A Showdown Over Gene Fragments

A private treasure-trove of genetic data has become such a hot property that researchers are talking about spending millions of dollars to duplicate it and make the information public

When top genome researchers gathered in Washington, D.C., last week for *Science*'s annual conference on the human genome, they came to pursue different agendas in public and private. In the open sessions, the talk ranged from the latest refinements in DNA sequencing to the ethics of genetic testing. But in offstage strategy meetings, the focus was on the commercial world of gene hunting.

The main events, both on the podium and backstage, took place on 4 October. Donna Shalala, secretary of Health and Human Services, spoke to the open session about the importance of genetic research as a means of preventing disease. Afterwards, a group of top scientists—including Francis Collins, director of the National Center for Human Genome Research (NCHGR)—hurried out of the hotel ballroom, climbed a flight of stairs, and slipped into Room 15, where the Wellcome Trust (a British philanthropy group) had convened a private meeting. Behind closed doors, about 30 scientists and executives met to discuss a vexing problem—the growing commercial control of genetic data. The focus of the meeting was on a private database owned by a partnership that has adopted an unorthodox gene-hunting approach and pursued it aggressively with lots of cash and cutting-edge technology. As a result, it has a virtual monopoly on a key type of data: expressed sequence tags (ESTs), which are unique fragments of genes expressed in human tissue. In a 4-hour session, participants debated whether to agree to restrictions the partnership may place on use of this data, or to try to duplicate the work and make it freely available. They emerged with no conclusions, but the sentiment was strongly in favor of constructing a public data bank.

RICK KOZAK

TIGR Team. Craig Venter *(left)* and William Haseltine have 35,000 gene fragments already in the bank.

This isn't the first time the commercial side of the genome project has erupted in contentiousness. Last month, the news broke that a team of university, government, and company scientists had won the race to identify a major breast cancer gene, and that patent rights on its sequence are likely to be licensed to Myriad Genetics, a profit-making company (see box on p. 209). But the sweeping scope of commercial investments in ESTs has raised concerns to a new level.

When the Wellcome meeting was planned several months ago, according to geneticist Michael Morgan, a Wellcome Trust officer, the objective seemed tame enough. It was to get the community talking about a possible new genetic map based on ESTs and on longer stretches of complementary DNA (cDNA) which include ESTs. These cDNAs are copies of working genes as they are expressed—or used to make protein—in tissue. Most publicly funded mapping efforts have focused on the entire genome. But less than 5% of the genome includes genes that code for proteins; most of it appears to regulate gene expression or be cluttered with "junk." For that reason, some researchers would put a higher priority on targeting expressed genes. They would capture ESTs and cDNAs and build a physical map by tracing these expressed genes to precise locations on the chromosomes. Moreover, by sequencing cDNAs, it might be possible to acquire data for gene-based medicine faster.

The official topic of the Wellcome Trust meeting was the cost and feasibility of following this alternative approach. But it took on another purpose as well—ventilating feelings of "intense anger" and "frustration" that had built up in the academic community in recent weeks, Morgan says. Researchers were upset that private claims on cDNA sequences would create barriers to the free exchange of information. Some also may have resented proprietary claims that might interfere with their own commercial ventures. If any outfit was cast in the role of Frankenstein that afternoon, it was The Institute for Genomic Research (TIGR), based in Gaithersburg, Maryland. "They're coming after us with torches and pitchforks," said Leslie Platt, TIGR's chief operating officer.

TIGR was actually just one of the targets. Itself a nonprofit research institute, TIGR is joined through complex ties to a profit-making venture known as Human Genome Sciences Inc. (HGS) of Rockville, Maryland. And both TIGR and HGS are bound through contractual commitments to the pharmaceutical company SmithKline Beecham. TIGR and HGS, with SmithKline's generous backing, have amassed an enormous trove of information on human ESTs. They aren't the only companies collecting such data, but they're the only ones ready to make a lot of it available.

TIGR is offering to share much of its data with universities and other nonprofit institutions—if they sign contracts promising to respect TIGR's and HGS's proprietary rights and to provide previews of relevant publications. This offer, on terms that are becoming increasingly common in biological research, seems monstrous to some—so monstrous that leading lights in the genome community are backing a rival venture that would repeat a lot of work done by TIGR and HGS but place it in a public data bank. The power behind this proposed venture: Merck & Co., a major competitor of SmithKline, eager to break SmithKline's lock on ESTs.

