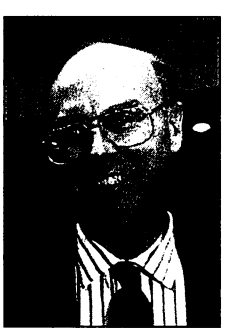
GENOMICS

Fruit Fly Genome Yields Data and a Validation

WASHINGTON, D.C.—The humble fruit fly has just soared to the top of the genome charts. Using an approach dismissed as unworkable a mere 2 years ago, a team of publicly and privately funded scientists announced last week that they had decoded more than 97% of the genome of *Drosophila melanogaster*. As with all genome projects, parts are missing: The team sequenced only gene-containing regions, and about 1600 gaps remain. Even so, *Drosophila*, which has been long studied by geneticists, is the largest creature ever to be sequenced, genomewise, and only the second multicellular organism. What makes this milestone especially noteworthy, however, is that it validates the controversial "shotgun" approach. As such, it could pave the way for a public-private effort to complete the human genome, said J. Craig Venter, president of Celera Genomics in Rockville, Maryland, the private half of the team.



Fly catchers. Gerald Rubin *(left)* and J. Craig Venter *(below)* orchestrated a public-private venture to sequence the fruit fly genome.

The last two big successes of the genome project, the nematode (*Science,* 11 December 1998, pp. 1972, 2012) and human chromosome 22, recently published in *Nature* (*Science*, 24 September 1999, p. 2038), were both done using the "clone-by-clone" approach. This involves determining the order of the bases in a series of overlapping clones, whose locations on the chromosomes are known.

In May 1998, Venter stunned the genome community when he said he would tackle the human genome with the whole-genome shotgun approach that he had pioneered on microbial genomes (*Science*, 18 June 1999, p. 1906). To "shotgun" a genome researchers shred the entire genome into random pieces, sequence all the pieces, and then reassemble them in the correct order with the aid of a supercomputer. At the time, critics argued that Venter would be unable to put the millions of DNA fragments back together. As a test case, Venter teamed up with Gerald Rubin and the Berkeley Drosophila Genome Project to try the fruit fly.

The effort "worked better than anyone expected," Rubin reported at the annual meeting of the American Association for the Advancement of Science, which publishes *Science*. Geneticists and molecular biologists are ecstatic. "[Venter and Rubin] have really pushed the envelope of what's possible," raved Daphne Preuss, a geneticist at the University of Chicago. Added geneticist Lawrence Goldstein of the University of California, San Diego: "The quality of what I saw was really exceptional."

One key to their success was an assembly program designed by Celera's Eugene Myers. In short order, the program was able to assemble the 120 million bases into 26 long stretches, or "scaffolds." Myers relied on existing genome maps to order these stretches. Still, the program left 1800 gaps, which Myers reduced to 1600 by adding sequence data from his academic collaborators. What's more, the shotgunned data matched already finished fly sequence quite well. Myers is confident that this approach will work on the far larger human genome. But skeptics are waiting to see how difficult the remaining gaps are to close, a task Rubin's team is taking on, before giving the thumbs-up.

Meanwhile, analyses so far suggest the fruit fly could have as many as 13,000 genes, half of whose functions are unknown, said Celera's Mark Adams. With the sequence in hand, Goldstein expects research to "catapult ahead." For Rubin, this achievement is sweet because everyone worked together well: "It has been one of the most pleasurable scientific experiences that I've had in my academic career."

–ELIZABETH PENNISI

INTELLECTUAL PROPERTY

HHS Probes Genesis of Gene Sequencer

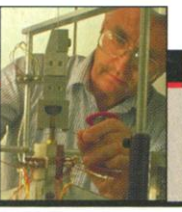
During the past 6 months, biologist Leroy Hood and members of his former lab at the California Institute of Technology (Caltech) in Pasadena have become ensnared in a tangled federal probe of the origins of the DNA sequencing machines that now play a central role in decoding the human genome. Responding to subpoenas, the researchers have been turning over files from more than 15 years ago to inspectors from the U.S. Department of Health and Human Services (HHS).

Hood's Caltech lab developed the key technology behind the sequencing machines and the reagents needed to run it that now are marketed by PE Corp. At issue in the HHS probe is whether Hood's lab used grant money from the National Science Foundation (NSF) as part of that research. If it did, then Caltech, which holds the patent on the technology, may improperly have received royalties from sales of the machine to government researchers.

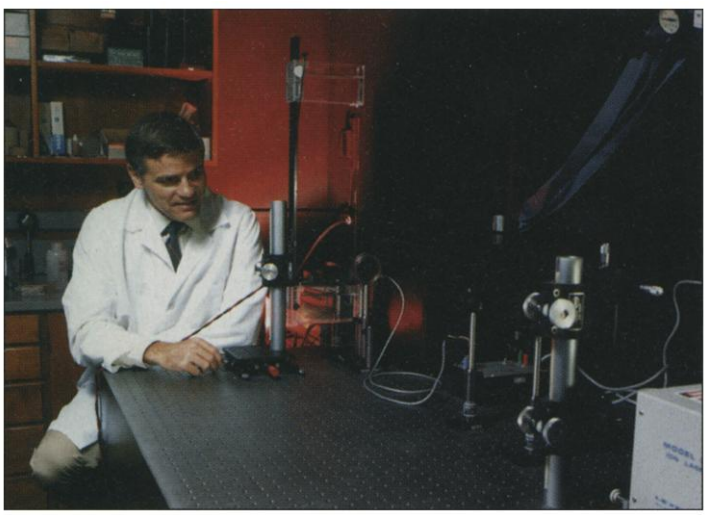
Nobody is accusing the researchers of wrongdoing, and Hood and Caltech vigorously deny that NSF funds were involved in the key research. But the issue has developed into a cause célèbre since the *Los Angeles Times* broke the story last week. A member of Congress is concerned that the federal government may have been ripped off, and Caltech president David Baltimore has responded with a public statement.

