

# Coming together

KEEPING TOGETHER | WORKING TOGETHER

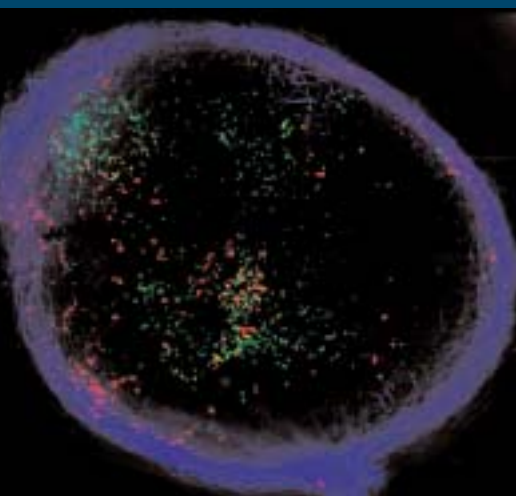


The **CBR Institute**  
for Biomedical Research

Chairman and  
President Letter

Adhesion Molecules  
and Inflammation  
Research Group

Autoimmunity and  
Allergy Research Group



**Team Effort** A snapshot of a lymph node (outlined in purple) in a living mouse: Through actual physical encounters, red-labeled dendritic cells arriving via a lymph vessel (bottom right) deliver news about foreign antigens in the body to immune cells (T lymphocytes tagged with green-fluorescent dye).

Dynamic visualization of these interactions using multiphoton intravital microscopy reveals how T cells become activated. This understanding holds great promise for the eventual development of new and effective ways to treat cancer and autoimmune diseases. *Image courtesy of Thorsten Mempel, Ph.D., von Andrian lab.*



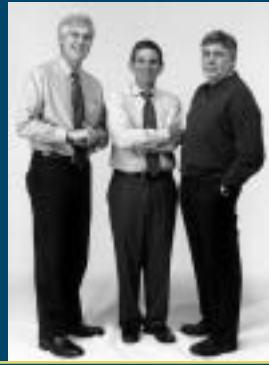
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# Together we succeed

THOMAS EDISON WAS ONCE ASKED WHY HE EMPLOYED A TEAM OF 21 ASSISTANTS. HE REPLIED, “IF I COULD SOLVE ALL THE PROBLEMS MYSELF, I WOULD.”

Sarcasm aside, he was absolutely correct: Teamwork and collaboration are essential to scientific discovery. No one, not even a genius, can do it alone.

Even when a solitary mind conjures a breakthrough insight – the Eureka moment, an exception in itself – the translation of that idea into something provable, tangible, and beneficial to society always depends upon the intelligence and hard work of colleagues and supporters. The idea’s fruition may occur on the far horizon, by a child now learning about Marie Curie or the human genome.

Now more than ever, The CBR Institute for Biomedical Research is thriving on collaboration, on the sharing of ideas and resources among our scientists and between CBRI and other research institutions. We are also collaborating vigorously with public and private funding sources, who share our mission of pursuing basic research to strengthen immune defense and harness inflammation. Our vision is to open doors to new therapies and cures for illnesses ranging from cancer to heart disease to arthritis to Alzheimer’s disease.

Teamwork requires more than recruiting talented people. It demands a dogged focus on specific goals and an institutional framework that provides the expertise, facilities, financial resources, and – yes – the community spirit to reach those goals. Accordingly, we have recently undergone a process of strategic planning that identifies our strengths, defines our needs, and clarifies our mission within the general areas of immunology and inflammation. This endeavor has illuminated “bridges” that span the breadth and diversity of our expertise. It has brought us closer together as a community. (See executive summary of the Strategic Plan on page 25.)

What exactly does CBRI do? The answer can now be found in four Areas of Research Concentration pursued across our 21 distinct laboratories. Investigators have further defined several scientific challenges within each research area.

## **This is what we do:**

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**ADHESION MOLECULES AND INFLAMMATION** – five CBRI labs pursue research in this area. They investigate cell-surfaces molecules that are crucial to cell growth, pathogen detection, inflammation, and wound repair. This is a new field of study and we are at its forefront. As proof, CBRI’s Timothy Springer received, with Eugene Butcher, the highly prestigious Crafoord Prize in 2004 for his discoveries about adhesion molecules.

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**IMMUNE DEFENSES AGAINST INFECTIOUS DISEASES, VIRUSES, AND TUMORS** – six CBRI labs conduct path-breaking work in this area. They are discovering how immune cells succeed in fighting dangerous pathogens and cancer.



- **AUTOIMMUNITY AND ALLERGY** – six CBRI labs are doing research in this area. Autoimmunity is characterized by an attack of the immune system against the body’s own healthy tissues, leading to illnesses such as lupus and Graves’ disease.

- **GENETICS OF CANCER AND IMMUNODEFICIENCY** – four CBRI labs conduct this research, which gives hope to patients with rare immune deficiencies and examines how cancer can result from failures in genetic repair.

Inside this Annual Report, you will learn more about our Areas of Research Concentration and the CBRI laboratories within each area. You will see how the labs pursue unique work and how they collaborate on common goals. And you will learn how this collaboration results in breakthrough discoveries. For more in-depth information on CBRI research, see our new and improved Web site at [www.cbrinstitute.org](http://www.cbrinstitute.org). Visitors can search by research concentration, laboratories, or by “Diseases We Fight.”

One form of collaboration is the Program Project Grant, in which biomedical research institutions in Boston and around the world work together on major research projects. These publicly-funded mega-grants can be extremely productive, as they meld diverse talents and scientific outlooks. An excellent example of this at CBRI is a five-year, \$12 million effort to create new strategies for combating bioterrorism, led by Senior Investigator Judy Lieberman.

The new Center for Human Cell Therapy (see article on page 12) is another model of collaboration. This far-reaching initiative, funded at \$12.6 million over five years, is led by CBRI Senior Investigator Leslie Silberstein, in tandem with scientists at Massachusetts General Hospital and Dana-Farber Cancer Institute.

Overall in fiscal year 2004, CBRI received \$30.7 million in research funding from the National Institutes of Health, and \$4.5 million in private gifts and grants – record totals, both. Our successful fundraising efforts are more and more focused on building the Institute’s endowment. A strong endowment will enable us to launch bold research initiatives, help establish young investigators, and acquire new research space.

Finding cures for disease is not the equivalent of sending a man to the moon; it is closer in scope to sending thousands of men and women to hundreds of moons and planets. We can get there, ultimately, but only by working together, by finding new ways to combine our talents for the greater good. CBRI is devoted to the cause of basic research leading to improved human health, and we ask you to join us in support of this worthiest of goals.

Sincerely,

Fred S. Rosen, M.D.  
President

Alan J. Strassman  
Chairman

# A healing vision

## ADHESION MOLECULES AND INFLAMMATION RESEARCH GROUP

What, you may ask, are adhesion molecules? And why do they matter?

