2002 ANNUAL REPORT

TOOLS FOR BETTER HEALTH

BOSTON BIOMEDICAL RESEARCH INSTITUTE

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MISSION STATEMENT

The **BOSTON BIOMEDICAL RESEARCH INSTITUTE** (BBRI) is dedicated to basic biomedical research to promote the understanding, treatment and prevention of specific human diseases. The areas of investigation concern the structure and function of muscle proteins, mechanisms of cell communication, and the control of cell growth and gene function. A major focus is muscle cell biology which has implications for muscle-related diseases such as asthma, stroke, and heart failure. When appropriate, the Institute collaborates in clinical studies of patients to apply the results of basic research to problems of human health and the cure of disease. BBRI is an independent, not-for-profit institution.

BOSTON BIOMEDICAL RESEARCH INSTITUTE

MESSAGE FROM THE DIRECTOR

HENRY PAULUS, Ph.D.

After two years in Watertown and with the extraordinary support of the members of its Board of Trustees and Corporation, together with good friends and foundations, BBRI is beginning to reap the full benefits of our new research facility. We have been able to attract five new members to our research faculty, three of whom established their research programs at BBRI within the past year. We have also been able to expand existing research programs by providing adequate space for our core research facilities and have established a new Cell Biology Core Facility. Finally, we have been able to strengthen the staff of our research programs by attracting outstanding young scientists through the BBRI Scholar program. Let me expand on each of these in turn.

BBRI's unique collaborative research environment and its new state-of-the-art laboratory space have been great assets in the recruitment of new scientists. However, another important requirement for successful recruitment is the availability of startup funds for establishing new research programs. Startup funds come from BBRI's Annual Fund, which — as noted in the Development Report — has grown to the record level of one-half million dollars in the past year. This has been a great asset in attracting the three scientists who established their research programs at BBRI in the past year. We are pleased to welcome Drs. Lucia Rameh, Jeff Miller, and Toshio Kitazawa, whose research programs are described in this report.

Progress in experimental science depends in large part on the development of new research tools, which often consist of sophisticated instruments that need to be housed in the institutional core facilities. One example is the crystallography facility that was established at BBRI in 1996. BBRI's new research building in Watertown was designed to be able to accommodate large new instruments, and in the past two years, four new major pieces of state-of-the-art equipment have been acquired. These include a protein sequencer, an isothermal calorimetry workstation, a confocal microscope, and a flow cytometer. The first three were funded through the award of shared equipment grants from the National Institutes of Health, for which BBRI scientists competed successfully, the last through a challenge grant from the Kresge Foundation. The BBRI community rose brilliantly to the Kresge challenge by raising $1.2 million to fund the establishment and long-term operation of a Cell Biology Core Facility. A large section of this Annual Report is devoted to the description of BBRI's major research instruments and how they can advance biomedical research.

The staff list at the end of this Report numbers 30 postdoctoral fellows. Postdoctoral trainees make a vital contribution to BBRI's intellectual environment. It is primarily through them that the research faculty carries out their educational mission by passing on their scientific insights and research expertise to a younger generation of scientists. At the same time, inquisitive young scientists bring new perspectives to research problems that can lead their mentors' research programs into innovative directions. In order to attract the best doctoral candidates to BBRI, the Institute established in 1997 the prestigious position of BBRI Scholar, which is awarded competitively to outstanding postdoctoral applicants. The BBRI Scholar program has indeed brought exceptionally able and productive young scientists to BBRI. Thanks to the consistent growth of BBRI's Annual Fund, we can now appoint three BBRI Scholars every year and hope to be able to increase this number in the future. To recognize friends and foundations whose generosity has allowed this important program to grow, two of the Scholar positions have been named in their honor: the Endré Balazs Scholar and the Arthur K. Watson Scholar.

Its collegiality and multidisciplinary character make BBRI an exciting place for doing research and undoubtedly contribute to its successes. Another important element that allows BBRI to thrive is the very special partnership between its scientists and the members of the its Board and Corporation and the many friends who provide us with advice, guidance, and the funds that supported the initiatives that I have described in this message. On behalf of my colleagues, let me express my heartfelt appreciation to our partners in this exciting enterprise.

MESSAGE FROM THE PRESIDENT

David A. Gibbs, Sc.D.

Though the past year has been a very challenging one for our nation in many ways, I am pleased to be able to report on another year of accomplishments at BBRI. The talented and dedicated scientists at BBRI continue to advance the frontiers of knowledge about how the human body works.

In the Fall of 2001, Dr. Andrew Bohm of our x-ray crystallography group along with collaborators from the University of Chicago solved the three-dimensional structure of edema factor, one of the three deadly toxins of the anthrax bacillus. This was an important and very topical discovery that received attention from around the world. On behalf of everyone at BBRI, thank you to each of the donors that helped to fund and launch the crystallography program at BBRI in 1996. It is rewarding to see the quality of research being conducted by Drs. Bohm, Dominguez, Grabarek and Harrison.

In June of 2002, BBRI signed an option and license agreement with Wyeth Pharmaceuticals for the Alzheimer's vaccine technology developed at BBRI by Dr. Vic Raso. The agreement gives Wyeth the option to license BBRI's technology for the development of vaccines against beta-amyloid plaques, which are thought to be causative agents of Alzheimer's disease. Alzheimer's affects four million Americans today and will afflict an estimated fourteen million Americans by the middle of this century unless a way for preventing or curing this devastating disease is found. Dr. Raso's study may contribute toward finding such a way.

The past year also saw the successful renewal of BBRI's Smooth Muscle Program Project Grant (PPG) for another five years from the National Institutes of Health (NIH). The PPG involves nine BBRI scientists and their research groups – Drs. Dominguez, Grabarek, Graceffa, Lehrer, Lu, Mabuchi, Stafford, Tao and Wang. Together these groups collaborate to study the regulatory mechanisms in smooth muscles that control vital functions in our body such as blood pressure, breathing, digestion and childbirth. The fact that the PPG, under the leadership of Dr. Albert Wang, will have been funded continuously for fifteen years is testimony to the importance and quality of the research at BBRI.

As you will read in this Annual Report, access to shared scientific equipment is essential to BBRI's scientists. Over many years BBRI has been very successful in securing shared instrumentation grants from the National Institutes of Health and the National Science Foundation to fund new equipment, but there is a constant need for additional funding from private contributions. The purchase, operation and replacement of state-of-the-art equipment was the focus of a Science Initiative Challenge Grant from The Kresge Foundation. Through the wonderful support of fifty-seven donors and the tremendous efforts of many people including Campaign leaders Allie Blodgett, Jake Layton, Donna Fisher and Ty Howe, BBRI was able to raise $1.2 million to receive $400,000 from The Kresge Foundation. You can read more about this and other fundraising accomplishments later in this Annual Report.

