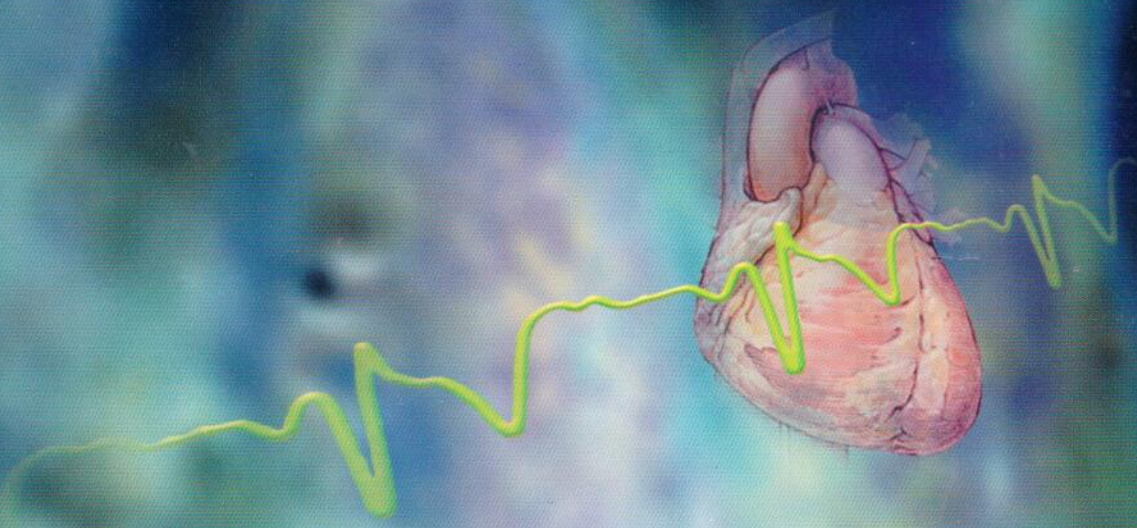
BOSTON BIOMEDICAL RESEARCH INSTITUTE



disease models

ANNUAL REPORT 2004

table of contents

Who We Are

The Boston Biomedical Research Institute (BBRI) is an independent, not-for-profit institution dedicated to basic biomedical research to promote the understanding, treatment and prevention of specific human diseases, and to the training of research scientists. Investigations focus on structure and function of proteins that control cellular communication, muscle contractility, cell movement, growth and differentiation and on the underlying causes of human disease from the study of disease models and development of novel therapeutics. In a uniquely collaborative environment that fosters innovative, multidisciplinary research, our mission is to advance the frontiers of human knowledge in the biomedical sciences and to develop cures for disease.

Message from the President

John R. Layton

We must all champion the excellence of the Institute and bring wider attention to the importance of the discoveries being made here.

Enthusiasm for excellence. Not only does this phrase characterize what goes on in the labs at BBRI, it also can be used to frame the year just past. Our most notable achievement last year was to bring on as Director, Dr. Charles Emerson. As Charlie indicated at our 2003 Annual Meeting, his attraction to taking the position grew the more he learned about the excellence of the science at BBRI, and as he witnessed the enthusiasm for basic science, and for BBRI specifically, that characterizes the BBRI community.

In his first year as Director, Charlie has focused on developing various avenues building on our existing scientific excellence. One example has been the development of the Postdoctoral Fellows Association, a program that improves the postdocs' experience by giving them broader exposure to different aspects of scientific research.

Charlie's enthusiasm for BBRI has been infectious and has led to many important discussions about our future, and what will need to be done to secure it. These discussions have encouraged Charlie to lead a strategic planning process for the Institute, in order that we can plan appropriately for the longer term. It is likely that a key element of the outcome of this process will be an ambitious long-term goal to build on BBRI's existing excellence by attracting new scientists of the highest caliber to join our faculty.

The recruitment of Dr. Eric Sundberg from the Keck Center for Structural Biology at the University of Maryland is a major step in this direction. Eric joined BBRI on July 1, following a faculty search led by Celia Harrison. Eric's expertise revolves around how proteins interact, so his work will directly benefit many of our existing research programs. We are very pleased to welcome him onto the team. Page four of this report goes into greater detail about Eric's research.

Communicating our enthusiasm about BBRI is absolutely vital if we wish to enhance its reputation for scientific excellence. To attract the highest caliber of postdoctoral candidates, we must all champion the excellence of the Institute and bring wider attention to the importance of the discoveries being made here. This can be a daunting task, especially for those of us who are somewhat scientifically-challenged. Going beyond the notion that our scientists all seek innovative solutions to improving human health can suggest the need for a depth of knowledge that non-scientists lack.

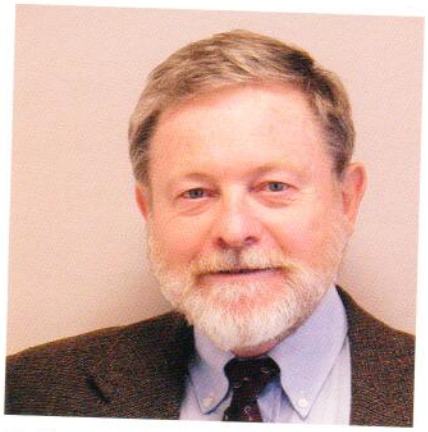
One way that may help all of us to communicate our mission better is through understanding BBRI's work on disease models. Five such disease models currently under investigation at BBRI are highlighted in this year's Annual Report. This year's featured group all relate to Degenerative Disease and Injury, and we look forward to presenting other areas of disease model research at BBRI in future reports.

Enthusiasm for excellence certainly characterizes our increasing involvement in the local community. Our first-ever Walk for Science raised $20,000 to help cover a variety of programs designed to foster an appreciation for science in the larger community. The Walk concluded with a Science Expo for Watertown High School students, who presented posters on their science projects. It was invigorating to see these young scientists interact with each other and with our scientists. Their enthusiasm for science was unmistakable, and Board member Jillian Darling deserves special recognition as the driving force behind this very successful event.

Further evidence of an enthusiasm for excellence at BBRI can be found in the fact that BBRI received $470,595 from 147 donors last year. The average individual donor gift of $770 speaks volumes about the commitment that our donors have to furthering basic research. On behalf of everyone at BBRI, I thank each and every one who gave so generously to BBRI last year. I could not perform the President's job without enthusiastic support from members of the Board, committee members, and the people who work at BBRI – scientists and non-scientists alike – who make my job a real pleasure. A very heartfelt thanks from me to all who have contributed so much to the betterment of the Institute and the health of mankind. Keep it up, team!

Message from the Director

Charles P. Emerson, Jr., Ph.D.



Disease research at BBRI is growing naturally, based on an evolving interest in using disease models to uncover basic mechanisms and our strength in protein research.

My first year at BBRI has been one of the most exciting and challenging of my career as I have moved my lab and family to the Boston area and assumed the directorship of this special Institute. During this transition, I have especially appreciated the warm welcome that we have received from the entire BBRI community of scientists, postdoctoral fellows, administrators and trustees. This has allowed me to devote time to learning about the research activities of the Institute's scientists. In this report, I want to share with you some highlights of this past year and some of the important, and in some cases unexpected, discoveries I have made about BBRI.

Much of my time during this past year has been devoted to better understanding the strengths, accomplishments and ambitions of this Institute. I have drawn on my scientific and research administrative experience at other institutions to identify areas for improvement and strategic opportunities to strengthen our ongoing research to build our scientific excellence. I have learned a great deal about BBRI and the aspirations of our scientists by organizing bi-weekly faculty and postdoc research lunches, which provide a forum for discussion and critique of existing and newly-brewing ideas. Additionally, I have met individually with all of our scientists to learn about their research programs, funding, and goals. The scientific discourse that has emerged over the year has highlighted areas of existing research excellence at BBRI, and identified many new research opportunities for our scientists. The interdisciplinary, collaborative research environment at BBRI is very different from those prevalent in academic institutions with department-based programs and provides our scientists with the flexibility, freedom and time to creatively pursue innovative basic and disease research. The level of technical and intellectual collaboration at BBRI is impressive and is a major driver of our research programs. I am also discovering opportunities for our scientists to develop new collaborative programs based on shared interests not previously recognized. One important challenge during the coming years will be to encourage our scientists to build new interactions and collaborations in areas of mutual interest and to identify sponsored and private funding sources to support these new research areas.

This year also has highlighted for me the excellence of protein research at BBRI in the fields of protein structure and conformational dynamics, protein modification, and protein-protein interactions. Work being done at BBRI is directed towards understanding key cellular and physiological mechanisms that regulate muscle contractility, cell movement, embryonic development, and metabolism. The Human Genome Project has provided us with a remarkable dictionary of all of the 30,000 genes and their encoded proteins in our genome, and more than half these encoded proteins were previously unknown. BBRI scientists now have great opportunities to investigate how newly discovered proteins interact with already known proteins to control key cellular and physiological processes as well as to discover their functions in the body and to investigate the underlying causes of human disease, and to develop cures.

Another exciting discovery I made at BBRI this year is that disease research activity at BBRI is growing naturally, based on an evolving interest in using disease models to uncover basic mechanisms and our strength in protein research. This interest also is greatly nurtured by our unique interactive and interdisciplinary research environment that favors innovative work, and by the extraordinary advances in knowledge of genes and basic biological mechanisms that have occurred over the past 20 years. These rapid advancements in our knowledge are propelling discoveries of the biological basis of human diseases and providing the technology and knowledge for development of novel therapeutics. I have experienced the power of this transition period in my own research, which has led me into areas of cancer therapeutics based on research to identify genes that control tissue formation and regeneration.

BBRI is becoming a leader in developing the basic and disease "Discovery Research Engine," which is a theme of this year's Annual Report. This report highlights for the first time the disease model research ongoing at BBRI in the area of Degenerative Disease and Injury as well as provides an

overview of the broad base of excellent basic, disease and therapeutic research ongoing at BBRI. This report has been a platform for me to crystallize my thoughts and ideas about BBRI, its current research and the possibilities we have to define our future.

Basic and disease model research at BBRI has gained further momentum this year through the recruitment of two exceptional investigators with research programs in areas of protein research related to human disease. Dr. Eric Sundberg joins us as a newly appointed BBRI Scientist from the Keck Center for Structural Biology at University of Maryland (see Page 4). Eric's research combines the use of X-ray crystallography, biophysics and genetics to discover basic mechanisms that dictate how proteins interact, using the superantigens as a protein model. His work will lead to the development of drugs that can block the toxic activity of these proteins in the treatment of bacterial infections or exposure to toxins as bioterrorism agents. Dr. James Fessenden joins BBRI as a newly appointed Instructor from Harvard Medical School. He will investigate the ryanodine receptor to understand how this channel protein controls the flow of calcium ions in and out of muscle cells to regulate muscle contraction as well as to develop drug therapeutics to treat a diversity of human genetic heart diseases resulting from mutations that disrupt the structure of this receptor. Eric and Jim's research programs will significantly enhance protein research at BBRI and our emerging research on disease models and therapeutics.

In addition to digging deeply into research at BBRI this year, I have greatly enjoyed and benefited from my work with Albert Wang, Deputy Director, Alan Kaye, CFO, and Simon Welsby, Director of Development, with whom I have worked to understand and enhance the administration of research and its support at BBRI. I also have enjoyed working closely with our Trustees, whose tireless energy and enthusiasm for the Institute and its research are constant reminders of the importance and value of our scientific mission.

We have had many notable successes at the Institute this year. The research productivity of our scientists has grown, as evidenced by the continued increase in sponsored research, which has doubled in the last five years. Also notable are the excellent publications of our scientists, postdoctoral fellow and associates, which are highlighted for the first time in this Annual Report. We also launched a new website, www.bbri.org, designed by Walter Stafford and a team of faculty, postdocs and trustees, which better projects the research and training programs at BBRI as well as the science of our investigators. There have been many successes this year, but none so important as the newly established BBRI Postdoctoral Association, which is described below. The postdoctoral fellows at BBRI are remarkable in their accomplishments and enthusiasm. Support for our postdoc program and the recruitment of talented postdoctoral fellows is one of our highest priorities to support scientific excellence at BBRI.

I would like to thank all members of the BBRI community for their strong support and encouragement over the past year. As I enter my second year as Director, I look forward to the challenges ahead as we join together to develop a strategic plan to establish new programmatic and faculty recruitment initiatives and to identify the financial support that will be required to shape our future as a leading biomedical research institute.

BBRI Postdoc Association

With the guidance and encouragement of Dr. Emerson, this past year saw the creation of the BBRI Postdoc Association. The Postdoc Association (PDA) works to promote intellectual exchange and to enhance the educational and social experience of postdoctoral fellows at BBRI by sponsoring career development seminars, a scientific speakers program, and social outings and by providing a more formal conduit between the postdoctoral community and the administration and the faculty. During this inaugural year, the PDA sponsored seminars by Dr. Malcolm Gefter of Praecis Pharmaceuticals, Dr. Judith Gallant of Wyeth Pharmaceuticals, Dr. Douglas Fambrough of Oxford Bioscience Partners and Judy Foreman, science writer for *The Boston Globe*, among others. To increase scientific interactions between postdocs, and between postdocs and faculty, the PDA also began a bi-weekly series of "chalk talks," when postdocs discuss their research in an informal setting. The PDA is lead by a Steering Committee, elected by the postdoctoral fellows. Currently the Steering Committee members are Dr. Marie-Annick Forget, Dr. Andrew Mazurkie and Dr. Atsuko Polzin.

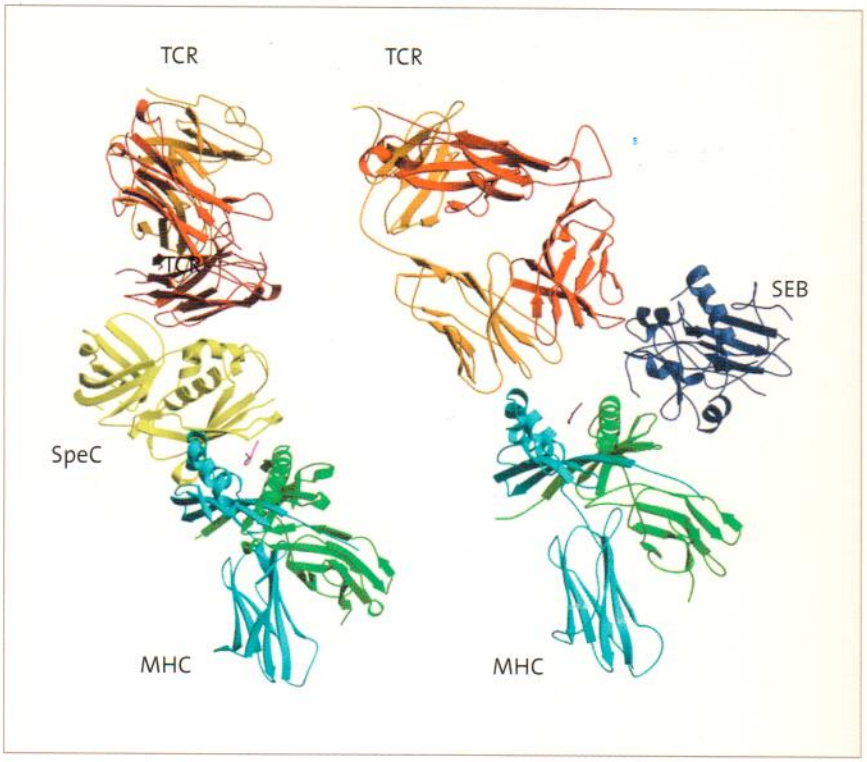
Front (L-R) Renjian Alan Huang, Valerie Carricaburu, Andrew S. Mazurkie, Samudra S. Gangopadhyay, Alena Lieto, Xing-bin Ai, Eunhee Lee, George J. Dimopoulos. Center (L-R) William A. Marganski, Mark L. Bannister, Frederic Kerff, Stefan Girgenrath, David Hayes, Sung Haeng Lee, Ambrus Toth. Back (L-R) Philip Nickson, Marie-Annick Forget-Dubois, Atsuko N. Polzin, Malgorzata Anna Boczkowska, Steven Munevar, David Chereau, Grzegorz Rebowski, Jaya Pal Gangopadhyay, Mahasweta Girgenrath, Beenu Moza, Jolanta Kordowska, Yana Khalina.

