From Insight to Impact

The Broad Institute
2011 Annual Report
"We are unafraid to take on the toughest challenges. Every time we confront a problem that once seemed insurmountable, we take another step toward better therapeutics for patients."

- TODD GOLUB
In the more than two years I have had the privilege of serving as the chair of the inaugural board of the Broad Institute, it has become ever more manifest to me not only that the institute is uniquely positioned to position medicine for future generations, but more fully how that excitement potential is being realized in real time, day in and day out.

The Human Genome Project demonstrated that the traditional, small-scale model of biomedical research was no longer equal to the potential for progress in medicine and health. Ten years ago, Eric Lander emerged from the race to sequence the genome convinced that the next phase of work would require a new form of scientific community. It would have to set bold goals and apply teamwork to accomplish them; focus on scale, process and efficiency; marry breakthrough technological capabilities with individual creativity; share data rapidly and freely to accelerate the pace of discovery. The Broad Institute was conceived as a response to those needs and has been producing a cascade of high-impact results across a broad spectrum of biomedical puzzles and targets of opportunity.

The Broad engages the future, thinks strategically about what might be possible five and ten years hence, even beyond. This is a community unafraid to tackle challenges that others dismiss as impossible. Transforming medicine requires erecting bridges across the wide gap between fundamental insights and novel therapies. This in turn, requires assembling teams of bright and resourceful people who can collaborate across seldom connected islands of skill and expertise. Within the Broad community, extraordinary scientists are traversing the bridges of scientific discovery, often building them as they go.

The Broad Institute draws additional strength from its distinguished and deeply-engaged Board of Directors, proven innovators from industry and the academy – themselves bridge builders. It’s a great pleasure to work with these colleagues who are committed to the institute’s success, inspired by the quality of its people, and energized by their wholehearted embrace of this pivotal moment in the history of medicine and human health.

Many board members have expressed their deep commitment through philanthropy, as well. And so do many others. All of us are deeply grateful for the generosity of the Broad’s friends and supporters.

Diana Chapman Walsh
Chair of the Board of Directors
IT’S A COLLECTION LIKE NO OTHER: 100,000 customized molecules designed to fill in where nature left off. Known as Diversity-Oriented Synthesis (DOS) compounds, these chemicals (named “small molecules”) are a critical part of an effort at the Broad Institute to integrate chemistry and biology in order to develop new therapies for the most daunting human diseases.

“DNA sequencing shines a powerful light on human health. It tells us what can go wrong when disease strikes. But a gap remains between understanding disease and developing effective therapies,” explains Stuart Schreiber, Ph.D., a core member and director of the Chemical Biology Program at the Broad. “We need the science of small molecules to deliver on the promise that human biology holds for human health.”

Systematic, high-throughput DNA sequencing has deepened our understanding of the human genome over the last decade. Using a similar comprehensive, high-tech approach, scientists at the Broad have identified biological targets and synthesized small molecules that can travel through the body to hit those targets – hopefully without a trail of toxic side effects. In some cases, these small molecules are used as probes to deliver new information about disease biology. In other cases, the small molecules take aim at proteins that have been deemed “undruggable.”

“Chemistry is the key ingredient moving forward if we are to take advantage of the massive investment made in understanding biology through...”

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“Our mission - our moral obligation - is to create a transformative collection of new chemical matter that will make a difference for human health.”

- MICHAEL FOLEY

genomics,” says Michael Foley, Ph.D., director of the Chemical Biology Platform at the Broad.

Ever more-powerful sequencing technologies offer an unprecedented range of potential new drug targets. But genomics discoveries will not mean anything for human health without new chemistry. “DOS is new chemistry capable of effectively interfacing with the new targets,” adds Foley. “The Broad is one of the few places that has made a meaningful investment in new chemistry in the last five years.”

In effect, scientists are creating a new cosmos, systematically populat ing it with odd molecular shapes and structures not found anywhere else. Inspired by the chemistry found in “natural products” - potent small molecules found in nature that have been the basis for many drugs - scientists in the Broad’s Chemical Biology Program and Platform deploy automated incubators, computerized imaging systems, and robotic screening systems to accelerate the pace of discovery.

The diverse array of chemicals in this cosmos is intended to cover a range of chemical space far broader than that of existing small molecule collections. As Schreiber explains, compounds found in most of these collections are limited – either too simple in design or too similar to each other – and have difficulty hitting the most critical targets in the disease process.

“A library that contains a more diverse range of molecular shapes provides more hits for the more challenging biological targets,” he says.

How are these molecules assembled?

A DOS compound starts with tiny chemical fragments that are joined in the lab to create numerous versions of a molecule. These versions are built in three-dimensional structures.

“In the Broad DOS collection, we have taken a systematic approach to synthesizing compounds according to their physical properties,” explains Jeremy Duvall, Ph.D., DOS chemistry manager. A compound with a particu lar three-dimensional structure may bind to a target, another version with the same molecular signature but just a slightly different three-dimensional structure may miss it entirely.

The DOS collection is designed to include all of the three-dimensional variations of each compound. “No one has ever done that before,” says Foley.

“Our mission - our moral obligation - is to create a transformative collection of new chemical matter that will make a difference for human health,” says Foley.

Broad researchers share their DOS compounds widely in a public database and document the milestones and approaches used to design, create, and evaluate them. Says Foley, “The more we can encourage people to share data, the better off society is going to be.”

When scientists at the Broad Institute set up a small pilot screen to find drugs against malaria using 8,000 compounds from the 100,000 compound Diversity-Oriented Synthesis (DOS) collection, they were only intending to take this small “informa tion set” out for a test drive. The informed set was selected to represent the diversity of the entire collection. Each compound in the screen was present with its full complement of alterna tive three-dimensional structures. But researchers got a hit quickly, and now have accelerated their hunt for new compounds.

Developed in collaboration with Oday Wirth, Ph.D., Broad senior associate member and chair of the Department of Immunology and Infectious Diseases at the Harvard School of Public Health, that pilot screen and the systematic process Broad scientists pursued to develop a lead compound is highlighted in a paper published in ACS Medicinal Chemistry Letters. The hit cluster included a compound with strong antimalarial activity at an unusually low concentration. The most potent compound was selected for further work up by the Broad’s medicinal chemistry team.

“if we had not included all of the three-dimen sional structures for each compound in the pilot screen, we quite possibly would have missed this,” says Benito Munoz, Ph.D., director of medicinal chemistry within the Broad Institute’s Chemical Biology Platform. The team optimized the compound, and showed that it is active in low doses against two P. falciparum strains in vitro and, in fact, is more potent than antimalarial agents in common use.

Researchers are now studying how this anti malarial compound and others are metabolized in vitro in mice and in humans using microsomes, which are subcellular liver structures. Com pounds that are more stable in the presence of microsomes are more likely to be metabolically stable. Morgan’s team will select those compounds with the best overall metabolic stability for in vivo animal studies.

