and phosphoproteomics of biological samples in health versus disease using the MS technology. Specifically, proteome and phosphoproteome of oral fluids such as whole saliva, parotid secretion and gingival crevicular fluids are determined in healthy individuals versus patients with periodontal disease. These investigations are aimed at defining biomarkers for early detection of both oral and systemic diseases.

**Ulrike Schulze-Spate, DMD, Ph.D.**

The bones of the skeleton are mineralized structures that also contain cells that regulate its structure and function. The two major types of cells are bone-forming cells (osteoblasts) and bone-resorbing cells (osteoclasts) that work in a dynamic equilibrium in all bones of the body throughout the lifetime of an individual. Balance is achieved by continuous remodeling of bone in response to growth, injury and aging. This highly sensitive biological system is dysregulated in pathological bone disease where the balance between bone formation and resorption is disturbed with resulting bone weakening.

My research focuses on identifying pathomechanism associated with bone metabolism and includes the following specific parts. Part 1 investigates the transcriptional regulation of bone-resorbing osteoclasts during development and activity both in vivo and in vitro. Part 2 focuses on bone cell development in 3-dimensional scaffolds. Part 3 is a translational project that investigates bone formation and remodeling in vivo after supplementing patients with Vitamin D3 and Calcium compared to a placebo group after undergoing sinus augmentation surgery.

**Philip Trackman, Ph.D.**

Research in Dr. Trackman’s laboratory is focused on the regulation of extracellular matrix accumulation in mineralized and non-mineralized normal tissues, and in pathologies in which extracellular matrix accumulation is affected. Studies, which utilize cell culture, animal models, and human tissues, encompass a wide range of experimental approaches derived from the disciplines of biochemistry, enzymology, cell biology, and quantitative biology. Goals of these studies are to obtain a greater understanding of the molecular and cellular basis for gingival overgrowth and other fibrotic diseases, and to understand mechanisms of osteopenia that occurs as a complication of type I diabetes. Several important milestones in these fields have been published by Dr. Trackman’s laboratory. Recent important findings show that oral fibroblasts are resistant to the effects
of certain inflammatory factors, and that this resistance contributes to the elevated expression of connective tissue growth factor (CCN2/CTGF). This growth factor, in turn, contributes to gingival overgrowth and oral fibrosis. In addition, the laboratory is investigating a role for the process of epithelial to mesenchymal transition as an underlying mechanism that contributes to all forms of gingival overgrowth. The mechanism by which lysyl oxidase acts as a tumor suppressor is another important focus for the laboratory. Dr. Trackman’s group has made the novel discovery that the tumor suppressor function of lysyl oxidase resides in the propeptide region of the proenzyme precursor. This propeptide is released from the proenzyme by extracellular proteolytic processing, and the released propeptide inhibits growth of tumor cells and tumor formation. A focus of the laboratory is to identify mechanisms by which the lysyl oxidase propeptide can suppress tumor formation or tumor growth. Dr. Trackman’s laboratory works in collaboration with the laboratories of Dr. Gail Sonenshein and Dr. Kathrin Kirsch of Boston University School of Medicine, Department of Biochemistry on this project. The potential use of this peptide as a pharmacologic agent has been patented.

Thomas Van Dyke, DDS, Ph.D.
For the past 25 years, Dr. Van Dyke has focused on phagocyte cell function. He works with neutrophils, macrophages, and destructive periodontal disease. Dr. Van Dyke is particularly interested in regulation of acute and chronic inflammation. His work in this area focuses on the role of low molecular weight lipid molecules that mediate resolution of inflammation in periodontal and other inflammatory diseases.

PATHOLOGY AND LABORATORY MEDICINE

Daniel G. Remick, M.D., Professor and Chairman
The laboratory focuses on investigating the inflammatory response with particular emphasis on soluble mediators of inflammation, the cytokines. We are attempting to determine how the inflammatory response results in tissue/organ injury and death. To achieve this goal the laboratory uses a variety of methods ranging from whole animal models to isolated cells with reporter gene constructs. The primary theme which ties together all of the projects is the careful measurement of cytokines. Cytokines are peptide mediators of the inflammatory response which represent critical components. They have been successfully modulated to improve health in patients with severe diseases. One of the projects in the lab uses an animal model of sepsis. The primary push is to understand the immunopathology of sepsis, determine why organs fail and why mice die. Another project looks at how oxidants regulate chemokine expression. The third project examines the immunopathology of a novel model of murine asthma. For this model we immunize and challenge mice with a house dust extract which contains high levels of cockroach allergens. The ultimate focus of the lab is to understand the reaction to inflammation so that it may be modulated to improve health outcomes.

Christopher Andry, Ph.D.
Operational improvement in diagnostic laboratory services and organ and tissue procurement in an academic medical center; inflammation and periodontal disease and healthcare disparities for people with cognitive disabilities. While these areas are disparate in nature they represent examples of the broad opportunities present in the department of pathology and laboratory medicine.

Kazem Azadzoi, M.D.
Our research introduces a new concept in the pathophysiology of lower urinary tract symptoms (LUTS) associated with erectile dysfunction (ED). The etiology of LUTS is poorly understood and the close association of LUTS and ED remains a clinical mystery. We have attempted to present a unifying concept, namely pelvic arterial insufficiency, as underlying the common clinical problems of LUTS and ED. We realize that each disorder has a complicated multifactorial etiology. However, in view of growing evidence from clinical and basic research, we are increasingly convinced that ischemia is an important etiological factor in ED-associated LUTS. Certainly, atherosclerosis can explain the marked association of these conditions with increased age and their association with vascular risk factors. In
addition, the fact that the penile, bladder, and prostate smooth muscle alterations seen clinically can be reproduced in our experimental model of pelvic ischemia lends further credence to our unifying hypothesis. Our clinical studies have shown that human pelvic perfusion correlates with LUTS as well as erectile dysfunction. We also found that human bladder non-compliance correlates with decreased bladder blood flow. Our studies with experimental models have shown that pelvic ischemia exposes the bladder, prostate and penis to repeating cycles of oxidative stress as these organs undergo smooth muscle contraction and relaxation for regular physiologic activities. Oxidative stress under ischemic conditions triggers a cascade of molecular events involving oxidative stress-responsive genes, stress proteins, antioxidant defense mechanisms, growth factors, prostaglandins and leukotrienes leading to smooth muscle dysfunction, microvascular damage, neurodegeneration and fibrosis. Treatment with antioxidants appears to delay or prevent these changes. Our current studies extend the previous findings to cellular and molecular mechanisms of oxidative and nitrosative injury and the roles of stress-responsive genes, antioxidant enzymatic system, S-nitrosylation, and mitochondrial and endoplasmic reticulum stress proteins in smooth muscle dysfunction, vasculopathy and neurodegeneration of the ischemic bladder, prostate and penile erectile tissue. Another goal is to develop newer prophylactic and therapeutic strategies against LUTS and ED.

Brygida Berse, Ph.D.

My research focuses on the signal transduction pathways regulating gene expression in neuronal cells. The main line of studies relates to the two genes coding for acetyltransferase (ChAT) and vesicular acetylcholine transporter (VChT). They exhibit unusual genomic organization, i.e. the latter is entirely contained within the first intron of the former. This provides a very unique model to study coordinated regulation of genes involved in related functions, but it also presents specific challenges for promoter cloning and analysis. Cellular responses to extracellular factors, i.e. protein phosphorylation, nuclear translocation of transcription factors, promoter activity and specific mRNA accumulation are studied in neuronal cell lines and in primary neuronal cultures. Methods include tissue culture, mammalian cell transfection, recombinant DNA techniques, reporter gene assays, siRNA, RT-PCR, Northern blotting, EMSA, Western blotting, and HPLC. Other studies in the laboratory pertain to cross-talk between various signaling pathways in neuronal cells, developmental expression of neuronal-specific genes, and the effects of DNA methylation on promoter activity.

Jan Krzysztof Blusztajn, Ph.D.

Prenatal programming of brain development and aging by essential nutrient availability during gestation. We study the effects of perinatal availability of an essential nutrient, choline, on brain development and aging in experimental animals. This research endeavors to determine why it is that supplementation with choline during critical perinatal periods in rats and mice cause a long-term facilitation of visuospatial memory which persists until old age. To this end we are utilizing biochemical, neuroanatomical, and behavioral techniques in a highly unified experimental design. Our studies to date have focused on the development of the basal forebrain cholinergic system, hippocampal MAPK and CREB signaling, and on the developmental patterns of brain gene expression. Recent data prompted us to test the hypothesis that the actions of choline are mediated by an epigenetic mechanism involving DNA methylation. We found that prenatal availability of choline alters global DNA methylation and patterns of DNA methylation of key genes (e.g. insulin-like growth factor II, Igf2) whose expression is known to be regulated by this process. We are vigorously pursuing the testing of the methylation hypothesis [both as it relates to DNA and histones] and we are producing genetic mouse models that help us understand the mechanism of action of choline. Induction and maintenance of neuronal neurotransmitter phenotype: focus on basal forebrain cholinergic neurons. Our second interest is the regulation of the expression of the cholinergic phenotype, i.e. of the genes coding for proteins involved in the synthesis and the storage of the neurotransmitter, acetylcholine. Our current research centers on the molecular mechanisms whereby bone morphogenetic protein 9 (BMP9) induce the cholinergic phenotype in neuronal precursor cells. We focus on the basal forebrain cholinergic neurons (BFCN). These cells are important for such functions as learning memory and attention.
found that BMP9 is a candidate for an endogenous differentiating factor for BFCN, and possibly also for a maintenance trophic factor for these cells in adulthood. These possibilities are being tested using purified BFCN, isolated by fluorescence-activated cell sorting. The key question that we wish to answer is what are the signaling pathways and transcription factors that allow BFCN to express their cholinergic phenotype.

Steven A. Bogen, M.D., Ph.D.
Dr. Bogen’s research group focuses on applied (translational) projects in the area of cancer detection and diagnosis, with an emphasis on new technology development. As a result of this translational focus, the work has resulted in more than a dozen U.S. patents. Most of the patents relate to products that are now commercialized. The group is currently working with combinatorial peptide libraries expressed in phage as a discovery platform, for two projects. The first is an investigation of the role of antigen in triggering gammopathies. We developed a method to identify the antigen to which a patient’s serum antibody binds, without any other clues as to the antigen’s identity. The group first applied this technology to the analysis of paraproteins from patients with multiple myeloma. In addition, the group is using the platform to identify serologic markers associated with diseases for which there are no effective clinical assays.

Vladimir A. Botchkarev, M.D., Ph.D.
Molecular mechanisms controlling hair follicle growth in health and disease. Our research is focused on four major projects: 1) delineating the role of BMP-antagonist noggin in the control of hair follicle development and cycling; 2) analyzing the role of p53 and its target genes in chemotherapy-induced hair loss; 3) control of apoptosis in autoreactive CD8 cells in autoimmune hair loss; molecular mechanisms regulating hair pigmentation

Selwyn A. Broitman, Ph.D., FACG
Molecular approaches to cancer of the large bowel.

Nancy L.R. Bucher, M.D.
Molecular mechanisms that may regulate normal hepatocyte proliferation (as in liver regeneration); cultures of freshly isolated normal rat hepatocytes grown as three-dimensional spheroids more realistically reflect hepatocyte behavior in vivo than do almost universally studied monolayers. Immediate early genes activated by cell isolation regain normal quiescence after a few days in spheroids, but never in monolayers. Freshly isolated rat hepatocytes cultured as monolayers or 3-dimensional spheroids. Spheroids much more closely reflect behavior of normal hepatocytes in vivo; DNA synthesis is suppressed, despite presence of a potent growth factor (EGF) and expression of the immediate early genes shuts off, opposite to monolayers.

Bohdana F. Burke, M.D.
Quantitative immunohistochemistry in determination of estrogen and progesterone receptors.

Wellington V. Cardoso, M.D., Ph.D.
Our research is focused on the molecular regulation of lung development. We are investigating how respiratory progenitor cells are initially specified in the foregut and how they generate the different cell types characteristic of the mature lung. We investigate the mechanisms by which cell fate and morphogenesis are couple during formation of the airways. For this, we use functional mouse genetic approaches, organ and cell culture, genome wide screen, in situ hybridization and other strategies to study the role of specific pathways in the developmental programs of the lung. This research provides insights into basic mechanisms of lung development and progenitor cell biology. It also has an impact on our understanding of the pathogenesis of conditions such as lung immaturity and pulmonary hypoplasia, and mechanisms of repair in the adult lung.