Our new Scientist

Eric J. Sundberg, Ph.D., Scientist

"Eric is an exceptionally talented new investigator whose studies complement and enhance BBRI's excellence in protein research."

Charles Emerson, Director



Two ways in which superantigens can interact with receptor molecules on the surfaces of immune system cells. The superantigens, streptococcal exotoxin C (SpeC) and staphylococcal enterotoxin B (SEB), crosslink T cell receptors (TCR) and class II major histocompatibility complex (MHC) molecules differently. Understanding the structural characteristics of the complexes formed between superantigens and their immune system cell surface receptors is crucial to the development of effective therapeutics.

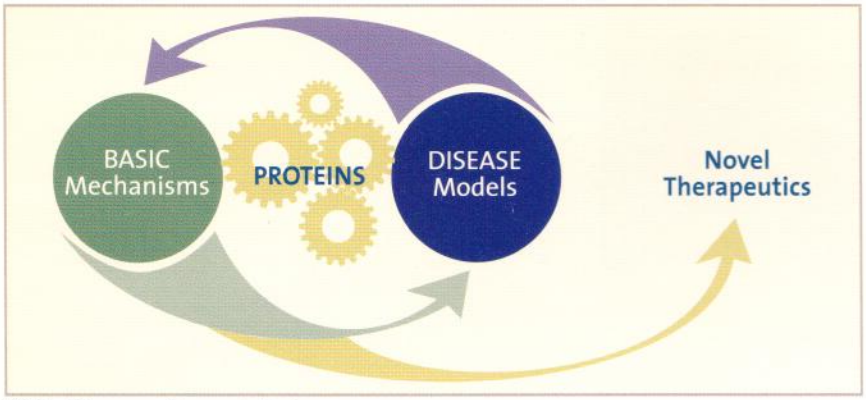
Dr. Eric Sundberg comes to BBRI from the Center for Advanced Research in Biotechnology, part of the University of Maryland Biotechnology Institute, where he was a research assistant professor. This appointment followed postdoctoral work at the same institute during which he was a recipient of an Arthritis Foundation Postdoctoral Fellowship. He received his Ph.D. from Northwestern University.

Eric aims to develop potent inhibitors of the superantigen disease pathway and investigate more effective cancer immunotherapies.

Eric's research focuses on understanding the molecular mechanisms by which superantigens, a family of bacterial toxins, cause disease and on the development of drugs that can counteract superantigen-mediated illness. Superantigens interact with receptor molecules on the surfaces of immune system cells to induce abnormally high levels of cellular proliferation and the subsequent release of immune signaling chemicals. This over-stimulation of the immune system has been implicated in numerous human diseases, including toxic shock syndrome, food poisoning and autoimmune disorders. On account of these disease implications, some superantigens have been classified as bioterrorism agents. The development of therapeutics against superantigen-induced disease, against which no drug or vaccine is currently available, is therefore critical not only to the improvement of public health but also to our overall national defense against bioterrorism. Using structural, energetic and functional analyses combined with molecular evolution and protein design techniques, Eric aims to develop novel therapeutic molecules that serve as potent inhibitors of the initial steps in the superantigen disease pathway. Eric also plans to use structural approaches to investigate the design of more effective cancer immunotherapies by leveraging the immune system's responses to tumors.

Introduction

Disease Models at BBRI: Degenerative Disease and Injury



BBRI's Discovery Research Engine

Disease models are providing unprecedented opportunities to develop novel drug, stem cell and gene therapeutics for a diversity of diseases.

BBRI scientists are dedicated to fundamental discovery research that aims to inform our understanding of the normal functions of the human body, as well as identify novel therapeutic approaches for treatment of human diseases. Our scientists accomplish this aim not only by studying the basic biological mechanisms by which our bodies function, but also by studying mechanisms which are not functioning properly, using experimental models of human disease. Disease models enable a scientist to simplify a problem and study it experimentally in a way that is not possible using human subjects. These models are providing a deeper understanding of how the body normally works as well as unprecedented opportunities for scientists to develop novel drug, stem cell and gene therapeutics for a diversity of diseases.

Today, translating fundamental biomedical discoveries to therapeutics for disease is becoming more and more streamlined, thanks to the development of new technologies, such as high throughput screening and the Genome Project, which has provided for the first time a lexicon of all of the 30,000 or more human genes, the majority of which were previously unknown. Each of these genes encodes a unique protein that carries out a specialized function in the body. The exciting challenge ahead is to translate this wealth of gene information into an understanding of the functions of proteins in specific biological processes and in disease.

BBRI scientists have recognized expertise in the fields of protein structure and conformational dynamics, protein modification and protein-protein interactions. Indeed, at the core of BBRI's science is our excellence and breadth in protein research. Thus, as the focus of much biomedical research shifts from gene discovery to investigations of protein function in this post-genome era, BBRI scientists have the expertise and facilities to investigate key cellular and physiological mechanisms in a way not possible at most institutions. Discovery research at BBRI is further enhanced by the Institute's unique, multidisciplinary environment, which encourages scientists to interact and collaborate, heightening creativity and promoting an environment ripe for innovation.

The study of proteins is critically important to diseased-based research because proteins carry out all of life's functions and as such are targets of therapeutics for disease. The focus of BBRI research on proteins and their biological functions using basic and disease model approaches, therefore, provides opportunities for us to rapidly translate our discoveries into novel therapeutics.

Understanding proteins and how they function drives the "Discovery Research Engine" at BBRI, as graphically represented in the above figure. Today the work of BBRI scientists centers on understanding how specific genes and their encoded proteins function in five specific fundamental biological processes: muscle contraction, cell shape and movement, embryonic development and tissue regeneration, protein function and modification, and cellular communication, as illustrated in the overview of BBRI Today at the end of this report. In this report, we highlight the research of five laboratories, each focused on the area of Degenerative Disease and Injury. The scientists featured employ a range of disease models to conduct their work: two animal models, a molecular model, a cell culture model, and an organ model. These models are shedding light on the mechanisms of cell death, tissue injury, repair, and remodeling, opening the door to new therapeutics for muscular dystrophy, cardiac ischemia, Alzheimer's disease, malignant hyperthermia, cardiac myopathy, cancer and wound healing.

We hope you will enjoy learning about these five innovative projects currently underway at BBRI. Each provides an excellent example of how disease model research can both inform our understanding of the normal functions of proteins in the body as well as identify novel therapeutic approaches for treatment of human disease. Yet the projects in this report are just the tip of the iceberg. Degenerative Disease and Injury is just one of five areas of disease research at BBRI – including Cancer, Reproductive Health, Bacterial Pathogenesis, and Metabolic Disorders — where our "Discovery Research Engine" is producing novel therapeutic approaches to disease.

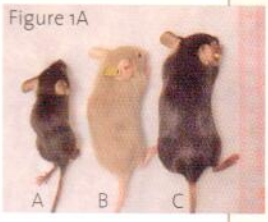
Congenital Muscular Dystrophy, Type 1A

Jeffrey Boone Miller, Ph.D., Senior Scientist

The congenital muscular dystrophies are caused by genetic defects that can lead to severe muscle weakness, with symptoms often beginning in infancy or very early childhood. Dr. Jeffrey Miller's laboratory at BBRI is studying one of these diseases, Congenital Muscular Dystrophy Type 1A, or CMD1A, which is a devastating, recessive genetic disease that prevents normal neuromuscular function from the time of birth and usually leads to death in the first few years of life. The disease is caused by mutations in a human gene called Lama2. Human Lama2 encodes the a2 subunit of laminin, which is an extracellular signaling protein that is found on the extracellular surfaces of nerve, skeletal muscle and skin cells.

Dr. Miller's laboratory is conducting experiments designed to identify therapies for CMD1A, with a focus on interventions that inhibit a type of cell death termed apoptosis, or programmed cell death (see Figure 2). Though apoptosis is a normal process that is used to remove damaged cells from the body, as well as to shape tissues and organs in the embryo during development, an excess of apoptosis, as occurs in some diseases, can cause excessive tissue loss and be deleterious. Preventing such excessive programmed cell death might thus restore the normal balance of cell life and death and ameliorate disease.

As a disease model for human CMD1A, Dr. Miller's laboratory is studying mice in which the Lama2 gene has been made nonfunctional. In their preliminary work, Dr. Miller's lab has shown that muscle disease in the Lama2-deficient mice is ameliorated by genetic alterations that inhibit programmed cell death. Specifically, both the growth (Figure 1A) and the survival (Figure 1B) of Lama2-deficient mice are greatly improved when apoptosis is inhibited by genetically removing a protein termed Bax, which promotes cell death. These findings provide new insight into the normal function of laminin-a2 as a signaling protein that instructs muscles that they are healthy and identify Bax as a drug target for the development of pharmacological therapeutics to treat CMD1A muscular dystrophy. This work will appear in the *Journal of Clinical Investigation*.



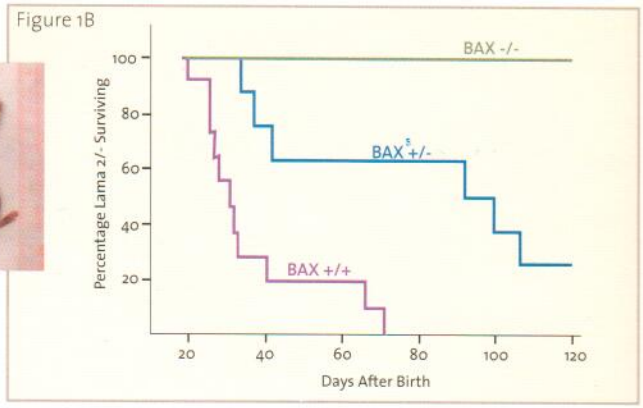


Figure 1A: Improvement of muscle function in Congenital Muscular Dystrophy by genetic inactivation of the Bax cell death gene. Mouse A is a six week old mouse that lacks Lama2 and is a model for human Congenital Muscular Dystrophy Type 1A (CMD1A). The CMD1A dystrophic Mouse A is smaller and has a paralyzed left hind limb, compared with Mouse C which is a normal mouse. Mouse B also lacks Lama2, but is genetically modified to be less susceptible to cell death by genetic inactivation of Bax. As a result, the genetically-modified Mouse B is larger and has greatly improved neuromuscular function.

Figure 1B: Improvement of the life span of mice with Congenital Muscular Dystrophy by genetic inactivation of the Bax cell death gene. Mice that are Lama2- deficient (Lama2 -/-) but have normal Bax genes (Bax +/+) are dystrophic and die within 70 days after birth (red line). Lama2-deficient mice that have no functional Bax genes (Bax -/-) (green) or one functional Bax gene (Bax+/-) (blue) however, survive much better and live much longer.

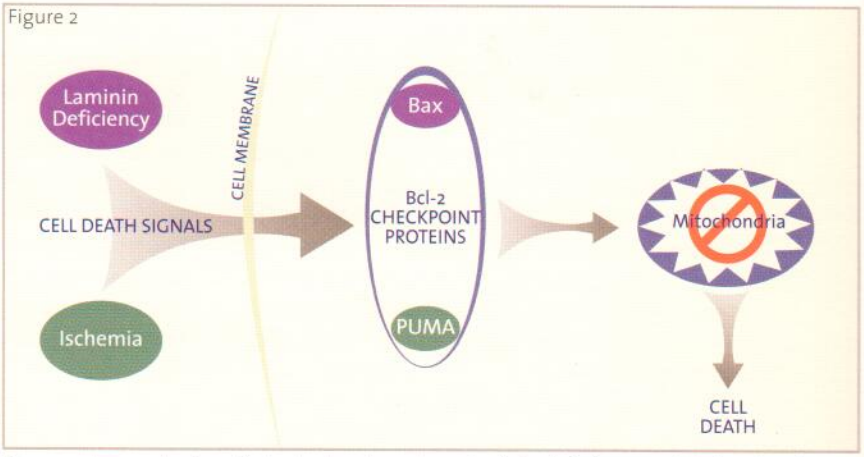


Figure 2: In apoptosis, cell death signals such as laminin deficiency and ischemia relay a message through the cell membrane to mobilize Bcl-2 checkpoint proteins such as Bax and Puma to deplete the energy production and nutrients in the cell mitochondria, resulting in cell death.

Dr. Miller's laboratory is now working to screen for Bax drug inhibitors to treat CMD1A in the Lama2-deficient mouse model as well as to determine if additional neuromuscular degenerative diseases, such as Limb-Girdle Muscular Dystrophies, can be ameliorated by targeted alterations of Bax and other Bcl-2 checkpoint proteins.

Ischemic Heart Disease

Peter Erhardt, M.D., Ph.D., Scientist

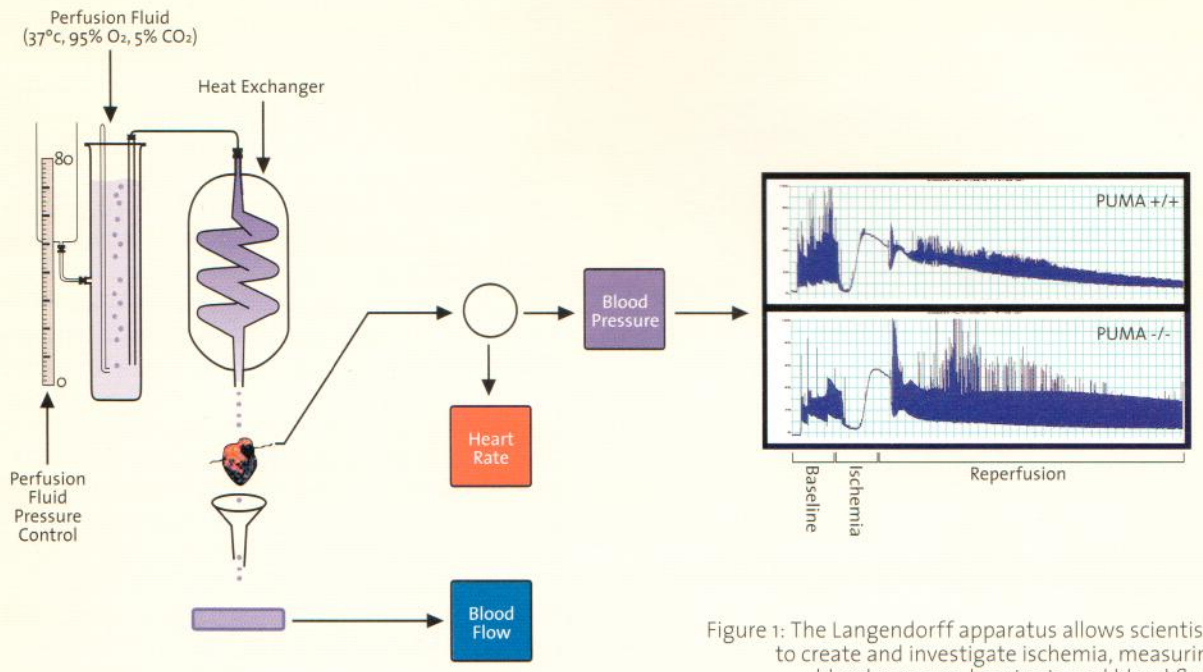


Figure 1: The Langendorff apparatus allows scientists to create and investigate ischemia, measuring blood pressure, heart rate and blood flow.