The year 2002 has also seen the continuation of BBRI's commitment to outreach programs. For the first time BBRI participated in the Biomedical Science Careers Program Student Conference. This biennial conference attended by more than 600 students aims to assist and encourage members of underrepresented minorities to pursue careers in biomedical science. BBRI faculty members Drs. Coluccio, Langsetmo, Leavis, Lu, Paulus, Wang and Wohlrab all volunteered their time to serve as mentors to the young people in attendance. And once again BBRI presented $2,500 Scholarships to two outstanding Watertown High School students. George Troung will be attending Tufts University to study biology and Sandra Volz will be attending Northeastern University to study marine sciences.

Basic research at BBRI benefits from a dynamic partnership that relies on the commitment and generosity of a growing number of friends who support vitally important research initiatives and on the quality of our scientists and their ability to attract funding from the National Institutes of Health. The energy of this partnership ensures that the research programs at BBRI continue to thrive.

NEW BBRI SCIENTISTS

Dr. Toshio Kitazawa, Senior Scientist, came to BBRI from Georgetown University Department of Physiology where he was an Associate Professor. He received his Ph.D. from University of Tokyo Department of Pharmacology.

Dr. Kitazawa's research focuses on how molecular signals are passed along in smooth muscle cells. The functions of many of our internal organs rely on the delicate control of smooth muscle contraction. Smooth muscle disorders contribute to many diseases, such as hypertension, coronary vasospasm, and asthma. Smooth muscle contraction requires reversible phosphorylation of myosin regulatory light chains. Such phosphorylation is triggered by a rise in the level of the intracellular calcium, which turns on an enzyme called myosin light chain kinase (MLCK). Contraction also results from a decrease in phosphorylation, promoted by another enzyme called myosin phosphatase (MLCP). For example, activation of certain receptors leads to a decrease in the MLCP activity and enhances smooth muscle contraction at a given calcium level (calcium sensitization). Cyclic GMP, on the other hand, is a potent physiological messenger for vasodilation, because it decreases the contractility at a given calcium level via an increase in the MLCP activity (calcium desensitization). Dr. Kitazawa has proposed that most smooth muscle stimulants cause an up-regulation of MLCK and a down-regulation of MLCP, resulting in a large sustained contraction. Reciprocally, nitric oxide causes a down-regulation of MLCK and an up-regulation of MLCP. Dr. Kitazawa investigates calcium sensitization and desensitization through modulation of MLCP in order to explore the mechanism of smooth muscle pathology.

Dr. Jeffrey Miller, Senior Scientist, came to BBRI from Massachusetts General Hospital and retains his title as Associate Professor of Neurology at Harvard Medical School. He received his Ph.D. in Biochemistry from University of California, Berkeley.

Dr. Miller's research group focuses on three areas of neuromuscular biology and disease. First, they are testing possible ways to inhibit the muscle wasting and loss of muscle function that is found during normal aging and in neuromuscular diseases such as muscular dystrophy. Second, they are examining how the small number of stem cells in adult muscle normally function and how they might be used in cell replacement therapies. Third, they are using new gene analysis methods to examine how environmental contaminants (e.g. PCBs, pesticides) cause adverse effects on the nervous system during pregnancy and throughout life. The laboratory's goals are to understand how certain neuromuscular problems arise and might be ameliorated.

Dr. Lucia Rameh, Scientist, came to BBRI from Harvard Medical School, Beth Israel Deaconess Hospital where she was an Instructor in the Department of Medicine. She received her Ph.D. in Biochemistry from the Universidade de Sao Paulo, Brazil.

In contrast to simple unicellular forms of life, such as bacteria and yeast, cells in complex, multi-cellular organisms differentiate to perform specialized functions and utterly depend on each other. This interdependence necessitates intercellular communication to drive development and to assure the well-being of the whole organism. Dr. Rameh's laboratory studies how normal cells communicate with each other, and how a break-down in communication leads to disease at the organism level, such as cancer or diabetes. They are investigating a class of molecules, collectively known as phosphoinositides, that participate in this basic process of cell-cell communication. Like the Ctrl key in a computer keyboard, phosphoinositides serve a broad range of functions in cells, but need to work in concert with other signals to cause a specific outcome. By systematically disrupting the normal functions of phosphoinositides in cells, Dr. Rameh's research group seeks to understand their role in health and to design strategies that interfere with the disease process.

INTRODUCTION

Albert Wang, Ph.D., Senior Scientist and Deputy Director

One of BBRI's many strengths is its state-of-the-art instruments. Over the years we have been quite successful in getting shared instrumentation grants from federal agencies. This is primarily because of the collaborative nature of the Institute, in which we all take great pride. Not only is a given instrument here used by a large number of scientists, but sharing it also fosters great synergism among the users. The recent successful completion of The Kresge Foundation Science Initiative Challenge Campaign enabled us to establish a Cell Biology Core Facility, which adds two more useful tools to our list – the flow cytometer and the confocal microscope. I thought we might take this opportunity to briefly introduce some of BBRI's shared instruments. In this Annual Report, we highlight eight major pieces of equipment housed at the Institute. I wish to thank my colleagues who took time from their busy schedules to write about their favorite instrument. Contributors include: Drs. Bohm, Erhardt, Hansen, Langsetmo, Lehrer, Lu, Mabuchi and Stafford. Personally, I learned a lot from reading their descriptions of such a great collection of equipment and will always keep a copy handy for myself. I hope you will enjoy reading these accounts as much as I did.

ANALYTICAL ULTRACENTRIFUGES

Walter Stafford, III, Ph.D., Senior Scientist

Analytical ultracentrifugation has been found invaluable in the elucidation of information about the mass, structure and interactions of macromolecules. In his book "The Molecular Biology of the Gene" J.D. Watson characterized analytical ultracentrifugation as perhaps the most striking contribution of physical chemistry to the study of biological macromolecules.

An analytical ultracentrifuge is a very high speed centrifuge with an optical system for viewing the sedimentation process. At its top speed of 60,000 rpm, it will develop an acceleration of 200,000 times the force of the earth's gravity (g). At forces of this magnitude, very small particles and protein molecules can be sedimented. Sedimentation takes place in much the same way as a glass of freshly squeezed orange juice separates. The heaviest particles settle out first and the smallest ones last. The sedimentation in a glass of orange juice occurs at 1 x g, of course, so only the very large particles of pulp will settle out. Protein molecules, on the other hand, are extremely small by comparison and, therefore, require much greater force to make them settle out. Most proteins will move only about 1/4 inch in several hours at 60,000 rpm. The optical system of the analytical ultracentrifuge allows one to measure the speed of movement of the protein molecules. By measuring the speed as well as the rate of spreading of the boundary between the water and the protein solution, one can calculate both the mass and the shape of the protein particles. For example, if two proteins have the same mass but different shapes, the more compact protein will sediment faster than a protein that is more extended. By measuring the sedimentation velocity of a protein of known mass, one can deduce its general shape. Interactions between molecules can also be studied because of the increase in mass of the complex that is formed when two proteins interact to form a new protein particle.

Sedimentation takes place in much the same way as a glass of freshly squeezed orange juice separates.

