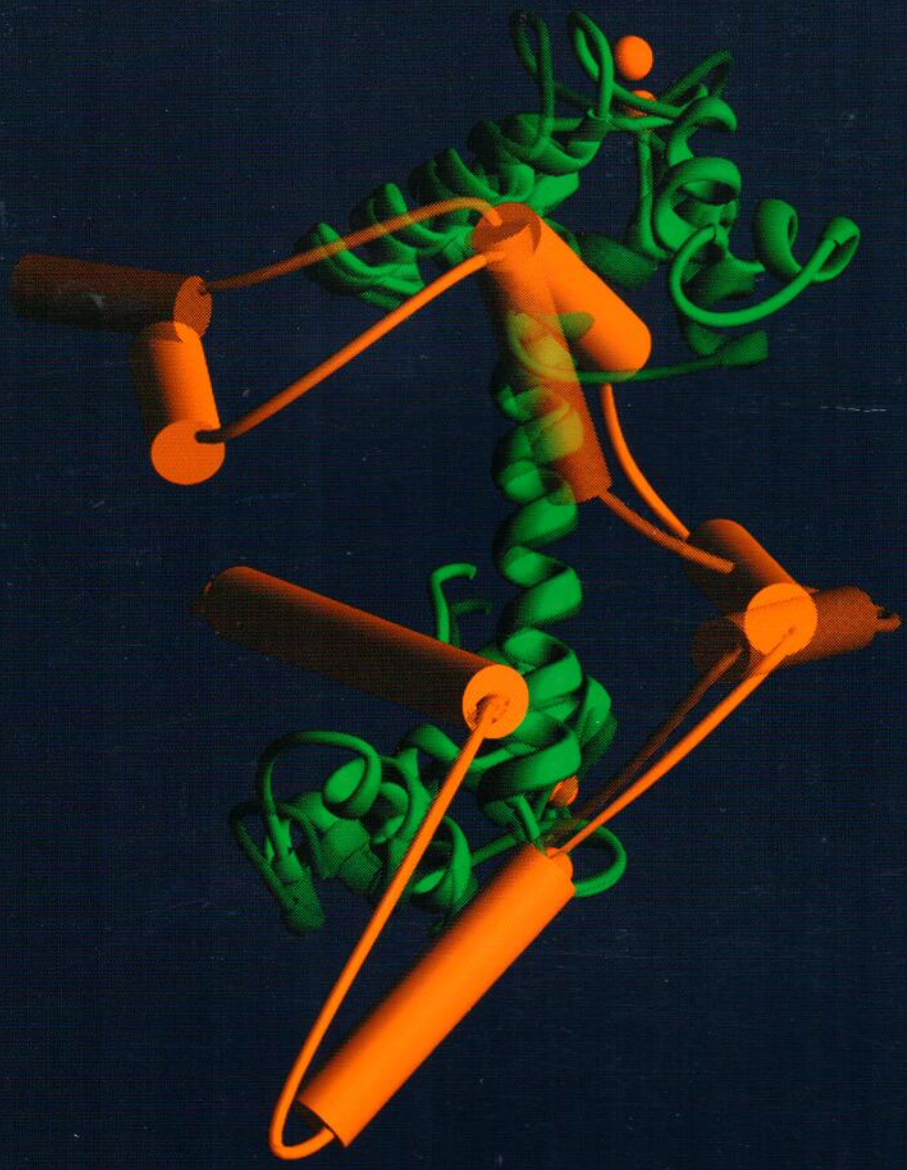
BOSTON BIOMEDICAL RESEARCH INSTITUTE



ANNUAL REPORT 1999

THE FUTURE HOME OF

BOSTON BIOMEDICAL RESEARCH INSTITUTE

"The new facility has clearly been scientist-designed (with good help from DTS Shaw Associates) and will be a tremendous boost to the programs of the Institute. The floorplan maximizes lab space and keeps administrative space to a bare-bones level. The larger facility will allow us to continue this era of remarkable growth in the number of active research groups—and in the size and productivity of each group. This will give us the critical mass to allow each program to "take wing" and reach its full potential which, of course, translates into an increasingly rapid pace of discovery of new potential cures and technologies."

— Kathleen G. Morgan, Ph.D., Message from the Director

HISTORY OF BBRI

1950 The Retina Foundation is founded by Charles Schepens.

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

1961 John Gergely joins the Foundation to initiate a program in muscle research which subsequently became internationally prominent.

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

1964-66 The research facilities at 20 Staniford Street are enlarged and scientists in other areas of basic biomedical research, such as bioenergetics and developmental biology, are recruited so as to provide a well-rounded biomedical research program to complement the Institute's clinical eye research efforts.

1970 The Retina Foundation evolves into two separate institutions: the Boston Biomedical Research Institute, which is granted a rent-free 50-year lease of one-half the space at 20 Staniford Street, and the Eye Research Institute of the Retina Foundation, which is now known as the Schepens Eye Research Institute.

1972-1979 BBRI's muscle research program makes fundamental contributions to the characterization of the proteins that constitute skeletal muscle. These included the elucidation of the role of the troponins, which are important regulatory components of skeletal and heart muscle and have come to play a key role in the early diagnosis of heart attacks.

1982 BBRI files its first patent application in the area of immunotechnology and receives corporate research support for further research in this field. This patented technology has now been licensed to a biopharmaceutical company for use in cancer immunotherapy.

1990's A major program in smooth muscle research is initiated at BBRI with the support of a $6 million program project grant from the NIH.

1995 With the appointment of Kathleen Morgan as BBRI's Director, the Institute focuses on three major areas - cell motility, cell communication and cell growth - and begins an aggressive faculty recruitment program in these research fields.

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

MISSION

Boston Biomedical Research Institute

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.

MESSAGE FROM

The President

Just prior to the start of 1999, Dr. Sam Lehrer, BBRI Senior Scientist, gave an invited talk at the International Institute for Advanced Research Symposium 1998 entitled "Cooperativity in the Regulation of Muscle Contraction". Fittingly, the operative word "cooperativity" fairly describes the activity of the BBRI family this year.

My message last year spoke of the necessity of implementing a facilities plan consistent with BBRI's vision of its future programs. Sale of our lease at 20 Staniford Street and purchase of property at 64 Grove Street, Watertown occurred early in fiscal 1999. The site selection, financing, planning and construction of this new research facility have been the focus of our energies this year.

