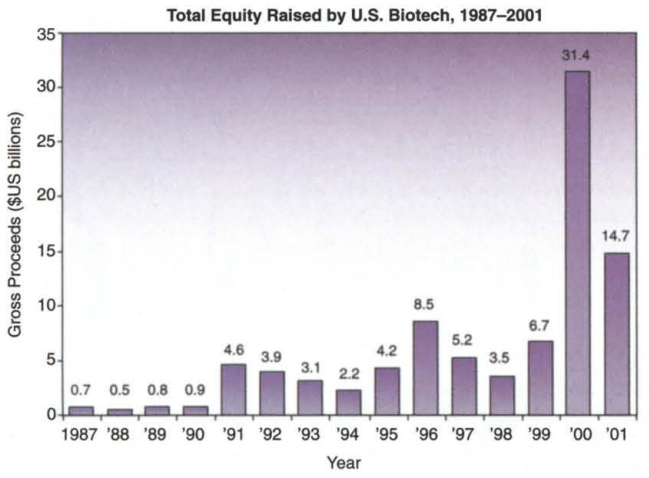
Private investment in genomics boomed in 2000–01; now there's a glut of sequence data and many firms are struggling to deliver drugs

After the Gold Rush: Gene Firms Reinvent Themselves

Genomics companies have a problem today like the one that confronted petroleum-rich nations a few decades ago: too much production. DNA sequencers in both the private and public sectors have pumped out billions of bytes of data. Much remains in private hands, but a lot is pouring into public databases, contributing to a general glut. As a result, pharmaceutical firms and academic labs that once were willing to pay a premium to see new genes now have more than enough in hand, and genomics companies are scrambling to develop fresh products.

In the past, many of these firms could count on outside financing to help support growth. Fad-conscious investors put unprecedented amounts of money into launching biotechs in the mid- to late 1990s. Many were "shoveled through on the word genomics," says one industry analyst. And that led to the largest ever boom in public investment. It peaked in 2000 when biotech companies raised more money in 1 year—over $30 billion—than in the previous 6 years combined, according to *Signals*, an online magazine of bioindustry analysis (see graph). Company founders bought gleaming new technologies to surf the genome: sophisticated computers, gene-hunting software, and exotic mice engineered to lack single genes. But now, says Steven Dickman, a principal at Techno Venture Management—a venture capital company based in Boston, Massachusetts, and Munich, Germany—"the perception is that the market is swimming" in genome-based data.



Expectations. Investors pumped billions of dollars into biotechnology through 2001. Human Genome Sciences, a genomics firm that made *Business Week*'s cover in 1995, now has $1.57 billion in cash and six drugs in clinical trials.

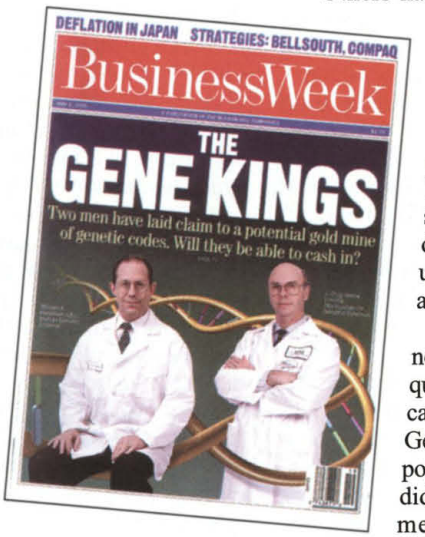
Investors and pharmaceutical companies—the biotechs' biggest customers—want marketable products rather than raw data, and that means drugs. Genomics firms are trying to innovate in many ways to meet that demand. "It's the nature of the beast," says Robert Nussbaum, branch chief of the intramural program at the National Human Genome Research Institute (NHGRI) in Bethesda, Maryland. "Companies have to go where the money is." One strategy is to home in on proteins that are important in disease processes, coming up with targets for new drugs that are not only attractive but "validated" and "druggable," in the current jargon. Another tactic is to go for an overhaul, de-emphasizing basic genetics and shifting resources into focused therapeutics. Yet another—for firms than can afford it—is to buy a company that already has plans to make drugs.

Even as they try these strategies, firms are continuing to recruit basic scientists to help them make sense of the biology. "We are looking for full professors who have spent 30 years trying to understand the biochemistry of a target," says Jay Lichter, executive vice president of business development at SEQUENOM, based in San Diego, California.

That's good news for academics, but there could be a downside, too: As the field moves closer to commercial applications, companies are likely to become more protective of their research data, refusing to share a rich new source of information about human biology.

Renovate or die

Only the nimble can keep their footing in this treacherous marketplace. Already, some early genomics firms have fallen by the wayside. For example, DoubleTwist in Oakland, California, which specialized in selling access to a gene database and bioinformatics tools, went out of business in March after burning through $76 million from investment capital firms and other sources.



Others have been bought out, such as Gemini Genomics, based in Cambridge, U.K., which merged in a stock swap with SEQUENOM in May 2001. SEQUENOM is pinpointing genes that affect human health, drawing on resources such as clinical and genetic data from a wide range of population groups, including twins and disease-affected families.

