In 2004, two extraordinary universities – Harvard and MIT – and two extraordinary philanthropists – Eli and Edythe Broad – launched a bold experiment in biomedicine. In founding the Broad Institute of MIT and Harvard, they sought to define a new kind of research institution for the 21st century.

The Broad Institute began as a ten-year experiment, with an unprecedented gift from the Broad family ($200 million with instructions to spend it within a decade) and a union of two world-leading research centers (the Whitehead/MIT Center for Genome Research, a flagship of the Human Genome Project, and Harvard’s Institute for Chemistry and Cell Biology, a pioneer in therapeutics).

The experiment was risky. It required reaching across different disciplines, different institutions and different research cultures. We had no idea whether such a model could succeed. But, in a remarkably short time, the Broad Institute grew into a vibrant community involving more than 1,500 scientists across Boston with collaborations across the world.

In 2008, the partners declared the experiment a success and, with the additional generous gift of a $400 million endowment from the Broad family, agreed to establish the Broad Institute as a permanent institution closely affiliated with MIT, Harvard, and the Harvard-affiliated hospitals.

In 2009, the Broad Institute formally made this transition to permanence – with its legal incorporation and under the stewardship of a wise Board of Directors (page 44).

This is our first Annual Report. For this occasion, I have tried to express in the accompanying essay (p.6) the core beliefs and aspirations that animate the Broad community.

We invite you to join us in our mission, which will ultimately be measured by the impact of this generation on the health of our children and our children’s children.

Sincerely,
Opportunity & Responsibility
The Broad Institute is not a typical research institution. Its mission and organization flow from two core beliefs — that:

1. This generation has a historic opportunity and responsibility to transform medicine by using systematic approaches in the biological sciences to dramatically accelerate the understanding and treatment of disease.

2. To fulfill this mission, we need new kinds of research institutions, with a deeply collaborative spirit across disciplines and organizations, and having the capacity to tackle ambitious challenges.

A historic opportunity and responsibility to transform medicine

Biological science in the 20th century made breathtaking progress in our understanding of life. The molecular biological approach, which took hold at mid-century, revealed the fundamental principles of life. With increasingly powerful tools, its reach gradually extended from the simplest viruses to bacteria, yeast, fruit flies, and mice. By the turn of the century, scientists had read the entire DNA sequence of the human genome.

The mission of the next scientific generation is to bring the full power of this revolution to the study of human disease. To fulfill this responsibility, the scientific community needs to:

Complete the comprehensive picture of the molecular components of life. The Human Genome Project was only a first step in laying out the “Periodic Table” of life. We need a comprehensive picture of all the functional elements encoded by the human genome — including the regulatory controls, genes, RNAs, proteins, and metabolites. We also need a systematic catalogue of their genetic variation across the human population and their evolutionary variation across a wide range of species.

Define the biological circuits that underlie cellular responses. Cellular components work together in biological “circuits” that determine a cell’s identity, integrate information from outside the cell to make decisions, and that carry out cellular responses. We must move from the “parts list” to a comprehensive identification and understanding of all of the circuitry.

Discover the molecular basis of all major inherited diseases. The fundamental cellular pathways underlying most inherited diseases remain a mystery, hampering efforts at prevention and treatment. By comprehensively studying the full range of genetic variants in the human population, it should be possible to identify those genes and biological pathways that influence susceptibility to disease, and to create new experimental disease models to propel the development of effective treatments.

Discover the mutations that lead to all major types of cancer. Cancer is a genomic disease, in which cells accumulate specific mutations that confer new, often deadly properties. Without the ability to read these changes, oncologists have had only blunt instruments to treat cancer. With our new genomic and chemical technologies, we need to develop systematic catalogues of all the molecular changes in the cancer genome; classify tumors not merely by the cell type affected (breast, lung, kidney, and so on) but by the cellular pathways that are altered; develop more powerful and less toxic cancer therapies; and develop new tools for the early detection of cancer and monitoring of targeted cancer treatment.

Discover the molecular basis of all major infectious diseases. Viruses, bacteria, and other pathogens are responsible for an enormous burden of disease,>
especially in developing countries. Each pathogen has its own strategy, involving a complex and dynamic interplay between pathogen and host. Tackling infectious disease will require comprehensively defining the components and pathways in both the pathogen and the host that are essential for the pathogen to resist attack and cause disease. We then need to turn this knowledge into effective vaccines, rapid diagnostics, and new kinds of therapeutics.