Ischemic heart disease is one of the leading causes of morbidity and mortality. It is elicited by the narrowing or blockade of the heart's own arteries, the coronary arteries. As a consequence, blood flow becomes insufficient to supply the heart muscle with oxygen and nutrients, a condition that results in chest pain (angina pectoris) and death of heart muscle cells, ultimately leading to heart attack (myocardial infarct). The extensive cell loss in ischemic heart disease, also known as coronary artery disease, ultimately leads to heart failure, where the heart can no longer pump enough blood to supply other tissues.

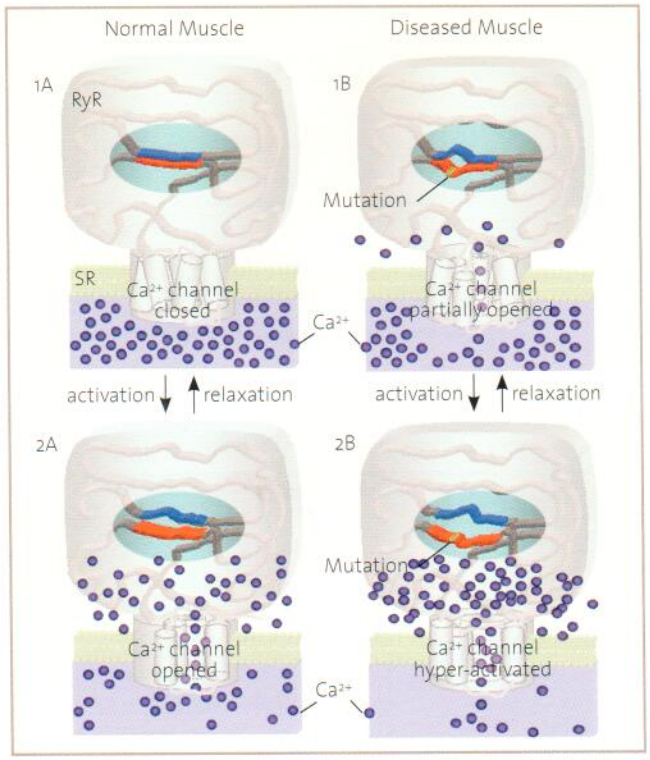
A research project in Dr. Peter Erhardt's laboratory at BBRI aims to prevent irreversible cardiac cell loss caused by ischemic heart disease, thereby salvaging heart muscle and allowing recovery of heart function. The project focuses on a protein called PUMA – p53 upregulated modulator of apoptosis. Apoptosis is a form of cell death that is regulated by the Bcl-2 group of checkpoint proteins, including PUMA (see Figure 2, page 6). PUMA is believed to play a critical role in the death of cardiac muscle cells after an ischemic episode. Dr. Erhardt's hypothesizes that by blocking PUMA after the re-institution of blood flow to the heart muscle, cardiac cell death will be significantly attenuated.

To test this hypothesis, Dr. Erhardt's lab is using a disease model system known as the Langendorff heart in which blood substitutes are pumped through isolated mouse hearts. The Langendorff apparatus (see Figure 1, this page) allows scientists to create and investigate ischemia (blocked blood flow) and reperfusion (re-introduction of blood flow) in a mouse heart. To assess the role of PUMA in cardiac cell death, Dr. Erhardt is comparing a normal or "wild-type" mouse heart during ischemia and reperfusion with a mouse heart in which the PUMA gene has been mutated or "knocked out". The hearts are subjected to a brief 20-minute period of ischemia followed by several hour recovery period of reperfusion. The left ventricular performance of both hearts is monitored during the experiment by a data acquisition system that measures blood pressure, heart rate, and blood flow.

In his studies, Dr. Erhardt has found that in a normal mouse heart, only 30% of cardiac muscle function is recovered after reperfusion, while in the PUMA "knockout" heart the recovery of function is as high as 90-100%. The striking recovery of PUMA "knockout" hearts to ischemic damage identifies PUMA as a primary target for therapeutic intervention to block heart muscle damage following heart attacks. Potential therapies based on Dr. Erhardt's work include drugs designed to inhibit PUMA function in cardiac muscle cells during ischemia and reperfusion as well as restoration of damaged cardiac muscle by the implantation of stem cells in which PUMA has been "knocked out."

Malignant Hyperthermia and Cardiac Myopathy

Noriaki Ikemoto, Ph.D., Senior Scientist



A molecular model for calcium channel disease.

Calcium ion controls many cellular processes, including muscle contraction, and is stored inside a vesicle called the sarcoplasmic reticulum (SR). The release of calcium from the SR must therefore be carefully controlled to avoid abnormal calcium signaling. Many muscle diseases are caused by defects in the control of calcium release. One of these is malignant hyperthermia, which is a condition provoked by inhalable anesthetics leading to uncontrolled muscle contraction and overheating of the body. Malignant hyperthermia has been the cause of many tragic deaths in the dentist's chair and on the operating table.

Dr. Noriaki Ikemoto's laboratory at BBRI is using a molecular model to research the underlying physiological defect in this disease, which they have discovered to be the aberrant release of calcium through a calcium channel protein called the ryanodine receptor (RyR). In the resting state of normal muscle, the RyR calcium channel is closed (Figure 1A). In diseased muscle, however, the RyR calcium channel is partially open even in the resting state (Figure 1B). This leads to leaky calcium channels and abnormally elevated calcium concentrations in the muscle cell. Muscle contraction is induced when physiological activators open the muscle channel so as to rapidly release calcium into the muscle cell (Figure 2A). The opening of RyR calcium channels from malignant hyperthermia patients is hypersensitive to activators of muscle contraction (Figure 2B). Malignant hyperthermia is caused by mutations in the gene encoding the skeletal muscle type RyR. The aberrant calcium release through a mutant RyR calcium channel is also the underlying mechanism of some types of cardiac disease, such as arrhythmogenic ventricular cardiomyopathy and stress-induced polymorphic ventricular tachycardia: two potentially fatal cardiomyopathies, and also reveals how the channel normally works.

In searching for critical domains of RyR involved in the pathogenic mechanism of these diseases, Dr. Ikemoto's lab paid particular attention to the fact that the reported sites of malignant hyperthermia mutations are not randomly distributed in the RyR molecule. Instead, they are localized to two rather restricted regions: the terminal and central domains (see Figures 1 and 2). Based on this observation, Dr. Ikemoto proposed a 'domain-switch' model that involves interactions between the so-called terminal and central domains of RyR as the mechanism for calcium channel regulation. The model assumes that in the resting or non-activated state of normal muscle, the terminal and central domains make close contact, i.e. they are in a "zipped" or "off" configuration (Figure 1A). If a mutation should occur in one of the domains, the interaction of this domain with its mating domain will weaken, causing a partial "unzipping", and creating a partially open calcium channel. Calcium leaking through the open channel results in abnormally high concentrations of calcium in the muscle cell. (Figure 1B). When normal muscles receive a signal to contract, the interdomain contacts are weakened, leading to an "unzipped" or "on" configuration of the domain switch. This leads to calcium channel opening, calcium release, and muscle contraction (Figure 2A). In diseased muscle, the domain switch that is already partially unzipped (cf. Figure 1B) is turned to the fully open configuration even by very weak stimuli, such as inhalable anesthetics, or to an abnormally open configuration by normal stimuli, causing the hyperactivation effects that are seen in individuals genetically disposed to malignant hyperthermia (Figure 2B).

According to the Ikemoto lab's recent work in collaboration with groups in Japan, Australia and Great Britain, an essentially identical domain switch-based mechanism can explain the pathogenesis of some cardiac diseases, such as cardiac hypertrophy. Fortunately, it is now possible, thanks to scientists' understanding of the mechanism of calcium release, to treat these conditions with drugs. The most widely used drug for treating malignant hyperthermia is dantrolene. Recently, research showed that dantrolene stabilizes the zipped configuration of the domain switch and prevents unwanted domain unzipping caused by mutations. In collaboration with a group at Yamaguchi University, Dr. Ikemoto's group also recently found that a new chemical compound, JTV519, prevents abnormal unzipping of the domain switch of cardiac RyR and the subsequent calcium leak. JTV519 has shown promise as a treatment for the early stages of heart failure, thereby preventing severe heart failure.

Alzheimer's disease

Victor A. Raso, Ph.D., Senior Scientist

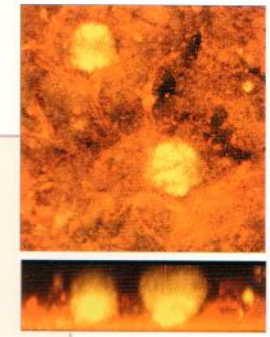


Figure 1. Confocal reconstruction of a Thioflavin stained section of a brain from a transgenic Alzheimer's mouse. The Alzheimer's plaques appear yellow while the surrounding brain tissue and blood vessels are red. The panel below is a 90 degree tilt of the 3-dimensional reconstruction shown above.

Figure 2

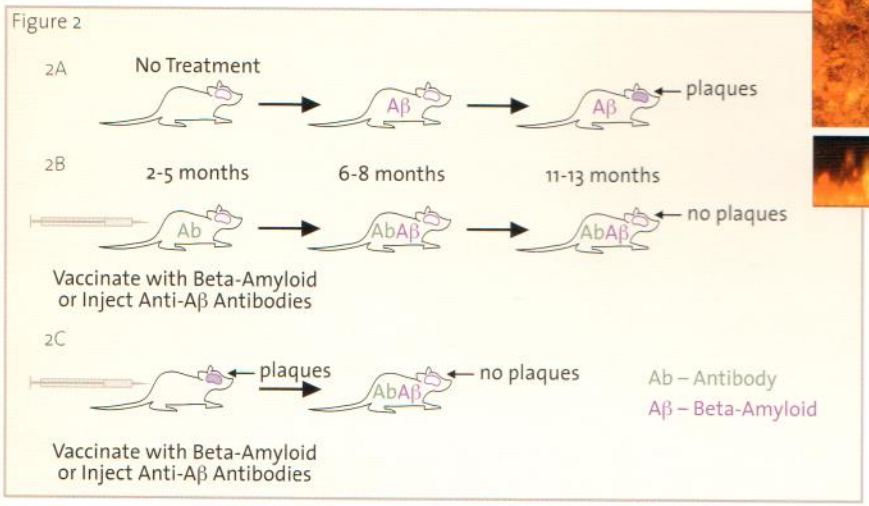


Figure 2. Alzheimer's mouse model 2A received no treatment and developed brain plaques. But the injection of antibodies decreased concentrations of beta-amyloid in the blood and brain and prevented formation of plaques in young mice (2B) and reduced the number or size of pre-established plaques in old mice (2C).

Alzheimer's disease is a progressive form of dementia which involves the parts of the brain that control thought, memory and language. This devastating disease affects 4.5 million Americans today and will afflict 14 million Americans by the middle of this century unless a way for preventing or curing the disease is found.

Dr. Vic Raso's laboratory at BBRI is currently refining a novel approach for controlling Alzheimer's disease that holds great promise for conquering this presently incurable condition. Their approach involves the use of a unique antibody-based vaccine that targets the protein thought to be responsible for Alzheimer's disease, known as beta-amyloid (ß-amyloid). Because Dr. Raso's research is focused on understanding how antibodies work to recognize and modify proteins, he became interested in designing antibodies that would interact with and destroy ß-amyloid. This protein occurs normally in our bodies but its function has not yet been discovered. However, ß-amyloid molecules can stick to each other to form aggregates that can precipitate and form harmful deposits in the brain called plaques. These aggregates or plaques are the most likely cause of the memory loss and dementia that are the hallmarks of Alzheimer's and they also play a role in numerous other neurological diseases (Figure 1).

To evaluate the effectiveness of using the body's own immune system to reduce ß-amyloid plaques in the human brain, Dr. Raso' s group began by adopting a transgenic mouse model of Alzheimer's that was developed elsewhere. They designed and produced specific vaccines and antibodies targeted to ß-amyloid and administered them to the transgenic mice. Results from this and other laboratories showed that the immune response against ß-amyloid produced anti-ß-amyloid antibodies in these animals. As the scientists anticipated, the continued presence of these antibodies effectively decreased concentrations of ß-amyloid in the blood and brain, thereby preventing formation of ß-amyloid plaques in young mice (Figure 2B) and reducing the number or size of pre-established plaques in old mice (Figure 2C). These results suggest that vaccination might be used to prevent Alzheimer's in people who have a genetic predisposition or who show early signs and symptoms, and also for treating patients actually suffering from Alzheimer's.

Dr. Raso's lab next tested the Alzheimer's vaccines in pre-clinical studies in non-human primates at the New England Regional Primate Research Center. The primates mounted an unexpectedly strong immune response to a single injection of the vaccine. Most importantly, the highly sensitive primates were perfectly healthy and showed no signs of autoimmune disease at the conclusion of the trials, proving to be compatible with the anti-ß-amyloid antibodies that had been circulating in their bodies.

The Alzheimer's vaccines are now being further tested in human clinical trials, and Dr. Raso's lab is working to refine the vaccine technology to solve problems of brain inflammation that arose during the first stage of the trials. This involves the production of miniaturized human antibodies that bind to and clear ß-amyloid plaques and are small enough to escape being recognized by the body's immune cells, which is thought to be the cause of the inflammation. A ß-amyloid vaccine that can safely be used in humans may help lower the incidence of Alzheimer's disease and reduce the terrible toll of suffering experienced by its victims and their families.

Dr. Raso has secured one U.S. patent (and others are pending) for this innovative and high impact approach to treating and preventing Alzheimer's disease. This patent and the pending patent applications have been recently licensed to a major pharmaceutical company who is committed to continue human clinical trials with the goal of gaining regulatory approval to offer this vaccine to those at risk for this devastating disease.