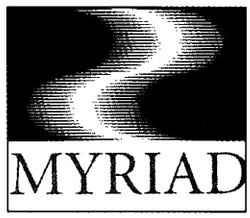
All these agendas clashed last week at the Wellcome Trust meeting. And while nothing was resolved, the reverberations will continue for months.

Riding the TIGR

This debate over ESTs has been brewing for years, says TIGR's director, J. Craig Venter. He traces it back to the late 1980s, when he was an intramural researcher at the National Institutes of Health (NIH) looking for new ways to identify genes active in the brain. Venter says he set out in the traditional way—hunting for stretches of chromosomal DNA and attempting to sequence them. But Venter says this proved to be extremely slow work, and "I'm an impatient person." He and his postdocs began looking for short cuts that might make it possible to capture data more rapidly. The key elements of their strategy: Look for messenger RNAs in brain tissue, tag them by capturing short stretches of genetic material (ESTs), use robots to sequence them, and rely on powerful

NIH in Danger of Losing Out on *BRCA1* Patent

The discovery of *BRCA1*, a cancer susceptibility gene which in its defective forms accounts for about 130,000 breast cancers in the United States alone, was a welcome event (*Science*, 23 September, p. 1796 and 7 October, p. 66). But as reported in the 7 October issue of *The Cancer Letter*, the celebrations barely had time to die down before a duel over proprietary ownership of the gene began. At issue: whether the National Institutes of Health (NIH), which contributed both researchers and funds to the successful search, will get to share patent rights to the gene with the University of Utah and the biotechnology firm Myriad Genetics Inc. of Salt Lake City.



The stakes are high because the patent—if it issues—is a potential money spinner, providing its holders with a 17-year monopoly on the sale of diagnostic tests and therapeutics developed from *BRCA1*. If NIH owned a share of the patent, it would not only get a cut of the royalties on the sales, but it would also have a say in which companies receive licenses to develop the products and under what conditions.

The search for *BRCA1* was conducted by a mega-team—45 researchers spread across the University of Utah, Myriad, the pharmaceutical giant Eli Lilly of Indianapolis, Montreal's McGill University, and the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. But the patent application has been filed by the University of Utah, and the NIEHS investigators are not named as co-discoverers. The university has agreed to license commercial use of the patent exclusively to Myriad, which has sublicensed rights to Lilly, and to a Lilly subsidiary, Hybritech of San Diego.

The patent filing has spurred NIH's patent lawyers to examine their options. "It's a very sensitive issue. We're looking at it," says NIH Director Harold Varmus. Although no one contacted by *Science* would reveal exactly what NIH is demanding, Varmus's spokesperson Anne Thomas confirmed that "[NIH] patent lawyers are in discussions with their counterparts at the University of Utah."

For their part, the Utah scientists—including Mark Skolnick, who from his joint appointment at Myriad and the University of Utah oversaw the whole consortium, and Myriad director of research Alexander Kamb—defend the patent application. Without patent protection, neither Myriad nor any other company can afford to invest the resources needed to develop *BRCA1*-based therapeutics or tests, Skolnick says. What's more, Kamb points out, Myriad and its corporate sponsor Lilly contributed the lion's share of funds and personnel to the *BRCA1* isolation effort. Half of the 45 people who co-authored the *BRCA1* article are employed by Myriad, and an additional six by Lilly. Myriad's president and CEO Peter Meldrum says Lilly put $4 million into the project, and in April of 1993, Myriad raised another $10 million in a private placement offer. NIH, meanwhile, funded the six-person NIEHS team. NIH also provided approximately $2 million in research grants to the University of Utah, according to David Goldgar, a senior member of the university's *BRCA1* team.

But, in fact, the dueling parties' contributions of time, dollars, and people power have less to do with determining who is legally entitled to hold the patent than do their intellectual contributions. "To be a co-inventor," says patent attorney Max Hensley of Gilead Sciences in Foster City, California, "you must have had a role in the conception of the invention." What constitutes inventorship is one of the murkiest areas of patent law, and liable to lead to unpredictable rulings when patent disagreements result in litigation. For that reason, says Hensley, "it's certainly better for all parties to sit down and discuss these things before they go to court."