Reinvent the process of therapeutic discovery and development to make it vastly more effective and efficient. Pharmaceutical science has not kept pace with biomedical discovery: It currently targets only a tiny fraction of human gene products for therapeutic benefit, focusing primarily on those already proven “druggable” and using only a limited range of laboratory assays. Moreover, academic researchers tend not to engage in therapeutic development because the required tools are out of reach. We need to reinvent therapeutic science to make it accessible to the creative energies of a new generation of researchers. This will require new ways to synthesize chemicals of unprecedented diversity; to carry out high-throughput screening on living cells and tissues; to discover molecules that modulate defective pathways and rapidly identify their targets; to optimize efficacy and safety; and to find biomarkers to increase the accuracy and efficiency of clinical trials. Together, these efforts can propel a renaissance in therapeutic science.

New kinds of research organizations
The work of this scientific generation is about integration. It requires a comprehensive view of the billions of bases in the human genome, the tens of thousands of components in biological systems. It requires combining biology, chemistry, mathematics, computation and engineering with medical science and clinical research. It requires diverse infrastructure, and a wide range of scales and time horizons. The traditional model of each scientist’s laboratory as a self-sufficient island—which was widely successful in biomedical research in the 20th century and remains appropriate for many purposes today—cannot alone address the biomedical challenges...
outlined above. Nor does the traditional model of organizing science along disciplinary lines enable the progress we seek, which is catalyzed only by the convergence of multiple perspectives. The challenge of integrative science is particularly acute for young scientists. Alone, they cannot acquire all the expertise, create the full range of infrastructure or raise all the support needed to take bold risks.

We need new models for research organizations that:

Unleash the creativity and ambition of a new generation of scientists by giving them a supportive, vibrant, and collaborative intellectual environment and access to cutting-edge capabilities. Creative and ambitious scientists are the secret ingredient of scientific progress — bringing fresh ideas, boundless energy and a sincere desire to change the world. But these young researchers face serious challenges in assembling all the pieces needed to pursue their dreams — collaborations, capabilities, infrastructure, funding. We need to lower these barriers by building communities that help scientists from different fields and institutions come together around common challenges, empowering them to share expertise, create common infrastructure, and obtain seed funding.

Complement individual creativity with the power of industrial-strength teamwork. Academic laboratories typically consist of a professor and trainees: there are few positions in academia for world-class professional scientists of the sort found in industry. There are enormous returns for bringing the power of professional scientific teams to help tackle basic research challenges.

Nurture a deeply collaborative environment. Successful collaboration depends on institutional culture, which must actively promote and reward open communication across laboratories, disciplines and institutions.

Act nimbly. To encourage creativity, an organization must be able to move quickly. It must take risks on new approaches and new structures that fly in the face of conventional wisdom.

Tackle bold projects. To meet the range of biomedical challenges ahead, an organization must be able to mount projects at any scale, from a single individual to teams of hundreds of scientists.

Share openly. Seizing the opportunity before us requires creating methods, tools, and massive data sets, and making them available to the entire scientific community. Rapid and free sharing can dramatically accelerate the cycle of progress.

Reach globally. Biomedicine must focus on the medical problems of the entire world, not just advanced economies. Furthermore, it must include scientists in developing countries as true partners in the endeavor, bringing their unique knowledge to promote scientific advancement.

What is the Broad Institute?
The Broad Institute is the response of the Harvard and MIT communities to these core beliefs and their challenges. The Broad Institute is:

• A new kind of research institution aimed at propelling the transformation of medicine by focusing powerful new approaches on the understanding and treatment of disease.
• A collaborative community that unites more than 150 faculty and more than 1,500 scientists from across MIT, Harvard and the Harvard-affiliated hospitals — and beyond — with the aim of empowering and supporting a new generation of scientists to tackle ambitious challenges in basic biology and disease.
• A scientific community with deep, multidisciplinary and integrated programs in cancer, infectious disease, metabolic and psychiatric diseases, as well as research in genome biology, chemical biology, cellular circuitry, and computational biology.
• A scientific community enabled by world-leading, professionally-led platforms, providing unparalleled infrastructure ranging from genome sequencing to therapeutic discovery and development, and making it possible to tackle projects at any scale.
• A flagship for many of the most ambitious international scientific projects of our time.
• A community with a longstanding commitment to rapid and free data sharing and to international collaboration, born of a history in the Human Genome Project.
• An experiment in how to organize biomedical science for the 21st century.
Who is the Broad Institute?
The Broad community brings together a diverse group of undergraduate and graduate students, postdocs, professional scientists, administrative professionals, and faculty from across our Partner Institutions (see sidebar). We aim to cultivate a culture and environment that encourages scientific creativity, in which all participants (regardless of role and seniority) “own” the scientific mission of the institute, and in which ambitious, energetic, and bright researchers are empowered intellectually and appropriately resourced to tackle even the most difficult biomedical challenges.