Simply put, adhesion molecules are sticky cell-surface molecules that govern cell-to-cell interactions and are crucial for inducing inflammation, wound repair, pathogen detection, and cell differentiation.

CBRI is pushing the bounds of adhesion molecules research. For instance, researchers at the Institute are discovering the role of adhesion molecules in the homing of immune cells to injured tissues, and the recruitment of blood-clotting platelets to the site of wounds.

That knowledge – a collaboration of visionary minds and new imaging tools that follow cells in live animals and even capture the way molecules bend – is leading to new treatments for diseases like psoriasis, heart disease, juvenile diabetes, and Alzheimer's disease.

The five CBRI investigators in the Adhesion Molecules and Inflammation Research Group are pursuing key scientific challenges that include:

**1**  
**Understanding how adhesion molecules work at the molecular level.**

*Senior Investigator Timothy Springer's* discoveries about the behavior and structure of adhesion molecules have led to new clinical treatments for autoimmune diseases such as psoriasis. Understanding the behavior of adhesion molecules is also central to the research of *Senior Investigator Leslie Silberstein*, the director of a new center at CBRI devoted to developing cell therapies for disease.

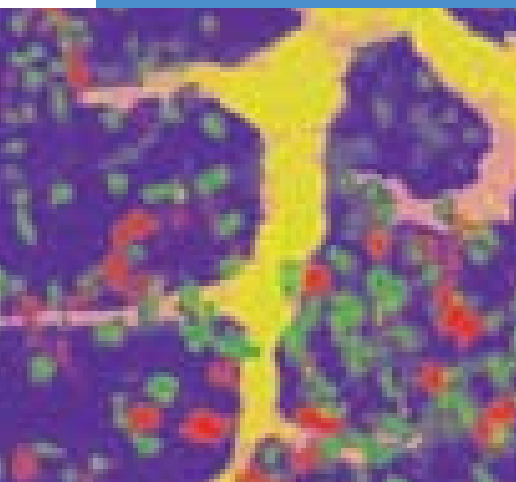
**2**  
**Predicting the structure of molecules.**  
With intense focus, *Junior Investigator Motomu Shimaoka* seeks to predict the changing shapes of adhesion molecules and, therefore, manipulate their conformations for therapeutic means.

**3**  
**Understanding the biophysics of how adhesion molecules enter and exit from the bloodstream.**

Using state-of-the-art imaging techniques that he has created, *Senior Investigator Uli von Andrian* is acquiring insights that indicate how and why these cells enter, or fail to enter, both healthy and infected tissues.

**4**  
**Searching for small molecules that impede the function of adhesion molecules and lead to ways of preventing inflammatory diseases.**

The lab of *Senior Investigator Denisa Wagner* conducts breakthrough research on the role of adhesion molecules in inflammatory processes such as atherosclerosis. She and CBRI colleagues plan a drug discovery endeavor that may provide new means for treating heart disease and healing wounds.



CBRI's intravital microscope captures, within a live mouse, the movements of T cells (green) and dendritic cells (red) in the vicinity of a lymph node (yellow/purple). Understanding the migration and tag-team interaction of immune cells will lead to better therapies for enhancing and blocking immune responses. *Courtesy, von Andrian lab.*



CBRI IS A WORLD LEADER IN ADHESION MOLECULES AND INFLAMMATION RESEARCH, PROVIDING VITAL INFORMATION FROM THE SUB-MOLECULAR LEVEL TO THAT OF THE WHOLE ORGANISM. | FOR INSTANCE, RESEARCHERS ARE LEARNING TO INFLUENCE THE MOVEMENT OF ADHESION MOLECULES, AS WELL AS RELATED INFLAMMATORY AND IMMUNE CELLS, AND THIS WORK IS LEADING TO NEW THERAPIES FOR ILLNESSES SUCH AS PSORIASIS, RHEUMATOID ARTHRITIS, MULTIPLE SCLEROSIS, AND HEART DISEASE. LEFT TO RIGHT: TIMOTHY SPRINGER, Ph.D., LESLIE SILBERSTEIN, M.D., MOTOMU SHIMAOKA, M.D., ULI VON ANDRIAN, M.D., Ph.D., AND DENISA WAGNER, Ph.D.



SIX CBRI INVESTIGATORS CONDUCT PATH-BREAKING RESEARCH INTO **AUTOIMMUNE DISEASES**, IN WHICH THE BODY'S IMMUNE SYSTEM INAPPROPRIATELY ATTACKS HEALTHY TISSUE, OR SELF. | THEIR RESEARCH TARGETS ILLNESSES SUCH AS LUPUS, CROHN'S DISEASE, TYPE 1 DIABETES, REPERFUSION INJURY, HEREDITARY ANGIOEDEMA, AND GRAFT VS. HOST DISEASE (TRANSPLANT REJECTION). | **ALLERGY**, CHARACTERIZED BY AN IMMUNE SYSTEM OUT OF BALANCE, IS ANOTHER KEY CONCERN OF THE RESEARCH GROUP. | LEFT TO RIGHT: AL DAVIS, M.D., CHESTER ALPER, M.D., ANJANA RAO, Ph.D., MICHAEL CARROLL, Ph.D., STEFAN FESKE, M.D., AND MANJUNATH NARASIMHASWAMY, M.D.

# Defending your self

## AUTOIMMUNITY AND ALLERGY RESEARCH GROUP

About five percent of Americans suffer from some form of autoimmune disease, in which immune cells attack the body's own healthy tissue, or self. Some autoimmune diseases are well-known, such as lupus, rheumatoid arthritis, type 1 diabetes, and multiple sclerosis. Rarer forms are Graves' disease, myasthenia gravis, and Hashimoto's disease.

As much as 20 percent of Americans struggle with allergy, which is a generally less severe manifestation of an immune system out of kilter.

In autoimmune responses, immune cells are not properly eliminated during their development in the thymus gland and elsewhere. These cells recognize and attack "self molecules," and the persistence of these cells can cause pathological conditions that damage or erode tissues.

Working together, CBRI investigators in the Autoimmunity and Allergy Research Group have identified scientific challenges including:

**1** Understanding how immune cells acquire tolerance of healthy tissue.

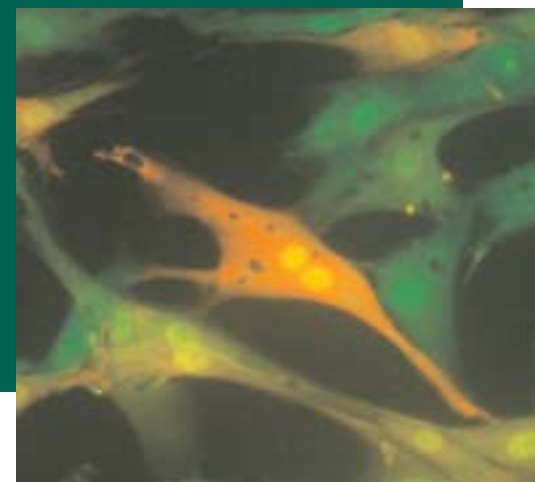
In particular, *Senior Investigator Anjana Rao* has made important discoveries about the signaling processes that enable immune cells to tolerate – effectively, to leave alone – healthy tissue. A possible outcome of the research would be drugs that block "intolerant" proteins or induce targeted tolerance of transplanted organs. *Junior Investigator Stefan Feske* is taking special aim at how the immune system is regulated via cellular signals that move through "calcium channels."