Sedimentation analysis gives us a tool for the quantitative characterization of individual proteins and their interactions. Examples of proteins and interactions that have been studied quantitatively by sedimentation analysis are smooth muscle myosin, transcription factor with DNA, and antigens with antibodies.

CALORIMETERS

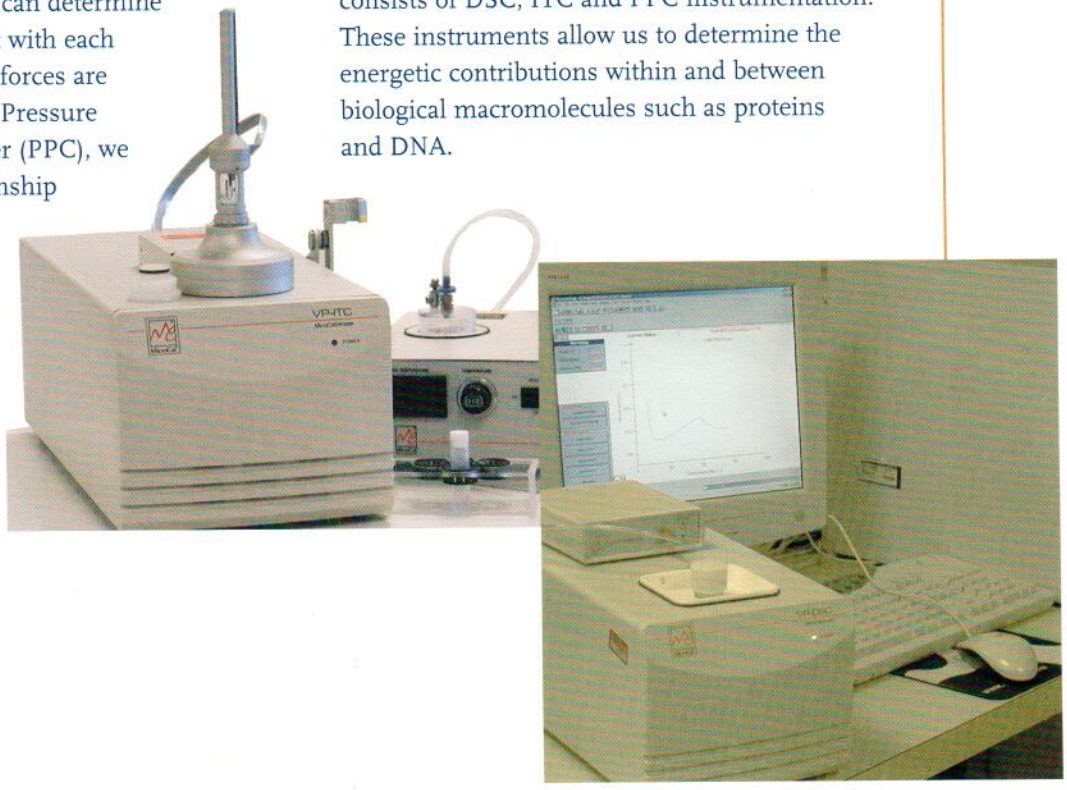
Knut Langsetmo, Ph.D., Instructor

Heat is a fundamental part of all chemical reactions, including the reactions that take place in a living organism. Therefore, the ability to measure the heat absorbed or released during a reaction provides us with a universal means to follow biological processes. As the name suggests, a calorimeter measures heat. We have the capability to make three different kinds of heat measurement. With a Differential Scanning Calorimeter (DSC), we can measure changes in the heat capacity of a solution as it is heated. This is typically used to determine the stability of a whole macromolecule or its parts. An Isothermal Titration Calorimeter (ITC) measures the heat of interaction between molecules; from such measurements we can determine how tightly they interact with each other and what types of forces are involved. Finally, with a Pressure Perturbation Calorimeter (PPC), we can measure the relationship between heat and pressure, the thermal coefficient of expansion. From this measurement over a range of temperature, we can determine the change in volume during a reaction, further characterizing its basic nature.

Calorimetric methods measure the heat involved in biological processes without modifying the components themselves.

It has long been thought that there is a relationship between the structure of a macromolecule and its function. Understanding the link between them would greatly improve our ability to understand the causes of diseases and to develop new treatments. Key to understanding this link is knowing the various contributions to the energy of a given reaction. In this regard, calorimetric methods are particularly useful since they measure the heat involved in biological processes without modifying the components themselves. From measuring the heat involved, we can have a more fundamental description for the structure-function relationships of macromolecules.

Through a successful grant proposal, BBRI scientists recently obtained funding from the NIH for a Calorimetry Workstation, which consists of DSC, ITC and PPC instrumentation. These instruments allow us to determine the energetic contributions within and between biological macromolecules such as proteins and DNA.



CONFOCAL MICROSCOPE

Steen Hansen, Ph.D., Scientist

Confocal microscopy has revolutionized biological imaging of 3-D structures and living organisms.

Microscopes are used to visualize objects that are too small for the naked eye to see. In biology and medicine, a variety of microscopes exist which are specialized to generate images of everything from individual molecules to entire living organisms. The confocal microscope or, more accurately, the confocal laser scanning microscope is an instrument designed to generate optical sections of cells, subcellular structures, as well as small organisms such as embryos, worms, fruit flies etc.

The confocal microscope utilizes a laser, which excites fluorescent molecules that are either present in cells or attached to molecules inside cells. The emitted fluorescent image is magnified by a fluorescence microscope and measured by a "detector" (i.e. a photomultiplier tube). In front of the detector is a pinhole that only allows light from the focal point of the lens to pass through. In this setup, the pinhole is said to be "conjugate" to the focal point, hence the term "confocal" microscope. As a result, all the light that reaches the detector is always in focus, in contrast to a conventional microscope, where, unless the specimen is completely flat, much of the light is out of focus and therefore creates a blurred image. To generate an image, the laser beam is scanned across the specimen by mirrors, thus the term "scanning" laser confocal microscope. The image, however, doesn't exist until it is assembled in a computer. By moving the level of the pinhole up and down, it is also possible to generate images from different layers of a thick specimen, which can be reconstructed in 3-D by a computer.

Confocal microscopy has revolutionized biological imaging of 3-D structures. Whereas previously it was necessary to cut these structures into slices and manually reconstruct images from these slices into 3-D, the confocal microscope can do all this for us by computer. Equally important, since the need for cutting sections is avoided, the confocal microscope can also be used to image living organisms. The advantages have made the confocal microscope a household instrument for biomedical research that is widely used.

