

Innovations

Broad Institute: Bringing Genomics to Real-World Medicine

In June 2003, the scientific and medical communities at MIT, Harvard University and its affiliated hospitals, and the Whitehead Institute banded together as collaborating partners to form the Eli and Edythe L. Broad Institute based in Cambridge, MA. The Broad Institute, established with initial funding from a \$100 million philanthropic donation from the Los Angeles-based Broad family, was primarily viewed as a marriage between the Whitehead Institute's Center for Genome Research (WICGR) and the Harvard Institute of Chemistry and Cell Biology (ICCB). Eli Broad, founder and chairman of AIG SunAmerica, Inc., explains, "The purpose of the Broad Institute is to create a new type of research institute to build on the accomplishments of the human genome project and to move to clinical applications to both prevent and cure diseases."

The nascent institute includes four core faculty members leading four foundational programs in genomics, chemical biology, medical and population genetics, and cancer medicine. When fully staffed over the next five years, the institute will have 12 core faculty members on board at the new 230,000-square-foot Cambridge facility, scheduled to be completed in 2006. Among the four core members are former ICCB Director Stuart Schreiber and former WICGR Director Eric Lander, who now directs the Broad Institute. "In the early days, when Eric and I were discussing formally merging these two institutions, my thinking was that the Broad represented the promise of integrating genomics and chemical biology," recalls Schreiber. But today, that idea too narrowly describes the Institute's mission. "It is the integration of genomics and chemical biology in partnership with the medical side of cancer, psychiatric disease, infectious disease, and metabolic disease," says Schreiber. Within the scope of the Broad's current research effort are the four founding scientific pro-

grams, three initiatives in metabolic, infectious, and psychiatric disease, five scientific platforms, and 11 major projects. Researchers also participate in numerous other projects, many involving partners from outside of the MIT and Harvard communities and a few with for-profit companies.

Complex Human Genetic Diseases

"Today, we are constantly reminded that the human genome sequence is just a reference that by itself is of very little value," says Schreiber. To add that value, the Broad has chosen to focus on medical arenas with a significant underlying genetic ba-

"[The Broad Institute] is the integration of genomics and chemical biology in partnership with the medical side of cancer, psychiatric disease, infectious disease, and metabolic disease." —Stuart Schreiber, Broad Institute faculty member

sis rather than Mendelian diseases in which a single gene change is strong enough to cause disease. One example is the Psychiatric Disease Initiative (PDI), dedicated to finding the multiple genes contributing to schizophrenia and bipolar disease risk. In 2004, the Broad Institute recruited Edward Scolnick, former president of Merck Research Laboratories, as director of the PDI, where he works with Pamela Sklar, who has been researching psychiatric disease genetics for the past six years. "Ed Scolnick provides a vision of disease that takes into account what the real challenges are and the

combination of approaches needed to solve the big problems in psychiatric disease," says Schreiber. "And he was able to nucleate a group of colleagues in the area."

"The Broad is unique because it is a collaborative institute and it allows expensive and complicated technology and the people who know how to use it to be applied in collaborative ways to major medical problems that otherwise would be very difficult to do," says Scolnick. "The people, technology, and funding are here now at this unique time to apply the best of this so-called postgenomics era to significant medical projects." Adds Sklar, "I am now in a position where I can be at the forefront of developing genetic analyses and techniques and apply them very rapidly to psychiatric disease. That had been missing in the field of psychiatric research as a whole."

"Eric Lander has set up the Broad Institute in a very efficient way to have core technologies and core groups operate in large collaborative projects in much the same way a company laboratory does," says Scolnick, though he adds that it does not yet have financial resources available to it on the scale of a pharmaceutical company like Merck. This means the research pace is slower than in a company environment. "But no company has the technology that is available here to be able to do the things with genetics that the Broad can do," he says.

Network of Collaborations

Two years after its founding, the Broad includes 60 associated faculty members, drawn from MIT, Harvard and its hospitals, and the Whitehead Institute. "That is what is most impressive about the Broad," says Michael Snyder, Director of the Yale Center for Genomics and Proteomics, whose center is also pursuing advances in genomics re-

search. "They have clearly attracted some of the leading figures in their fields." Each member of the Broad community, including the four core faculty members, retains membership in his or her home department and institution. Associate members participate with the Broad on two-year membership cycles.

