Boston Biomedical Research Institute

THE POWER OF OBSERVATION

CANCER BIOLOGY
INTEGRATIVE PROTEIN BIOLOGY
CARDIOVASCULAR BIOLOGY
REGENERATIVE BIOLOGY

Annual Report 2008

THE FRUIT FLY

Fruit flies are useful in quickly and efficiently establishing the function of genes in signaling pathways in a whole animal instead of cell lines, which do not always accurately reflect normal functions of genes. In addition, because one can do genetics in fruit flies, it is easy to determine the consequences of disrupting a gene, something which takes a great deal of time and effort in other animal models. The information gleaned from fly studies allows us to make predictions and conduct focused experiments in vertebrates to identify genes that are essential for life and are responsible for human genetic disorders.

Director's Letter

I am pleased to share with you my enthusiasm and excitement about our current research as well as the many accomplishments Boston Biomedical Research Institute has achieved over the past 40 years of our independence as a research organization.

The Institute has had a long and rich history of research excellence since our beginnings in 1949 as the Retina Foundation. However, it was not until 1968 that Hungarian scientist Endre Balazs recruited fellow Hungarian John Gergely to join him in developing a new entity to be called Boston Biomedical Research Institute. Soon after, Drs. Balazs and Gergely began the recruitment of other distinguished scientists, including D. Rao Sanadi, Barbara Wright, and Peter Davison to establish an institute with a broad base for biomedical research.

Over the ensuing forty years, researchers at Boston Biomedical have made many important contributions to the understanding of how the body works making the Institute an internationally recognized center of excellence for research in muscle biology and disease. A few highlights of our accomplishments include the following:

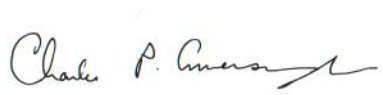
- The Institute's muscle research program made fundamental contributions toward understanding the molecular signals that control contraction of heart, skeletal and smooth muscles. Troponins, which are important protein regulators of skeletal and heart muscle contraction, are now routinely used as biomarkers in the early diagnosis of heart attacks.
- The development of a therapeutic use of hyaluronan in retinal surgery has saved the sight of many thousands of patients, and is used in the treatment of arthritic joints.
- Molecular structures of major muscle proteins were determined to reveal their functions in muscle contraction.
- The invention of an immunization approach for the treatment of Alzheimer's disease. A Phase III clinical trial involving passive immunization is currently being conducted by Wyeth-Ayerst.
- The elucidation of the mechanism of protein splicing is now being investigated as a therapeutic target in multidrug-resistant tuberculosis.
- Institute scientists are investigating the role and therapeutic potential of programmed cell death in muscular dystrophies and heart ischemia.

- The Institute was awarded funds to establish a new Senator Wellstone Muscular Dystrophy Cooperative Research Center supported by the National Institutes of Health (NIH). The goal of the Center is to organize collaborative initiatives to conduct basic and therapeutic research that will lead to treatments for facioscapulohumeral dystrophy (FSHD) for which there are currently none.

One of my most rewarding jobs as director is to introduce new friends to the Institute, to tell them about the high caliber of our research and about our unique culture of collaboration, which supports the creativity of our scientists and gives them a competitive edge in the increasingly difficult world of NIH and foundation funding. The Wellstone Center is proof that the Institute is a world-class leader in biomedical research. I relish every opportunity to tell the story of how our research excellence, unique collaborative spirit and agile administration enabled us to compete successfully for this prestigious Center award.

This past year has brought major funding successes that come from our stellar multidisciplinary research in Cancer Biology, Cardiovascular Biology, Integrative Protein Biology, as well as Degenerative Diseases and Regenerative Biology, and our strong collaborative spirit. Three of our newer investigators, Drs. Oliver King, Moonkyoung Um and Martin Duennwald, received funding for an exciting project to develop an innovative animal imaging technology that will uniquely enable development of therapeutics for Huntington's and Parkinson's diseases using mouse models. These three investigators each bring to our research table their specialized expertise in computational biology, mouse genetics and biochemistry in a truly multidisciplinary and collaborative project.

This is a remarkable time for Boston Biomedical Research Institute, and I invite all of you to join in celebrating our many achievements of the last 40 years and to usher in the next 40 years of research excellence.



Charles P. Emerson, Jr., Ph.D.
Director and Senior Scientist

40TH YEAR OF INDEPENDENCE BOSTON BIOMEDICAL RESEARCH INSTITUTE

1949 | The Retina Foundation is founded by Charles Schepens.

1951 | The laboratory of the Retina Foundation is established in a tenement house on 30 Chambers Street of Boston's old West End, with Endre Balazs as the first full-time member of the research staff creating a program centered on the biology and physical chemistry of hyaluronic acid, a key component of joint and eye fluids.

1961 | John Gergely joins the Foundation to initiate a program in muscle research which subsequently becomes internationally prominent. This program makes fundamental contributions to the characterization of the proteins that constitute skeletal muscle. These include the elucidation of the role of the troponins, which are important regulatory components of skeletal and heart muscle now known to play a role in the early diagnosis of heart attacks.

1962 | The Institute of Biological and Medical Sciences of the Retina Foundation moves into a new building at 20 Staniford Street in Boston. The building is erected, at the cost of $2 million, on land made available by the urban development project in the West End of Boston.

1964–69 | The research facilities at 20 Staniford Street are enlarged and scientists in other areas of basic biomedical research, such as bioenergetics and developmental biology, are recruited so as to provide a well-rounded biomedical research program to complement the Institute's clinical eye research efforts.

1968 | The Retina Foundation evolved into two separate institutions: the Boston Biomedical Research Institute, which is granted a rent-free 50-year lease of one-half the space at Staniford Street, and the Eye Research Institute of the Retina Foundation, which is later known as the Schepens Eye Research Institute.

1982 | Boston Biomedical files its first patent application in the area of immunotechnology and received corporate support for further research in this field. This patented technology is later licensed to a biopharmaceutical company for use in cancer immunotherapy.