Thomas Christensen, Ph.D.
Mechanisms involved in the pathogenesis of fibrotic lung injury analyzed by quantitative image analysis and its amelioration by drug intervention using experimental animal models; development of sensitive and accurate amyloid typing by immunoelectron microscopy for diagnostic purposes.
Cytoskeleton and neurodegeneration: This project is aimed at elucidating the relationship between neurodegeneration-associated genetic backgrounds and cytoskeletal rearrangements in neurites of specific neuronal populations in Alzheimer’s disease (AD) and Huntington’s disease (HD) models. Cytoskeletal neuritic abnormalities are neuropathological hallmarks of many neurodegenerative diseases, including AD and HD. However, the mechanisms by which these abnormalities may lead to neurodegeneration remain unclear. Actin and tubulin are two major cytoskeletal proteins indispensable for normal neurite development and regenerative response upon injury or neurodegenerative stimuli. Our preliminary studies show that actin capping protein β2-subunit (Capzb2) is necessary for normal growth cone morphology, neurite length and arborization in hippocampal neurons. In addition to regulating microfilament assembly, Capzb2 binds tubulin and, in the presence of microtubule-associated protein tau, affects microtubule polymerization in vitro, a process that is necessary for neurite outgrowth. Accordingly, Capzb2 silencing in hippocampal neurons results in short, poorly branched neurites with abnormal growth cones. Interestingly, the levels of Capzb2 protein are altered in the hippocampi of AD patients and in the heads of caudate nuclei and prefrontal cortices of HD patients. These data suggest that Capzb2 may play a role in the neurodegeneration associated with AD and HD. We want to test the hypothesis that Capzb2 may support the regenerative response of neurons following degenerative stimuli by coordinating the rearrangement of the actin and microtubule cytoskeleton in the growth cone. Firstly, we want to determine how changing levels of Capzb2 may modify morphology of neurites and/or neuronal survival in aged AD and HD transgenic mice in vivo. Secondly, we want to establish how mutations associated with AD or HD modulate the effects of Capzb2 on neurite outgrowth, growth cone morphology, and microtubule polymerization in cultured neurons. It is likely that these experiments will improve our understanding of the mechanisms by which AD- and HD-associated genetic backgrounds influence neurite morphology and lead to cytoskeletal abnormalities that may contribute to neuronal demise. It is also likely that these studies will provide insight into the potential of cytoskeletal regulators to affect the development of neuritic abnormalities and the progression of neurodegeneration in AD and HD. II. miRNAs in schizophrenia and bipolar disorder: This project applies a novel approach towards the search for biological markers for bipolar disorder (BD) and schizophrenia (SCH). Recently, small non-coding RNA molecules (microRNAs, miRNAs) were shown to regulate the expression of human CNS genes involved in cell processes and functions negatively affected in neuropsychiatric disorders, such as synaptic development and maturation, learning and memory. Exosomes are well-characterized category of secretory vesicles that have been recently shown to contain mRNA, including miRNA. The interesting property of exosomes is that they are able to attach themselves to recipient cells and release their content including genetic regulatory material such as miRNAs. Our preliminary data indicate that exosomes isolated from frozen postmortem brain tissue also contain well-preserved miRNA. To test the hypothesis that exosomal miRNA content reflects disease specific-aberrations, we compare exosomal miRNA content in PFCs (Brodmann area 9, BA 9) of patients with BD, SCH and controls to establish BD exosomal miRNA profile. Exosomes are extracted from the frozen postmortem PFCs (BA 9) from the patients diagnosed with SCH, BD and matching controls obtained from Harvard Brain Tissue Resource Center (McLean 66 cohort). To establish cell-type specific miRNA profile in BD we are collaborating with Advanced Tissue Research Center at Harvard NeuroDiscovery Center (Dr. Charles Vanderburg) to use laser capture microscopy (LCM) mapping of neurons and glia in brain regions participating in mood manifestations (BA9, BA24 and ventral striatum) in BD and control samples from McLean 66 cohort. We want to test the hypothesis that major cell- categories in different but interacting brain regions display specifically altered miRNA profiles in BD in comparison to controls. Upon LCM mapping, neuronal and glial miRNAs are obtained using an miRNA extraction kit designed for small amount of miRNA (Molecular Devices Corporation), followed by a sensitive amplification protocol for each of the examined areas. miRNA profiles, both exosomal and cellular are established using liquid phase miRNA multiplex bead arrays (Luminex) and subjected to...
computational analysis. It is likely that these experiments will improve our understanding of the mechanisms by which the signaling may be altered in BD and SCH. It is also likely that novel regulatory miRNAs may emerge as potential biological markers for BD and SCH.

Mark S. Eller, Ph.D.
Our research focuses on the cellular responses to replicative stress encountered during the replication of G-rich human telomeric DNA. We have documented that DNA oligonucleotides homologous to this DNA (repeats of TTAGGG) (T-oligos) induce DNA damage responses similar to those from telomere disruption without actually altering the telomere structure. We hypothesize that during telomere replication, secondary structures formed in telomeric single-stranded DNA inhibit replication and cause the induction of DNA damage responses that facilitate telomere replication and the eventual restoration of the proper telomere structure and the presence of T-oligos at the telomere at this time exaggerates this response. Our research also focuses on the use of these T-oligos to inhibit the growth of cancer cells as a potential new anti-cancer therapy.

Douglas V. Faller, M.D., Ph.D.
The major focus is the study of the basic molecular and cellular biology of transformed cells and tumors. We are determining the mechanisms by which retroviruses and their oncogenes cause tumors, defining the ways in which viruses and oncogenes control host cell gene expression. One special interest of the laboratory involves viral regulation those cellular genes encoding cell cycle-regulating molecules, DNA repair and growth factors or and cytokines. We analyze the molecular mechanisms by which oncogene-transformed cells become autonomous of growth factor requirements, elucidating growth-factor signal transduction pathways in normal and transformed mesenchymal and lymphoid cells, and the ways in which signaling pathways are disrupted or circumvented in tumor cells. We also study the role of oncogenic proteins in transcription, development, cell cycle control and arrest, and programmed cell death. Another area of focus is signaling by steroid hormones in breast and prostate cancer cells.

Mark Flomenbaum, M.D., Ph.D.
Dr. Flomenbaum's interests include all aspects of forensic medicine and pathology; and medical death investigation.

Caroline Attardo Genco, Ph.D.
Work in Dr. Genco's laboratory is focused on three areas; 1) Innate Immune Responses to Mucosal Pathogens; 2) Regulatory Mechanisms in Bacterial Pathogens; and 3) Pathogen Induced Chronic Inflammatory Disorders.

Innate Immune Responses to Mucosal Pathogens
We are examining the interactions of several mucosal pathogens with both phagocytic and non-phagocytic cells. Work with *N. gonorrhoeae* has established that distinct proinflammatory responses are observed in different compartments of the female lower genital tract (endocervical, ectocervical and vaginal cell lines). Using these cell lines we have demonstrated that infection with *N. gonorrhoeae* inhibits the apoptotic response of these cells. *N. gonorrhoeae* may thus establish infection by inhibiting the apoptotic response to infection, thereby resisting killing from both the host cell and the innate immune response. Current studies are focused on defining the role of toll-like receptors and intracellular signaling receptors in *N. gonorrhoeae* induced proinflammatory responses in epithelial cells. Work with *P. gingivalis* has demonstrated the invasive capabilities of these organisms for endothelial cells and has defined specific cell signaling pathways involved in this response. We have shown that 2 adhesins of this organism, the major and minor fimbriae proteins bind to and signal through TLR2 for an inflammatory response in human aortic endothelial cells. Furthermore both the major and minor fimbriae proteins can signal through TLR4 if the accessory proteins MD2 and CD14 are present. Our recent studies are focused on defining intracellular signaling receptors and pathways utilized by *P. gingivalis* to induce IL-1ß secretion in endothelial cells.

Regulatory Mechanisms in Bacterial Pathogens
This work is focused on understanding mechanisms utilized for bacterial colonization, and in particular in the ability of in vivo environmental factors to modulate bacterial gene expression. Transcriptional regulatory mechanisms have been defined on a global level in the pathogenic Neisseria species. We have established that the expression of virulence factors in these organisms is controlled by a global regulatory protein (ferric uptake regulator protein, Fur). We have established that the transcriptional regulatory protein Fur controls the expression of numerous genes that are required for the virulence of *N. meningitidis* and *N. gonorrhoeae* and have established that many of these genes are expressed in vivo during mucosal gonococcal infection in both men and women. Current studies are aimed at examining the regulation and expression of Fur-regulated genes in vitro and in vivo directly in clinical specimens. We have also recently identified a novel mechanism for Fur-mediated regulation through small regulatory RNAs (sRNA) in both *N. meningitidis* and *N. gonorrhoeae*. We have established that in *N. meningitidis* the sRNA, NrrF functions independently of the cofactor RNA-binding protein, Hfq. Current studies are focused on defining how NrrF functions independently of Hfq and on identifying additional sRNAs using high-density oligonucleotide microarrays together with computational analysis.

**Pathogen Induced Chronic Inflammatory Disorders**

Chronic inflammation culminates in devastating events, results in significant host pathology, and is associated with a number of human diseases including autoimmune diseases, infectious diseases, neoplastic diseases, and inflammatory atherosclerosis. Our studies focus on two pathogens associated with chronic inflammation, *Chlamydia pneumoniae* and *Porphyromonas gingivalis*. *C. pneumoniae* is a respiratory pathogen that causes a mild, usually asymptomatic pneumonia. *P. gingivalis* induces a local host inflammatory response that results in inflammatory bone destruction, which is manifested as periodontal disease. Normally, the acute inflammatory response is self-limited, working to contain these infections until the adaptive immune response is activated. However, under some circumstances, a chronic inflammatory state can ensue, resulting in additional host pathology. Recently, both *C. pneumoniae* and *P. gingivalis* have been implicated in the pathogenesis of chronic inflammatory plaque formation although how these pathogens induce and maintain chronic inflammation is not well defined. Our laboratory has defined the role of specific innate immune signaling pathways in immune cells that contribute collectively to pathogen-induced chronic inflammation. We are examining in vitro model systems for platelets, endothelial cells, and macrophages. Using defined animal models of inflammation we are characterizing the roles of innate immune pathways in inflammatory processes in vivo. Enhanced understanding of the roles of specific innate immune signaling pathways, which participate in proinflammatory mediator expression and functional immune responses will provide a promising avenue for novel therapies for chronic inflammatory disorders.

**David A. Goukassian, M.D., Ph.D.**

Dr. Goukassian's research work to date has explored cellular responses to UV-induced DNA damage and the development of DNA oligonucleotide-based therapy for prevention of UV-induced mutagenesis and carcinogenesis. Current research work is heading towards development of a novel treatment modality for various UV- and other environmental carcinogen-induced human tumors including, but not limited to skin, breast, prostate and lung cancers. In our earlier work we have demonstrated an age-associated decreases in DNA repair capacity, attributable at least in part to decreased induction of the p53 tumor suppressor protein and transcription factor by DNA damaging agents and a subsequently reduced induction of p53-regulated DNA repair proteins that appear to be rate limiting. We have been and are studying DNA damage-inducible responses, that we named SOS-like response, in various DNA repair-efficient and – deficient murine models of Xeroderma Pigmentosum (XP) groups A and C, melanoma prone Tyr-Hras/Ink4-Arf null murine model, and in adult human skin ex-vivo. We have
shown that application of various telomere homolog oligonucleotides induce DNA damage responses. In particular, we have shown that pre-treatment with thymidine dinucleotide, prior to damaging irradiation, enhances repair of UV-induced DNA photoproducts and reduces mutation frequency in irradiated skin of rodents. In an ex-vivo model of human skin organ-culture, we extended our knowledge to adult human skin. Our future studies will thus explore both the molecular events underlying carcinogenesis due to environmental carcinogens and a novel approach to cancer prevention and treatment in humans.

Dr. Goukassian’s current research projects are directed towards identifying additional telomere homolog oligonucleotides-induced anti-cancer mechanisms/effects including, but most likely not limited to activation of anti-angiogenic and anti-inflammatory pathways. In fact, he has already shown very convincingly that treatment of human cells in vitro and mouse and human skin in vivo with telomere homolog oligonucleotides leads to down-regulation of COX-2 expression, an enzyme up-regulation of which is strongly implicated in the development and progression of colon, skin and breast cancers. In addition, he is also examining the effect of intratumoral injections of telomere homolog oligonucleotides on regression of established UV-induced neoplasms – squamous cell carcinomas (SCCs) and basal cell carcinomas (BCC), which may represent a novel non-surgical modality for cancer treatment. These studies include also evaluation of T-oligo effects on tumor angiogenesis in vivo and examination of underlying molecular mechanisms of anti-angiogenic effects of T-oligo in various tumor cell lines and endothelial cells in vitro.

Joel M. Henderson, M.D., Ph.D.

My primary research focus is the role of mechanical forces in podocyte injury and glomerulosclerosis. The podocyte is a highly specialized and structurally intricate cell that plays a critical role in the maintenance of glomerular barrier structure and function. These cells are subjected to a unique mechanical environment, and alterations in this environment may cause podocyte injury and glomerulosclerosis. Podocyte injury has been implicated in the pathogenesis of glomerular damage in a wide spectrum of kidney diseases. Specific projects that I am working on that are aimed toward understanding the role of mechanical forces in podocyte injury include: 1) characterization of contractile protein expression in podocytes; 2) measurement and modulation of traction force generation by cultured wild-type and mutant podocytes; 3) cultured wild-type and mutant podocyte response to normal and increased levels of mechanical stretch; 4) development of a transgenic mouse model with altered contractile protein expression in the podocyte; 5) observation and measurement of podocyte structural and functional changes in vivo using multi-photon fluorescence microscopy. As a renal pathologist, I also collaborate with other researchers to help evaluate and understand kidney pathology and pathophysiology in a variety of animal models and human specimens.