In keeping with the organizational structure of the Institute, the entire faculty has been involved in site selection and planning of the facility. Grove Street was selected by faculty consensus. Laboratory design, from the broad concept of open laboratory space to the detail of laboratory color scheme was decided by faculty vote in concert with DTS Shaw Associates, the architects. The many faculty meetings, led by Dr. Morgan, were often spirited as opinions were strongly voiced, but issues were always resolved and choices made in a timely manner. The faculty is to be commended for the cooperative spirit shown throughout the process.

A special construction finance committee lead by trustee Mr. Shane and composed of faculty members Dr. Morgan and Dr. Wang and corporation members Mr. Henderson, Mr. Layton, Ms. Huang and myself guided the financing of the project working with BBRI's Chief Financial Officer, Thomas McQuaid, and the bond underwriters, State Street Bank and Trust Company. Construction oversight is provided by the joint committee of Drs. Grabarek, Morgan and Paulus of the faculty and corporation members Dr. Blout, Dr. Comb, Mr. Getschow, Mr. Nunes, Mr. Shane and myself, in concert with Thomas McQuaid and the Siena Construction Corporation.

"We could not have achieved what we have today without the exemplary cooperation among all the BBRI family. I cannot thank you enough."

In October 1998 we set a very ambitious target to locate, construct and occupy a new laboratory. We are currently mid-way through construction and remain on schedule. Beginning with site selection to the current construction phase, we could not have achieved what we have today without the exemplary cooperation among all of the BBRI family. I cannot thank you enough.

The new laboratory is but one step in fulfilling our vision of performing critically important research in cell motility, cell growth and signal transduction in the 21st Century. Expanding our research programs and increasing our faculty with the bright stars of the future are important steps. Funding this future will require a major commitment from all of us, but with the "cooperativity" demonstrated so far I am confident we shall reach our goal.

— David A. Gibbs, Sc.D.

MESSAGE FROM
The Director

This has been a year when our motto: "Laying the Foundation for a Healthier Future" seems especially appropriate. Not only have BBRI scientists been pushing back the frontiers of our knowledge with their cutting edge fundamental research, but we've also had the pleasure of literally watching as a new foundation for BBRI has been laid at 64 Grove St.

The new research facility has clearly been scientist-designed (with good help from DTS Shaw) and will be a tremendous boost to the programs of the Institute. The floorplan maximizes lab space and keeps administrative space to a bare-bones level. The larger facility will allow us to continue this era of remarkable growth in the number of active research groups—and in the size and productivity of each group. This will give us the critical mass to allow each program to "take wing" and reach its full potential which, of course, translates into an increasingly rapid pace of discovery of new potential cures and technologies.

In the past year we've seen discoveries from our signal transduction group on the kinases, PAK, MAPK, PKC, PI-3K and PDK. That may sound like alphabet soup to many of you, but these discoveries relate to potential cures for inflammatory disease, heart failure and cancer. Our cell growth group has reported advances on heat shock proteins, catalytic antibodies

"Our primary mission continues to be the performance of fundamental biomedical research, which promotes the understanding, treatment, and prevention of human diseases."

and protein splicing which have resulted in very real technological advances, invention disclosures and patents pending, some of which are already listed on our homepage (www.bbri.org). These advances offer promise of progress in the battles against heart failure and Alzheimer's disease and in providing new tools for the genetic modification of plants and animals as better sources of food and biopharmaceuticals. Our motility/cytoskeleton group has visualized the molecular basis of movement with the sophisticated techniques of crystallography, fluorescence and mass spectroscopy and optical tweezers. Again, these techniques are not household terms, but cell movement is fundamental to processes ranging from brain development to cancer metastasis.

Modern science is becoming increasingly sophisticated and, hence challenging to communicate. But, to quote the Medical Foundation: *"Basic research is the key to progress in science and medicine. There can be no new treatments, no new cures, without the new knowledge that basic research provides."* Our supporters realize this and we thank them.

This issue of the Annual Report is focused on tracking one specific area of investigation in which the BBRI has played a leading role over several decades—the troponin story. We know now that troponin is necessary for the heart to beat and for us to move our arms and legs. Since 1996, troponin has been widely used as one of the earliest indicators of heart attacks. Recently mutations have been linked to certain types of hereditary heart disease and, through a spectacular example of scientific serendipity, troponin has been identified as one of the most promising candidates for cure of cancer by antiangiogenesis therapeutics.

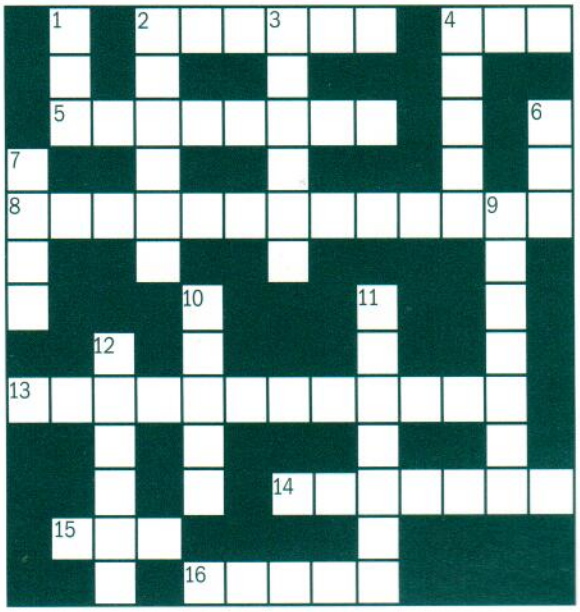
I hope you enjoy reading the story and, as always, if you'd like to learn more, don't hesitate to stop by and ask for a tour of our new facility!

— Kathleen G. Morgan, Ph.D.

