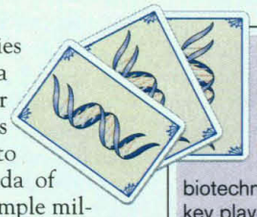
The Genomics Gamble

Drug companies, biotechs, and Wall Street investors are putting their money down on efforts to unlock the secrets of human DNA. But when will genomics deliver on its promise of next-generation treatments?



Dollars and dreams of better ways to prevent and treat disease are driving efforts to find and decode human genes. In this special issue, *Science* takes an in-depth look at biotechnology's second wave, including the key players, companies, and technologies. Separate articles examine the conflicts over the control of DNA sequence data, patenting, and regulation—vital issues that will have to be resolved if genomics is going to realize its potential.

After visitors to the laboratories of Sequana Therapeutics in La Jolla, California, wend their way past the battalion of robots that spray human DNA into tiny plastic wells, the armada of black boxes that copy each sample millions of times, and several more squadrons of LCD-lit machines that separate the genetic material by weight or extract the exact sequence of nucleotides that code for genes, each person is given a most unusual gift: a box for a compact disc labeled "Human Genotype." The box bears the visitor's name above a surreal illustration of a broken DNA double helix, sprawled across a desert landscape like an ancient ruin. Chromosome-shaped clouds float in the air. And in one corner, in Greek, are the words "know thyself." Open it up and the box is empty. But it won't be that way for long, according to an accompanying booklet. In less than 5 years, it predicts, humans will be able to carry their entire genetic blueprint on a CD, "which will evoke a revolution in many areas of our lives."

Whether or not Sequana's breathless prediction comes true, the crusade to identify every human gene—collectively known as the "genome"—already is changing the landscape of the biotechnology industry, big pharmaceutical companies, and academia in a way that would itself have seemed surreal a few years ago. The drive is fueled by the international Human Genome Project, which plans by 2003 to sequence the 3 billion adenines (A), cytosines (C), guanines (G), and thymidines (T) found in the 23 chromosomes of each human. And just as quickly as the "high-throughput" sequencing machines have been spitting out these ACGTs, a raft of powerful new technologies is beginning to make sense of the data. "We've gone through a period where it was the gene of the year, to gene of the month, to, pretty soon, gene of the day," says Harvard University Nobel laureate Walter Gilbert.

Gilbert, who in a 1991 *Nature* editorial first detailed how this surge of genetic knowledge was changing the paradigm of biomedical research, co-founded a genomics company, Myriad Genetics in Salt Lake City, that last October brought the revolution into the clinic with a test for genetic mutations that increase a woman's risk of breast cancer. Other genomics companies have gene-based diagnostics that they hope to market this year. The even grander dream is that a better understanding of the links between genes and disease could give rise to a new generation of highly effective drugs that treat causes, not just symptoms.

Dazzled by the commercial possibilities, venture capitalists, the big drug companies, and Wall Street are all swooning over genomics, pouring millions of dollars into start-ups, the impact of which is being felt from Boston to Beijing. While less than 10 years ago, genomics companies struggled mightily to find investors, today "it's very difficult to talk to venture capitalists unless you call yourself a genomics company," says George Poste, who heads R&D at SmithKline Beecham Pharmaceuticals, which helped launch the genomics gold rush by making a $125 million deal in 1993 with a then-fledgling start-up, Human Genome Sciences (HGS) in Rockville, Maryland.

Genomics is having a profound impact on established biotechs, too. As an editorial in last November's *Nature Biotechnology* snickered, many of these companies seem to have "undergone collective corporate psychoanalysis and have discovered that deep down they are all really 'genomics' companies." In an odd role reversal of lumbering "big pharma" and fleet-footed "bio," the editorial also noted, the few biotechs that earn big profits from having brought products to market—like California's Amgen, Genentech, and Chiron—have been slow in (or ultrasecretive about) climbing on the genomics bandwagon. "All of the [biotechs] are going to be forced to broaden into genomics," asserts the University of Washington's Leroy Hood, who pioneered the development of high-throughput DNA sequencers and co-founded Darwin Molecular in Seattle.

It gets more surreal still. Many of the companies that fly under the genomics flag have adopted business plans that bear little resemblance to those of traditional biotechs. Rather than staking their fortunes on cloning a blockbuster drug or two, genomics companies are generating serious revenue early on by selling information, such as leads on possible drug targets, to big pharma. "Their business strategies are just as innovative as their research strategies," says Carl Feldbaum, president of the Biotechnology Industry Organization in Washington, D.C.

