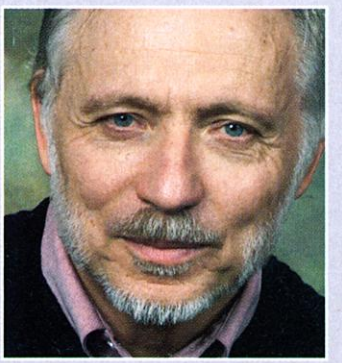
UNSUNG HERO: ELBERT BRANSCOMB

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.

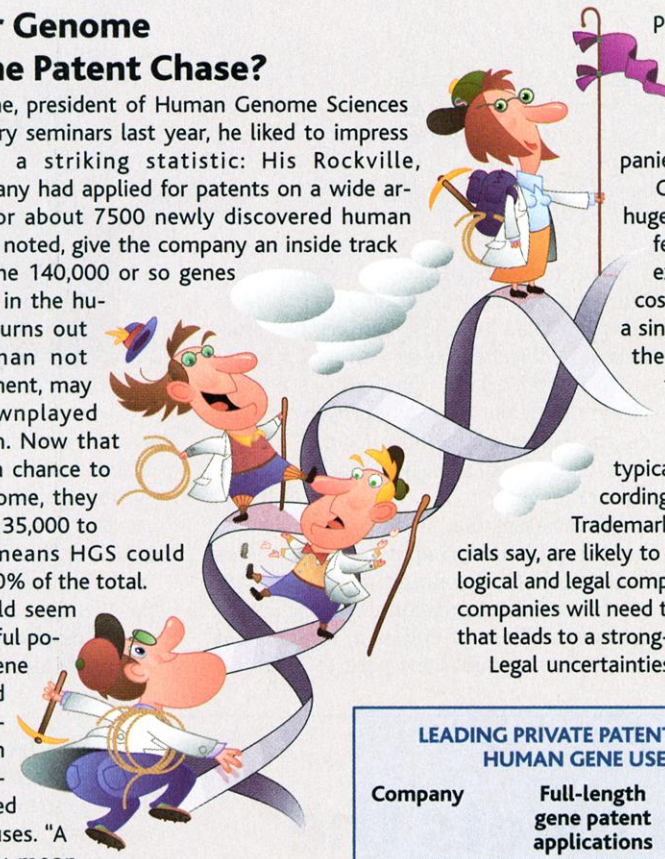
CREDITS: (TOP TO BOTTOM) JOINT GENOME INSTITUTE; ILLUSTRATION: TERRY E. SMITH

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

Will a Smaller Genome Complicate the Patent Chase?

When William Haseltine, president of Human Genome Sciences (HGS), spoke at industry seminars last year, he liked to impress his audiences with a striking statistic: His Rockville, Maryland–based company had applied for patents on a wide array of medical uses for about 7500 newly discovered human genes. Those filings, he noted, give the company an inside track on exploiting 5% of the 140,000 or so genes that he estimated are in the human genome. But it turns out that Haseltine, a man not known for understatement, may unwittingly have downplayed HGS's patent position. Now that researchers have had a chance to survey the entire genome, they believe it contains just 35,000 to 45,000 genes. That means HGS could have claims on up to 20% of the total.



Although that would seem to put HGS in a powerful position, the shrinking gene count could be a mixed blessing for the company and others, from universities to governments, that have rushed to lay claim to gene uses. "A smaller genome may mean more people pursuing claims on the same real estate," says Mark Edwards of Recombinant Capital, a biotech consulting firm in Walnut Creek, California. As a result, firms may spend millions of dollars over the next decade battling to convince patent examiners and judges that they were the first to invent uses for a particularly valuable swath of DNA.

In the long run, it will be quality—not quantity—that counts. Genes themselves cannot be patented, only the uses to which the information can be put. "The real question is: 'How many of the genes represent legitimate targets for drug development?' " asks Stephen Bent, a patent attorney with Foley & Lardner in Washington, D.C. "No one yet knows, but finding [commercially valuable genes] is probably not appreciably easier if the total pool is 45,000 instead of 100,000. You are still searching for that needle in a haystack." Indeed, Randy Scott, chair of Incyte Genomics in Palo Alto, California, which claims ownership of the most patents related to human genes, says that "the actual number of loci is an interesting academic issue, but it is not at all relevant to our business," which focuses on selling genetic information and helping other companies develop new drugs.

Companies that have tried to lock up rights to huge numbers of genes in the hope of snaring a few with valuable uses could find that to be an expensive strategy. Patent experts estimate it costs $100,000 to $500,000 simply to maintain a single patent over its 10- to 20-year life-span in the United States and other industrialized nations. And actively preventing other companies from infringing is far more costly; in the United States, for instance, legal defenses typically cost $1.6 million per contested patent, according to statistics compiled by the U.S. Patent and Trademark Office (PTO). Gene patent fights, PTO officials say, are likely to be even more expensive because of their biological and legal complexity. To recover such costs, Bent notes, most companies will need to cash in on at least one "blockbuster" patent that leads to a strong-selling product.