The Troponin Story

BASIC RESEARCH AND SERENDIPITY

Many of us enjoy solving crossword puzzles. Each clue poses an intellectual challenge, and as we progress, the letters of the words with which we fill the blank spaces provide additional clues, so that the puzzle gradually becomes easier until we have the satisfaction of seeing every space in the square filled with a letter. To us scientists, basic research represents a similar challenge, except that the puzzle has no boundaries. While the answers that we find improve our understanding of nature and through medical applications inevitably improve our lives, the new questions lead us to ever new problems that we could not even have imagined when we began. This is what makes basic biomedical research so exciting: no matter how esoteric the question with which we start, we cannot predict where our search will lead us, and along the way we may happen upon solutions to apparently unrelated medical problems. This process of unexpected discovery — or serendipity — is inherent in the very nature of basic research. The story told in this year's Annual Report is an excellent illustration of this aspect of basic biomedical research. It starts with a simple biological problem — how does muscle contract? — continues on a long journey that leads to the discovery of ever more complex molecular machines, and along the way leads us to insights into inherited forms of heart disease as well as to unexpected medical applications, including, early markers for heart attacks and possible inhibitors of tumor growth.



PROLOGUE

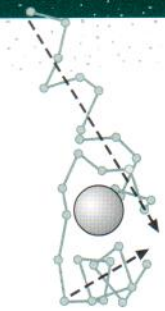
However, before we start with our story, a bit of background. The muscles in our arms and legs let us lift objects, write or walk. The muscles in our heart pump blood through our bodies. The muscles in our blood vessels control our blood pressure. The modern study of muscle contraction can be traced back to 1939 and the work of a Russian husband-and-wife team, V.N. Engelhardt and M.N. Lyubimova, who found that

1971

1965, Ebashi discovers troponin as the transducer through which calcium ion triggers muscle contraction. In 1971, Gergely and Greaser (BBRI) identify the three components of troponin: TnC, TnI and TnT.

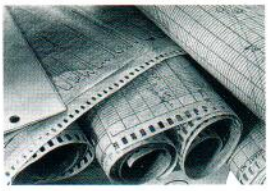
1975

Potter and Gergely (BBRI) measure the binding of calcium ions to TnC and correlate it to the control of muscle contraction.



1980'S

Tao, Gergely, Grabarek, Leavis and others at BBRI analyze the structure of TnC and its interaction with calcium and the other troponins by resonance energy transfer and cross-linking.



the fibrous protein in muscle extracts, which was called "myosin", was able to hydrolyze ATP, the major source of metabolic energy, in a process that seemed to play an important role in muscle contraction. Shortly thereafter, the Hungarian biochemist and Nobel laureate, Albert Szent-Györgyi, and his associates found that the so-called "myosin" actually contained two proteins, myosin and a new protein, actin. When a mixture of actin and myosin was extruded through a fine needle, "actomyosin" threads were formed. A very exciting discovery was that addition of ATP caused contraction of these actomyosin threads, reproducing in the test tube what actually happens in muscle. The next important observation was that calcium ions are required for muscle contraction and that the removal of calcium produces relaxation. This posed a great scientific challenge: how can a small metal ion, a single atom, trigger the contraction of the comparatively enormous muscle fibers? An important clue came from the observation that actomyosin reconstituted from highly purified actin and myosin was unable to respond to calcium. The scene shifts now to 1963 and the laboratory of the Japanese biochemist, Setsuro Ebashi, who began to search for proteins that would make purified actomyosin responsive to control by calcium. He discovered such a protein and named it "native tropomyosin" because it resembled tropomyosin, a protein that had been discovered in England by Kenneth Bailey in 1946, but without a clue about its role in muscle. Ebashi's group began to analyze this protein in the hope of discovering how it could act as the transducer through which calcium triggers muscle contraction.

ACROSS

2 The tissue in our bodies that allows us to move and breathe and lets our heart pump blood.

4 Component of troponin that inhibits muscle contraction and can be used to diagnose heart attacks within two hours and may find use in the treatment of metastatic cancer. (abbrev.)

5 A group of proteins that play an essential role in the control of muscle contraction by calcium ion.

8 An activity that furthers our understanding of nature and thereby helps us control nature, often in unanticipated ways.

13 A Hungarian biochemist who received the Nobel prize for the identification of vitamin C and discovered the role of actin and myosin in muscle contraction.

14 An as yet unknown medical application of troponin research that will be discovered in the year 2001.

15 The major source of metabolic energy in cells, which drives many processes such as muscle contraction.

16 More of it was spent by American consumers in Kmart stores in a recent month than by NIH on all research related to muscle, heart and cardiovascular disease in an entire year. The equivalent of ATP for basic research.

DOWN

1 Component of troponin that binds tropomyosin, can be used to diagnose heart attacks within two hours, and is defective in the inherited disease, hypertrophic cardiomyopathy. (abbrev.)

2 A major component of the contractile apparatus of muscle that can be considered its motor.

3 A serious disease produced by cells that undergo uncontrolled proliferation, which may be prevented by TnI on the basis of experiments in an animal model.

4 An abnormal growth of cells or tissue.

6 A US government agency whose mission is to uncover new knowledge that will lead to better health for everyone. One mechanism by which this mission is executed is the award of research grants to conduct basic biomedical research by academic institutions throughout the United States. (abbrev.)

7 An independent organization that has made important contributions to the advancement of our understanding of nature, particularly with respect to muscle contraction and its control. (abbrev.)

9 A metal ion that plays an important role in the control of biological processes, especially muscle contraction where it serves as the messenger between the nerve impulse from the brain and the contractile machinery.

11 One of the founders of BBRI who established a world-renowned muscle research group at the Institute.

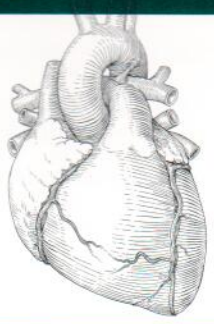
12 Something all of us strive for and which has greatly benefited from basic biomedical research.

1990

Grabarek, Tao and Gergely (BBRI) find how the calcium switch in muscle works by locking the structure of TnC so that it can no longer respond to calcium.

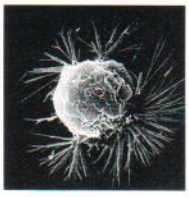
1995

Measurement of TnI or TnT released by heart muscle is shown to be an early diagnostic test for heart attacks, which is now used in millions of patients every year.