**2** Discovering what controls the interaction of immune cells with each other. In this realm, *Investigator Manjunath Narasimhaswamy* is researching how

immune T cells "grow up" to carry out different missions. His work may contribute to the development of new therapies for Crohn's disease. *Senior Investigators Al Davis* and *Michael Carroll* specialize in the complement system, a set of proteins that comprise our first line of immune defense. Davis' work focuses on hereditary angioedema, while Carroll is unlocking the immunological wrongdoing behind lupus and reperfusion injury, a dangerous surgical complication.

**3** Learning how genetic variation contributes to autoimmunity and allergy. *Senior Investigator Chester Alper* studies immune function within the genes of the major histocompatibility complex, or chromosome 6. His research sheds light on genetic predisposition to autoimmune diseases and explores the behavior of molecular switches that are key for the genetic expression of autoimmunity.

Connective tissue cells (dyed green) with a calcium channel CaT2 (in orange). Calcium channels ferry a form of calcium, calcineurin, through the cell membrane. Calcineurin plays a critical role in signalling the immune system in neurons, cardiac and muscle cells, and blood cells. *Courtesy of the Feske lab.*



# Getting down to basics

## GENETICS OF CANCER AND IMMUNODEFICIENCY RESEARCH GROUP

It is astounding, the immune system's ability to produce antibodies that target billions of different pathogens assailing the body. The capacity to mount a specific immune response lasts a lifetime and requires complex signaling pathways and rearrangements of DNA, with the constant attention of DNA repair proteins. Breakdowns in this repair process, however, can lead to cancers that affect millions of people.

Immunodeficiency diseases, disabling and frequently fatal, can result when defects in genes disrupt the normal growth and behavior of immune cells. Researchers at CBRI are striving to understand these compromised genes and, thereby, contribute to therapies for scores of diseases, such as Severe Combined Immunodeficiency, which almost exclusively afflict children.

Moreover, this research is producing far-reaching discoveries about the

basic operations of the immune system. From such studies emerge insights that seed the ground for new therapies addressing every disease with an immunological connection.

CBRI investigators in the Genetics of Cancer and Immunodeficiency Research Group have defined scientific challenges that include:

**1**  
Discovery of the products of defective genes and their effects on the immune system.

CBRI President *Fred S. Rosen* (not shown in photo) is a world leader in this area. Among a lifetime of accomplishments, he has identified the genetic bases of Wiskott-Aldrich syndrome, a rare and sometimes fatal immunodeficiency.

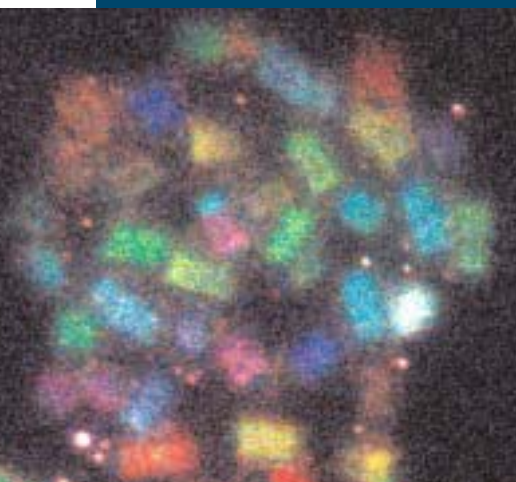
**2**  
Modeling the basis of immunological diversity.

The laboratory of *Senior Investigator Frederick Alt* has produced a stream

of fundamental discoveries regarding the genetics of immunity, work that one day may lead to new anti-cancer and anti-aging therapies. One of CBRI's outstanding young scientists, *Junior Investigator Jayanta Chaudhuri* is dedicated to expanding our understanding of DNA repair and how it contributes to the immune diversity that protects us from many diseases, including cancer.

**3**  
Developing mouse models for various types of lymphoma and other cancers, and for tolerance related to autoimmunity.

*Senior Investigator Klaus Rajewsky*, for instance, has revolutionized medical research with novel gene-targeting techniques that assist laboratories around the world. His mouse model for Hodgkin's disease may lead to new therapies for patients with that dangerous form of leukemia.



Glittering like crystals, these chromosome pairs from a cancerous tumor have been isolated for study with CBRI's spectral karyotyping system (SKY). Helping to reveal the very complex genetics of cancer, SKY employs an interferometer, a fluorescent microscope, a laptop computer, and a special camera. *Courtesy, Alt lab.*



THE VAST DIVERSITY OF HUMAN IMMUNE RESPONSES DEPENDS UPON GENETIC SHUFFLING THAT CAN GO AWRY AND LEAD TO CANCERS SUCH AS HODGKIN'S DISEASE AND BURKITT'S LYMPHOMA. IMMUNE DEFICIENT ILLNESSES, INCLUDING WISKOTT-ALDRICH SYNDROME AND SEVERE COMBINED IMMUNODEFICIENCY, CAN RESULT WHEN GENE DEFECTS SUBVERT NORMAL IMMUNE CELL BEHAVIOR. FOUR CBRI INVESTIGATORS DELVE INTO THE **GENETICS OF CANCER AND IMMUNODEFICIENCY**. THEIR WORK NOT ONLY TARGETS SPECIFIC DISEASES, BUT PRODUCES BASIC INSIGHTS ABOUT DISEASE PROGRESSION AND AGING. LEFT TO RIGHT: KLAUS RAJEWSKY, M.D., FRED ALT, Ph.D., AND JAYANTA CHAUDHURI, Ph.D. NOT PICTURED HERE IS CBRI PRESIDENT FRED S. ROSEN, M.D.



WORKING TOGETHER WITH GREAT VERVE, SIX CBRI INVESTIGATORS SEEK TO UNDERSTAND AND HARNESS THE BODY'S IMMUNE DEFENSES AGAINST INFECTIOUS DISEASES, VIRUSES, AND TUMORS.

THEY PURSUE PROJECTS THAT MAY LEAD TO NEW THERAPIES AND CURES FOR AIDS, TUBERCULOSIS, AND PATHOGENS SUCH AS CHOLERA, AS WELL AS UNLOCK THE BASIC FUNCTIONS OF THE IMMUNE SYSTEM. | IN ADDITION, THEY ARE COMBINING ENERGIES TO DEVELOP NEW MEANS TO COUNTER BIOTERRORIST ATTACK. LEFT TO RIGHT: HIDDE PLOEGH, Ph.D.,

PAT FRASER, M.D., ANNE GOLDFELD, M.D., JUDY LIEBERMAN, M.D., Ph.D., PREMLATA SHANKAR, M.D., AND TOMAS KIRCHHAUSEN, Ph.D.