CASE STUDY

‘Test drive’ yields promise with malaria

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The sequencing platform is a dynamic foundation
A Platform in action

The Broad’s Genome Sequencing Platform, one of the leading contributors to the Human Genome Project, operates at 320 Charles Street in the same space where much of the work on this historic project was accomplished. The space, techniques, and technology driving the platform’s research have changed dramatically since the Human Genome Project’s completion in 2003, but the commitment to harnessing powerful technologies to transform medicine remains. The technologies to transform medicine continues to grow, and the commitment to completing the Human Genome Project’s historic project was accomplished. The space, techniques, and technology driving the platform’s research have changed dramatically since the Human Genome Project’s completion in 2003, but the commitment to harnessing powerful technologies to transform medicine remains. The platform designs and carries out large-scale genome sequencing projects, generating massive quantities of genomic data, to excess of 300,000 billion bases of DNA data. The machine produces millions of genome sequence reads and up to a gigabyte of data. The sequencer can produce millions in just a few hours, an Ion Torrent instrument, allows for high-throughput HiSeq desktop versions.

The sequencing platform is powerful and vast – tens of thousands of samples are sequenced here every year. But it is also agile. In just a few hours, an Ion Torrent sequencer can produce millions of reads tiny electric current generating a gigabyte of data. The machine is inherently collaborative, Nusbaum writes new computational tools to assemble the genome. The projects tackled are diverse, but all have a common thread: deep collaboration across disciplines, boosted by the fundamental differences, and interpreted. The sequencing platform is powerful and vast – tens of thousands of samples are sequenced here every year. But it is also agile. In just a few hours, an Ion Torrent sequencer can produce millions of reads tiny electric current generating a gigabyte of data. The machine is inherently collaborative, Nusbaum writes new computational tools to assemble the genome. The projects tackled are diverse, but all have a common thread: deep collaboration across disciplines, boosted by the fundamental differences, and interpreted. The sequencing platform is powerful and vast – tens of thousands of samples are sequenced here every year. But it is also agile. In just a few hours, an Ion Torrent sequencer can produce millions of reads tiny electric current generating a gigabyte of data. The machine is inherently collaborative, Nusbaum writes new computational tools to assemble the genome. The projects tackled are diverse, but all have a common thread: deep collaboration across disciplines, boosted by the fundamental differences, and interpreted. The sequencing platform is powerful and vast – tens of thousands of samples are sequenced here every year. But it is also agile. In just a few hours, an Ion Torrent sequencer can produce millions of reads tiny electric current generating a gigabyte of data. The machine is inherently collaborative, Nusbaum writes new computational tools to assemble the genome. The projects tackled are diverse, but all have a common thread: deep collaboration across disciplines, boosted by the fundamental differences, and interpreted.
Engineering a way to predict drug safety

The path to drug development is long, requiring significant investments of money and time. But obstacles often spawn ambitious goals—and bold experiments. Sangeeta Bhatia, Ph.D., a senior associate member at the Broad Institute, and her collaborators believed they could tackle a critical challenge for drug development. They wanted to create a way to test for toxicity long before a medicine coursed through a patient’s liver.

To do this, Bhatia and her colleagues fashioned a three-dimensional version of the human liver by encapsulating highly functional human liver cells in an artificial substrate. This substrate—a sliver that looks something like a contact lens—can be implanted into mice.

Bhatia’s research at MIT, where she is a professor of health sciences and technology, stems from her desire to build new liver cells and tissues that can sustain normal human life after liver injury.

“To start, we wanted to build a higher fidelity model of the human liver,” says Bhatia, who is also director of the Laboratory for Multiscale Regenerative Technologies at the David H. Koch Institute for Integrative Cancer Research at MIT. “We can use a model of the human liver to cut drug development costs and make drugs safer for patients.”

To test whether the implanted liver tissue truly mimics the functional and molecular activity of the human liver cells, and not the mouse host, Bhatia teamed with Broad core member Todd Golub, M.D., and David Thomas, M.D., an associate researcher at the Broad and instructor of medicine at Harvard Medical School. This is not a small task—the liver performs over 500 different functions. There are 83 different enzymes involved in liver detoxification alone.

Thomas and his colleagues developed a set of molecular tools known as probes to survey the expression and function of a range of enzymes involved in the human liver’s activity.

“It was important to identify the effects of the three-dimensional microenvironment in which the engineered liver tissue is produced,” explains Bhatia. Golub and Thomas developed an assay to define the best environments for the liver cells.

Researchers examined 83 genes encoding drug metabolism enzymes and transcription factors found exclusively in human liver tissue. They found that most of the enzymes are expressed in the engineered tissue, including the handful of enzymes that account for 90 percent of drug metabolism. And the engineered human liver cells implanted in the mouse reacted to a test drug while the innate mouse liver cells did not.

Tools like in vivo artificial human liver tissue could ultimately be used to study liver cell metabolism, hepatotoxicity, or drug potency. Adds Bhatia, “This tool provides a critically important step in the development of a robust system for experimental therapeutics.”

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— SANGEETA BHATIA

Illustration / Sigrid Hart

Confocal fluorescence micrograph depicting human liver cells (green) and co-encapsulated fluorescent nanoparticles (red).
RNA TOOLS

Turning down genes—and watching what happens

A LITTLE MORE THAN A DECADE AGO, researchers discovered an ancient mechanism that cells use to silence genes. Like a dimmer switch turning down a light, RNA interference (RNAi) dials down gene activity, interfering with protein production or other cellular functions, in simple organisms as well as in humans. Scientists have seized on RNAi as a tool to “turn down” genes to determine what they do.

In order to take full advantage of RNAi technology for disease research, four scientists at the Broad Institute launched The RNAi Consortium (TRC) to build a library of RNAi reagents to target every gene in the human and mouse genomes. The consortium team evolved into the Broad RNAi Platform, and the vision of TRC’s founders materialized in a more concrete form: a large, well-characterized collection of RNAi reagents that is openly shared with the scientific community. The platform has collaborated with nearly 100 different research groups, and scores of other groups have published results using these reagents on their own.

“The broad goal of the RNAi Platform is to better understand the functions of the entire human genome,” says platform director David Root, Ph.D. “We need to quickly assess the role genes play in disease susceptibility in order to transform medicine.”

RNAi screens in cell lines are used to identify the genes that cancerous tumors need to survive—their Achilles’ heels—in a collaboration of the Cancer Program known as Project Achilles. RNAi is also used to study other cancer cell properties, such as the ability to migrate and differentiate. Other Broad projects use RNAi to reconstruct the network of genes involved in immune response.

The platform team is building a comprehensive set of reagents for perturbing genes. The range of genes targeted is also expanding to include “non-coding” genes, which are transcribed into RNA but do not lead to production of a protein. These genes appear to play roles in development, gene regulation, and more.

Broad researchers are constantly improving methods. They are developing better ways to transfer reagents into cells, mix them in pools, and test them in mice. They are also incorporating increasingly sophisticated readouts of cell states and behaviors, and new ways to interpret all the data.

“The great tools we’ve developed—and our deep expertise in applying RNAi—keep advancing the forefront of functional genomics,” Root says.

PROTEOMICS

Uncovering the biomarkers of disease

PROTEINS ARE tantamount diagnostic tools. A vial of blood contains a rich sea of proteins, some of which rise and fall in accordance with disease response and recovery. But pinpointing proteins is an incredibly complex task. Unlike DNA, which has fixed chemical properties and structure, proteins come in all shapes, sizes, and concentrations that change over time. Many key protein biomarkers are only present at infinitesimal levels in blood. Some potential biomarkers, or indicators of disease, have been identified over the years, but few have been approved for clinical use.