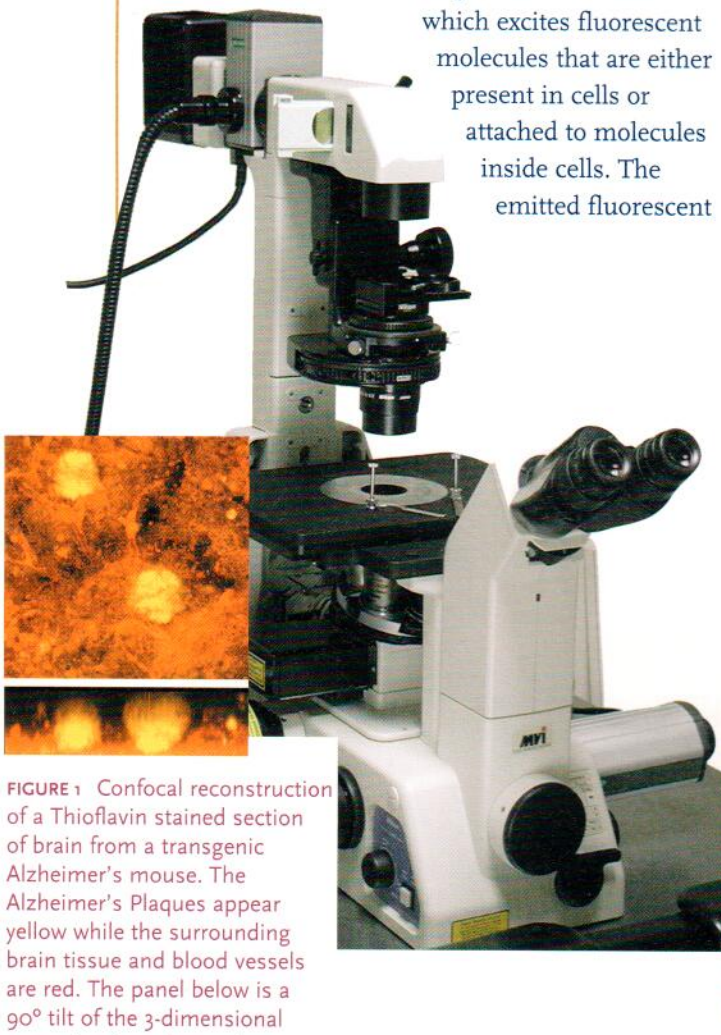


FIGURE 1 Confocal reconstruction of a Thioflavin stained section of brain from a transgenic Alzheimer's mouse. The Alzheimer's Plaques appear yellow while the surrounding brain tissue and blood vessels are red. The panel below is a 90° tilt of the 3-dimensional reconstruction shown above.

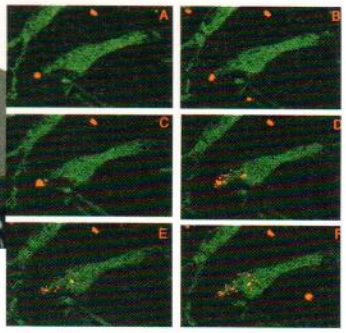


FIGURE 2 Three hour time-lapse images (A-F) of a brain microglial cell (stained green) in the process of ingesting and breaking apart an artificial Alzheimer's Plaque (stained red).

Figures provided by Vic Raso

FLOW CYTOMETER

Peter Erhardt, Ph.D., Scientist

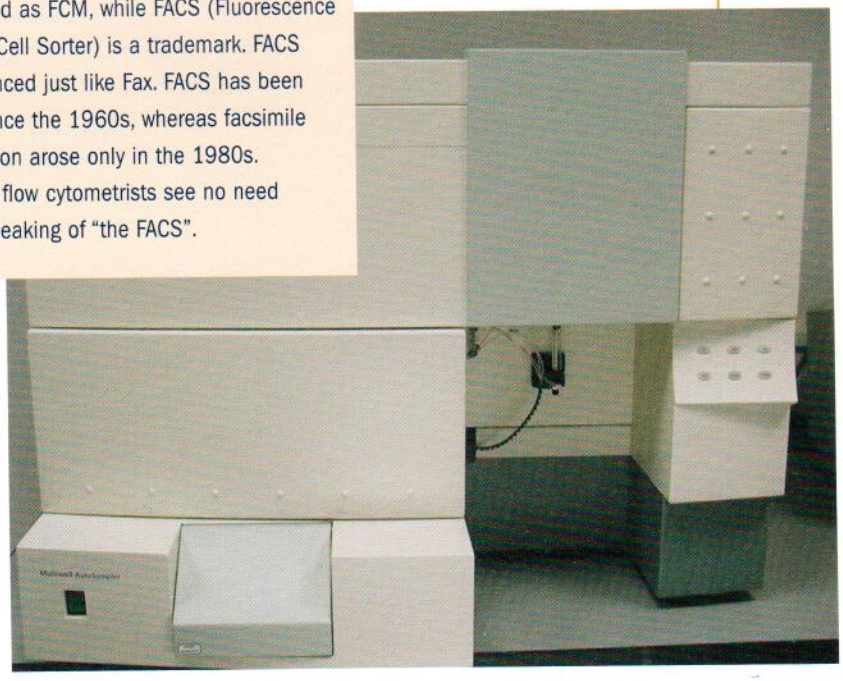
Flow cytometry (FCM) is a method for quantifying the types of cells in a mixture. It may be used simply for cell analysis or it can be used for cell sorting, where the subpopulations are physically separated from each other and used for further experiments. No other method allows as rapid a quantitative and detailed analysis of subpopulations of cells as FCM. It is popular for both research and clinical diagnosis, because it can quickly and inexpensively analyze a large number of samples (30-50 samples/hour), much faster than the best hematologist.

No other method allows as rapid a quantitative and detailed analysis of subpopulations of cells as flow cytometry.

To do the analysis, fluorescently labeled live or fixed cells in single-cell suspension are passed single-file as a fine stream through a laser beam. Each cell scatters some of the laser light and also emits fluorescent light excited by the laser. The cytometer typically measures several parameters simultaneously for each cell: a) the low-angle forward scatter intensity, approximately proportional to the cell diameter; b) the orthogonal (at 90° angle) scatter intensity, approximately proportional to the quantity of granular structures within the cell; and c) fluorescence intensities at 3-4 wavelengths. The computer records the data and displays them graphically.

The use of flow cytometers has been increasing since they became commercially available in the early 1970s. There are about 7,000 flow cytometers in use worldwide. In research, fluorescent antibodies are often used to measure specific cell components such as surface receptors, expression of a transgene or binding of viruses, or hormones to their receptors. Another typical measurement is the amount of total DNA per cell for analyzing the growth and death of cells. FCM also has important clinical applications in diagnosis, prognosis, and optimization of therapy. For example, FCM can distinguish subtle changes in the types of blood cells to discriminate between different types of blood cell cancers (e.g. leukemias and lymphomas).