John Kim, Ph.D.

Asthma represents an important health problem in the United States and is among the most common respiratory complaints seen by physicians in the outpatient setting. While the magnitude of the problem affects nearly 36 million Americans, understanding of the pathogenesis of asthma at this time is limited.

We developed a novel murine model of asthma which is induced by a house dust extract that contains cockroach allergens and endotoxin. The house dust was collected from the house that has asthmatic children and then extracted into PBS. Pulmonary expression of inflammatory mediators, recruitment of leukocytes, and airway hyper-responsiveness were significantly increased following immunization and challenge with the house dust extract. All of these data demonstrate that we have been successful in establishing a unique murine model of asthma-like pulmonary inflammation. My studies have been focused on expanding our understanding of asthma by using our well-established mouse model:

1) The role of tumor necrosis factor in asthma, potentially novel mediators for new insights into the pathogenesis of this asthma like pulmonary inflammation. In a previous study, we demonstrated a brisk and significant increase in tumor necrosis factor within the
bronchoalveolar lavage fluid immediately after pulmonary challenge with the house dust extract. Given the increase in TNF, it would represent a logical target for inhibition and blockade of the pulmonary inflammatory response to the house dust extract. Blockade of TNF by using antibody resulted in a reduction of the pulmonary and inflammation demonstrated by reduced recruitment of inflammatory cells and airway hyper-responsiveness.

2) Exacerbation of Asthma by Air Pollution. The urban atmosphere is heavily polluted and increased ambient air pollutants including ozone, nitrogen oxide, and particulate matter are correlated with dramatic increases in the risk of pre-existing respiratory disease such as asthma. We seek to determine the pathways and mediator responsible for exacerbation of pulmonary inflammation and airway hyperresponsiveness by diesel particular matte suspension in our mouse model of asthma.

3) Treatment of asthma using herbal extract mixtures. So-Cheong-Ryong-Tang (SCRT), also known as Xiao-Qing-Long-Tang (in China) and Sho-Seiryu-To (in Japan) has been used to treat bronchial asthma and allergic rhinitis for centuries while its mechanism for reducing bronchopulmonary inflammation in asthma yet to be elucidated. This study investigates whether the herbal extract, SCRT administered before allergen challenge would inhibit the pulmonary inflammation and airway hyperresponsiveness in a mouse model of asthma.

Darrell M. Kotton, M.D.
Research interests are in the area of stem cell biology and gene therapy: 1) The role of bone marrow-derived stem cells in lung injury repair is evaluated in specified mouse models of lung injury. 2) Embryonic stem cell differentiation into lung epithelial cells: development of an ex vivo platform that models lung epithelial cell development from undifferentiated mouse embryonic stem cells. Regenerative medicine applications for healing the injured lung using lineage-directed embryonic stem cells are also studied. 3) Gene therapy of lung diseases using lentiviral vectors: lentiviral transduction of hematopoietic stem cells followed by transplantation, or intratracheal delivery of lentiviral vectors is used to overexpress or knockdown genes in mouse models of lung disease. More information available at www.kottonlab.com.

Thomas C. King, M.D., Ph.D.
Applications of molecular pathology to patient diagnosis.

Neil Kowall, B.S., M.D.
Human neuroanatomy; immunocytochemistry and enzyme histochemistry of the brain; neuropathological basis of neurological disorders; animal models of neurological diseases.

Martin Kroll, M.D.
We investigate the dynamics of normal and pathological states by developing mathematical models. Our knowledge of normal physiology, cell processes and pathology requires integration into a systematic view. Our approach is to develop a systematic view of biological processes (Systems Biology). The step to Systems Biology became necessary when our information concerning biology systems revealed that operated as highly complex organizations. The development of mathematical models of normal physiology and disease allows one to gain insight and understanding of these processes. The gained knowledge allows for improved experimental studies and creation of mental image, thereby improving the ability to intervene in the disease process. Systems Biology approaches offer the ability to predict the outcome of complex biological processes as well as form a basis to understand the reasoning in living systems. It represents a union of experimental, modeling and computational methods. It serves as a bridge between the biological and physical sciences.

In the past we have studied the deterministic behavior of the glucose-insulin axis, pupil function, blood perfusion in skin and the effect of PTH on bone formation. Currently, we are investigating the dynamics of BNP in heart failure and blood coagulation.
Shinichiro Kurosawa, M.D., Ph.D

Objective: My overall goal is to bring new therapeutics and novel diagnostics to patients through our pre-clinical non-human primate models of human diseases.

Key words: Clinical Hematology, Critical Care Medicine, Blood Coagulation and Inflammation, Sepsis and Septic Shock, Pre-clinical in vivo models, Biodefense Pathogens

Highlights of Key experiences: My background includes sets of experience to conduct translational research.

- Served as a member of the central evaluation committee for Phase II and Phase III clinical trials.
- PI for conducting the clinical trials within the institutions.
- Seven plus years of Consultative Hematology experience, focusing on the abnormalities in hemostasis and coagulation. About half of the patients were at the Intensive/Critical care units.
- Conducted basic investigation of structure-function relationship analyses of Protein C anti-coagulant pathway members at the molecular levels.
- Group leader in the Primate research, where research was performed in an investigational ICU setting.

Research Interests In the Translational Research:

Our laboratory focuses on studying host responses in the field of translational medicine. We have established multiple pre-clinical in vivo models. We continue our efforts to establish, standardize and validate models, so that the system will help provide means for filling the gap between bench and bedside. Most recently, we are applying high throughput technology to evaluate host responses at molecular level. The results from our models frequently feed back to the basic research and vice versa, providing us unique sets of hypotheses. The availability of the model and the novel hypotheses will give our students and postdoctoral fellows a unique advantage. We can also help our collaborators, who have proved the concept using mouse models, by moving the project beyond rodent biology. We are committed to bring new diagnostics and therapeutics in order to improve/save human lives.

Innovation/Exploration:

Hold three patents concerning novel diagnostic approaches. One of which was successfully licensed to a French diagnostic company, and now commercially available. If the critical findings are not properly protected as intellectual properties, it is unlikely that the technology will benefit patients down the line.

Marc E. Lenburg, Ph.D.

Our laboratory uses high-throughput genomic methods coupled with bioinformatics to detect the physiological effects of tobacco-smoke exposure and smoking-related diseases such as lung cancer and chronic obstructive pulmonary disease (COPD). This work is centered on developing biomarkers for diagnostic, prognostic, and pharmacogenomic clinical applications but also involves data mining and experimental approaches to understand the regulatory networks and related biological processes that underlie variability in the response to tobacco smoke and contribute to smoking-related disease pathogenesis. Developing data-analysis techniques to support these translational bioinformatics goals is another area of focus for the lab. Several examples of current projects include: the discovery of cancer specific non-coding transcripts and splice variants using high-throughput cDNA sequencing; understanding the molecular basis of clinical heterogeneity amongst COPD patients with an aim toward tailored therapy; understanding how microRNA contribute to the regulation of tobacco-exposure and disease-specific patterns of gene expression; and developing non-invasive tests for early-stage lung-cancer diagnosis and assessment of lung-cancer risk.

Adam Lerner, M.D.

Our lab has two central research interests:

1) Cyclic nucleotide phosphodiesterases (PDEs) as therapeutic targets in human lymphoid malignancies. We have found that inhibition of the PDE4 cAMP PDE family induces apoptosis in primary leukemic cells from patients with B-CLL. In the absence of
exogenous stimulation of adenylate cyclase, addition of a PDE4 inhibitor activates both PKA and EPAC, a cAMP-activated Rap1 GDP exchange factor. Surprisingly, expression of EPAC is unique to B-CLL among circulating hematopoietic cells and activation of EPAC is anti-apoptotic, suggesting that it may play a pathophysiologic role in this disease. PDE4 inhibitors confer their most dramatic apoptotic effects in conjunction with either radiation or glucocorticoids such as dexamethasone. PDE4 inhibitor-mediated PKA activation in primary human B-CLL cells increases levels of glucocorticoid receptor and augments glucocorticoid-induced GRE transactivation. Inhibition of PKA blocks glucocorticoid-mediated apoptosis in CLL. We recently examined how CLL cells differ from normal hematopoietic cells with regard to their sensitivity to PDE4 inhibitor-mediated cAMP accumulation, CREB phosphorylation and gene expression (J. Immunol. 2009, 182:5400-5411). We hope to learn how to best exploit this potential “Achilles heel” as a means to improve the treatment of CLL.

2) The role of the AND-34/NSP family in resistance of human breast cancer cells to antiestrogen therapy. We cloned AND-34 and demonstrated that it associates with the focal adhesion adapter protein p130Cas and that over-expression of AND-34 activates the small GTPases Rac and Cdc42. In an unbiased study of initially antiestrogen-sensitive breast cancer cell lines, Dorssers et al determined that over-expression of either the human homologue of AND-34, called BCAR3 or NSP2, or p130Cas induced resistance to the clinically used antiestrogens tamoxifen and faslodex. Among three highly related gene family members, only AND-34 induces anti-estrogen resistance as well as cyclin D1 promoter activation. AND-34 over-expression leads to Rac activation as a result of its ability to activate PI3K, but such Rac activation is not sufficient for anti-estrogen resistance as all three gene family members activate Rac. Among NSP family members, only AND-34 induces p130Cas serine phosphorylation (Cellular Signaling 2009: 21:1423-35). Our recent AND-34 knockout mouse shows rupture of the ocular lens shortly after birth (Molecular Vision 2009;15:685-699). We are now focused on determining the biochemical mechanisms for AND-34’s unique ability to induce anti-estrogen resistance as well as the normal physiologic roles of these gene family members.

Ann Marshak-Rothstein, Ph.D.
My laboratory is primarily interested in factors regulating T and B lymphocyte activation, function, longevity, and apoptosis, especially in animal models of systemic autoimmune disease. We have found that those autoantigens or autoantigen complexes capable of co-engaging the B cell antigen receptor and a member of the Toll-like receptor family can efficiently activate autoreactive B cells. The main interest of the lab is to further characterize the autoantigens involved in this mode of activation scheme and to further delineate the unique functional properties of B cells stimulated by BCR/TLR coengagement. Other projects in the lab have focused on the lymphocyte abnormalities associated with the lpr and gld mutations, lesions that result in the failure to functionally express the Fas and Fas-ligand molecules, respectively. Specific ongoing projects include: (1) B cell stimulatory activity of defined dsDNA fragment immune complexes; (2) unique patterns of gene expression elicited by TLR/BCR co-engagement; (3) effects of TLR activation on BCR-mediated signaling cascades; (4) effects of TLR inhibitors on the development and progression of systemic autoimmune disease; (5) the role of Fas/FasL interactions on the in vivo persistence of tumor specific T cells; (6) pro-inflammatory and anti-inflammatory aspects of soluble and membrane-bound FasL; (7) therapeutic applications of forced FasL expression on tumor cells; (8) specific targeting of naturally formed FasL microvesicles to tumor populations; and (9) role of metalloproteinase cleavage on FasL function in vitro and in vivo.

Aubrey Milunsky, M.D., D.Sc.
Gene mapping and cloning for neurological and other genetic disorders as well as genetic mutation screening by Mass Spectrometry.

Mary J. Murnane, Ph.D.
Our laboratory has been focused primarily on the characterization of proteolytic profiles as indicators of colorectal tumor staging and the development of markers for cancer diagnosis, prognosis and followup that may provide better identification of individual patients for
particular treatment protocols. In this work we have studied cathepsins B, H, L and D as well as matrix metalloproteinases 2 and 9 and the relationship of these markers to alterations in oncogene and tumor suppressor genes as well as the role of gene methylation in the regulation of MMP-9. We utilize proteinase activity assays (spectrophotometric and electrophoretic), western blotting, ELISA assays and various molecular assays for this work. We are also interested in the characterization of abnormal proteolytic enzyme activities and their post-translational processing events in human primary cancers as a means of elucidating pathways by which cancer develops.

Barbara Nikolajczyk, Ph.D.

Projects in the Nikolajczyk lab focus on understanding how immune system cells modulate systemic inflammation in type 2 diabetes patients. Inflammation is strongly implicated in the most dire complications of type 2 diabetes, including cardiovascular disease and stroke. We are focusing on two cell types that promote inflammation in these patients: monocytes and B cells.

Project 1: Recent work indicates that blocking activity of the pro-inflammatory cytokine IL-1β through infusion of a natural inhibitor of IL-1β, IL-1 receptor antagonist (IL-1ra), decreased systemic inflammation in type 2 diabetes patients. IL-1ra infusion also increased insulin sensitivity in the same study. Overall, this work indicated that decreasing IL-1β production/activity using methods that are less invasive yet more stable than IL-1ra infusion will be effective in combatting the many complications that account for both morbidity and mortality associated with type 2 diabetes. Monocytes are well known to produce significant amounts of pro-inflammatory cytokines and are potent producers of IL-1β. Our most recent work recapitulates demonstrations that fresh ex vivo monocytes from type 2 diabetics hyper-produce IL-1β. These cell also hyper-produce IL-1β in response to stimulation. Recent time course analyses in the Nikolajczyk lab demonstrate that although IL-1β production by monocytes from diabetic patients vs. healthy donors is elevated, peak IL-1β production is significantly delayed (p<0.03) in monocytes from type 2 diabetics compared to healthy donors. This findings indicates that the fundamental mechanisms regulating IL-1β production are altered in diabetes. Our analysis of interactions between transcription factors and the IL-1β promoter in monocytes from type 2 diabetics is beginning to identify protein/DNA and protein/protein interactions that explain both IL-1β hyper-production and the delayed peak of IL-1β production. The goal of this work is to first fully characterize differences suggested by our ongoing work, then to design small molecule inhibitors that would block key events in IL-1β production by monocytes from type 2 diabetic patients.