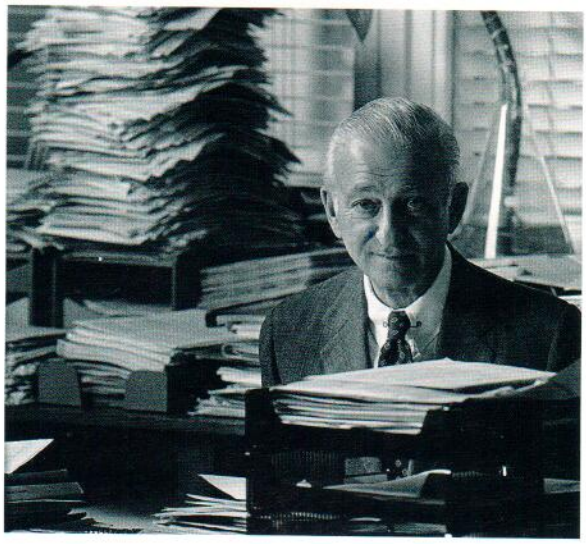
1999

Scientists at Children's Hospital, Boston, in collaboration with Tao (BBRI) discover that TnI inhibits the growth of blood vessels to tumors.



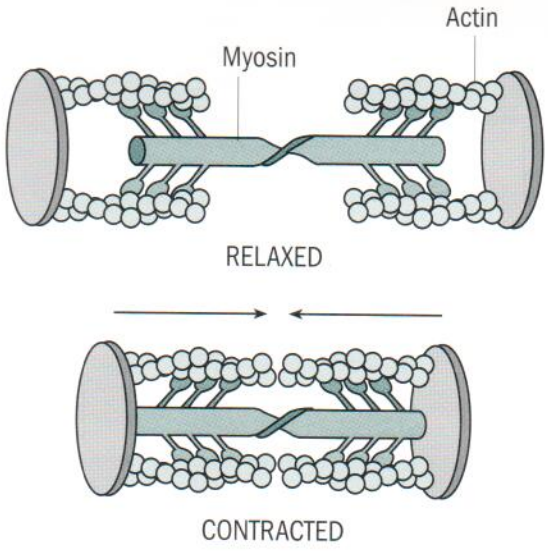
DISCOVERY OF THE TROPONINS

To Setsuro Ebashi's surprise, as he purified his preparation of tropomyosin, its ability to make muscle contraction responsive to calcium was lost. The component that was lost turned out to be a new protein fraction, which he named troponin. Together with pure tropomyosin, troponin could make muscle contraction responsive to calcium. Evidence from several laboratories suggested that troponin was composed of more than one protein. The important breakthrough came in 1971 in the laboratory of John Gergely at BBRI. John Gergely had briefly worked with Albert Szent-Györgyi, first in Hungary and later at NIH, and subsequently became one of the founders of BBRI and director of its muscle research group. At BBRI, John Gergely and his postdoctoral fellow, Marion Greaser, undertook the fractionation of troponin from rabbit muscle and found that it was composed of three different proteins, which together restored full calcium sensitivity to muscle contraction. In 1973, Marion Greaser and John Gergely published a classical paper which assigned names and functions to the three troponins: Troponin C binds calcium, troponin T binds to tropomyosin, and troponin I inhibits the hydrolysis of ATP by actomyosin and thereby muscle contraction. In scientific shorthand, these are known as TnC, TnT, and TnI, respectively.



John Gergely

Over the next few years, intense research on the three components of troponin ensued, both at BBRI and throughout the world. Indeed, this was one of the most exciting periods in muscle research, because it had become possible to reproduce the complex process of muscle contraction and its control in the test tube, using just six highly purified proteins: Myosin, actin, tropomyosin, and the three troponins. When filaments made from these proteins were treated with ATP and calcium ions, they would contract; when calcium was removed, they would relax again.



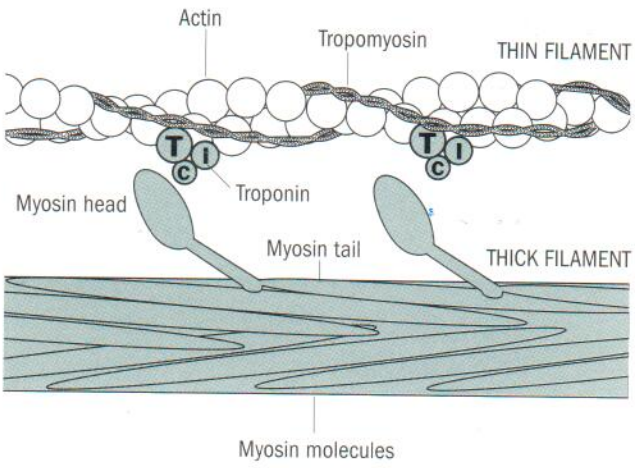
Each muscle fiber is a bundle of myofibrils, which in turn are made up of thousands of myofilaments. There are two types of myofilaments: The thin filaments, composed primarily of actin, and the thick filaments, composed of myosin. The contractile apparatus consists of two sets of actin filaments, attached at one end to a disc, facing each other and connected by myosin filaments. The thick myosin filaments have projections sticking out like arms that grab the actin molecules. The hydrolysis of ATP causes the arms to pull the actins with their attached discs towards each other; this causes the muscle to contract.

HOW DOES CALCIUM TRIGGER MUSCLE CONTRACTION?

While all the components of the regulatory system in muscle and their role in switching muscle contraction on and off had been described by the early seventies, the molecular mechanism of muscle regulation was far from clear and became the subject of intense studies at BBRI and in several other laboratories. As we said before, the function of troponin is to make the contractile machinery sensitive to calcium ions. Thus TnC, the calcium binding component of troponin, became the subject of detailed scrutiny. As soon as Marion Greaser had purified TnC, his colleague at BBRI, John Collins, undertook the difficult task of determining the

order in which its 159 amino acids are arranged. The outcome was very interesting: TnC contains four segments similar to segments found in other calcium binding proteins. Each of these segments represents a calcium binding site and has a characteristic structure consisting of two helices connected by a loop. This type of structure was given the name EF-hand by Robert Kretsinger of the University of Virginia. It is the loop that captures the calcium ion, while the helices make important connections within the TnC molecule and with other troponin components.