Wound Healing

Steen Hansen, M.D., Ph.D., Scientist

These findings will expand our understanding of tissue and organ regeneration as well as identify the cellular processes that malfunction during tumor formation in cancer.

Life is dangerous. Few people make it through without physical injuries along the way. While the accomplishments of medical intervention are often considered noteworthy, the capacity of our bodies to regenerate is usually taken for granted. Yet there is nothing trivial about the processes involved in the healing of wounds. Whether it is a simple skin cut, an intestinal infection, or major surgery, repair processes have to take place that involve proliferation and migration of cells as well as production of molecules that form scaffolds whereupon the cells rest. Moreover, the cells must be able to communicate with their neighbors and the local environment in order to regenerate the damaged tissue. Finally, the cells must be able to sense when to stop growth and migration once the damage has been repaired. Thus, the processes involved in wound healing and regeneration utilize mechanisms similar to those that build and shape tissues and organs in embryos and malfunction in cancer.

Dr. Steen Hansen's lab at BBRI, which includes Dr. Marie-Annick Forget-Dubois and Dr. Scott Frank, focuses on wound healing mechanisms in polarized epithelial cells. Such cells line the inner surfaces of most of our organs such as the lungs, gastrointestinal tract, liver, pancreas, and kidney, as well as the mammary and prostate glands. Using a cell culture model to conduct their studies, the Hansen lab simply grows epithelial cells in culture and creates "wounds" by scraping off lanes of cells with micropipettes (Figure 1). The complexity of these experiments lies not in generating the wound but in the manipulation of cells and their proteins prior to wounding and the methods used to study wound closure. By genetic means the scientists can either eliminate proteins of interest from the cells and/or produce an excess of proteins, which have been engineered to inhibit or increase their normal function. They then utilize a combination of biochemical and high resolution cellular imaging techniques to study how the wounds are filled and where the proteins are located as cells at the wound edge divide and migrate into the wounded areas. These experimental tools permit scientists to ascribe specific functions to given proteins in the wound healing process.

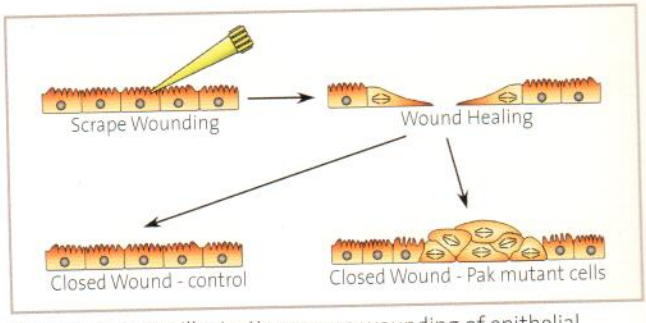
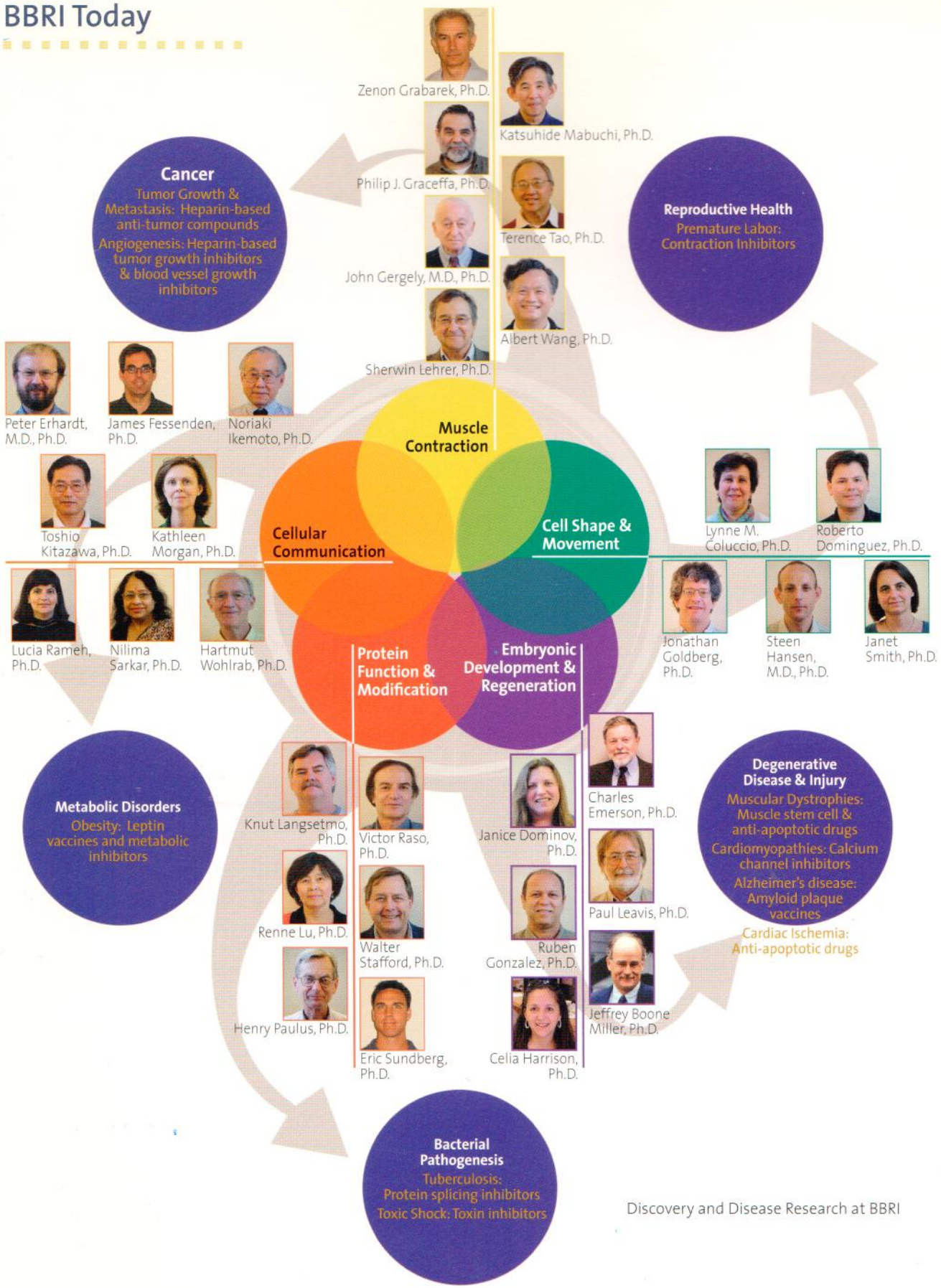


Figure 1: Cartoon illustrating scrape wounding of epithelial cells. Using a pipette tip (yellow), rows of cells are scraped away (upper left panel). This leads to a proliferative and migratory response in cells adjacent to the wound (upper right panel). In normal cells, the wound heals and the site of the wound is no longer distinguishable (lower left panel). In contrast, in cells in which Pak function is inhibited, the cells continue to proliferate after wound closure resulting in cells piling up on one another akin to what in observed in cancerous epithelial cells (lower left panel).

The proteins on which this research is focused were first identified as constituents of protein complexes on the inside of cell membranes contacting the surface below to attach cells to the extracellular matrix substrate. In collaboration with Dr. Zegers, at the University of Cincinnati, the Hansen lab has recently shown that two of these membrane-localized proteins, termed Pak and PIX, are also located at contact points between neighboring cells. In fact, they found that Pak and PIX shuttle back and forth from locations beneath the cell to between cells during wounding and wound closure. In cells adjacent to the initial wound, Pak and PIX shuttle from cell-cell junctions to contact points with the surface below them, and during wound closure, these proteins return to their original location at the contact junctions between neighboring cells as the cells reconnect with one another. Importantly, these scientists also found that inhibition of Pak function during wound healing causes cells to form abnormal cell-cell contacts during wound closure (see figure). Therefore, these findings, indicate that Pak and PIX have important functions in orienting cell movement and cell growth during wound healing.

Dr. Hansen and his lab members are currently expanding the scope of their research by investigating the roles of other components of the Pak and PIX protein complex in epithelial wound healing. They anticipate that their findings will expand our understanding of tissue and organ regeneration as well as identify the cellular processes that malfunction during tumor formation in cancer.

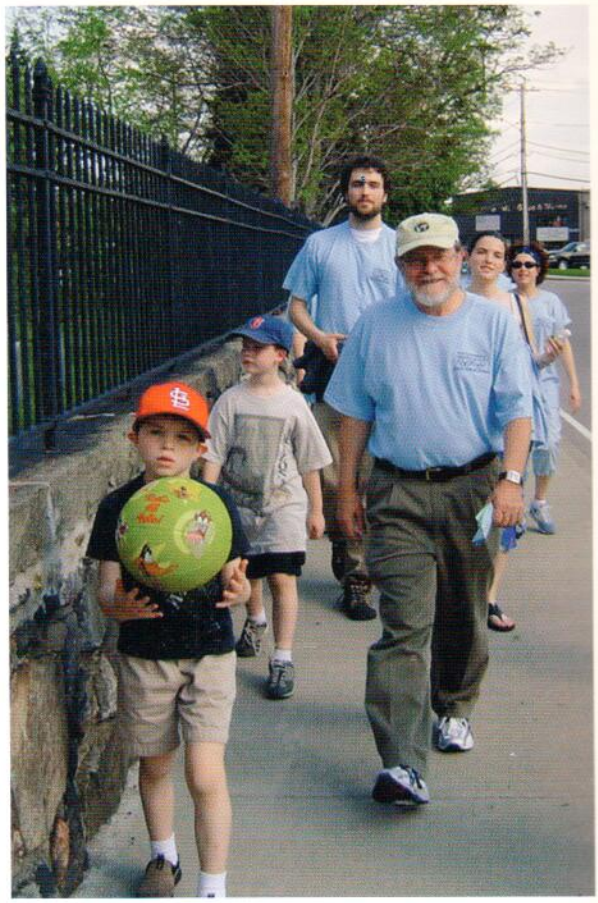
BBRI Today



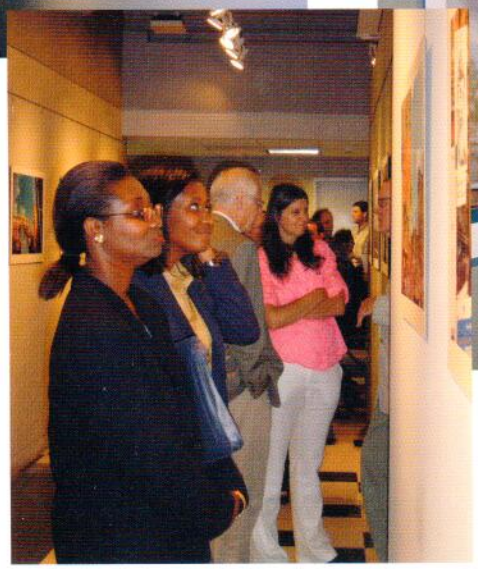
Discovery and Disease Research at BBRI

Community Outreach

BBRI is committed to informing our community about the importance of basic biomedical research for improved human health. To accomplish this goal, BBRI offers a range of community outreach programs. These programs include Exploring Science lectures on topics of general scientific interest, Conversations in the Corridor, an open house where members of the community are invited to speak with the scientists about their latest research, and a range of Science Education Outreach programs, including student and teacher internships, scholarships and classroom visits, which aim to introduce young students to the broad career opportunities in the field of science. Through all of these efforts, BBRI shows its commitment to building the public's awareness of the excitement and promise of basic biomedical research.



BBRI's first ever Walk for Science and Science Expo was more than just a fundraiser. It was a chance for Watertown High School students to display their science projects to BBRI scientists and members of the community. At right, Dr. Charles Emerson BBRI's Director, participates in the Walk For Science with his sons and staff members.



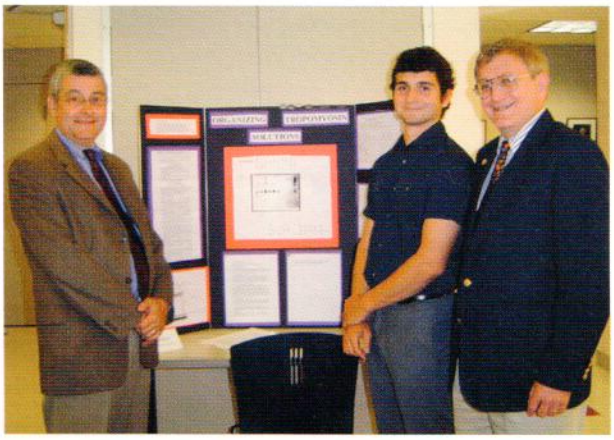
BBRI Trustee Stuart Watson (above left), and members of the community (center) enjoy an exhibit in BBRI's lobby Gallery by photographer Kwesi Budu Arthur (above).

As part of its Science Education Outreach Program, BBRI invites local students into the laboratories for internships each summer. Pictured above are the 2004 summer students who spent their vacation immersed in research and experiments alongside BBRI's scientists. Standing, left to right, are Tanina Bianchi, Debbie Sarkes, Jenny (or Ying) Jiang, Debbie Waung, Laura Leisinger, and Chen Bai. Seated, left to right, are Daiva Nevidomskyte, Sabah Malek, Diana Mujalli, Michael Riley, and Gaurav Giri.

"This has been better than any after-school activity I've been involved in. There's no better way to learn science than being in a lab."

Andrew Bisbas, high school student intern

BBRI's Science Education Outreach Programs include visits to area high schools to teach the students about the type of research being conducted at the Institute. Above, Deputy Director Albert Wang speaks to the Belmont High School Science Club.



Above, Watertown High School student Andrew Bisbas (center) displays his project at the Science Expo with Watertown High School he appears with Acting Headmaster P. Michael Noftsker (left) and Watertown High School Science Coordinator George Buckley (right).

Each year two scholarships are awarded to students from Watertown High School who have an excellent academic record and an interest in studying science in college. The 2004 winners were Rachel Thornton, who will be studying Biology at Harvard University, and Andrew Bisbas, who will study Biology at Cornell.

Development Report

Jillian Hosford Darling, Chair

Philanthropy will play a central role in BBRI's ongoing efforts to become an epicenter of cutting edge basic scientific research from which springs new insight into potential therapies to treat human disease.

I am very pleased to share with you some highlights from BBRI's 2004 fundraising efforts. Dr. Charles Emerson joined our institute as Director in fiscal year 2004, bringing with him a wealth of enthusiasm and plans for new initiatives that will enhance BBRI's excellence in discovery research. Gaining financial support for Dr. Emerson's plans for growth in the areas of faculty recruitment, new technologies and educational outreach in the local community, as well as ongoing funding for our existing programs, is the task of the Development team comprised of BBRI's staff, faculty and trustees, who together work tirelessly to raise funds for BBRI. They have done an excellent job this year and I thank them wholeheartedly for their dedication to BBRI.

Strong teamwork and the generosity of our friends and supporters will be vitally important as we continue the tradition of scientific excellence at BBRI, shaping our future through a strategic planning effort led by Dr. Charles Emerson. The Institute's progress will require strategic collaborations and significant resources. Philanthropy will play a central role in BBRI's ongoing efforts to become an epicenter of cutting edge basic scientific research from which springs new insight into potential therapies to treat human disease. We are looking forward to engaging our donors in this process and keeping them informed as the plan develops.