Chromosome clouds also are racing across the academic sky. Today, most prominent geneticists have links with the genomics industry—and not simply to harvest some of the bumper crop of new biodollars. Genomics companies have resources for gene hunting that academia simply cannot match. "It's impossible to ignore the way things have changed in the last 3 years in human genetics [because of industry]," says Francis Collins, head of the U.S. National Center for Human Genome Research (NCHGR). "Gene hunting used to be a purely academic exercise."

Still, while opportunities clearly abound, genomics biotechs themselves would be wise to heed Sequana's counsel to "know thyself." Their grip on genetic information—their lifeblood—may be tenuous. Patent protection of much sequence data is uncertain (see p. 780), and ever more genetic information is becoming available free of charge through public databases (see p. 777). Already, many scientists are concerned that, as powerful as the new high-throughput technologies are, the genomics industry is in danger of making the same mistake that the previous wave of biotechs made: hyping itself to the hilt (see sidebar on p. 770). "Genomics is not going to be the Holy Grail—get off that idea," cautions William Rutter, chair and co-founder of Chiron.

Moreover, although genetic information is swelling databases at a prodigious rate, there is a vast distance between knowing DNA sequences and helping people live longer, healthier lives. Scientists still are debating such fundamental questions as how many genes there are amid the vast stretches of DNA that has no known function (see sidebar on p. 769). Only about 1% of the human genome has been fully sequenced so far, and precious few links between genes and common diseases have been discovered, largely because many genes work in concert

in complex biological pathways.

All of which suggests that the genomics industry is in its infancy. "The amount of DNA information is going up by a factor of 10 every 5 years, which means in 1985 we knew 1% of what we know now," says Harvard's Gilbert. "And we're not anywhere near the end of the process. It's like the computer chips. That's the only other aspect of society changing as rapidly."

Marrying genomics and biotech

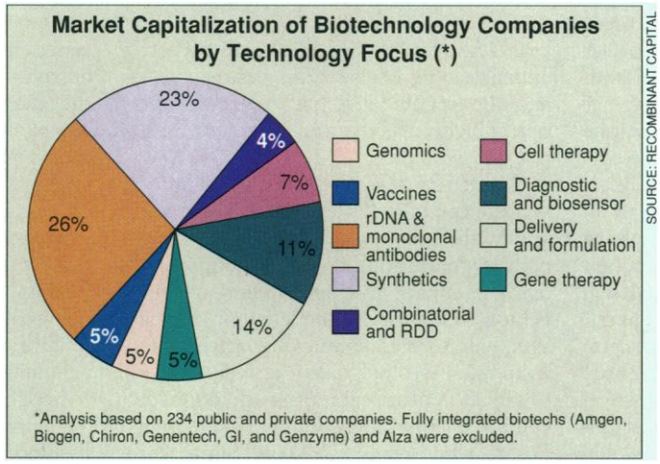
In the mid-1980s, biotechnology began flirting with genomics, but the relationship didn't take off immediately. Among the earliest players was Collaborative Research, a small Boston-area biotech that tried to exploit a gene-mapping technique known as restriction fragment length polymorphisms, or RFLPs. Like flags used by surveyors, RFLPs serve as markers along the chromosomes for gene-hunting researchers, allowing them to pinpoint disease-causing genes by tracing the inheritance of DNA differences among related individuals. The technique led to the publication of the first, albeit crude, map of the human genome. In its 1987 annual report, the company crowed that the promise RFLPs held "to diagnose the common diseases exposes us to a massive commercial market."

In the spring of 1987, Gilbert began fishing for money to launch Genome Corp. This would-be biotech hoped to sell drug companies access to a database of genomic information derived largely from the new DNA-sequencing machines that had been developed by Hood, then at the California Institute of Technology, and co-workers.

Neither Collaborative Research nor Genome Corp. realized their dreams. Collaborative Research, which in 1994 changed its name to Genome Therapeutics, now focuses primarily on sequencing the genomes of pathogens. "Making markers and a map were not commercially viable approaches," says former Collaborative Research consultant Mark Skolnick, who helped develop the RFLP technique and now is at Myriad. "It was an example of being ahead of the times." Genome Corp. never even came to be. "It was just years too early for people to recognize the value of the idea," says Gilbert, who notes that when the stock market crashed in 1987, his funding for the nascent company collapsed.

In October 1990, the Human Genome Project was launched with great fanfare by double-helix co-discoverer James Watson, who then headed the effort for the National Institutes of Health (NIH). But even that did not attract a critical mass of private investors. J. Craig Venter, head of The Institute for Genomic Research (TIGR) in Rockville, Maryland, recalls co-chairing a meeting back then on the genome project and the pharmaceutical industry. "There was very little interest from the industry," he says.