# Fighting the good fight

## IMMUNE DEFENSE RESEARCH GROUP

The immune system is a spear as much as a shield, and one of its sharpest instruments is the aptly-named killer T cell, a key player in our adaptive immune system. Killer T cells – in league with dendritic and other immune cells – are responsible for destroying infection before it takes over.

These warriors defend the body from diseases including AIDS, tuberculosis (TB), and hepatitis, as well as myriad infectious agents that occur naturally or are manufactured as weapons of bio-terrorism.

AIDS, for instance, remains a worldwide epidemic. Almost 3 million people died of AIDS in 2003, and 38 million people are infected globally (about 400,000 in the United States). Tuberculosis kills 2 million people per year, with almost one-third of the world's population carrying the germ. In a hellish

partnership, one-third of people with HIV/AIDS are co-infected with TB.

CBRI investigators in the Immune Defense Research Group have agreed on key scientific challenges including:

**1**

**Understanding the regulation of T cell response in chronic infections.**

With TB and AIDS in mind, *Investigator Anne Goldfeld* researches the complex factors that result in protective immune responses, with the long-range goal of developing immuno-therapies that eradicate or control these diseases.

**2**

**Understanding how to regulate and manipulate killer T cells at the molecular level.**

*Senior Investigator Hidde Ploegh's* research is providing new insights into the biology of T cell interactions with their target cells. Using state-of-the-art confocal microscopy, *Senior Investigator Tomas Kirchhausen*

studies the complex machinery of the cell as it brings infectious materials inside its bounds.

**3**

**Discovering the role of programmed cell death (apoptosis) in immune defense.**

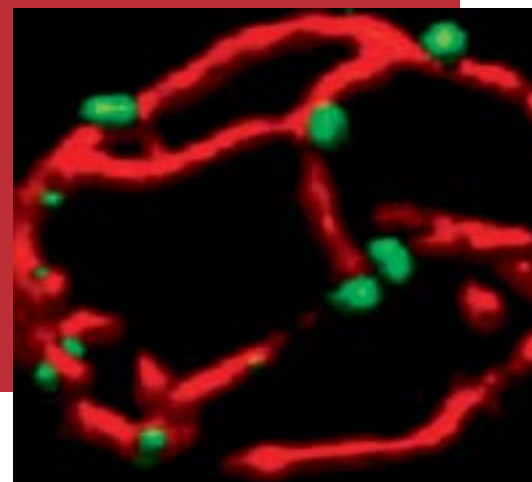
*Investigator Premlata Shankar* seeks to develop RNA Interference-based gene therapy – ultimately inducing cell death – for viral infections such as AIDS, hepatitis, and bio-terrorism agents. In addition, *Junior Investigator Patricia Fraser* is using molecular epidemiology to identify subsets of individuals who bear excess risk for certain autoimmune and infectious diseases.

**4**

**Methods for inducing T cells specific for cancer and for viruses.**

*Senior Investigator Judy Lieberman* is developing a unique AIDS vaccine, now in primate trials, that elicits long-lasting T cell immunity to HIV.

Still image from a “molecular movie” of a mitochondria organelle within a living yeast cell, captured with CBRI's confocal microscope. Green spots correspond to Dnm1p, a protein that regulates mitochondrial fission. The image appeared on the cover of *Molecular Biology of the Cell*, August 2003. *Courtesy of the Kirchhausen lab.*



by Leslie Pray

# Translation creation

## CBRI AND RESEARCH PARTNERS JUMP-START NEW FIELD OF CELL THERAPY

IT'S A WONDERFUL THING TO MAKE A BIOMEDICAL DISCOVERY THAT ILLUMINATES THE BODY'S INNER WORKINGS OR UNCOVERS A HIDDEN DISEASE PROCESS. BUT IT'S JUST AS IMPORTANT TO TAKE THAT DISCOVERY AND, BY POOLING RESOURCES AND TALENT, CONDUCT THE INNOVATIVE AND OFTEN NEGLECTED WORK THAT ENABLES THE DISCOVERY TO BECOME A NEW THERAPY THAT IMPROVES LIVES.

This kind of creative translation of brilliant discoveries into effective realities – bridge building, so to speak, between fundamental research and clinical application – is the mission of the Center for Human Cell Therapy. Established in October, 2004, and located primarily at the CBR Institute, the Center is an inspired collaboration between CBRI, Children's Hospital Boston, Massachusetts General Hospital, and the Dana-Farber Cancer Institute.

Made possible by a \$12.65 million, 5-year grant from the National Institutes of Health (NIH), the Center will facilitate bench-to-bedside development of cellular therapies – including therapies based on adult stem cells and, conceivably, embryonic stem cells – for the treatment of damaged and diseased tissue. In so doing, the Center plans to take on an array of illnesses such as cancer, heart disease, Parkinson's disease, kidney disease, diabetes, and other devastating conditions. The potential also exists to develop new means to repair and even grow organs for transplantation.

"We're very fortunate, it's a new type of endeavor," says Leslie Silberstein, M.D., senior investigator at CBRI and director of the Center. "The NIH has never funded something like this before." More translational research centers are likely to spring up around the country, however, reflecting the primacy of this approach in the NIH's new strategic "roadmap." The NIH is reacting to increased public and Congressional pressure for tangible rewards from the doubling of the NIH budget over the past five years.

The Center for Human Cell Therapy, primarily, is the brainchild of Silberstein, who is director of the Joint Program in Transfusion Medicine at the Brigham and Women's Hospital, Dana-Farber Cancer Institute, and Children's Hospital Boston. Dr. Silberstein is also the principal investigator and director of a NIH-funded, post-doctoral training program that prepares M.D.s and Ph.D.s for careers in transfusion medicine.

Joining Silberstein at the Center are co-directors David Scadden, M.D., of Mass General, and Jerome Ritz, M.D., of Dana-Farber. Drawing upon

the enormous breadth and depth of expertise at Harvard-affiliated medical institutions (there are 17 of them, including the CBR Institute), the Center is a timely solution to the growing gap between basic scientific research and clinical transfusion medicine. Until now, translational work in this field has been done piecemeal in laboratories or conducted with private funding.

The heart of the Center – the Translational Cell Therapy Laboratory – is housed at the CBR Institute and will be staffed by eight to ten scientists and technicians. One key project will be the development of sophisticated cell culturing and manipulation techniques. Feeding into the main lab are a handful of "shared resource cores" located either at CBRI (the flow cytometry core) or at nearby institutions. For instance, the tissue manufacturing/regulatory core has been set up at Dana-Farber.