Pictures opposite page, from left to right: Co-founders Drs. Endre Balazs and John Gergely. Co-founder, Dr. John Gergely. Below from left to right: Trustees Emeriti, Ernest Henderson, III and William Tyler. Co-founder, Dr. Endre Balazs and Chairman of the Board John French. Founding President, Carol Lord Means and Dr. Endre Balazs. Director, Dr. Charles Emerson, Jr. and Dr. John Gergely.




1990s | A major 15-year program in smooth muscle research is initiated at the Institute with the support of three consecutive $6 million program project grants from the National Institutes of Health.

1996 | A challenge grant from a leading Boston foundation provides the cornerstone for the establishment of a major structural biology facility at the Institute for the analysis of proteins at the atomic level.

2000 | The Institute moves to a new state-of-the-art research facility in Watertown, Massachusetts. The new facility allows 50% more space for the expansion of its faculty.

June 2003 | Completing its $6.5 million *A Campaign for BBRI: Intellectual Partners for the Future of Science*, the Institute meets two major challenge grants from the Kresge Foundation and an anonymous foundation.

September 2003 | Boston Biomedical recruits Dr. Charles Emerson, formerly Chair of the Department of Cell and Developmental Biology at the University of Pennsylvania, to serve as its Director.

2006 | With the completion of a five-year strategic plan, the Institute forms four interdisciplinary programmatic initiatives that focus on disease-based basic research, build upon, and bring together the unique strengths of the Institute. Programmatic areas include Cancer Biology, Cardiovascular Biology, Integrative Protein Biology, Degenerative Disease and Regenerative Biology.

2007–2008 | The Institute welcomes eight researchers, both junior and senior, to establish labs further strengthening the four programmatic initiatives. The opening of the Senator Wellstone Muscular Dystrophy Cooperative Research Center takes place at Boston Biomedical, and the Institute celebrates its 40th year of Independence.

WHERE THE RUBBER MEETS THE ROAD

CANCER BIOLOGY

SARAH WILCOX-ADELMAN, PH.D.

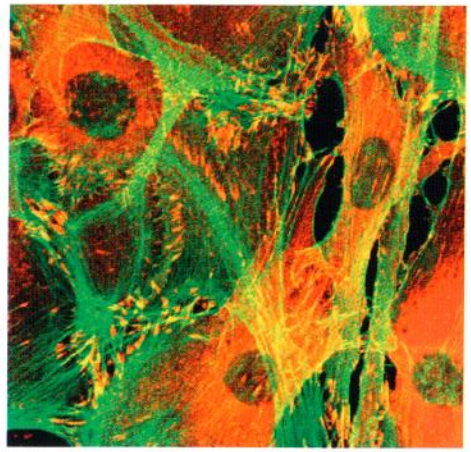
To understand the role of Syndecan-4 in cell movement, picture a cell as a car. In order to move in tissues of the body, a cell needs the ability to connect with a non-moving support—the matrix proteins underneath the cell, like collagen for example, serve as a road to "support" the cell. The type of matrix proteins at different locations in tissues determines whether cells move and how fast—whether the road is slippery, rough or impassible. The cell's receptors on its surface are the wheels that provide environmental cues to activate the cellular motors to enable cell movement. Syndecan-4 is such a receptor that enables "rubber to hit the road".

The human body is composed of trillions of individual living cells that make up our tissues and organs. Most cells behave as they should, multiplying just enough to compensate for the wear and tear of the tissue. Yet some cells undergo mutations that make them proliferate too rapidly: these are potential cancer cells. By a process called *metastasis*, they often escape and establish tumors elsewhere in the body. Scientists at Boston Biomedical Research Institute seek to understand how the body works and how to intervene when the body malfunctions.

Scientists at Boston Biomedical Research Institute are uniquely positioned to investigate the mechanisms of normal cell growth and the factors that lead to metastasis and tumor formation. Their expertise in the study of proteins is widely recognized, and the Institute has powerful research tools for the study of cells, such as laser scanning and spinning disk confocal microscopes and sophisticated cell sorters. In addition, the Institute has a tradition of interdisciplinary collaboration, and complementary approaches that can therefore be brought to bear on a single research problem.

Much of the research on cancer is focused on tumors that are derived from stem cells which give rise to the most deadly types of cancer such as pancreatic and small-cell lung cancer. But let us describe briefly just one type of investigation, which involves the cell-surface receptor syndecan-4.