2004 proved to be a banner year of support of BBRI's Educational Outreach Programs which continue to thrive and grow. I am pleased to report that a new donor, the Leon Lowenstein Foundation gave a generous grant to fund a new teacher internship program, in which high school science teachers spend the summer doing research in the lab of a BBRI scientist. The teachers then take the scientific techniques and approaches utilized during the internship and translate them into a classroom project to be conducted during the following school year. BBRI's 2004-2005 teacher intern is Mr. Thomas LaRocca from Watertown High School, who spent the summer doing research in the laboratory of Dr. Sam Lehrer. Many thanks to the Leon Lowenstein Foundation for making this unique collaborative educational project possible.

In May we held our first ever Walk for Science. This event attracted nearly 100 walkers and the support of local businesses including Acusphere, Inc. who closed their laboratories for the day enabling all of their employees to participate in the walk. Together we raised $20,000 to be used to fund scholarships to local high school seniors, student and teacher internships and classroom visits from area schools to our laboratories.

Following the Walk for Science, Watertown High School held their Student Science Exhibition at BBRI, an engaging event where students displayed their science projects to the walk participants, discussed their projects and answered questions. Many thanks to George Buckley, WHS Science Coordinator, for his role in helping make possible this wonderful collaborative community event which aims to promote science as a career for young people.

Through the generosity of our loyal donors we raised $470,595 in support of the 2004 Annual Fund. Thanks to the efforts of the Stewardship Committee, led by Allie Blodgett, we are happy to report that we had a 14% increase in new donors. Annual Fund dollars are critical to the Institute as they provide vital unrestricted support which helps provide the infrastructure to BBRI scientists in their pursuit of new knowledge.

In July BBRI's faculty, staff and trustees gathered at the home of Jake Layton to honor Director of Development and Public Affairs, Simon Welsby with a BBQ and "roast." Our thanks go to Simon for seven dedicated years of service to BBRI, during which time he oversaw the raising of over $10 million for BBRI and helped lead A Campaign for BBRI to success. We wish him and his family all the best as they 'cross the pond' and Simon settles into a new position at the University of Leeds in England.

My year as chair of the development committee was an immensely rewarding experience because I was able to be a party to wonderful friendships and the amazing generosity and sincerity of our donors. Thank you all for your generosity and support of BBRI!

Annual Fund Donors

Each fall BBRI hosts Conversations in the Corridor, an open house where friends of the Institute come in and speak to the scientists about their research. Above, Dr. Charles Emerson discusses his research on cell signaling with BBRI President Jake Layton, Corporator Winston Henderson, and Vice President Ty Howe.

Explorer

Bang-Woel Lu Foundation
The Thoracic Foundation
Arthur K. Watson Charitable Trust

Benefactor

Dr. Endre A. Balazs & Dr. Janet L. Denlinger
Jane B. Cook 1992 Charitable Trust
Alice Willard Dorr Foundation
Mrs. Greta Brown Layton
June Rockwell Levy Foundation
Leon Lowenstein Foundation, Inc.

Patron

Mr. Andre Balazs
Allie Flather Blodgett
Mr. & Mrs. Chilton S. Cabot
Drs. Peter and Jane Coleman, in honor of Dr. Terence Tao
Mr. and Mrs. John R. Layton
G. Gorham Peters Trust

Sponsor

Carole and John Benning
Howard C. Connor Charitable Foundation
Ms. Jillian Hosford Darling
Eastern Bank Charitable Foundation
Dr. Douglas M. Fambrough
Donna Cohen Fisher
Lynn and Richard Jachney
Mr. and Mrs. Geoffrey Nunes
Dr. Henry Paulus
The Shane Foundation
Jane H. Stephenson

Members of the community enjoy the reception for Rich Wilson's Exploring Science lecture.

Supporter

Dr. Robert. P. Bondaryk
Thomas R. and Linda DiBenedetto
Mr. and Mrs. Thomas P. Eddy
Dr. Charles P. Emerson, Jr.
Mr. and Mrs. John B. French
Dr. and Mrs. John Gergely
Dr. and Mrs. David A. Gibbs
Mr. Alan L. Kaye
Mr. Peter O. Kliem
Eli and Anne W. Manchester
Anne and Galen Stone
Edmund G. Sullivan
Drs. Albert and Li-Wen Wang

Associate

John E. Abele
Dr. Elkan R. Blout
Nancy E. Concannon
Dr. Leslie R. Coney
Mrs. Frederic G. Corneel
David C. Crockett
Mrs. Edith LaC. Dabney
Mr. and Mrs. Nelson J. Darling, Jr.
David C. de Sieyes
Dr. Josefina Bondoc DeBaere
Jacquelyn M. Findlay
Ms. Kate Sides Flather
Mr. and Mrs. Albert M. Fortier, Jr.
Alden French, III
John Gergely, Jr.
Gregory S. Getschow
Ms. Ellen W. Griggs
Mr. Nathaniel S. Howe, Jr.
Dr. and Mrs. Noriaki Ikemoto
Mr. and Mrs. Charles C. Ives, II
Dr. Ann R. Karnovsky
Nancy Kivel
Thomas and Barbara Leggat
Drs. Sherwin S. and Liane Rief Lehrer
Mr. and Mrs. Cornelius J. McCarthy
Mr. George McCarthy
Justin P. Morreale
Mrs. Caroline B. Nash
New England Biolabs
Mrs. John T. G. Nichols
Mr.and Mrs. Richard D. Phippen
Mr. and Mrs. Vincent F. Raso
William and Pamela Sartorelli
Peter and Nancy Sholley
Mrs. Anne G. Smith
Drs. Walter and Sue Stafford
Mr. and Mrs. William B. Tyler
Mr. Josef H. von Rickenbach
Watertown Savings Bank
Mr. Stuart H. Watson

Annual Fund Donors *[continued]*

BBRI Corporator Carole Benning and faculty members Dr. Albert Wang and Dr. Henry Paulus at the 2003 Annual Meeting.

Friend

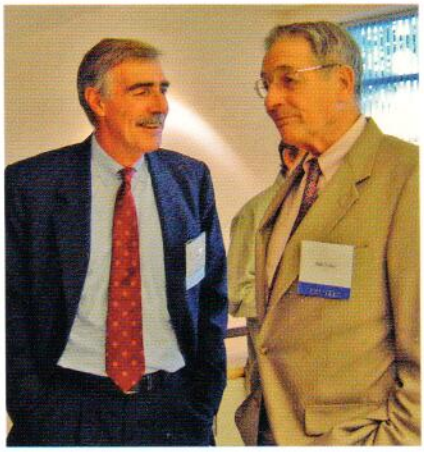
Dr. Nile and Lee Albright
Mrs. Lavinia C. Almy
Ms. Marianne E. Balazs
Victor N. Baltera, Esq.
Andrew J. Bendheim
Carole Smith Berney
Mr. and Mrs. Garrett D. Bowne, III
Mr. David E. Brook
Pat and Don Brouillette
Dr. Penelope Stohn Brouwer
Gurdon S. Buck
Consuelo Calabro, in memory of Frederick Engelhardt
Aliceann L. Caron
Marilyn Carson
Lillian M. Clancy
Dr. Barb Cohen
Kent Coit and Gail Mazzara
Margaret A. Congleton
Dr. and Mrs. Keith Crawford
Dr. and Mrs. Peter F. Davison
William Elfers
Paul Farber
Newell Flather
Mr. and Mrs. John S. Foster
Hollis French, II
Diana and Ronald Garmey
Robert M. Gottlieb and Margo L. Rosenbach
Dr. and Mrs. Philip Graceffa
Thomas McLean Griffin
Joanie Johnson
Susan Kahn, in memory of Frederick Engelhardt
Lise Kaye
Todd and Diane Keiller
John W. Ketchum and Dinah Lane
Ms. Angeline B. Kounelis
Sandra and Stanley Kwiatkowski, in memory of Frederick Engelhardt
Kyu Won Lee
Mr. and Mrs. R. Willis Leith
Sandy and Eileen Leith
Ronald W. Lennox and Therese Feng
Mr. and Mrs. John Lowell
Mrs. John A. Marks, in memory of Frederick Engelhardt
Dorothy J. McDonnell
Victoria Bailey Miller
Jeffrey L. and Jacqui Morby
E. Joyce Munger
Mr. and Mrs. George A. Page, Jr.
Robert and Mary Beth Palladino
Gladys Poor
Carlos M. Samour
Drs. Satyapriya and Nilima Sarkar
Dr. and Mrs. Robert C. Seamans, Jr.
Ross E. Sherbrooke
John F. Sherrerd
Mr. Homer A. Skinner
Henry S. Slayter
Margaret Smith and Jim Bell
Stephen and Brigitte Steadman
Mr. and Mrs. Richard D. Stone
Lena M-L Sundgren
Harry and Dotty Syrigos
Drs. Ludwik and Irma Szymanski
W.J. Nealon Commercial Realty
Eustis Walcott
Mr. and Mrs. Monte J. Wallace
Ms. Joan D. Wheeler

Gifts in Kind

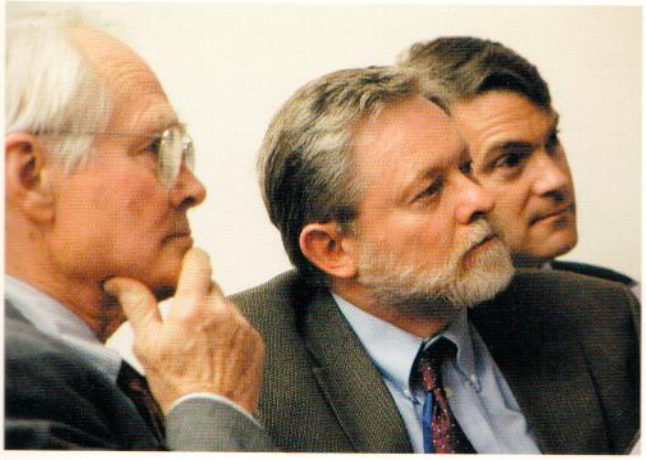
John Sumida

Matching Gifts

Deutsche Bank
Hewlett-Packard Company
Saucony, Inc.
The Prudential Foundation



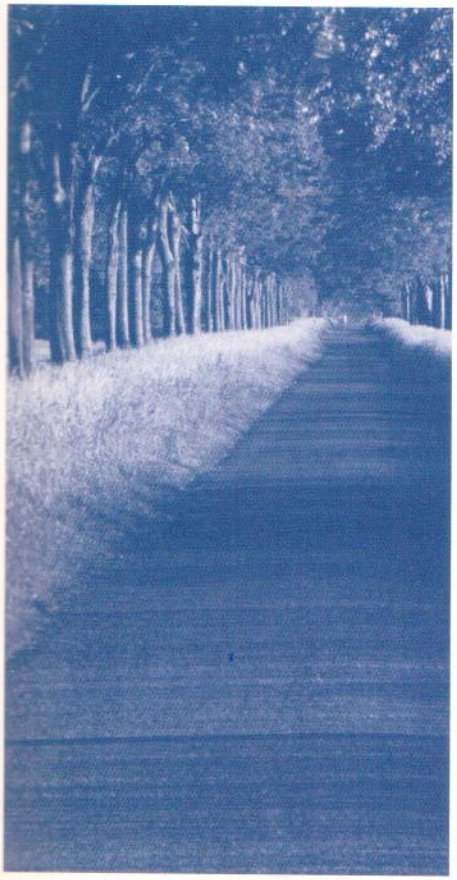
Exploring Science lecturer Rich Wilson speaks with BBRI Overseer William Tyler.



BBRI Board Chairman Jack French (left) listens to remarks at the 2003 Annual Meeting, along with Director Charles Emerson (center) and Board President John Layton (right).

Foundations & Businesses

Apple Lane Foundation
The Endre A. Balazs Foundation
Bell Family Charitable Gift Fund
Bingham McCutchen
Biogen
Peter & Jane Coleman Fund
Nancy Concannon Rev. Trust 2002
Howard C. Connor Charitable Foundation
Jane B. Cook 1992 Charitable Trust
Alice Willard Dorr Foundation
Eastern Bank Charitable Foundation
Elfers Foundation, Inc.
Hurdle Hill Foundation
Kenwood Foundation
June Rockwell Levy Foundation
Leon Lowenstein Foundation, Inc.
Loring, Wolcott, & Coolidge Fiduciary Services
Bang-Woel Lu Foundation
Marsh USA, Inc.
Morby Family Charitable Foundation
New England Biolabs
G. Gorham Peters Foundation
The Shane Foundation
Sherrerd Charitable Lead Annuity Trust
Sholley Foundation, Inc.
The Tamarack Foundation
The Thoracic Foundation
Vicam Limited Partnership
W.J. Nealon Commercial Realty
Watertown Savings Bank
Arthur K. Watson Charitable Trust
Thomas J. Watson Foundation



The Discovery Society

The Discovery Society is a wills and bequests program formed in 2003 that encourages our close friends to consider including the Institute in their estate plans. We would like to recognize and thank the following individuals who have chosen to become members of the Discovery Society. Their generosity is greatly appreciated, and will help ensure that BBRI will be here for many years to come, performing innovative biomedical research for the better health of future generations.

Anonymous
Allie F. Blodgett
Lillian Clancy
John B. French, Esq.
Philip Graceffa, Ph.D.
Ernest Henderson, III
Mira Jelin
John R. Layton
Eli Manchester, Jr.
Geoffrey Nunes, Esq.
Henry Paulus, Ph.D.
Jane H. Stephenson
Albert Wang, Ph.D.
Simon D. J. Welsby

We hope that all of our supporters will consider including Boston Biomedical Research Institute in their estate plans. For information on joining The Discovery Society, please contact Virginia Sullivan, Associate Director of Development and Public Affairs at (617) 658-7711.

Board of Trustees

Corporation Members and Scientific Advisors

Officers

John B. French, *Chairman*
John R. Layton, *President*
Allie Flather Blodgett, *Vice President*
Nathaniel S. Howe, Jr., *Vice President*
Jane H. Stephenson, *Vice President*
Geoffrey Nunes, *Treasurer*
Harry Johnson, *Secretary-Clerk*
Charles P. Emerson, Jr., Ph.D., *Director*
Chih-Lueh Albert Wang, Ph.D., *Deputy Director*

BBRI Trustees and Overseers. Seated (L-R) Josefina Bondoc DeBaere, John R. Layton, Charles P. Emerson, Jr., John B. French, Allie Flather Blodgett, William B. Tyler. Standing (L-R) Albert Wang, David A. Gibbs, Stuart H. Watson, Jillian Hosford Darling, Jane H. Stephenson, Victoria Bailey Miller, John Gergely, Nathaniel S. Howe, Jr.

