# Sharing the Glory, Not the Credit

Greeted by chamber music and an honor guard, leaders of the public and private groups sequencing the human genome filed into the White House last June, shook hands with the president, and pledged to support each other's endeavors. Within weeks, this show of amity dissolved. Over the summer and fall, the teams withdrew to their labs, muttering about the doubtful quality and accessibility of each other's research. The grumbling continued until December, when the two decided to part company at the finish, collaborating only on a single publication date. The result: Two reports on the human genome are coming out this week—a privately funded version in *Science* and a publicly funded version in *Nature*.

The falling-out over the final reports is just a footnote to the huge effort to complete the sequencing of the human genome. But it highlights a philosophical disagreement over how such data should be shared (see sidebar on p. 1192). It also reveals how the rules of scientific publishing, usually rigid, become flexible when the stakes are high. Journal editors are accustomed to telling authors what a paper must disclose and what kind of supporting data must be released. But in this case, the authors themselves—because they were offering a big prize—sought to write the rules. Scientists in the public sequencing group also sought to shape the rules that would apply to the paper from the rival private group. As they courted the authors of these hot papers, the journal editors invited comments on data release, received sharply clashing recommendations, and chased an elusive consensus.

The imbroglio, which reached a peak in the last few months, first broke into public view in March 2000. At that time, the private genome group—headed by J. Craig Venter, president of Celera Genomics in Rockville, Maryland—was still discussing the idea of pooling data and publishing results with the public group, headed by Francis Collins, director of the U.S. National Human Genome Research Institute. Several public-group scientists led by Eric Lander, director of the Whitehead/MIT Genome Center in Cambridge, Massachusetts, had spearheaded efforts to work out a compromise. But the talks broke down.

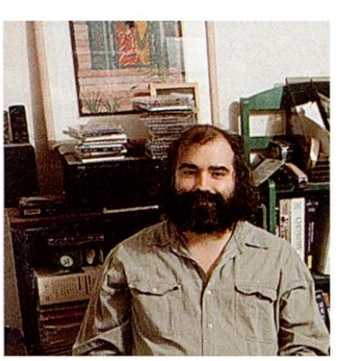
**All smiles.** Venter, Patrinos, and Collins (*left to right*) celebrating a truce in June; by December, hostilities had resumed.

That failure became evident when an official at the Wellcome Trust, the British charity that supports one of the largest nonprofit sequencing teams, the Sanger Centre in Hinxton, U.K., leaked a letter to the press from Collins to Venter (*Science*, 10 March 2000, p. 1723). In the letter, Wellcome officials and U.S. scientists charged that Celera was trying to maintain control over the jointly produced genome data for 5 years and claim intellectual property rights on uses of those data in secondary technologies, such as gene chips. When Celera did not respond quickly, the publicly funded scientists declared the negotiations over. They had insisted that data be deposited immediately in a public database, with no commercial conditions attached. Celera wanted to guard against data piracy by retaining the information on its own Web site, with certain restrictions: Users would not be able to resell the information or use it for other commercial purposes.

Addressing a congressional hearing on 6 April, Venter denied that he wanted exclusive control of the genome data. "We will release the entire consensus human genome sequence freely to researchers on Celera's Internet site when it is completed," he said. But the public group leaders say they had trouble nailing down the details of Celera's conditions on how its data could be used.

By the time of the much-publicized June ceremony at the White House, the two groups had stopped talking about a pooled database and agreed to "coordinate" but not to collaborate, as Collins explained in June. Collins and Venter still held out hope that they might release their reports in the same journal. At the time of publication, Collins and Venter explained in June, the public group would deposit its sequence data in the free public database GenBank, whereas Celera would release data through its own Web site.