Project 2: A second focus of the Nikolajczyk lab is to understand how B cells contribute to type 2 diabetes inflammation in individuals with and without confounding periodontal disease. We have found B cells in type 2 diabetes patients and in periodontal disease patients (who are normoglycemic) have elevated responses to toll-like receptor ligands and that cytokine production is activated/ blocked by TLR ligand cross-talk. Therefore, these B cells are fundamentally altered such that they unexpectedly respond to inflammatory stimuli. Ongoing analyses are characterizing these responses as well as the underlying molecular mechanisms driving them. Preliminary evidence suggests B cells from these two inflammatory disease cohorts respond differently to toll-like receptor (TLR) ligands. Furthermore, our studies suggest that B cells will respond differently to anti-inflammatory treatments as compared to monocytes, raising the possibility that treatments based on monocyte studies alone will be prone to unexpected outcomes in clinical trials involving alteration of TLR protein function. Our studies are aimed at identifying targets for alleviating the over-production of pro-inflammatory cytokines generally associated with the devastating complications of isolated and co-occurring systemic inflammatory diseases by focusing on an unappreciated source of cytokines in diabetics, B cells.

References:
PMID: 18566416

Michael J. O’Brien, M.D., M.P.H.
The morphologic and molecular genetic pathways of the adenoma-carcinoma sequence in colorectal neoplasia has been a long-term interest. I currently direct the Pathology Review Center of a multicenter clinical trial, based at MSKCC, New York, that is designed to compare the impact of single screening colonoscopy to programmatic fecal occult blood testing on outcomes that relate to colon cancer prevention. In collaboration with Dr. Shi Yang and Dr. Frank Farraye at BUSM I am pursuing clinical epidemiologic and tissue based molecular genetic studies of the role of hyperplastic type polyps in the evolution of colorectal cancer. Our laboratory studies are focusing on the methylation of CpG islands of promoter regions of suppressor and mutator genes in hyperplastic polyps and associated colorectal neoplasms. We are also interested in clarifying the morphologic characteristics of hyperplastic type polyps that indicate risk for progression to cancer. Our goal is to explore the extent to which the potentially preventable or reversible phenomenon of gene methylation contributes to the overall incidence of colorectal cancer and to put these laboratory studies into the clinical context of cancer prevention and surveillance.

Carl J. O’Hara, M.D.
Currently I am working on three major areas related to Amyloidosis. 1) The assessment of Amyloid deposition in 33-40 autopsies on patients with Primary (AL) Amyloidosis, evaluating the spectrum of organ involvement and addressing the issue of organ tropisms for amyloid deposition. 2) Study of over one hundred bone marrow specimens from Amyloid patients treated with high doses of melphalan followed by stem cell transplantation. We are evaluating the overall effect of therapy on plasma cell volumes and other parameters before and after treatment. 3) A study of lung involvement by amyloid looking at the extent of involvement and anatomic location of amyloid deposits related to clinical parameters of lung function and radiographic findings.

Hee-Young Park, Ph.D.
Epidermal melanocytes play a critical role in providing protection from sun-induced damages by synthesizing melanin. My laboratory is interested in understanding the signaling pathways that regulate melanin synthesis, as well as physiological agents that modulate melanin synthesis. We are now studying how a small molecule Bone Morphogenetic Peptide-4 (BMP-4) exerts its regulatory effects on many of the proteins involved in making melanin. We are also interested in examining how DNA damages affect the biology of melanocytes using DNA-damage mimicking oligo nucleotides. My laboratory is also interested in examining the biological processes involved in cutaneous wound healing and also wounds that do not hear in the timely manner.

Nader Rahimi, Ph.D.
A crucial aspect of many of human diseases such as cancer, inflammatory diseases, and age-related macular degeneration is the formation of new blood vessels known as angiogenesis. Our laboratory is studying molecular mechanisms of angiogenesis and its application to human diseases, in particular its role in cancer and ocular diseases. A brief description of the current projects is outlined below.
Elucidation of angiogenic signaling of VEGFR-2: Our systematic analysis of VEGFR-2 during the past 10 years has identified key signaling pathways activated by VEGFR-2. Activation of VEGFR-2 stimulates a number of key signal transduction pathways in endothelial cells. Activation of PI3 kinase (phosphoinositide 3-OH kinase), requires tyrosine phosphorylation of Y799 and Y1173 on mouse VEGFR-2 (Y801 and Y1175 on human VEGFR-2) which stimulates endothelial cell survival and proliferation. Phosphorylation of Y1173 on VEGFR-2 also is responsible for activation of PLCγ1 (phospholipase Cγ1), which stimulates endothelial cells tubulogenesis and cell growth. Src kinases are also activated by VEGFR-2 and contribute to VEGFR-2 mediated cellular events. In particular, c-Src kinase directly through its Src homology 2 (SH2) domain and indirectly via c-Cbl binds to phospo-Y1057 (Y1059 in human VEGFR-2) of VEGFR-2. In turn, c-Src kinase phosphorylates VEGFR-2 at multi-docking site, Y1173 and also catalyzes tyrosine phosphorylation of IQGAP1 and acts as an adaptor to bridge IQGAP1 to VEGFR-2. IQGAP1 activates b-Raf and mediates proliferation of endothelial cells. c-Cbl, an ubiquitin E3 ligase also is activated by VEGFR-2 and mediates ubiquitination of PLCγ1 resulting in the inhibition of its activity and with it angiogenesis. The current projects in our laboratory are focused in the identification of additional signaling molecules involved in VEGFR-2 signaling, and to determine molecular mechanisms of their activation by VEGFR-2 and their biological importance in pathological angiogenesis.

Role of ubiquitin pathway in angiogenesis: Attachment of ubiquitin to proteins regulates a broad range of key cellular events such as proteosomal degradation, tumor suppression, inflammation, cell cycle progression, and modulation of signaling pathways. Together with ubiquitin activating enzyme E1 and ubiquitin-conjugating enzyme E2, E3 ubiquitin ligases catalyze the ubiquitination of a variety of biologically significant protein substrates for targeted degradation through the 26S proteasome, as well as for non-proteolytic regulation of their functions or subcellular localizations. Our recent work has identified Casitas B-lineage lymphoma (c-Cbl) E3 ubiquitin ligase as a negative regulator of angiogenesis. Upon stimulation by VEGF, VEGFR-2 recruits and activates c-Cbl. As a result of activation by VEGF, c-Cbl ubiquitinates PLCγ1 and inhibits VEGFR-2/PLCγ1 driven angiogenesis. We are currently investigating role of c-Cbl ubiquitin E3 ligase and other related proteins in angiogenesis and mechanisms involved in this process. In particular, we are studying role of ubiquitin E3 ligases in ubiquitination of VEGFR-2, and its major substrate, PLCγ1. Various in vivo and in vitro models of angiogenesis including genetically engineered mouse models are used to determine role of ubiquitin pathway in VEGFR-2 signaling and angiogenesis.

Identification of novel genes involved in the tumor growth and angiogenesis: Completion of the human genome project has created a great opportunity to translate this unprecedented scientific accomplishment into tangible improvements in the diagnosis and the treatment of human diseases. A recent work in our laboratory has identified a number of novel and uncharacterized transmembrane proteins through a unique strategy of bioinformatics coupled with cell culture-based analysis of human genome. Preliminary results have demonstrated unique expression profiles of several of these uncharacterized transmembrane proteins throughout a variety of human organs and tumor cell lines. The overall goal of this project is to establish role of these novel gene products in angiogenesis and tumor growth and metastasis. Various biological assays including, in vivo mouse model, conditional knockout strategy and in vitro cell culture system are used to elucidate function of these gene products in angiogenesis and tumor growth. These studies will provide insight into aspects of tumor development that have been poorly explored because the expression and function of these transmembrane proteins has remained uncharacterized.

Maria Ramirez, Ph.D.
The main focus of my research is the differentiation of lung epithelial cells during mammalian development. We are currently studying two developmental events at the molecular level: the initial determination and specification of the endoderm to become lung epithelium and the differentiation of alveolar type I cells to form the air-blood barrier perinatally. Molecular mechanisms that initiate lung formation from the embryonic foregut:
Between embryonic days 8.0 and 9.5 of mouse development the multipotent ventral foregut gives rise to the thyroid, lung, liver and pancreas. Combination of growth factors and signaling molecules from the foregut itself and neighboring embryonic structures instruct the cells of the foregut endoderm to start a gene expression program that will determine the fate of endoderm cells. Using extremely sensitive methods for dissection of small tissues and analysis of gene expression, we have identified new and known genes expressed during differentiation of endoderm cells into lung epithelial cells. Chromatin remodeling and DNA methylation genes significantly change their expression level coincident with the formation of the lung primordium. Based on these findings and the importance of chromatin modifications in the regulation of cell fate decisions in other developing systems, we are evaluating whether chromatin modifications and DNA methylation participate in initiation of lung development by establishing patterns of gene expression in the embryonic foregut, inducing lung cell fates. Lung alveolar type I cell morphogenesis: The extensive distal lung gas-exchange surface that supports respiration at birth forms in the last 2-3 days of gestation in mice. This process requires differentiation of epithelial type I and type II cells, vascular remodeling and thinning of the mesenchyme. Differentiated epithelial type I cells are commonly defined by the expression of cell specific genes, the extended and attenuated cell shape, and the location within the distal lung. During lung development, progenitor cuboidal epithelial cells remodel their apical and basolateral plasma membranes and cytoskeleton resulting in cell flattening, thinning and spreading. These processes, to which we refer collectively as cell flattening, are a hallmark of type I cell differentiation and are required for alveolar sac enlargement perinatally, and for repairing the lung epithelium after injury in the adult. We are studying epithelial type I cell flattening during development using models of normal and altered lung epithelial morphogenesis, focusing in the membrane enlargement and cytoskeleton reorganization that take place to increase the surface area covered by epithelial type I cells 25-100 fold during type I cell morphogenesis.

Carol L. Rosenberg, M.D.
Molecular genetics of breast cancer, translational studies: This lab investigates the molecular and genetic alterations that are important early in human breast carcinogenesis. Our overall goal is to identify the abnormalities characterizing early cancer development, even before the tissue is histologically fully malignant. We hypothesize that these genetic abnormalities are biologically meaningful and clinically relevant. In testing this hypothesis, we (and others) have shown that cancer-related abnormalities can be present in hyperplastic lesions and even in histologically normal epithelium. We study primary human tissues, and we ask questions and employ techniques suitable to that material, including laser capture microdissection, loss of heterozygosity and copy number alteration, mRNA and miRNA expression [measured by microarray and quantitative PCR], and immunohistochemistry. Since we attempt comprehensive genetic analyses of the data, the work is multidisciplinary, and collaborations with pathologists, geneticists, surgeons and bioinformaticians and biostatisticians are crucial. In addition, we have projects ongoing with organizations both inside and outside BUMC, including the Framingham Heart Study and the Nurses' Health Study-Benign Breast Disease Substudy. Identifying and understanding the landscape of molecular and genetic abnormalities in premalignant and histologically normal tissue should generate novel markers of breast cancer risk, uncover mechanisms implicated early in cancer initiation and progression, and identify new targets for cancer prevention and treatment. This work has been supported by funds from the NCI, the Department of Defense, the LaPann Fund and the Susan G Komen, Mary Kay Ash and Avon Foundations.

Neil B. Ruderman, MD/D.Phil.
Areas of Interest: Diabetes and Metabolic Disorders
Our research focuses on the effects of exercise and fuels such as glucose, free fatty acids (FFA), and amino acids, on cellular metabolism, signal transduction and gene expression. For example, increases in plasma FFAs are observed in people with obesity, the metabolic syndrome and type 2 diabetes. All of these disorders are associated with a
pro-inflammatory state, endothelial cell dysfunction and a predisposition to atherosclerotic vascular disease. Thus, we have undertaken studies to determine the effects of excess FFAs on skeletal muscle, liver, macrovascular endothelial cells and microvascular pericytes. We have found that FFAs, and especially the saturated FFA palmitate, increase the activity of the pro-inflammatory transcription factor NF-kappaB in all cells tested thus far. We have also discovered that palmitate, but not the monounsaturated fatty acid oleate, increases ceramide accumulation, causes endoplasmic reticulum (ER) stress, and even apoptosis. Another significant focus of our lab is the study of the fuel and stress sensing enzyme AMP-activated protein kinase (AMPK). AMPK is activated by exercise, anti-diabetic drugs such as metformin and troglitazones, and by a number of hormones including adiponectin, which when present at high levels appears to protect against type 2 diabetes and coronary heart disease. We found that activation of AMPK can prevent most of the metabolic and biological abnormalities caused by exposure of cells to excess FFAs, suggesting that activation of AMPK may be a target for the treatment or prevention of metabolic disorders that are associated with elevated FFA levels. Finally, we are actively studying whether under conditions of fuel surfeit, as would occur in type 2 diabetes, obesity, and the metabolic syndrome, AMPK may be downregulated. It is our hypothesis that this could lead to decreases in the normal functions of AMPK (such as regulation of \( \frac{\text{oxidation of fatty acids by mitochondria}}{\text{mitochondria}} \)) which in turn lead to the accumulation of triglycerides and other lipids in tissues such as skeletal muscle and liver. It is also our hypothesis that the latter could play a causal role in the pathogenesis of insulin resistance and the development of a pro-inflammatory state.