One major European genomics pioneer—Genset, headquartered in Paris—ran short of cash this year. Founded in 1989, Genset had staked out a leading position in developing drug candidates for nervous system and metabolic disorders. But the company's stock price dropped from a high in the $70s at the height of the biotech craze to about $1 per share in May, and the company could not come up with the money to bring a promising new fat-busting hormone to clinical trials. In July, as Genset closed its research facility in San Diego, the Geneva-based biotech Serono began a cash buyout of Genset stock.

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Even deep-pocketed companies are feeling the pressure. Incyte Genomics in Palo Alto, California, and Celera Genomics in Rockville, Maryland—which started as DNA sequencers—both are now trying to define themselves as experts in target validation and drug development. Celera this year took a $2.8 million charge against operating income and laid off 16% of its workforce as a consequence of restructuring efforts. In addition, Celera last November purchased Axys Pharmaceuticals in South San Francisco—known for its expertise in small-molecule development—and recently declared that the number of employees assigned to "therapeutic programs" has grown from 40 to 327. The revamped Celera has no drugs in clinical trials as yet but has set its sights on drugs for oncology, inflammation, and coagulation.

Genomics underground. Jonathan Rothberg launched the New Haven, Connecticut, firm CuraGen in his basement.

Incyte has also begun moving aggressively in this direction. To lead its drug-development effort, the company last November brought in two former DuPont executives, Paul A. Friedman and Robert Stein, and in March, the company leased space from DuPont in Newark, Delaware, and built a new laboratory with 80 new research and drug-development positions. The company is focusing on cancer and inflammation and hopes to use 14,000 patented full-length DNA sequences to expand to other diseases.

As these ex–genomics firms rush to embrace drug development, they are finding others ahead of them: the ones that wrote drug discovery into their initial mission statements. One of the first to do so was Human Genome Sciences (HGS) in Rockville, Maryland. Founded in 1992, the company began selling target information in 1993. But once it was up and running as a drug-development enterprise, it gradually stopped selling data on the most "druggable" of its gene candidates. In July, the company held $1.57 billion in cash and short-term investments.

Today, HGS is ahead of its peers in the clinical competition, with six drugs in human trials—including the first to be discovered solely through genomics methods—and three others approved for clinical testing. "We have 1060 employees, and half of those are in drug development, not drug discovery," says William Haseltine, chair and chief executive officer, adding, "Those [biotech companies] that rely primarily on genomic data have made a serious error."

Target hunt

Some high-profile young firms are now marketing "target validation," a form of protein research, as a means of bridging genome studies and pharmaceutical development. Take CuraGen, a genomics-based start-up headquartered in New Haven, Connecticut. The company was born, literally, in the basement of molecular geneticist Jonathan Rothberg, who saw the medical promise of genetics while studying fruit fly genetics at Yale in the late 1980s. "There was just no payoff in studying one gene at a time," Rothberg says, so he decided to plumb the whole genome "as a machine," using computers.

After winning $10 million in federal grants, Rothberg courted investors, who bet millions more on CuraGen's target-discovery technology. Its researchers use sophisticated bioinformatics to scan the genome, sort the unknown genes into categories, and then identify those that might have a disease-causing role. To date, the company has come up with 8200 genes that it says represent the "pharmaceutically tractable genome," for which drugs can be made using current technologies validated in cell- and tissue-based assays. The focus is on drugs for common diseases, such as cancer and diabetes.

CuraGen initially raised funds by selling targets and access to the company's technologies. For example, as a start-up, CuraGen made a deal with Genentech in South San Francisco, gaining access to $26 million to use when needed. If Rothberg had accepted all the money up front, Genentech could have taken over. "Instead, I squirreled away that money for a rainy day," Rothberg says. In exchange, Genentech picked up more information about its own targets plus rights to develop some of CuraGen's candidates. Genentech also acquired access to CuraGen's technologies and some CuraGen stock. Some of the "credit," as Rothberg calls it, is still on tap, thanks to CuraGen's parsimonious strategy.

In February 2001, Rothberg negotiated an unprecedented $1.46 billion deal with Bayer of Germany. For the first time in biotech history, CuraGen says, large pharma was splitting both profit and risk on a final product. Bayer bought $85 million in CuraGen stock. Then the companies set up a 5-year plan in which CuraGen agreed to provide Bayer with 80 targets related to obesity and diabetes—each validated to Bayer's liking. If any become drugs, CuraGen will share in development costs and get 44% of eventual profits. "We are not getting cash for targets," says Richard Shimkets, CuraGen's director of drug discovery. "We are getting ownership."

Right now CuraGen is betting on its own drug candidate, a growth factor dubbed CG53135, set to enter clinical trials for patients with ulcerative colitis. CuraGen plans to take the drug all the way to phase III clinical trials and then partner with a large company for marketing and development.