Trustees

Elkan R. Blout, Ph.D.
Jillian Hosford Darling
Josefina Bondoc DeBaere, Ph.D.
Janet L. Denlinger, Ph.D.
Thomas R. DiBenedetto
Edward G. Fey, Ph.D.
Donna Cohen Fisher
Judah Folkman, M.D.
David A. Gibbs, Sc.D.
Ellen W. Griggs
Ernest Henderson, III
W. Lynn Jachney
Peter O. Kliem
Eli Manchester, Jr.
Victoria Bailey Miller
Stuart H. Watson

Overseers

Donald G. Comb, Ph.D.
David C. Crockett
John Gergely, M.D., Ph.D., D.Sc.M. (hon.)
John A. Shane
William B. Tyler

Corporation Members

Gregory M. Antonopoulos
Paula S. Apsell
Courtney Arrington,M.D.
Andre Balazs
Endre A. Balazs, M.D.
Marianne E. Balazs
Victor N. Baltera
Carole Lund Benning
Andrew Bohm, Ph.D.
Robert P. Bondaryk, Ph.D.
David E. Brook
Penelope Stohn Brouwer
George D. Buckley
Chilton S. Cabot
Daniel V. Calano, Jr.
Gordon C. Cheng
Lillian M. Clancy
Barb Cohen, Ph.D.
Peter S. Coleman, Ph.D.
Nancy E. Concannon
Leslie R. Coney, Ph.D.
S. Allen Counter, Ph.D.
Keith Crawford, M.D., Ph.D.
Roberto Crea, Ph.D.
William E. Cress
Martha Davenport
Peter F. Davison, Ph.D.
David C. de Sieyes
Thomas P. Eddy
Douglas M. Fambrough, Ph.D.
Kate Sides Flather
Albert M. Fortier, Jr.
Alden French, III
Diana O. Garmey
Ronald Garmey
John Gergely, Jr.
Gregory S. Getschow
Robert Gottlieb
Susan Hager
Meg D. Hamilton
Mary Louise Henderson
Vivian Wenhuay Chen Huang
Charles C. Ives, II
Mary Eliot Jackson
Edward C. Johnson, 3d
James K. Joyal
Ann R. Karnovsky, Ph.D.
Lise D. Kaye
James B. Keegan
Nancy M. Kivel, M.D.
Thomas E. Leggat
Sherwin S. Lehrer, Ph.D.
William A. Lowell
Jane L. Lundquist
Cornelius J. McCarthy
George J. McCarthy
Justin P. Morreale
MaryBeth Palladino
Robert M. Palladino
Harry Parsekian
Henry Paulus, Ph.D.
Mrs. Richard D. Phippen
Charles E. Procknow
Vincent F. Raso
Carlos M. Samour, Ph.D.
D. Rao Sanadi, Ph.D.
William A. Sartorelli
Gary C. Shaw
Peter B. Sholley
Robert Simmons
Gilbert L. Steward, Jr.
Anne B. Stone
Galen L. Stone
Edmund G. Sullivan
Kenneth L. Swan
Henri Termeer
Norman R. Veenstra
Josef von Rickenbach
Eustis Walcott
Simon D. J. Welsby
Clyde Younger

Scientific Advisors

Paul T. Matsudaira, Ph.D.
Charles C. Richardson, M.D.
Dagmar Ringe, Ph.D.
Thomas P. Stossel, M.D.

Committees of the Board

Budget, Finance & Audit
Geoffrey Nunes, *Chair*
Charles P. Emerson, Jr., Ph.D. *(ex officio)*
David A. Gibbs, Sc.D.
Alan L. Kaye, CPA
John R. Layton *(ex officio)*
Thomas E. Leggat
Eli Manchester, Jr.
Vincent F. Raso, CPA
Chih-Lueh Albert Wang, Ph.D.

Development
Jillian Hosford Darling, *Chair*
Allie Flather Blodgett
Chilton S. Cabot
Thomas P. Eddy
Charles P. Emerson, Jr., Ph.D. *(ex officio)*
Donna Cohen Fisher
Kate Sides Flather
Diana O. Garmey
Gregory S. Getschow
Ellen W. Griggs
Nathaniel S. Howe, Jr.
Charles C. Ives, II
John R. Layton *(ex officio)*
Virginia Sullivan
Chih-Lueh Albert Wang, Ph.D.
Simon D. J. Welsby

Education
Peter O. Kliem, *Co-Chair*
Paul C. Leavis, Ph.D., *Co-Chair*
Elkan R. Blout, Ph.D.
Penelope Stohn Brouwer
Daniel V. Calano, Jr.
Charles P. Emerson, Jr., Ph.D. *(ex officio)*
John R. Layton *(ex officio)*
Gary C. Shaw
Chih-Lueh Albert Wang, Ph.D.
Simon D. J. Welsby
Hartmut Wohlrab, Ph.D.

Executive
Allie Flather Blodgett
Jillian Hosford Darling
John B. French
Nathaniel S. Howe, Jr.
John R. Layton *(ex officio)*
Jane H. Stephenson
Simon D. J. Welsby

Governance
W. Lynn Jachney, *Chair*
Allie Flather Blodgett
Charles P. Emerson, Jr., Ph.D. *(ex officio)*
John B. French
David A. Gibbs, Sc.D.
Harry Johnson
Peter O. Kliem
John R. Layton *(ex. officio)*
Geoffrey Nunes
Jane H. Stephenson
Chih-Lueh Albert Wang, Ph.D.
Simon D. J. Welsby

Investment
Thomas R. DiBenedetto, *Chair*
Elkan R. Blout, Ph.D.
Chilton S. Cabot
Charles P. Emerson, Jr., Ph.D. *(ex officio)*
David A. Gibbs, Sc.D.
Alan L. Kaye, CPA
John R. Layton *(ex officio)*
William A. Lowell
Geoffrey Nunes
Vincent F. Raso, CPA
Chih-Lueh Albert Wang, Ph.D.

Patents & Technology Transfer
Edward G. Fey, Ph.D., *Chair*
Elkan R. Blout, Ph.D.
Jillian Hosford Darling
Charles P. Emerson, Jr., Ph.D. *(ex officio)*
David A. Gibbs, Sc.D.
Nathaniel S. Howe, Jr.
Alan L. Kaye, CPA
Todd S. Keiller *(consultant)*
John R. Layton *(ex officio)*
Henry Paulus, Ph.D.
Chih-Lueh Albert Wang, Ph.D.
Stuart H. Watson

Public Relations
Jane H. Stephenson, *Chair*
Lynne M. Coluccio, Ph.D.
David C. de Sieyes
Charles P. Emerson, Jr., Ph.D. *(ex officio)*
Harry Johnson
John R. Layton *(ex officio)*
Virginia Sullivan
Simon D. J. Welsby

Stewardship
Allie Flather Blodgett, *Chair*
Keith Crawford, M.D., Ph.D.
William E. Cress
Jillian Hosford Darling
Josefina Bondoc DeBaere, Ph.D.
Charles P. Emerson, Jr., Ph.D. *(ex officio)*
Donna Cohen Fisher
John B. French
Ellen W. Griggs
Nathaniel S. Howe, Jr.
John R. Layton *(ex officio)*
William A. Lowell
Victoria Bailey Miller
Henry Paulus, Ph.D.
Jane H. Stephenson
Anne B. Stone
Virginia Sullivan
Chih-Lueh Albert Wang, Ph.D.
Simon D. J. Welsby

Newly elected Trustees and Corporators at the 2003 Annual Meeting, (L-R) Josefina Bondoc DeBaere, Nancy M. Kivel, Victoria Bailey Miller, Mary Beth Palladino, Robert M. Palladino, Marianne E. Balazs, Andrew Bohm, George D. Buckley, Alden French, III, Henry Paulus.

Message from the Treasurer

Geoffrey Nunes

These are truly "exciting times" at BBRI's state-of-the-art facility in Watertown MA. BBRI's collaborative research programs, led by Dr. Charles P. Emerson, Jr. continue to thrive and gain momentum. In fact, Dr. Emerson's accomplishments during his first year at BBRI were truly remarkable. Dr. Emerson has worked closely with the Boston area scientific community: he has fostered relationships with prominent biotech leaders, deans of universities and colleges and chief executive officers at other prominent independent research institutes; he has increased BBRI's visibility and begun positioning the Institute to increase its collaborative research initiatives and educational programs; he has put internal processes in place to help ensure that existing scientists will flourish; he has identified promising alternative funding opportunities; and last but not least he has provided strong leadership by implementing a formal mentoring program, which has fostered a team spirit. The Board of Trustees has embraced the collective vision of Dr. Emerson and the faculty, and looks forward to assisting BBRI to achieve the strategic initiatives required to position the Institute as a leader in cutting edge biomedical research while ensuring its financial strength for the future.

The Statements of Financial Position indicate that total assets at June 30, 2004 had increased to approximately $45,379,000 from $42,347,000 at June 30, 2003. This increase reflected a growth in grants receivable of $1,573,000, or 20% over the prior year, to $9,368,000 as of June 30, 2004. Investments approximated $15,669,000 on June 30, 2004, an increase of approximately $1,487,000 over the prior year. The investment portfolio had a solid year with an annual total return of 15.1%.

The Statements of Activities indicate that BBRI revenues from grants and contracts of approximately $11,470,000 for the year ended June 30, 2004, reflected growth of 21% over the prior year. Revenue from federal agencies represents approximately 96% of such revenue. During the last fiscal year the Institute was awarded ten new grants from the National Institutes of Health and one new grant from the National Science Foundation.

Charitable giving remains a critical revenue source for BBRI. Philanthropic giving during the fiscal year was used to support the BBRI Scholars program as well as other research and educational initiatives. Fiscal year 2004's total contributions approximated $558,000. Unrestricted, temporarily restricted and permanently restricted contributions approximated $444,000, $60,000 and $54,000, respectively. BBRI appreciates each and every donor's generous support. We hope you will continue to assist BBRI in reaching its goal of expanding our friends, advocates and supporters. This will be a primary focus over the next few years as BBRI prepares to meet the challenges formulated by Dr. Emerson and his scientific colleagues in their strategic planning process that will enable it to continue to develop its excellence in basic and disease related research.

Unrestricted investment income of $1,871,000 for the year ended June 30, 2004 increased $1,478,000 over the prior year, due primarily to strong stock market performance.

Other income includes net royalty income of $55,000 relating to an Alzheimer's vaccine technology. The gross royalty revenue of $100,000 was allocated in accordance with BBRI patent policy.

Total expenses of $12,445,000 increased approximately $1,205,000 or 10.7% over the prior year due primarily to growth in research initiatives. BBRI continued its cost containment efforts taking advantage of various purchasing consortiums and affiliation memberships. BBRI routinely solicits competitive bidding to ensure it receives the best price, service and quality from vendors and independent contractors.

BBRI significantly improved its operating performance for the fiscal year ended June 30, 2004, as the increase in unrestricted net assets was $1,478,000, an increase of $2,350,000 over the prior year. As previously noted, the investment portfolio generated a 15.1% return in fiscal year 2004 versus a 3.3% return in fiscal year 2003. BBRI easily exceeded its debt service coverage ratio requirement of 110% for the fiscal year ended June 30, 2004 and increased its liquidity ratio (a measure of unrestricted cash and investments available to satisfy outstanding bond debt) to 101% as of June 30, 2004 from 89% at June 30, 2003.

The Investment Committee's discipline and diligence in achieving the performance and asset allocation of our portfolio, with guidance from our investment advisor New England Pension Consultants, was reflected by the strong performance achieved. The Committee continued to reposition and diversify the portfolio during the year to help reduce risk and preserve principal with a goal of maximizing total return. Once again, I would like to thank Tom DiBenedetto for his leadership of the Investment Committee as well as the other members for continuing to share with us their expertise.

Respectfully submitted,
Geoff Nunes, Treasurer

Statements of Financial Position

June 30, 2004 and 2003

ASSETS	2004	2003
Cash	$ 1,180,636	$ 921,496
Grants receivable	9,367,984	7,794,153
Unconditional promises to give	566,214	722,652
Investments	15,668,709	14,181,202
Prepayments, deposits and other receivables	223,663	150,861
Trustee-held funds	1,244,594	1,244,688
Property and equipment	14,971,033	15,517,841
Deferred compensation investments	2,155,693	1,813,629
Total assets	**$ 45,378,526**	**$ 42,346,522**
LIABILITIES AND NET ASSETS		
Accounts payable and accrued expenses	$577,388	$811,577
Accrued interest expense	379,056	385,202
Deferred income	9,074,340	7,608,262
Note payable	8,143	10,056
Bonds payable	15,895,000	16,190,000
Deferred compensation payable	2,155,693	1,813,629
Total liabilities	**28,089,620**	**26,818,726**
NET ASSETS		
Unrestricted	14,661,863	13,183,469
Temporarily restricted	485,930	82,541
Permanently restricted	2,141,113	2,261,786
Total net assets	**17,288,906**	**15,527,796**
Total liabilities and net assets	**$ 45,378,526**	**$ 42,346,522**

Copies of our complete, audited financial statements are available upon request from the Chief Financial Officer, Boston Biomedical Research Institute.

Statements of Activities

For the years ended June 30, 2004 and 2003

CHANGES IN UNRESTRICED NET ASSETS	2004	2003
Revenues		
Grants and contracts	$ 11,470,152	$ 9,454,776
Contributions	443,962	406,723
Investment income	1,870,738	392,107
Other income including licensing fees, net	57,149	5,921
Total unrestricted revenues	13,842,001	10,259,527
Net assets released from restrictions	81,354	109,324
Total unrestricted support	**13,923,355**	**10,368,851**
Expenses		
Salaries and benefits	7,433,636	6,710,931
General support and services	2,069,051	1,661,649
Occupancy costs	1,061,271	947,199
Interest Expense	905,526	919,635
Depreciation	975,477	1,000,929
Total expenses	**12,444,961**	**11,240,343**
Increase (Decrease) in unrestricted net assets	1,478,394	(871,492)
CHANGES IN TEMPORARILY RESTRICTED NET ASSETS		
Contributions	60,000	50,000
Investment income	250,363	1,361
Net assets released from restrictions	(81,354)	(109,324)
Reclassification of prior years' net assets	174,380	—
Increase (Decrease) in temporarily restricted net assets	403,389	(57,963)
CHANGES IN PERMANENTLY RESTRICTED NET ASSETS		
Contributions	53,707	730,651
Investment income	—	30,640
Reclassification of prior years' net assets	(174,380)	—
Increase (Decrease) in permanently restricted net assets	(120,673)	761,291
Increase (Decrease) in net assets	**1,761,110**	**(168,164)**
Net assets at beginning of year	**15,527,796**	**15,695,960**
NET ASSETS AT END OF YEAR	**$ 17,288,906**	**$ 15,527,796**