David J. Salant, MBBCh

Structural biology of glomerular epithelial cells (podocytes), proteomic analysis of components that constitute the glomerular filtration barrier, and mechanisms by which antibody and complement alter their function and morphology.

Jacqueline Sharon, Ph.D.

The current research goals of the laboratory are to develop immunotherapies and elucidate the mechanisms of protective immunity against inhalational tularemia, an acute lethal infectious disease. Tularemia is caused by the gram-negative intracellular bacterium Francisella tularensis, which has been classified as a Category A Select Agent – a likely bioweapon. The high virulence of F. tularensis and the threat of engineered antibiotic resistant variants warrant the development of new therapies to combat this disease. We are developing antibody-based therapies for post-exposure treatment of tularemia and testing them in an inhalational mouse model of tularemia.

David Sherr, Ph.D.

The Sherr laboratory employs state-of-the-art cellular and molecular technologies to research three specific areas of basic and applied science: 1) mechanisms through which environmental chemicals suppress the immune system (the Apoptosis team) http://www.cireeh.org/pmwiki.php/Main/ATeam, 2) molecular signaling leading to environmental carcinogen-induced and spontaneous breast cancers (the Breast Cancer team) http://www.cireeh.org/pmwiki.php/Main/BTeam, 3) development of vaccines for the treatment of cancer and primary amyloidosis (the Cancer/Amyloid Immunotherapy team) http://www.cireeh.org/pmwiki.php/Main/CTeam. The common element in these 3 disciplines is the involvement of an environmental chemical receptor, the aryl hydrocarbon receptor (AhR), in the suppression of the immune system and in maintaining tumor cell growth.

Barbara E. Slack, Ph.D.

Our laboratory is currently engaged in studying the proteolytic processing of the amyloid precursor protein (APP) of Alzheimer’s disease. APP proteolysis by beta- and gamma-secretases releases an amyloidogenic protein, Abeta, which forms insoluble deposits in the brain in AD. We study the mechanisms by which receptor-coupled signaling pathways activate another class of proteases, known as alpha-secretases, which cleave APP within the Abeta domain, precluding the formation of amyloid, and releasing a soluble, neurotrophic
fragment known as sAPPalpha. In addition, we are interested in understanding the role of F-spondin, an extracellular matrix protein and putative ligand for APP, as a regulator of APP proteolysis and function.

Avrum Spira, M.D.

Our laboratory research interests focus on applying high-throughput genomic and bioinformatics tools to the translational study of lung cancer and Chronic Obstructive Lung Disease (COPD). The primary research focus of our lab is to determine how cigarette smoking affects intra-thoracic (lobar bronchi) and extra-thoracic (mouth and nasal) airway epithelial cell gene expression and to use this information to develop a non-invasive genomic biomarker for lung cancer that can identify that subset of smokers who have, or are at risk for developing, lung cancer. Our lab has also begun to explore how this molecular "field of injury" in airway epithelium reflects information about the perturbation of specific oncogenic pathways within an individual, potentially allowing personalized genomic approaches to lung cancer chemoprophylaxis and therapy. This airway "field of injury" concept is also being extended to explore the molecular pathways that contribute to the pathogenesis of Chronic Obstructive Lung Disease, as well as identify non-invasive measures of the biological response to tobacco exposure that can be applied to large-scale population studies as part of the NIH/NIEHS Genes and Environment Initiative. Additionally, our lab is interested in understanding the underlying mechanisms of smoking-related disease risk and is seeking to identify microRNA alterations and DNA polymorphisms that are associated with the gene-expression changes characterizing the airway field of injury. Please see our website at www.pulmonomics.org for additional details.

Deborah J. Stearns-Kurosawa, Ph.D.

So why is it that some people get a bacterial infection, feel lousy for a few days, take antibiotics and then forget about it when they go back to class or work, but other people get the same infection and die in two weeks in the intensive care unit? It's all about what pathogen is invading and how our bodies respond to the infection. It's a highly orchestrated response that requires input from our immune, coagulation, neurologic, and inflammatory pathways. And this in turn requires coordinated responses from cells and molecules in each of these pathways. If the response is too much, too little, too short, too long, too soon, too late, too fast, then the disintegration begins leading to multiple organ failure, shock and death. We have multiple projects in the laboratory to identify contributions at the host, organ, cellular, molecular and genetic level that contribute to different responses to infection. We want to identify the point where this disintegration process remains reversible, so that patients can be identified earlier with better prognosis and less morbidity.

Current laboratory interests include:

- **Study of B.anthracis** (anthrax) infection in a clinically relevant nonhuman primate animal model. Our laboratory altered the disease paradigm by demonstrating the significant contribution of the host septic response to the lethality of anthrax infection and showed how adjunctive therapeutics can be beneficial. Model characterizations include physiology changes, metabolic indicators, biomarkers of coagulation, inflammation and innate immunity, and antigen-specific B cell responses after challenge with bacteria, toxins or spores. Therapeutics are studied at different disease stages and vaccine approaches are evaluated and validated in the primate models for application in both civilian and military populations.

- **Study of enterohemorrhagic E.coli** (EHEC) infection and the Shiga-like toxins from these bacteria. The prototypic bacterium is the E.coli O157:H7 strain, a frustratingly persistent public health problem from contaminated water, undercooked hamburger, spinach, uncooked cookie dough, bean sprouts, petting farms, etc. Antibiotics made the disease worse and EHEC infection is the leading cause of kidney failure in young children in the US. We are developing clinically-relevant animal models to test therapeutics that work in the blood stream, in the intestinal tract and inside cells where the bacterial toxins invade. Immunoprofiling studies focus on innate and adaptive immunity responses to identify evidence-based vaccine approaches.

- **Study of how other pathologic conditions contribute to septic responses.** One school of thought is that the decades of failed clinical trials to treat severely septic patients may be because research models have not taken into account co-morbidity contributions.
Patients often are burdened with multiple problems, like obesity, diabetes and/or autoimmune disease, at the time they get a severe bacterial infection. Each of these health problems have their own set of contributions to the pathways that respond to bacterial infection, and very little is known about how responses are altered accordingly.

Martin Steffen, M.D., Ph.D
My lab works on developing the tools of systems biology for mammalian cells, emphasizing the technique of mass spectrometry. Our guiding biological focus is cancer biology, and our interests are both at the level of basic research and clinical application. One area characterizes proteomic differences between normal and diseased tissue, specifically measuring the phosphorylation status of tyrosine kinases, to develop signatures to classify human tumors. Future efforts are aimed at applying this approach to predict drug susceptibilities. We are also exploring the interaction of the immune system and prostate disease, with the goal of improving early detection of prostate cancer. Thirdly, we are profiling brain microvessels in stroke-prone rats in order to understand disease pathogenesis.

Sam Thiagalingam, Ph.D.
Our major research focus continues to be on the use cancer genomics and biology, employing primarily breast and colon cancers as model systems. We hope to contribute to the elucidation of the multi-modular molecular network (MMMN) cancer progression models as the road map to dissect the complexity inherent to cancer through these studies. Our approach to achieve this overall goal is to undertake research under the following topics: (i) The Smad signaling connection to colon cancer metastasis; (ii) The Smad signaling connection to breast cancer metastasis/bone metastasis; (iii) Development of therapeutic approaches to breast cancer by targeting TGF-beta signaling events; and (iv) hBub1 is a suppressor of p53 mediated cell death. Recently, we have also become interested in the role of epigenetics in the pathogenesis of major psychiatric disorders such as schizophrenia (SCZ) and bipolar disorder (BD). Because of the overwhelming evidence for the role of environmental factors in the presentation of the major psychiatric disorders, we hope to decipher a direct correlation between the altered epigenome and SCZ and BD. Our pioneering studies analysing the LOH frequencies of colon cancer showed that SMAD4 is the major target tumor suppressor gene localized to the minimally lost region on chromosome18q. As a follow up of these studies, we are working to unravel the molecular basis of SMAD4 inactivation in advanced metastatic colon cancer. Furthermore, overactivation of the signaling cascade mediated by increased levels of TGF-beta has been implicated in high incidence of breast cancer metastases. We have devised an interdisciplinary research strategy to test the inhibitors of TGF-beta signaling as potential therapeutic agents for advanced breast cancer. We have also continued to maintain an interest in understanding the connection between genomic instability and cancer at the molecular level. Our genetic and epigenetic studies of lung cancer and the examination of the literature have enabled us to propose an academically simplified scheme to explain the complexity in cancer progression as a process that consists of various alterations in a multi-modular molecular network (MMMN) defined by a cascade of modular events encompassing multiple targets within each module. We are in the process of developing strategies to validate the MMMN model for breast cancer with the hope of paving the way for developing similar models for other cancers as well as the other complex diseases. Furthermore, in a series of studies on post-mortem brain samples, by investigating DNA methylation and polymorphisms of COMT and RELN in bipolar disorder and schizophrenia, we demonstrated that differential epigenetic modification of these genes play a significant role in the pathogenesis. We plan to extend these preliminary observations to establish a logical relationship between epigenetic changes and schizophrenia and bipolar disorder by analyzing candidate genes and a wide spectrum of genes. Detailed descriptions of the research projects can be found at: http://people.bu.edu/samthia/index.html.

Peter Thomas, Ph.D.
1) Role of carcinoembryonic antigen (CEA) in the liver and its influence on the development of hepatic metastases; 2) sialoglycoconjugates of colon tumor cell surfaces and their relationship to differentiation and formation of metastases; 3) 'interrelationship between Kupffer cells and other cells of the hepatic sinusoid; 4) metabolism of bacterial endotoxins
and their interaction with Kupffer cells and cytokine production in the development of hepatic disease.

**Mina Yaar, M.D.**

Current research interest focuses on DNA damage and repair and induction of DNA damage response in cancer cells that are resistant to apoptosis and/or senescence. My research involves investigation of the molecular mechanisms that initiate the response to DNA damage in normal cells and aberrations that occur in malignant cells. In addition, I examine both in vitro and in vivo the ability of different molecules to arrest malignant progression by inhibiting cancer cell proliferation and inducing their apoptosis.

**PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS**

Faculty with a primary or secondary appointment in the Department of Pharmacology and Experimental Therapeutics has their names marked with two asterisks (**). Faculty members who are participating in the NIGMS Biomolecular Pharmacology Training Grant have their names marked with one asterisk (*). Faculty who are in the department, but who are not accepting students are indicated with a dagger (†). Refer to [http://www.bumc.bu.edu/busm-pm/fac/faculty/](http://www.bumc.bu.edu/busm-pm/fac/faculty/) for links to a more detailed description of research interests, a list of representative publications and a picture, where available.

**David H. Farb, Ph.D., Professor and Chair of Pharmacology.**

Research Interests: Abnormal activation of amino acid receptors has been implicated in the etiology of psychiatric disorders such as anxiety, depression, schizophrenia, as well as of convulsive disorders. Impaired cognition is a common symptom of these and other neurological disorders, including neurodegenerative disorders, and the development of cognitive enhancers would provide significant symptomatic relief for many patients. Ongoing studies provide a strong foundation for constructing models of steroid hormone interactions with excitatory and inhibitory amino acid receptors in the brain and spinal cord. This knowledge may lead to new strategies for the treatment of psychiatric and cognitive disorders. The role of neuroactive steroids and small molecule modulators in the control of GABA, glycine, and glutamate (NMDA and non-NMDA) receptors is being investigated using a multidisciplinary approach that includes the techniques of molecular biology, cell biology, mouse transgenics, patch-clamp neurophysiology, and in vivo chronically implanted high density electrode recordings of neuronal ensembles in freely moving rats and transgenic mice.

*Carmela Abraham, Ph.D., Professor of Biochemistry.*

Research Interests: Dr. Abraham’s laboratory studies the mechanisms of normal brain aging and the etiology of Alzheimer’s disease (AD). Dr. Abraham is studying the function of the amyloid precursor protein (APP) and a novel protease involved in the degradation of the amyloid beta peptide (A-beta) in order to understand the etiology of AD and design possible treatments. Dr. Abraham’s laboratory also investigates normal human brain aging and uses the rhesus monkey as a model. Specifically, they are interested in the expression of gene products that could contribute to the destruction of myelin. They have found, using microarray analyses, that the anti-aging gene, Klotho, is downregulated in the aging brain and are now characterizing the role of Klotho and ways to elevate its expression.