Caltech officials, the researchers themselves, and lawyers from PE all say they

CREDITS: (CLOCKWISE FROM TOP) G. BERNARD/ANIMALS ANIMALS; R. KOZAK; PAUL FETTERS FOR HHMI



are baffled by the probe. It's unclear who would owe money to the federal government, and the amount at stake may total less than a million dollars, says PE attorney Joseph Smith. Indeed, one of the most puzzling aspects of the affair is why the HHS Inspector General's (IG's) office launched the probe in the first place. Officials from the office decline comment. But the researchers involved are not so reticent. "What they're doing is wrong," says Hood, who's now at the University of Washington, Seattle. "It's a witch-hunt."



Man and machine. Leroy Hood and the automated four-color sequencer, developed in his lab at Caltech in the 1980s.

CREDIT: R. J. PAZ/CALTECH

The probe focuses on a 1980 change to patent law known as the Bayh-Dole Act and a 1988 contract between Caltech and Applied Biosystems Inc. (ABI), a company that PE later purchased. Bayh-Dole encourages universities to patent inventions developed with government money but stipulates that the government should not pay a royalty fee if it uses the invention.

Although the Bayh-Dole Act has been widely praised for helping to move technology from universities to industry, it has created a perplexing dilemma: It's often difficult to separate how labs spend their federal and private funding. Hood says his lab developed what's known as the four-color fluorescent dye DNA sequencer in the early 1980s with money from the Weingart Foundation, Monsanto, the Baxter Foundation, and Upjohn. Hood's lab then received grants from the National Institutes of Health (NIH), but Hood says he used that money solely for studying the immune system.

PE attorneys note that the Hood lab first filed a patent on the DNA sequencer in January 1984, 20 months before receiving an NSF grant in September 1985. John Wooley, an NSF officer who led a team of reviewers on a site visit in March 1985, confirms that the machine was already operational then. "We saw it working, and we saw sequence data," says Wooley, who is now an official at the University of California, San Diego.

At the time, however, Caltech and the researchers made some statements that have come back to haunt them. In June 1986, Caltech and NSF both issued press releases in conjunction with a *Nature* paper about the machine; all of these documents note NSF's support of the research. "It was a courtesy to NSF," says Baltimore: "As far as we can tell, this falls into the category of 'No good deed goes unpunished.' " Tim Hunkapiller, who is named in the patent for the sequencer and now runs Discovery Bioscience in Seattle, blames Hood's "grantsmanship" in part for the acknowledgments to NSF.

According to PE attorney Smith, Caltech further confused the issue in 1988 when it included language in a license agreement with ABI that said the university would not receive royalties for DNA sequencers sold to the federal government. But Smith, who helped craft the document, says the Caltech attorneys mistakenly included this language because a postdoctoral student in Hood's lab received an NIH fellowship—which Bayh-Dole explicitly exempts.

Why the HHS IG's office became interested in this case in unclear, because NSF does not fall under its jurisdiction. In the past, however, the IG has criticized NIH for not closely monitoring whether universities comply with Bayh-Dole when they patent NIH-funded inventions. And NIH has purchased several PE sequencing machines—which now cost up to $300,000—and the expensive reagents needed to run them. *Science* has learned that NIH has passed on to the IG complaints that it received from a Boston lawyer, George Corey, that questioned the government funding of Hood's lab during the time it developed the DNA sequencer. Corey did not want to discuss the matter publicly.

If the genesis of the probe is uncertain, so are the stakes. "We don't even know the answer to that," says Baltimore. PE pays Caltech a royalty of 2% on sales of its sequencers, but Smith says the company already gives the government a 6% discount on the few sequencers it purchases. That "the government [is] trying to get anything here is really kind of silly," says Smith. Texas Representative Ralph Hall, the ranking Democrat on the House Science Committee, doesn't think it's silly at all. "We have been looking into charges that the American taxpayers may have been overcharged for these sequencers," Hall told the *Los Angeles Times*. The General Accounting Office (GAO) also has a congressional mandate to look into government-wide compliance with Bayh-Dole and has issued three reports on the topic in the past 2 years. With this combination of Congress, HHS, GAO, patent lawsuits, and the media, Caltech's role in the development of the DNA sequencer will likely remain in the spotlight for months to come. **–JON COHEN**

With reporting by Eliot Marshall, Leslie Roberts, and Elizabeth Pennisi.

GENE PATENTS

Patent on HIV Receptor Provokes an Outcry

For the past 5 years, a biotech company that set out to methodically sequence and commercialize human genes has been telling the world that it would beat everyone else to the Patent Office. Last week, that company—Human Genome Sciences Inc. (HGS) of Rockville, Maryland—made good on its boast. It won a U.S. patent on a human gene that plays a key role in HIV infection. The gene codes for a cell surface receptor called CCR5 that HIV uses to gain entry to a cell. The news gave HGS a big boost: Its stock, after declining a week before, skyrocketed on 16 February to a record high, $188 per share,