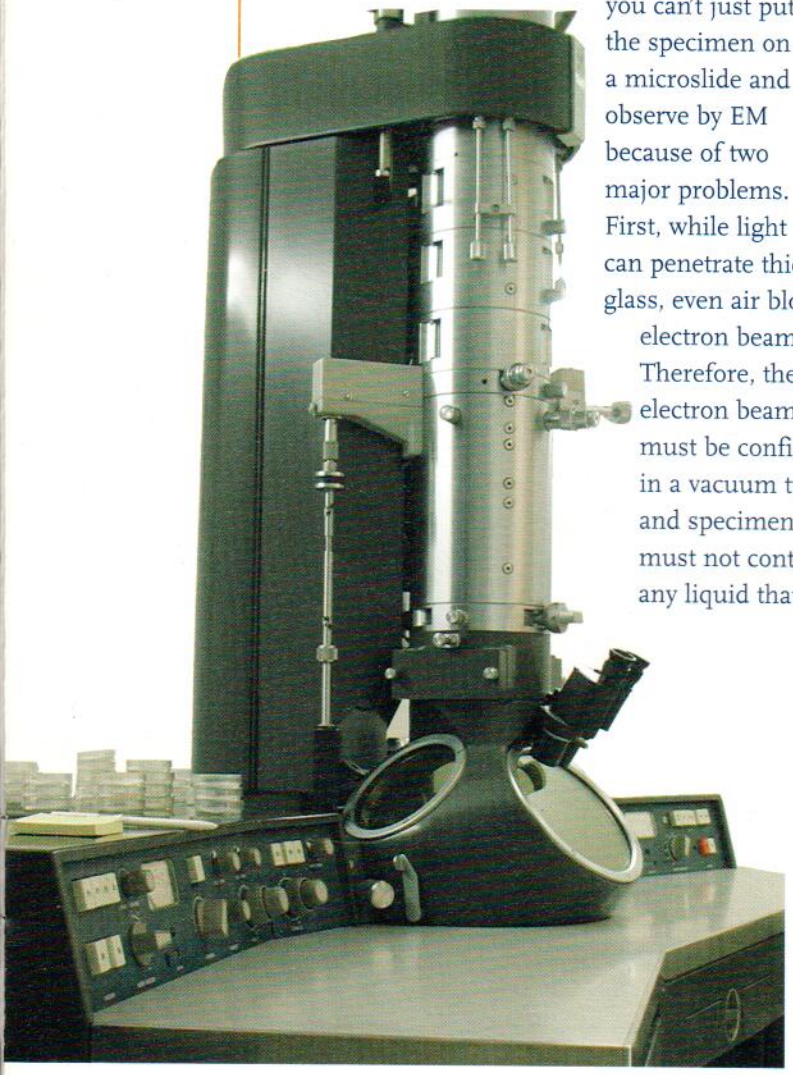
FACS, but no Fax. BBRI owns a flow cytometry instrument called FACSCalibur that can perform both cell analysis and cell sorting. Flow cytometry is a generic term and is abbreviated as FCM, while FACS (Fluorescence Activated Cell Sorter) is a trademark. FACS is pronounced just like Fax. FACS has been around since the 1960s, whereas facsimile transmission arose only in the 1980s. Therefore, flow cytometrists see no need to stop speaking of "the FACS".



ELECTRON MICROSCOPE

Katsuhide Mabuchi, Ph.D., Senior Research Associate

An electron microscope (EM) enables us to magnify objects much more than the light microscope (LM) can. A bacterium looks like a grain of rice with LM, while you can see its detailed inside features with EM. How does EM provide so much higher magnification? Light travels like a wave; different colors of light have different wavelengths. For example, blue light has a shorter wavelength than red light. The wavelength of light sets the limit on the size of the object you can see. EM uses electron beams, which can also be viewed as waves but with much shorter wavelengths than light, hence allowing us to see smaller objects.



But unlike LM, you can't just put the specimen on a microslide and observe by EM because of two major problems. First, while light can penetrate thick glass, even air blocks electron beams. Therefore, the electron beams must be confined in a vacuum tube and specimens must not contain any liquid that may vaporize in the vacuum. This means it is impossible to observe a biological specimen as is. Secondly, biological specimens are almost transparent to electron beams, just like glass to light, and internal structures are not revealed unless they are "stained." Among the many ways to visualize samples is a technique called "rotary shadowing," in which protein molecules are coated with a thin layer of a heavy metal (e.g. platinum). Because heavy metals block electron beams, they can reveal the shape of transparent objects.

Electron microscopy uses electron beams, which can also be viewed as waves but with much shorter wavelengths than light, hence allowing us to see smaller objects.

EM helps scientists to visualize the surface of cells, the structure of membranes and particles inside the cell, and the shape of individual protein molecules. From the images of these biological elements it is often possible to deduce their functions. For example, the current theory about how muscles contract was proposed based on the shapes and movement of myosin and actin filaments observed with EM.

MASS SPECTROMETER

Renne Lu, Ph.D., Senior Scientist

The mass spectrometer is an instrument for determining the mass of molecules. During the past decade, mass spectrometry has been increasingly applied to biological sciences thanks to advances in the development of matrix-assisted laser desorption ionization (MALDI) techniques, which facilitate vaporization and ionization of biological samples from a solid state into the gas phase. When a molecule carrying a positive or negative charge travels through a long tube in an electric field, its velocity depends on its charge and its mass: the smaller a mass per charge is, the faster the molecule will travel. If the time required to reach the detector at the other end of the tube is measured, the mass of the molecule can be calculated. This new type of instrument, which BBRI purchased using grants awarded by NIH and NSF, is called MALDI-TOF (time of flight) mass spectrometer.

The ability of the mass spectrometer to analyze a complex mixture and its superb sensitivity make this instrument one of the most powerful tools in proteomics during the current post-genomic era.

The precision offered by MALDI-TOF mass spectrometry allows us to detect minute changes in the mass of a molecule. Mass spectrometry can therefore be used in a wide range of applications in research laboratories or pharmaceutical companies. Common applications include quality control of synthetic peptides and drugs, verification of proteins and protein fragments generated by recombinant DNA techniques, and identification of phosphorylation and other post-translational modifications of proteins, which are often critical for the regulation and functions of proteins.

The ability of the MALDI mass spectrometer to analyze a complex mixture and its superb sensitivity make this instrument one of the most powerful tools in proteomics during the current post-genomic era. An unknown protein may be cleaved into smaller fragments chemically, or by an enzyme and the masses of the fragments in the mixture can be determined by mass spectrometry. Upon comparison of the results with information in the genomic database, the original parent protein can be unambiguously identified. This instrument also allows the identification of proteins associated with certain diseases, either up- or down-regulated, or binding partners of a molecule with known functions.

