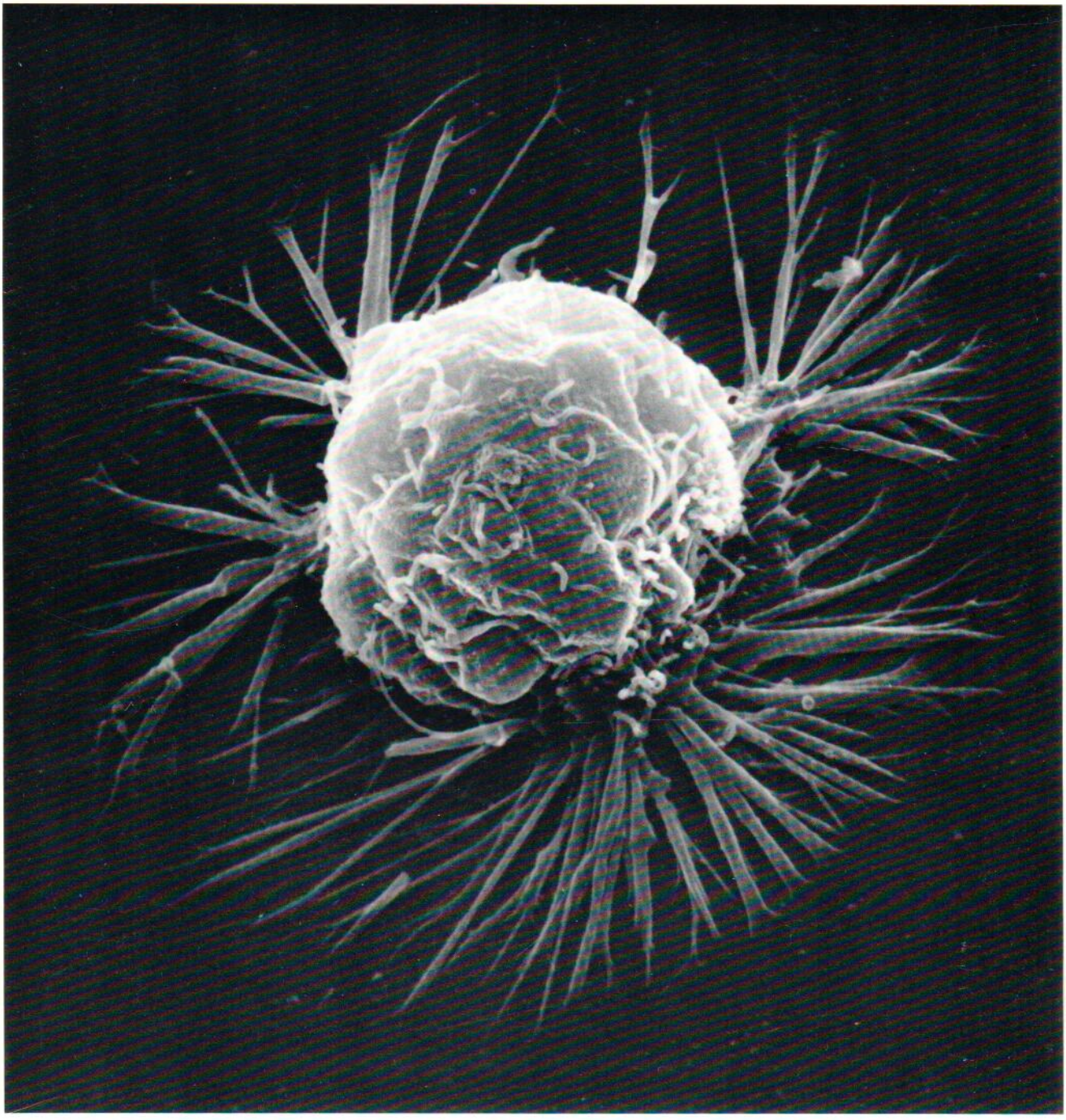
Boston Biomedical Research Institute

1992 Annual Report



Boston Biomedical Research Institute is dedicated to basic biomedical research, which promotes the understanding, treatment and prevention of specific human diseases. One major focus is muscle cell biology and its implications for neuromuscular and other muscle-related diseases such as asthma, hypertension, malignant hyperthermia and gastrointestinal disorders. Results of research are published in leading scientific journals. When appropriate, the Institute collaborates in clinical studies of patients to apply the results of basic research to problems of human health, the cure of disease and the development of new medicines. Boston Biomedical Research Institute is an independent, not-for-profit institution.

Cover Photo
A human breast cancer cell, as revealed in three-dimensional detail by scanning electron microscopy. (Courtesy National Cancer Institute, Bethesda, Md.)

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This has been an active and involved year for the Trustees whom we have called upon to devote more time than they might have expected to the affairs of the Institute. They have responded with great goodwill and cheerfully participated in the ongoing long range planning of the Institute.

As indicated in last year's report, the joint search process while stimulating was also cumbersome, as the Institute and Harvard Medical School needed to proceed with both joint and separate approval processes. Ultimately, after careful and thoughtful deliberation, the Trustees determined not to pursue further the candidacy of the scientist whom Harvard and the search committee recommended as the most qualified person for the joint position of Executive Director of the Institute and Professor at the Harvard Medical School. Our reluctance to proceed did not reflect on the professional qualifications of the candidate, but rather indicated a doubt on the part of the Trustees that the candidate was the right person to lead the Institute at this time. There were also significant financial implications in some of the candidate's proposed changes for the Institute which the Trustees felt could not be undertaken at present. As a result, the search for a new Director of the Institute is suspended at the moment but is expected to resume later this year.

In the process of working through the issues involved in the consideration of candidates, it became clear that the Trustees needed to consider in greater depth than we are able to at our periodic meetings, questions of the mission and goals of the Institute and its internal organization and structure. As a result, the Trustees met at an all day retreat in May which had been well prepared in advance by a committee of Trustees with the help of a professional consultant. This event, while not an uncommon one for other organizations, was a first for the Institute, and from all indications was a great success. Naturally, all problems and issues are not solved or resolved in one all day session, but following on from the decisions made at this retreat, joint faculty and Trustee committees have been formed to further study and report on a number of topics. These include the mission of the Institute, the organizational structure of the Institute, the roles and responsibilities of Trustees and Incorporators and techniques for better communication between the faculty and Trustees. Some of these committees have already completed their work and others are ongoing, but it is clear that their efforts and the cooperative nature of the undertakings is generating a renewed sense of purpose and vitality at BBRI, among both faculty and Trustees. One concrete result of these activities is the recently adopted mission statement which is printed on the inside front cover of this Annual Report. Also, it is expected that some of the proposed organizational changes of the Institute (most notably the elimination of traditional departmental boundaries among the faculty, to be replaced by less formal groupings among scientists working in similar or related fields) will require bylaw amendments to be adopted at this year's annual meeting.