Because they are so focused on their own work, most basic researchers are not thinking about the regulatory requirements and technical challenges to overcome before an idea can progress beyond mouse studies



THE POWER OF THREE: THE NEW CENTER FOR HUMAN CELL THERAPY IS A VISIONARY, COLLABORATIVE ENTERPRISE LED BY (LEFT TO RIGHT) DAVID SCADDEN, M.D., MASSACHUSETTS GENERAL HOSPITAL; LESLIE SILBERSTEIN, M.D., THE CBR INSTITUTE; AND JEROME RITZ, M.D., DANA-FARBER CANCER INSTITUTE.

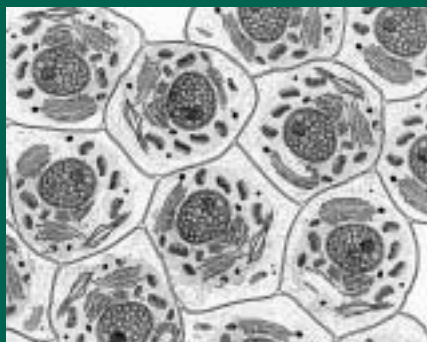


Illustration of a cluster of normal cells. The therapeutic use of healthy cells – in particular, immune cells and stem cells – is a new field with enormous potential for treating disease. *Courtesy, National Cancer Institute.*

toward clinical applications in humans.

According to Silberstein, “CBRI has an outstanding cadre of basic scientists. A lot of individuals have made major discoveries in their laboratories. However, we have a backlog of discoveries that need to be translated.” The Center, he says, is a powerful vehicle for translating new knowledge into treatments. “CBRI is best known for its high quality science, but we’re coming full circle.”

The circle started with Edwin Cohn, the founder of the CBR Institute. In the 1940s, Dr. Cohn and the large team he mobilized developed a revolutionary procedure (known as Cohn fractionation) to separate out the active proteins of plasma, such as the blood-clotting agent albumin, for therapeutic means. These products were employed on WWII battlefields, where delivering liquid blood plasma was all but impossible without refrigeration. Cohn fractionation saved thousands of lives then and continues to save lives today, in emergency rooms and on the battlefields of Iraq and Afghanistan.

“The impact of Cohn fractionation on human medicine and the world has been immense,” says Silberstein. Indeed, the spirit of Edwin Cohn lives at the Center for Human Cell Therapy, a venture melding the past of his discoveries about blood with present-day discoveries about inflammation and immune defense.

**THE GOAL OF THIS COLLABORATION: A FUTURE IN WHICH CELLS JOIN DRUGS AS A POWERFUL MEANS OF HEALING.**

### IT TAKES A VISION

On the cusp of a major new endeavor, one can’t help but want to put things

into perspective. And that’s exactly what Leslie Silberstein has done.

He isn’t your typical scientist. “I never had any formal research training,” he says with a smile and a shrug. He received his M.D. from the University of Leiden, The Netherlands, in 1977. After several years of training in clinical hematology and oncology, he took his first job as the assistant director of the blood bank at the University of Pennsylvania medical center. There, he says, “I reinvented myself. I started going to people’s labs in my spare time and learning how to do research. I guess I was lucky and worked hard. I got my first grant after five years and have been funded [by NIH] ever since.”

“I like looking at the big picture,” he states. “I get as much, even more, satisfaction bringing together people of different backgrounds and expertise and building something that wasn’t there before. For twenty years, my career goal has been to make transfusion medicine an academic discipline.” Reflecting back on his days at Penn, he adds: “I wanted to take transfusion medicine from what it was at that time – delivering safe blood to hospitals – to the next step, which is to develop these new forms of cellular therapies. Otherwise, the field was going to die. It just wasn’t going to further develop.”

### 21ST CENTURY TRANSFUSION MEDICINE

In 1818, James Blundell performed one of the first successful human blood transfusions. Blundell didn’t come up with the idea himself. He was inspired by his mentor John Henry Leacock who, experimenting with cats and dogs, had established that donors and recipients had to be of the same species. Leacock published his findings, then sailed for Barbados and never transfused again. Blundell

kept working and later became the “father of blood transfusion.”

Although its roots lie in the ground prepared by Leacock and Blundell, as well as by Edwin Cohn, human cell therapy is a decidedly 21st century medicine. For most of its history, blood transfusions involved transferring whole pints of blood. Only in the last five to ten years have physician-scientists been able to isolate, manipulate, grow, and transfuse with cells alone. Thus the term, “cellular therapy.” Silberstein points to the practice of isolating and repairing the defective genes of immune cells in patients who would otherwise die of immune deficiency. That, he says, is one of the best success stories to date. Bone marrow transplantation, too, is a successful procedure in which the stem cells of bone marrow revive the destroyed hematopoietic (blood-related) and immune systems of patients with cancer.

As an example of the type of project the Center will fund, researchers have identified a new immune cell in the bone marrow and demonstrated its efficacy at attacking cancer in an animal model. But extrapolating animal model results to humans poses an immense challenge, particularly for scientists who have no expertise in isolating their cell of interest from human tissue or growing them under FDA/GMP (Food and Drug Administration/Good Manufacturing Practice) conditions.

How, for example, do you purify and grow human cells without killing them? How do you manipulate them outside the body so that they retain all their other characteristics? And what steps ensure that the manipulated cells get to their intended destination after they are introduced into the body? After you’ve figured that out, says Silberstein, “then you can start to think about getting funding

to put [the therapy] into clinical trial.”

By providing the money and resources for that initial translational step, which federal funds don't normally cover, the Center will both streamline the translational process for new therapies and improve existing ones. Silberstein points to Graft vs. host disease, a complication associated with bone marrow transplants, in which transplanted immune cells attack the recipient's tissues.

Imagine, he says, having the knowledge to neutralize those attack cells, “to improve upon the magic bullet and improve the quality of life for bone marrow transplant recipients.”

The Center will accept proposals from scientists at Harvard-affiliated institutions. David Scadden, co-director of the Center from MGH, foresees a stream of projects, with two or three ongoing at any time. The key, he says, sounding as much like a cheerleader as a researcher, is to establish a pipeline of projects, to keep the momentum going.

Most projects, Scadden estimates, are expected to take from six months to a year to complete, after which researchers should be well equipped with the knowledge necessary to finish the translational process and enter clinical trials. While the Center's researchers will act deliberately and incrementally, developing strict, standardized approaches to manufacturing cells and tissues, their work may seem fast compared to the glacial pace at which most discoveries now move into the realm of testing and clinical practice.

Indeed, the first round of research proposals should be funded by early 2005. According to Jerome Ritz, co-director of the Center from Dana-Farber, clinical trials could begin within a few years on patients with a

type of head and neck cancer. After completion of the initial translation phase, volunteer patients would receive injections of donated immune T cells that have been modified according to methods developed at the Center. Given good results, the patients would then receive injections of their own modified T cells, a procedure that eliminates problems related to genetic incompatibility.