Better biomarkers are urgently needed to improve diagnosis and treatment for a variety of diseases, including cancer, cardiovascular disease, and infectious diseases.

Steven Carr, Ph.D., director of the Broad Institute’s Proteomics Platform, leads a team that is developing a powerful new approach to detect and verify biomarkers. Earlier this year, he and his colleagues put this technique into practice, using the search for heart attack biomarkers as a test case. They were able to detect minute levels of new biomarkers, some of which appear in the blood just 10 minutes after a heart attack—a detection strategy that could be applied to a variety of diseases by following up on the most promising protein candidates.

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Illustration/Sigrid Hart

Creatine kinase, shown here, is a known heart attack biomarker. Steven Carr and colleagues are developing a promising technique to verify known biomarkers like this protein and to detect new biomarkers of disease.
Diagnosing a heart attack quickly is critical. Heart attacks kill more than 600,000 people in the United States every year. But if a doctor can accurately and rapidly diagnose a patient, the patient can immediately receive medication or catheter-based treatment. For years, researchers have looked for proteins or biochemicals in the blood that are released when heart cells are injured, but the ones that scientists have identified were only detectable several hours after the injury. Many key protein biomarkers are only detectable at the nanogram-per-milliliter level or below. A smattering of potential biomarkers of disease have been detected over the years, but very few have been approved for clinical use.

Carr and colleagues at the Broad and at Massachusetts General Hospital developed a new, systematic approach to detect and verify biomarkers and put this “pipeline” into practice. The researchers explained that what is most exciting about the research is the potential of applying this detection strategy to a variety of diseases and following up on the most promising protein candidates.

“Proteomics is not a static technology,” Carr says. “Rapid advances in mass spectrometry are driving change, enabling us to detect and quantify signals that were once beyond our grasp.”

The mission of the Broad’s Proteomics Platform is to leverage detection strategies to provide new insights into gene function, drug targets, and the molecular basis of disease. With dramatic advances in proteomics technologies, including mass spectrometry, Carr’s team can tackle biomedical problems with an unprecedented degree of sensitivity and specificity.

Carr and his team are using new strategies to bridge the gap between discovery and clinical validation of biomarkers. Their next step will be to measure candidate proteins in a large, diverse population.

The researchers’ ultimate goal is to develop diagnostic tools that can be implemented in the clinic to identify or predict disease. Carr describes the Broad Institute’s close collaboration with the Harvard-affiliated hospitals as critical to this mission. “We wouldn’t be able to do this work alone – the clinical questions drive our investigations,” he says.

“We urgently need better diagnostic tools for diseases like cancer, chronic illnesses, and infectious disease. We’re developing a new approach because improvements in clinical care depend on our ability to detect and intervene early.”

– STEVEN CARR
CANCER

Translating genomic knowledge into impact

Scientists in the Broad’s Cancer Program started by envisioning where cancer treatment needs to be. They then set their sights on these far shores – effective new therapies – and began to build a bridge to get there. Thanks to generous philanthropy and a close relationship with partner hospitals, the gap is narrowing.

Cancer Program researchers see three challenges:

- Developing a comprehensive catalog of all genes frequently mutated in tumors, across cancer types, to understand how genes drive the disease. With powerful new sequencing technologies and a blossoming international collaboration, this goal is already within sight in the next five years.

- Translating this genomic knowledge into a “therapeutic road map” showing the right targets for drug development, by identifying the critical vulnerabilities and mechanisms of resistance, for all cancers.

- Creating and applying powerful new chemical and biological tools to discover and develop effective cancer therapies.

These major challenges require collaborations that cut across the traditional scientific boundaries of biology, chemistry, medicine, computational science, and engineering. Members of the Cancer Program collaborate closely with scientists in the Chemical Biology Program and nearly all of the institute’s platforms, especially the RNAi Platform, the Genome Sequencing Platform, and the Chemical Biology Platform.

“With every resource that we build and every challenge that we tackle, we narrow the gulf between the far shore and where we stand.”

– Todd Golub
Cancer researchers at the Broad use systematic approaches to understand the genetic changes underlying cancer and develop more effective therapies. In this illustration, a tumor (in green) begins dying upon exposure to a targeted drug delivered via the bloodstream. Broad scientists also aim to learn how tumors respond to drugs and why some develop resistance.

Using the Broad’s powerful new sequencing technologies to read massive amounts of DNA information, Cancer Program director and Broad founding core member Todd Golub and his colleagues are now unveiling genetic blueprints for deadly cancers such as multiple myeloma, prostate cancer, melanoma, and breast and ovarian cancer.

These researchers have created a host of projects to connect those genomic discoveries to the underlying biology of disease, to identify targets for treatment, and to discover chemicals that can modulate cancer cells. These projects are:

**Target Accelerator.** Broad scientists have developed powerful ways to identify the role of key cancer-related proteins in the cells.

**Project Achilles.** Using tools developed in the Broad’s RNA interference (RNAi) Platform, scientists can identify cancer’s weak spots and make them a focus of new therapeutics.

**Cancer Therapeutics.** Scientists are using new chemical methods to attack cancer’s most important targets, including those once deemed “undruggable.”

**Drug Resistance.** Scientists are launching a systematic effort to predict in advance how tumors may become resistant to cancer drugs and to develop ways to stop them from doing so.
Summary: Many cancerous tumors initially respond to treatments, only to subsequently develop drug resistance, allowing the cancer to come back. Broad researchers are probing how resistance develops—and providing a guide to how to prevent it.

Half of all melanomas—the most deadly form of skin cancer—harbor a mutation in a gene called BRAF. The FDA recently approved a powerful new drug that inhibits mutated BRAF and causes tumors to shrink in many patients. The success, however, is short-lived: the cancer comes back within a year.

“The big question now is: How does resistance occur and how can we use that knowledge to develop therapies that will circumvent resistance?” says Levi Garraway, M.D., Ph.D., a medical oncologist and associate professor at Dana-Farber Cancer Institute, and a senior associate member at the Broad Institute.

Garraway’s team has developed powerful tools to answer these questions. They “turned on” 600 different kinase genes in melanoma cell lines to see which ones have the ability to make cells resistant to the drug. They discovered several ways in which melanoma cells can become resistant: BRAF’s sister proteins could step in and reactivate uncontrolled growth; other kinases could bypass BRAF; and mutations in downstream genes could reactivate the pathway. Remarkably, they showed that patients with resistant tumors showed similar mutations.

And, they have found chemicals can block some of these resistance pathways. The team has recently expanded the project to study resistance to additional cancer drugs.

While Garraway’s work focuses on the changes within cancer cells, resistance may also arise from neighboring non-cancer cells in the tumor—known as the tumor’s microenvironment. A team led by Todd Golub, Cancer Program director, has developed ways to systematically screen for factors secreted by cells in the microenvironment that can cause cancer cells to become drug-resistant. They recently discovered that neighboring fibroblasts in the laboratory—and in patients—can secrete a growth factor that can bypass BRAF and produce resistance. Excitingly, they found that this mechanism of resistance can be blocked with existing drugs.