Last year's report mentioned the planning for a capital fund drive. In view of the temporary suspension of the search for a new Director as the Institute reviews some of the basic issues alluded to above, plans for a capital campaign are proceeding slowly and informally at the present time; however, this has only been delayed not abandoned, as an increase in endowment funds remains a long-term need of the Institute. Of equal importance is the continued support of the Institute's Annual Fund drive, which provides much-needed unrestricted operating funds.

In addition to all of this administrative and planning activity which, as indicated, has involved faculty as well as Trustees, it is particularly pleasing to report that there have been many positive scientific developments during the year, both in terms of new research grants and with respect to recruitment of new scientists. These developments are outlined in more detail in John Gergely's report.

In preparation for retirement, in June of this year Dr. Rao Sanadi resigned his position as department director while retaining his appointment as senior scientist. He was one of the original group of scientists forming BBRI when, 23 years ago, it became a separate entity from the Retina Foundation. Dr. Sanadi has been a leader in research on mitochondrial enzymes for many years, and he has served several terms as BBRI's Executive Director. His plans now include travelling to consult in his native India on the medical problem of lactose intolerance, which is prevalent in India, and on how biotechnology might be used to alleviate the problem.

We continue to be most grateful to individuals and institutions who support the Institute on a regular ongoing basis with unrestricted gifts. These donors, who are recognized elsewhere in this report, provide us with the necessary flexibility to respond to the more stringent NIH funding procedures which affect us along with all organizations who operate in large measure with NIH grants. Among the restricted-use gifts we received this year, I want especially to express our gratitude to the trustees of the Amelia Peabody Charitable Fund for their outstanding endowment grant to BBRI.

John B. French

Report of the Executive Director

While the funding level at NIH has not markedly improved, this has been a good year for BBRI. Of the grants that were pending a year ago, seven have been funded, including one to Zenon Grabarek - his first from NIH. The most significant of the new awards is a program project grant on smooth muscle, a field of research started at BBRI by the late Jack Seidel some years ago. This multi-investigator operation is headed by Albert Wang and involves - in addition to Albert - Phil Graceffa, Sam Lehrer, Zenon Grabarek, Terry Tao, Renne Lu and Eddie Mabuchi, as well as two investigators from the University of Texas and Rice University, respectively. This grant, totalling $6,000,000 for a five year period, will go a long way toward stabilizing BBRI's funding. BBRI's budget for fiscal '93 shows a healthy 43% increase over that of fiscal '92. Grants that have to date been approved for funding currently total $18,000,000, representing about 50% of the estimated cumulative budget of BBRI over the next five years. Several applications for NIH grants are currently undergoing NIH peer review, and we hope that a good percentage will receive funding (for current grants, see Table on page 20 of this Report).

I am happy to report that we have been successful in attracting Peter Coleman as a Senior Scientist. He has relinquished his position as Professor of Biology at New York University and is adding a new and exciting facet to the research of the Institute. His work deals with the modification within the organism of various proteins that play a role in a wide range of processes such as control of normal growth and diseases of the nervous system and cancer. Another addition to the staff is Brenda Williams, who will assume her position next spring. She comes from the National Institute for Medical Research at Mill Hill, London. Her work will focus on the process by which the various cells in the brain acquire their characteristic properties, the so-called process of differentiation, which is of recognized importance from the point of view of multiple sclerosis. We shall provide her with initial support and hope that her research accomplishments to date will make it possible for her to compete successfully for an NIH grant. Peter Prevelige, who has received a Shannon Award from NIH, joined us in October from MIT.

This has been a busy year for faculty and members of governing boards alike, as should be clear from the President's report, chiefly owing to the search for a senior scientist to become Executive Director of BBRI. Although this round did not culminate in an appointment, it has produced useful insights, and it should benefit all of us in making decisions for the Institute's leadership in the future. Problems of a financial nature, the pros and cons of affiliation with an academic institution, the nature of the internal organization of BBRI, and future trends in research - all emerged as important factors that will undoubtedly be before our eyes in the years to come. One tangible result of last year's activities is the proposed new organizational structure for BBRI that would eliminate formal departments and department directors. It is a recognized fact that conditions have changed so that to count on the existence of several well defined departments may not be advantageous in the future, and a more integrated research program for the Institute as a whole will be more in tune with both the changes that have taken place in the staff over the years as well as the funding situation throughout the country. These changes would make it difficult, if not impossible, to create and maintain departments based on a sizable number of investigators of closely related interests. Yet another by-product of the search was the recognition of the need for continued recruitment of principal investigators at all levels.

In the course of the past year we also had lively discussions concerning the relation of basic research and applied medical research, including biotechnological applications. To many of us it seems that a small institute can make its influence best felt throughout the scientific community by focussing on important problems of fundamental importance. However this is not inconsistent with encouraging contact with the medical community and bringing to light possible applications to medical problems and, through the patent process, to assure that opportunities for commercial exploitation and beneficial discoveries are not lost. Past research at BBRI on the structure of hyaluronic acid, the role of calcium in the regulation of muscle contraction, the involvement of the sarcoplasmic reticulum in malignant hyperthermia, the role of asbestos in generating so-called free radicals, the possibility of cancer detection and cure with the use of antibodies has contributed to the body of knowledge that informs medical thinking in cardiology, oncology and the area of muscle diseases.

I have high hopes for the future of BBRI. The new initiatives in the research program and the enhanced involvement of Trustees and Corporation Members in the affairs of the Institute will help assure that the next decades will see the Institute prosper.

John Gergely

CANCER

INTRODUCTION

That cancer is among America's leading killers, second only to cardiovascular disease, is a disturbing thought. No one – neither layman nor scientist – is immune from the anxiety and fear that rise up when the word "cancer" is discussed in a personal context. In part, our phobia is justified because of two facts: first, current medical statistics tell us that cancer is likely to strike as many as 1 out of every 3 Americans during their lifetime, and perhaps 20% of those afflicted will die of the disease; second, as cancer progresses, the body finds it more difficult to handle its growing tumor burden, clinical treatment can be protracted, and enduring it is invariably unpleasant. Cancer rarely ever cures itself. For the disease to be successfully treated, modern medical practice often requires that the cancerous tissue literally be cut out, and, in addition that radiation therapy and/or potent drugs be administered, which have unpleasant side effects such as nausea and loss of hair.

It used to be believed that cancer was not really a single disease like polio or tuberculosis, whose causes are traced to infection by a unique and well-understood virus or bacterium, but rather that there were more than 100 different types of human tumors, benign as well as malignant, each type affecting a different kind of cell or tissue, be it brain, pancreas, breast, or white blood cells. But, as explained below, the discoveries of modern molecular biology have caused us to change our point of view.