Better still would be to agree on commercial rights at the start of a collaboration. "Intramural researchers are supposed to have a formal agreement if they enter into in any form of collaboration with a partner in industry or university," says Barbara McGarey, deputy director of NIH's Office of Technology Transfer.

The NIEHS investigators had no such agreement with the University of Utah and Myriad, however. According to NIEHS team leader Roger Wiseman, the team tried to establish a Cooperative Research and Development Agreement (CRADA) with Myriad, "but it was never completed due to concerns from the Lilly cooperation." These concerns, he says, had to do with the CRADA's fair-pricing clause—a standard clause in NIH's CRADA agreements that drug companies hate because it gives the government leverage over the price of ensuing products (see *Science*, 22 October 1993, p. 496). A CRADA might not have avoided the current brouhaha, however. The agreements ensure that the industrial partner gets first dibs on a license if the government laboratory ends up holding the patent, but don't necessarily specify ahead of time who would be named on the patent.

Despite its lack of agreement regarding the commercial spoils, the NIEHS team did show foresight over how the academic glory would be divvied up: Two years ago, the NIEHS and Utah teams co-signed a document detailing the order of authorship in "the unlikely event" that they isolated *BRCA1*.

–Rachel Nowak

computers to analyze the data. They hoped to use the unique sequences of these ESTs, whose functions would be completely unknown, to reach into databases and human tissue to fish out whole genes.

Although Venter's lab continued to receive NIH intramural funding, he claims that NIH's top officials declined to provide funds to scale up his processes and zero in rapidly on cDNAs. For example, when his lab collaborated with Applied Biosystems Inc. on the first automated gene sequencer, his work was financed not by NIH but primarily by the Department of Defense. By last year, Venter and his top staff had quit the government, teamed up with HGS, and made a pledge to deliver commercially valuable data to HGS and SmithKline Beecham.

In a short time, TIGR and HGS had assembled a battalion of 80 sequencing machines and built up a collection of 300 libraries of cloned human genetic material. They poured tens of millions of dollars into computerized analysis of the sequence data, and began to sequence not only the short EST fragments but also full-length genes themselves. According to HGS president William Haseltine, this joint effort has produced more than 35,000 unique ESTs and will soon be able to identify 80% of all major human genes.

Claims like this may sound grandiose, but they recently gained credibility when Bert Vogelstein of Johns Hopkins University went hunting for genes in the HGS-TIGR database. Vogelstein, who had already identified several human colon cancer genes, was also aware of a proofreading gene in bacteria—one that corrects errors in DNA. If humans have a similar gene, Vogelstein speculated, defects in it might open another route to cancer. Vogelstein made a one-time agreement with HGS-TIGR that allowed him to search the EST database for traces of a human gene that might resemble the bacterial version. The search took minutes: Vogel-

stein immediately found a human proofreading gene that, when mutated, appears to be responsible for several types of cancer.

Vogelstein is not the only one who's gaining respect for this database. C. Thomas Caskey, a geneticist at Baylor College of Medicine in Houston and president of the international Human Genome Organization (HUGO), says he tested it 2 weeks ago. "There's a gene I've been interested in for quite some time—a gene of no economic value but great biologic interest," Caskey says. His lab had studied bacterial versions, but "never the mammalian genes." He tried the HGS-TIGR database: "In a minute and a half we got a strike ... and now we have the gene. It was beautiful to see how quickly it worked."

Caskey, Collins, and other leaders want an equivalent public source of data and clones to construct a physical map of ESTs and cDNAs on chromosomes. Some EST mapping has already begun at NCHGR using Venter's early NIH data. Researchers mix radiolabeled EST sequences with large sets of tagged somatic cell DNA and search for a match. By that means, they have identified the chromosomes from which some ESTs come, but it will take more money and a lot more work to build a detailed map.

Money in the bank

It is precisely because TIGR's database is so powerful that academic scientists are concerned about private control of it. Venter and Haseltine are now proposing to share it widely, but only on condition that users give HGS-TIGR first option on commercial rights to genes whose discovery it may assist. The owners also want to be notified 30 to 60 days before data derived from it are published. This presents a dilemma: While the database could provide the raw material for a powerful new map of human genes, many academic scientists are leery of collaborating with TIGR on a venture that may cramp their right to publish while steering business to HGS and SmithKline Beecham. They seized the opportunity at the Wellcome Trust meeting last week to air their concerns. Haseltine and Venter were not invited at first, but when they learned of the meeting, they were allowed to come and quell rumors.