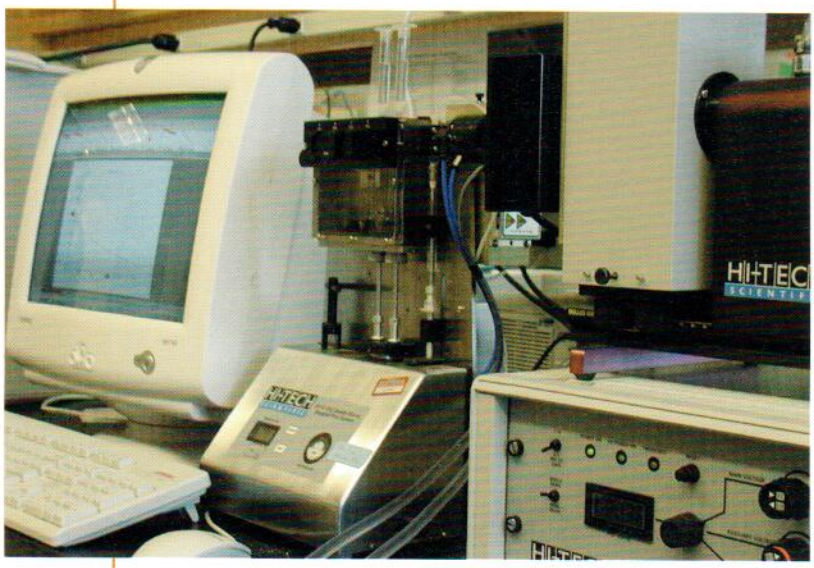
STOPPED-FLOW FLUORESCENCE INSTRUMENTATION

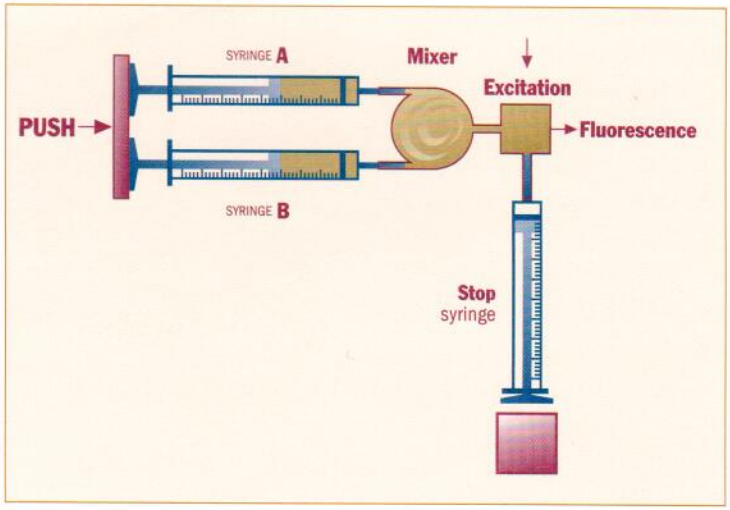
Sam Lehrer, Ph.D., Senior Scientist

Often a biochemist or biophysicist wishes to measure how fast a substance interacts with another, for example, a substrate binds to an enzyme. This can be done in a simple spectrophotometer if either molecule contains a probe whose spectral properties change during the binding process and if the contents can be mixed faster than the substrate binds to the enzyme. Hand mixing usually takes several seconds; if the reaction is more rapid than that, a faster mixing system becomes necessary. Also, most proteins do not have a sensitive amino acid side chain located in the right place in the structure to have its spectral properties perturbed by the interaction (i.e., an intrinsic probe). To solve these problems, we use a Stopped-Flow instrument which can mix solutions in a couple of milliseconds and use extrinsic probes that we attach to the protein which are sensitive to the interaction under study. Fluorescent probes are good choices because of their high sensitivity. A simplified schematic of the basic components of a stopped-flow fluorescence instrument is shown below.

A stopped-flow instrument can mix solutions in a couple of milliseconds and measure the dynamics of interacting proteins.

The stopped-flow instrument measures the dynamics of interacting proteins. With this instrument we can measure, for example, how fast myosin interacts with actin thin filaments using mutant proteins, e.g. those associated with muscle diseases. Since many biologically important processes function by producing changes in the millisecond time range, it is useful for studying a variety of physiological and pathological systems.





After filling the drive syringes with solutions A and B (one of which contains molecules with the fluorescent probe), the syringes are pushed within a millisecond. Solution A is rapidly mixed with B and enters a spectrophotometer cell. After the flow is stopped the change in fluorescence is monitored.

X-RAY CRYSTALLOGRAPHIC FACILITY

Andrew Bohm, Ph.D., Principal Scientist

To see the individual atoms within a molecule, one must use light with a very short wavelength. This light falls in the X-ray region of the electromagnetic spectrum, far outside of the visible light region to which our eyes are sensitive. The electron beams used for electron microscopy also have short wavelengths, but they interact so strongly with molecular samples that the object of interest is usually destroyed before complete data can be collected. X-rays are much gentler, and in fact they tend to go through objects rather than interacting with them at all. This property makes X-rays very useful for medical imaging, but causes experimental hurdles when we use them to see biological molecules.

The crystal scatters far more X-rays than a single molecule would, and allows us to take pictures of the scattering pattern to develop a complete 3-D model of the molecule.

When X-rays do interact with an object, they are scattered by it. A mathematical formula allows us to convert the pattern of scattered X-rays into an image of the object. To image a sample with X-rays, we must present the X-ray beam with a crystal composed of the molecule we are studying. The crystal (with millions of similarly oriented copies of the molecular sample) scatters far more X-rays than a single molecule would, and allows us to take pictures of the scattering pattern. By rotating the crystal while taking a series of these pictures, we can develop a complete 3-D model of the molecule, with precise coordinates for every atom.

This process requires a great deal of specialized machinery and computer power. Producing defect-free crystals of a given sample often takes years, and since only a small fraction of the X-rays that strike the crystal are scattered by it, we need to use an X-ray generator that is much more powerful than those used for medical imaging. The intensity of this X-ray beam requires that we cool the sample using a liquid nitrogen system during data collection. We also use a very sensitive X-ray detector to record the patterns produced by the scattered X-rays. BBRI's X-ray diffraction facility was established five years ago and is currently used by four laboratories.

DEVELOPMENT REPORT

John R. Layton

With many competing philanthropic priorities facing us during a very difficult year for our nation, we recognized early in the year that success in our fundraising efforts would require an especially strong commitment to BBRI's mission from our volunteers and from the Institute's loyal contributors. I am happy to report that basic biomedical research continues to be a compelling cause worthy of philanthropic support, judging from the extraordinary generosity shown by donors to BBRI.

The dedication and persistence of BBRI's Board of Trustees, Faculty and development team enabled the Institute to meet some very important challenges in the past year. Our successes, which were the result of many hours of hard work by many people, were due to the generosity of the individuals, foundations and businesses listed in this Annual Report. On behalf of all the Trustees of the Institute, I offer sincere thanks to all of those generous contributors.

In June, 2001, The Kresge Foundation issued a challenge to BBRI – if the Institute could raise $1.2 million by June 1, 2002, a challenge grant of $400,000 would be provided to establish a Cell Biology Core Facility, equipment many of our scientists find helpful in their research. Through the generosity of many friends, including gifts from BBRI scientists and members of the staff, we successfully concluded the Kresge Science Initiative challenge. Through this challenge, we raised a total of $1.6 million and broadened our base of donors. I especially want to thank our Challenge Campaign Co-Chairs, Donna Fisher and Ty Howe, for their tireless and effective leadership of this effort. Thanks also to Allie Blodgett, who has been an undeniable force in our fund-raising efforts.