Legal uncertainties over the patentability of uses of gene fragments also cloud the picture. A blockbuster gene may, for example, turn out to be covered by a patchwork of patents, with one firm winning the right to use the complete gene while others lock up related uses for fragments of the same sequence. Evolving patent rules in the United States and Europe are making patenting the uses of small fragments harder. But if the fragment patents came first, their owners could force whole-sequence patenters to cough up royalties, says Stephen Kunin, a PTO expert on gene patenting. The good news, Kunin notes, is that a smaller genome could speed the PTO's process of identifying and rejecting the thousands—if not tens of thousands—of redundant applications that have been filed on gene uses that are already spoken for. If fewer genes are indeed up for grabs, he adds, "a lot of people are going to discover that they lost the race to the patent office."

–D. M.

LEADING PRIVATE PATENTERS OF HUMAN GENE USES

Company	Full-length gene patent applications	No. of U.S. patents
Incyte Genomics	7000+	560
Human Genome Sciences	7500+	162
Celera Genomics	unknown	(hopes to get 100–300)
Hyseq	5500	0
Millennium	500+	50+

ILLUSTRATION: TERRY E. SMITH

pharmaceutical companies with deep pockets are pumping billions of dollars a year into a wide range of genomics companies. These cash streams not only fuel research and product development but also give some companies "some ability to decide whether or not to show profits. Everything hinges on how much they choose to spend on R&D," explains Alexander Hittle, a stock analyst with A.G. Edwards & Sons in St. Louis, Missouri.

Toolmakers to trailblazers

Although the hundreds of companies involved in genomics are often hard to pigeonhole, and they can reshape themselves in a single board meeting, they are often placed in one of three major categories. At one end of the spectrum are the toolmakers, which sell the machines, chemicals, chips, and computer codes that make it possible to sequence raw DNA, characterize gene expression, and search for meaningful patterns in the data. Among these are Affymetrix of Santa Clara, California, which makes gene chips that give researchers the ability to screen the activity of scores of genes at a time, sequencing machine–maker Applied Biosystems of Foster City, California, and bioinformatics software developer Informax of Rockville, Maryland. The toolmakers are among the first to show profits, in large part because—like the peddlers who sold shovels, food, and blankets to gold miners—they typically demand payment whether or not their customers ever strike it rich. Applied Biosystems, for instance, made a profit of $186 million last year, primarily on sales of sequencing machines and reagents. Affymetrix could be profitable within a year or so.

The second category is the service sector. Companies such as Incyte Genomics of Palo Alto, California, and Celera, for exam-

ple, are making their names as gene discoverers and information brokers, selling up-to-date information on genes and their products to companies searching for drugs and diagnostic tests. Although Incyte may move into the black this year, profits in this sector are uncertain, because the demand for privately held information may shrink as public databases grow. Indeed, to hedge against that development, both companies are reformulating themselves, having applied for patents on genes that could involve them more directly in drug development and staking claims in the new field of proteomics (see below and sidebar, p. 1194).

The third category consists of the drug discoverers like Millennium and Human Genome Sciences (HGS) of Rockville, Maryland, both of which are helping other companies find drugs and diagnostics while trying to develop their own. HGS has focused on finding proteins that can be used as drugs, and Millennium has established itself as an ambitious technology pioneer, attempting to use concepts borrowed from the steel, computer, and other established industries to scale up and speed drug discovery. Under its 1998 deal with Bayer, for instance, Millennium promised to identify 225 new drug targets within 5 years, in exchange for up to $465 million in cash and the right to commercialize up to 90% of the discoveries. (Bayer, which has already received nearly 100 targets, decides which 10% it keeps.) Such alliances, believes Edwards of Recombinant Capital, are the future of commercial genomics, especially as companies try to tackle diseases that involve a dozen or more genes. But profits in this business aren't likely to materialize for years. Millennium, for instance, expects to spend nearly $400 million on research this year, report losses of $125 million, and remain in the red for at least another 4 or 5 years.