Peter Coleman using the High-Performance Liquid Chromatography equipment

There is one general and most significant feature recognized by both clinicians and scientific researchers alike – **all cancer cells proliferate uncontrollably**. Now, if humans were single cell organisms like bacteria, this might not pose much of a problem, since then our "object in life" would be merely to reproduce our unicellular selves as efficiently as possible. But since we are complex multicellular beings that contain over a *trillion* cells, the uncontrollable proliferation of a single aberrant tumor cell ultimately disrupts the delicate balance demanded by Nature if all our different cells and tissues are to work harmoniously together to make us function normally. Thus, cancer, left unchecked, makes our bodies progressively abnormal and unable to survive. The end result of such increasing abnormality is reached when, due to the growing tumor, the functional imbalance among our many cells and tissues reaches a limit no longer compatible with life. This is why cancer is so insidious.

All of us are aware that a lot of private and federal money continues to be well-spent on "cancer research". The outstanding medical achievements purchased with this money have included the discovery of more sensitive methods of cancer detection. This is important because it has been shown that if cancer is detected early, then clinical treatment is more certain of success. But what about the prospects of curing cancer outright?

THE ROLE OF BASIC RESEARCH

Let's not fool ourselves. It is generally recognized that the development of completely successful methods for treating cancer will not be forthcoming until scientists in the laboratory learn much more about the basic biology of cancer. Learning about the basic biology of any human disease involves many hours of painstakingly careful, detailed (and expensive) research well before such fundamental scientific findings can become part of the arsenal of clinical treatment.

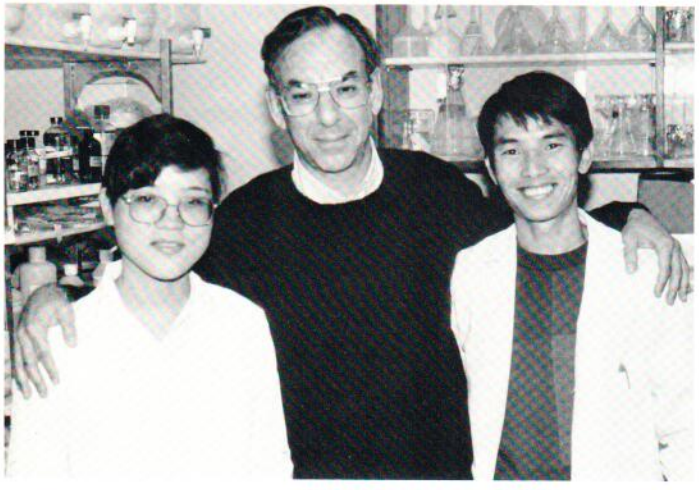
WHAT ARE ONCOGENES?

A major breakthrough in our understanding of the basic biology of cancer was the discovery of ***oncogenes***. These are genes which can cause our cells to "transform" from their normal into a cancerous state. After intensive research during the 1970's and 1980's, scientists were startled to learn that oncogenes are produced when otherwise normal genes within normal mammalian cells undergo a change, or mutation, which then renders them capable of causing cancer. Prior to this change or "mutational event", these otherwise normal mammalian genes are called *proto*-oncogenes (that is, *potential* cancer-causing genes). This means that our own proto-oncogenes have the capacity to undergo mutation and that this mutation may trigger the transformation of a normal cell to a cancer cell. It is sobering to realize that we humans always carry the benign, i.e., the unmutated, forms of the oncogenes in our chromosomes. Indeed, our normal cells bear the seeds of their own destruction!

The molecular details of how oncogenes promote this transition from a normal to a cancerous state are beginning to unravel only because of the power of basic research investigation. Our current understanding, at least insofar as clinical relevance is concerned, is still far from adequate. Yet, we know some important facts.

For instance, oncogenes (and proto-oncogenes), as part of the cell's DNA, encode information for making proteins which often turn out to be enzymes — enzymes being those vital protein molecules in all cells that take charge of speeding the chemical processes of life. Many of these oncogene-encoded enzymes are responsible for chemically modifying the molecular structure of certain other key cellular proteins, and by doing so, they actually *control* the way such key proteins perform specific tasks in the cell.

Think of the specific protein that the oncogene-encoded enzyme will modify as a kind of switch. Then consider that in the normal cell this protein switch is supposed to be "on" for a defined, limited time. Let's assume that after the oncogene-encoded enzyme chemically modifies the specific protein switch, it now remains "on" all the time. Surely, after a little while the cell will recognize that something different is happening, and indeed the presence of a constantly "on" switch will inevitably lead to a progressively different series of chemical events that change the behavior of the cell. Now, most cells in our bodies do not divide, or do so infrequently. But — continuing with our example — if the "on" switch *controls cell division* via a complex cascade of events, then the effect of the oncogene (remember, the switch was left "on", abnomally) ultimately is to encourage cells to keep multiplying *uncontrollably*!



Peter Coleman (center) with Willa Cai and Wenlong Ying

HOW DO ONCOGENES ACTUALLY WORK? A BRIEF STORY ABOUT *RAS*

Over years of research, biologists have devised the convention of calling specific genes by three-letter names. Thus, scientists designate oncogenes by names such as *ras*, *myc*, *erb*, *myb*, and many others that have been discovered since 1980. Since genes are pieces of DNA that code for the expression of individual proteins, each of these oncogenes specifies production of a unique protein. The daunting task of basic research in the biology of cancer is to answer three fundamental questions: **1)** What is the protein product of each oncogene? **2)** What does the protein do (e.g., is it an enzyme)? and **3)** How does the protein's molecular function in the cell correlate with the development of cancer (carcinogenesis)?

The story of the cellular oncogene *ras* and its protein product offers some insights into what we mean when we speak of "basic cancer research". The *ras* oncogene is a mutated form of a normal gene that codes for a protein called p21^{ras} (scientific jargon used to specify a **p**rotein with a molecular weight of **21**,000). What's special about *ras*? Scientific interest was sparked dramatically when it was found that one subtype of the mutant *ras* oncogene occurs in 95% of tumors isolated from pancreatic cancer patients, 40% of colon cancer patients, and 50% of patients with adenocarcinomas of the lung; overall, *ras* is present in about 30% of all human cancers! The fact that many different kinds of human cancer possess this mutant *ras* oncogene is strong evidence that just a few kinds of our normal proto-oncogenes, having undergone a mutation and acting in concert through their protein products, may be linked to the ultimate cause of cancer. Thus, the question now becomes: What is the function fulfilled by the p21^{ras} protein in our cells?

Many members of the *ras* family of proteins are now known. In the broadest sense, all of them act similarly — *as signalling molecules.* The p21^{ras} protein (both the non-mutant form in normal cells and the oncogene-derived mutant form in tumors) is known to behave as a "modifier" of the way in which various other cellular proteins function.