Successfully concluding the Kresge Science Initiative challenge provided a tremendous boost to the Institute's comprehensive fundraising effort, *A Campaign for BBRI: Intellectual Partners for the Future of Science*, which was announced in the Institute's most recent newsletter. The goals of the campaign are to increase the number of scientists and postdoctoral fellows at the Institute, to increase and improve laboratory space and equipment, to establish a pilot fund for innovative scientific ideas and to create science education outreach programs for local students.

Including the funds received from the Kresge Foundation, we have raised $5.6 million thus far in our campaign effort, which is, by far, the most money BBRI has ever raised in a campaign. In reaching this amount, we owe a debt of gratitude to the many generous donors who contributed during the silent phase of this campaign, as well as to those who helped us meet the Kresge Foundation challenge.

We are not about to rest on our laurels. We are now undertaking a generous $250,000 challenge grant from the Fidelity Non-Profit Management Foundation which, when complete, will allow BBRI to establish a Pilot Fund Initiative for the development of novel scientific ideas. This fund will provide a competitive annual award to the most innovative pilot project proposed from among BBRI's faculty. Such projects are often deemed too "early" to receive support from national funding agencies.

Finally, I am happy to report that BBRI's Annual Fund continues to break new ground. In 2002, we raised $499,262, an increase of 7% over the amount raised in 2001, and a new record for the Annual Fund at BBRI. The Annual Fund is of critical importance because it supports research initiatives that are not covered by research grants. As we reach out to you in the coming year to tell you more about these initiatives and about BBRI's latest scientific accomplishments, we hope you will choose to help us build a strong future for the world-class biomedical research programs at BBRI!

Thank you, again, to all those who contributed so generously of their time and their financial resources to BBRI in the year just ended.

GIFTS & PLEDGES TO A CAMPAIGN FOR BBRI:
INTELLECTUAL PARTNERS FOR THE FUTURE OF SCIENCE

To make the most of the many opportunities for growth that our new state-of-the-art research facility in Watertown provides, BBRI has launched a comprehensive fundraising campaign. Our goals are to raise the resources needed to increase the Institute's scientific staff and provide for the associated expansion of laboratory space within the building, to purchase new scientific equipment, to expand our postdoctoral fellowships program, to launch a pilot fund for novel scientific ideas, and to establish science education outreach programs to benefit local students. A Campaign for BBRI: Intellectual Partners for the Future of Science is making good progress with $5.6 million raised to date. As the campaign gains momentum, we would like to pause and thank the following individuals, foundations and corporations who have made the leadership phase of this first major fundraising campaign for BBRI such a success:

$1,000,000 and Up

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$500,000 - $999,999

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Dr. Mahlon Hoagland (l), keynote speaker at the 2001 Annual Meeting, greets BBRI Trustee Dr. Elkan Blout.

(l-r) BBRI Trustee Donna Fisher, George Kaye, and Corporator Josef von Rickenbach at the 2001 Annual Meeting.

* *In 2001, BBRI Corporator Frederic G. Corneel passed away. All of us will miss his good counsel and kind support.*

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An integral part of A Campaign for BBRI has been The Kresge Foundation Science Initiative, a challenge grant which BBRI successfully completed in June, 2002. With the dedicated support of the donors listed below, BBRI raised $1.6 million to establish a Cell Biology Core Facility which benefits the research of numerous groups of scientists in their ongoing studies into diseases such as cancer, Alzheimer's disease, heart disease and stroke. We offer our sincere thanks to the following supporters:

BBRI Vice President Allie Blodgett views cells through the confocal microscope in The Kresge Foundation Cell Biology Core Facility.

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Very special thanks to Sterling Hager, Inc. for Public Relations services provided

* *In 2001, BBRI Corporator Frederic G. Corneel passed away. All of us will miss his good counsel and kind support.*

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TREASURER'S REPORT

Geoffrey Nunes

BBRI's research continues to thrive in its new state-of-the-art facility in Watertown. At the same time strides are being made in cost containment by constantly reviewing existing relationships with vendors. Once again, the administrative and support staff remained at constant levels, whereas BBRI experienced growth in scientific personnel, including the addition of three new principal investigators along with their research staffs. In fact, since the implementation of our strategic plan six years ago we have successfully recruited thirteen scientists.

A review of the Statements of Financial Position indicates that investments approximated $13,750,000 on June 30, 2002, a decrease of almost $1,698,000 over the prior year. As investors are aware, the stock market woes continued during this past year, leading to an annual total return of –7.7%.

A review of the Statements of Activities indicates that BBRI revenues from grants and contracts of approximately $8,727,000 reflected strong growth of 10% over the prior year, resulting in the second straight year of double digit growth. Revenue from federal agencies represents approximately 91% of revenue from grants and contracts.

Philanthropic giving once again was significant as BBRI continued in its leadership phase of *A Campaign for BBRI: Intellectual Partners for the Future of Science.* Fiscal year 2002's total contributions approximated $1,735,000. As we enter the next phase of the campaign, we hope you will continue your generous support of BBRI and assist us with our goals to expand our friends, advocates and supporters. Unrestricted contributions of approximately $578,000 decreased $1,436,000. However, this decrease reflects BBRI's strategic planning, which included raising permanently and temporarily restricted contributions of $957,000 and $200,000, respectively, to help establish the Cell Biology Core Facility (an endowment and equipment fund) as well as begin raising contributions for the Fidelity Non-Profit Management Foundation permanently endowed Pilot Fund Initiative, which will generate the seed money necessary to help secure future federal funding.

We suffered less of an investment income (loss) primarily due to a reduction in unrealized losses over the prior year. These unrealized losses, along with some realized losses as a result of portfolio rebalancing, caused BBRI's debt service coverage ratio (a target established in bond agreements) to be less than 110% for the fiscal year ended June 30, 2002. Trustees and management, together with an independent consultant, are formulating a plan to bring the ratio well above 110%. Other income includes net royalty income of $132,000 relating to an Alzheimer's vaccine technology (see President's report for further details). The gross royalty revenue of $400,000 was allocated in accordance with BBRI patent policy and includes a fund in the amount of $96,000 available for research in the laboratory of the inventor.

Total expenses of $10,942,000 increased approximately $841,000 over the prior year due primarily to growth in research initiatives. During the fiscal year the Institute was awarded fifteen new grants from Federal Government sources, most of which came from the National Institutes of Health. Additionally, BBRI received three grants from the American Heart Association, and one each from the American Federation of Aging Research, the Merck Foundation and the Muscular Dystrophy Association.

The Investment Committee reviews performance and asset allocation with our investment advisor, New England Pension Consultants, on a quarterly basis. The Committee rebalanced the portfolio during the year to help reduce risk and preserve principal given the bond covenants which focus on short-term results. I want to take this opportunity for a special thank you to Ernest Henderson III, who has served as Treasurer of BBRI since November 1983. Under his leadership the Investment Portfolio grew from approximately $1,200,000 to $13,750,000 as of June 30, 2002. I also would like to thank the members of the Investment Committee for their assistance during the past year.