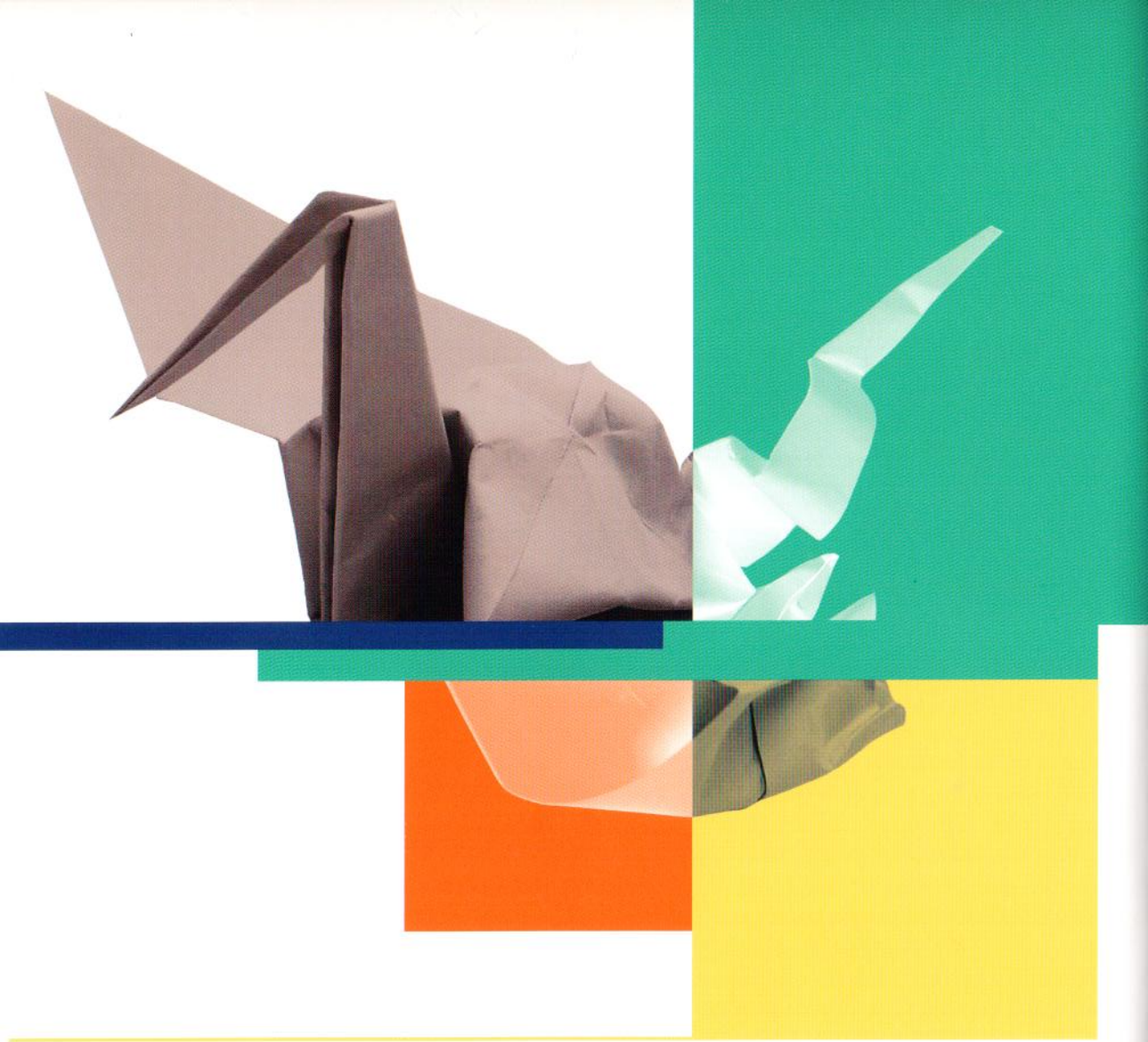
Syndecan-4 localizes to the surface of cells and serves as a receptor that binds to proteins in the extracellular matrix. In order to define the biological role of syndecan-4, especially whether it functions in cell propagation, mutant cells were studied in which the gene for syndecan-4 was inactivated. These cells indeed moved much more slowly, suggesting that syndecan-4 plays a role in locomotion and may be an important factor in the ability of tumor cells to undergo metastasis. The research study also threw interesting light on the role syndecan-4 played in angiogenesis (the formation of new blood vessels from existing blood vessels). Endothelial cells (which compose blood vessels) showed impaired angiogenesis when syndecan-4 was not present. Tumors require a blood vessel supply to grow and this ability may be compromised when syndecan-4 is absent. These studies indicate that syndecan-4 may play an important role in tumor formation, both in terms of cell growth and metastasis, and may be a potential therapeutic target. Thus what seemed to be the investigation of a relatively esoteric protein is turning out to lead to the understanding both of normal cell migration as well as cancer metastasis.



Migrating endothelial cells—actin cytoskeleton is stained in green and vinculin-containing focal adhesions are red. The yellow staining is the co-localization of green and red together.

THE SETBACKS OF MISFOLDING

REGENERATIVE BIOLOGY



MARTIN L. DUENNWALD, PH.D.

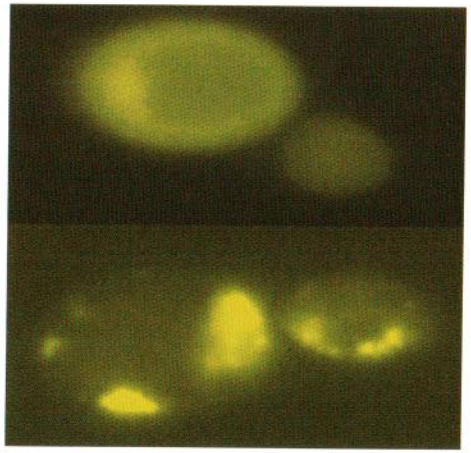
In order to function properly, proteins, the major workhorses inside our cells, must attain a specific three-dimensional conformation. Proteins fold into this conformation in a process that is reminiscent of origami. The origami artist folds plain paper into complex defined objects and likewise proteins are folded into complex and defined structures. Whenever this protein misfolding goes awry it has detrimental consequences to human health as documented by degenerative diseases including muscular dystrophies as well as Alzheimer's, Parkinson's and Huntington's diseases.

Understanding how specific genes and their encoded proteins function in biological processes like muscle contraction, cell movement, embryonic development and tissue regeneration, provide the platform for researchers to identify new, more strategic therapeutic targets for the next generation of drug discovery.

Forging a connection between basic discovery and medical application, scientists at Boston Biomedical Research Institute study neurodegenerative disease and regenerative biology. The Institute's ongoing effort to understand how muscles grow and deteriorate, leading to tissue loss and dysfunction, and what role specific proteins play in body structures will help discover new ways to promote muscle regeneration. Boston Biomedical Research Institute's scientists are studying several different muscular dystrophies to identify their particular molecular defects and to determine possible modes of intervention. Congenital muscular dystrophies are caused by genetic defects that lead to severe atrophy of muscle tissue. Important in these studies are mouse models which carry the same mutation as the affected humans. These studies have revealed that programmed cell death plays an important role in the atrophy of dystrophic muscle and that its improvement can suppress the disease symptoms. Studies are also underway in exploring the use of adult muscle stem cells for restoring dystrophic muscle tissue. The National Institutes of Health recently awarded nine million dollars to launch a unique collaboration of researchers, clinicians, patients, government research agencies and pharmaceutical / biotech companies to study the causes and potential treatments for facioscapulohumeral muscular dystrophy (FSHD), a muscle weakening and disabling disease that affects, at the least, one in 20,000 individuals worldwide. The award will create the first Senator Wellstone Muscular Dystrophy Cooperative Research Center to focus on FSHD and will be headquartered at Boston Biomedical Research Institute. The Wellstone Center will enable basic, translational and clinical research—the full "discovery pipeline"—in order to understand how muscles grow and deteriorate and to develop new therapies for those with FSHD.