Knowing how tumors evade drugs can guide strategies to effectively treat melanoma while preventing resistance with targeted drugs in combination. This systematic approach is a model for making headway in other cancers.

“We should anticipate that resistance is a likely scenario. We need to be on top of that by understanding, early on, what are the likely paths tumor cells can take to become resistant and how to stop them,” says Golub. “That could have a huge impact.”

Targeting resistance

Broad researchers have uncovered several mechanisms of resistance to BRAF inhibitors in melanoma: BRAF’s sister proteins could step in and reactivate the pathway; other kinases could bypass BRAF; downstream elements like MEK are mutated; and factors from other cells trigger proliferation and survival of tumor cells.

CANCER CASE STUDY

MITOCHONDRIAL DISORDERS

Stepping stones to common disease

Against the white background of a PowerPoint slide, the words, “Not a single proven therapy” stand out in bold type. Vamsi Mootha, M.D., a senior associate member at the Broad Institute and physician-scientist at Massachusetts General Hospital, pauses for a moment and points to the text. “This is what motivates us,” he says.

Mitochondrial diseases take many forms but are uniformly fatal. Although collectively they affect at least 1 in 4,000 live births, these disorders are considered rare. They fall under the category of orphaned or neglected diseases, deemed unprofitable areas of research by pharmaceutical companies. But a growing body of evidence suggests that understanding these rare diseases could help researchers unlock the mechanisms of more common illness, including diabetes, neurodegenerative diseases such as Parkinson’s disease, and cancers such as gliomas, all of which are also linked to the mitochondria.

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Mitochondria: the cell’s powerhouses

Mitochondria are responsible for producing 90 percent of the energy cells need to grow and survive. If the mitochondria in cells are compromised, the parts of the body that need energy the most—the heart, brain, liver, muscles, and lungs—can become damaged. With more than 1,000 mitochondrial proteins identified, Broad researchers can now study the role these proteins play in human disease.

“I like to think of mitochondria as the hub of a wheel with spokes reaching out into all of these other diseases. If we can understand what goes wrong in these rare disorders, we’ll have a huge advantage in studying the common diseases.”

– VAMSI MOOTHA

Mootha and his colleagues are pursuing the genetic mutations that lead to mitochondrial diseases, but first, they needed a map of the more than 1,000 mitochondrial proteins, collectively known as the mitochondrial proteome. In the past decade, they have begun to crack open the field by mapping out and sequencing all of the regions of DNA that code for mitochondrial proteins. These projects, known as MitoCarta and MitoExome, are beginning to bear fruit.

Through the MitoCarta project, researchers identified nearly 1,100 genes involved in mitochondrial function. Building on this work, Mootha and his collaborators are embarking on the MitoExome project, which aims to match hundreds of disease phenotypes (physical characteristics) with genetic abnormalities. The team has already identified 10 mitochondrial disease genes.

Over the last seven years at the Broad, we’ve developed a genomic foundation for tackling these disorders,” Mootha says. “We’ve identified all of the protein components in the organelle, we’re using evolutionary genomics to understand how those components are wired together, and we’re now using sequencing technologies to scan all of those proteins to establish a molecular diagnostic. The momentum is building—we’re poised to take on these diseases.”

Working with the Broad’s Metabolite Profiling Platform, Mootha and his team are establishing biomarkers of mitochondrial disease. These biomarkers can be used together with sequencing to recruit patients for clinical trials and to monitor a patient’s response to treatment. With a parts list and diagnostic biomarkers in hand, the team will be ready for the next important step: creating new therapeutics. By partnering with the Broad’s Chemical Biology Platform, Mootha and his colleagues hope to identify drugs that act on the mitochondria, which could spur new treatment options for neglected patients.

“Our long-term vision is to develop novel therapeutics and companion diagnostics,” Mootha says. “If we can discover drugs to treat these rare diseases, the same molecules could be useful for common diseases that impact hundreds of millions of people.”

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MORE THAN ONE-THIRD of the world’s population is infected with tuberculosis. Ten percent of these 2 billion people will become sick with active TB in their lifetime. And, each year, roughly 2 million will die. TB is the leading cause of death from a curable disease and the second-leading cause of death from infectious disease worldwide.

The problem has been worsening over the past decade. TB and HIV share a catastrophic synergy, with each potentiating the other. Moreover, drug-resistant forms of the TB microbe, *M. tuberculosis*, are rapidly emerging.

What makes TB such a global scourge is that it is devilishly hard to treat. Whereas most bacterial infections can be cleared with two weeks of treatment, patients must take an antibiotic for nine months to kill the bacterium (or up to three years for strains resistant to conventional therapy). On top of that, TB infections can be hard to diagnose.

Beyond these clinical challenges, TB is also daunting for scientists to study in the laboratory. It can take weeks to grow it in a test tube, and it requires extensive biosafety protection in the lab. Finally, TB tends to attract little commercial interest because it is largely a disease of the developing world and the prospects for profit are low.

The Broad Institute has made a deep commitment to tackling TB, including understanding why it eludes short-course treatments and developing better diagnostics and therapies. “If we can understand the essential functions of TB and the basis of resistance, we would have a much better idea how to target it,” says Broad core member Deborah Hung, M.D., Ph.D., who is also an infectious disease physician at Massachusetts General Hospital and Brigham and Women’s Hospital. An assistant professor in the department of microbiology and molecular genetics at Harvard Medical School, she trained in both synthetic chemistry and bacterial genetics. “We’re capitalizing on the genomic approaches and advanced technologies here at the Broad.”

The Broad’s TB program is led by Hung, director of the Infectious Disease Program, and draws on the strengths of a number of the Broad’s programs and platforms, including the Chemical Biology Platform for high-throughput chemical screening, the Genome Sequencing Platform and Genome Sequencing and Analysis Program, and the Proteomics Platform. Sarah Grant, M.D., a pulmonologist at Brigham and Women’s Hospital who works with Hung, also is exploring how a subset of TB cells is able to persist for many months in the face of antibiotic treatment—and to develop compounds that can block this ability. Working with the Broad’s Chemical Biology and Genome Sequencing platforms as well as the Genome Sequencing and Analysis Program, she narrowed in on compounds that will reveal more about the mysterious microbe.
Turning up new genetic clues

FAMILY HISTORY IS A strong risk factor for psychiatric diseases, pointing to the influence of genetic inheritance. But finding the genes responsible for these devastating disorders has eluded scientists for decades.

That’s finally changing. Using powerful genomic technologies and thousands of patient samples, researchers at the Broad Institute and their collaborators have found a growing collection of genes linked to three psychiatric diseases: schizophrenia, bipolar disorder, and autism. Mark Daly, Ph.D., a senior associate member of the Broad and chief of the Analytic and Translational Genetics Unit (ATGU) at Massachusetts General Hospital, coordinates analysis for the Psychiatric Genome-Wide Association Study Consortium, which pulls together studies from around the world involving tens of thousands of patients.

"Each time we find additional genes we get more specific insight into the disease," Daly, who is also co-director of the Broad’s Program in Medical and Population Genetics, says. “The role of genetics is to identify which processes and cell types are connected to each disease. We can then focus our understanding and eventual therapeutic development on those connections.”

In schizophrenia, some of the genes are related to calcium channels, which govern how signals travel between brain cells.