The biochemistry of how p21^{ras} acts inside the cell is the subject of intense research, but already is known to involve three features. Feature #1. - The p21^{ras} protein binds a molecule called **g**uanosine **t**ri-**p**hosphate (GTP), and clips off one phosphate to make **g**uanosine **d**i-**p**hosphate (GDP), which stays bound to p21^{ras}. Feature #2. - When the GTP is bound, i.e., *before* the phosphate is clipped off, p21^{ras} is "active" and can form complexes with various other proteins in the cell, many of which are associated with the cell's surrounding membrane called the plasma membrane. In the case of the normal *ras* protein, this active GTP-bound form is short-lived, as are the complexes it makes with other proteins. But, in contrast, the mutant oncogene *ras* protein seems to hang onto its GTP for a much longer time than the normal *ras* protein before clipping off the phosphate, and, thus, remains in the "active" state. As time passes, the cell accumulates a higher amount of the "active" (GTP-bound) p21^{ras}. Feature #3. - Virtually all members of the *ras* protein family become structurally modified by having a fatty molecule attached to one end of the p21^{ras} protein. This fatty molecule is called an isoprenyl chain, and the result is that p21^{ras} becomes, as the biochemists say, ***isoprenylated.***

Recent basic research has revealed the following consequences of the three features just mentioned. First, the active (mutant) GTP-bound, isoprenylated p21^{ras} protein, when it forms complexes with various other cellular proteins, particularly those associated with the cell membrane, signals a sequence of yet-to-be-understood events in the cell which result in transformation and the

Willa Cai and Wenlong Ying discussing the synthesis of chemical "tags" for prenylating enzymes

genesis of a cell whose control over proliferation has been lost — in other words, a cancer cell arises. Second, and most interestingly, this transforming phenomenon will not happen if, somehow, the isoprenylation of the mutant $p21^{ras}$ can be prevented.

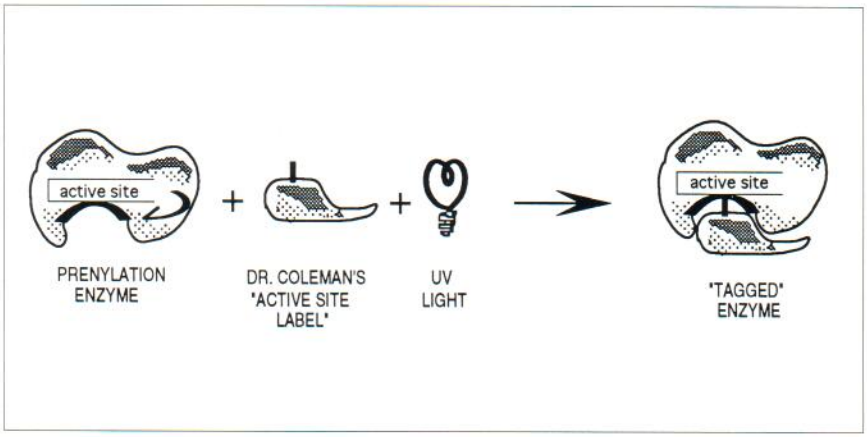
It turns out that the isoprenylation of $p21^{ras}$ can indeed be prevented! Unfortunately, scientists find that the current method, which prevents isoprenylation of the *ras* protein, also blocks one of the most important metabolic pathways required for life — the synthesis of cholesterol. So there must be a better way to prevent the isoprenylation of the *ras* protein without shutting down cholesterol synthesis as well. But to find the "better way" requires deeper knowledge about the molecular machinery of cells that allows proteins like *ras* to become isoprenylated. And this now brings us to a description of some of the basic cancer research currently underway at BBRI.

HOW DOES CANCER GET STARTED? ISOPRENYLATION OF PROTEINS

Protein isoprenylation, which was discovered only about 7 years ago, cholesterol synthesis, cell division and cancer are all intimately linked phenomena, according to Peter Coleman, who just joined BBRI in June as Senior Scientist after many years as Professor of Biochemistry at New York University. A major research investigation currently underway in Dr. Coleman's laboratory involves the enzymes responsible for protein isoprenylation and their role in the control of cell division and cancer.

Dr. Coleman explains, "We know that of the thousands of cellular enzymes, a few specific ones control the process of protein isoprenylation, such as that of the *ras* protein family. Along with other scientists around the world, my lab is exploring the molecular characteristics of these special enzymes. This work is in its early stages, and though we are making exciting progress, the extent of our understanding is not yet mature enough to apply our knowledge to the arsenal of medical weapons against cancer. Surely, that day will come as we continue to uncover the molecular acrobatics of these growth-regulating enzymes and learn precisely how they function in our cells."

In order to gain the necessary understanding of these protein-prenylating enzymes, Dr. Coleman has devised a most promising experimental approach. Using a unique type of chemical which he synthesizes, he figured out a way of "tagging" these prenylating enzymes precisely at that location on their molecules where they carry out their catalytic function— at their so-called "active site". The method is interesting because it makes use of *ultraviolet light* as the means of activating his chemical labels for tagging the prenylating enzymes, as the diagram below illustrates:



Once the enzyme is "tagged", Dr. Coleman says, two vital pieces of knowledge will become accessible to scientists. For one thing, it will become possible for them to cut apart the "tagged" enzyme into small fragments, and isolate the one that contains the chemical label fastened to it. In this way scientists can learn precisely where on the molecular structure of the prenylating enzymes they perform their chemistry; in other words, the exact amino acids and their shape in space at the "active site". Second, it also becomes possible to think seriously about designing, using today's advanced computer technology, man-made molecules as potential anti-cancer drugs that could fit, like a hand in a glove, into this precisely defined active site, and by blocking it, prevent the enzyme from working.

If the function of the protein-prenylating enzymes is crucial to the complex picture of cell growth and proliferation (and thus cancer), as in the case of *ras* oncogene protein, then it is an equally crucial item on today's scientific research agenda for scientists to discover exactly how these enzymes work, how their functions in the cell are controlled, and how one might modify these functions when they go awry.

HOW DOES CANCER GET STARTED? -TUMOR PROMOTERS AND THE PHOSPHORYLATION OF PROTEINS

We have just seen that the modification of certain proteins by isoprenylation can lead to uncontrolled cell proliferation and ultimately to cancer. This does not mean that cancer has a biochemically unique cause. On the contrary. The onset of cancer also involves other types of modification such as protein phosphorylation, the process by which phosphate is chemically joined to proteins. This insight has come from the study of specific molecules known as tumor promoters.

John Badwey and Jia-Bing Ding

Exposure of an organism to certain chemicals can increase the likelihood that it will develop cancer. Such chemicals are called tumor promoters. Some of the most powerful tumor promoters are natural products of plants and blue-green algae. The list includes exotic substances with tongue-twisting names such as phorbol esters, okadaic acid, and calyculin A, but also chemicals that are found in familiar objects such as celery stalks. For many years, the biochemical mechanisms by which these tumor-promoting compounds predisposed a tissue to malignancy were completely unknown. However, investigations in several laboratories have dramatically increased our knowledge in this area over the last decade. One such study is being carried out in the laboratory of John Badwey, a Principal Scientist who came to BBRI from the Harvard Medical School in 1989.