Boston Biomedical scientists also seek to understand neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's diseases and the role protein misfolding plays in such diseases with the goal of developing regenerative therapeutics for treatment of these disorders. Because of our traditional strength in the biophysical and molecular analysis of proteins, Boston Biomedical is strongly positioned to analyze the molecular basis of these disorders to discover ways to correct the folding defects. The therapeutic agents currently being explored by Institute scientists include small molecule drugs against Huntington's, hormonal intervention for Parkinson's and a vaccine strategy against Alzheimer's disease. The neurodegenerative group is working to establish a new platform in monitoring neurodegeneration and how this can lead to the efficacy of new drugs.

Elucidating basic biological mechanisms leads to a fuller understanding of disease which, in turn, provides an avenue to explore novel therapeutics. The goal of scientists at Boston Biomedical Research Institute is to conduct cutting-edge research moving us one step closer to improving human health for generations to come.



The simple model organism yeast recapitulates major aspects of Huntington's disease. The top image shows yeast cells expressing a normal protein. The protein is distributed throughout the entire cell and is not toxic. The bottom image shows yeast cells expressing the protein that causes Huntington's disease. The disease-protein forms aggregates and is toxic.

LIKE A HOUSEHOLD PLUMBING SYSTEM

CARDIOVASCULAR BIOLOGY

JAMES L. SHERLEY, M.D., PH.D.

The human heart and blood vessels are a living pumping and plumbing system of remarkable ability. Imagine if all the faucets in your home were removed, but your plumbing system could release water exactly when and where you needed it. You think, "Shower," and shower water would instantly appear and stop when you were done. This is what our cardiovascular system does with blood for the organs of our body by using a special type of muscle called smooth muscle, which is a major focus of cardiovascular research at Boston Biomedical.

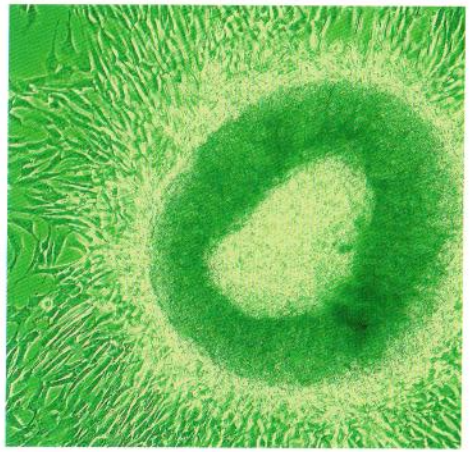
The cardiovascular or circulatory system is responsible for delivering oxygen and distributing nutrients to virtually all the cells in one's body and for the removal of carbon dioxide and other waste material. Smooth muscle, one of the research specialties of Boston Biomedical Research Institute, is essential to the control of these functions. Smooth muscle cells regulate the movement of fluids and gases within the body, determining how much blood (or air in the case of lungs) flows to the brain, hands, feet and elsewhere.

The cardiovascular system is composed of the heart, blood vessels and blood. The regular contractions of the heart send blood into flexible tubing called arteries, which carry oxygen-rich blood to every inch of the human body. Arteries branch out and divide into tiny capillaries, which have such thin walls that oxygen, nutrients and minerals are then able to pass through to enter surrounding organs and tissues. At all levels, arteries contain in their walls smooth muscle cells that contract or relax to control the inner arterial diameter, which in turn controls the rate of blood flow. Moreover, substances targeted for disposal are transported back into the blood through the capillaries to veins, which also have a smooth muscle cell layer, and back to the heart, being purified en route.

Similar to a plumbing system with automatic on and off switches, smooth muscle cells establish the regulatory systems that govern how much blood goes where. Smooth muscle will determine independently how much blood flows to all parts of the body at any given moment on any given day. Depending on whether the body is at rest or in motion, smooth muscle is an important determinant of the appropriate amount of oxygen and nutrients to keep the bodily systems functioning. Unlike smooth muscle, skeletal muscle operates under voluntary control and responds when it receives directives from the brain to contract, lift or lengthen. By contrast, smooth muscle operates without our awareness, based on physiological and environmental cues.

When functioning well, smooth muscle also protects the core organs of the body: the kidneys and liver, for example. However, when smooth muscle functions less well, the arteries and lungs can be affected. Blood pressure is regulated by the contraction and relaxation of smooth muscle cells within arterial walls. When the steady flow of oxygen-rich blood for the heart itself is obstructed or diminished causing malfunction of arterial smooth muscle, the result could be coronary disease. Conditions like asthma are due to abnormally thickened bronchial smooth muscle that causes oxygen to move more slowly through the lungs and then to the rest of the body. In these diseases, smooth muscle cells become either overgrown or become fibrotic, acting like concrete around the arteries and airways. These conditions cause a range of cardiovascular and pulmonary disorders resulting from the malfunction of the human "plumbing system".

Scientists at Boston Biomedical Research Institute have a long tradition of seeking to understand the underlying reasons for loss of function in smooth muscle as it relates to the cardiovascular system. More recently, scientists are also developing a smooth muscle research program to address destructive diseases of the lung like emphysema. Once these mechanisms are more clearly discerned, researchers can move toward innovative interventions to treat or prevent the harmful effects of smooth muscle cells that have gone awry.



Pictured above is an image of smooth muscle cells in a culture dish migrating out of an artery.

IN THE NICK OF TIME

INTEGRATIVE PROTEIN BIOLOGY

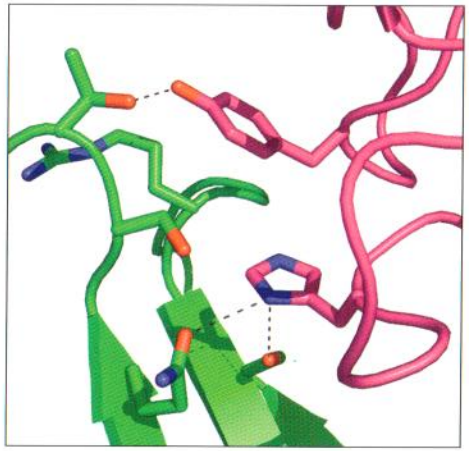
ERIC J. SUNDBERG, PH.D.