*Karen N. Allen, Ph.D., Associate Professor of Chemistry.*

Research Interests: Research in the Allen group is concerned with diverse aspects of protein structure, function, and ligand design. The lab employs a multidisciplinary approach involving state-of-the-art X-ray crystallography and spectroscopy, molecular modeling, enzymology, and molecular biology to address fundamental problems at the interface of enzymology and structural biology. Current projects focus on the aldolase isozymes, the dolichol pathway enzymes, and the haloacid dehalogenase superfamily.

*Salomon Amar, D.M.D., Ph.D., Professor of Periodontology and Oral Biology, Boston University Goldman School of Dental Medicine.*
Research Interests: Dr. Amar devotes approximately 70% of his time to research in cell and molecular biology. His interests focus on the control of TNF-α and other cytokine gene expression in inflammatory diseases; the role of infection in cardiovascular disease and obesity; the application of “omics” approaches to mapping of signaling pathways; and the characterization of cells and extracellular matrix macromolecules in wound healing and tissue regeneration.

*David Atkinson, Ph.D. Professor of Physiology and Biophysics.

Research Interests: Dr. Atkinson’s research efforts aim to provide detailed structural and conformational information on the molecular organization and interactions of lipids and proteins in plasma lipoproteins. The primary approaches use the techniques of X-ray/neutron scattering, protein crystallography, structural electron microscopy/image processing, nuclear magnetic resonance, calorigraphy, circular dichroism, and molecular modeling to probe the structure and physical properties of lipoproteins, lipoprotein apoproteins and lipid/apoprotein reassembled model systems.

*Irving J. Bigio, Ph.D. Professor of Biomedical Engineering, Electrical & Computer Engineering, Physics.

Research Interests: The focus of Dr. Bigio’s research is the development of minimally-invasive diagnostics and therapeutics based on optical and photonic technologies. Ongoing projects include: 1) Development of fiber-optic probes to perform spectroscopic measurements on tissue in vivo and noninvasively to instantly detect early cancer and other pathologies in situ. 2) Fiber-optic probes to measure drug concentrations in tissue, local spatial profiles and local kinetics, noninvasively and in real time. 3) Sensors to monitor the response of tumors to specific treatments. 4) Optical methods for noninvasive imaging of neuronal activation and brain function.

*Victoria M. Bozotna, Ph.D. Associate Professor of Medicine and Physiology.

Research Interests: The research focus is on ion channels and mechanisms of calcium signaling in a variety of cell types. Methodologies include patch clamp, high resolution confocal and deconvolution imaging, and molecular and biochemical techniques (including knock-out mouse models) to study single channels and whole-cell currents, regulation of membrane potential, intracellular calcium, vascular tone, and expression, activity and localization of several major determinants in calcium signaling cascades. The large part of her recent research is devoted to studying store-operated channels and capacitative calcium entry pathway in vascular smooth muscle cells, cardiac myocytes, platelets, T-lymphocytes, astrocytes and beta cells.

†Charles Cantor, Ph.D. Professor of Biomedical Engineering and Pharmacology (leave of absence), Chief Scientific Officer at Sequenom, Inc.

Research Interests: Dr. Cantor’s major research effort is the development of novel methods for detection and modulation of cells that express specific nucleic acid sequences. His laboratory is using split fluorescent protein complementation to view specific transcripts in living cells. Such methods may also allow novel in vivo imaging modalities. Similar approaches are being explored to alter the properties of specific cells in living organisms. It is possible that such methods will mature into extremely specific targeted intervention methods with high therapeutic indices.

**Jiang-Fan Chen, M.D., Ph.D., Associate Professor of Neurology and Pharmacology.

Research Interests: Dr. Chen’s research focuses on the neurobiology of adenosine and the A2A adenosine receptor and the role they may play in the development and treatment of neuropsychiatric disorders. Dr. Chen has developed an A2A receptor knockout mouse model and couples this genetic approach with pharmacological manipulation to explore the pathophysiological role of A2A receptors in animal and cellular models of neuropsychiatric disorders. The knowledge derived from these studies may provide the neurobiological basis for rational development of A2A receptor agents as treatment strategies for neuropsychological disorders, ranging from Parkinson’s disease to drug addiction.

†Aram Chobanian, M.D., President Emeritus of the University, Boston University; University Professor; Professor of Medicine and Pharmacology, John I. Sandson Distinguished Professor of Health Sciences.
*Dominic A. Ciraulo, M.D., Professor and Chairman of Psychiatry.

Research Interests: Dr. Ciraulo’s research interests focus on addiction psychopharmacology. He is the Principal Investigator of the National Institute on Drug Abuse and The BUSM Medication Development for Stimulants Center, and the Principal Investigator on grants from the National Institute on Alcohol Abuse and Alcoholism that study the role of medications and psychosocial therapies in the treatment of alcoholism. His research also examines the relationship between animal and human models for screening of medications to treat addiction. The medication development program incorporates the latest neuroimaging technologies in collaboration with the Brain Imaging Center at Boston University School of Medicine.

*Richard A. Cohen, M.D. Professor of Medicine.

Research Interests: The research programs of the Vascular Biology Unit are directed towards an integrative molecular understanding of abnormal vascular endothelial and smooth muscle cell function in diseased blood vessels and its contribution to abnormal vascular reactivity, hypertrophy, inflammation, and atherogenesis. Research projects focus on the mechanisms by which vascular risk factors associated with diabetes mellitus, hypercholesterolemia, and hypertension lead to abnormal production of vasoactive factors from the endothelium and also how they alter the smooth muscle cell response. These factors include nitric oxide, prostanoids, oxygen–derived free radicals, cytokines, and growth factors. Experimental approaches employ cell physiology of cultured endothelial and smooth muscle cells with measurements of intracellular calcium and oxygen–derived free radicals, coupled with studies of molecular signaling. The influence of altered production of endothelial factors and signaling cascades on inflammatory responses and cell adhesion is studied as it applies to the development of atherosclerotic lesions, particularly in diabetes. Post-translational modification by tyrosine nitration and thiol oxidation of proteins studied by immuno/affinity labeling and mass spectrometry has been shown to alter the function of endothelial cell nitric oxide synthase, sarcoplasmic reticulum ATPase, endothelial nitric oxide synthase, p21ras, manganese superoxide dismutase, and prostacyclin synthase. S-glutathiolation has been demonstrated as a reversible thiol modification that modulates cell signaling. Proteomic approaches are being used to screen proteins for oxidant modifications that occur as physiological mechanisms or are a consequence of excess reactive nitrogen species.

**Pietro Cottone, Ph.D., Assistant Professor of Pharmacology.

Research Interests: Dr. Cottone is co-director of the Laboratory of Addictive Disorders. Dr. Cottone’s research interests focus on the neurobiological substrates of motivated behaviors including feeding and addiction. The major goal of Dr. Cottone’s research is identifying the biological bases of and potential treatments for obesity and eating disorders. Current studies concern the role of stress in compulsive eating and palatable food dependence. Areas of focused research include the investigation of the neurobiological bases of stress-related disorders such as anxiety and depression. Dr. Cottone’s studies are carried out on environmental and genetic animal models, using behavioral, biochemical, and molecular approaches.

*Charles Delisi, Ph.D. Metcalf Professor of Science and Engineering and Dean Emeritus, College of Engineering.

Research Interests: The Biomolecular Systems Laboratory develops and applies computational/mathematical methods, and high throughput experimental methods, to analyze changes in gene and protein expression profiles of cells in response to various endogenous and exogenous signals. In collaboration with the Fraunhofer Center for Manufacturing Innovation, and the Departments of Chemistry and Physics, Dr. DeLisi is developing and applying new DNA and peptide microarray technologies for fingerprinting the complete molecular state of a cell. Examples include the response to ligands (drugs, toxins, hormones), and changes that occur as normal cells mature, differentiate, and progress toward disease. The long-range goal is to relate expression patterns to pathways, pathways to networks, and networks to function.
**Gerald Denis, Ph.D.** Assistant Professor of Pharmacology and Medicine, Cancer Research Center.

Research Interests: Dr. Denis is exploring mechanisms of transcriptional control mediated through bromodomain proteins, a newly described class of co-activators and chromatin regulators. In particular, he is studying the double bromodomain protein Brd2 and its associated multiprotein complex. In transgenic mice, B cell-restricted constitutive expression of Brd2 transcriptionally activates cyclin A, causing B cell leukemia and lymphoma similar to the diffuse large B cell type of human non-Hodgkin lymphoma. His results have broad significance for understanding adaptive immunity, B cell malignancy and transcriptional control. In translational studies, he has used this model to identify new targets for immunological and anti-cancer agents.

**Howard Eichenbaum, Ph.D.** University Professor; Director, Center for Memory and Brain; Director, Cognitive Neurobiology Laboratory; Director, Center for Neuroscience, Professor of Pharmacology.

Research Interests: Dr. Eichenbaum’s major research goals are elucidation of the function of the hippocampus and the functional organization of the medial temporal lobe memory system. Specific projects include: 1.) Hippocampal and cortical coding, a study to assess the functional correlates of single neuron and neuronal ensemble activity in the cortex and hippocampus of rats performing memory tasks, 2.) Hippocampal lesions or localized NMDA receptor KO and memory, projects that will characterize the roles of the hippocampus and parahippocampal region in rats and mice, 3.) The effect of aging on hippocampal behavioral physiology and memory performance in rats, 4.) A study to test the hypothesis that schizophrenia is associated with decreased function of corticolimbic NMDA receptors.

*Lindsay A. Farrer, Ph.D.* Chief, Genetics Program; Professor, Depts. of Medicine, Neurology, and Genetics and Genomics, Boston University School of Medicine and Depts. of Epidemiology and Biostatistics, Boston University School of Public Health.

Research Interests: Dr. Farrer’s research investigates genetic risk factors in familial neurodegenerative and other chronic diseases. In collaboration with other laboratories worldwide, his group has localized genes causing rare and common disorders including Alzheimer disease (AD), age-related macular degeneration, dependence on illicit substances (cocaine, opiates, nicotine, and alcohol), complications of sickle cell disease, Wilson disease, Machado-Joseph disease, Waardenburg syndrome, asthma, and metabolic syndrome. Many of these projects are collaborative and multi disciplinary efforts aimed at linking human genetic variation to biological mechanisms and developing novel therapeutic targets.

**Jane Freedman, Ph.D.** Professor of Medicine and Pharmacology.

Research Interests: Coronary artery plaque rupture leads to platelet-dependent thrombosis and myocardial infarction. The major research initiatives in this laboratory include an emphasis in the molecular regulation of pathways contributing to thrombosis, vascular disease, and how these factors contribute to acute coronary syndromes. The main topics include: platelet signaling pathways, molecular regulation of platelet nitric oxide and reactive oxygen species, and the role of inflammation in thrombosis.

**Terrell T. Gibbs, Ph.D.** Associate Professor of Pharmacology.

Research Interests: Dr. Gibbs’ research efforts focus on the pharmacology of neurotransmitters and neuromodulators, and on mechanisms of modulation and regulation of neurotransmitter receptor function, including up-regulation, down-regulation, desensitization, and tolerance. Current studies concern the acute and chronic effects of modulators of amino acid receptor function, including benzodiazepines, barbiturates, and steroids. Computational and electrophysiological methods are used to evaluate thermodynamically plausible models for receptor function. Methodologies include the use of radioligand and/or electrophysiological techniques of studying receptor function.

*Robert C. Green, M.D., M.P.H.* Professor of Neurology, Genetics and Epidemiology.

Dr. Green’s research interests are in early and preclinical detection, treatment and prevention of Alzheimer’s disease. He is the Clinical Core director and Associate Director.
for the Boston University Alzheimer Disease Core Center. Dr. Green is also a co-
Principal Investigator on Boston University’s NIH-funded MIRAGE (Multi-Institutional 
Research in Alzheimer’s Genetic Epidemiology) Study, a consultant on the NIH-funded 
Cache County Memory and Aging Study and is the Boston site director of the NIH-funded 
ADAPT (Alzheimer’s Disease Anti-Inflammatory Prevention Trial) Study, one of the first 
large-scale intervention trials to prevent the development of Alzheimer’s disease in at-risk 
family members. Dr. Green is also Principal Investigator and Director of the REVEAL 
(Risk Evaluation and Education for Alzheimer’s disease) Study, a multi-center project 
funded by the National Human Genome Research Institute and the National Institute on 
Aging to develop genetic risk assessment strategies for individuals at risk for Alzheimer’s 
disease.

*Mark W. Grinstaff, Ph.D. Professor of Biomedical Engineering, Chemistry and 
Ophthalmology.
Research Interests: The Grinstaff group pursues highly interdisciplinary research in the 
areas of biomedical engineering and macromolecular chemistry. In one current research 
project, his group is designing, synthesizing, and characterizing novel dendrimers, 
termed “biodendrimers,” for tissue engineering and biotechnological applications. These 
new biomaterials are being evaluated for the repair of corneal lacerations, for the 
delivery of anti-cancer drugs, for the delivery of DNA, and as temporary biodegradable 
scaffolds for cartilage repair. In a second project, his group is creating novel polymeric 
coatings termed “interfacial biomaterials” that control biology on plastic, metal, and 
ceramic surfaces.