Protein phosphorylation is one of the control mechanisms by which the growth of cells and a variety of other important biological functions are regulated. These functions include combating bacterial infections, a process which has been studied in Dr. Badwey's laboratory for some years. Addition and removal of phosphate to and from proteins is carried out by two types

of enzymes, respectively called protein kinases and protein phosphatases. In 1982, it was discovered that tumor promoters, such as the phorbol esters, stimulate the activity of a particular kind of protein kinase. Other tumor promoters such as okadaic acid and calyculin A were found to inhibit the major protein phosphatases in cells. Note that the stimulation of protein kinases and the inhibition of protein phosphatases achieve the same net effect – a build-up in the amount of phosphorylated protein. All of the most powerful tumor promoters that have been characterized to date increase the amount of phosphorylated proteins in cells. Major questions remain about this process. Does cancer result from increases in one particular type of phosphorylated protein or of several different kinds? What are the normal functions of these phosphorylated proteins in cells? Do tumor promoters mimic chemicals that are normally involved in cellular regulation? Dr. Badwey, together with Jia-Bing Ding, a research fellow, is studying the interactions of tumor promoters with white blood cells. One hopes their work may provide answers to some of these questions. The insights gained from this research may play an important role in cancer prevention.

John Codington (center) with Samantha Matson and Zibin Wu

HOW CAN CANCER BE DETECTED? EPIGLYCANIN AND HUMAN CARCINOMA ANTIGENS

The unprecedented progress in the biomedical sciences during recent years has resulted mainly from the development of new techniques in molecular genetics. Yet, despite the accumulation of vast amounts of information on the biology of cancer, including the discovery of oncogenes and their possible role in cancer, very little has actually changed during this period with regard to the ways in which cancer is diagnosed and treated. Needless to say, current methods fall far short of what is needed in the face of the nearly epidemic proportions in which malignant diseases are occurring in our modern societies. Research by John Codington, who came to BBRI as a Senior Scientist in 1986 from the Massachusetts General Hospital, offers hope for improved methods for the diagnosis and therapy of carcinomas (that is, cancers derived from epithelial tissue), which account for more than 80% of all cancers and include cancers of the breast, prostate, colon and lung.

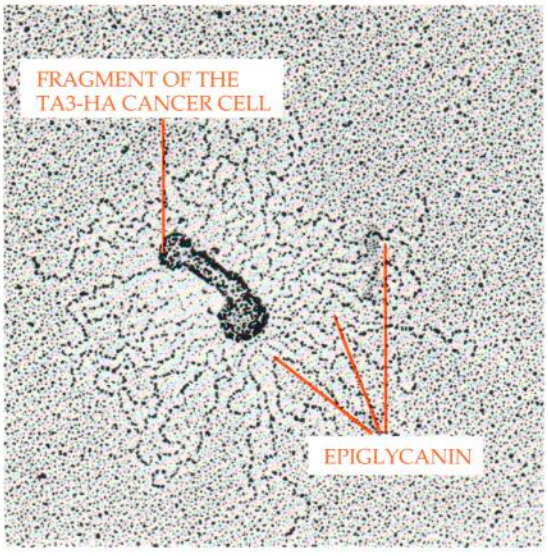
This story began in Dr. Codington's laboratory at the Massachusetts General Hospital with the 1972 discovery of a long filament-like glycoprotein molecule in breast cancer cells from a certain strain of mouse. Glycoproteins, which are molecules composed of both protein and sugar chains, are often found associated with cell surfaces. This glycoprotein, which Dr. Codington christened "epiglycanin," was found to be present in high concentrations at the surface of the carcinoma cells and was seen by electron microscopy to cover the cell very much like

spruce trees might cover a mountain in Vermont. Indeed, this glycoprotein coat was found to protect the cancer cells from attack by the body's own white blood cells and antibodies, and its presence enabled these cancer cells to grow in all strains of mice, as well as in certain other species, such as the rat and the hamster. The ability of the malignant cells to escape destruction was found to be due, in part, to the large proportion of sugar in the epiglycanin molecule. The protein backbone of epiglycanin, to which the sugar chains are attached, represents only about 20% of its mass, the rest being the sugar portion. When viewed in the electron microscope, isolated molecules of epiglycanin appear as elongated rods. They are also seen as long filaments emanating from the surface of carcinoma cells or from membrane particles isolated from the cell surface, as shown in the illustration below.

Unexpectedly, Dr. Codington discovered that an antibody to epiglycanin, produced in a rabbit which had been immunized with epiglycanin, recognized not only epiglycanin but also a related glycoprotein present in human carcinoma cells. This glycoprotein, which he called Human Carcinoma (HC) antigen, like epiglycanin in the mouse, is shed into the blood from proliferating cancer cells. It was possible to detect very small amounts of the HC antigen in the blood by using a test employing the rabbit antibody and radioactive epiglycanin. This test was employed in double-blind studies of serum or plasma obtained from humans with or without carcinomas. Blood from about 75% of the cancer patients tested was found to contain the HC antigen, whereas little or no antigen was detected in the blood from normal individuals.

With the support of biotechnology funds, a program of research was initiated at BBRI in 1986 to study the possibility of developing a reliable immunoassay for the HC antigen with mouse monoclonal antibodies to epiglycanin, rather than the rabbit antibody. Such a test might achieve worldwide use to diagnose the presence of cancer and to monitor the effectiveness of cancer therapy in patients. Dr. Codington is now testing large numbers of monoclonal antibodies to epiglycanin for their capacity to identify the HC antigen and is collaborating with Dr. Svein Haavik of the University of Oslo in the development of a diagnostic immunoassay and the characterization of the HC antigen. Prospects for the future success of this project appear good.

It is anticipated that monoclonal antibodies specific for the HC antigen might also be used in the radio-imaging of tumors and in the immunotherapy of cancer. In collaboration with Dr. Rashid Fawwaz of the College of Physicians and Surgeons, Columbia University, Dr. Codington is investigating



By electronmicroscopy, epiglycanin can be seen attached to a fragment of the surface of the TA3-HA cancer cell. (Magnification 64,000X)

whether a monoclonal antibody specific for the HC antigen, after labelling with a radioisotope, can be used for establishing the locations of tumors in the cancer patient. Another project, which is being performed in collaboration with Dr. Soldano Ferrone of New York Medical Center, examines the possibility that antibodies against HC antigen-specific antibodies, so-called anti-idiotypic antibodies, can be used in cancer immunotherapy.