Leadership

The unique, “experimental” nature of the Broad Institute aims to balance the best of academia and industry, individual-initiated and industrial-scale science, and the excitement and ideas of newer scientists with the insights and experience of more established scientists, all across multiple institutions and disciplines. These kinds of “creative tensions” demand a novel approach to leadership. A Leadership Group composed of Core Faculty (currently six), Program and Platform directors, and senior administrators gathers weekly to share ideas, assess the status of projects, and discuss future directions. Far from being cumbersome, this combination of talents and perspectives at the level of Broad leadership ensures that the institute remains nimble and effective in the scientific paths it pursues.

The Broad Institute’s partner institutions

Meeting the challenges of biomedicine requires bringing together world-class expertise across many disciplines, exceptional and creative scientists, and unprecedented technological resources. All of these can be found within a unique three-mile radius around the Broad Institute, and all of them are critical elements in this young organization’s amazing success to date. The Boston area’s pre-eminent biomedical research organizations — the Massachusetts Institute of Technology, Harvard University and its affiliated major teaching hospitals (Beth Israel Deaconess Medical Center, Brigham and Women’s Hospital, Children’s Hospital, Dana-Farber Cancer Institute, and Massachusetts General Hospital) all bring their particular strengths to the Broad, weaving them together in a collaborative effort to completely transform medicine and biology.
Organization
The Broad Institute encompasses three types of scientific organizational units, each of which is tightly integrated with the others: Core Faculty Laboratories, Programs, and Platforms.

Core Faculty Laboratories
Each Core Faculty member leads a laboratory consisting of students, postdocs, and scientific staff. These laboratories are similar in their structure and membership to laboratories at Harvard, MIT, and the hospitals; however, rather than being embedded in a department in which every faculty member is from the same discipline (e.g., Genetics, Chemistry, Infectious Disease), the Core Faculty labs are physically adjacent to scientists from other disciplines and interests. Moreover, the trainees in the Core Faculty laboratories are typically engaged in one or more Broad Programs, and often benefit from and collaborate with the Broad Platforms, as described below.

Current Core Faculty include:
David Altshuler, M.D., Ph.D.
Todd R. Golub, M.D.
Deborah Hung, M.D., Ph.D.
Eric S. Lander, Ph.D.
Aviv Regev, Ph.D.
Stuart L. Schreiber, Ph.D.

Programs
At their core, Broad Programs are intellectual communities of scientists that bring together Associate and Core Members, their labs, and Broad staff around a shared scientific focus. Members meet regularly to share ideas between labs, catalyze collaborations that extend beyond the capabilities of any individual lab or institution, and to launch and execute ambitious projects with the potential for a transformative impact in their field.

Current Programs include:
Cancer
Defining the genomic basis of cancer, understanding its weaknesses, and driving new therapeutic and diagnostic approaches.

Genome Biology
Uncovering all the functional elements of the vertebrate genome and describing their gene regulatory machinery, and comprehensive cataloguing of thousands of microbial and insect vector genomes.
Epigenomics
Applying genome-wide profiling of DNA methylation, histone modifications and regulatory proteins to understand the role of chromatin in genome regulation during cellular differentiation and in diseased states.

Cell Circuits
Deciphering functions and interactions of critical molecular components in cells through novel applications of proteomics, RNAi and other technologies, with the goal of systemically reconstructing cellular circuits.

Psychiatric Disease
(The Stanley Center for Psychiatric Research)
Unraveling the genetic and molecular basis of psychiatric disease, particularly bipolar disease and schizophrenia, with the ultimate aim of improving diagnosis, treatment and, if possible, prevention.

Metabolism
Pioneering new approaches for systematically investigating and targeting the metabolic basis of human disease, ranging from Mendelian syndromes to complex disorders such as diabetes, obesity, and cardiovascular disease.

Medical and Population Genetics
Understanding how multiple forms of genomic variation contribute to susceptibility to a range of human diseases and to individual responses to therapy.

Chemical Biology and Novel Therapeutics
Integrating innovative small-molecule chemical biology and genome biology to yield therapeutics matched to patients’ genomic signatures.

Infectious Disease
Building and applying genomic tools to understand the mechanisms behind infectious diseases and comprehensively defining the critical pathogen-host molecular interactions in order to transform approaches to finding effective vaccines, diagnostics, and novel therapeutics.