“These are among the first really solid biological clues that we have strong confidence in,” says Daly. “The next step is to take these genetic clues forward into a deeper understanding of the disease.”

Daly and his colleagues are also analyzing samples from genome-wide association studies of diabetes, which pulls together studies from around the world involving tens of thousands of patients.

"We need to find all genetic variations, common and rare, that influence the risk of psychiatric disorders,” says Steven McCarroll, Ph.D., director of genetics for the Stanley Center for Psychiatric Research at the Broad. “The recent results are important because they tell us not only that that’s possible, but that the work will lead us to specific and actionable areas of human biology. They are not just random hits on the boardroom of the genome.”

“I look forward to the day when we can look back on these early genetic discoveries and say: That was the turning point that led to truly important therapies for patients!”

- MARK DALY

Gerstner Family Foundation gift supports groundbreaking effort in ADHD

Attention deficit hyperactivity disorder, or ADHD, is one of the most common behavioral disorders in children, and often continues into adulthood. Yet, the genes that underlie it remain unknown.

To accelerate the understanding of the genetics of this disorder, Louis V. Gerstner, Jr., has pledged $4.6 million through the Gerstner Family Foundation to launch the ADHD Initiative at the Broad.

"Progress in nearly every major disease depends upon the support of a few visionary leaders, who are willing to fund research at the earliest, most critical stages," says Broad Institute director Eric Lander. "Louis is a remarkable visionary — laying a critical foundation that will ultimately give rise to an entire field of research."

Led by Mark Daly, Ph.D., and Benjamin Neale, Ph.D., the initiative builds on longstanding collaborations between the Broad and Massachusetts General Hospital. Recent successes include unearthing genetic insights into other common disorders such as inflammatory bowel disease, autism, and type 2 diabetes.

With support from the Gerstner Family Foundation, these investigators will tackle a disease that affects nearly 5 percent of children in the United States. Preliminary studies point to common genetic variations in ADHD patients, but rigorous studies have not been possible. “Our ability to identify genetic factors has been limited by the paucity of large sample collections,” says Neale, an assistant investigator and founding research affiliate at the Broad. “The Gerstner gift will enable us to drive progress in this critical area.”

A pool of roughly 15,000 patient samples will be collected. That resource will be the backbone for a flagship project that applies powerful new tools to examine patients’ genomes and identify the variants associated with ADHD.

“I’m deeply grateful to Lou for his generosity and vision,” says Daly, a senior associate member of the Broad and co-director of the Program in Medical and Population Genetics, and chief of ATGU. “This will enable the first steps in a long-term strategy to make an impact on the understanding, treatment, and clinical care of ADHD.”
Scientists at the Broad Institute and Massachusetts General Hospital have uncovered new components in a critical pathway that allows immune cells to detect viral invaders.

**CASE STUDY**

**CELL SIGNALING NETWORKS**

**The wiring that underlies human health**

When Aviv Regev arrived at the Broad Institute in 2006, she hoped to deepen her study of human cells—ranging from cancer cells to stem cells and immune cells. As she peered more deeply into how cells make decisions—to divide, die, make insulin, or differentiate into a new cell type—she set an ambitious goal: to catalog all the biochemical circuits inside human cells and to determine which configurations lead to disease.

“Our vision is to understand all the layers of information in a cell’s circuitry explaining how the cell operates,” explains Regev, Ph.D., a core member at the Broad Institute, and MIT associate professor. “If you know how the cell is wired in fine detail, you can open up vast areas of new research that ultimately will transform human health.”

And cells are like computers, she adds. “They receive external information, monitor their own internal states, and make decisions—all done using cellular circuits of interacting molecules. We use the word ‘circuit’ because it immediately invokes an integrated circuit that is wired together for some functional purpose.”

A computational biologist by training, Regev has long been fascinated by cell circuitry and cellular signaling. “But it was only when I came to the Broad that I had the ability to do the right experiments in order to unravel the networks in a systematic way,” she explains. “The Broad’s systematic research approach allows us to marry the problem of understanding how cells compute with the vision and ability to develop tools to find the answers.”

The study of the intricacies of cell circuitry shows that it truly takes a network, cutting across research interests and institutions and drawing on many technology platforms and areas of biological expertise. “Our work has shown that you can choose one cell type and very systematically—one layer at a time—decipher its circuits,” Regev says. “You perturb, measure, and model.”

“The impact, she says, will be lasting, as scientists make data, discoveries, and tools available to the global community. “One of our strengths at the Broad is our network of programs, platforms, and people, working together to advance the study of human health and disease everywhere.”
“Our work in cell circuitry involves a diverse team of scientists at the Broad across multiple disciplines, from proteomics to chemistry. The deeper our understanding of how cellular networks function, the better our understanding of human disease.”

– NIR HACOHEN
“Biology isn’t just about observing. We can change something and see if we can make it better. We can build something that doesn’t exist now.”

– FENG ZHANG

Feng Zhang is intent on unraveling the most intimate mysteries of the brain. Zhang, a core faculty member of the Broad and an investigator at the McGovern Institute for Brain Research at MIT, is designing new molecular tools that allow scientists to study individual cell types and manipulate their activity. His groundbreaking approach is opening up new areas of research that ultimately will transform the understanding of psychiatric and neurodegenerative diseases.

“The genome-engineering tools that we’ve been developing give researchers the power to study a specific group of cells, or to insert a mutation into a specific gene,” Zhang says. “That’s the piece that’s been missing – precise ways to test hypotheses.”

While a graduate student, Zhang, working with his Stanford University advisor Karl Deisseroth and a fellow student, Edward Boyden (now also on the MIT faculty), conceived a powerful way to use light to control the activity of neurons. Their idea was to use a protein from green algae that responds to light by opening or closing a pore in the cell membrane. The scientists created transgenic mice in which the gene encoding this protein was turned on in specific types of neurons. By using fiberoptics to deliver light into the brain, they could control the activity of target neurons.

The technique – called optogenetics – has taken the neurobiology world by storm.

“We can systematically look at one type of cell at a time to figure out what each one does, and how they work with each other,” Zhang says. “The team has successfully demonstrated the power of optogenetics in studying motor function, sleep, and the reward system. “The way the brain is put together is very important to neurological and psychiatric diseases.”

Feng Zhang, Ph.D.

ENGINEERING THE GENOME

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Continued next page
problems, such as autism or schizophrenia,” says Zhang. “A lot of them involve the way cells are connected in the brain.”

Since coming to the Broad, Zhang has undertaken another path-breaking project. His idea is to use a new kind of protein, called TAL effectors, that can be customized to bind to a specific location in the genome. After developing ways to build TAL effectors in a matter of days, Zhang and his team have been perfecting applications of these versatile proteins. They have developed ways of using TAL effectors to insert a new DNA sequence, change a single base of DNA, delete a region of genetic material, and more. The technique opens up new ways of investigating many disease areas, including cancer, infectious diseases, and diabetes. Zhang is working with researchers from many Broad groups, including the Epigenomics Program and RNAi Platform, to use TAL effectors to engineer and manipulate genomes.