In order to learn how the binding of calcium can trigger a change in TnC, James Potter and John Gergely at BBRI undertook careful biochemical and physicochemical studies. They measured the binding of calcium to TnC very precisely and found that the binding of only two of the four calcium ions occurred in a concentration range at which calcium is known to control muscle contraction, whereas the other two calcium ions seem to play a structural role. During the next decade, many interesting features of TnC were uncovered at BBRI through the work of Paul Leavis, Sam Lehrer, Zenon Grabarek, Albert Wang, and others, as well as through the contributions from other laboratories throughout the world. Yet, the structural transition in TnC induced by calcium was still difficult to visualize. The situation changed in 1986 when the 3D structure of TnC was solved simultaneously by research groups in Canada and in the USA using X-ray crystallography. The structures provided very important clues about the mechanism of TnC function. It was proposed that when calcium ions bind to two of the loops, the helices flanking the loops, which are stuck together in the absence of calcium, open and grab hold of the inhibitory component, TnI, thus triggering muscle contraction.

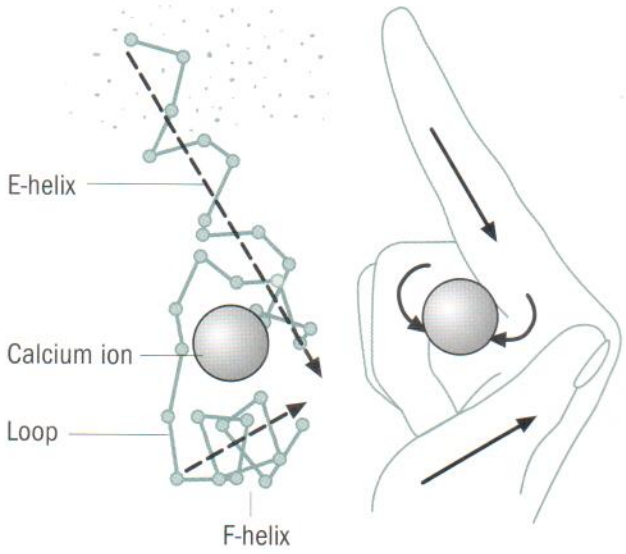


A portion of the thick and thin myofilaments in molecular detail. The thin filament appears as two twisted strands of nearly spherical actin molecules, entwined by strands of tropomyosin, each tropomyosin molecule spanning about seven actins. Much of our knowledge on tropomyosin comes from research at BBRI by Sam Lehrer and Phil Graceffa. The troponin complex (shown only schematically) sits on the surface of the actin chain, with the elongated TnT making direct contact with tropomyosin. Calcium ions induce a change in the shape of TnC, which in turn alters the interaction of TnC with TnI and TnT, ultimately causing a slight movement of tropomyosin on the actin filament. This makes room for the myosin head to grab the actin chain and move it, using the energy provided by the hydrolysis of ATP.

GENETIC ENGINEERING AND MOLECULAR RULERS

How can one prove that this is how the calcium switch actually works? Scientists at BBRI addressed this problem by taking advantage of the rapid progress in genetic engineering, which permitted the precise replacement of individual amino acids in a protein, a process known as site-directed mutagenesis. By substituting the amino acid cysteine for the natural amino acid at carefully selected sites in TnC, Zenon Grabarek and his colleagues introduced a chemical bond between the cysteines that reversibly locked TnC in the calcium-free conformation. Such a TnC mutant was inactive as a calcium switch no matter how much calcium was around unless its structure was unlocked by breaking the constraining bond. In a different approach Terence Tao and colleagues combined site-directed mutagenesis with a sophisticated biophysical technique called resonance energy transfer. This method measures the transfer of radiant energy between two types of chemical groups attached to a protein at specific sites, a fluorescent donor and an acceptor. The donor is excited by irradiation with UV light, then a part of the excitation energy is transferred to a nearby acceptor causing a decrease in donor fluorescence. Because the efficiency of energy transfer depends on the distance between the donor and the acceptor, this technique can serve as a so-called molecular ruler. BBRI scientists were among the pioneers to apply this technique to the study of proteins. Terence Tao and his colleagues used energy transfer technique to measure exactly how far the helical segments of TnC move apart when calcium binds and found the change to be in excellent agreement with the prediction.

Together the two types of experiments provided irrefutable proof that indeed calcium causes opening of two EF-hands in TnC and that this change is the key transition involved in regulation of contraction. Later it became clear that a similar mechanism is used by other EF-hand type calcium binding proteins for regulation of many intracellular processes.



Two helical segments of TnC, indicated by the dotted arrows labeled E- and F-helix, are represented by the extended forefinger and thumb, respectively, and the loop connecting the helices by the curve middle finger, which encloses a marble-sized object, the calcium ion.

GETTING TO KNOW YOUR TEAM

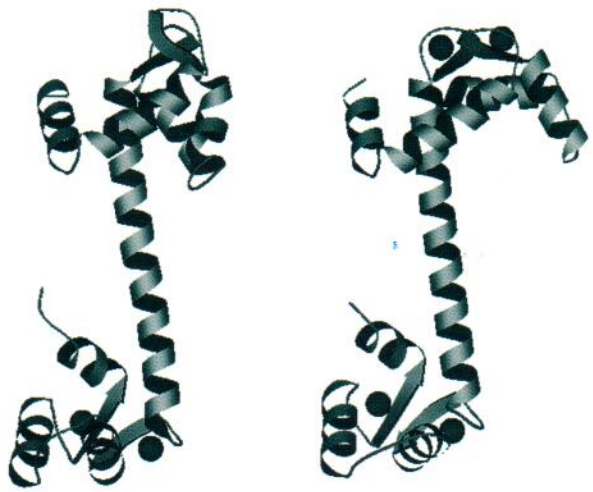
Once you know the players, their characters and habits, you want to know how well they play together. In the world of proteins, this means to identify the sites at which proteins interact, both in terms of particular amino acids and in three dimensions. We have made great progress in this respect, but the task is by no means accomplished. Unfortunately TnC is the only troponin component whose 3D structure is known at the moment. Numerous attempts in several laboratories to crystallize and solve the structures of the other troponin components and their complexes have so far been unsuccessful. Thus the only way we can obtain information on how the troponin components interact with each other and thereby transmit the regulatory calcium signal to the entire thin filament come from indirect biochemical measurements. One way is to chemically cross-link two proteins, then break them into small fragments and identify the pieces that contain segments of both proteins. In this way the interaction sites can be mapped to specific amino acids in each protein. In order to figure out how these interaction sites are arranged in space, the resonance energy transfer technique is very useful. Reactive cysteine residues are introduced in various positions by site-directed mutagenesis and labeled with energy donors or acceptors so as to allow the measurement of energy transfer between these sites. A large number of such experiments have been performed at BBRI by the research groups of John Gergely and Terence Tao. These studies have yielded the model of the TnC-TnI interactions and its calcium dependence that is shown on the cover of this report. Although just a small step and not yet the final answer, it is through many small steps of this sort that complex biological problems are solved.