*Science* and *Nature* were competing for the papers, and the authors let both journals know that they were looking for the best terms. In June, Donald Kennedy succeeded Floyd Bloom as editor-in-chief of *Science*, taking charge of months-old negotiations. Members of the public consortium had by then made abundantly clear that they did not want *Science*, or *Nature* for that matter, to allow Celera an exception to the traditional practice that genomic data be released in GenBank. One respected scientist in this



## UNSUNG HERO: JIM KENT

**Jim Kent, a bioinformatics graduate student at the University of California, Santa Cruz, wrote a program in just 4 weeks that pieced together the rough draft of the human genome for the public consortium—producing an assembly called the "golden path."**

CREDITS: (TOP TO BOTTOM) RICK KOZAK; DON HARRIS/UC SANTA CRUZ

## Celera and *Science* Spell Out Data Access Provisions

When J. Craig Venter announced in 1998 that his company, Celera Genomics of Rockville, Maryland, intended to sequence the human genome, he also promised that he would make the results freely available. This week, the promise is coming due. *Science* is publishing Celera's report, and Celera is publishing the underlying genomic sequence data on its own Web site (www.celera.com). According to terms negotiated between the company and *Science*, any reader will be able to view Celera's assembled genome at no cost through the Web site—or by obtaining computer disks from the company. Celera is also asking users to register and agree to specific conditions.

At a press briefing last week, Venter described the conditions as they apply to several broad categories of readers:

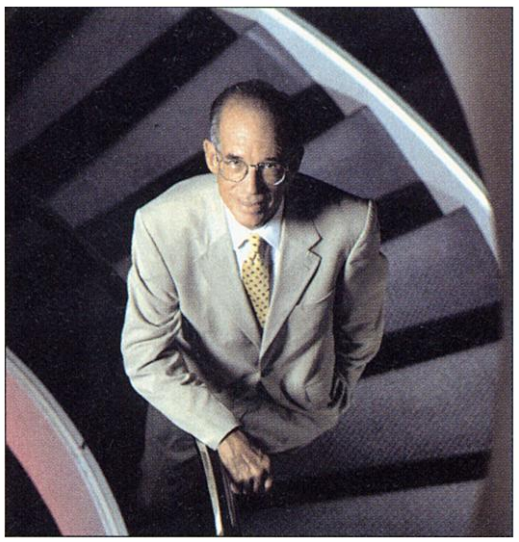
First, nonprofit researchers who want to search the database or download batches of DNA sequence (up to 1 megabase per week) may do so by mouse-clicking their agreement to a form on the Celera site. It requires that they not commercialize or distribute the data. However, they may use the information in research, in scientific articles, and in patents.

Second, academic users who want to download more than 1 megabase per week must submit a signed letter from an institution official agreeing to the terms above.

Third, scientists in industry or with commercial connections may use the data at no cost for the purpose of validating the results in the *Science* paper, after signing a materials transfer agreement promising not to use the data for commercial purposes.

Fourth, those who want to use the data for commercial purposes must first negotiate an agreement with the company.

–E.M.



**Man in the middle.** *Science* Editor-in-Chief Donald Kennedy received a barrage of e-mails about the terms for publishing the Celera paper.

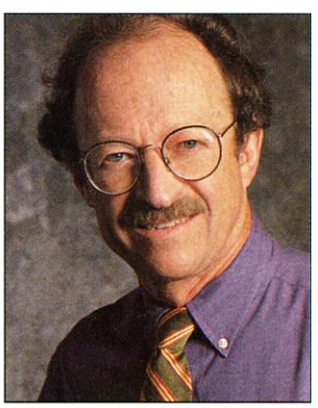
field who asked to remain anonymous says that "jealousy" over scientific credit played a big part in the split.

"I got a very thoughtful memo from Eric Lander" about publishing genome data, Kennedy recalls. It laid out "three or four license terms that he thought would not be reasonable and a general one that he thought would be OK." Serious negotiations began in September, with editors at *Science* running between the two camps. Editors worked out what they viewed as a balanced plan, requiring Celera to release data freely to academics but allowing the company to protect its database by requiring readers to obtain access at a company site and register as academic or commercial users. Nonprofit scientists would have free access, Celera said, but those with commercial connections would have to pay. Commercial users would also be bound by other intellectual property conditions.