Grants & Fellowship Awards

June 30, 2004

National Institutes of Health			
Dr. Ai	Signaling Role of Qsulf in Embryonic Neural Tube	9/03 - 5/05	87,000*
Dr. Bohm/Grabarek	Molecular Basis for Inhibition of Edema Factor	3/04 - 2/06	101,000*
Dr. Bohm	Functional Studies of the Yeast Poly (A) Polymerase	9/99 - 8/03	198,000
Dr. Bohm	Catalytic Mechanism and Regulation of Mammalian Adenylyl Cyclase	9/99 - 2/05	510,000
Dr. Bohm	Mechanism of Poly (A) Polymerase Processivity	7/02 - 6/07	1,839,000
Dr. Coluccio	Myosin-I Mediated Processes in Liver Cells	8/97 - 7/03	1,407,000
Dr. Coluccio	Molecular Mechanism of a Mammalian Class I Myosin Motor	2/04 - 1/08	1,500,000*
Dr. Dominguez	Atomic Structure of Smooth Muscle Caldesmon	3/00 - 2/05	1,761,000
Dr. Dominguez	Structure of the Smooth Muscle Myosin Phosphatase	9/03 - 11/08	2,465,000*
Dr. Dominov	Enhancement of Myoblast Chemotactic Migration	9/02 - 6/04	210,000
Dr. Erhardt	Prevention of Myocardial Ischemic Injury by RAF/ERK	4/03 - 3/07	1,471,000
Dr. Emerson	Control of Muscle Protein Synthesis during Myogenesis	9/03 - 6/05	1,336,000*
Dr. Emerson	Sonic Hedgehog Target Genes in Development and Cancer	12/03 - 11/06	1,900,000*
Dr. Gangopadhyay	CaMK II Variants and Vascular Smooth Muscle Function	4/04 - 3/07	156,000*
Dr. Graceffa	Smooth Muscle Thin Filament	8/01 - 7/05	1,892,000
Dr. Hansen	Rnd Effector Molecules in Epithelial Cell Transformation	3/03 - 2/08	2,365,000
Dr. Harrison	Structure-Function Study of Angiogenic Protein, Ephrin	7/01 - 6/05	1,261,000
Dr. Ikemoto	Structure and Function of Sarcoplasmic Reticulum	4/02 - 3/07	3,030,000
Dr. Ikemoto	Regulation of Normal and Diseased Cardiac Ca2+ Channels	4/03 - 3/07	1,682,000
Dr. Kitazawa	G Protein Mediated Ca2+ Sensitization in Smooth Muscle	4/02 - 11/03	320,000
Dr. Kitazawa	Mechanism of Ca2+ Sensitization in Smooth Muscle	6/02 - 5/07	2,876,000
Dr. Lehrer	Tropomyosin and the Regulation of Muscle Contraction	2/01 - 1/05	2,106,000
Dr. Miller	Molecular Physiology of Respiratory Muscles	11/01 - 6/05	1,921,000
Dr. Miller	Neurotoxicogenomics and Child Health	11/01 - 8/06	1,506,000
Dr. Miller	Pathogenesis of Laminin-Alpha2 Deficiency	9/02 - 8/06	1,291,000
Dr. Morgan	Regulation of Contraction and Growth of Blood Vessels	3/00 - 2/05	1,762,000
Dr. Morgan	Contraction of Vascular Smooth Muscle Cells	4/01 - 3/05	1,023,000
Dr. Morgan	Signaling & Uterine Contractility during Pregnancy	8/03 - 6/08	1,696,000*
Dr. Rameh Plant	The Role of PtdIns-5-P in Cell Function and Signaling	6/03 - 3/08	1,752,000
Dr. Raso	Immunotherapeutic Agents to Treat Alzheimer's Disease	9/00 - 8/05	1,958,000
Dr. Sarkar	Function of Polyadenylate Sequences in Bacterial RNA	9/98 - 8/03	1,567,000
Dr. Smith	Role of cGMP signaling in Dictyostelium chemotaxis	11/03 - 12/07	1,343,000*
Dr. Tao	Molecular Interactions of the Myosin Phosphatase Subunits	2/00 - 1/05	1,282,000
Dr. Tao	Mechanism of Calcium Regulation in Striated Muscle	6/03 - 5/08	3,109,000
Dr. Tao	A Stroboscopic Time-Resolved Spectrofluorometer	3/04 - 2/05	158,000*
Dr. Wang (Pro. Proj.)	Molecular Mechanism of Smooth Muscle Regulation	12/02 - 11/07	9,133,000
Dr. Wang	Regulation of Myosin Light Chain Kinase by Phosphorylation	1/02 - 12/04	96,000
National Science Foundation			
Dr. Erhardt	Mechanism of Cell Survival Mediated by the B-Raf Kinase	6/00 - 5/04	309,000
Dr. Stafford	Development of Software for Real-Time Display and Analysis of Sedimentation Velocity Data	1/04 - 8/05	44,000*
Department of the Army			
Dr. Rameh Plant	The Role of Novel Phosphoinositide Pathways in Breast Cancer	10/01 - 7/04	473,000
U S Department of Agriculture			
Dr. Miller	Muscle Cell Growth and Development	11/01 - 4/04	236,000
American Heart Association			
Dr. Dominguez	X-Ray Study of Smooth Muscle Actin and its Complex with a Caldesmon Fragment	1/02 - 12/05	300,000
Dr. Janet Smith	Cyclic GMP Signaling by GBP-A and B in Dictyostelium	1/02 - 12/05	260,000
CONRAD			
Dr. Gonzalez	Leptin Peptide Antagonists	12/02 - 11/04	260,000
EMD Pharmeceuticals			
Dr. Stafford	Characterization of EMD72000	10/02 - 10/03	60,000
Muscular Dystrophy Association			
Dr. Miller	Dysferlinopathy Model Studies	7/02 - 6/05	105,000

*New grants in Fiscal Year 2004

BBRI Faculty Publications

July 1, 2003 to June 30, 2004

Ai, X., Do, A. T., Lozynska, O., Kusche-Gullberg, M., Lindahl, U., Emerson, C. P. Jr. (2003) QSulf1 remodels the 6-O sulfation states of cell surface heparan sulfate proteoglycans to promote Wnt signaling. *J Cell Biol* **162**, 341-51.

Bacchiocchi, C., Graceffa, P. & Lehrer, S. S. (2004). Myosin-induced movement of αα, αβ, and ββ smooth muscle tropomyosin on actin observed by multisite FRET. *Biophys J* **86**, 2295-307.

Batters, C., Arthur, C. P., Lin, A., Porter, J., Geeves, M. A., Milligan, R. A., Molloy, J. E. & Coluccio, L. M. (2004). Myo1c is designed for the adaptation response in the inner ear. *EMBO J* **23**, 1433-40.

Braquart-Varnier, C., Danesin, C., Clouscard-Martinato, D., Agius, E., Escalas, N., Benazeraf, B., Ai, X., Emerson, C. P. Jr., Cochard, P. and Soula, C. (2004) A subtractive approach to characterize genes with regionalized expression in the gliogenic ventral neuroepithelium: identification of chick sulfatase 1 as a new oligodendrocyte lineage gene. *Mol Cell Neurosci* **25**, 612-628.

Carricaburu, V., Lamia, K. A., Lo, E., Favereaux, L., Payrastre, B., Cantley, L. C. & Rameh, L. E. (2003). The phosphatidylinositol (PI)-5-phosphate 4-kinase type II enzyme controls insulin signaling by regulating PI-3,4,5-trisphosphate degradation. *Proc Natl Acad Sci USA* **100**, 9867-72.

Chang, J. D., Field, S. J., Rameh, L. E., Carpenter, C. L. & Cantley, L. C. (2004). Identification and characterization of a phosphoinositide phosphate kinase homolog. *J Biol Chem* **279**, 11672-9.

Chen, Y. & Lehrer, S. S. (2004) Distances between tropomyosin sites across the muscle thin filament using luminescence resonance energy transfer: Evidence for tropomyosin flexibility. *Biochemistry.*

Correia, J. J., Johnson, M. L., Laue, T., Stafford, W. F. & Williams, R. C. (2004). Spinning with Dave: David Yphantis's contributions to ultracentrifugation. *Biophys Chem* **108**, 23-42.

Correia, J. J., Laue, T. & Stafford, W. F. (2004). Preface to wFestschrift for Dave Yphantis. *Biophys Chem* **108**, 1-4.

De Marzi, M. C., Fernandez, M. M., Sundberg, E. J., Molinero, L., Zwirner, N. L., Llera, A. S., Mariuzza, R. A., & Malchiodi, E. (2004) Cloning, expression and interaction of human T cell receptors with the bacterial superantigen SSA, *Eur J Biochem.*

Dominguez, R. & Graceffa, P. (2003). Solution Properties of TMR-Actin: When Biochemical and Crystal Data Agree. *Biophys J* **85**, 2073-4.

Emerson, C. P. Jr. and Hauschka, S. D. (2004) Embryonic origins of skeletal muscles. In: *Myology* (A.G. Engel and C. Franzini-Armstrong, eds.) Vol. 1, third edition, McGraw-Hill, NY. 3-44.

Eto, M., Kitazawa, T., Brautigan, D. L. (2004) Phosphoprotein inhibitor CPI-17 specificity depends on allosteric regulation of protein phosphatase-1 by regulatory subunits. *Proc Natl Acad Sci USA* **101**, 8888-93.

Fessenden, J. D., Perez, C. F., Goth, S., Pessah, I. N., Allen, P. D. (2003) Identification of a key determinant of ryanodine receptor type 1 required for activation by 4-chloro-m-cresol. *J Biol Chem* **278**, 28727-35.

Frickel, E. M., Frei, P., Bouvier, M., Stafford, W. F., Helenius, A., Glockshuber, R. & Ellgaard, L. (2004). ERp57 is a multifunctional thiol-disulfide oxidoreductase. *J Biol Chem* **279**, 18277-87.

Gangopadhyay, J. P., Grabarek, Z., and Ikemoto, N. (2004)Fluorescence probe study of Ca2+-dependent interactions of calmodulin with calmodulin-binding peptides of the ryanodine receptor. *Biochem Biophys Res Commun.*

Gelinas, A. D., Toth, J., Bethoney, K. A., Langsetmo, K., Stafford, W. F. & Harrison, C. J. (2003). Thermodynamic Linkage in the GrpE Nucleotide Exchange Factor, a Molecular Thermosensor. *Biochemistry* **42**, 9050-9.

Gelinas, A. D., Toth, J., Bethoney, K. A., Stafford, W. F. & Harrison, C. J. (2004). Mutational Analysis of the Energetics of the GrpE.DnaK Binding Interface: Equilibrium Association Constants by Sedimentation Velocity Analytical Ultracentrifugation. *J Mol Biol* **339**, 447-58.

Gonzalez, R. R. & Leavis, P. C. (2003). A peptide derived from the human leptin molecule is a potent inhibitor of the leptin receptor function in rabbit endometrial cells. *Endocrine* **21**, 185-95.

Gonzalez, R. R., Leary, K., Petrozza, J. C. & Leavis, P. C. (2003). Leptin regulation of the interleukin-1 system in human endometrial cells. *Mol Hum Reprod* **9**, 151-8.

Gonzalez, R. R., Rueda, B. R., Ramos, M. P., Littell, R. D., Glasser, S. & Leavis, P. C. (2004). Leptin induced increase in leukemia inhibitory factor and its receptor by human endometrium is partially mediated by interleukin 1 receptor signaling. *Endocrinology* **145**, 3850-7.

Graceffa, P. & Dominguez, R. (2003). Crystal Structure of Monomeric Actin in the ATP State: Structural Basis of Nucleotide-Dependent Actin Dynamics. *J Biol Chem* **278**, 34172-80.

Guan, R., Xiang, Y., He, X., Wang, C., Wang, M., Zhang, Y., Sundberg, E. J., & Wang, D. (2004). Structural mechanism governing cis and trans isomeric states and an intramolecular switch for cis/trans isomerization of a non-proline peptide bond, *J Mol Biol* **341**, 1189-1204.

Harrison, C. J. (2003) GrpE, a nucleotide exchange factor for DnaK. *Cell Stress & Chaperones* **8**, 218-224.

Ikemoto, N. (2004) Intra-molecular domain-domain interaction - A key mechanism for calcium channel regulation of ryanodine receptors in "Ryanodine receptors: structure, function and dysfunction in clinical disease" edited by X. H. Wehrens and A. R. Marks.

Je, H. D., Gallant, C., Leavis, P. C. & Morgan, K. G. (2004). Caveolin-1 regulates contractility in differentiated vascular smooth muscle. *Am J Physiol Heart Circ Physiol* **286**, H91-8.

Khapchaev, A. Y., Krymsky, M. A., Sidorova, M. V., Bespalova, Zh. D., Wang, C. L., Shirinsky, V. P. and Vorotnikov, A. V. (2004) Novel phosphospecific antibodies for monitoring phosphorylation of proteins encoded by the myosin light chain kinase genetic locus. *Biochemistry* (Moscow) **69**, 789-98.

Kitazawa, T., Polzin, A. & Eto, M. (2004). CPI-17-deficient smooth muscle of chicken. *J Physiol* **557**, 515-28.

Kobayashi, S., Yamamoto, T., Parness, J. & Ikemoto, N. (2004). Antibody probe study of Ca2+ channel regulation by interdomain interaction within the ryanodine receptor. *Biochem J* **380**, 561-9.

Lamia, K. A., Peroni, O. D., Kim, Y. B., Rameh, L. E., Kahn, B. B. & Cantley, L. C. (2004). Increased Insulin Sensitivity and Reduced Adiposity in Phosphatidylinositol 5-Phosphate 4-Kinase {beta}-/- Mice. *Mol Cell Biol* **24**, 5080-5087.

Li, X. D., Mabuchi, K., Ikebe, R. & Ikebe, M. (2004). Ca2+-induced activation of ATPase activity of myosin Va is accompanied with a large conformational change. *Biochem Biophys Res Commun* **315**, 538-45.

Li, Y., Je, H. D., Malek, S. & Morgan, K. G. (2004). Role of ERK1/2 in uterine contractility and preterm labor in rats. *Am J Physiol Regul Integr Comp Physiol* **287**, R328-35.

Lykke-Andersen, K., Schaefer, L., Menon, S., Deng, X. W., Miller, J. B. & Wei, N. (2003). Disruption of the COP9 signalosome Csn2 subunit in mice causes deficient cell proliferation, accumulation of p53 and cyclin E, and early embryonic death. *Mol Cell Biol* **23**, 6790-7.

Miller, J. B. & Emerson, C. P. Jr. (2003) Does the road to muscle rejuvenation go through Notch? *Sci Aging Knowledge Environ* **48**, pe34.

Mitra, P., Zhang, Y., Rameh, L. E., Ivshina, M. P., McCollum, D., Nunnari, J. J., Hendricks, G. M., Kerr, M. L., Field, S. J., Cantley, L. C., Ross, A. H. (2004) A novel phosphatidylinositol(3,4,5)P3 pathway in fission yeast. *J Cell Biol* **166**, 205-11.

Nowak, J. A., Malowitz, J., Girgenrath, M., Kostek, C. A., Kravetz, A. J., Dominov, J. A. & Miller, J. B. (2004). Immortalization of mouse myogenic cells can occur without loss of p16INK4a, p19ARF, or p53 and is accelerated by inactivation of Bax. *BMC Cell Biol* **5**, 1.

Nyitrai, M., Stafford, W. F., Szent-Gyorgyi, A. G. & Geeves, M. A. (2003). Ionic interactions play a role in the regulatory mechanism of scallop heavy meromyosin. *Biophys J* **85**, 1053-62.

Paolini, C., Fessenden, J. D., Pessah, I. N., Franzini-Armstrong, C. (2004) Evidence for conformational coupling between two calcium channels. *Proc Natl Acad Sci USA*.