MEDICAL ADVANCES

Our story so far has described a logical progression of experiments that have yielded ever deeper insights into how our muscles contract and relax. We can easily see the impact of this basic research on biology, but what about medicine? Let us look at what would have been a typical justification of a grant application to the National Institutes of Health in 1970 for funds to study the structure and function of troponin: "It is important to understand how muscle contraction is controlled by calcium so that we can discover what has gone wrong in disorders such as cardiac arrhythmias, genetic diseases which are caused by defective troponin, or heart failure."

Now let us review, with 30-year hindsight, the medical advances that have resulted from troponin research. Cardiac arrhythmias are now widely treated with an important class of drugs known as calcium-blockers that attenuate the excitability of heart muscle and thereby eliminate irregularities of heartbeat. An inherited, albeit rare disorder, hypertrophic cardiomyopathy, has been discovered to be caused by mutations in the genes for myosin, tropomyosin, TnT, or TnI. The basic studies on TnI by Yin Luo and others at BBRI may yield insights into the causes of this serious disorder, which can lead to sudden death. Although no treatments are yet available for familial hypertrophic cardiomyopathy, the dawning era of gene therapy offers hope for a complete

cure. But the health benefit of troponin research that has had the greatest impact was the development of a quick test for heart attacks. About 1.5 million Americans suffer heart attacks each year, but many times that number rush to emergency rooms with chest pain. Until 1995, these patients were taken to intensive care units until a diagnostic test could confirm whether a heart attack had indeed occurred, a procedure that required more than two hours and gave an incorrect diagnosis 5% of the time. In 1996, a new test was developed, based on the release of TnT or TnI by damaged heart muscle, which can be run in 20 minutes using a shirt-pocket device and is effective within just two hours after the onset of chest pain. Millions of such tests are now run every year and are helping to assure that patients receive proper care for heart attacks as soon as possible, while heart damage is still reversible, while at the same time preventing the unnecessary use of intensive care units for patients whose chest pains have other causes.

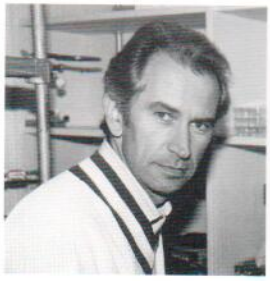


The crystal structure of troponin C (TnC) and its modulation by calcium ion. At low concentrations of calcium, no calcium ions are bound to the loops at the top of TnC and the two helices at the top right are folded against its central helix region. At high calcium concentrations, two calcium ions (blue balls) bind to the top loops of TnC and the helices at the top right swing to the right and open a large cleft, in which TnC grasps a portion of TnI, thereby pulling the inhibitory TnI regions away from actin and allowing the muscle to contract, as illustrated on the cover of this Report.

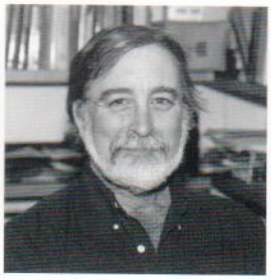
SERENDIPITY

A totally unanticipated potential health benefit of troponin research is the use of TnI in cancer therapy. In order to proliferate rapidly, metastatic cancer cells have to stimulate the growth of blood vessels so that they can obtain nutrients and oxygen; if the growth of new blood vessels is inhibited, cancerous tumors become dormant and shrink dramatically. This concept was advanced by Judah Folkman at the Boston Children's Hospital in the 1970s, and several inhibitors of blood vessel growth, known as angiogenesis inhibitors, are already in clinical trials for the treatment of cancer. A year ago, scientists at the Boston Children's Hospital and MIT discovered that cartilage, which traditionally is devoid of blood vessels, contains a potent inhibitor of blood vessel growth. With the collaboration of Terence Tao at BBRI, the active substance could be identified as TnI. Although TnI has not yet been tested clinically, it was found to be one of the most potent angiogenesis inhibitors known based on tests in an animal model system involving lung metastasis of a particularly aggressive melanoma. The identification of TnI as a potential anticancer agent might be considered just stroke of luck – however, scientists like to call it serendipity, because such "unlikely" spin-offs of basic biomedical research, although unpredictable, are the rule and not the exception.

Terence Tao



Zenon Grabarek



Paul Leavis

Yin Luo

Development Report

This has been a very busy and productive year for the development team. Our focus has been two-fold – the ever important Annual Fund and preparation for a major campaign in support of our new research home in Watertown.

Thanks to the wonderful support of our very loyal group of donors and to the hard work of the Development Committee and the Development Office we achieved a record Annual Fund performance this year - $440,000. This represents 14% more than our target of $385,000 – marvelous! These funds are invaluable to BBRI because there is a significant part of the Institute's research programs which cannot be funded through grants from the National Institutes of Health and voluntary health agencies. Your contribution has helped provide for essential scientific equipment and support for a number of important research initiatives, including seed funding for brilliant young scientists at the start of their careers of discovery.

"Thanks to the wonderful support of our very loyal group of donors ... we achieved a record Annual Fund performance this year - $440,000."

The Feasibility Study for our major fundraising campaign was completed this spring – special thanks to all those individuals who were interviewed. The findings were very interesting and stimulating and give us reason to move forward with confidence and plan the campaign in earnest. Clearly BBRI's new research facility, with its state-of-the art laboratories and increased research space will be a very conducive setting for our scientists and will give us the room to expand our faculty and science programs. In order to make this expansion happen and realize the full potential of BBRI's new research home, we will need to provide increased philanthropic support through a major campaign. More information about this exciting project in the months ahead.