Lander objected to these terms as "discriminatory" and "absolutely unacceptable," says Kennedy. Lander declined to comment publicly, saying he wanted to see the final terms (which were being finalized at the time; see sidebar). Colleagues say he argued forcefully in November that authors of scientific papers must share data freely with all readers—not just with academics. Biotech scientists, several people argued, would find it impossible to accept Celera's terms and would be excluded from examining the results. Harold Varmus, former director of the National Institutes of Health (NIH) and now president of the Memorial Sloan-Kettering Cancer Center in New York City, is sympathetic to Lander's view. "This is a complicated world now," Varmus says. "It's not just people in industry who have commercial connections; many people in academia do." Whitehead/MIT Genome Center scientists, for example, are involved in a 5-year consortium—funded by Affymetrix Inc. of Santa Clara, California; the Bristol-Myers Squibb Co. of Princeton, New Jersey; and Millennium Pharmaceuticals of Cambridge, Massachusetts—that aims to put genomic information on digital chips.

In October, Kennedy solicited advice from several other experts, who identified previous scientific papers in which readers were required to obtain supporting data from an independent Internet site. Some limited free access to nonprofit scientists. "This horse had already left the barn," Kennedy concluded. This interpretation prompted a new uproar in late October.

Members of the public genome project mobilized opposition. Warnings poured in to Kennedy by e-mail from well-known biomedical researchers, including molecular biologist Marc Kirschner of Harvard University; Bruce Alberts, president of the National Academy of Sciences (NAS); and Varmus. Varmus's letter, dated 5 November, was cosigned by other heavyweights, including David Baltimore, president of the California Institute of Technology in Pasadena; J. Michael Bishop, chancellor of the University of California, San Francisco; Arthur Levinson, CEO of Genentech in South San Francisco; Edward Scolnick, president of Merck Research Labs in Rahway, New Jersey; Kenneth Shine, president of the Institute of Medicine in Washington, D.C.; and Maxine Singer, president of the Carnegie Institution in Washington, D.C. They wrote to "express our concern" that *Science* might allow authors of an unspecified paper to "restrict availability" of the raw data. Doing so, they argued, might "open the door to similar withholding of information by future authors, with unfortunate consequences. ..." They urged *Science* to get more advice before taking this "unprecedented step."



**Leading critic.** Harold Varmus believes the protests improved the terms for access to Celera's data.

Kennedy says he weighed the advice and criticism. *Science*'s editors consulted with an intellectual property expert at NIH and with Tom Cech, president of the Howard Hughes Medical Institute in Chevy Chase, Maryland, a nonprofit organization that had already agreed to subscribe to

CREDITS: SAM KITTNER

## Bermuda Rules: Community Spirit, With Teeth

The "Bermuda Rules" may sound like standards for lawn tennis, but in fact they are guidelines for releasing human sequence data. Established in February 1996 at a Bermuda meeting of heads of the biggest labs in the publicly funded genome project, the rules instruct competitors in this cutthroat field to give away the fruits of their research for free. "The whole raison d'être for the communal effort was to get useful tools into the hands of the scientific community as rapidly as possible," says Francis Collins, director of the U.S. National Human Genome Research Institute in Bethesda, Maryland. But the rules also offer another benefit: They discourage the patenting of genes by sequencing labs, an activity executives of big pharmaceutical companies seem to despise as much as some academics do. The insistence on quick, unconditional release of data also lies at the heart of the dispute between publicly funded genome scientists and the private company that has just produced a draft version of the human genome, Celera Genomics of Rockville, Maryland.

At the 1996 Bermuda gathering sponsored by the Wellcome Trust, a British charity that funds large-scale sequencing at the Sanger Centre in Hinxton, U.K., scientists agreed to two principles. First, they pledged to share the results of sequencing "as soon as possible," releasing all stretches of DNA longer than 1000 units. Second, they pledged to submit these data within 24 hours to the public database known as GenBank. The goal, according to a memo issued at the time, was to "prevent ... centers from establishing a privileged position in the exploitation and control of human sequence information."