Samantha Matson and Zibin Wu doing an antibody capture assay

HOW CAN CANCER CELLS BE KILLED? THE QUEST FOR THE "MAGIC BULLET"

In 1898 Paul Ehrlich proposed the idea of using a molecular carrier with affinity for a particular organ to deliver a drug to its designated target. Ideally, the activity of a therapeutic agent might in this way be sharply focused on a diseased tissue, while normal, healthy cells would remain unaffected. A testimony to the attractiveness of this simple concept is the fact that today, nearly one hundred years later, we are still striving to bring it to fruition. Despite this ardent quest, we are still not certain whether a "magic bullet" strategy can, in fact, provide the basis for a truly effective and practical mode of cancer therapy. Continuing efforts toward this end are nevertheless justified because rapid biotechnological advances are providing new tools for the design of very sophisticated "bullets". However, in order to design such targeted drugs, it is essential that we understand the molecular, cellular and pharmacological mechanisms that underlie their action.

Conventional surgery can excise tumors en masse. But surgery holds no answer for tumors disseminated widely throughout the body. On the other hand, to be successful a magic bullet approach must target and identify individually every malignant cell in the body and kill *only* these. The enormity of this task is illustrated by the fact that even a malignant tumor the size of a small marble can contain over a *billion* cells, and frequently a cancer patient's tumor is tens of times larger. Elimination of these cancer cells must be accomplished in the presence of a vast excess of normal cells, which the magic bullet, like a guided missile, must leave unharmed. Indeed, this would be a tremendous accomplishment! Until recently, realization of the full potential of the magic bullet approach has been stymied by a lack of suitable technology. However, there is new promise in this approach through the combined application of modern methods of toxicology, genetic engineering and the production of special immunological molecules called "monoclonal antibodies".

Dr. Vic Raso, a Senior Scientist who joined BBRI in 1988 from the Dana Farber Cancer Institute, is applying these techniques to his research program's goal of recognizing, attacking and ultimately killing *only* cancer cells. Dr. Raso tells us that monoclonal antibodies, produced in the laboratory by cells grown in tissue culture outside of the living animal, comprise a class of immunologically active proteins tailored to recognize and bind tightly to

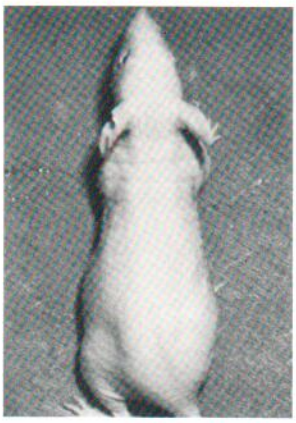
specific regions of other molecules. Each monoclonal antibody will seek out a unique portion of another molecule's structure. In a mixture of thousands of different molecules, one, and *only one* molecule can be selectively recognized by a specific monoclonal antibody and will bind to it to the exclusion of all other molecules in the mixture, even those that resemble (but do not exactly match) the one against which the monoclonal antibody was designed. Dr. Raso explains that cancer cells possess on their surface certain molecules that distinguish them from normal cells. So the first task is to search out these cancer-specific molecules and attempt to construct a spectrum of monoclonal antibodies that would recognize and bind *only* to these specific cancer cell surface "marker" molecules, a concept so important that research on this aspect alone is ongoing worldwide.

Dr. Raso's interest in applying aspects of toxicology to cancer was stimulated by the knowledge that certain non-human toxic proteins (such as the bacterial diphtheria toxin, or DT) kill human cells. DT does this by blocking the cell's ability to synthesize its own proteins. DT is lethal only when a particular portion of its molecular structure is taken into the cell. Given all the above, he asks: How might these two features of cancer cell recognition and selective cell killing be technologically linked so that a future clinical program would be able to target only cancer cells with a monoclonal antibody, then selectively kill them with a cellular toxin like DT?

Using a model system consisting of mice with tumors of human origin, Dr. Raso has already demonstrated that DT (to which mice are normally insensitive) kills all of the human tumor cells and dissolves large solid human tumor masses, while leaving the mouse unscathed and fully recovered within 10 days! Now, via genetic engineering and other state-of-the-art laboratory methods, he is attempting to devise efficient use of structurally altered yet potentially lethal toxin molecules, such as a modified version of DT. The key feature of such altered toxins is that they are *engineered* so that they cannot penetrate cells by themselves, although, if they could find their way inside, they would be lethal, as with native (unmodified) DT. Dr. Raso has available several such modified toxin molecules. They may be likened to disarmed bombs waiting for someone to set the "on" switch and make them explosive. This might be achieved if, somehow, the modified toxin could be complexed with molecules - say monoclonal antibodies - that carried them into cancer cells and then released them. But how might such a selective entry *only into cancer cells* be accomplished? How could the scientist fool only the cancer cell into taking up the disguised toxin, while leaving all normal cells unaware of the potential molecular executioner in their midst?

Applying the ingenious methods of modern biological research, there may now be a way. Suppose that a monoclonal antibody were to be constructed that would not only specifically recognize and latch onto

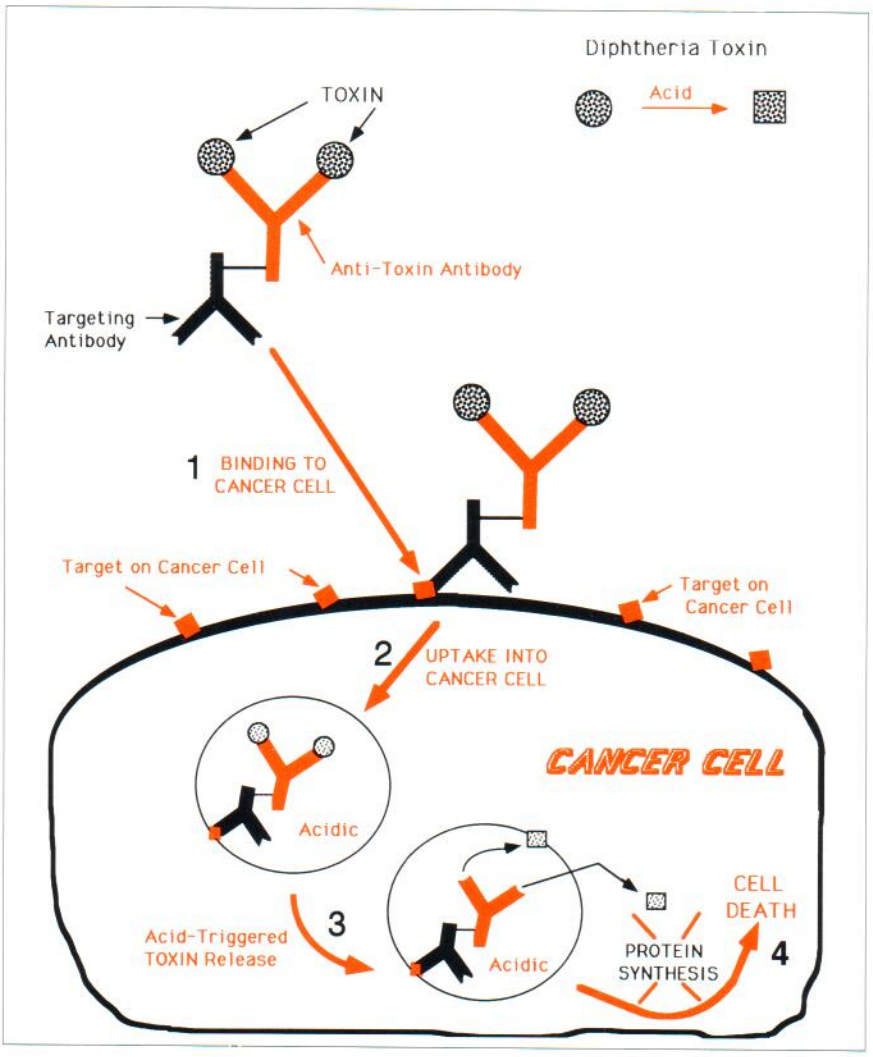
A mouse with advanced cancer tumor of human origin