Other potential projects may include the development of cells that speed healing of cartilage in knees and a cellular vaccine for cancer. In the latter case, researchers at the Center would genetically enhance the ability of certain cells to stimulate an immune response to a protein expressed on cancer cells.

### **JUST THE BEGINNING THERE ARE AS MANY POTENTIAL CELL THERAPIES AS THERE ARE CELL TYPES.**

“I think we are just at the beginning of understanding all the differences,” Silberstein says of the hundreds of different blood cell types that likely exist. “The challenge is going to be finding those that are viable for therapeutic applications.” Viability includes factors such as the cells' ability to function in concert with the body's natural cells, as well as the level of harmful side effects that may result from cellular intervention.

Blood cells are only one type of cell suitable for cellular therapy. The Center will also team up with the new Harvard Stem Cell Institute, which opened its virtual doors in 2004. (David Scadden is co-director of the Institute.) The focus of the Institute is so-called “proof-of-principle” research: for example, can a stem cell become a muscle cell? Once this kind of vital question is answered, the

Institute will function as an indispensable resource for the Center for Human Cell Therapy. There the next level of questions can be tackled. For example: if a stem cell can be made into a muscle cell, how are those cells maintained under conditions necessary for clinical success?

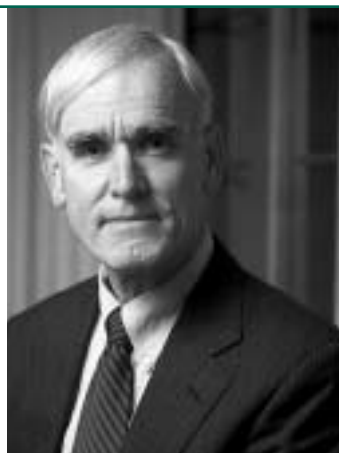
Research with embryonic stem cells is not currently scheduled, but the three directors of the Center envision a possible role for this kind of work in the future, in accordance with federal funding regulations and using approved embryonic stem cell lines. The Center may seek private funding for embryonic stem cell research, if it is adopted.

Not only is Leslie Silberstein's vision bringing the CBR Institute full circle – back to the type of translational research that Edwin Cohn pioneered – there is also a good chance that the collaboration inherent to the Center may breed other productive partnerships. As Silberstein explains, “The idea is to attract other basic scientists to studying human cells. Not everything that we learn from mouse cells holds up in human cells. This becomes even more relevant if you want to put human cells into people as a therapeutic measure.”

That is the goal – an eminently achievable one, given the Center's freedom to innovate and its emphasis on collaboration and selfless cooperation. Co-directors Silberstein, Scadden, and Ritz – coming from three very distinct institutions – harmonize on this point: the Center's work is all about breaking the logjam between discovery and delivery, between research and results.

“Nothing would give me more gratification,” says Dr. Silberstein, “than to look back after ten years and see that we were on the right track.”

## FINANCIAL REPORT



Fiscal year 2004 may be remembered most as the year when The CBR Institute for Biomedical Research changed its name, celebrated its 50th anniversary, and completed a strategic plan. However, it was also a year of expansion of research space – the first such expansion since a move to the Warren Alpert Building in 1992.

Dr. Fred Rosen took over leadership of the Institute in 1987 with a vision of transforming the organization into a world-class research institute that could flourish in the competitive world of the 21st century. Competition for research funds and gifts would not only be with other independent research institutes performing “basic science” research, but also with universities and major teaching hospitals that perform clinical research. He recognized that attracting and retaining world-class scientists required first-class research facilities.

That move in 1992 doubled the Institute’s research space and came with a great amount of financial risk. New NIH grants were required to cover the costs of the space. Dr. Rosen executed a plan that was equal to his vision: he recruited a group of the best scientists in the nation who were able to secure the NIH grant base required to pay for this new, state-of-the art research space.

As the graph on the facing page demonstrates, the Institute’s research operations have grown by an average of 18 percent per year over the past five years, with total operating expenditures increasing from \$19.0 million in 1999 to \$35.7 million in 2004. During that time period, grant funding awarded to our scientists by the National Institutes of Health (NIH) increased by 65 percent.

During the past year, the Institute’s research operations increased by 17 percent and NIH grant activity grew by 13 percent. Our NIH growth far surpassed the increase of 3.7 percent in the overall NIH budget. CBRI’s investigators have taken advantage of new NIH funding opportunities by obtaining grants in the areas of bioterrorism and translational research. The Institute has achieved a position of national prominence, ranking 15th among the 89 members of the Association of Independent Research Institutes when measured by the level of NIH grant funding.

We moved into 8,000 square feet of additional research space in the Warren Alpert Building during the fiscal year, a commitment that increased our space in that building by 30 percent. This was the first phase of the Institute’s strategic plan that includes an intermediate-term goal of adding a total of 28,000 square feet of space and a long-term goal of consolidating all operations in a single research facility.

As the Institute continues to implement its strategic plan by recruiting new investigators and taking on additional research space, it will be important to keep in mind the fundamentals that have contributed to its past financial success. They include utilizing all space efficiently and effectively and making sure that the investigators who occupy the space have sufficient full-overhead (primarily NIH) grants to accommodate the cost of the space.

Handwritten signature of Theodore M. Cronin in black ink.

Theodore M. Cronin,  
Vice President of Finance  
& Chief Financial Officer

Handwritten signature of Walter M. Pressey in black ink.

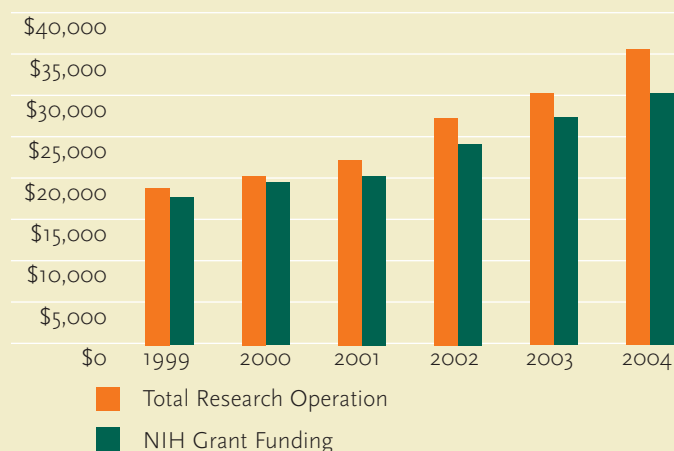
Walter M. Pressey  
Treasurer

## Selected Financial Data\*

Fiscal Year Ended June 30, 2004  
(Dollars in thousands)