The spark that set the genomics industry on fire was a 21 June 1991 paper in *Science* (p. 1651) by Venter, who was then with NIH, and co-workers outlining a shortcut to characterizing genes. Genes are notoriously elusive because they account for only about 3% of human DNA. Scientists debate what the rest of the DNA is for: Much of it looks like evolutionary junk, while other regions regulate gene expression and other functions. Venter's work basically helped researchers separate the wheat from the chaff.



5% solution. While still small, genomics companies' share of the biotechnology industry is growing.

When DNA is translated to messenger RNA (mRNA), the only portion of genetic code retained is the information needed to make a protein. In effect, mRNA is all gene. Venter's key contribution was to devise a quick and dirty system for identifying these genes. After making complementary DNA (cDNA) to the mRNA—DNA is easier to work with—Venter found that sequencing a small region gave him enough information to search existing databases and determine whether it was similar to known genes from other organisms. These gene pieces, which he called expressed sequence tags, or ESTs, thus provided a cheap, rapid way to skim the genome for practical information.

The commercial possibilities of the approach were manifest immediately, the first of which was a controversial (and ultimately futile) attempt by NIH to stake a claim on these unknown genes. The controversy—and "constant press coverage"—says Venter, helped jump-start the industry (*Science*, 15 January 1993, p. 300). One person to take notice was the late venture capitalist Wallace Steinberg, who encouraged Venter to leave NIH and head TIGR, which would be largely funded by the new company, HGS (see p. 778).

SmithKline played a major role itself in building the biotech genomics industry by committing $125 million to HGS in 1993 for exclusive access to its database of ESTs. "Up until that deal, there was nothing like it in biotech," says Venter. HGS's CEO William Haseltine, a former AIDS researcher at Harvard's Dana-Farber Cancer Institute, says he is surprised at how quickly the pharmaceutical industry responded when it saw the potential power of genomics to discover novel drugs. "The pharmaceutical companies were much more receptive than the scientific community as a whole," says Haseltine. By the end of 1994, four other budding genomics companies had made deals with big pharma totaling more than $140 million.

Pharma's market

Today, eight genomics biotechs have gone public and a few dozen smaller start-ups are attracting serious attention. These companies come at genomics from every conceivable angle, and many, including HGS, are continually reinventing themselves to keep up with each other and with the flood of new technologies. Stock analysts—four of whom wrote fat reports about genomics last year—generally divide the genomics companies into three broad categories—large-scale sequencers, positional cloners, and those that do functional genomics—although the categories are losing some of their meaning because of the protean nature of the companies.

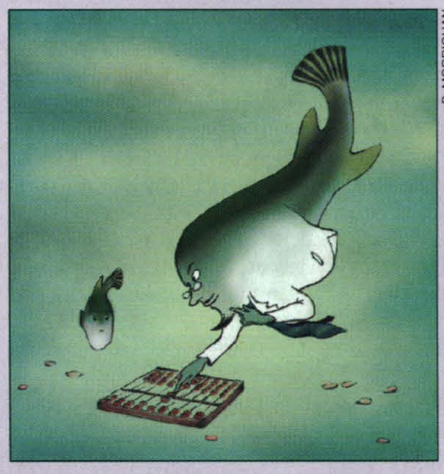
HGS, the prototypical large-scale sequencer, sells exclusive access to its database of ESTs to big pharma. Incyte Pharmaceuticals in Palo Alto, California, HGS's main rival, sells nonexclusive access to its EST database. Genome Therapeutics in Waltham, Massachusetts, and Microcide in Mountain View, California, are taking a similar approach with the genotypes of pathogens.

The positional cloners, in contrast, sift through the genomes of individuals from families that have specific diseases and try to determine which genes cause the disease. Companies that analysts have labeled as positional cloners include Sequana; Myriad; Millennium Pharmaceuticals in Cambridge, Massachusetts; Darwin; Genset in Paris; and Mercator Genetics in Palo Alto, California. They distinguish themselves in

How Many Genes Are There?

When J. Craig Venter, head of The Institute for Genomic Research (TIGR) in Rockville, Maryland, co-authored a July 1994 paper in *Nature Genetics* postulating that there are 60,000 to 70,000 genes in the human genome, he says he received an irate phone call from one of his biggest supporters. "What the hell do you think you're doing, saying there are only 60,000 genes?" the caller yelled.

The caller was the late entrepreneur Wallace Steinberg, who played an instrumental role in forming the nonprofit TIGR and its main corporate backer, Human Genome Sciences (HGS), also in Rockville. According to Venter, Steinberg hollered, "I just sold 100,000 genes to SmithKline Beecham!"—a reference to the landmark deal he cut that gave the large pharmaceutical company access to HGS's database of gene fragments, known as ESTs (see main text). Steinberg "was seriously concerned," says Venter. "He was always trying to raise the number of genes, because he saw them as a commodity."



