Genome Project Goes Commercial

Venture capitalists are pouring money into new companies. Most researchers welcome the trend, but it is bringing new worries about conflicts of interest

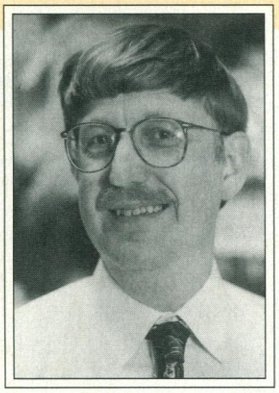
One year's heresy is the next year's dogma, or so it's starting to seem in the Human Genome Project. A year ago, James Watson resigned as head of the project after battling a wealthy entrepreneur who was trying to recruit academic researchers to join a new company. Now genome research has become a veritable hotbed of capitalism. More than 30 leading genome scientists are cutting deals with venture capitalists and new companies are springing up around the country. And this time around, virtually everybody—including Watson—is welcoming the trend.

Researchers are happy in part because Wall Street is bringing fistfuls of much-needed cash to the project. This year alone, private investors are expected to match as much as half of the $170 million the federal government will spend, with most of the investment going into new ventures. Eight genome-related companies were established in the past year, a half-dozen are in the planning stages, and several established biotech firms are moving aggressively to join the craze. Indeed, so many venture capitalists have discovered the genome that some top researchers have had dozens of them visit in search of a deal. Overnight, it seems, "the project has evolved from solely a public effort to a joint public and private effort," says Frank Ruderman, vice president for development at Genomyx Inc., a company set up 4 years ago by Genentech Inc. that is only now finding enough investor interest to go semipublic.

Welcome as this influx of cash is, however, it is raising concerns about conflicts of interest and it is renewing the debate over intellectual property rights (see box on page 302). Most of the researchers contemplating links with the private sector do not intend to leave their current academic research positions; instead, they plan to hold equity in the companies and spend some portion of their time there. Since the federal government is funding their academic research, it may be difficult to avoid the appearance that public funds are being used for private gain. The issue is hardly new, since the entire biotech industry was founded on similar arrangements (see Conflicts of Interest special section, 31 July 1992). But in an effort as high-profile as the Human Genome Project, even the appearance of a conflict of interest could be politically damaging if crusading congressmen such as Representative John Dingell (D–MI) choose to single it out for investigation.

"I'd hate to see [the project] caught up in sullying over an appearance of conflict of interest."

–Francis Collins



PAULINE LUBENS

Researchers like Watson argue, however, that the benefits of industrial participation far outweigh the potential drawbacks. Academic labs launched the project and are well on their way to finishing genetic maps. But now it's time to move to large-scale sequencing, he says, and industry is best at that kind of factory-like production. Academic-industrial partnerships make sense, Watson suggests, because much of the technology is already being developed in university labs, so "maybe the places that are doing the mapping should be involved in the sequencing as well." Watson adds that his fierce opposition to a company that wealthy entrepreneur Frederick Bourke was trying to start last year (*Science*, 7 February 1992, p. 677) was based not on the concept of such a company, but on Bourke's attempts to lure researchers away from top academic labs to join him in the private sector.

Taking the plunge

In fact, Watson is so enthusiastic about the potential for private-sector involvement that he is helping establish a company himself, although he will have no financial stake in it. The company, as yet unnamed, is expected to be a collaboration between researchers at Cold Spring Harbor Laboratory, which Watson directs, and Brookhaven National Laboratory to develop high-speed sequencing technology. Funding will come from the Long Island Venture Fund, a new fund being set up by the Long Island business community to encourage the commercialization of technologies at Cold Spring Harbor, Brookhaven, and the State University of New York, Stony Brook.

Watson is not the only big name who is dipping his toes into the waters of commerce. Harvard Nobelist Walter Gilbert, who tried unsuccessfully to start a gene mapping company in 1987—prompting a fierce debate over the propriety of mixing commercial interests and genome research—found the investment climate a lot more receptive this time. He has joined University of Utah geneticist Mark Skolnick in a company devoted to developing cancer therapies by tracing genes turned up by the genome project. Called Myriad Genetics Inc., the company has backing from Eli Lilly & Co. and the investment banking firm Spencer Trask Inc. Buoyed by swelling Wall Street interest in the project, Myriad is about to go semipublic; a "private placement" early this year will allow wealthy investors to buy stock.