FINANCIAL
STATEMENTS OF FINANCIAL POSITION

JUNE 30, 2002 AND 2001

	2002	2001
Assets:		
Cash	$ 809,876	$ 520,284
Grants receivable	6,101,263	4,981,270
Unconditional promises to give	889,522	417,140
Investments	13,749,823	15,447,786
Prepayments, deposits and other receivables	125,895	168,704
Trustee-held funds	1,245,148	1,281,381
Property and equipment	16,269,056	16,564,454
Deferred compensation investments	1,798,647	2,217,224
Total assets	**$ 40,989,230**	**$ 41,598,243**
Liabilities and net assets:		
Accounts payable and accrued expenses	$ 640,141	$ 240,524
Accrued interest expense	391,140	391,140
Deferred income	5,988,342	4,798,037
Bonds payable	16,475,000	16,745,000
Deferred compensation payable	1,798,647	2,217,224
Total liabilities	**25,293,270**	**24,391,925**
Net assets:		
Unrestricted	14,054,961	16,438,854
Temporarily restricted	140,504	187,904
Permanently restricted	1,500,495	579,560
Total net assets	**15,695,960**	**17,206,318**
Total liabilities and net assets	**$ 40,989,230**	**$ 41,598,243**

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

FINANCIAL
STATEMENTS OF ACTIVITIES

FOR THE YEARS ENDED JUNE 30, 2002 AND 2001

	2002	2001
Changes in unrestricted net assets		
Revenues:		
Grants and contracts	$ 8,726,563	$ 7,942,481
Contributions	578,473	2,014,487
Investment income	(1,127,514)	(1,743,133)
Other income including licensing fees (net)	147,245	257
Total unrestricted revenues	8,324,767	8,214,092
Net assets released from restrictions	233,227	46,074
Total unrestricted support	**8,557,994**	**8,260,166**
Expenses		
Salaries and benefits	6,338,189	5,680,793
General support and services	1,655,951	1,677,110
Occupancy costs	969,985	812,632
Interest Expense	938,735	948,997
Depreciation	1,039,027	981,475
Total expenses	**10,941,887**	**10,101,007**
Decrease in unrestricted net assets	(2,383,893)	(1,840,841)
Changes in temporarily restricted net assets:		
Contributions	200,000	
Investment income	(14,173)	(25,544)
Net assets released from restrictions	(233,227)	(46,074)
Decrease in temporarily restricted net assets	(47,400)	(71,618)
Changes in permanently restricted net assets:		
Contributions	956,755	
Investment income	(35,820)	(65,341)
Increase (decrease) in permanently restricted net assets	920,935	(65,341)
Decrease in net assets	**(1,510,358)**	**(1,977,800)**
Net assets at beginning of year	**17,206,318**	**19,184,118**
Net assets at end of year	**$ 15,695,960**	**$ 17,206,318**

GRANT AND FELLOWSHIP AWARDS
JUNE 30, 2002

		GRANT TERM	DOLLARS
NATIONAL INSTITUTES OF HEALTH			
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. Coluccio	Myosin-I Mediated Processes in Liver Cells	8/97 - 7/03	1,407,000
Dr. Dominguez	Atomic Structure of Smooth Muscle Caldesmon	3/00 - 2/05	1,761,000
Dr. Graceffa	Smooth Muscle Thin Filament	8/01 - 7/05	1,892,000*
Dr. Harrison	Structure / Function Analysis of Molecular Chaperones	7/98 - 6/03	1,237,000
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. Kitazawa	G Protein Mediated Ca2+ Sensitization in Smooth Muscle	4/02 - 11/02	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. Lehrer	Calorimetry Work Station	3/02 - 2/03	151,000*
Dr. Lu	Procise Protein Sequencing System	5/02 - 4/03	147,000*
Dr. Miller	Molecular Physiology of Respiratory Muscles	11/01 - 6/05	1,921,000*
Dr. Miller	Neurotoxicogenomics and Child Health	11/01 - 8/02	1,506,000*
Dr. Miller	Gene Arrays in Developmental Neurotoxicology	11/01 - 9/02	119,000*
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. Paulus	Mechanism of Protein Splicing in Mycobacterium	4/97 - 3/02	1,403,000
Dr. Rameh Plant	Diabetes & Endocrinology Research Center	10/01 - 3/02	13,000*
Dr. Raso	A Binary System for Cell-targeted Delivery	3/99 - 2/02	246,000
Dr. Raso	Vaccine to Elicit Catalytic Anti-cocaine Antibodies	4/99 - 3/03	471,000
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. Tao (MERIT)	Proximity Relationship among Muscle Proteins	5/96 - 3/02	2,201,000
Dr. Tao	Molecular Interactions of the Myosin Phosphatase Subunits	2/00 - 1/04	1,282,000
Dr. Wang (Pro. Proj.)	Molecular Mechanism of Smooth Muscle Regulation	12/97 - 11/02	8,171,000
Dr. Wang	Regulation of MLCK by Phosphorylation	1/02 - 12/04	96,000*
Dr. Wohlrab	Phosphate Path within Homodimeric Mitochondrial PTP	5/98 - 4/03	1,412,000
NATIONAL SCIENCE FOUNDATION			
Dr. Erhardt	Mechanism of Cell Survival Mediated by the B-Raf Kinase	6/00 - 5/03	309,000
Dr. Smith	Role of Two Novel cGMP Binding Proteins in Dictyostelium	9/01 - 6/03	205,000*
DEPARTMENT OF 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 CANCER SOCIETY			
Dr. Bohm	Structure of G-Beta Gamma / Effector Complex	1/99 - 12/02	342,000
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. Foster	Structural Investigation of Muscle Thin Filaments using 3D Helical Reconstruction of Electron Micrographs	7/01 - 6/03	57,000*
Dr. Janet Smith	Cyclic GMP-Dependent Myosin Regulatory Light Chain Phosphorylation in Dictyostelium	7/00 - 6/02	99,000
Dr. Janet Smith	Cyclic GMP Signaling by GBP-A and B in Dictyostelium	1/02 - 12/05	260,000*
AMERICAN FEDERATION OF AGING RESEARCH			
Dr. Erhardt	Regulation of Cardiomyocyte Survival by MDM2	7/01 - 6/02	49,000*
CONRAD			
Dr. Leavis	Contraceptive Potential of Novel Embryo-derived Peptides that Modulate Maternal Immunity	12/00 - 11/01	126,000
MARCH OF DIMES			
Dr. Coluccio	Mechanochemical Properties of Mammalian Myosin I's	6/98 - 5/03	310,000
Dr. Dominguez	Structural Biology of Caldesmon - based Thin Filament Regulation	2/00- 1/02	100,000
MERCK FOUNDATION			
Dr. Ikemoto	Banyu Fellowship Award in Cardiovascular Medicine	4/02 - 3/04	80,000*
MUSCULAR DYSTROPHY ASSOCIATION			
Dr. Miller	Cell Death Genes in Developing & Dystrophic Muscle	11/01 - 6/02	56,000*

**New grants in fiscal 2002*

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