P. MORRIGHAN

Fishy estimate. Sydney Brenner contends that humans and puffer fish have the same number of genes—about 60,000.

In addition to annoying his sponsor, Venter's lowball estimate helped stir up a debate among his colleagues. More than a century after Austrian monk Gregor Mendel first detailed how genetic material was passed from one generation to the next, researchers still don't know how many genes we're all walking around with. The essential problem is that our genes are hidden in a haystack of apparently meaningless genetic information. Only about 3% of the 3 billion individual units known as "bases" that make up DNA actually code for proteins, which is the simplest definition of a gene. Until the international Human Genome Project is completed in 2003, scientists will not know for sure the number of genes in human chromosomes.

But that doesn't lessen the certainty of the many scientists today who say they already know the answer. At the low end is Sydney Brenner, who launched the field of nematode genetics. Brenner is unequivocal: "We know almost exactly: 60,000 genes," he says. "There isn't much room for much more. In fact, it may be less than that." Brenner, who heads the Molecular Sciences Institute in La Jolla, California, has been studying the genome of the fugu, or Japanese puffer fish. It has 360 million bases, and his lab finds a gene every 6000 bases, yielding 60,000 total genes. Brenner assumes that this number is true across species. "If our genes turn out to be bigger, there will just turn out to be fewer of them," he insists.

Venter's estimate is based on an analysis of the ESTs that have been sequenced. But one problem with calculations based on gene fragments is that several ESTs may come from the same gene, a redundancy that would not be detected unless their sequences overlapped—a shortcoming Venter tried to correct for in his *Nature Genetics* paper by estimating various redundancy frequencies.

C. Thomas Caskey, head of the genome project at Merck & Co., guesses 80,000 to 100,000. He's working with an EST database put together by Robert Waterston and colleagues at Washington University in St. Louis. Caskey says they have identified 42,000 to 43,000 unique genes and are still counting. "The curve certainly hasn't flattened," he says. "If it was 60,000, we'd see more of a flattening of the curve."

The co-founder of the genomics company Darwin Molecular in Seattle, Leroy Hood of the University of Washington, ups the ante a bit, but with a dose of humility. "I suspect it will be a lot more than 100,000 in humans. But any number anyone gives you is just a wild guess," he says. Joining Hood on the high end, but without the caveat, is William Haseltine, head of HGS, who says the company's EST database already has identified 90% of human genes. "There are 120,000 to 150,000 genes," Haseltine declares, adding that only HGS and its main competitor, Incyte Pharmaceuticals, would really know.

But Randy Scott, scientific director of Incyte—which has a massive EST database similar to HGS's—doesn't claim to know. "We're pretty comfortable that we're in the range of 80,000 to 100,000, but we're still discovering," says Scott. "I think people are fairly naïve about the complexity of the data, and that's why you get these rip-roaring debates."

Brenner takes a humanistic view of the debate. "People like to have a lot of genes," says Brenner. "It makes them feel more comfortable. To be only eight times more complicated than *E[scherichia] coli* is an insult." And having more genes in the database makes investors feel more comfortable, too. **–J.C.**

part by the quality of the family samples they obtain. Large families in isolated areas with good genealogical records are especially valuable.

Functional genomics companies attempt to tease out the specific roles particular genes play. Some, like Affymetrix and Synteni, both in the San Francisco Bay area, and Combion in Pasadena, California, are developing "array technologies" that can rapidly analyze which genes are turned on, or expressed, in a given tissue or cell. Researchers hope that the ability to analyze hundreds of genes simultaneously and to compare patterns of gene expression in diseased and healthy tissue will reveal the complicated pathways that cause disease.

Other functional genomics companies compare the genes in humans to those in various species. This can give researchers clues to what functions newly discovered human genes perform. Exelixis in Cambridge, Massachusetts, specializes in the genetics of the fly. "What I don't think any of us fully dreamed of until recently was that at the structural and functional level genes would be so homologous, that we were looking at little people with wings," says Exelixis co-founder Corey Goodman, a developmental geneticist at the University of California, Berkeley. Across town at NemaPharm, a company co-founded by developmental geneticist Robert Horvitz of the Massachusetts Institute of Technology (MIT), the nematode worm is the model. Across the Atlantic in Cambridge, England, Hexagen exploits the mouse.

The driving force behind this boom continues to be the pharmaceutical industry, which to date has cut more than $1 billion worth of collaborative deals with genomics companies (see figure on p. 772). What's in it

for big pharma? Drug companies now spend hundreds of millions of dollars and several years bringing a drug from lab bench to pharmacy shelf. Many set their sights on a growth rate of about 10% annually, says Jurgen Drews, president of global research at Hoffmann-La Roche, but he contends that the companies do not have enough drugs in the pipeline to keep up the growth rate. That's where genomics fits in.

