Human Cancer Genome Project Moving Forward Despite Some Doubts in Community

The Human Cancer Genome Project, a proposed 10-year, $1.5 billion effort to achieve “a comprehensive genomic analysis of cancer,” is preparing to launch its 3-year pilot project as soon as next year. But some disagreement remains about how best to dissect the genetics of cancer and ultimately find cures. And although the project’s planners intend to seek new funding for the main project and not put investigator-initiated grants at risk, some cancer researchers are worried that the project will indirectly depress available funds.

The goal of the genome project is to identify all the functional gene mutations and other abnormalities in common tumor types. Once accomplished, this information could lead to more individualized drug therapy and the development of drugs against newly discovered targets. “We know cancer is a genetic disease, and I think it’s a very worthwhile investment to find all the genetic alterations that occur in major cancer types,” said Victor Velculescu, M.D., Ph.D., of Johns Hopkins Medical School in Baltimore. “The reason is, most of them are funded from R01 grants, and they’re afraid this [project] is going to compete for their funding.” Hartwell argued for a pilot project focused intensively on a single cancer site to discover what can be learned from a comprehensive analysis. “Then you can make an intelligent argument as to how much it should be expanded,” he said, “and whether it’s worth depleting some of the R01 pool to do it, or whether it’s worth going to Congress for new funding.”

Such a single-cancer approach is under consideration for the pilot phase, and Francis Collins, M.D., Ph.D., director of the National Human Genome Research Institute (NHGRI), said he expects the larger comprehensive project to yield “an awful lot of discoveries.” “The project we’re planning needs to be really bold and ambitious,” Collins said. “Doing this on a small scale is not likely to be successful.”

Not everyone agrees. “I think you’d probably get more bang for your buck if you do investigator-driven research than these megaprojects,” said Rene Bernards, Ph.D., head of the division of molecular carcinogenesis at the Netherlands Cancer Institute in Amsterdam.

Linking Mutations to Drugs

The cancer genome project originated when NCI director Andrew von Eschenbach, M.D., asked Hartwell and Eric Lander, Ph.D., director of the Broad Institute in Cambridge, Mass., to oversee a study of technology opportunities in cancer as part of von Eschenbach’s plan to eliminate death and suffering from cancer by 2015.

From those discussions, Hartwell drafted a proposal for a biomarker project and Lander’s group wrote the proposal for the cancer genome project. After Lander presented the project proposal to the National Cancer Advisory Board in February, the project moved forward quickly, with planners hoping to release several requests for applications (RFAs) to the outside scientific community as soon as possible. In late July, cancer experts from many different fields held a workshop in Washington, D.C., to lay out options for structuring a pilot project, which should be up and running next year. An external scientific committee is now making decisions on issues like tumor focus, technology choices, and sample collection. The NCI and NHGRI have each committed $50 million to the pilot project.

The overall cancer genome project is driven in part by recent scientific findings about how specific cancer-related mutations can affect drug response. These include the 2004 discovery that somatic mutations in the epidermal growth factor receptor (EGFR) gene in lung tumors can predict patient response to the drug gefitinib (Iressa) and the 2003 discovery that mutations in the c-Kit gene can predict response to the drug imatinib (Gleevec).

These and other discoveries of novel mutations in cancer genes gave hope that large-scale sequencing of tumors will enable individualized drug therapy for existing drugs—and discovery of new drugs. At the same time, tumors don’t arise just from gene mutations. Abnormal gene copy number; gene silencing through methylation and other epigenetic mechanisms; and gene translocations, amplifications, and deletions also contribute in various degrees, depending on the tumor. The cancer genome project will also analyze these phenomena. “Sequence is just one kind of information,” said Collins. “What we’re trying to do here is to learn everything we possibly can from every kind of technology.”

Still, mutation detection will probably be the single biggest part of the cancer...
launched programs to and several drug companies have now important BRAF mutations in melanoma, in 2000, the project discovered the impact, has delivered mixed results. Begun Sanger Institute’s Cancer Genome Project, according to planning documents. The NCAB report suggested a comprehensive genomic analysis of roughly 12,500 tumor samples—250 samples from each of 50 major cancer types. “As sequencing technology improves and costs fall, it should become possible to resequence all human genes in all samples,” reads the report.

**A Worrisome Precedent?**

Despite the $100 million commitment by two NIH institutes, some in the cancer research community are not yet convinced that large-scale sequencing of tumors will be worth the investment. “I think everyone would say, ‘Yes, it would be useful to have the sequence,’” said Stephen Elledge, Ph.D., a Harvard Medical School geneticist. “The real question is, if we have $1.5 billion in new cancer money, is that what we want to do with it? What’s the quickest way to get a cure for the disease?”