Morgan of the Wellcome Trust said there developed "quite a debate" in Room 15 as to whether the terms being offered by Venter and Haseltine would "encumber the public database" with intolerable conditions. Representatives of some institutions, including the Howard Hughes Medical Institute, disclosed that they would agree to let their scientists sign the restrictive data agreements. Others said they would not. One of those who spoke firmly against using the HGS-TIGR database to construct a public map, according to Morgan, was Collins. The NCHGR chief, he says, was "extremely certain there was no possibility of bridging the gap between the public and private sector" in a joint mapping project unless Haseltine and Venter "removed all strings on any reagents to be mapped." Collins could not be reached for comment after the meeting. Morgan said he believed Wellcome might be "thinking along the same lines as Francis [Collins]."

HANK MORGAN

Industrial approach. SmithKline Beecham has poured millions into HGS-TIGR's automatic sequencing effort.

In taking a skeptical view, Collins is representing map makers in the universities and in his own agency. For example, Eric Green, staff scientist at NCHGR, says he won't be using any proprietary data. "I don't want to find that I've spent the last 4 years of my life building a map that I intend to have as openly available as possible, only to find that some of the key rivets in it have strings attached. I operate in the public domain; that's why I take this attitude," says Green, who pronounces TIGR as "tigger," unlike Venter, who calls it "tiger." Besides, the work done by TIGR "isn't brain surgery," Green adds: "All that stands between us and what TIGR has done is money."

Although money may continue to be in short supply, one new option has raised hopes for a public EST map. It is the offer from Merck last week to finance a duplicate EST database and to share it with all comers—no strings attached. HGS-TIGR may be unable to prevent this by patenting their ESTs. The Patent and Trademark Office (PTO) has ruled that EST fragments whose functions are unknown cannot be patented because their utility is not clear. The PTO reached this conclusion when NIH tried to patent the EST sequences Venter produced while he was on the government payroll; earlier this year, NIH Director Harold Varmus decided not to appeal the ruling. Merck executives insist that by helping to publish EST sequences, their aim is to encourage the free exchange of data. But, as HGS staffers note, it would also undermine Merck's competitor, SmithKline Beecham.

The Merck initiative has yet to be nailed down in detail, however. One holdup, ironically, is a proprietary concern from another quarter—an academic institution that holds commercial rights to a key element of the proposed database. The plan, according to Merck executive Keith Elliston, is to support the development of a high-quality library of human cDNA clones by M. Bento Soares at Columbia University. These clones would be shipped to Washington University in St. Louis, where Robert Waterston and Richard Wilson would sequence ESTs. The data would be quickly checked for quality and released to the public by way of the National Center for Biotechnology Information at NIH (GenBank) within 24 to 48 hours. Merck wouldn't even see the sequences until after they had been deposited, says Elliston.

Merck is ready to sign contracts, but as *Science* went to press, it hadn't worked out the legal arrangements with Columbia University, which is seeking reimbursement for the use of Soares's cloning technology. Columbia spokesperson Elaine Metcalf confirmed that legal negotiations are under way but declined to reveal details. However, she did confirm that NCHGR's Collins encouraged the university to help create a public EST database.

Even though the initiative hasn't been firmed up, Caskey, as president of HUGO, drew up a statement last week to guide the effort. The recommendations, endorsed by many at the Wellcome Trust meeting, include sequencing the cDNA clones, placing them on a physical map with a resolution of 100,000 base pairs, making the data "freely available" to all researchers, and making the clones themselves available with "no encumbrances."

Venter, meanwhile, says he's delighted that leaders of the genome program have belatedly come to recognize the value of ESTs. But he believes the community is overreacting to the intellectual-property restrictions sought by HGS and TIGR, pointing out that they are no more burdensome than those required by other biotechnology companies. Scientists may be frightened by the massive scale of TIGR's data gathering and don't quite know how to respond, says Venter.

None of the participants in the debate is ready to predict how it will be resolved. HUGO is planning the first of a series of open meetings in 4 months to discuss the matter again. By then, researchers will have had time to digest HGS-TIGR's terms, and prospects for the Merck venture will be clarified. It will be an interesting fall in the genome community.

–Eliot Marshall