*James A. Hamilton, Ph.D. Professor of Physiology and Biophysics.
Research Interests: Dr. Hamilton’s laboratory is developing and applying novel physical 
approaches to study of obesity, metabolic syndrome, and cardiovascular disease. 13C 
NMR methods pioneered in his laboratory have been used to describe the interactions of 
fatty acids and drugs with binding sites on albumin, and new studies are currently 
correlating important details predicted by NMR with recent x-ray crystal structure. His 
laboratory has determined the complete solution structure of several intracellular fatty 
acid binding proteins (FABP) by multi-dimensional NMR and is studying the molecular 
details of ligand binding to FABP. New fluorescence approaches have been developed to 
characterize the diffusion of fatty acids into adipocytes and evaluate the effects of drugs 
and inhibitors on fatty acid uptake. A newer focus of research is on imaging 
methodologies, mainly magnetic resonance imaging (MRI), of fat tissue and 
atherosclerosis. These studies extend from animal model systems (mouse and rabbit) to 
humans. The work emphasizes interactions of different disciplines on translation of basic 
biophysics to human disease aspects.

*Michael Hasselmo, Ph.D. Professor of Psychology.
Dr. Hasselmo’s laboratory research concerns cortical dynamics of memory-guided 
behavior, including effects of neuromodulatory receptors and the role of theta rhythm 
oscillations in cortical memory. Neurophysiological techniques are used to analyze 
effects of modulators on synaptic and neuronal activity in cortical circuits in the rat, and 
computational modeling is used to link this physiological data to behavior. Experiments 
using multiple single-unit recording in behavioral tasks are designed to test predictions of 
the computational models. Areas of focused research include episodic memory function 
and theta rhythm dynamics in hippocampal formation. Research addresses physiological 
effects relevant to Alzheimer’s disease, schizophrenia and depression.

**Alan Herbert, MB.ChB., Ph.D. Associate Professor of Pharmacology and Neurology.
Dr. Herbert’s laboratory has just completed a whole genome scan of families from a 
community-based population that involved typing 100,000 single nucleotide 
polymorphisms per individual and identified a common variant that increases risk of 
obesity. The closest gene INSIG2 is involved in the regulation of fatty acid synthesis. 
Another variant affecting a gene in the same pathway, ACACA, is associated with 
leanness. Dr. Herbert is in the process of initiating a high-throughput screen of candidate 
drugs for these genes as targets, using a chemical library available through the Center 
for Methodologies and Library Development at Boston University. Analysis of other traits
is also underway, potentially providing insight into pathways of addiction and genes that predict successful neurological aging.

**Gary B. Kaplan, M.D. Professor of Psychiatry and Pharmacology.**
Research Interests: In addiction, cognitive and motivational brain regions are responsive to salient environmental and contextual drug cues that serve as triggers for continued vulnerability to relapse. Our research examines drug reward and craving responses to drug-associated cues and contexts in animal models. Extinction is a form of learning that can reduce the rewarding properties associated with drug cues and contexts but such learning occurs over long periods of time. Our translational research examines the neural mechanisms underlying extinction of conditioned drug reward and drug priming induced reacquisition of conditioned drug preferences. To study long term changes in synaptic plasticity in extinction of conditioned drug reward, we examine regulation of transcription factors is relevant limbic and cortical circuitry. To enhance extinction learning, we utilize translational pharmacological approaches using N-methyl-D-aspartate (NMDA) glutamate and aminobutyric acid (GABA) receptor agonists and examine behavioral and neurochemical effects of these agents. By understanding the behavioral and the neural mechanisms for enhancement of drug related reward extinction, we hope to block craving and relapse in clinical populations.

*Catherine Klapperich, Ph.D. Assistant Professor, Biomedical Engineering and Manufacturing Engineering.*
Research Interests: The Biomedical Microdevices and Microenvironments Laboratory (BMML) is focused on the design and engineering of manufacturable, disposable microfluidic systems for low-cost point-of-care molecular diagnostics. We are currently working on devices for the detection of infectious diarrhea, influenza and MRSA. They are also studying the interactions between cells and synthetic microenvironments. Specifically, we are interested in building culture systems in vitro that mechanically mimic the physiological environment. These synthetic microenvironments are intended for use in diagnostics, high throughput drug screening, and to enable previously impossible basic science studies. Currently we have projects aimed at recapitulating the microenvironments of the breast, cochlea and neural tissue.

**Conan Kornetsky, Ph.D. Professor of Psychiatry and Pharmacology.**
Research Interests: Dr. Kornetsky’s research is directed toward the determination of neuronal mechanisms involved in the behavioral effects of drugs. Much of this research is focused on the brain’s motivational systems that are directly related to the rewarding effects associated with abused psychomotor stimulants and opioids. Methodologies include stereotaxic surgery for implanting intracerebral stimulating electrodes and/or cannulae directly into specific brain sites, psychophysical determination of thresholds for various types of intracerebral electrical stimulation, intravenous drug self-administration in rats, quantitative determination of cerebral metabolic rates in specific brain areas using 2-[14C] deoxyglucose, and brain-stimulation reward in knockout mouse models.

†Vidhya Kumaresan, Ph.D. Research Assistant Professor of Pharmacology.
Overall research objective is to study neuronal activity-dependent plasticity and its relevance for brain disorders. The current focus of Dr. Kumaresan’s research is to understand the neurobiological bases of addiction to psychostimulants. Recidivism to drug abuse is a major hurdle in the successful treatment of addiction. Illicit drug use usurps neural circuits involved in survival enhancing behaviors. The goal is to elucidate the cellular and molecular underpinnings of drug-induced enduring neural plasticity in these circuits using a combination of behavioral, cellular and molecular approaches. In particular, Dr. Kumaresan employs a novel approach of using cell-permeable peptides that disrupt protein-protein interactions in vivo in order to study ongoing behavior. These approaches are expected to lead to successful treatment of relapse precipitated by drug re-exposure, drug-associated cues and stress. Knowledge gained from these studies will also be applicable to the treatment of other brain dysfunctions involving persistent memories such as PTSD.
**Susan E. Leeman, Ph.D.** Professor of Pharmacology.

Research Interests: Dr. Leeman's work focuses on the two peptides, substance P (SP) and neurotensin, which were isolated and chemically defined in her laboratory. Projects that are currently underway include: 1. the role of glycosylation of the NK1 receptor on its signal transduction pathways, 2. the roles of SP in several models of inflammation in the gastrointestinal tract, including post-surgical cell adhesion formation, and the effect of non-peptide SP antagonists. 3. the role of LITAF, a newly described transcription factor participating in TNF alpha synthesis in macrophages obtained from inflamed colonic tissue.

**Adam Lerner, M.D.** Associate Professor of Medicine and Pathology.

Research Interests: Dr. Lerner studies the potential use of cyclic nucleotide phosphodiesterase inhibitors as novel therapeutic agents for the treatment of human lymphoid malignancies. He has found that PDE4 inhibitors not only induce apoptosis in primary human chronic lymphocytic leukemia (B-CLL) cells but also augment the ability of glucocorticoids to induce B-CLL apoptosis, and he is elucidating the mechanisms of these phenomena. He also studies AND-34, an SH2 domain-containing protein that he has shown binds to the focal adhesion protein p130Cas. His current work focuses on understanding the signaling pathway by which AND-34 over-expression induces anti-estrogen resistance in human breast cancer cells.

**John R. Murphy, Ph.D.** Professor of Medicine.

Research Interests: The research interests of Dr. Murphy’s group includes the design, expression, and characterization of diphtheria toxin-related cytokine fusion proteins, the molecular basis of diphtheria tox gene regulation, and the molecular mechanisms by which large hydrophilic proteins are transported into eukaryotic cells. They have shown that the delivery of the diphtheria toxin catalytic domain from the lumen of early endosomes to the cytosol of target cells requires the participation of Hsp90, thioredoxin reductase, and other cytosolic translocation factors. In addition, they have recently demonstrated the molecular mechanisms for formation of the metal ion dependent active form of the diphtheria toxin repressor, DtxR. Studies are in progress to identify small peptides activators as a unique approach to antimicrobial agent development.

**Susan Perrine, M.D.** Associate Professor of Pediatrics, Medicine, and Pharmacology; Director of the Hemoglobinopathy-Thalassemia Research Unit

**John A. Porco, Jr., Ph.D.** Professor of Chemistry and Pharmacology.

Research Interests: Research activities in the Porco group (people.bu.edu/porcogrp) involve the development of new methodologies for organic synthesis and their application to synthesis of complex natural products and analogues. Targets for synthesis include pharmacologically active compounds where the preparation of structural variants will allow investigation of key regulatory interactions with biomolecules. Dr. Porco and colleagues have also established the Boston University Center for Chemical Methodology and Library Development (CMLD-BU, cmld.bu.edu) for development of methodologies for the stereocontrolled synthesis of complex molecule libraries for biological screening.

**Tyrone M. Porter, Ph.D., Assistant Professor of Biomedical Engineering.**

Due to its relatively low cost, portability, and beamforming capabilities, ultrasound is an ideal tool for noninvasive evaluation and treatment of a broad range of medical ailments, including vascular occlusions and cancer. Research in the Medical Acoustics Laboratory (MedAL), led by Dr. Tyrone Porter, is focused on the design and fabrication of ultrasound technology to improve upon the diagnosis and treatment of debilitating diseases. This includes the development of targeted ultrasound contrast agents for molecular imaging applications and nano-sized vesicles that release drugs when exposed to acoustic fields. The combination of diagnostic and therapeutic technology may potentially lead to noninvasive image-guided treatment of diseases.

**Katya Ravid, Ph.D., Professor of Biochemistry.**

Research Interests: The cells of all blood lineages arise from pluripotent hematopoietic stem cells that reside in the marrow. The bone marrow also contains stem cells of other lineages, including fat, vascular etc. Our research is focused on two interrelated projects that bear on mechanisms associated with the development of blood and vascular
pathologies: (1) Studies in the lab center on molecular mechanisms involved in cell cycle control during the development of bone marrow megakaryocytes into platelets, a process that includes cellular polyploidization prior to platelet fragmentation. We also identified mechanisms of polyploidy in vascular smooth muscle cells, and found that the degree of polyploidy serves as an excellent biomarker for aging; (2) Ongoing studies explore the role of vascular and bone marrow cell (progenitors and mature) adenosine receptors in vascular regeneration during injury or atherosclerosis. Transgenic and knockout mouse models are used to assist in exploring mechanisms in vivo.

**Karen Reed, Ph.D., Associate Research Professor of Surgery and Associate Professor of Pharmacology.**

Dr. Reed’s research focuses on two areas medically and economically relevant to gastroenterology. One area involves the molecular and cellular characterization of proinflammatory regulators of intra-abdominal adhesion formation while the second area focuses on the etiology of inflammatory bowel disease (IBD). In the area of adhesion formation we have demonstrated that a specific substance P receptor antagonist reduces post-surgical adhesion formation and that this response involves tissue plasminogen activator (tPA), matrix metalloproteinases and oxidative stress. In similar studies we have also shown that HMG-CoA reductase inhibitors reduce adhesion formation. These studies have led to several publications and awards including a paper in the Proceedings of the National Academy of Sciences and a “Best Poster Presentation” award at the international meeting of the Peritoneal Access Society held in Belgium. I am also extremely interested in understanding the pathogenesis of IBD. I have been involved in research to characterize the involvement of the transcription factor NFkB, as well as its upstream activators and downstream mediators, in intestinal inflammation in the rat. I have also contributed to research investigating the role of substance P as well as the transcriptional regulator, LITAF, in intestinal inflammation.

*Douglas L. Rosene, Ph.D. Professor of Anatomy and Neurobiology.**

Research Interests: Dr. Rosene’s research interests center on identifying the neurobiological basis of normal learning and memory and related cognitive functions in the normal brain and the disruption of these processes in neurodegenerative diseases, localized neurological damage such as stroke and by stressors such as malnutrition. To accomplish this, multidisciplinary studies of animal models use combinations of behavioral, neurohistochemical, neurophysiological and neuroanatomical techniques to study these cognitive functions. Studies use the rhesus monkey as a model of normal aging, of cerebrovascular disease and neurological damage as well as a rat model of prenatal malnutrition.

**Shelley J. Russek, Ph.D. Professor of Pharmacology.**

Research Interests: The research of Dr. Russek’s laboratory is focused on gene regulatory mechanisms responsible for the expression and function of neurotransmitter receptors in the normal and diseased brain. Using genomic strategies that include chromatin immunoprecipitation, DNA and receptor pull-down, single cell imaging, and delivery of viral vectors into animals, the laboratory uses the interface between in vitro and in vivo models to test mechanisms of disease and to develop novel genetic therapies for disorders such as epilepsy, autism, and Rett’s syndrome.

**Valentina Sabino, Ph.D., Assistant Professor of Pharmacology.**

Dr. Sabino is co-director of the Laboratory of Addictive Disorders. Dr. Sabino is currently researching the neurobiology of addiction and stress-related disorders. Studies on addiction aim to understand the neurobiological substrates of alcohol abuse and dependence, by exploring the role of central neurochemical systems in excessive alcohol drinking. She is working toward the development of new therapeutic agents to alleviate alcohol addiction. Animal models for excessive drinking are studied in order to identify compounds for potential clinical development. Research is also conducted on the neurobiology of stress-related disorders such as anxiety and depression. The laboratory uses environmental and genetic animal models of disease, with a multidisciplinary approach to understand the neurobiology of psychiatric disorders and to develop novel therapies.
**Scott Schaus, Ph.D.** Associate Professor of Chemistry and Pharmacology.