Platforms
Broad Platforms are professional scientific organizations that bring together the technological, informatics, and management expertise necessary to create unmatched technological capabilities for undertaking Broad projects, and to carry out projects that are challenging in scope and/or scale. Broad Platforms are led by and composed of professional staff scientists who have deep expertise in each scientific area, and the organizational skills required to push the frontier of rapidly evolving technologies, carrying out projects that could not be undertaken within a single research laboratory. Platform and Program scientists work closely together, and with other collaborators around the world, to tackle critical challenges in understanding human biology and disease.

Current Platforms include:

Genome Sequencing – with the world’s largest and most advanced DNA sequencing capacity including sample preparation and applications development.

Genetic Analysis – with the world’s largest installation for the development and application of high-throughput genotyping and gene expression analysis.

Chemical Biology/Novel Therapeutics – with the academic world’s largest and most advanced chemical compound library-building capability and state-of-the-art screening facilities.

RNAi – with world-leading capabilities in loss- and gain-of-function genetic approaches to systematically discover mammalian gene functions and interactions.

Biological Samples – with state-of-the-art ability to receive, process, provide quality control, and to prepare, store, and retrieve hundreds of thousands of patient biospecimens.

Imaging – with the state-of-the-art ability to computationally analyze large sets of biological images.

Proteomics – with groundbreaking capabilities to identify and quantitatively analyze proteins and their modifications to understand biology, define drug mechanism of action, and to identify proteins relevant to disease (for example, biomarkers) and health.

Metabolite Profiling – with standard-setting capabilities to quantitatively analyze endogenous metabolites in virtually any type of biological sample.

Honors and Awards
The success of Broad’s unique scientific culture, which supports and empowers the work of our many researchers, is reflected – at least in part – in the prestigious honors and awards bestowed on many Broad members this past year.

Significant honors and awards in 2008-2009 have included:

Lasker Award for Basic Medical Research
Gary B. Koren

Paul Marks Prize for Cancer Research
Matthew L. Meyerson, David Sabatini

Doris Duke Distinguished Clinical Scientist Award
Marcus Attefield

Doris Duke Innovation in Clinical Research Award
James E. Bradner, Benjamin L. Ebert, and Joel N. Hirschhorn

Howard Hughes Medical Institute Early Career Scientist Award
Bradley E. Bernstein, Michael Lahm, Peter Reddien, and Aviv Regev

NIH Director’s New Innovator Award
Pardis Sabeti and John L. Rein

NIH Director’s Pioneer Award
Aviv Regev

Merck Irving S. Sigal Memorial Award
Drs. Hung, Richard and Hindia

Rosenthal Memorial Award – American Association for Cancer Research
Todd Golub
The critical role of education

The Broad Institute is fundamentally committed to educational outreach through many formal and informal programs for all age groups.
Today you give us room to fly.”

The Broad Institute of Harvard and MIT was founded in 2003 and launched in 2004 as a groundbreaking ten-year experiment in scientific organization and culture, testing how effective venture philanthropy and inter-institutional collaboration could be in propelling biomedical progress. In only half that time, the institute’s founders were able to declare the experiment a resounding success.

On September 4, 2008, Eli and Edythe L. Broad announced to a large gathering of Broad members an unprecedented $400 million endowment gift— in addition to their previously pledged $200 million— to make the Broad Institute a permanent institution within the biomedical landscape. The announcement event included talks by Eli Broad, Massachusetts Governor Deval Patrick, Harvard President Drew Faust, MIT President Susan Hockfield, Nobel Laureate David Baltimore, and Broad Institute Director Eric Lander.

“Over my lifetime I’ve made a lot of different investments, and our investment in the Broad Institute has without question yielded the greatest returns,” said Eli Broad. “We’re now making a $600 million bet that the Broad will be the place where the greatest scientific discoveries take place.”

With the Broads’ endowment of $400 million the Broad Institute has transitioned to a permanent, nonprofit 501(c)(3) organization. Harvard and MIT remain at the heart of Broad, continuing to help govern the institute (see page 44 – Board of Directors).

“Every good experiment leads to the need for more experiments,” said Eric Lander. “What we really need to know now is not whether we can create a successful institute, but whether we, as a community and as a world, can transform human health. That answer will take decades. With Eli and Edythe’s gift of a permanent endowment, we can focus on this goal five years ago. Now you give us room to experiment. Today you give us room to fly.”

Short History of the Broad Institute

The Broad Institute, founded in 2003 and launched in 2004, evolved from more than 15 years of unique research efforts in the Boston/Cambridge area. The Whitehead/MIT Center for Genome Research (CGR) was a flagship of the Human Genome Project (HGP) that reached its successful conclusion in 2003. The scale of the HGP was an early experiment in new models for interdisciplinary teamwork, attracting professional scientists, and learning how to tackle large-scale challenges.