Drews calculates that drug companies now work with just 417 "targets," or human enzymes, receptors, and ion channels known to play a role in diseases (excluding those caused by pathogens). He thinks genomics could boost this number by at least an order of magnitude. He figures that there are 100 "important" diseases that are caused by five to 10 genes each (most common diseases are polygenic), yielding perhaps 500 to 1000 disease-related genes. Most are part of signaling pathways and regulatory cascades, he says. So assume each gene's protein product interacts with three to 10 other proteins, and there are 3000 to 10,000 targets-in-waiting. "[Genomics] is a much more mechanical way to find drug targets," says Drews.

Cecil Pickett, executive vice president of discovery research at Schering-Plough, points out that a pharmaceutical company doesn't need to derive many drugs from a genomics-company collaboration to make it worth the price. "Two or three targets that would yield marketable drugs—that would have an impact," says Pickett.

Not only do pharmaceutical companies expect genomics to deliver them more targets, they also believe that this surge of genetic information will help them develop drugs more quickly. Says C. Thomas Caskey, who heads the genomics program at Merck & Co.: "If you just had genomic science, you'd say it will percolate along, but it is coming along when industry is having a revolution in other areas." For example, he

Hype Surrounds Genomics Inc.

Boosters of the burgeoning genomics industry often give the impression that discovering a new disease gene is tantamount to discovering a new treatment. But history shows that identifying the enemy isn't the same as stopping it. For instance, researchers discovered the mutated gene that causes sickle cell anemia 40 years ago, but there still is no cure—and that's not surprising, says Robert Weinberg, a specialist in cancer-causing genes at the Massachusetts Institute of Technology. "For a number of genetic diseases, knowing the genes might not help the patient one whit," he says.

Weinberg is not alone in expressing concern about hype in genomics. Other academics, researchers at older biotech companies and big pharmaceuticals, and even some stock analysts and scientists who have started genomics companies worry that the promise of genomics is being oversold. "Hype and speculation in some cases have gone to absurd levels," says J. Craig Venter, head of The Institute for Genomic Research, a Rockville, Maryland, nonprofit.

> **"For a number of genetic diseases, knowing the genes might not help the patient one whit."**
>
> **Robert Weinberg, MIT**

The main concern is not that genomics is a sham, but that it could take a long time to produce substantial financial returns. "We're talking about understanding the computer of life—the most difficult thing mankind has ever understood on this planet," says Thierry Soursac, the general manager of RPR Gencell in Santa Clara, California—a division of the drug company Rhône-Poulenc Rorer that does some genomics work, but primarily focuses on cell and gene therapy. Soursac says he has high hopes for genomics but low regard for the way Wall Street investors talk about its potential: "If it takes 20 years, it will be an extraordinary accomplishment. But for Wall Street, if it takes 2 years, it will be too long." Michael Steinmetz, vice president of preclinical R&D at the pharmaceutical company Hoffmann-La Roche, agrees. "The timeline has been completely underestimated," he says.

If Soursac and Steinmetz are correct, it wouldn't be the first time biotechnology has gone down this road. Earlier waves of biotech companies were heavily criticized for overselling technologies like monoclonal antibodies and gene therapy. "Biotech doesn't exactly have a clean record in this regard," acknowledges David Galas, head of Seattle's Darwin Molecular, who says the process of starting up a biotech makes it difficult to avoid hype. "Once you have an idea for a company, you want to sell it to investors. It's just sell, sell, sell all the way along the line."

Indeed, in part because of the hype, some older biotechs, such as Chiron of Emeryville, California—which is part of a "functional genomics initiative" with Genetics Institute and Genentech—have pointedly resisted transforming themselves into genomics companies. "Obviously, genomics information will provide, over some time frame, tremendous insight into humans and other organisms," says William Rutter, head of Chiron. "But in the time frame of our lives, I'm not at all sure there will be a lot of direct impact."

The brass at Genetics Institute, a Cambridge, Massachusetts, company that makes products based on proteins secreted from cells, also blanches at the idea of being labeled a genomics company. Steven Clark, the company's vice president of research, is confident that genomics will eventually lead to new treatments. But "is this really going to revolutionize drug discovery?" asks Clark. "I don't know."

Daniel Kisner, president of Isis Pharmaceuticals, a start-up biotech in Carlsbad, California, asserts that many of the current crop of genomics biotechs will not survive. "[The industry is] highly competitive and already overbuilt," says Kisner, who previously was an executive at Abbott Laboratories and, before that, a top official at the U.S. National Cancer Institute. "I don't know what these people are going to be doing in 5 years unless they begin to use their chemistry programs to make more clear drug discoveries."