Our body is a complex machine whose moving parts are proteins, similar to the workings of a sophisticated clock. Scientists used to think that the body could be fully understood in terms of the structure of its individual proteins, but such a "parts list" is as uninformative in understanding its operation as a list of all the gears and wheels in a clock would be. This is because proteins, like the gears in a clock, do not work in isolation but mesh together, often in different ways depending on the mode in which the clock is operating, be it as an hourly timekeeper, as a stop watch, or as an alarm clock.

The proteins constitute the machinery of the body, both as the major components of cells, tissues and organs and as catalysts of the thousands of chemical reactions that are essential for our bodies to grow, digest food, breathe, move our muscles, and even to think. Almost always working with other proteins, they define highly integrated molecular networks. Changes in the ways proteins operate or interact with others can sometimes signal disease. A major aim of Boston Biomedical Research Institute's program in Integrative Protein Biology (IPB) is the study of proteins and their interactions within the context of larger biological systems. Doing so in both normal and diseased states allows us to determine those significant differences that will provide novel avenues for therapeutic strategies.

Boston Biomedical Research Institute has a long tradition of excellence in the study of proteins, particularly in the study of the interactions between proteins. The Institute's scientists have made many important contributions to the development of biophysical techniques for the study of how proteins interact and take pride in our state-of-the-art instrumentation for such studies. Using biophysical approaches, they are able to study the interaction of proteins and obtain important mechanistic and structural information, and have made basic contributions with regard to how proteins in muscle interact and control the contractile process. On the other hand, considering that many thousands of proteins interact in any single cell in a highly dynamic manner, it is not possible to study all of these interactions by biophysical methods. Rather, one has to take a short-cut to identify a few of these interactions which are relevant to specific biological problems, for example interactions that differ in normal and cancerous cells.

One of these short-cut approaches is called Tandem Affinity Purification (TAP). This involves attaching a TAP-tag to a protein of interest to allow its purification from a mixture of thousands of other proteins by a simple but powerful method known as affinity purification. A TAP-tagged protein is introduced into a cell of interest, where it interacts with all its usual partners. When researchers break open the cell and re-isolate the TAP-tagged protein by affinity purification, the tagged protein will still be bound to all its interaction partners and these will be isolated together with the tagged protein like fish on a baited hook. The identification of these proteins is done with the Institute's state-of-the art mass spectrometer. This powerful TAP-tag approach is currently being applied to the study of the signal-transduction pathways in cultured cells of a stem-cell cancer of the type that leads to pancreatic cancer, and has already led to the identification of several proteins previously unknown to be involved in cancer. These novel protein-protein interactions can now be studied by the biophysical techniques that have historically formed the foundation of the Institute's protein studies in order to understand the signaling mechanisms that underlie the uncontrolled growth of these cancer cells.



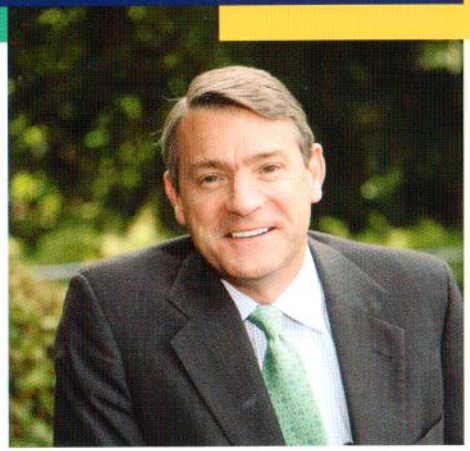
A close-up view of a protein-protein interaction as seen by X-ray crystallography. A bacterial toxin (in magenta) interacts with an immune receptor (in green). This results in hyper-stimulation of the human immune system causing a potentially lethal condition known as toxic shock-like syndrome. These types of atomic interactions are similar to those that drive molecular recognition between all proteins.

President's Letter

Abu Ali al-Hasan Ibn al-Haytham (965 – 1039 A.D.), the Persian scientist who lived during the Islamic Golden Age, was a Renaissance man, even before there was a renaissance. Not only did al-Haytham make significant contributions to such varied scientific fields as anatomy, astronomy, mathematics, medicine, musicology, ophthalmology, philosophy, physics, psychology, and visual perception, he has been named as one of the most influential thinkers in the second millennium, as well as the greatest scientist of the Middle Ages. While his most significant individual achievements were in the field of optics, he is also credited with pioneering the modern scientific method. Today, scientists at Boston Biomedical follow the process al-Haytham developed, employing rigorous experimentation to verify theoretical hypotheses to explain phenomena that have been observed.

In honor of its 40th anniversary as an independent Institute, I am pleased to share the following observations about BBRI: the Institute is flourishing scientifically. Boston Biomedical has been awarded New England's first Wellstone Center grant, one of six Congressionally-mandated centers in the country, established in honor of the late Senator Paul Wellstone, to develop therapies for various muscular dystrophies. The Institute was able to develop this grant proposal—which was awarded the best score and which required collaboration with other research organizations, biotech companies, and a patient advocacy organization—in less than half the time it normally takes. In addition, three of our scientists, who were recruited last year, have developed a novel neurodegenerative disease research program to develop therapeutics to combat Alzheimer's, Parkinson's and Huntington's diseases. They have been awarded grant funding from a prestigious local foundation. Also, BBRI scientists have recently far surpassed the national average in achieving R01 funding from the National Institutes of Health, attesting to the Institute's scientific excellence.

Since the completion of our strategic plan a couple of years ago, we have also achieved great success in recruiting top-notch scientists to the Institute from some of the most prestigious scientific organizations in the country. This year, we are lucky to have Markus Hardt join us from the University of California at



San Francisco. Markus is an expert in the use of mass spectrometry to study proteomics, which will, among other benefits, enhance our scientists' ability to identify disease biomarkers.