The Bermuda policy, which replaced a 1992 U.S. understanding that such data should be made public within 6 months, has had a significant impact on the field. For example, Collins claims, it has already enabled the identification of more than 30 disease genes. Both Collins and Ari Patrinos, director of the U.S. Department of Energy's office that funds genome research, backed the Bermuda push for openness. "We felt it would strengthen international cooperation," Patrinos says. "Scientists are by their very nature hoarders. They're chewing on the data all the time, and they never think they're ready" to let go, he adds. By adopting this formal mechanism, members of the consortium assured each other that no one would be squirreling away caches of data or quietly patenting genes. The policy also delivered a clear symbolic message, Patrinos says: "We all believe that the genome belongs to everybody."

When sequencers met in Bermuda again in 1997, they reaffirmed their pledge and added an explicit directive against patenting newly discovered DNA. Failure to cooperate, U.S. officials made clear, could be a black mark in future grant reviews. Although the message seemed to challenge private DNA databases by undermining their claims to exclusivity, large pharmaceutical firms welcomed it, because they would benefit if there were fewer patent holders to buy off.

Alan Williamson, a former executive at Merck, the pharmaceutical giant in Whitehouse Station, New Jersey, embraced the policy enthusiastically. "Putting data out immediately was a good thing," he says, because it encouraged the sharing of research tools without letting legal contracts get in the way. But he wishes sponsors of this research had taken active steps to make it difficult for others to patent and sell this genetic information—for example, by filing their own noncommercial patent claims that might block other claimants. Biomedical companies, he argues, should compete on the commercially difficult work—developing drugs—not on profiting from research tools such as DNA databases.

**Care to share?** NIH's Francis Collins is a strong advocate of rapid data release.

Indeed, Merck was so certain that this was the right approach that beginning in 1994, the company poured tens of millions of dollars into creating a nonprofit database of gene fragments known as expressed sequence tags (ESTs). The Merck Gene Index, as it is called, was designed to counter privately owned genetic databases and a surge in gene patenting led by such companies as Human Genome Sciences in Rockville, Maryland, and Incyte Pharmaceuticals in Palo Alto, California. These companies sell genetic information, patent uses for newly discovered genes, and seek to obtain royalties for the use of their patents—by big pharmaceutical firms and all other users. Merck also contributed to a free database of mouse ESTs, which are useful in identifying human disease genes.

In a similar defensive move, 10 companies joined with the Wellcome Trust in 1999 to create a nonprofit database of human genetic variations garnered from the genome, known as single-nucleotide polymorphisms (SNPs). SNP maps may be extremely valuable someday in identifying disease genes and standardizing gene-based medical therapy, and several companies had already begun to gather them in private collections.

Quarreling over the principles of the Bermuda Rules broke out again when Celera announced that it would sequence the entire human genome. Its business plan, according to president J. Craig Venter, is to collect and process genomic data more efficiently than research outfits can do for themselves. The company would appear to have no incentive to give information away, but Venter grabbed headlines in 1998 when he declared that he would finish a rough draft of the genome earlier than the publicly funded effort and give everyone free access to Celera's sequence. Ever since then, Venter and the advocates of the Bermuda Rules have been arguing about what "free access" means. **–E.M.**

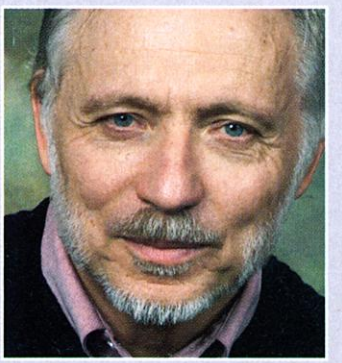
Celera's private database. In a conference call, Kennedy received encouragement from Harvard chemist George Whitesides, molecular biologist James Hudson of Research Genetics Inc. in Huntsville, Alabama, geneticist Nina Fedoroff of Penn State University, and half a dozen others. After proposing additional improvements in the terms of data release—including the use of materials transfer agreements that would let viewers have free access to the data but give Celera legal protection against data piracy—Kennedy decided that the terms were fundamentally acceptable.