“TAL effector technology represents a major advance in gene manipulation in animals,” says Michael Brown, M.D., a Nobel laureate and professor of molecular genetics and director of the Jonsson Center for Molecular Genetics at UT Southwestern. “Zhang has performed an extremely valuable service to the entire community of biologists by making all of his methods and reagents available to any academic for a nominal fee. His generosity should be a model for all who develop pioneering technologies.”

To Zhang, openly sharing his methodologies and techniques is natural. “When you’re building tools, it’s important to get them out into the community,” he says. “The Broad has a system in place for sharing and collaborating, and that’s what I believe in. Too. You build a tool, send it out, people use it and tell you it’s not working well, and you fix it. That kind of feedback drives things forward.”

“Biology isn’t just about observing,” he says. “We can change something and see if we can make it better. We can build something that doesn’t exist now. That’s what got me interested in the field. Its capacity to be transformed.”

Brian Hubbard, Ph.D.

As director of the Broad Institute’s Therapeutics Discovery and Development (TDD) Platform, Brian Hubbard aims to transform the process of drug discovery and the treatment of human disease by developing and applying new drug discovery technologies. His group is focusing on classes of protein targets that are generally viewed as “undruggable” and patient populations currently left untreated by the biopharmaceutical industry.

“Our goal is targeting new mechanisms that are emerging from studies of human biology, and working in an open, collaborative environment to establish proofs of concept,” he says. “The platform brings together experts from academia and industry to drive innovation in solving therapeutics challenges widely considered intractable. Like other Broad initiatives, TDD works with Broad programs and platforms in an integrated, collaborative, and overarching effort to transform the understanding and treatment of disease.”

The platform does not aim to duplicate drug discovery activities being pursued by large pharmaceutical and biotech companies, according to Hubbard. Instead, the goal is to address critical unmet needs not being tackled elsewhere. TDD integrates its ideas with industrial-strength execution, bringing to bear the Broad’s capabilities in areas ranging from Diversity-Oriented Synthesis to Gene Expression High-Throughput Screening to laboratory-based target identification.

Hubbard brings extensive knowledge of drug discovery and development to the Broad. Before arriving in 2011, he was senior director of cardiovascular diseases at Merck, where he was responsible for strategy and execution of research. His focus was primarily atherosclerosis research.

Prior to his work at Merck, Hubbard was director of cardiovascular and metabolism research at Novartis Institutes for Biomedical Research. He also did research into metabolic diseases and obesity at Millennium Pharmaceuticals. He has received numerous awards during his industrial career, including elite scientific recognition awards at Millennium, Novartis, and Merck.

“At the Broad, we aim to do more than just bring a few therapies to patients in need; we hope to revolutionize the entire drug discovery process.”
The Broad's deeply collaborative community bridges multiple institutions and partners in industry, connecting researchers with each other and across MIT, Harvard, and more than 20 other Harvard-affiliated hospitals who work together to address the most critical problems in biomedicine.

"Broadies" take on “impossible” problems, transcending disciplines and fusing experimental, computational, and clinical science into a new biology.

“The Broad is without peer in its expertise and leadership in genomics and therapeutic discovery.”

— MYRIAM HEIMAN

Myriam Heiman's journey to the Broad Institute was driven by a central question: What are the root causes of neurodegenerative and psychiatric diseases? And for Heiman, who joined the Broad in early 2011 as a core member, this question hinges on the longstanding problem in neuroscience of cell identity in the structurally diverse environment of the nervous system.

Heiman holds a joint appointment with the Picower Institute for Learning and Memory at MIT, and she is an assistant professor of neuroscience in the Department of Brain and Cognitive Sciences at MIT. The brain contains many different types of cells, all with unique functions and unique ways of breaking down. In many neurodegenerative diseases, for example, certain cells are affected early in the disease process — but the reason remains a mystery. “How one studies individual cell types in very complex tissues is a fundamental question that has, for many decades, hampered neuroscience research,” she says.

After studying basic genetics in yeast for her graduate work at Johns Hopkins University, Heiman pursued this question during her postdoctoral research with Paul Greengard and Nathaniel Heintz at the Rockefeller University. The scientists took a genetic approach to solving the problem. Using molecular tags, they were able to biochemically purify all the messenger RNA — representing the proteins being made in the cell — from a single cell type.

“It’s a very simple idea, but very powerful because we haven’t had this kind of molecular access before,” she says. "It’s a very exciting new ability to investigate what is being done by particular types of cells at particular times — during normal function and in diseased states. If we can understand what’s going on in the vulnerable cell types, then we may understand the etiology of these diseases,” she says. This sort of molecular profiling allows investigators to study individual neuron populations among the myriad cell types that constitute the mammalian nervous system.

At the Broad, Heiman and her team use molecular profiling, biochemical analysis, and mouse models of disease, including Huntington's and Parkinson's diseases, to investigate the basis of selective vulnerability in disease. They also want to know how normal aging enhances this vulnerability.

“One commonly observed feature of many of these diseases is they’re only seen in advanced age,” Heiman says, “despite the fact that the genetic risk factors are present from birth. We can now ask what diseases causing changes occur very early in the course of an illness, before symptoms develop. We’re certainly not the first people to ask these questions,” she adds. “The difference is that we now have the ability to probe at the molecular level — comprehensively and with great cellular resolution.”

Heiman’s team also is interested in basic neurodevelopmental questions. “We try to understand what happens to cells as they age, to get a full perspective of what is defining cellular identity at the molecular and cellular level as these cells are born, mature, and then age,” she says.

Heiman hopes that her approach can accelerate research into psychiatric disease and other diseases with selective cell deficiencies, such as cancer. By working with Huntington's disease, caused by mutation of a single gene, she hopes to prove the strength of her model and demonstrate its promise in untangling other diseases.

“We hope that we can use the simplicity of this model and the lessons we learn to gain insights into other complex diseases,” she says. She collaborates closely with computational biologists and scientists in the Proteomics Platform, “The Broad is without peer in its expertise and leadership in genomics and therapeutic discovery, as well as in the study of cellular circuitry and molecular phenotypes in disease,” she says.
Paul Blainey’s 3.5-cm microfluidic chip sorts single cells and amplifies their genomes to prepare for sequencing.

Paul Blainey is intent on harnessing the power of small. An expert in analytic systems at both the single-molecule and single-cell levels, Blainey, newly arrived as a core member of the Broad Institute, has developed a microfluidic platform that allows him to segregate individual cells and directly sequence their genomes.

This, in turn, allows scientists to determine genomic sequences from organisms that have not been successfully cultured in the lab – unknown microbes that could provide insights into fundamental aspects of microbial evolution and drive a deeper understanding of the population structure of human pathogens.

At the Broad, Blainey plans to continue developing new applications of microfluidics in single-cell and single-molecule science. He has devised a system based on single-molecule assays to measure how certain proteins move along DNA, using simple microfluidics to stretch DNA and fluorescent protein labels to monitor the movement. The work revealed that the proteins stay in contact with DNA as they slide along it, and that they spin around the DNA helix as they move. In his new role, Blainey plans to develop microfluidic technology to make these single-molecule assays easier to perform, in addition to searching for new classes of polypeptides that move along DNA by sliding.