Same mouse, fully recovered within 10 days of treatment with 1 microgram of diphtheria toxin

tumor cells but at the same time grasp the modified toxin. Such a man-made *hybrid monoclonal antibody* molecule would then carry the modified toxin "piggy-back", while it became selectively bound to, and then entered, cancer — but no other —cells. Such a complicated molecular delivery vehicle would indeed constitute a "magic bullet" against cancer because only those cells possessing the tumor-specific surface marker molecule would be targeted. Dr. Raso's strategy, then, is to create a molecular complex consisting of the cancer cell-specific *hybrid* monoclonal antibody linked at one end to the modified toxin; the other end of the antibody, in turn, would selectively bind to the cancer cell's surface. Such a complex is illustrated in the accompanying diagram.

The ultimate goal of Dr. Raso's molecular manipulations is, of course, to insure that once a cancer cell takes up this nominally disarmed toxin, and the toxin is released in its active lethal state inside, then the cancer cell, and *only* the cancer cell, will die. If the power of modern basic research continues to provide us with such marvelous insights and promising new methods, Paul Ehrlich's dream of the "magic bullet" may soon become reality in our struggle to conquer cancer.



Magic bullet delivery system

PUBLICATIONS

September 1991 - August 1992

An important part of research is the communication of scientific discovery so that the knowledge gained can help new research as well as benefit clinical studies directed towards curing or preventing disease. The dissemination of new research findings is achieved primarily by publication in scientific journals. Over the past year, BBRI investigators have published the following papers:

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Ikemoto, N., B. Antoniu & J-J. Kang, 1992. Characterization of "depolarization"-induced calcium release from sarcoplasmic reticulum in vitro with the use of membrane potential probe. Biochem. Biophys. Res. Commun. 184: 538-543.

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THANKSGIVING DINNER
AT BBRI - ERI

Zenon Grabarek, Terry Scott, and two ERI colleagues enjoy turkey and all the fixings

Pat Brouillette takes a moment's respite before dessert

Tino Bozzella keeps the cider glasses coming

Mary Caulfield, John Gergely, and Carol Burke await the "next seating"

Thank you!

It is a great pleasure to report that the Amelia Peabody Charitable Fund has established a generous endowment for support of a second Amelia Peabody Senior Scientist at BBRI. This resource is pivotal to our success in recruiting outstanding senior scientists. Another crucially important foundation grant is enabling us to bring aboard next spring a young researcher whose innovative work in developmental biology will further broaden our horizons.

All told, members of our Board and Corporation together with other good friends - the individuals, foundations, and businesses listed on these two pages - contributed over $120,000 to the Annual Research Fund, which is unrestricted, and another $376,000 for restricted uses. The Annual Research Fund provides for such essential and ongoing needs as seed money to test promising new research leads, while the restricted-use funds this year are largely capital gifts contributed to support recruitment of scientists and related needs.

Many, many thanks for your support in furthering BBRI's unique contributions to the ongoing fight against disease. Your gifts make an important difference at BBRI!

William B. Tyler
Chairman

Foundations and Businesses which generously gave us their support and encouragement in fiscal 1992:

Anonymous
Analytical Biotechnology Services
The Boston Foundation/Leith Family Fund
Combined Jewish Philanthropies of Greater Boston/Sumner & Carol KaufmanFund
Connor Foundation
Eaton Foundation
Elfers Foundation
Henderson Foundation
Hurdle Hill Foundation
Evander Lewis Family Foundation
Lynn Jachney Charters, Inc.
Millipore Foundation
New England Biolabs
Amelia Peabody Charitable Fund
G. Gorham Peters Trust
The Harold Whitworth Pierce Charitable Trust
Fred M. Roddy Foundation
Theo M. Sanders Fund
The Shane Foundation
Sholley Foundation
Tamarack Foundation
Taplin Charitable Lead Trust
John J. Vecchi, CPA
Zoion Research, Inc.

The friends who contributed major restricted-use gifts:

Anonymous
Ernest and Mary Louise Henderson
Amelia Peabody Charitable Fund

The friends who contributed the unrestricted gifts which comprise the Annual Research Fund:

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John Shane, Trustee and former President, speaking about the desk display of DNA that he presented to each of the retiring members of the Corporation

Corporation member Ruth Darling with newly-elected member Charlie Ives

Peter Kliem, newly-elected Trustee, with Board member Jack Buchanan

Early arrivals for a meeting of the Nominating Committee: seated, Katherine Babson and Kent Coit; standing, Edgar Davis, Joe McCullen (Committee Chairman), and John Gergely

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Gifts were given in memory of
Horace W. (Hoddy) Cole
-by Pamela and Robert Adams
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Geoffrey Nunes
John and Jane A. Paine
Paul and Miriam Rooney
Elizabeth C. Stephens
Mr. and Mrs. William A. Whittemore
Jack Seidel
-by Mrs. Julius C. Ritter
Elizabeth Maclean Slayter
-by Hugh Maclean

Corporation member Ron Garmey (center) with new Corporation members Robert Greeley and Tom DiBenedetto

BBRI Treasurer, Ernie Henderson, with new Corporation member Allie Blodgett

New Corporation member Kent Coit with (at left) his wife, Gail Mazzara, and Ana Maria Garcia, wife of senior scientist Terry Tao.

Corporation member Bernie Fields (center) with Rao Sanadi, Director of the Department of Cell & Molecular Biology, and John Gergely, Executive Director

BOSTON BIOMEDICAL RESEARCH INSTITUTE, INC.