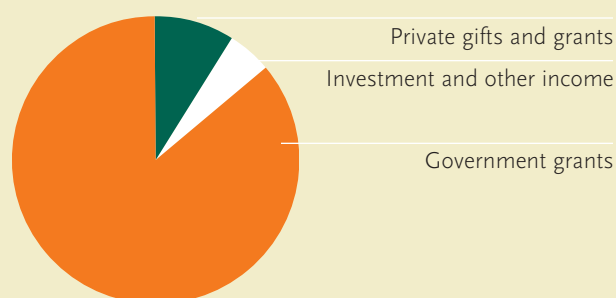
### GROWTH IN OPERATIONS

over a five year period



### REVENUES

FY 2004



### TOTAL OPERATING EXPENSES

#### BALANCE SHEET

Cash and investments	12,327
Other assets	2,454
Property and equipment	3,214
<b>Total Assets</b>	<b>17,995</b>
Accounts payable and accrued expenses	3,316
Deferred revenues	304
Notes payable	3,738
Unrestricted net assets	8,090
Temporarily restricted net assets	549
Permanently restricted net assets	1,998
<b>Total Net Assets</b>	<b>10,637</b>
<b>Total Liabilities and Net Assets</b>	<b>17,995</b>

#### UNRESTRICTED REVENUES & EXPENDITURES

<b>Revenues</b>	
Government grants	30,688
Private gifts and grants	3,299
Investment and other income	1,758
<b>Total Revenues</b>	<b>35,745</b>
<b>Expenditures</b>	
Research direct costs	21,203
Facilities and administrative	13,650
Fund raising and other	875
<b>Total Expenditures</b>	<b>35,728</b>
<b>Increase in Net Assets – CBR Institute</b>	<b>17</b>
<b>Net Loss – Subsidiary – CBRL</b>	<b>(411)</b>

\* This financial summary is derived from the financial statements, audited by KPMG, LLP. Copies of these statements are available upon request.

## GIVING AT CBRI



We are extremely grateful for our donors. Philanthropy is increasingly important to the CBR Institute and, thus, to the patients who will benefit from the fruits of our research in coming generations. Gifts provide two ingredients essential for our world-class institution: financial stability during a time of stalled support from the federal government, and financial flexibility to seize discoveries and convert them into new, potentially productive lines of research.

Thus, we deeply appreciate the gifts, grants, and commitments from individuals, private foundations, and corporations that the Institute received in fiscal year 2004. Gifts and multi-year commitments totaled \$4,453,000, an increase of 40.6 percent over FY 2003. Cash income from private sources totaled slightly more than \$4 million, an amount equal to approximately 15 percent of our operating budget. Overall, we are gratified that gift transactions have tripled during the previous four fiscal years. CBR's strong growth is noteworthy in the context of philanthropy nationwide, which only last year began to recover from its nadir during 2000-2002.

The year witnessed several major awards from private foundations, which included: \$1,134,000 from the Ellison Medical Foundation; \$750,000 from the Sandler Program for Asthma Research; and \$150,000 from the American Society of Hematology Foundation. Generous distributions from the estate of CBRI's late trustee and benefactor, Allen Latham, Jr., bolstered the Institute's endowment, as well as the endowment of the Latham Family Professorship.

In October 2003, the CBRI community took time to observe our 50th birthday and reflect on the Institute's remarkable achievements. Nearly 1,000 individuals participated in events related to the anniversary: a scientific symposium, celebratory dinner cruise in Boston Harbor, the gala in Boston's Westin Hotel, and an enthusiastically received program for Boston public school students at the Museum of Science. Honoring our past, we never ceased working, however, to ensure promising opportunities for private support of the Institute's work in the future. Several factors bode well for continued growth in giving to CBRI.

First is the commitment of our volunteers and friends, exemplified by the energy and growth of the CBRI Associates Program. Second is the remarkable creativity of our investigators and staff. Next is the projected health of our operating budgets, a very important factor in maintaining the confidence of our donors. We completed a strategic plan during the fiscal year that defines our mission and lays the groundwork for critical work during the next decade with the promise to improve health care for everyone. Our potential is great; the executive summary of the plan is included for your review in this report.

Finally, the Institute launched a new Web site in 2004, which vividly communicates our research and its benefits for patients. As the importance of our discoveries and their clinical potential become more apparent, CBRI is vigorously encouraging new donors outside of our traditional giving communities to support our mission.

A handwritten signature in black ink that reads "Laurence W. Herron". The signature is fluid and cursive, with a long horizontal line extending from the end.

Laurence W. Herron  
Vice President for Development & External Relations

**CAPITAL GIFTS & COMMITMENTS FOR ENDOWMENT,  
RESEARCH, AND FACILITIES**

American Association for the Advancement of Science  
American Cancer Society  
American Foundation for AIDS Research  
American Heart Association  
American Society of Hematology  
Aplastic Anemia Foundation  
Arthritis Foundation  
Biogen Corporation  
Brian Brandt  
Cancer Research Institute  
Dr. John F. and Mary Adele Crigler  
Dana Foundation  
Damon Runyon Cancer Research Foundation  
Donald C. and Joyce Eckart  
The Ellison Medical Foundation  
European Molecular Biology Organization  
Jonathan A. French Charitable Trust  
Dr. Robert J. and Muriel Haggerty  
Charles H. Hood Foundation  
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Irvington Institute for Immunological Research  
Israel Binational Research  
Jeffrey Modell Foundation  
Estate of Allen Latham, Jr.  
Ruth N. Latham Charitable Trust  
Latham Family Educational Trust  
Leukemia & Lymphoma Society  
Lymphoma Research Foundation  
Jill and Frederick H. Lovejoy, M.D.  
Joan MacPherson  
Katherine MacPherson  
March of Dimes Birth Defects Foundation  
Multiple Myeloma Research Foundation  
National Cancer Institute of Canada  
Oxford Fund, Inc.  
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Martin Peretz  
The Perkin Fund  
Pew Latin American Fellows Program in the Biomedical Sciences  
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Sirna Therapeutics  
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**GIFTS FOR OPERATIONS  
CBRI Fellows  
\$20,000 & Above**

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Mitchel Sayare  
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WRG Foundation for William R. and Adele Grant

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\$10,000 & Above**

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Joseph Perini Memorial Foundation

**Edwin J. Cohn Society  
\$1,000 & Above**

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## OUR TEAM 2004 – 2005



The CBR Institute is much more than talented individuals. It is talented individuals working together to produce path-breaking results in biomedical science. Indeed, the most important aspect of medical research is collaboration, a value that CBRI considers paramount both inside its walls and with its scientific partners all over the world.

Over 330 people work at the CBR Institute, from senior scientists overseeing large laboratories to support personnel that keep our state-of-the-art facilities safe and humming along. In the past year we have launched new efforts to enhance the sense of community here. Collaboration on a shared mission that leads to new therapies and cures for dread diseases is our overriding goal.

One excellent example is our new orientation program, in which employees learn about multiple aspects of the Institute – including history, safety, technology transfer, institutional funding, and public affairs issues – in order to become ambassadors for CBRI as it seeks to raise its public profile and expand the scope of its research.