He hopes his work at the Broad and MIT, where he is an assistant professor in the Biological Engineering Department, will allow these technologies to find a broad range of important applications quickly. “The Broad is the best place in the world to do this kind of work.”
“I am convinced that genomics will be one of the ways to find out how to make people live longer, better lives.”
ARLOS SLIM HELÚ gets right to the point.
Sitting at a large oval table in his spacious Mexico City office, he explains to his visitors why he invests in genomic medicine.

“I am convinced that genomics will be one of the ways to find out how to make people live longer, better lives,” he says.

Gesturing across the table to his son Marco Antonio Slim Domit, he says, “Tony can tell you in three words what we need for health: new, better solutions.”

Mr. Slim warms to the topic of why he has devoted considerable resources to an initiative that bears his family’s name: the Slim Initiative for Genomic Medicine.

“It’s the challenge,” he says. “We are clear that the way to finish poverty is with employment. But to become employed you first need to have good health, and then good education. We think genomics is the right way to improve health.”

Part of the Carlos Slim Health Institute, the Slim Initiative is funded by the 25-year-old Carlos Slim Foundation, whose public health programs initially focused on improving maternal and child health through nutrition and immunizations, especially in rural areas of Mexico. The foundation also promotes education, the arts, sports, historic restoration, and digital literacy among other causes.

In 2010 the health institute expanded its vision to include basic biomedical science in the form of genomics. Through a three-year,
$65 million agreement with the Broad Institute, the Slim Initiative brings together experts from the Broad and from Mexico, including the National Institute of Genomic Medicine of the Mexican Secretariat of Health, known by its Spanish acronym INMEGEN.

The relationship forged with the Broad has twin goals. One is to unlock biological secrets through a better understanding of genetic factors underlying disease. The other is to invest in human capital. So far the Slim Initiative has helped to train more than 1,500 Mexican experts. INMEGEN scientists collaborate with their Broad counterparts in a flourishing exchange of ideas, sharing access to advanced technology and providing educational opportunities for researchers and students in both Cambridge and Mexico City.

“It is important to accelerate the development of research in genomics here,” Mr. Slim says.

Because the project is Mexican at its heart, it focuses on diseases that have a profound impact on Mexicans and Latin Americans: diabetes and cancer. The Slim Initiative also studies kidney disease that has a profound impact on Mexicans and Latin Americans: diabetes and cancer.

Diabetes is among the most common inherited diseases in Latin America, yet the role played by genetic risk factors is not well understood. Answers may lie in unlocking biological secrets through a better understanding of genetic factors underlying disease.

“Mexican and Latin American populations have been poorly represented in the human genome,” says Miguel Betancourt, M.D, who oversees the Slim Initiative as global solutions director of the Carlos Slim Health Institute. “Epidemiology tells us there are differences in type 2 diabetes and cancer in this population. We want to see what the role of the Latin American genome is.”

Such an ambitious project requires private-public partnerships, Dr. Betancourt says. Governments can’t do everything.

“The same is true for genomics,” he says. “Every single thing we do – telemedicine for pregnant women, vaccines for neglected diseases, genomics for other diseases – is translated for public use.”

But don’t call it “philanthropy.”

“Think of it as social investment. We need to have a return on our investment for Mexican society: stronger institutions, better-trained researchers, better services for the population,” says Dr. Betancourt, a pediatrician who joined the Carlos Slim Health Institute after serving in the Mexican Secretariat of Health. “It is important that the research is jointly done in Mexico. We don’t want to just be sample givers.”

In Mexico and Latin America, the Slim family’s imprint touches daily life through telecommunications, real estate, retail, construction, and cultural institutions they have built. Now 72, Mr. Slim devotes more time to the foundation, he has stepped back from some leadership roles, and his children have come to the fore in the family businesses.

His son-in-law, architect Fernando Romero, designed Museo Soumaya, the soaring art museum named after Mr. Slim’s late wife, Soumaya Domit. Its treasures include Impressionist paintings, Mexican masterpieces, religious artifacts, and a top floor devoted to sculpture holding the largest collection of Rodins outside France. People can visit the museum free of charge.

His office in Lomas de Chapultepec in Mexico City has an art gallery and towering bookcases with art tomes in his office. An image of Lebanon, where his parents were born, hangs on a wall. A worn copy of futurist Alvin Toffler’s book, Las Guerras del Futuro, lies open, facedown on his table.

Mr. Slim shares a prediction with his son Marco Antonio, Dr. Betancourt, and Slim Initiative associates assembled around his table.

“What vaccines were in the past, I think genomics will be in the future,” Mr. Slim says. “The work we are doing with the Broad Institute is very important not just for Mexico, but worldwide.”
The Slim Initiative for Genomic Medicine is a two-way street, with researchers and information moving in both directions as part of the international collaboration. David Altshuler and Angela Schwarz, two young scientists from the National Institute of Genomic Medicine (INMEGEN) in Mexico City, spent a short sabbatical at the Broad Institute as part of the initiative. The effort focuses on diseases that have a profound impact on Mexicans and Latin American diabetes and cancer, as well as kidney disease in affected families.

“The most important part of this collaboration is to bring knowledge back to Mexico, to start to do sequencing analysis,” Dr. Schwarz says on the last day of her three-month stay at the Broad. Trained as a physician, she is working on her Ph.D. in biomedical science while studying cancer genomics.

Dr. Altshuler, who is a computational biologist, notes that the international collaboration also highlights interdisciplinary connections among researchers. “It’s another way to do science,” he says.

At a regularly scheduled visit by INMEGEN scientists to the Broad, decisions are being made about the direction of a Slim Initiative project on diabetes. During a discussion led by Broad founding core member David Altshuler and leaders from Mexico City, milestones in the genetic analysis of Mexican samples are reported. Experts from Mexico and the University of Southern California weigh in with their results from relevant studies, generating excitement and thoughtful consideration of where resources need to go. Two years into the three-year initiative, the Slim Initiative diabetes project is exploiting new methodologies to accelerate diabetes research and Latino genomics.

“I think the Mexican population is a model for identifying genetic risk factors in diabetes that haven’t been identified before,” says Teresa Tusié, principal investigator for the Slim Initiative diabetes project and chief of the area of Molecular Biology and Genomic Medicine at the Institute of Biomedical Research at the National Autonomous University of Mexico. Altshuler is excited about the scientific progress being made, and he especially values the opportunity to work together, across borders.

“In the long run, the most important thing is forming relationships and a team,” he says.

At INMEGEN in Mexico City, scientists explain what the Slim Initiative means to them.

Alfredo Hidalgo Miranda, champion of the breast cancer project at INMEGEN, says his work simply couldn’t happen without the Slim Initiative. Four years ago he and his colleagues embarked on a project to characterize genomic alterations in breast tumors from Mexican patients. While survival rates are lower among Latinx women, little is known about the genetics of breast cancer in this population. Working with samples from a local hospital specializing in breast disease, the INMEGEN researchers analyzed tumors looking for genetic variation, such as when stretches of DNA are present in excess copies or missing altogether.

For a more comprehensive analysis, the team needed more firepower. They got it when the Slim Initiative project was launched. Dr. Hidalgo Miranda was able to sequence his samples and do joint analysis with a team at the Broad.

“The Slim Initiative has made things happen. It allowed us to do sequencing of tumors that would have been impossible to do here,” he says. “It’s a good example of how to produce information that is useful for the Mexican population.”