With the financiers now lining up, it is hard to imagine that there was a time not so long ago when the genome project's economic worth was widely questioned. In 1987, Gilbert recalls, "venture capitalists weren't interested. They asked how [a genome company] could make commercial sense." But times have changed. "Today there are ten-fold more [markers], and the role of genetic information is ten-fold more obvious to everybody," Gilbert says. "It's reached critical mass—the genome project is moving quite rapidly. I'm delighted to see it work out."

Other well-known figures in the genome community joining the bandwagon include University of California, San Francisco (UCSF), geneticist David Cox, Eric Lander of the Whitehead Institute for Biomedical Research, and Daniel Cohen, director of the French Généthon gene mapping center. Cox, fellow UCSF geneticist Richard Myers, and Dennis Drayna, a former Genentech researcher, will be part of Mercator Genetics Inc., another company developing therapeutics from genome research. They've already incorporated and are working out final details before looking for a location. Lander and Cohen are at an earlier stage, and are now in discussion with two venture capital firms about setting up a similar therapeutics company.

Bourke is also back, with a venture based around the sequencing technology of Leroy Hood of the University of Washington. After

SOME NEW AND PLANNED GENOME-RELATED COMPANIES

Company Name	Research Focus	Main scientists	Main financial backing	Status
SEQ Ltd. Princeton, NJ	DNA sequencing, technology development	Kevin Ulmer	Johnston Associates Inc.	Incorporated 1987, main funding 1992
Incyte Pharmaceuticals Inc. Palo Alto, CA	cDNA sequencing	Randy Scott	Schroder Ventures Phoenix Partners	Incorporated 1991
(Operating under Darwin name; see below) Seattle, WA	DNA sequencing	Leroy Hood	Frederick Bourke	Inc. 1992, planned merger with Darwin 1993
The Institute for Genomic Research Rockville, MD	cDNA sequencing	Craig Venter, Mark Adams, Chris Fields	Human Genome Sciences Inc.	Incorporated 1992
Myriad Genetics Inc. Salt Lake City, UT	Cancer genes	Mark Skolnick, Walter Gilbert	Eli Lilly & Co. Spencer Trask Inc.	Incorporated 1990, main funding 1992
Mercator Genetics Inc. San Francisco area	Disease genes	David Cox, Richard Myers, Dennis Drayna	Robertson Stephens & Co.	Incorporated 1992
Sequana Therapeutics Inc. San Diego area	Polygenic disease genes	Peter Goodfellow, Anthony Monaco, Hans Lehrach	Avalon Medical Partners D. Blech & Co.	Incorporated 1992
(Not yet decided) Cambridge, MA	Disease genes	Eric Lander, Daniel Cohen, Jeffrey Friedman	Mayfield Fund; Kleiner, Perkins, Caufield & Byers	Under discussion
Human Genome Sciences Inc. Rockville, MD	Disease genes	Craig Rosen William Haseltine	Health Care Investment Corp.	Incorporated 1992
Darwin Molecular Technologies Inc. Seattle, WA	Applied molecular evolution; cancer, inflammatory disease genes	Mark Pearson Gerald Joyce	George Rathmann Ronald Cape	Incorporated 1992
Nanotronics Inc. San Diego, CA	High-speed sequencers	Glen Evens Michael Heller	Birndorf Biotechnology Dev., Enterprise Partners	Incorporated 1992
(Not yet decided) Long Island area	High-speed sequencers	William Studier Thomas Marr	Long Island Venture Fund	Under discussion
Genomyx Inc. San Francisco, CA	Long read-length sequencers	Thomas Brennan	Genentech Inc.	Inc. 1988, planned private placement, 1993
Genome Systems Inc. St. Louis, MS	Gene library screening	David Smaller	Gold Biotechnology Inc.	Incorporated 1992

trying unsuccessfully to raid top genome laboratories for talent, Bourke is now planning a merger with Darwin Molecular Technologies Inc., a new Seattle, Washington-based company backed by George Rathmann, the CEO of ICOS Corp., and Ronald Cape, the former chairman of Cetus Corp. Darwin is already up and running, having lured Mark Pearson, a member of the genome project's national advisory board, away from DuPont Corp.