The Massachusetts Institute of Technology's Eric Lander, who co-founded the genomics company Millennium Pharmaceuticals in Cambridge, Massachusetts, concedes that genomics is hyped, but questions whether it's overvalued. If you compare the market valuation—the number of shares of stock multiplied by the selling price—of the public genomics company with that of the big pharmaceuticals, genomics only accounts for about 0.5% of the total, he says. "Do we believe genomics has increased the value of pharmaceutical development by 0.5%?" asks Lander. "I'm willing to say yes. Maybe it's undervalued." William Haseltine, head of the genomics company with the highest valuation, Human Genome Sciences, has this to say to the skeptics: "They won't be skeptical very long." The clock's ticking. –J.C.

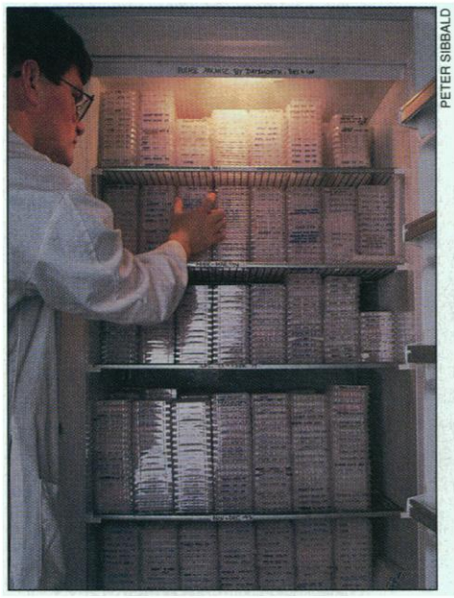
says, the simplicity of making recombinant proteins today is being matched by the power of combinatorial chemistry, a new way to construct giant libraries of potential drugs by synthesizing thousands of variations on each chemical theme (*Science*, 31 May 1996, p. 1266). Bioinformatics, the use of high-powered computing to navigate the river of genetic and other biological information flowing out of the world's laboratories, also is allowing drug developers to travel kilometers in the same amount of time that they used to move ahead by meters (*Science*, 2 August 1996, p. 588). Says Caskey, "Could [this drug-discovery revolution] have happened without genomics? A lot of it would have. But it's a combination of these technologies."

Green genes

While big pharma has been stuffing money into one pocket of genomics biotechs, Wall Street has been stuffing money into the other. "For the investors, it's a large psychological kicker that these pharmaceuticals are putting out enormous investments in something that pharmaceuticals on their own cannot create," says Reijer Lenstra, a stock analyst with Smith Barney in New York City who wrote an overview of genome companies last September.

All told, genomics companies make up only 5% of the biotechnology sector, according to Mark Edwards, whose company, Recombinant Capital in San Francisco, analyzes the biotechnology industry (see pie chart on p. 768). But that figure downplays the punch these companies have packed on Wall Street. Consider the amount they have raised in initial public offerings (IPOs). Last year, the top two IPOs in all of biotech were Genset and Affymetrix, both of which reaped nearly $100 million. Millennium also ranked high on the list, netting about half that amount. Sequana and Genome Therapeutics, both of which had gone public earlier, took in more than $30 million each when they returned to the Street with what is known as a "subsequent offering" of stock. "Investors have rewarded these companies to a degree that, cynically, I wouldn't have thought possible," says Elizabeth Silverman, a stock analyst with New York's Punk, Ziegel & Knoell, who puts out a monthly "genomics digest."

One key reason investors love these young companies is because, unlike traditional biotechs, many have a "product" right away: the information they sell to big pharma. Take Incyte, which itself raised more than $30 million in a 1995 subsequent offering. This company began in 1991 as a traditional biotech, aiming to develop therapeutic proteins and partnering with Genentech to pay for human trials of their candidate drugs. When early data looked disappointing and Genentech backed out, Incyte decided to shift into large-scale sequencing of ESTs and to develop a bioinformatics team that could make a state-of-the-art EST database, to which outsiders could buy a subscription. "What's different about genomics from most of biotech is the tools themselves have value," says Roy Whitfield, Incyte's CEO. "Think of gold mining. In biotech before, people were staking out claims and trying to mine. [Now we're] making a business out of selling tools to miners."



PETER SIBBALD

Filled to capacity. This lab freezer at Human Genome Sciences Inc. often stores as many as 144,000 genes.