Boston Biomedical is flourishing in other ways, as well. The Board of Trustees is more involved than ever in working to ensure that the Institute's future remains bright. We were all deeply saddened and diminished by the passing last winter of esteemed Trustee, M. Judah Folkman, losing his brilliance, wisdom, perspective, caring and wry humor. We are fortunate that Judah's widow, Paula, graciously agreed to complete his term as Trustee. The Institute has made substantial progress to fund the Dr. Elkan R. Blout Distinguished Israeli Biomedical Research Program, and I am hopeful that we will soon host our first Blout fellows at the Institute. Just as Ibn al-Haytham relied on the work of others to help him in his "searching for truth and knowledge," Boston Biomedical depends on the thoughtfulness and generosity of its donors and volunteers to make advances in its mission to improve human health. On behalf of everyone connected with the Institute, please accept my sincere gratitude for your help in that endeavor. I would also like to express my heartfelt appreciation to our Chairman, Jack French who will be stepping down after 14 years of service. Jack has been extremely instrumental in the progress of Boston Biomedical and we thank him for all his time and efforts and look forward to his ongoing support.

In closing, my hypothesis—based on the observations above, and my confidence that Boston Biomedical will attract additional philanthropic support for its programs—is that the Institute, with its nimble organizational structure and deeply collaborative and multidisciplinary approach to biomedical research, will have an even more significant impact on improving human health in its next 40 years than it had during its first 40 years. Please join me in toasting BBRI's bright future.

John R. Layton
President

Vision for the Future

I look forward to every opportunity to tell new friends and donors about all our successes and our ambitious plans for the coming year, as we continue to raise private and public research dollars to support our four interdisciplinary programmatic initiatives that focus on disease-based basic research and build upon our unique strengths. These programmatic areas are gaining momentum at a rapid pace and are bringing us closer to new therapies for cancer, heart disease, asthma, emphysema, neurodegenerative diseases and muscular dystrophies. These diseases have touched all of our lives, and those of our friends, family and colleagues at the Institute. A key to the success of these programs is continued faculty recruitment.

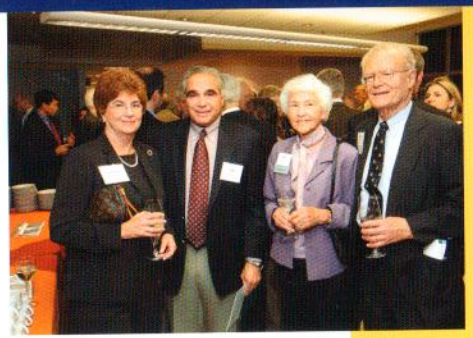
Once again, our unique culture of collaboration and efficient research administration, together with our recent investment in state-of-the-art instrumentation have made it possible for us to recruit a cohort of seven exceptionally talented and accomplished junior and senior scientists, and we continue our success. This year we will welcome a new investigator, Dr. Markus Hardt, who is an expert in biomarker discovery in cancer, coming to us from the University of California at San Francisco. His research program will add strength and vitality to both our cancer and integrative protein biology programs. We will continue to need resources to retain and recruit our most highly valued assets—exceptional investigators who energize our emerging program.

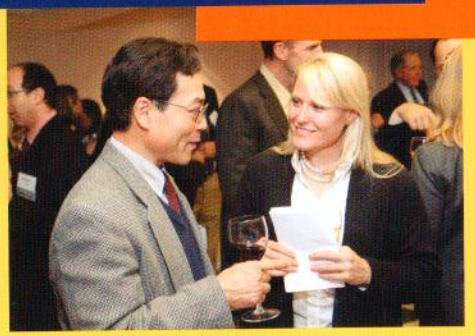
Looking forward, we seek to expand the faculty from our present 27 principal investigators to 30 and to double the number of post-doctoral fellows we train. With the strongest possible faculty, we hope to double our federally funded grant base. We will continue to keep our administration lean and efficient, so that nearly every dollar can be directed toward the research goals of the Institute, and we will continue to encourage a culture of collaborative partnerships which bring about results and innovative ideas more quickly.

I would be remiss if I did not emphasize the tremendous appreciation our scientific staff has for our Trustees, our Corporators and our supporters. The Institute is strong and vibrant, and we could not have accomplished all we have without your ideas and contributions. I am excited to be celebrating the 40th anniversary of this remarkable institution with so many of you.

Charles P. Emerson, Jr., Ph.D.
Director and Senior Scientist

Philanthropic Highlight: Annual Meeting 2007





Institute supporters and friends celebrated the year's success and joined Boston Biomedical in thanking donors for their ongoing support.

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Mr. Chilton S. Cabot and Ms. Mary Ann Spadafora
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Mrs. Margaret A. Congleton
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Jacquelyn M. Findlay
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Dr. and Mrs. M. Judah Folkman
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Mr. and Mrs. Alden French II
Diana and Ronald Garmey
Ms. Mimi Hewlett
Mr. and Mrs. Sturtevant Hobbs
Mr. and Mrs. Charles C. Ives II
Dr. Sherwin Lehrer and Dr. Liane Reif- Lehrer
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Ms. Ellen Page
Mr. and Mrs. Vincent D. Parenti
Mr. and Mrs. Harry Parsekian
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Mr. and Mrs. Richard D. Phippen
Mr. and Mrs. Wayne Pierce
Mr. and Mrs. Malcolm G. Pluskal
Mr. Murray Sachs
Pierrette E. Samour, in memory of Carlos M. Samour
Mr. Richard L. Sampson
Drs. Nilima and Satyapriya Sarkar
Dr. and Mrs. Robert C. Seamans, Jr.
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Mr.and Mrs. Eustis Walcott
Mr. and Mrs. Monte J. Wallace
Mr. and Mrs. Alexander Web III, in honor of Dr. Xingbin Ai
Mr. and Mrs. Simon D.J. Welsby
Mrs. Joan D. Wheeler
Mrs. Constance V.R. White

BUSINESS AND FOUNDATIONS

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The Darling 1982 Charitable Annuity Lead Trust
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THE ELKAN R. BLOUT DISTINGUISHED ISRAELI POSTDOCTORAL FELLOWSHIP PROGRAM

Mr. Nicholas S. Brill
Dr. Douglas M. Fambrough
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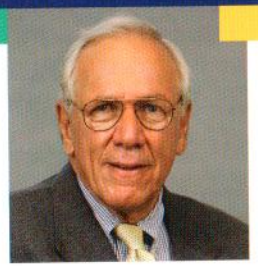
Treasurer's Report



Boston Biomedical Research Institute invested significantly in its research enterprise during the past fiscal year in order to rebuild its grant base and diversify its revenue streams. As a result, the Institute made great scientific progress in accordance with its strategic planning initiatives in the areas of Cancer, Proteomics, Cardiovascular and Regenerative Disease during fiscal year 2008. Recruitment of eight new faculty members has led to many new collaborations and exciting opportunities at the Institute. Implementation of those scientific initiatives identified in Boston Biomedical's strategic plan is working well as evidenced by an increase in grant awards of approximately $14,800,000 in the last year. Under Charlie Emerson's leadership, Boston Biomedical has recently been awarded a grant from the NIH to establish New England's first Senator Wellstone Muscular Dystrophy Cooperative Research Center.