The new Center for Human Cell Therapy, headquartered at CBRI, is a great example of how we collaborate with other premier research institutes, in this case Massachusetts General Hospital and Dana-Farber Cancer Institute. Among many benefits, this venture is likely to produce new technologies for harvesting individuals' cells and using them therapeutically in patients.

Another new area of collaborative energy at CBRI is research into countering bio-terrorism. For instance, Senior Investigator Judy Lieberman, M.D., Ph.D., is leading a multi-institute project focused on RNA Interference as a tool against this emerging threat. However, in a sense, CBRI's move into bio-terrorism research is history repeating itself. Our founder, Edwin J. Cohn, pioneered the fractionation of blood into healing components, such as blood-clotting albumin, employed on the battlefields of World War II and still today in Iraq and Afghanistan.

Top-notch facilities enable our scientists to make breakthrough discoveries. In FY 2004 we christened a new multi-photon, intra-vital microscope, which captures the traffic of immune cells in living animals, as well as expanded cell sorting and confocal microscopy core facilities. In addition, our bio-level 3 facility, for the handling of sensitive pathogens, is now undergoing a \$300,000 renovation to support bio-terrorism research.

Finally, we've increased our research space by leasing an additional 8,000 square feet. This step partially addresses the space shortage which has restricted CBRI's ability to absorb greater amounts of funding from public and private sources, and it gives us room to develop our farm team of promising young investigators. The space expansion is a component of our overall strategic plan, which calls for the eventual gathering of CBRI staff under the same roof.

All of these measures – enhanced staff orientation, path-breaking research collaborations, cutting-edge facilities – will further spur the collaborative spirit of the Institute as we perform the basic research today that leads to cures tomorrow.

A handwritten signature in black ink, appearing to read "Michael Lanner". The signature is fluid and cursive, with a long horizontal stroke at the end.

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Executive Vice President  
Chief Administrative Officer

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## CBRI STRATEGIC PLAN: EXECUTIVE SUMMARY

Approved by  
Board of Trustees,  
2004

For 50 years The CBR Institute for Biomedical Research, Inc. (CBRI) has contributed to Boston's leadership in biomedical research and commercial biotechnology. CBRI advances human health by discovering new knowledge about immunology and inflammation. This mission includes training research fellows for the next generation of academic and industrial leaders in biomedicine as well as the transfer of technology to industry for the development of medical treatments and cures. One of America's premier independent research institutions,

**CBRI IS RECOGNIZED AMONG RESEARCHERS WORLDWIDE FOR ITS BREAKTHROUGHS THAT INCREASE THE BODY'S ABILITY TO FIGHT DISEASE AND TO HEAL.**

The Institute is affiliated with Harvard Medical School.

CBRI's work in recent years has increasingly centered on immunology, immune defense, and inflammation.

**IMMUNOLOGY** studies the structure and function of the immune system, which contains the organs, tissues, cells, and cell products that protect the human body from disease. Immune system research influences most aspects of medical discovery, healthcare, and disease management.

**IMMUNE DEFENSE** is the coordinated, complicated reaction of the immune system to fight disease-causing agents, including viruses, bacteria, and other types of infection. Immune defense also helps to keep damaged cells from becoming malignant. In addition, it will play an important role in developing treatments for autoimmune diseases and immunodeficiency, as well as protections against bioterrorism.

**INFLAMMATION** is the gathering of immune system cells and molecules at a site of infection. Though a positive response to infection, inflammation is harmful when prolonged or misregulated. Heart disease, Alzheimer's disease, ulcers, and frailty in old age are among conditions linked with chronic inflammation.

CBRI pursues its mission in a field – biomedical research – that a recent report by the Brookings Institution described as “uncertain, time-consuming, and expensive.” Though scientifically powerful, CBRI faces challenges on several fronts:

- Heavy dependence on public funding through the National Institutes of Health (NIH);
- Inadequate capital base (endowment);
- Discoveries may take a generation to bear fruit in the clinic;
- Modest public profile;
- Existing physical facilities limit growth; and
- Executive leadership in transition.

To meet these challenges, the Institute's strategic plan must articulate well-defined scientific and management initiatives to meet the following objectives:

- Global leadership in research on immune defense and inflammation;
- Sufficient facilities and space for its researchers;
- A broader base of funding;
- A strong brand and wider public recognition;
- An executive structure that balances scientific and business components; and
- A smooth transition to new leadership.

To ensure *global leadership in research*, the Institute will:

- Focus institutional resources, fiscal and human, on research related to immune defense and inflammation;
- Organize four areas of research concentration: adhesion molecules and inflammation; autoimmunity and allergy; genetics of immunodeficiency and cancer; and immune defense against viruses, tumors, and infectious diseases;
- Identify specific research goals in each area and appoint area leaders to coordinate the work and resources of each concentration toward these goals;
- Recruit six new investigators: two junior investigators in adhesion molecules; one junior investigator in autoimmunity; two junior investigators in genetics of immune deficiency and cancer; and one senior investigator in immune defense against viruses and infections; and
- Pursue short-term and long-term needs for space and facilities. During the next five years, CBRI will lease up to 30,000 square feet of additional space, beginning with 8,000 square feet in January 2004. CBRI will review options and come to a decision for consolidating the Institute's operations in a single location during this five-year period.

To promote *financial strength*, the Institute will:

- Seek to increase NIH funding from \$26.9 million to \$38.0 million annually through the utilization of additional research space and the productivity of new investigators;
- Enact fiscal policies to:
  - 1) Encourage balanced operating budgets;
  - 2) Maintain CBRI's high indirect cost recovery through the controlled, strategic use of low-overhead grants;
  - 3) Invest institutional funds to recruit and equip junior investigators and meet targeted institutional research objectives;
  - 4) Direct capital expenditures towards core, shared equipment and other facilities; and
- **SEEK TO BROADEN THE INCOME BASE THROUGH AN ENLARGED ENDOWMENT, GROWTH IN UNRESTRICTED ANNUAL GIVING, PHILANTHROPIC SUPPORT FOR CURRENT OPERATIONS,** licensing fees and royalties from the transfer of technologies to the commercial sector and privately sponsored research. This will require:
  - 1) An endowment of \$20 million in three years and \$50 million in five years;
  - 2) A \$5 million base of annual philanthropy or an amount equal to 10 percent of CBRI's annual operating budget, whichever is greater;
  - 3) \$500,000 minimum annual income from licensing fees for technology and royalties from the commercial use of CBRI technology; and
  - 4) An increase in sponsored research income from \$600,000 to \$800,000 annually.

To increase *public awareness and appreciation*, the Institute will:

- Complete the branding study begun during 2003 and implement an institutional brand, which communicates the Institute's values and products comprehensively; and
- Employ marketing to translate the excellence of CBRI's institutional mission into financial support.

To insure *future leadership*, the Institute will:

- Appoint a scientific director by December 2004 and a new president by June 2005.

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**Editorial**

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**2004 Annual Report**