Sequana has a different focus but a similar business strategy. "Biotechnology is a handmaiden to the pharmaceutical industry," says Sequana's CEO Kevin Kinsella, whose seed capital firm, Avalon Ventures in La Jolla, California, has launched 16 biotechs. Sequana, too, has little interest in developing drugs itself and instead sells information to big pharma. "For a biotechnology company, the worst thing that can happen in the '90s is for a lead product to go to clinical trials," says Kinsella. "Investors hear a huge sucking sound."

The information that Sequana sells differs markedly from access to a database of sequences. Pharmaceutical companies hire Sequana to hunt for genes that cause specific diseases and, if possible, unravel what the genes do. The foundation of the business is the tens of thousands of DNA samples from well-characterized patient populations that Sequana acquires from more than two dozen collaborations with academic groups. In addition to its fleet of high-throughput machinery, Sequana analyzes these samples with a large bioinformatics team. "The nice thing about our business is we've set up an industrialized version of positional cloning," says Kinsella. "It's a sausage machine. All you need is sausage meat at the beginning to get sausage at the end."

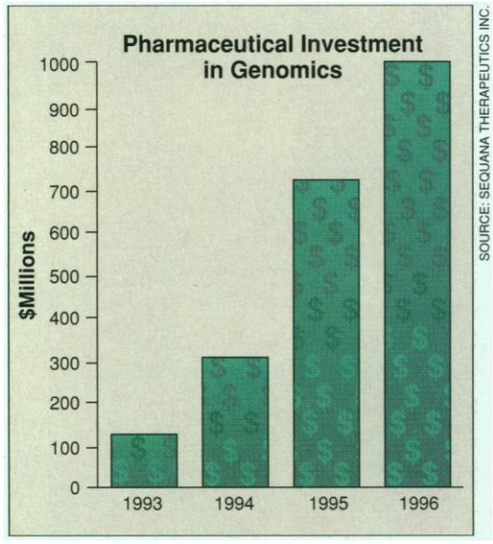
Millennium's business model differs from that of the rest of the pack because in addition to amassing a portfolio of multimillion-dollar deals to find drug targets for big pharma, it has retained substantial rights to develop drugs in-house.

Myriad may develop treatments, although it sees itself primarily as a diagnostics company, which has allowed it to bring its breast cancer predisposition test to market quickly (*Science*, 25 October 1996, p. 496). "We decided we wouldn't have to sell on 'Trust me, in 10 years there will be a product,'" says Myriad's Skolnick. Peter Meldrum, the company's CEO, adds that "Our revenue stream is not relying on a revenue stream from big pharma." Myriad also envisions its market expanding once genetic diagnostics are used to determine which patients should take which drugs, a field called pharmacogenetics (see p. 776).

Incyte's Whitfield stresses that whatever a company looks like today could change tomorrow. "One thing you can't do in genomics is take a static view," says Whitfield. "This time last year we had three partners. We have 10 now." And consider how HGS, the company that kicked off genomania, has changed. Its database of ESTs is no longer SmithKline's exclusive hunting preserve: Last summer, the two companies decided to let three other pharmaceuticals in—with deals worth $140 million. "We've already saturated SmithKline with [drug-target] opportunities," says HGS's Haseltine. HGS also has branched into pathogen and agricultural genetics. And it intends to bring products to the clinic itself, as early as next year. "From our perspective, we've formed a therapeutics company," says Haseltine.

In addition to these changes, genomics companies also have begun to partner with—or snap up—other biotechs. Sequana collaborates with a La Jolla, California, neighbor, Aurora Biosciences (a maker of high-throughput screens for genetic targets), and in July bought NemaPharm. In August, Incyte bought Combion. In November, England's Chiroscience bought Darwin. HGS, owing to its interest in developing treatments itself, has links with antisense developer Isis in Carlsbad, California, and Genetic Therapy Inc. and vaccine-developer MedImmune, both of Gaithersburg, Maryland. Affymetrix is collaborating with Genetics Institute, which, in turn, announced in September that it was partnering with Chiron and Genentech on a new "functional genomics initiative." Sequana's Kinsella

explains that the way to win the game is to do everything: "The more genomics companies we link ourselves with, the more we migrate up the food chain and the less and less we'll be butting heads with academics."



High rollers. By 1996, drug companies had invested more than $1 billion in genomics biotechs.

Acadenomics

A psychoanalyst would have a field day exploring the relationship between genomics companies and academia. Although the two can merge beautifully, each complementing the other's weaknesses, at times, it is a love-hate relationship fraught with fierce competition. Although some researchers say the flood of new genomics companies simply is redefining the focus of academic investigators, increasingly, scientists concur with the University of Washington's Hood that "most academics aren't going to begin to have the resources to really be competitive on their own."