At the same time, a similar new approach to chemical biology began at Harvard in the mid-1990s, leading to the creation of the Institute of Chemistry and Cell Biology (ICCB). The ICCB sought to bring novel approaches to chemistry and high-throughput chemical screening to academia.

In 2000, scientists at CGR and ICCB saw the similarities in their visions and began to seek a way to institutionalize their efforts in a new kind of research organization. It was clear that the organization would need to span MIT, Harvard, and the Harvard-affiliated hospitals—an unprecedented collaboration. And it was made possible by the visionary philanthropic investment of Eli and Edythe L. Broad.

Founded in 2003 and launched as a ten-year experiment in scientific culture and organization, the founding partners declared the Broad Institute a success in 2008, and agreed to make it a permanent 501(c)(3) nonprofit research institute.
As a young medical resident at Massachusetts General Hospital ten years ago, Sekar Kathiresan had the foresight to begin collecting blood samples from his patients. When powerful new technologies were developed at the Broad, making it possible to scour the entire genome for genes that play critical roles in the risk of disease, Kathiresan was ready. Drawing on blood samples from his patients and from others around the globe, Kathiresan and his colleagues are now cracking open the genetic secrets of heart disease, a leading cause of death in the developed world.

Working with many collaborators, Kathiresan (now an Associate Member at the Broad, as well as the director of preventive cardiology at MGH) has identified many of the more than 100 different genes that are now known to be associated with early heart attacks or abnormal levels of cholesterol and triglycerides in the blood.

Two years ago, Kathiresan found that a blood test measuring a set of genetic variants might help predict who is at a high risk of a heart attack. “Compared to a single measurement of cholesterol in the blood, gene variants are something you’re born with, so they may be a better indicator of your true cholesterol burden over a lifetime,” he says.
Finding missing ‘lincs’ in the genome

John Rinn found his way to the Broad community two years ago, within weeks of joining Beth Israel Deaconess as a newly minted assistant professor of pathology. He brought his passion for a new kind of RNA with him. Ever since graduate school, Rinn had been determined to understand the role of lincRNAs (large intergenic noncoding RNAs), part of the genome once dismissed as meaningless filler.

As a postdoctoral researcher at Stanford University, he identified a lincRNA called HOTAIR, which regulates other critical genes. Although some scientists contended that the few known lincRNAs were exceptions to the rule, Rinn came to the Broad with the idea that there might be many more – and with a 10-year plan to define them all. Within a year, he and his collaborators at Broad uncovered nearly 3,000 lincRNAs in the genome, many of which appear to play key roles in cancer and the immune system.

Rinn, now an Associate Member, says the Broad has enabled his lab “to make discoveries in months that would have taken years anywhere else. We’ve opened up the wardrobe and entered into the mysterious world of noncoding RNA. Now we need to find the mechanisms by which these creatures act.”
Some mutated genes drive cancer; others are simply along for the ride. To identify potential cancer drivers that might be weaknesses, or “Achilles’ heels,” Senior Associate Member Bill Hahn and his colleagues created a comprehensive set of genomic tools based on a new technology known as RNA interference. These molecular probes can systematically turn off or tamp down the activity of specific genes, much like a dimmer on a light switch. Jesse Boehm, a former graduate student in Hahn’s lab and now a full-time scientist at Broad, and his colleagues are using these new tools in a collaborative effort known as Project Achilles, which aims to eventually survey all human genes in at least 500 cancer cell lines to find cancer’s weak points.

As just one example of the many discoveries that have flowed from this effort, Hahn, Boehm, and their colleagues found that tumor cells that carry a mutation in KRAS, a cancer-causing gene considered nearly impossible to develop drugs against, have a key genetic weakness – an Achilles heel. This vulnerability suggests a new way of fighting the numerous tumors that carry KRAS mutations.

“The Broad research environment resembles a permanent scientific retreat,” Boehm says. “Interesting ideas are continuously simmering and new concepts and paradigms emerge from collaborative efforts.”
Of the tens of thousands of proteins coded by the human genome, less than one percent is considered “druggable,” that is, able to be targeted by a drug. Angela Koehler’s prey is the other 99 percent: the “undruggable” proteins that can play key roles in cancer and other devastating diseases.

To stalk such elusive targets, Koehler and her colleagues assembled a transformative collection of chemical compounds from a diverse array of sources, including natural products. She and others also built a powerful tool called a Small Molecule Microarray, which enables scientists to rapidly screen many thousands of chemical compounds in search of one that might bind to a protein and modulate its function.