Paulus, H. (2003) Inteins as targets for potential antimycobacterial drugs. *Front Biosci* **8**, s1157-65.

Phelps, A. & Wohlrab, H. (2004). Homodimeric Mitochondrial Phosphate Transport Protein. Transient Subunit/Subunit Contact Site between the Transport Relevant Transmembrane Helices A. *Biochemistry* **43**, 6200-6207.

Polyak, E., Standiford, D. M., Yakopson, V., Emerson, C. P. Jr., Franzini-Armstrong, C. (2003) Contribution of myosin rod protein to the structural organization of adult and embryonic muscles in Drosophila. *J Mol Biol* **331**, 1077-91.

Rameh, L. E. (2003). Type 2 PIP4-kinases. In *Handbook of Cellular Signalling*, Academic Press: pp 129-133.

Rufo, P. A., Lin, P. W., Andrade, A., Jiang, L., Rameh, L. E., Flexner, C., Alper, S. L. & Lencer, W. I. (2004). Diarrhea-associated HIV-1 APIs potentiate muscarinic activation of Cl- secretion by T84 cells via prolongation of cytosolic Ca2+ signaling. *Am J Physiol Cell Physiol* **286**, C998-C1008.

Shin, H.-M., Morgan, K. G. (2003) Vasodilation by Banhabackchulchunmatang, a Chinese medicine, is associated with negative modulation of PKCalpha activation and NO production. *Life Sciences* **74**, 723-732.

Shin, J. H., Mahadevan, L., Waller, G. S., Langsetmo, K. & Matsudaira, P. (2003). Stored elastic energy powers the 60-µm extension of the Limulus polyphemus sperm actin bundle. *J Cell Biol* **162**, 1183-1188.

Sontag, C. A., Stafford, W. F. & Correia, J. J. (2004). A comparison of weight average and direct boundary fitting of sedimentation velocity data for indefinite polymerizing systems. *Biophys Chem* **108**, 215-30.

Stafford, W. F. & Braswell, E. H. (2004). Sedimentation velocity, multi-speed method for analyzing polydisperse solutions. *Biophys Chem* **108**, 273-9.

Stafford, W. F. & Sherwood, P. J. (2004). Analysis of heterologous interacting systems by sedimentation velocity: curve fitting algorithms for estimation of sedimentation coefficients, equilibrium and kinetic constants. *Biophys Chem* **108**, 231-43.

BBRI Faculty Publications

July 1, 2003 to June 30, 2004

Sundberg, E. J. & Mariuzza, R. A. (2004). Antibody structure and recogniton of antigen, in *Molecular Biology of B Cells, VII. Function and Application of Immunoglobulins*, Federick W. Alt, Tasaku Honjo and Michael S. Neuberger, ed., Elsevier Academic Press, London. Review.

Sundberg, E. J. & Mariuzza, R. A. (2004). Structural and energetic aspects of immunological protein-protein interfaces, in *Proteomics and Protein-Protein Interactions: Biology, Chemistry, Bioinformatics and Drug Design*, Gabriel Waksman, ed.

Sundberg, E. J., Andersen, P. S., Schleivert, P. M., Karjalainen, K., & Mariuzza, R. A. (2003). Structural, energetic and functional analysis of a protein-protein interface at distinct stages of affinity maturation. *Structure* **11**, 1151-1161.

Terrak, M., Kerff, F., Langsetmo, K., Tao, T. & Dominguez, R. (2004). Structural Basis of Protein Phosphatase 1 Regulation. *Nature* **429**, 780-784.

Tokumitsu, H., Hatano, N., Inuzuka, H., Ishikawa, Y., Uyeda, T. Q., Smith, J. L. & Kobayashi, R. (2004). Regulatory mechanism of Dictyostelium myosin light chain kinase A. *J Biol Chem* **279**, 42-50.

Wang YL, Burridge K, Dembo M, Gabbiani G, Hanks SK, Hosoya H, Janmey P, Karlsson R, Lindberg U, Mabuchi I, Otey C, Rottner K, Small JV, Wang C. L., Zigmond S. (2004) Biomedical research publication system. *Science* **303**, 1974-6.

Wang, F., Thirumurugan, K., Stafford, W. F., Hammer, J. A., 3rd, Knight, P. J. & Sellers, J. R. (2004). Regulated conformation of myosin V. *J Biol Chem* **279**, 2333-6.

Wang, S., Ai, X., Freeman, S. D., Pownall, M. E., Lu, Q., Kessler, D. S. & Emerson, C. P. Jr. (2004). QSulf1, a heparan sulfate 6-O-endosulfatase, inhibits fibroblast growth factor signaling in mesoderm induction and angiogenesis. *Proc Natl Acad Sci USA* **101**, 4833-8.

Wennerberg, K., Forget, M. A., Ellerbroek, S. M., Arthur, W. T., Burridge, K., Settleman, J., Der, C. J. & Hansen, S. H. (2003). Rnd proteins function as RhoA antagonists by activating p190 RhoGAP. *Curr Biol* **13**, 1106-15.

Wier, W. G. & Morgan, K. G. (2003). alpha(1)-Adrenergic signaling mechanisms in contraction of resistance arteries. *Rev Physiol Biochem Pharmacol* **150**, 91-139.

Wohlrab, H. (2004) Novel inter- and intrasubunit contacts between transport-relevant residues of the homodimeric mitochondrial phosphate transport protein. *Biochem Biophys Res Commun.* **320**, 685-8.

Yang, J., Swaminathan C. P., Huang, Y., Guan, R., Cho, S., Kieke, M.C., Kranz, D. M., Mariuzza, R. A., & Sundberg, E. J. (2003). Dissecting cooperative and additive binding energetics in the affinity maturation pathway of a protein-protein interface. *J Biol Chem* **278**, 50412-50421.

Zavala-Ruiz, Z., Sundberg, E. J., Stone, J. D., DeOliveira, D. B., Chan, I. C., Svendsen, J., Mariuzza, R. A., & Stern, L. J. (2003). Exploration of the P6/P7 region of the peptide-binding site of the human class II MHC protein HLA-DR1. *J Biol Chem* **278**, 44904-44912.

Zegers, M. M., Forget, M. A., Chernoff, J., Mostov, K. E., ter Beest, M. B. & Hansen, S. H. (2003). Pak1 and PIX regulate contact inhibition during epithelial wound healing. *EMBO J* **22**, 4155-65.

New Patents & Patent Applications

Pending U.S. Patents

Development and biological effects of leptin peptide antagonists (LPA's), Ruben Rene Gonzalez, Paul Leavis, filed 5/7/2004

Methods for delaying or inducing labor, Kathleen Morgan, Yungpig Li, filed 7/15/03

Methods for preventing or reducing ischemia/reperfusion induced myocardial cell death, Peter Erhardt, filed 4/13/2004

Inhibition of FGF signaling, Charles Emerson, Xingbin Ai, filed 2/13/2004

Protein Phosphatase 1 for rational drug design, Roberto Dominquez, filed 5/26/ 2004

Issued U.S. Patents

US 6,582,945: Immunological control of ß-amyloid levels in vivo, Victor Raso, Issued 6/24/2003

Faculty & Staff

Director
Charles P. Emerson, Jr., Ph.D.

Deputy Director
Chih-Lueh Albert Wang, Ph.D.

Senior Scientists
Lynne M. Coluccio, Ph.D.
Charles P. Emerson, Jr., Ph.D.
John Gergely, M.D., Ph.D., D.Sc.M.(hon.)
Philip J. Graceffa, Ph.D.
Noriaki Ikemoto, Ph.D.
Toshio Kitazawa, Ph.D.
Paul Leavis, Ph.D.
Sherwin S. Lehrer, Ph.D.
Renne C. Lu, Ph.D.
Jeffrey Boone Miller, Ph.D.
Kathleen G. Morgan, Ph.D.
Henry Paulus, Ph.D.
Victor A. Raso, Ph.D.
Nilima Sarkar, Ph.D.
Walter F. Stafford, III, Ph.D.
Terence Tao, Ph.D.
Chih-Lueh Albert Wang, Ph.D.
Hartmut Wohlrab, Ph.D.

Principal Scientists
Roberto Dominguez, Ph.D.
Zenon Grabarek, Ph.D.
Celia J. Harrison, Ph.D.

Scientists
Peter Erhardt, M.D., Ph.D.
Steen Hansen, M.D., Ph.D.
Lucia Rameh, Ph.D.
Janet Smith, Ph.D.
Eric J. Sundberg, Ph.D.

Instructors
Janice A. Dominov, Ph.D.
James Fessenden, Ph.D.
Jonathan Goldberg, Ph.D.
Ruben Gonzalez, Ph.D.
Knut Langsetmo, Ph.D.

Senior Research Associates
Katsuhide Mabuchi, Ph.D.

Research Associates
Gong-Jie Cao, Ph.D.
Scott Frank, Ph.D.
Shu-Qin Jiang, Ph.D.

Fellows
Xingbin Ai, Ph.D.
Paul Balbo, Ph.D.
Mark Bannister, Ph.D.
Malgorzata Boczkowska, Ph.D.
Emma Borrego-Diaz, Ph.D.
Valerie Carricaburu, Ph.D.
Jamila Chahboune, Ph.D.
Yao Dong Chen, Ph.D.
David Chereau, Ph.D.
Robert Cleverly, Ph.D.
George Dimopoulos, Ph.D.
Raul de la Torre Medina, Ph.D.
Marie-Annick Forget-Dubois, Ph.D.
Brian Foster, Ph.D.
Jaya Pal Gangopadhyay, Ph.D.
Samudra S. Gangopadhyay, Ph.D.
Mashasweta Girgenrath, Ph.D.
Margarita Gonzalez, M.D.
Tomoyo Hamada, Ph.D.
Renjian Alan Huang, Ph.D.
David Hayes, Ph.D.
Hyun-Dong Je, Ph.D.
Frederic Kerff, Ph.D.
Shigeki Kobayshi, Ph.D.
Jolanta Kordowska, Ph.D.
Eun Hee Lee, Ph.D.
Sung Haeng Lee, Ph.D.
Yu Li, Ph.D.
Alena Lieto, Ph.D.
William Marganski, Ph.D.
Andrew Mazurkie, Ph.D.
Gretchen Meinke, Ph.D.
Philip Nickson, Ph.D.
Liuling Qin, Ph.D.
Atsuko N. Polzin, Ph.D.
Grzegorz Rebowski, Ph.D.
John Sumida, Ph.D.
Mohammed Terrak, Ph.D.
Ambrus Toth, M.D., Ph.D.

Emeritus Scientists
Peter S. Coleman, Ph.D.
Peter F. Davison, Ph.D.
Jen-shiang Hong, Ph.D.
Saroj Joshi, Ph.D.
D. Rao Sanadi, Ph.D.
Frank Sreter, M.D., D.V.M., Ph.D.

Adjunct Scientists
Leonard P. Adam, Ph.D.
Andrew Bohm, Ph.D.
Michael A. Geeves, Ph.D., D.Sc.
James S. Huston, Ph.D.
William J. Lehman, Ph.D.
Satyapriya Sarkar, Ph.D.
Michael Sherman, Ph.D.

BBRI Scholars
Atsuko Polzin, Ph.D., Arthur K. Watson Scholar
Alena Lieto, Ph.D., Endre A. Balazs Scholar
Ambrus Toth, Ph.D.

Research Assistants
Katie Archer, B.S.
Vincent Annese, B.S.
Magdalena Ardelt, B.S.
Amy Barber, B.S.
Mary Beermann, B.S.
Kelly Bethoney, B.S.
Brendan Broudeur, B.S.
Alex Chan, B.S.
Zhiwei Chen, B.S.
Daniel Chenkin, B.S.
Sheffali Dash, B.S.
Laetitia Favereaux, M.S.
Christy Fitzgerald, B.S.
Cynthia Gallant, B.A.
Cynthia Georges, B.S.
Jennifer Goldberg, B.S.
Elizabeth Gowell, B.S.
Hongqui Guo, M.S.
Vanessa Howarth, B.S.
Vanessa Jung, B.A.
Kazuyo Kitazawa, B.S.
Christine Kostek, B.S.
Allen Liu, B.S.
Zhaojiang Lu, B.S.
Jonathan Malowitz, B.S.
David Schrier, B.S.
Tina Silva, B.S.
Michelle Steffen, B.S.
John Stewart, B.S.
Devin Strickland, B.S.
Praveem Suraneni, M.S.
Ming-Jen Tsay, B.A.
Dania Villarnovo, B.S..
Jinghong Zhang, B.S.'
Rong Zhao, B.S.

Visiting Scientists
Richard Anderson
Corrado Bacchiocchi, Ph.D.
John Codington, Ph.D.
Sang-Jin Lee, Ph.D.
Yunping Li, M.D.
Malcolm Pluskal, Ph.D.
Gabriel O. Reznik, Ph.D.

Students
Yusra Al-Najjar
Sosie Bagdasarian
Chen Bai
Tanina Bianchi
Eugene Drokyansky
Gaurav Giri
Caitlin Harrington
Jenny Jiang
Scott Kaye
Laura Leisinger
Sabah Malek
Diana Mujalli
Daiva Nevidomskyte
Michael Riley
Debbie Sarkes
Drew Tsakos
Debbie W. Waung

Faculty & Staff [*continued*]

Administration

Alan L. Kaye
Chief Financial and Administrative Officer

Patricia Brouillette
Human Resources Manager

Paul M. Farber
Senior Accountant

Virginia Cahill
Financial Assistant

Aliceann Caron
Financial Assistant

Helene Clinton
Financial Assistant

Computer Services

Walter F. Stafford, III, Ph.D.
Dir. of Computer Services

Gary Henry
Assistant to Computer Services Director

Development & Public Affairs

Simon D.J. Welsby
Director of Development & Public Affairs

Virginia M. Sullivan
Associate Director of Development & Public Affairs

Sheena Frève
Development & Public Affairs Assistant

Facilities

Donald J. Gillis
Manager

Helga Ishizaka
Facilities Assistant

Alan Smith
In Vivo Facility Manager

Seth Hamor
In Vivo Facility Assistant

Amber Townes
In Vivo Facility Assistant

Oscar Bianchi
Carpenter/Shipping

Marie Narinkiewicz
Receptionist

Administrative Assistants

Mary Caulfield

Marilyn DeMont

Angela DiPerri

Dorothy Syrigos

Housekeeping

Naomi Ladino Lopez

Jian-Qing Yang

Editors

Charles Emerson, Albert Wang, Henry Paulus, Virginia Sullivan

Contributors

Peter Erhardt, Steen Hansen, Noriaki Ikemoto, Andrew Mazurkie, Jeffrey Miller, Vic Raso, Eric Sundberg

Photography

A special thank you to Alan Huang for his photography

Design

Beck Designs

Boston Biomedical Research Institute
64 Grove Street
Watertown, MA 02472
Tel: 617-658-7700
Fax: 617-972-1760
www.bbri.org

BOSTON BIOMEDICAL RESEARCH INSTITUTE
64 Grove Street
Watertown MA 02472
617 658-7700
617 972-1760 FAX
www.bbri.org