A more limited sequencing effort, the Sanger Institute’s Cancer Genome Project, has delivered mixed results. Begun in 2000, the project discovered the important BRAF mutations in melanoma, and several drug companies have now launched programs to find BRAF kinase inhibitors. But the project recently sequenced breast cancers and found few recurring somatic mutations. Sanger researchers sequenced the coding regions of all 518 protein kinases in 25 breast cancers and breast cancer cell lines, but most of the primary breast cancers had no somatic kinase mutations at all. Resequencing of the mutated genes in 56 other breast cancer samples yielded only three more functional mutations. “The results suggest that there is no commonly point-mutated and activated protein kinase gene in invasive ductal breast cancer,” concluded the paper’s authors.

The Sanger result “doesn’t cause me any anxiety at all,” said Collins. “I think what it shows is that if one wants to undertake this kind of analysis, you do need large numbers of samples, and you need to survey very large numbers of genes.”

Others take away different lessons. “You’re not going to find all the gold in the kinases,” said Hartwell. “And maybe … you’re not going to find the gold in sequencing. I’m personally much more interested in rearrangements and methylation than I am in point mutations.”

For some, the Sanger results raised doubts about the genome project sequencing plans. “The question is, how much information can you really get from resequencing tumor samples?” said Elledge. “And will you be able to figure out the real stuff from the noise? And if you are, how will that translate into cures for cancer?”

**A Functional Alternative?**

A different approach—one that has received little attention in genome project planning but, according to several researchers, should be—is functional genomics. It’s now possible to use “bar-coded” small-hairpin RNAs (shRNAs) to systematically knock out genes in human cells to determine their function, using the power of RNA interference. Until now, such large-scale knockouts had been possible only in model organisms. Using shRNA and cDNA (complementary DNA) “libraries,” one could, in theory, activate or knock out every gene to see if the cancer cells grow or die—and every phenotype in between—compared with normal cells, and then fish out the genes responsible.

“If we were to spend money on a functional genetic interaction map of the genome, including large-scale synthetic lethal screens, wouldn’t we be getting a lot more value for our money?” asked Bernards. “More targeted, rather than brainless, sequencing.” Bernards pointed out that sequencing would miss many key cancer genes. “There’s probably a whole range of spectacularly good cancer targets out there that are synthetic lethal with loss of Rb, loss of p53, loss of PTEN,” he said. “These genes may not be mutated in human cancer, and may not be amplified, and therefore would completely stay below the radar screen of this resequencing effort.”

Elledge also argued for a functional genetics approach. “Look for genes which, when you interfere with them, kill cancer cells and not normal cells,” he said. “These aren’t going to be genes that are mutant in tumors.”

The biggest limitation of this approach is that functional genetic screens can’t yet be done in many cell lines, and not at all in primary tumor samples. “The question is, are they able to scale to the level that this particular project aims to achieve in terms of getting an encyclopedic view of the causes of cancer?” said Collins. “I think, at the moment, most of those approaches are generally only workable [in] a small number of cell lines.” Bernards disagreed. “If you spend the kind of money they wish to spend on cancer genome resequencing, we could make a functional interaction map of spectacular size,” he said.

**The Case for Big Science**

Besides differences over scientific approach, there is concern that the project will generate a momentum of its own, even if the pilot project delivers disappointing results, and then not add much of value. Elledge said many colleagues wanted to see an independent evaluation of the pilot project’s data when it’s done. “They felt that there needed to be some sort of ‘go/no-go’ decision for whether or not these things should go forward, that shouldn’t be made by the people doing the work,” he said. Hartwell agreed. “There should be independent assessment of its execution and progress,” he said.

Lander said that the NIH-based peer review process and annual Congressional scrutiny will provide effective oversight for that evaluation. “There should be no expectations of infinite life for something like this,” he said. “The decisions for such a project have to be guided by data and productivity.”

The funding issue remains the biggest concern—and a legitimate one, Collins acknowledged. “The leadership of the NIH is equally concerned about not doing damage to the most critical part of our portfolio, which is the R01,” he said.
“At the same time, this is all very remi-
niscent of the debates that raged in the
scientific community more than 15 years
ago when the Human Genome Project
was being debated.”

Collins argued that the pilot project,
if successful, should be able to generate
the new funding. And, he added, R01
investigators will be greatly helped by
the new data, just as they were by the
Human Genome Project. “We should
always … try to achieve the right balance
between the investigator-initiated re-
search, which will always be the majority
of what we do, and then identifying
specific examples of large-scale, high-
throughput enterprises, which really can’t
be mounted by a single investigator, but
which can empower everybody,” he said.
“And when we see those, as we now do
for the cancer genome, it would be irre-
 sponsible not to move forward as quickly
as possible to make them come true.”

—Ken Garber