The Statements of Financial Position show a decrease in the Institute's investments of almost $4,175,000 at June 30, 2008 over the prior year. The vast majority of that decrease, $3,900,000 to be exact, was to implement a Board-authorized program to purchase new scientific equipment and provide needed Principal Investigator support for both established and new investigators. The remainder of the decline in our investments was due to a decline of – 0.4% in the value of our investment portfolio for the year. As most investors are aware, fiscal year 2008 was difficult for equity investments, making the modestly negative return our portfolio suffered appear comparatively strong.

As shown in the Statements of Activities, total unrestricted support for Boston Biomedical approximated $10,446,000 for the year ended June 30, 2008. Revenues from grants and contracts approximated $9,804,000, which is a decrease of $1,193,000 over the prior year. In 2008, 89% of the Institute's revenue from grants and contracts came from federal agencies. The Institute's success in securing federal funds in an increasingly competitive environment is a testament to the quality of scientific research being conducted. During the last fiscal year the Institute received seven new grants from the National Institutes of Health and three new foundation awards.

Charitable giving represents an important revenue source for Boston Biomedical, and the Board is committed to increasing revenues from this source in a significant way over the next several years. Total contributions approximated $539,000 during fiscal year 2008. Unrestricted, temporarily restricted and permanently restricted contributions approximated $417,000, $114,000 and $8,000, respectively. These contributions support important activities not covered by grants from federal agencies and not-for-profit foundations and associations, including support for investigators starting new research programs and purchasing scientific equipment. The Board of Trustees appreciates greatly each donor's generous support.

Total expenses of $13,582,000 increased approximately $591,000 or 4.5% over the prior year, due primarily to internal funding for new faculty members' research. The Institute maintains a lean administrative structure, and is committed to cost containment and purchasing efficiencies. My thanks go to Alan Kaye, the Institute's Chief Financial Officer, who works tirelessly to keep the Institute's finances in order.

Boston Biomedical's debt service coverage ratio (a target established in bond agreements) was less than the required 110% for the fiscal year ended June 30, 2008, due primarily to a lower funded grant base than in previous years, the expense of providing new investigator start-up packages for the newly recruited scientists, and unrealized losses on the equity portion of the investment portfolio. Trustees and management are formulating a plan to ensure the ratio stays well above 110%.

The Institute's liquidity ratio (a measure of unrestricted cash and investments available to satisfy outstanding bond debt) was 102% as of June 30, 2008, well above the level dictated in the bond documents.

Once again, Tom DiBenedetto deserves high praise for his continued professional leadership of the Investment Committee as do the other members for their expert guidance and insight. The Investment Committee continues to reposition and diversify the portfolio to help reduce risk while preserving principal, enabling the Institute to meet its short-term needs and maintain the desired targeted return.

Expanding our network of supporters, friends, and advocates is essential to the Institute's success over the next few years, as we continue to implement the strategic initiatives and scientific vision Dr. Emerson and his scientific colleagues have established. With that in mind, I encourage you to introduce your friends and colleagues to the Institute.

Respectfully submitted,

Geoffrey Nunes

Geoffrey Nunes, *Treasurer*

Financial Report

STATEMENTS OF FINANCIAL POSITION

	2008	2007
ASSETS		
Cash	$1,810,786	$1,496,890
Grants receivable	4,557,625	6,924,948
Unconditional promises to give	135,346	55,917
Investments	13,525,884	18,282,534
Prepayments, deposits and other receivables	173,739	153,295
Trustee-held funds	1,244,939	1,245,752
Property and equipment	13,522,511	13,576,129
Investments in limited partnerships	1,290,001	709,014
Deferred compensation investments	784,060	840,524
Total assets	**$37,044,891**	**$43,285,003**
LIABILITIES AND NET ASSETS		
Accounts payable and accrued expenses	$608,460	$608,294
Accrued interest expense	351,035	358,535
Deferred income	4,433,808	7,104,771
Note payable	—	1,259
Obligation under capital lease	300,497	108,392
Bonds payable	14,550,000	14,910,000
Deferred compensation payable	784,060	840,524
Total liabilities	**21,027,860**	**23,931,775**
NET ASSETS		
Unrestricted	12,925,653	16,061,719
Temporarily restricted	830,314	1,038,427
Permanently restricted	2,261,064	2,253,082
Total net assets	**16,017,031**	**19,353,228**
Total liabilities and net assets	**$37,044,891**	**$43,285,003**

STATEMENTS OF ACTIVITIES

	2008	2007
CHANGES IN UNRESTRICTED NET ASSET		
Revenues:		
Grants and contracts	$9,804,323	$10,997,688
Contributions	417,322	338,898
Investment income (loss)	(99,445)	1,994,042
Other income including licensing fees, net	32,558	3,168
Total unrestricted revenues	10,154,758	13,333,796
Net assets released from restrictions	291,608	462,911
Total unrestricted support	**10,446,366**	**13,796,707**
Expenses:		
Salaries and benefits	8,067,405	7,968,659
General support and services	2,090,891	1,734,457
Occupancy costs	1,420,618	1,384,655
Interest Expense	861,979	865,164
Depreciation	1,141,539	1,038,928
Total expenses	13,582,432	12,991,863
Increase (Decrease) in unrestricted net assets	(3,136,066)	804,844
CHANGES IN TEMPORARILY RESTRICTED NET ASSETS		
Contributions	114,081	372,700
Investment income (loss)	(30,586)	325,790
Net assets released from restrictions	(291,608)	(462,911)
Increase (Decrease) in temporarily restricted net assets	(208,113)	235,579
CHANGES IN PERMANENTLY RESTRICTED NET ASSETS		
Contributions	7,982	71,683
Increase in permanently restricted net assets	7,982	71,683
Increase (Decrease) in net assets	(3,336,197)	1,112,106
Net assets at beginning of year	19,353,228	18,241,122
NET ASSETS AT END OF YEAR	**$16,017,031**	**$19,353,228**

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

Philanthropic Highlight: The Next Generation of Discovery

Boston Biomedical Trustees, Corporators, and friends gathered to explore the labs of our Postdoctoral fellows at The Next Generation of Discovery.