Recently, Koehler and her collaborators used this tool to find a compound that blocks Sonic Hedgehog, an “undruggable” protein that controls the growth of several types of cancer cells.

“We may have 100,000 different proteins [in our bodies], mostly of unknown structure and function,” Koehler, a group leader in the Broad Institute’s Chemical Biology Program, says. “Here at Broad, we’ve assembled biologists, chemists, mathematicians, and physicists, to think together about ways to figure out what all those proteins do normally, and how to fix them in many different diseases.”
Soumya Raychaudhuri believed that there were important genetic connections about rheumatoid arthritis to be mined in the vast digital archives of scientific literature maintained online. But how could any single researcher comb through 250,000 studies? Raychaudhuri devised a solution: a computer program that could read through all the literature and look for genes that might share common ties to disease. The program, known as GRAIL (Gene Relationships Among Implicated Loci), takes a list of genetic regions associated with a particular disease and automatically assesses whether these regions contain genes that function together in the same cellular process or pathway. This has made GRAIL a broadly useful tool that can shed light on the biological basis of disease. So far, GRAIL has been used to unearth genes involved in cancer and Crohn’s disease, as well as rheumatoid arthritis.

A physician and a postdoctoral fellow in the labs of Mark Daly and David Altshuler in the Broad’s Medical and Population Genetics Program, Raychaudhuri says that the opportunity to think about the larger questions in biomedical research is one of the most attractive aspects of working at the Broad. He adds: “I hope that identifying these key pathways can guide us toward effective therapeutics.”
During graduate school, Pamela Sklar envisioned that when she finished her M.D.-Ph.D. program the genes responsible for mental disorders would be known. She soon realized, however, that progress in finding genetic risk factors for psychiatric disease was extremely slow. So Sklar, director of genetics for the Broad’s Stanley Center for Psychiatric Research, and her colleagues set off on a hunt for the genetic underpinnings of psychiatric disease at a scale never before attempted.

Sklar, also a senior Associate Member of the Broad, and her colleagues used powerful new analytical tools to scour the genomes of thousands of patients from samples collected over many years. Together with her collaborators, she found that the same large group of genetic variants was more common in all groups of schizophrenia patients, even though the DNA samples were collected by different researchers in different labs.

The findings point to a new way of understanding the biological basis of psychiatric disease. The researchers found that some of the variants are also implicated in bipolar disorder, suggesting that these two diseases share a common thread. “We could only accomplish this with the Broad’s great research capacities and expertise,” Sklar said. “We fully expect that future work will reveal meaningful pathways that will teach us about the biology of schizophrenia and bipolar disorder.”
Protein biomarkers buried deep in the blood can be powerful diagnostic tools, acting as early warning signs for doctors and patients in cancer and other diseases. Although thousands of these signposts have been uncovered, only a handful make it to the clinic. Susan Abbatiello, a Broad research scientist, and Steven Carr, director of the Broad’s Proteomics Platform, helped bridge that gap with a powerful method of detecting and quantifying even rare protein biomarkers in blood samples.

Their work, done in collaboration with other leading proteomic organizations across the US, demonstrated that the cutting-edge technologies developed at the Broad could provide a crucial step needed to unearth biomarkers that will be effective in detecting cancer at its earliest stages. Abbatiello and her collaborators hope to target up to 50 protein biomarkers in the blood that they suspect could play a role in breast cancer. “We’re not 100 percent sure which proteins play a role in the incidence of breast cancer. We’re developing these assays so we can test a larger number of samples,” Abbatiello says.

Working at the Broad, she says, “allows the freedom to pursue things that are interesting and challenging, and that may start an entirely new area of research.”
“The human epigenome is the next frontier of genomic research,” says Alexander Meissner, an Associate Member of the Broad Institute. While scientists have been studying epigenetic modifications - chemical changes that can turn genes on or off - for two decades, Meissner and his colleagues wanted to look at the big picture: they sought to map all epigenetic modifications across the entire genome, a technological feat that had never been done before. Such a map would allow researchers to see patterns, and determine how they affect human health.

Working together with his colleagues at the Broad and elsewhere, Meissner harnessed the latest genomic technologies to map out the epigenetic changes in a variety of cell types.

“Here at the Broad, the collaborations we have are critical in getting things done. If we tried to attack all the different levels ourselves, it would take a lot longer and might not even work,” says Meissner, who is also an assistant professor in the Department of Stem Cell and Regenerative Biology at Harvard University.