A heartfelt thank you to you and all our donors for continuing your generous support of BBRI – your belief in the importance of biomedical science and the hope it provides for potential new cures and therapies for disease is so important to everyone at BBRI!

— Allie Blodgett
Vice President & Development Committee Chair

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From left: Kathleen Morgan, Ph.D., BBRI Director, John French, BBRI Chair, Thomas McQuaid, BBRI Chief Financial Officer, State Representative Rachel Kaprielian, Sal Ciccarelli, Watertown Town Councilor, David Gibbs, Sc.D., BBRI President at the Groundbreaking Ceremony in Watertown, MA in May.

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Young Jin Choi, a Fellow working in the lab of Dr. Paul Leavis, discusses the cancerous cells viewed under the microscope with William Tyler at the Evening of Discovery.

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TOP — From left: Jillian Hosford Darling, Simon Welsby, BBRI's Director of Development & Public Affairs and Thomas Darling at the Annual Meeting in November.

BOTTOM — The Second Seidel Symposium entitled "Smooth Muscle Cells: Structure, Motility and Signaling" was successfully held at Marine Biological Laboratory at Woods Hole, Massachusetts from April 11-14, 1999. The international symposium was hosted by BBRI in honor of Dr. John C, Seidel, BBRI faculty member from 1961-1988. The symposium was attended by 134 scientists.

MATCHING GIFTS

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John Hancock Mutual Life Insurance Co.

Polaroid Foundation

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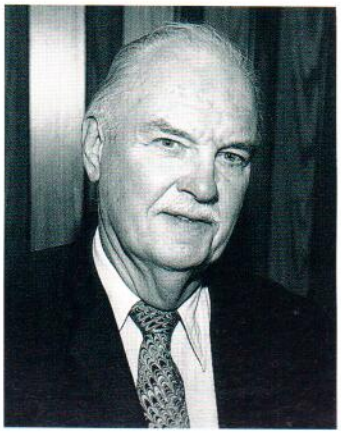
Treasurer's Report

In my annual report last year, it was disclosed that the Investment Committee, Budget and Finance Committee and the Special Facilities Finance Committees were exploring the implications of a move to a new facility. The results of that study have proved exciting with the decision to sell our leasehold interests in 20 Staniford St., Boston and certain lands and facilities in Townsend to our landlord, Schepens Eye Research Institute for $8,400,000.

The Committees recommended, and the Board of Trustees approved the sale of $17,000,000 of tax exempt bonds to finance the purchase and renovation of property at 64 Grove Street, Watertown. Our thanks to the many Trustees who expressed their support of the Institute through the purchase of bonds. According to State Street Bank and Trust's Public Finance Department, BBRI became the first small independent research institute in the country to obtain



"From an operations standpoint, BBRI had a tremendous year of growth with revenues from grants and contracts increasing 21% to over $6,266,000."

an investment-grade rating from both Moody's and Standard and Poor's rating services and to successfully issue tax exempt bonds.

From an operations standpoint, BBRI had a tremendous year of growth with revenues from grants and contracts increasing 21% to over $6,266,000. NIH related revenue represents approximately 90% of revenue from grants and contracts. The Institute was awarded eight new grants from the NIH representing approximately $6,000,000 of revenue over the life of the grants. Additionally, the Institute received grants from the American Cancer Society, the Hereditary Disease Foundation, Conrad and Pharming. Annual fundraising took a major leap forward with record-breaking donations of over $440,000, an increase of nearly 25%.

And finally, we are pleased to report that the Investment Committee recently engaged New England Pension Consultants as an advisor on strategy for our investment portfolio. The Committee will be looking at ways to preserve the principal of the portfolio while maximizing returns going forward.

Respectfully submitted,

— Ernest Henderson III, Treasurer

Statements of Financial Position

JUNE 30, 1999 AND 1998

ASSETS:	1999	1998
Cash	$414,426	$312,762
Grants receivable	4,139,194	3,280,609
Unconditional promises to give (restricted)	13,374	29,448
Investments	12,698,221	8,886,190
Prepayments, deposits and other receivables	100,008	137,683
Trustee-held funds	17,727,138	—
Construction-in-progress	4,226,847	—
Capitalized interest	75,607	—
Property and equipment	1,375,023	1,943,712
Deferred compensation investments	2,424,140	2,242,596
TOTAL ASSETS	$43,193,978	$16,833,000
LIABILITIES AND NET ASSETS:		
Accounts payable and accrued expenses	$651,438	$261,751
Accrued interest expense, net of income	128,646	—
Deferred income	4,150,406	3,396,889
Deferred compensation payable	2,424,140	2,242,596
Bonds payable	17,000,000	—
Total liabilities	24,354,630	5,901,236
NET ASSETS:		
Unrestricted	17,988,968	10,109,607
Temporarily restricted	352,414	353,716
Permanently restricted	497,966	468,441
Total net assets	18,839,348	10,931,764
TOTAL LIABILITIES AND NET ASSETS	$43,193,978	$16,833,000

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

Statements of Activities

FOR THE YEARS ENDED JUNE 30, 1999 AND 1998

CHANGES IN UNRESTRICTED NET ASSETS:	1999	1998
REVENUES:		
Grants and contracts	$6,266,489	$5,164,438
Contributions	439,511	340,546
Investment income	931,412	1,635,513
Other income including licensing fees	22,032	21,663
Total unrestricted revenues	7,659,444	7,162,160
Net assets released from restrictions	39,780	583,747
Total unrestricted support	7,699,224	7,745,907
EXPENSES:		
Salaries and benefits	4,684,666	4,298,300
General support and services	1,374,735	1,375,233
Occupancy costs	875,272	890,404
Depreciation	355,837	315,619
Fund raising	89,719	44,344
Total expenses	7,380,229	6,923,900
Increase in unrestricted net assets before extraordinary gain	318,995	822,007
Extraordinary gain on sale of leasehold	7,560,366	
Increase in unrestricted net assets	7,879,361	822,007
CHANGES IN TEMPORARILY RESTRICTED NET ASSETS:		
Contributions	2,310	14,531
Investment income	36,168	63,757
Net assets released from restrictions	(39,780)	(583,747)
(Decrease) in temporarily restricted fixed assets	(1,302)	(505,459)
CHANGES IN PERMANENTLY RESTRICTED NET ASSETS:		
Investment income	29,525	72,298
Increase in permanently restricted net assets	29,525	72,298
INCREASE IN NET ASSETS	7,907,584	388,846
NET ASSETS AT BEGINNING OF YEAR	10,931,764	10,542,918
NET ASSETS AT END OF YEAR	$18,839,348	$10,931,764