Faculty Publications July 2007 – June 2008

- Adamek, N., Coluccio, L. M. & Geeves, M. A. (2008). Calcium sensitivity of the cross-bridge cycle of Myo1c, the adaptation motor in the inner ear. *Proc Natl Acad Sci U S A* 105, 5710-5.
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- Gergely, J. (2008). Key events in the history of calcium regulation of striated muscle. *Biochem Biophys Res Commun* 369, 49-51.

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Philanthropic Highlight: Walk for Science Education

Members of the community joined Boston Biomedical Researchers, Board Members and friends, raising nearly $20,000 for the Third Annual Walk for Science Education presented by Enanta Pharmaceuticals.

Grants

National Institutes of Health

Dr. Coluccio		
Molecular Mechanism of a Mammalian Class I Myosin Motor	2/04–1/09	1,668,000
NCRR Shared Instrumentation Grant (SIG) Program	4/07–3/09	457,000
Role of Myosin 1c Adaptation in the Inner Ear	8/07–8/09	100,000 *
Dr. Dominov		
Apoptosis in Laminin-Alpha2 Deficiency	4/05–3/10	2,148,000
Dr. Erhardt		
Prevention of Myocardial Ischemic Injury by RAF/ERK	4/03–3/08	1,471,00
Dr. Emerson		
Control of Muscle Protein Synthesis during Myogenesis	7/05–6/10	4,258,000
Sonic Hedgehog Target Genes in Development and Cancer	12/03–11/07	1,900,000
Dr. Fessenden		
Molecular Mechanisms of RyR Activation by 4-CmC	8/05–4/08	389,000
Dr. Goetnick / Wilcox-Adelman		
Syndecan-4 signaling in Cell-matrix Interactions	3/06–2/09	1,285,000
Dr. Ikemoto		
Regulation of Normal and Diseased Cardiac Ca2+ Channels	2/08–11/11	1,923,000 *
Structure and Function of Sarcoplasmic Reticulum	4/02–3/08	3,030,000
Dr. Kitazawa		
Mechanism of Ca2+ Sensitization in Smooth Muscle	6/02–5/08	2,876,000
Dr. Leavis		
Dynamics of the Vascular Smooth Muscle Cytoskeleton	7/07–6/12	1,298,000 *
Dr. Lehrer		
Tropomyosin and the Regulation of Muscle Contraction	7/05–6/09	1,950,000
Dr. Lieto		
Role of Unconventional Myosin Myolc in Cell Motility	9/04–8/07	139,000

***New grants in fiscal 2008**

Dr. Miller

Pathogenesis of Laminin-Alpha2 Deficiency	9/02–8/07	1,291,000
Molecular Physiology of Respiratory Muscles	4/06–2/11	2,669,000

Dr. Morgan

Signaling & Uterine Contractility during Pregnancy	8/03–6/09	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. Sherley

Director's Pioneer Award	9/07–7/11	4,423,000 *
Kinetotoxic Mechanisms of Environmental Carcinogens	9/07–1/09	219,000 *
Molecular & Genomic Imaging Center	9/07–4/09	267,000 *

Dr. Smith

Cell Development and Function 3	11/03–12/07	1,343,000

Dr. Takayama

Role of Co-Chaperone, Bag 3, in Muscle Degeneration under Physiological Stress	7/07–4/11	1,540,000 *

Dr. Tao

Mechanism of Calcium Regulation in Striated Muscle	6/03–5/09	3,205,000

Dr. Wang (Pro. Proj.)

Molecular Mechanism of Smooth Muscle Regulation	12/02–11/08	10,356,000

United States Department of Agriculture

Dr. Miller

Poultry Muscle Development: Molecular & Cellular Biology	1/06–9/09	360,000

John W. Alden Trust

Dr. Dominov

Cell Death Mechanisms in a Congenital Muscular Dystrophy Model	6/07–5/08	25,000

American Heart Association

Dr. Khalina

Evaluation of Regulatory Properties of Smooth Muscle Thin Filaments using a Caldesmon Knockout Model	7/06–6/08	76,000

Cancer Research UK

Dr. Leavis

Optimization of Leptin Receptor Antagonist Peptides (LPA) & Studies on Bioavailability and Efficacy in a Tumor Model	1/08–12/09	425,000 *

Concern Foundation

Dr. Ai

Inhibitor of Hedgehog Autoprocessing as Endodermal Cancer Therapies	7/06–6/08	100,000

Ellison Medical Senior Science Award

Dr. Sherley

Identification of Chemical "Age Spots" on Immortal DNA Strands in Adult Stem Cells	12/07–9/08	50,000 *

Muscular Dystrophy Association

Dr. Ai

Regulation of Satellite Cell Development and Muscle Regeneration by Two Extracellular Herparan Sulfate 6-0 Endosulfatases	1/06–12/08	135,000

Dr. Miller

Apoptosis & Congenital Muscular Dystrophy (CDM) & LGND	7/05–6/08	300,000

Dr. Girgenrath

A Combinatorial Strategy to Treat Congenital Muscular Dystrophy	1/07–12/09	135,000

The Potts Memorial Foundation

Dr. Paulus

Development of a Novel Class of Drugs for Combating Drug-Resistant Tuberculosis	11/07–10/08	30,000 *

Sepracor

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