BALANCE SHEETS

AUGUST 31, 1992 AND 1991

	1992	1991
ASSETS		
CURRENT ASSETS		
Cash	$ 415,661	$1,231,708
Grants receivable	3,409,939	2,871,111
Prepayments, deposits and other receivables	168,404	166,434
Investments, at market value (cost 1992 - $4,927,072 1991 - $3,998,755)	5,771,907	4,748,327
Total current assets	9,765,911	9,017,580
FIXED ASSETS		
Leasehold improvements	1,935,632	1,935,632
Research equipment	4,893,498	4,782,484
Total	6,829,130	6,718,116
Less accumulated depreciation	5,514,645	5,278,790
Net fixed assets	1,314,485	1,439,326
	$11,080,396	$10,456,906
LIABILITIES AND FUND BALANCES		
CURRENT LIABILITIES		
Accounts payable and accrued expenses	$ 31,032	$ 60,837
Deferred grant income	3,643,024	3,118,424
Deferred fund (building)	115,702	115,702
Total current liabilities	3,789,758	3,294,963
FUND BALANCES		
Unrestricted	5,305,708	5,274,873
Restricted	670,445	447,744
Fixed assets	1,314,485	1,439,326
Total fund balances	7,290,638	7,161,943
	$11,080,396	$10,456,906

BOSTON BIOMEDICAL RESEARCH INSTITUTE, INC.

STATEMENTS OF REVENUES, EXPENSES AND CHANGES IN FUND BALANCES

FOR THE YEARS ENDED AUGUST 31, 1992 AND 1991

	1992	1991
REVENUES		
Grants and contracts	$4,256,384	$5,262,400
Unrestricted contributions	137,432	113,686
Restricted contributions availed of in current period	203,829	19,629
Property and equipment purchased	111,014	152,216
Investment income		
Interest and dividends	211,138	291,755
Realized and unrealized gains on securities during period	367,859	630,051
Total	5,287,656	6,469,737
EXPENSES (by department)		
Muscle Research	2,272,835	2,296,862
Cell and Molecular Biology	1,216,381	1,661,153
Metabolic Regulation	873,696	1,091,196
General Research	639,621	566,331
Fund Raising	74,931	65,252
Purchase of fixed assets	16,272	21,482
Depreciation	235,855	320,181
Write off - subsidiary advances	541	11,148
Total	5,330,132	6,033,605
EXCESS OF REVENUES OVER EXPENSES (EXPENSES OVER REVENUES)	(42,476)	436,132
Restricted contributions	375,000	96,129
Restricted contributions availed of in current period	(203,829)	(19,629)
FUND BALANCES, BEGINNING OF YEAR	7,161,943	6,649,311
FUND BALANCES, END OF YEAR	$7,290,638	$7,161,943

Copies of our complete, audited financial statements, certified by the independent accounting firm of John Vecchi, CPA, are available upon request from the Controller, Boston Biomedical Research Institute.

BOSTON BIOMEDICAL RESEARCH INSTITUTE, INC.

GRANTS, CONTRACTS AND FELLOWSHIPS

Principal Investigator	Title	Duration of Grant	Total Award
NATIONAL INSTITUTES OF HEALTH			
Program Project Grant			
Dr. Wang	Molecular mechanism of smooth muscle regulation	9/92 - 8/97	$ 6,000,000*
Research Grants			
Dr. Badwey	Synergistic stimulation and priming of neutrophils	7/90 - 6/95	960,000
Dr. Coleman	ATP binding site photoaffinity probes for F1 - ATPase	6/92 - 5/96	748,000*
Dr. Gergely (MERIT)	Biochemistry of muscle contraction	7/89 - 6/94	2,844,000
Dr. Grabarek	Calcium binding protein/target interactions	6/92 - 5/95	600,000*
Dr. Graceffa	Tropomyosin in muscle regulation	7/87 - 6/93	741,000
Dr. Ikemoto	Structure and function of sarcoplasmic reticulum	7/92 - 6/96	1,674,000*
Dr. Joshi	Molecular mechanisms of mitochondrial ATP synthesis	9/92 - 8/95	802,000*
Dr. Lehrer	Tropomyosin and myosin interaction in muscle	12/90 - 11/95	1,546,000
Dr. Lu	Structure-function relation in myosin	9/91 - 8/95	819,000*
Dr. Pande	Protein glycation: structure and stability of products	7/91 - 6/94	548,000
Dr. Paulus (Shannon)	Control of the aspartokinase isozymes in Bacillus	9/91 - 8/93	100,000*
Dr. Prevelige (Shannon)	Subunit interaction during icosahedral capsid assembly	9/92 - 8/94	100,000*
Dr. Raso	Targeting toxins with acid - triggered hybrid antibodies	12/89 - 11/94	1,234,000
Dr. Raso	Model to test the therapeutic value of toxin conjugates	9/92 - 8/95	769,000*
Dr. Stafford	Engineered anti - breast cancer single - chain Fv immunotoxin	6/90 - 5/95	646,000
Dr. Tao (MERIT)	Proximity relationship among muscle proteins	4/91 - 3/96	1,359,000
Dr. Volloch	Antisense intron as modulator of gene expression	12/88 - 11/93	1,289,000
Dr. Volloch (Shannon)	Mechanisms of RNA editing	9/91 - 8/93	100,000*
Dr. Wang	Comparative study of troponin C and calmodulin	7/88 - 6/93	631,000
Dr. Wohlrab	Proton-coupled inorganic phosphate transport	4/92 - 3/96	1,181,000*
Fellowships			
Dr. Kalapos	Identification of replication origin in the dystrophin gene	9/92 - 8/94	71,000*
Dr. Roten	Characterization of Bacillus subtilis aspartokinase I	9/92 - 8/94	53,000*
NATIONAL SCIENCE FOUNDATION			
Research Grants			
Dr. Lehrer	Microspectrofluorometry of oriented myofibrils	3/89 - 2/93	230,000
Dr. Paulus	Regulation of amino acid biosynthesis	3/92 - 8/94	160,000*
AMERICAN HEART ASSOCIATION			
Research Grants			
Dr. Joshi	Role of OSCP in mitochondrial energy coupling	7/91 - 6/94	32,000
Dr. Tao	Structure and function of genetically engineered calponin	7/92 - 6/95	176,000*
Dr. Wang	Caldesmon - myosin interaction in smooth muscle regulation	7/90 - 6/93	114,000
Established Investigator			
Dr. Wang	Caldesmon - Calmodulin - Its role in smooth muscle regulation	7/88 - 6/93	175,000
Fellowships			
Dr. Szczesna	Fluorescence microscopy of thin filament proteins in myofibrils	1/91 - 12/92	35,000
MUSCULAR DYSTROPHY ASSOCIATION			
Research Grant			
Dr. Ikemoto	Excitation - contraction coupling in malignant hyperthermia	7/91 - 6/94	126,000
OTHER			
Research Contract			
Dr. Codington	Carcinoma assay research project	3/92 - 2/93	277,000*

* New grants and contract awarded in Fiscal 1992

Design and production control
Furtado Communication Design

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