Grants and Fellowships

RESEARCH GRANTS

NATIONAL INSTITUTES OF HEALTH

Dr. Badwey	MAPK in the contractile phenotype of smooth muscle	3/96 - 2/01	$1,128,000
Dr. Badwey	Enzymes modulating second messengers in neutrophils	8/98 - 7/03	1,096,000 *
Dr. Badwey	A novel signalling pathway in neutrophils	5/96 - 4/99	533,000
Dr. Coluccio	Myosin-I mediated processes in liver cells	8/97 - 7/01	1,407,000
Dr. Graceffa	Smooth muscle and non-muscle caldesmon	5/93 - 4/99	748,000
Dr. Harrison	Structure / function analysis of molecular chaperones	7/98 - 6/03	1,206,000 *
Dr. Ikemoto	Structure and function of sarcoplasmic reticulum	9/96 - 8/01	2,416,000
Dr. Lehrer	Tropomyosin and myosin interaction in muscle	12/95 - 11/00	2,044,000
Dr. Morgan	Regulation of contraction and growth of blood vessels	7/96 - 6/00	713,000
Dr. Morgan	Contraction of vascular smooth muscle cells	4/97 - 3/01	768,000
Dr. Paulus	Mechanism of protein splicing in Mycobacterium	4/97 - 3/01	1,403,000
Dr. Raso	A binary system for cell-targeted delivery	3/99 - 2/01	246,000 *
Dr. Raso	Vaccine to elicit catalytic anti-cocaine antibodies	4/99 - 3/02	471,000 *
Dr. Sarkar	Function of polyadenylate sequences in bacterial RNA	9/98 - 8/02	1,419,000 *
Dr. Sherman	Molecular chaperones and protein phosphorylation	5/96 - 4/00	1,081,000
Dr. Tao (MERIT)	Proximity relationship among muscle proteins	5/96 - 3/01	2,201,000
Dr. Toker	Phosphoinositide 3-Kinase C signaling	12/98 - 11/03	1,385,000 *
Dr. Wang (Pro. Proj.)	Molecular mechanism of smooth muscle regulation	12/97 - 11/02	7,696,000
Dr. Wohlrab	Phosphate path within homodimeric mitochondrial PTP	5/98 - 4/02	1,412,000

AMERICAN CANCER SOCIETY

Dr. Bohm	Structure of G-Beta gamma / effector complex	1/99 - 12/01	342,000 *

CONRAD

Dr. Leavis	Development of antibodies against preimplant factor & invest contrac potential	10/98 - 9/99	58,400 *

DEFENSE ADVANCED RESEARCH PROJECTS AGENCY

Dr. Leavis	Embryonal factors as antiinfective agents	2/97 - 1/00	844,000

HEREDITARY DISEASE FOUNDATION

Dr. Sherman	Role of stress kinase & HSPS in Huntington-induced apoptosis	2/99 - 1/01	111,000 *
Dr. Stafford	Biophysical analysis of Huntington expanded repeats	9/97 - 8/98	53,000

MARCH OF DIMES

Dr. Coluccio	Mechanochemical properties of mammalian myosin I's	6/98 - 5/00	118,000

THE MEDICAL FOUNDATION-HARCOURT GENERAL CHARITABLE FOUNDATION, INC.

Dr. Toker	The role of protein kinase C in integrin-mediated tumor invasion	7/98 - 6/00	100,000

SPONSORED RESEARCH

Dr. Morgan	Asahi Chemical Ind. Co. Ltd.	7/98 - 4/99	15,000 *
Dr. Paulus	Pharming Technologies BV	1/99 - 12/99	99,300 *
Dr. Stafford	Analytical ultracentrifugation	5/97 - 7/98	60,000

NIH FELLOWSHIPS AND CONFERENCE AWARDS

Dr. Leinweber	Fellowship	7/98 - 6/01	81,000 *
Dr. Wang	Smooth muscle cells: Structure, motility & signaling	4/99 - 4/00	15,000 *

*New grants in fiscal 1999

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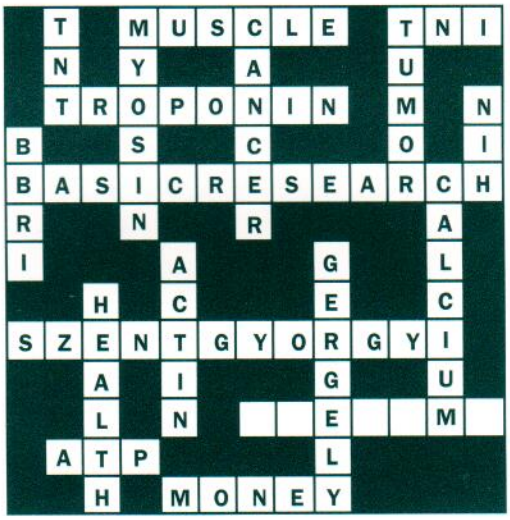
ANSWER TO PUZZLE ON PAGE 4



Front Cover—A model for the roles of troponin C (TnC) and troponin I (TnI) in the activation of muscle by calcium. The structure of TnC is known in atomic detail and the backbone is depicted as green coils. The red spheres are calcium ions. The atomic structure for TnI is not available. A low resolution model based on experimental work is presented here with orange cylinders and slender strands. The two superimposed images, one faint, one distinct, represent the structures in the absence and the presence of calcium, respectively. In the absence of calcium, the coils in the top right region of TnC are folded toward the center and the two TnI cylinders on either side of TnC interact with actin (which is not shown), causing muscle contraction to be inhibited. When calcium binds to TnC, these coils swing up and grasp the middle TnI cylinder, pulling the adjacent inhibitory regions away from actin and allowing the muscle to contract. Courtesy of Drs. Luo, Langsetmo, Gergely and Tao of BBRI.

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