HOW SOME GENOMICS FIRMS ARE FARING

	Stock price* (Year hi/low)	2000 Revenue ($ millions, % chg.)	Profit/Loss ($millions)	Type of company
Applied Biosystems	73 (43–160)	1388 (14%)	186.3	tool
Affymetrix	68 1/16 (42 5/16–163 1/2)	201 (84%)	–13.1	tool
Incyte Genomics	22 13/16 (19–144 1/2)	194 (24%)	–47 to –57	information/tool
Millennium Pharmaceuticals	43 9/16 (42 3/8–44 9/64)	213 (16%)	–75	tool/drug
Informax	11 1/2 (6 5/8–31 3/4)	17.1 (71%)	–21	tool
Myriad Genetics	71 1/2 (19–138)	34 (34%)	8.7	proteomics/drug
Lexicon Genetics	13 (8–49 1/2)	11.5 (342%)†	–18.5	information/tool
Human Genome Sciences	54 9/16 (25–116 3/8)	21.4 (–9%)†	–225	information/drug
Curagen	37 1/8 (18 3/8–128 1/4)	20.8 (38%)	–27	drug
Gene Logic	21 13/16 (13 15/16–152 1/2)	16.8 (25%)†	–18	information/tool
Celera Genomics	46.2 (27.8–276)	42.7 (247%)	–92.7	information
Hyseq	15 (9 5/8–139 1/2)	15.6 (143%)	–22.3	tool/drug
Biacore	42 (12 3/4–46 1/4)	28 (38%)	3.4	proteomics
Large Scale Biology	9.1 (5.5–33.5)	23.3 (45%)	–8.2	proteomics
Oxford Glycosciences	19.25 (17.25–23.1)	6.5 (2%)†	–10.3	proteomics
Ciphergen Biosystems	8.4 (6.75–39.4)	6 (96%)	3.4	proteomics

* as of 2/06/01; † partial-year figures.

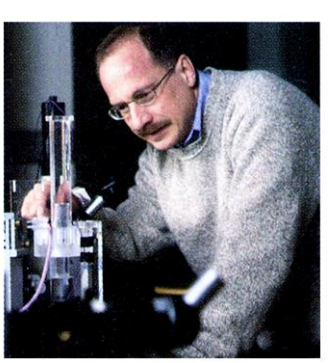
The proteomics generation

Toolmakers, information suppliers, and discovery companies are already looking beyond genomics to proteomics, the latest effort to demystify the functions of the proteins coded for by all those genes. Surveying genes is a good way of finding possible drug targets, the reasoning goes. But drug targets themselves are almost always proteins. And because proteins undergo significant changes after being built from their gene templates, researchers have recently set out to look for high-throughput methods to study them.

Many of these methods—two-dimensional gel electrophoresis, mass spectrometry, and protein binding studies—have been around for decades. But robotics and high-powered computers crunching massive amounts of data are making it possible to run these tests on a scale never seen before. "It's basically an old field being renewed because the technology has improved so much," says Amos Bairoch, a proteomics expert at the Swiss Institute of Bioinformatics in Geneva.

Still, working with that technology remains more difficult than sequencing genes. Whereas gene sequencing basically requires a single technology, proteomics today consists of a collection of nearly two dozen different techniques for analyzing a protein's function, its amino acid makeup, its three-dimensional structure, and the other proteins to which it binds. One benefit for companies entering the field is that there's plenty of room. "There is enough to be done that people don't need to collide head on immediately," says Bairoch.

Some proteomics groups may compete on the same turf anyway. Among the highest profile proteomics entrants are genomics powerhouses Celera and Incyte, both of which have made major moves into the field in the past year. In March, Celera raised nearly $1 billion on the stock market and announced that it was committing a sizable fraction to building a new proteomics research facility. In December, Incyte used money from its own recent stock offering to buy Proteome Inc., an early start-up in the field, to bolster its own burgeoning effort.



CREDIT: MARY LEVIN/UNIVERSITY OF WASHINGTON

UNSUNG HEROES: NORM DOVICHI & HIDEKI KAMBARA

An ocean apart, Dovichi (right) at the University of Alberta in Canada and Kambara at the Hitachi Co. in Tokyo independently hit upon a sequencing technology that greatly advanced the human genome project. The method, used in today's high-speed machines, uses laser beams to scan DNA being pumped through numerous capillary tubes, simultaneously identifying the bases by color-coded chemical tags.

Can Data Banks Tally Profits?

Celera's high-powered sequencing has achieved impressive results, but it hasn't yet translated into a healthy bottom line. Like most biotech start-ups, the nearly-3-year-old company has yet to turn a profit. And, although the company's stock rocketed after going public in May 1999, its price tanked over the past year, along with that of other biotechs, from a high of $275 a share to about $50 today.

Although the red ink—$234 million so far—is not unusual, Celera Genomics of Rockville, Maryland, faces a long-term problem, according to analysts. Much of the raw data its sequencers have chumed out is, or soon will be, freely available in public databases. All of which leads to the question: Just how is Celera going to tum a profit? That's still a big unknown, says David Molowa, a biotech analyst with J.P. Morgan Chase in New York City: "Celera's business model continues to be in flux."