Research Interests: Dr. Schaus’s research group concentrates on the development of novel technologies to investigate cellular processes such as cell cycle regulation, cell proliferation, and intracellular signaling. Genomic transcription profiling of both model organisms and mammalian cells is employed to validate drug targets and cellular response mechanisms. Current projects include the investigation of protein synthesis and amino acid biosynthesis regulatory mechanisms, MAPK cellular signaling pathways, and the development of microarray technologies.

†Cassandra Smith, Ph.D. Professor of Biomedical Engineering, Biology, and Director, Pharmacology, Molecular Biotechnology Research Laboratory.

†Temple F. Smith, Ph.D. Professor of Biomedical Engineering and Research Professor of Pharmacology, Director, Pharmacology, BioMolecular Engineering Resource Center.

*Jean-Jacques Soghomoni, Ph.D.** Associate Professor of Anatomy and Neurobiology.

Research Interests: The laboratory focuses on the functional neuroanatomy of the basal ganglia and the neurobiological basis of motor control, sensori-motor integration, and learning. His particular interest is the mechanisms of regulation of GABAergic neurons in the basal ganglia in the normal brain and in experimental models of Parkinson’s disease and the neuronal basis of L-DOPA-induced dyskinesias. Techniques include microdialysis, quantitative in situ hybridization histochemistry, immunohistochemistry, quantitative computerized image analysis and assessment of behavioral activity.

*Remco Spanjaard, Ph.D.** Associate Professor of Otolaryngology and Biochemistry; Research Assistant Professor of Biochemistry.

Research Interests: Dr. Spanjaard’s research addresses genetic mechanisms involved in several types of neoplasms. In one project he is studying a new class of RNA coactivator in the pseudouridine synthase (PUS) family that stimulates nuclear receptor-dependent gene regulation via a novel posttranscriptional modification of a highly unusual other RNA co-activator. In a second project he is studying a recently identified orphan member of the TNF receptor superfamily (TROY), which is uniquely expressed on primary and metastatic melanomas. In a third project, he is investigating the role of a p53-regulated, pro-apoptotic DNA damage response gene in breast cancer and chemotherapy resistance. Finally, he is investigating the identification and characterization of new tumor markers in head and neck squamous cell carcinoma that may serve as diagnostic/prognostic indicators and novel therapeutic targets.

**Thomas D. Tullius, Ph.D.** Professor of Chemistry and Pharmacology.

Research Interests: The Tullius laboratory focuses on developing and applying new chemical probe methods for determining the structure of DNA, RNA, and DNA-protein complexes in solution. His group introduced the use of the hydroxyl radical as a high-resolution chemical footprinting reagent for nucleic acids. They are using deuterium kinetic isotope experiments to obtain detailed information on the chemical mechanism of oxidative damage to DNA and RNA induced by the hydroxyl radical. A major project is developing a database of hydroxyl radical cleavage patterns of DNA to make structural maps of regions of the human genome involved in the regulation of gene expression and elucidate the rules by which DNA sequence is translated into three-dimensional structure.

*Carol T. Walsh, Ph.D.** Professor of Pharmacology.

Research Interests: Dr. Walsh’s research has included studies in gastrointestinal pharmacology, the toxicology of metal compounds, and pharmacokinetics. Her current interests include: 1.) the effect of transporter proteins on the pharmacokinetics of drugs and toxic substances, 2.) the impact of genetic variants on drug absorption, distribution and elimination, and 3.) the pharmacokinetics of protein therapeutics. Currently, Dr. Walsh is not conducting laboratory research and is involved in this training program in an administrative capacity as well as through service on qualifying and dissertation committees.

*Kenneth Walsh, Ph.D.** Professor of Medicine and Director, Whitaker Cardiovascular Institute.
Research Interests: Research in the Walsh laboratory has been focused in three areas. The major project investigates the signaling- and transcriptional-regulatory mechanisms that control both normal and pathological tissue growth in the cardiovascular system. Many of these studies involve analyses of the PI3-kinase/Akt/GSK/Forkhead signaling axis. This pathway is of critical importance in the regulation of organ growth and body size. Signaling through this pathway controls cellular enlargement (hypertrophy), cell death (apoptosis), and blood vessel recruitment and growth (angiogenesis). The second project investigates the role of the immune system in vascular disease. The formation of atherosclerotic lesions involves inflammatory cell interactions within the endothelium and subsequent extravasation into the vessel wall. Accelerated atherosclerosis is a critical factor contributing to the stroke and coronary heart disease that is a major cause of death among young women with systemic lupus erythematosus. The third project analyzes the actions of adiponectin on cardiovascular tissues. It is now recognized that adipose tissue functions as an endocrine organ and that obesity contributes to cardiovascular and metabolic disorders through an imbalance of cytokines. Adiponectin is an adipocyte-derived cytokine that is down-regulated in obese individuals. We have found that adiponectin has beneficial actions on the cardiovascular system by directly acting on the heart and blood vessels.

*David Waxman, Ph.D., Professor Biology and Medicine.
Research Interests: A major goal of Dr. Waxman’s laboratory is to elucidate the regulatory processes of cytochrome P450 gene expression, and their impact on patient responses to drugs, in particular, cancer chemotherapeutic agents. Model systems utilized in these studies include animal models (rats, gene knockout mice, immunodeficient scid mice), cell culture models, and in vitro, reconstituted biochemical systems. Projects include: (1) applications of cytochrome P450 in anti-cancer pharmacology, including cancer gene therapy; (2) role of PPAR and other orphan nuclear receptors in drug responses; (3) regulation of sex-dependent liver gene expression by growth hormone and other endocrine factors.

**Benjamin Wolozin, M.D., Ph.D., Professor of Pharmacology and Neurology.
Research Interests: Dr. Wolozin’s research investigates the pathophysiology of neurodegenerative diseases. Research on Parkinson’s disease focuses on the interaction between genetic factors implicated in this disease and environmental factors. His studies utilize cell culture, mammalian brain slice culture and transgenic lines of C. elegans, and results are then investigated further in transgenic/knockout mice and in human brain samples or cell lines from patients. His projects are also focused on identifying pharmacological strategies for Parkinson’s disease. The research on Alzheimer’s disease focuses on the interaction between the proteins that produce beta-amyloid and the genes that regulate cholesterol metabolism. Finally, Dr. Wolozin has an active epidemiological research program that examines the effects of FDA-approved medications on the incidence and progression of both Alzheimer’s and Parkinson’s disease.

*Joyce Y. Wong, Ph.D., Associate Professor of Biomedical Engineering.
Research Interests: Dr. Wong’s main research interest is in the development of new biomaterials that interact with living cells in novel ways. She is interested in questions relating to biocompatibility and control of cellular behavior at the cell-material interface for drug delivery and tissue engineering applications. Her approach includes direct measurement of physicochemical interactions between biological molecules and model biomembrane systems. Dr. Wong’s research uses a combination of approaches from materials science and engineering, polymer science and polymer physics, colloid and surface science, cell culture, and biophysics.

**Zhigang Xie, Ph.D., Assistant Professor Departments of Neurosurgery and Pharmacology.
Research Interests: Neural stem and/or progenitor cells (NSPCs) are promising cell sources for treating brain injury and degeneration. In addition, abnormal proliferation of NSPCs has also been linked to brain development disorders and brain tumors. Dr. Xie’s research interests include: (1) role of the centrosome in the proliferation of NSPCs during
mammalian brain development; (2) regulation of NSPC proliferation by genes that are linked to human brain development disorders; (3) mechanisms underlying the proliferation and migration of NSPC-like stem cells in brain tumors.

PHYSIOLOGY AND BIOPHYSICS

David Atkinson, Ph.D., Chairman
Structure and function of the plasma lipoproteins and apolipoproteins: the structural and molecular basis of lipid transport and the regulation of lipid metabolism in the body are investigated by X-ray crystallography, electron microscopy, and thermodynamic and spectroscopic methods.

Christopher W. Akey, Ph.D.
Structural electron microscopy and X-ray crystallography are being used to study the function of protein translocation channels (ribosome-ER channel, Legionella Type IVb secretory system), histone chaperones and molecules that form apoptosomes and related signaling complexes.

Esther Bullitt, Ph.D.
Research on the structure and function of macromolecular assemblies, using electron microscopy and computer image processing. Current studies focus on understanding adhesion of pathogenic bacteria via pili and on viral replication by RNA-dependent RNA polymerases.

M. Carter Cornwall, Ph.D.
Cellular and molecular mechanisms of dark adaptation and visual pigment regeneration in vertebrate retinal rod and cone photoreceptors. Optical methods (fluorescence, microspectrophotometry) as well as electrophysiological techniques (extracellular current measurements) are used at the single-cell level.

Fernando Garcia-Diaz, Ph.D.
Electrophysiology of membrane transport; expression and regulation of ion channels; development of cochlear ganglion neurons.

Hwai-Chen Guo, Ph.D.
Structure and function of proteins; X-ray crystallographic studies of factors involved in genetic regulation; structure-based design of DNA-binding proteins and enzymes by protein engineering techniques.

Olga Gursky, Ph.D.
Folding, structure, and stability of apolipoproteins, their peptide analogues and their complexes with lipids, analyzed by spectroscopic, calorimetric, and X-ray diffraction methods.

James A. Hamilton Ph.D.
Laboratory research focuses on fatty acid (FA) transport and arteriosclerosis. Structures of FA-binding proteins are determined by multinuclear 2-D and 3-D NMR. Transport of FA into cells is studied by new fluorescence approaches. Atherosclerotic plaques are studied by NMR and MR imaging.

James F. Head, Ph.D.
Crystallography is used to characterize protein-ligand and protein-protein interactions to understand how these interactions regulate physiological processes. Recent structures include the calcium-dependent photoprotein aequorin and a repressor protein associated with the regulation of antibiotic resistance in E. coli, MarR.

Haya Herscovitz, Ph.D.
Regulation of the assembly of apolipoprotein B (apoB) with lipids to form and secrete VLDL; chaperone-assisted folding of apoB. Biochemical, cell, and molecular biological techniques are used.

William Lehman, Ph.D.
Structural studies are carried out on the assembly, function, and regulation of actin-containing thin filaments in muscle and nonmuscle cells. Electron microscopy and 3-D image reconstruction are used to analyze thin-filament mechanisms.
Simon Levy, Ph.D.
Modulation of excitability of nerve cells by second messengers. Current projects include calcium regulation and detection in nerve cells, role of calcium-induced calcium release in the excitability of neurons, and mechanisms of light transduction in photoreceptors.

*Assen Marintchev, Ph.D. (See note below.)
His research encompasses the determination of the structure of the complex of human eIF5B-CTD with the eIF5 C-terminal tail by Nuclear Magnetic Resonance (NMR) to establish the molecular basis for binding affinity and specificity, together with identification of the roles of the eIF5B:eIF5:eIF1A interactions in translation initiation.

C. James McKnight, Ph.D.
Structure and function studies of peptides and proteins; macromolecular interactions; structure determination by multidimensional heteronuclear NMR; actin-binding proteins; lipoproteins.

Jeffrey R. Moore, Ph.D.
Research interests include molecular biomechanics of contractile proteins, the structure and function of motor proteins and calcium regulation of muscle contraction. We use laser traps and fluorescence microscopy to study the relationship between the structure, mechanics, and biochemistry of mechanoenzymes.

Judith D. Saide, Ph.D.
Assembly of proteins in the myofibrils of Drosophila flight muscle; identification and interaction of proteins that are associated with the Z-band and A-band. Approaches include monoclonal antibody production, immunoelectron microscopy, gene cloning, and bacterial expression of protein fragments.

Barbara A. Seaton, Professor, Ph.D.
Protein-membrane interactions of annexins, lung surfactant proteins, and blood coagulation proteins are studied using X-ray crystallography and complementary approaches such as mutagenesis and spectroscopy.

G. Graham Shipley, Ph.D.
Major research interests include membrane structure/function, membrane lipids, membrane receptors, and receptor-ligand interactions. Specific systems being studied using structural biology methods (e.g., protein crystallography, electron microscopy) are LDL receptor–LDL, insulin receptor–insulin, and ganglioside GM1–cholera toxin.

Donald M. Small, M.D.
Interests include the fundamental mechanism by which apolipoprotein B (apoB) is translated and translocated across the endoplasmic reticulum and assembled with lipids to form a nascent lipoprotein particle. Also of interest are the physical properties of lipids, fats, oils, detergents, proteins, and lipid-protein assemblies.

Raphael A. Zoeller, Ph.D.
Generation of mutant animal cell lines deficient in lipid biosynthesis. The use of somatic cell genetics to define roles of lipids in stroke, myocardial infarct, and neuromuscular diseases and to identify genes important for regulation of lipid metabolism.
* Dr. Marintchev just joined the BUSM Faculty in September, 2008, and is not yet a member of the GMS Faculty.