With his epigenomic maps in hand, Meissner’s laboratory is working to unravel how these epigenetic modifications are regulated during normal development, how this regulation changes in diseases like cancer, and how these marks can be altered or “reprogrammed.”
Mitochondria, tiny energy-producing "powerhouses" in human cells, are implicated in more than 50 devastating human diseases. But until recently, only half of the estimated 1,500 proteins that make up these tiny cellular machines had been defined, severely limiting researchers' knowledge of mitochondrial-based diseases. To shine light on a problem of such complexity and biomedical importance, scientists at the Broad attacked the problem from many angles.

Associate Member Vamsi Mootha and senior computational biologist Sarah Calvo and their colleagues integrated multiple genome-scale approaches, including mass spectrometry of mouse tissues. Through these combined efforts, they identified nearly all of the proteins that comprise mitochondria. They later mined this new mitochondrial parts catalog, dubbed "MitoCarta," and pinpointed genes that, when mutated, can cause severe metabolic diseases, including in infants.

When the team first applied for federal funding, the application was rejected because the review panel deemed the project too ambitious. They persisted, and when they eventually did receive funding, Mootha’s team completed the work three years ahead of schedule, due in large part to the scientific resources and expertise at the Broad, especially the Proteomics Platform. "A project of this scale could only be done here," Calvo says.
Governance

The Broad Institute’s transition in 2009 to a permanent 501(c)(3) biomedical research organization brought with it both great scientific potential and organizational challenges: in particular, the need to recruit highly accomplished individuals to provide thoughtful governance and leadership for the Institute.

Many exceptional people – all of whom believe deeply in the mission of the Broad Institute - have stepped up to offer wise counsel and careful stewardship of Broad’s organization, science, and culture.

Board of Directors
The members of the Broad Institute’s first Board of Directors include world-class leaders from science, law, education, and business. These distinguished individuals are charged with ensuring that the Broad successfully realizes the fulfillment of its mission to transform medicine.

CURRENT BOARD OF DIRECTORS MEMBERS INCLUDE:

Dennis Ausiello
Chief of Medicine at Massachusetts General Hospital; Chief Scientific Officer, Partners HealthCare

David Baltimore
President emeritus, California Institute of Technology; Nobel Laureate

Eli Broad
Founder, The Broad Foundation

Drew Gilpin Faust
President, Harvard University

Jeffrey S. Filer
Dean of the Faculty of Medicine, Harvard Medical School

Louis V. Gerstner, Jr.
Retired Chairman and CEO, IBM Corporation

Susan Hockfield
President, Massachusetts Institute of Technology

Seth A. Klarman
President, The Baupost Group, LLC

Eric S. Lander
President and Director of the Broad Institute; Professor, MIT; Professor, Harvard Medical School

William F. Lee
Co-managing Partner, WilmerHale

Arthur D. Levinson
Chairman, Genentech, Inc.

Philip A. Sharp
Institute Professor, Massachusetts Institute of Technology; Nobel Laureate

Patty Stonesifer
Former President, Bill & Melinda Gates Foundation; Senior Advisor to the Trustees of the Bill & Melinda Gates Foundation

Ratan N. Tata
Chairman of Tata Group

Diana Chapman Walsh
President emerita, Wellesley College

David Baltimore, Chair
President Emeritus, California Institute of Technology; Nobel Laureate

David Haussler
Director, Center for Biomolecular Science and Engineering, University of California, Santa Cruz

Richard Lifton
Chairman, Department of Genetics, Yale University School of Medicine

Vicki Sato
Former President, Vertex Pharmaceuticals; Professor of Management Practice, Harvard Business School

David Tirsch
Chair, Division of Chemistry and Chemical Engineering, California Institute of Technology

Harold Varmus
President & CEO, Memorial Sloan-Kettering Cancer Center; Nobel Laureate

The Board of Scientific Counselors (BSC), appointed by the Board of Directors, meets annually to review the institute’s scientific progress over the past year and to provide advice on future scientific directions to the Institute Director and to the Board of Directors.

THE BSC MEMBERS INCLUDE:

David Baltimore, Chair
President Emeritus, California Institute of Technology; Nobel Laureate

David Haussler
Director, Center for Biomolecular Science and Engineering, University of California, Santa Cruz

Richard Lifton
Chairman, Department of Genetics, Yale University School of Medicine

Vicki Sato
Former President, Vertex Pharmaceuticals; Professor of Management Practice, Harvard Business School

David Tirsch
Chair, Division of Chemistry and Chemical Engineering, California Institute of Technology

Harold Varmus
President & CEO, Memorial Sloan-Kettering Cancer Center; Nobel Laureate

‘Investors’

Many different individuals and organizations generously support the work of the Broad Institute. Their far-sighted contributions are, above all, investments in the future of human health.