Pediatric oncologist Gabriela Merced hopes to establish a biobank in Mexico for high-quality tumor samples from children. While childhood cancer survival is improving in Mexico, rates are still lower in the United States, or Canada, especially for leukemia.

“If you don’t collaborate, it is impossible to have results in pediatric cancer because the number of cases, fortunately, is small,” she says. “With the Slim Initiative project, I think we can do this.”

Claudia Rangel Escareño, a mathematician who works in computational genomics, says the Slim Initiative presents the opportunity to work with top researchers in the world doing genetic analysis.

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Connecting Communities

With new scientific approaches transforming our knowledge of human biology and disease, the Broad Institute is committed to opening the doors of science to the general public and to the next generation of young scientists.

Through public programs, educational programs, and online resources, we invite everyone to learn about exciting discoveries and what new knowledge means for them.

Public Lectures

Throughout the summer, Broad hosts its Midsummer Night’s Science lectures for the general public. The lecture series explores key advances in genomic research.

Educational Outreach Program

On-site programs bring local high-school students and teachers to the Broad to explore what it really means to be a scientist.

- Class visits bring more than 1,000 students each year for experiments, computer and paper-based activities related to current Broad research, tours of Broad labs, interactions with Broad scientists, and discussions of science careers.
- Summer internships allow a select group of high-school students to work one-on-one with scientific mentors.
- Teacher seminars bring educators into the Broad to learn about current research, tour Broad labs, and talk with scientists.
- Semester-long research projects provide opportunities for students to engage in independent research projects aimed at isolating and identifying microbes from the environment.
- Portable lessons are developed by Broad scientists and then delivered by science teachers in classrooms.

Diversity Initiative in Scientific Research

Programs engage underrepresented minorities at all levels in scientific training to pursue biomedical research.

- The Summer Research Program in Genomics (SRPG) is a nine-week undergraduate research program designed for students with an interest in genomics and a commitment to research.
- Minority Introduction to Engineering and Science at MIT (MITES) is a six-week residential, academic enrichment summer program that introduces high school seniors to engineering and science. Broad hosts 16 MITES students a year for a popular genomics internship.
- Broad Medical Fellows are medical students who work on an original research project in genomic medicine during an eight-week summer program.
- Broad Postdoctoral Fellows pursue up to three years of postdoctoral training in genomics through a program that prepares them for a research career.
- The Visiting Faculty Program provides scientists the opportunity to participate in leading genomics research.
These 15 high school students participated in the fall 2011 semester-long research project, and chose to investigate microbes from a wide variety of environmental sources, such as a spider web and a kitchen sponge.

Next up

They look like scientists. Wearing white lab gloves, wielding pipettes, and wondering what their mystery worm might be, 29 students from a greater Boston AP biology class work at stations in a Broad Institute lab. Tiny tubes contain proteins from a roundworm, a flatworm, and a mystery worm, plus a “ladder” of proteins they can use as a reference. They’ll send a small sample of each through a process called gel electrophoresis, a technique that uses electrical current to separate DNA, RNA, or protein molecules based on their size.

While they wait for the process to conclude, they open laptops to learn how to check an online database and try to identify an organism by using its protein sequences. “Chinese liver fluke?” asks one student. She holds that thought until after lunch, when the students break up into groups of four to talk with Broad scientists eager to share stories about their lives in science.

Researcher John Doench explains RNA interference for the students before describing his role in the RNAi Platform. RNAi, discovered in 1998, is an ancient mechanism that organisms use to silence genes. Scientists have seized this process to understand what genes do by selectively silencing them, one at a time, in laboratory experiments.

“Is that like hacking biology?” a student asks. Doench tells him yes. “Today’s discoveries become tomorrow’s tools.” Just as today’s students might become tomorrow’s scientists.

Reaching out

Bringing young minds into science

CASE STUDY

Steven
NEWTON NORTH HIGH SCHOOL
sock, tree bark

Porter
CAMBRIDGE RINDGE & LATIN SCHOOL
doorknob, hand

Amelia
CONCORD ACADEMY
fridge, spider web

Arum
Arcadia
CONCORD ACADEMY
grapes, toothbrush

Sofia
CONCORD ACADEMY
monkey bars, tea leaves

Adam
JOHN D. O’BRYANT SCHOOL
kitchen sponge, table

Kavin
BOSTON LATIN SCHOOL
school fountain water, tree bark

Daniel
NEWTON NORTH HIGH SCHOOL
feta cheese, his dog

George
BELMONT HIGH SCHOOL
carpet, refrigerator handle

Elizabeth
NEEDHAM HIGH SCHOOL
aquarium tank water, mouth swab

Josie
JOHN D. O’BRYANT SCHOOL
milk, children’s toy

Nick
BROOKLINE HIGH SCHOOL
dog, pillow

Mustafa
CAMBRIDGE RINDGE & LATIN SCHOOL
cheese, restroom

Ola
CONCORD CARLISLE HIGH SCHOOL
carpet, fence
Leadership

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The members of the Broad Institute’s Board of Directors include world-class leaders from science, law, education, and business. These distinguished individuals serve as wise and effective stewards of the institute, helping to drive the transformation of medicine that lies at the heart of the Broad Institute’s mission.

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Institute Professor, Massachusetts Institute of Technology; Nobel Laureate

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The ambitious projects undertaken by the Broad Institute would not be possible without the critical support and continued commitment of our donors, research sponsors, and friends. We would like to thank the following individuals and organizations for their investment in improving human health through their support of the Broad Institute.

Eli and Edythe L. Broad

Discussions 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 visionary generosity of the Broads ($100 million over ten years, subsequently doubled to $300 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.

The Stanley Medical Research Institute

The Broad Institute’s Stanley Center for Psychiatric Research was created in 2007 with the extraordinary support of a ten-year $100 million grant from the Stanley Medical Research Institute (SMRI). In April 2011, SMRI extended its support to fund the work of the Stanley Center through 2022. The mission of the Stanley Medical Research Institute is to discover the human genes that confer risk for bipolar disorder and schizophrenia and to use this information to develop new diagnostic tests and treatments for these illnesses.

Institute Carlos Slim de la Salud

In 2010 Carlos Slim Helú announced the launch of a major research project in genomic medicine to help accelerate progress in public health in Mexico and around the world. The major goal of this project, called the Slim Institute for Genomic Medicine, is to investigate the genomic basis of cancer in worldwide populations, and of type 2 diabetes in Mexican and Latin American populations. The Broad is collaborating in the $65 million project with the Carlos Slim Health Institute and Mexico’s National Institute for Genomic Medicine.

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Support

History of Operating Revenue

Balance Sheet

As of June 30, 2011 ($ in thousands)

Operating Revenue

From July 1, 2010 through June 30, 2011 ($ in thousands)

Operating Budget

As of June 30, 2011 ($ in thousands)

Financial Information

Balance Sheet

Total Assets $1,160,479
Total Liabilities $455,408
Total Net Assets $705,071

Operating Revenue

Operating Revenue ($ in millions)

As of June 30, 2011 ($ in thousands)

Balance of Operations

$11,258

Operating Budget

From July 1, 2010 through June 30, 2011 ($ in thousands)

Total Revenues $298,870
Total Expenses $287,612
SIDE POCKET FOR Q

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