NCHGR's Collins says that for an academic to compete in gene hunts of common disorders such as cancers, diabetes, or asthma, it's not enough to have an organized team, good technicians, and lots of money. "It's the kind of families you've collected," says Collins. "Obviously, many of the companies have moved into [finding DNA samples from quality families] by making liaisons with clinical groups that have no molecular biology experience. But the downside is some clinicians lose control."

Daniel Cohen, Genset's chief genomics officer, argues that unless they are collaborating with industry, academics should not bother searching for common disease genes. "If the number of genomics companies increases, all these [genomics] labs in academia will be obsolete," predicts Cohen, who until last year ran France's Center for the Study of Human Polymorphism, a nonprofit he co-founded that helped compile some of the best maps made of the human genome. To make better use of public funds, Cohen contends that academics should instead concentrate on basic knowledge and diseases that are rare or are predominant in developing countries, and thus hold little interest for profit-minded industry.

But instead of turning over clinical samples to biotechs doing genomics, Duke University—in what may be a harbinger for other academic institutions—has decided to launch its own biotech company. Allen Roses, Duke's chief of the neurology division, who is heading up a large hunt for the genetic basic of Parkinson's disease, believes that the company, which at press time had yet to be officially formed, will offer academics several advantages. Currently, the Parkinson's project has teams of researchers around the United States collecting blood samples from affected families. Duke's company plans to give all academic collaborators (10 other institutions are involved) a cut of any profits resulting from the work. Duke will funnel its own profits back into the school. What's more, Roses says, the researchers can offer study participants first access to any diagnostics or treatments that stem from the work.

Collins notes that NIH also is funding a new Center for Inherited Disease Research in Baltimore, which plans to isolate, sequence, and make sense of DNA in clinical samples collected by academics who don't have the means (or know-how) to do it themselves. "It will try to provide a facility for clinical investigators who have set up pedigrees and don't want to hand them over to a private concern, losing the opportunity to enjoy the detective work," says Collins. The center, which will be run by Johns Hopkins University, will open this spring.

Hood isn't worried about genomics companies leaving small academic labs out in the cold. "There's just an enormous opportunity in smaller labs to pick out interesting gene families in a way they never would have been able to before," says Hood. Eric Lander, head of the genome center at MIT's Whitehead Institute for Biomedical Research and a co-founder of Millennium Pharmaceuticals, also sees a bright future for academic geneticists: "I don't see much competition. I see specialization. Lots of academic problems make lousy industrial problems. We shouldn't be worried about bumping into each other."

Gene genies

If the fate of academic geneticists is uncertain, so is the fate of many genomics biotechs. Whenever there is this much growth in an industry, consolidation—and shake-outs—is inevitable. SmithKline's Poste says that he has long thought that many biotechs have a "delusion gene" for thinking that they will make it as pharmaceuticals themselves. He suggests that the survivors will be the ones that keep in mind what big pharma needs.

Poste also predicts that many pharmaceuticals, like SmithKline, will end up with a logjam of potential drugs to take into development. Genomics, he points out, amplifies the front end of drug discovery, but the tail end of drug development currently isn't getting a similar push from other breakthrough technologies. "That will create ever greater bottlenecks downstream," he says. "That certainly hasn't hit the industry yet."

The decrease in demand for targets is but one future problem for these biotechs. Another is that they will face increasing competition from in-house pharmaceutical genomics programs, which already are substantial at companies like SmithKline, Glaxo Wellcome, Rhône-Poulenc Rorer, and Merck. Companies such as HGS and Incyte will likely see less of a demand for their EST data as a public EST database put together by Merck and Washington University in St. Louis and, separately, Venter's TIGR puts more ESTs into the public domain. And as the Human Genome Project churns out more and more complete sequences, the utility of EST databases surely will change dramatically, too.

For biotechs that plan to make in-house drug development their mainstay, the biggest challenge they will face is deciding which leads to follow. Says Myriad's Skolnick, "The company that becomes large will be the one that [finds and exploits] a few important genes."

But for all the players involved in genomics, whether their paychecks come from a biotech or a university, the main challenge for years to come will be figuring out the function of genes. "What's really going to be the future is information that comes out of complex systems," says Hood, who thinks the combination of array technologies and comparative genetics with different species packs a powerful one-two punch. "In the '70s, '80, and even the '90s, biologists pretty much studied one gene at a time." In addition, biologists in what Whitehead's Lander has called the "postgenome world" will also have the ability to scan the entire genome for common gene variants, which should make it much simpler to find disease-susceptibility genes.

While it may take several decades before humans know themselves to the degree that the Sequana CD envisions, genomics already is allowing the species to know itself better than it ever has before. Now the question is how deftly can medical science use the information to move from knowing to healing thyself.

–Jon Cohen