A maturing venture

All this keen interest in commercialization on the part of top genome researchers is a sure sign of one thing: The genome project is coming of age. Four years after its inception, the initiative is on target in almost all areas, including physical and genetic mapping, sequencing, and work on the genomes of model species, such as the mouse and the roundworm. As a result, the venture capital community "is getting very excited—all the pieces are coming together," says Mark Levin, a venture capitalist with the Mayfield Fund. "The project is moving more quickly than anyone thought and people are starting to see how you could develop therapeutics from this."

The interest of the money men is being aroused at a time when venture capital investment in general, after plummeting for 4 straight years, is back. Last year more than $2 billion was invested in nearly 1100 companies of all sorts, a more than 30% rise from 1991. New money and a virtually untapped scientific project with vast potential for therapeutics and diagnostics is a heady brew, and investors are wasting no time in putting their money down on new genome ventures.

At the moment, the companies being set up fall into three main groups: those intending to do large-scale sequencing or mapping, taking over from the government—for a fee—much of the routine work of the genome project; more traditional biotechnology companies, like those of Gilbert and Cox, which will develop therapeutics from genome research; and those that intend to develop and sell the next generation of sequencing technology.

Kevin Kinsella, a venture capitalist with Avalon Medical Partners, which is planning a company centered on Peter Goodfellow, chairman of genetics at Cambridge University, and several other researchers, sees an explosion of genome-related startups as necessary for harvesting the practical fruits of the genome project. "On one hand," he says, "you've got universities, research institutes, and government laboratories, where all the work is going on. On the other hand, you've got pharmaceutical companies, which make all the drugs, but don't know anything about genes. We see the role of a [genome-related] company as a bridge between them."

Adds Lander, "If this project is going to succeed, it's going to have to be taken up by companies. And academic scientists need to be involved because tech transfer doesn't happen any other way." Why start a new company, rather than simply joining an established concern? "Existing small companies don't have the resources to do anything new, and existing big companies tend to be slow and clumsy," Lander explains.

Dealing with conflict

Lander, who directs the single largest genome grant ever, a recently awarded $24 million, 5-year center to map the entire human genome (*Science*, 4 December 1992, p. 1573), has had venture capitalists by the dozen visiting his laboratory over the past year looking for proprietary rights to the fruits of the genome project, but he turned them down flat. "Genomic maps are basic infrastructure," he contends. "They must be universally and freely available." He's been more receptive, however, to the idea of a company using publicly available maps to study particular genetic models of disease, such as mouse models of obesity. Yet before striking any deals,

NIH to Appeal Patent Decision

The National Institutes of Health (NIH) has won an internal battle in the Department of Health and Human Services (HHS) over its attempts to patent some of the early results of the genome project: thousands of gene fragments whose functions are unknown. Last year, HHS general counsel Michael Astrue blocked NIH from appealing a preliminary Patent Office ruling that such gene fragments cannot be patented without a known function (*Science*, 9 October 1992, p. 209). But Astrue left the government in November, and last week HHS, prodded by the Clinton transition team, gave NIH the green light to appeal. Agency officials expect to have the paperwork in well ahead of the 20 February deadline.

NIH officials have justified their efforts to patent the complementary DNA (cDNA) sequences partly on the grounds that it is preferable for the government to patent the genome than for private companies to do so. But it may be too late: *Science* has learned that at least one U.S. company has also filed for patent rights on thousands of cDNA sequences. And that company, Incyte Pharmaceuticals Inc., of Palo Alto, California, is gearing up its sequencing efforts to the point where it intends to find—and file patent applications for—as many as 100,000 cDNA sequences a year. After accounting for redundancies, that means the company will have sequenced the entire human cDNA library of 50,000 to 100,000 gene sequences by 1995, says Randy Scott, Incyte's vice president for research.

Incyte, one of more than a dozen new companies entering the genome arena (see accompanying article), is hoping that the information gained by sequencing cDNA will lead its researchers to genes that are involved in inflammatory diseases and other ailments. It calls the process "database discovery"—the company will use computers to search through the random cDNA sequences it has discovered, looking for homologies to known proteins. Such a link may give Incyte a clue as to the function of a gene, perhaps leading to a therapeutic agent. The company has no plans to release data until it publishes its findings, by which time, presumably, it will have attempted to patent everything it can.