Eli and Edythe L. Broad:
Discussions in 2002-2003 among Los Angeles philanthropists Eli and Edythe L. Broad, MIT, Harvard, and the Harvard-affiliated teaching hospitals shaped the vision for a new kind of research organization and community. The extraordinary generosity of the Broads ($100 million over ten years, subsequently doubled to $200 million) made it possible to formally announce the Eli and Edythe L. Broad Institute of MIT and Harvard in June 2003 and to launch it in May 2004. In September 2008, the Broads, Harvard, and MIT declared the new model a success. At the same time, the Broads announced that they would endow the institute with an additional $400 million, the largest single gift to a biomedical academic research center to date.

Foundations that have provided sponsored research support to the Broad:

American Kennel Club – C.H.F.
Bill & Melinda Gates Foundation
Burroughs Wellcome Fund
Doris Duke Charitable Foundation
Foundation for Research Science and Technology
Juvenile Diabetes Foundation
Medicines for Malaria Venture

Governmental Agencies:
The Broad Institute receives 90 percent of its annual funding from US government agencies, including:

National Institutes of Health (NIH)
National Cancer Institute
National Heart, Lung and Blood Institute
National Human Genome Research Institute
National Institute of Allergy and Infectious Diseases
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute on Drug Abuse
National Institute of Environmental Health Sciences
National Institute of General Medical Sciences
National Institute of Mental Health
NIH Office of the Director
National Center for Research Resources
National Science Foundation
US Department of Agriculture
Financial Information

Finances
On July 1, 2009, the Broad Institute made the formal transition to being a 501(c)(3) non-profit research institute with its own Board of Directors and endowment. For the previous five years, the institute operated as part of MIT. During this period, the Broad Institute doubled in size, adding new faculty, programs, and platforms. It also took occupancy of its current headquarters at 7 Cambridge Center in 2006, tripling its research space. The Broad has experienced an average annual growth rate of 22 percent over the last three years.

Broad Institute Historical Budgets for the Five Years FY05 - FY09 ($M)

<table>
<thead>
<tr>
<th>Year</th>
<th>Budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>$120.0</td>
</tr>
<tr>
<td>2006</td>
<td>$140.0</td>
</tr>
<tr>
<td>2007</td>
<td>$160.0</td>
</tr>
<tr>
<td>2008</td>
<td>$180.0</td>
</tr>
<tr>
<td>2009</td>
<td>$200.0</td>
</tr>
</tbody>
</table>

Results for FY09
The institute’s fiscal year begins July 1 and ends June 30. For the fiscal year ended June 30, 2009 (FY09), the Broad realized $221.69M in revenues and $217.95M of expenditures.

Statement of Activities - Total Operations FY 2009 ($ in Thousands)

<table>
<thead>
<tr>
<th>Sources</th>
<th>$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsored Revenue</td>
<td>189,281.2</td>
</tr>
<tr>
<td>Gifts</td>
<td>4,139.6</td>
</tr>
<tr>
<td>External Billing</td>
<td>5,976.9</td>
</tr>
<tr>
<td>Broad Gift &amp; Internal Reserves</td>
<td>21,296.4</td>
</tr>
<tr>
<td>Other Miscellaneous Income</td>
<td>1,000.0</td>
</tr>
<tr>
<td>Total Sources</td>
<td>221,694.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uses</th>
<th>$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salaries, Wages, Benefits</td>
<td>68,035.2</td>
</tr>
<tr>
<td>Materials &amp; Services</td>
<td>74,992.4</td>
</tr>
<tr>
<td>Facilities Expenses</td>
<td>30,187.0</td>
</tr>
<tr>
<td>Equipment/Depreciation</td>
<td>15,170.7</td>
</tr>
<tr>
<td>Subawards</td>
<td>15,298.2</td>
</tr>
<tr>
<td>Other Direct Expenses</td>
<td>14,269.4</td>
</tr>
<tr>
<td>Total Uses</td>
<td>217,952.9</td>
</tr>
</tbody>
</table>

Net Surplus / (Deficit) $3,741.2

Note: Results are unaudited; MIT financial statements did not separate the operations of the Broad Institute. These results are taken from internal summary reports. The institute’s first audited financial statements as a newly constituted 501(c)(3) organization will be based on the fiscal year ending June 30, 2010.

Broad Funding Sources FY2009 Actuals = $221.7M ($ in thousands)

- Federal $149,665
- Other $72,028
- Sponsored Grants, Gifts, Fellowships $29,418
- Collaborations with Industry $14,337
- Other Miscellaneous Income $1,000
- Broad Gift & Internal Reserves $21,296
- External Billing $5,976