Celera officials originally suggested that the company would make its money by selling subscriptions to its genome databases, which now include genomes of the human, fly, and parts of the mouse, along with a catalog of more than 3.5 million single-nucleotide polymorphisms, spots where the "letters" of the DNA sequence differ among individuals. Celera's president, J. Craig Venter, also said early on that the company would patent about 300 genes linked to diseases and make money by licensing rights to pharmaceutical companies to speed the discovery of new drugs (*Science*, 15 May 1998, p. 994).

That plan is making headway. Celera signed up its first set of database subscribers in early 1999. Since then, the company has made about 30 deals with pharma companies, universities, and research institutes, says Paul Gilman, Celera's head of policy planning. The terms of specific deals remain private. But Gilman says pharmaceutical companies pay from $5 million to $15 million a year, whereas universities and nonprofit research outfits typically ante up $7500 to $15,000 for each lab that is given access. In its 2000 annual report, Celera said it earned $43 million, primarily from subscription deals. And in a conference call with reporters last month, Celera Chief Financial Officer Dennis Winger suggested that the company could pull in twice that amount this year. As for patents, Gilman will say only that the company has filed for "some" and that it expects the eventual number to remain in the 100 to 300 range.

But even if Celera manages to keep adding new customers, many analysts question how long its trove of data will retain its value if much the same information is available elsewhere for free. Celera intends to retain subscribers, says Gilman, by staying one step ahead of the academic competition. That means designing a simple computer interface to access the human genome data and integrate them with data from other genomes and information on the proteins the genes encode. That way, even if the raw data are available elsewhere, Celera will still have an edge, says Gilman.

In any case, Celera is already looking beyond sequencing to a new horizon: proteomics. Last year, the company raised about $1 billion in a stock offering for a major new research effort to understand the role of the proteins coded for by genes. Although this is intended in part to feed new information into the database business, Gilman says the efforts will likely lead to discoveries of drug targets or new drugs that Celera will attempt to commercialize either in collaboration with pharmaceutical and biotech companies or possibly on its own.

That's a clear indication "that they want to get into the drug business in a limited way," says Franklin Berger, also a biotech analyst with J.P. Morgan Chase. And that, he says, would make Celera look more like a genomics-based pharmaceutical company like Millennium Pharmaceuticals of Cambridge, Massachusetts, than simply a data provider. Gilman agrees to a point but insists that unlike straight drug-discovery ventures, Celera will still be "grounded" in the online business. Berger, Mollowa, and other analysts applaud the shift toward drugs, as it proposes to exploit whatever moneymaking opportunities arise from the genome. But it also moves Celera into another arena with plenty of competition. **–R.F.S.**

Meanwhile in Europe, the Swiss start-up Geneva Proteomics is preparing a stock offering to raise money to set up a similar proteomics factory.

This proteomics gold rush suits the toolmakers just fine. Suppliers of well-proven proteomics technologies such as mass spectrometry, which can be used to identify different proteins, are already seeing their business jump. Meanwhile, companies like Ciphergen Biosystems of Fremont, California, which supplies protein-identification chips, are hoping to cash in as well. Still, these so-called "tool-kit" companies could face trouble down the road, says Craig West, another biotech analyst with A.G. Edwards & Sons. "Tool-kit firms are going to experience consolidation" as the proteomics field settles on a couple of key technologies as de facto standards, says West. And ultimately, West argues, the real money will flow to those who use the technology to find new blockbuster drugs. "It just doesn't seem to us that having the next cool way to find something out is viable for a long-term business model," he says.

What have you done for me lately?

Other analysts echo that sentiment in discussing the genome companies as a whole. Edwards, for instance, notes that as interesting as last month's Millennium-Bayer announcement was, the companies still have to show that they can move that speedily on a routine, sustained basis. Even then, some observers are skeptical that early agility will translate into substantially shorter drug development cycles, as major delays often occur during clinical trials and in the regulatory process. "We need a gene chip to speed up patients and the bureaucrats, not the science," jokes one analyst.

Industry executives see other challenges. Some wonder who will train their next generation of employees, as many of the best and brightest academics and graduate students have been lured into the private sector by stock options and hefty salaries. Others fret about how to keep the talent they've hired—and sometimes made wealthy—happy. The challenge, one exec told analyst Hittle, "is to find ways of keeping the job interesting enough so that millionaires want to come to work every day."

–DAVID MALAKOFF AND ROBERT F. SERVICE

CREDIT: BILLY COBLE/CELERA GENOMICS

UNSUNG HEROES: PETER LI & RICHARD MURAL

Bioinformaticist Li (right) came to Celera from the publicly funded Genome Data Base organization at the Johns Hopkins School of Medicine in Baltimore to lead the chromosome team with Mural, a co-author of gene-finding software called GRAIL. Their team validates DNA assemblies and locates them on chromosomes.