At this point, bioinformatics leaders raised objections. On 6 December, a former member of *Science*'s board of reviewing editors, geneticist Michael Ashburner of Cambridge University, distributed an open letter to these editors, urging them to quit and boycott *Science*. Another board member, cancer researcher Bert Vogelstein of Johns Hopkins

CREDIT: RICK KOZAK

## UNSUNG HERO: ELBERT BRANSCOMB

A U.S. Department of Energy (DOE) physicist, Branscomb got swept up in the genome program and became a bioinformaticist overnight, helping with genome mapping and later nudging DOE sequencing into high gear as director of the Joint Genome Institute in Walnut Creek, California.



University School of Medicine in Baltimore, Maryland, circulated a reply, saying he believed the final agreements "will meet the standard of public access to data that has been and continues to be *Science*'s policy." The next day, leaders of the public genome project voted to end discussions with *Science* and submit their paper to *Nature* (*Science*, 15 December 2000, p. 2042).

The decision to send the paper to *Nature* was not unanimous: Ari Patrinos, director of the U.S. Department of Energy's office that funds genome research, says, "It's no secret that I was advocating back-to-back publication in one journal, *Science*." But British members of the consortium were outraged by the deal with Celera. Lander adds: "We had to choose between two journals, and *Science*'s policy [on data release] wasn't clear." Although *Nature*'s editors haven't ruled out the use of private databases, the public consortium decided, Lander says, that it was "an easy choice" to submit a paper to them.

Varmus says that he believes the letters, including his own, improved the terms of data access. He recognizes that Celera cannot give away information it has spent hundreds of millions of dollars to acquire. But he argues that publishers need to find new ways to make data from private ventures available, because we are "now in an era of heightened commercialism" in which a great deal of genome and protein structure data will be in private hands. Says Patrinos: "This issue is not going to go away." Varmus hopes this episode will prompt a formal review—perhaps at the NAS—of "what publication really means." **–ELIOT MARSHALL**

# Genomania Meets the Bottom Line

When a drug company announces that it will start testing a new compound in humans, the news typically draws cursory notice from investors and stock analysts. After all, only a small fraction of candidate drugs ever make it to the pharmacy and on to a company's bottom line.

Last month, however, the financial savants took extra notice when Cambridge, Massachusetts–based Millennium Pharmaceuticals and European drug giant Bayer AG announced that they would soon put an anticancer drug into phase I clinical trials. What caught their eye was not the drug's potential profits, but the process the firms used to find it—and its speed. Aided by new technologies that enable researchers to rapidly screen thousands of genes and their protein products for potentially useful properties, the companies sped from gene identification to product testing in just 8 months, shaving at least 2 years off the typically long and costly drug-discovery process. "This is a major milestone for the pharmaceutical industry," crowed Bayer executive Wolfgang Hartwig.

Such expansive claims are not unusual in the biotechnology industry, which for more than a decade has hyped the profitmaking potential of sequencing human genes, only to see many of those claims founder in a sea of red ink. But the Millennium-Bayer announcement may be one sign that for-profit genomics—a loosely defined collection of commercial ventures that range from selling technologies, tools, and information to developing new drugs—is beginning to live up to its advance notices. "It's a wake-up call anytime you can punch years out of product development," says Mark Edwards of Recombinant Capital, a biotech consulting firm in Walnut Creek, California.


CREDITS: (TOP TO BOTTOM) JOINT GENOME INSTITUTE; ILLUSTRATION: TERRY E. SMITH

Still, many financial analysts remain wary of the growing genomics industry. Although a record number of self-proclaimed gene firms went public last year, and a few established firms saw their stock prices temporarily skyrocket in anticipation of the completion of the human genome, longtime observers note that most genomics companies have yet to turn a profit (see table on p. 1201). There are exceptions: Some genomics toolmaking companies and information brokers have impressive—and rising—earnings. But the industry is still too young to show that it can produce what Wall Street is really looking for: blockbuster drugs. Even some high-profile players, such as information broker Celera Genomics of Rockville, Maryland, are still struggling to figure out how they will ultimately make money (see sidebar on p. 1203).

Such uncertainty is typical of an emerging industry, analysts say. And just because many genomics companies are showing losses in annual reports doesn't mean they are in danger of closing up shop. Indeed, some companies—such as Celera—have banked so much money from stock offerings that they could survive for years at current spending rates. In addition, Bayer and bigger