Incyte appears to be the only company to admit publicly that it has filed for patents on uncharacterized cDNA. But others are sequencing cDNA, including Amgen Inc. and The Institute for Genomic Research (TIGR), the company set up last year by Craig Venter, the former NIH researcher whose cDNA sequences form the basis of NIH's patent claim. Amgen will not reveal its patent policy and Venter says that neither TIGR nor its spin-off companies will file for cDNA sequences of unknown biological function.

It is expected to take the Patent Office as much as a year to issue a final ruling on the patentability of cDNA. But it won't be alone in pondering the issue. Last month the congressional Office of Technology Assessment announced that it is launching a study on the propriety of gene patents, as well as the larger issues of intellectual property policies and their impact on research conduct, at the request of Senator Edward Kennedy (D–MA). The assessment should be finished by April 1994, in time for legislation on the issue, should Congress find it necessary to take matters into its own hands.

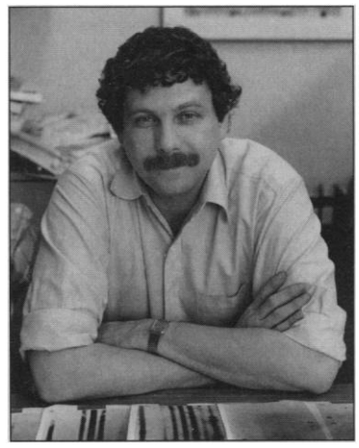
–C.A.

he's had to wrestle with potential conflict of interest issues that are typical of those faced by other top researchers who have moved closer to industry.

He emphasizes that no company he gets involved with will be allowed to have a special relationship with his genome center. Indeed, Lander's center has a policy forbidding patenting of maps or providing companies with advance access to data, and guaranteeing public release of data within 60 days of discovery. Nonetheless, Lander expects that his prominence both in the genome community and as its largest grantee will put him under the microscope and he is rightly concerned that conflict of interest could become an issue if he takes a share in a company.

That was made abundantly clear last month, when the National Institutes of Health's (NIH) National Center for Human Genome Research (NCHGR) received an anonymous letter questioning the propriety of various genome researchers—including Lander—becoming involved in genome-related companies. The letter charged that promises of prepublication release of data "ring hollow" when substantial financial gains are at stake and warned that conflicts of interest are a matter of "potential abuse, not actual abuse."

As it happens, Lander had already contacted NCHGR himself, asking for advice on the conflict issue before committing to any company. But, Lander points out, the type of financial ties the letter demonizes are not only legal but have been encouraged in biotechnology since the early 1980s as part of federal efforts to stimulate technology transfer. Indeed, since a company would have no proprietary rights to his research, Lander notes that his contemplated role in a company would easily be allowed within the tougher new NIH conflict of interest rules currently circulating in draft form in Washington. Still, with Dingell on the warpath again (*Science*, 28 August 1992, p. 1203) and a still-evolving threshold of inappropriate conflict, Lander agrees that the genome project, because of its visibility, may be held to a higher standard than biotech in general. "I'll go no further until all conflict issues are resolved in writing," he pledges.



M. LAMPERT/BOSTON

In demand. Eric Lander.

Skolnick, founder of Myriad Genetics, takes a different view: "In order to encourage private investment, you have to tolerate a certain amount of managed conflict. In life there are often trade-offs—one of the trade-offs is that some people with good ideas are going to get wealthy."

But Francis Collins, the University of Michigan geneticist who has been tapped to be the next genome project head, says he is still "worried" about the conflict issue. He notes that there was no resistance to a decision at a genome center directors' retreat last month to disclose financial holdings voluntarily, an unprompted move that suggests, he says, how seriously top genome researchers take the issue. But disclosure may not be enough, he warns. "The genome project has so much going for it, I'd hate to see it caught up in sullying over an appearance of conflict of interest."

Yet conflict isn't a problem, after all, without commercial potential. And as far as Wall Street is concerned, the genome project now has that in spades. From that perspective, conflict concerns may simply be the price of success. Dealing with these issues now, researchers argue, may prevent some tough questions later, before the profits start rolling in. And with a $7 million annual budget for research on the ethics of genome research, this is one project that shouldn't get itself into an ethical pickle.

–Christopher Anderson