"A lot of the interaction at the Broad is intended to enable larger collaborations that typically cannot be undertaken or are difficult to undertake at individual labs or to be funded in individual labs," says Patrick Kleyn, director of scientific planning at the institute. An example of that is the inhibitor RNA (RNAi) Consortium project. "That is a collaboration initially founded by a few investigators around Cambridge and Boston who came together realizing it would be more effective and efficient to pool resources," explains Kleyn. "It soon became clear it would make sense to make a library of inhibitory RNA clones, but it would require serious money and management." Building on the strengths of people with scientific expertise by providing the large-scale management experience, the Broad helped organize and currently is the base of operations for the RNAi Consortium. Announced in March 2005, the RNAi Consortium includes 11 biomedical organizations focused on creating a library of gene inhibitors based on RNA interference. The short RNA hairpin sequences created will be used to discover the key genes involved in normal physiology and disease by targeting 15,000 human genes and 15,000 mouse genes, the hope being that this will yield new targets for drug discovery. A total of 150,000 custom-designed short hairpin RNAs will be created and validated. All reagents and discoveries will be disseminated to the worldwide scientific community.

"The Broad is taking on big cutting-edge projects," says Snyder. One example cited is the International Haplotype Map Project, an international research effort mapping common patterns of human genetic variation known as haplotypes, led in part by the Broad's David Altshuler. "Clearly, David Altshuler is a leader in the field of genetic mapping, and the HapMap is a big, ambitious project that will be useful for

mapping genetic diseases, and that map will be very useful to many, many geneticists," says Snyder. "Similarly, Stuart Schreiber is a world leader in chemical biology genomics," says Snyder. "A lot of people collaborate with his group for screening, and I don't expect that to change even though many universities, including Yale, are setting up their own chemical genomics groups."

On select projects, collaborations also include for-profit companies. "Companies may participate with us in certain areas affecting global health, like malaria and TB, where they can contribute to societal benefit and can also enjoy the benefit of the goodwill," says Schreiber. "We hope to be a receptor for forward-thinking private sector companies like that." Yet Schreiber acknowledges that this type of research collaboration is the exception for a company. Kleyn adds that collaborations with for-profit companies would be considered only when there would be no restrictions on disseminating information into the public domain. "The funder would gain by overall acceleration of the field," he says. In the public/private RNAi Consortium project, pharmaceutical companies Bristol-Myers Squibb, Eli Lilly & Co., and Novartis AG and other academic centers are supplying \$18 million over three years to fund the production of inhibitory RNAs. "The companies benefit by working with the top researchers in the field and accelerating their own pipelines," Kleyn says, "and the institute benefits by getting the reagents, tools, the technologies out there into the public domain to advance medicine."

"The relationships we focus on with for-profit companies are those where the companies are comfortable with the idea that the project will be a public domain project," says Kleyn. The Broad Institute's collaboration with Novartis on the genetics of type 2 diabetes is an example. "There is an understanding that deciphering the genetics of complex disease is a fundamental, early-stage research program and unlikely to immediately deliver therapeutic benefit," says Kleyn. Adds Snyder, "The Broad already generates sequences they are putting out to the whole scientific community,

and lots of people use them. The information they generate will definitely be used very extensively. I would expect lots of collaborations between the Broad and others in the field, particularly as we learn more about them."

Multiple Funding Sources

Only about 10% of the Institute's funding derives from the original Broad gift. "That 10% is intentionally used to fund otherwise hard-to-fund research, the truest earliest research with no preliminary results based on good ideas," says Schreiber. "We encourage the growth of the Broad by asking for proposals for science that is very high risk but, if successful, would transform science and society." These projects are funded initially only for 12 months. The initial data produced are expected to enable the projects to generate their own sustaining funding. Ninety percent of the institute's funding comes from the government, philanthropic sources, and nonprofit institutions, and this funding supports more advanced science through the peer-review process. The bulk of that 90% also supports the scientific platforms.

"It is a fantastic time to do important work in medical illness with a genetic basis," says Scolnick. "I sensed that from the outside, but I now am really impressed that we are in a unique time to be able to apply modern human genetics to medical disease. Eric Lander wants the Broad to make seminal discoveries about currently very poorly understood diseases. He has a vision of what can be done to understand really difficult medical diseases with a genetic basis that is inspiring."

Alice A. McCarthy (alice@alicemccarthy.com) is a freelance science writer based in Gloucester, MA.