Approaching the challenge of drug discovery from a very different direction is Lexicon Genetics, a self-professed drug-discovery company that uses mouse genetics, headquartered in The Woodlands, Texas. It starts with animals rather than DNA databases and afterward moves to create chemicals that mimic the gene knockouts.

Launched in 1995, Lexicon has created a bank of 200,000 genetically engineered mouse embryonic stem cells that can be used to produce animal models of human disease. The company exploits an original gene-capture technique developed by co-founder and CEO Arthur Sands. The process inserts a nucleotide "cassette" randomly throughout the mouse genome to disrupt and deactivate gene-coding sequences. Company researchers industrialized the process with robots and created a hoard of potential embryos, representing defects in 35,000 genes, or an estimated 54% of the mouse genome.

Company	Stock close August 2000	Stock close August 2002	% change
Celera Genomics	108	9.45	–91%
CuraGen	41	5.81	–86%
Genset	27	3.1	–89%
Human Genome Sciences Inc.	156.31	15.06	–90%
Hyseq Pharmaceuticals Inc.	39.81	1.99	–95%
Incyte Genomics Inc.	79.75	6.12	–92%
Lexicon Genetics Inc.	30.63	5.22	–83%
Millennium Pharmaceuticals Inc.	130	12.26	–91%
Myriad Pharmaceuticals Inc.	134.88	17.17	–87%
SEQUENOM	28.75	2.43	–92%

CREDIT: (TOP) CURAGEN; (BOTTOM) SOURCE: CHARLES SCHWAB & CO.

The beauty of it, says Sands, is that each project can begin with its own animal model: the Lexicon knockout mouse. This strategy might help partners achieve big savings in preclinical drug research, he argues.

Lexicon, meanwhile, has built a drug-discovery infrastructure of its own. Using bioinformatics, researchers have picked out 5000 druggable genes to explore. Knockouts corresponding to each target are being grown and checked out in a mouse "hospital" where workups determine what ails each one.

Sands says that many drugs now fail before they get to clinical trials partly because "large pharmaceutical companies tend to place the in vivo aspects of drug discovery later in the process." Lexicon aims to reduce the risk by getting high-quality animal data early on: "We're now developing knowledge of the target function first and then pursuing compounds that hit those targets." But at the moment, Lexicon is struggling to make the strategy pay off. Even though the company raised $220 million in an initial public offering in April 2000 and $31.8 million privately, the company's stock is trading at $5.19 per share—down from a high of $49.25 in September 2000.

Data to share. Stephen Burley aims to have Structural GenomiX put many protein coordinates in a public repository.

Shortcut to the clinic

For those with enough cash, the quickest way to get a drugmaker is to buy one, as several genome research companies have done. For example, this is what happened at Structural GenomiX (SGX) near San Diego, California. It was launched 3 years ago by a group of crystallographers who wanted to create a proprietary database of protein structures. Using sophisticated software and x-ray crystallography, the company intended to determine the molecular structures of promising targets and sell the information.

But as market forces shifted, executives realized that it might not be possible to make a living just by selling data. A year and a half ago, SGX purchased a company called Prospect Genomics that uses computers to design drug candidates. The upgraded SGX aims not only to analyze target structures en masse but also to design drugs that fit those targets, cocrystallize the drug and its target, and analyze the shape of the final complex. SGX's chief scientific officer, Stephen Burley, says his team screens for other structures related to the target to identify potential side effects. The goal is to knock out toxicity problems before clinical trials.

Even with its upgrade, SGX had to scale back, retreating from a goal of characterizing 30,000 to 50,000 gene products to three areas: bacterial proteins, nuclear hormone receptors, and protein kinases. These are a better bet for drugs.

Millennium Pharmaceuticals, based in Cambridge, Massachusetts, also began by seeking to exploit genomics information for drug discovery but recently has focused on acquiring products. From 1996 to July 2000, Millennium sold seven of its genomics targets to Wyeth-Ayerst Laboratories for drug development. But in that same month, Millennium also acquired Cambridge Discovery Chemistry, based in Cambridge, U.K., a company that specializes in the chemical synthesis of small molecules. Since then, it has bought other drugmakers, including Xenova in Slough, U.K., in December 2001.

So far, Millennium has set out to test seven drugs in clinical trials, one derived from its gene databases. That might have buoyed investors. But Wall Street isn't so easily wooed these days. Millennium's stock chart looks like a downward-charging roller coaster. From a high of $146 in September 2000, its stock price has plummeted to a low of $11.54 in September 2002. But Millennium is not alone.

Also experiencing the Wall Street chill is Salt Lake City's Myriad Genetics. With diagnostic gene tests on the market for breast, prostate, and colon cancers, Myriad now emphasizes drug development. Recently, company executives announced losses attributed to the high cost of developing certain drug candidates, including a potential Alzheimer's medication, not derived from genomics databases. It is the only Myriad compound now being tested in people.

Stock price volatility doesn't necessarily spell doom for genomics-based companies; far from it. Today, at least eight therapeutics developed from genomics targets are in clinical trials, and biotech executives promise that hundreds more are on the way. Still, results might be years off—an eon in the financial world. "There is going to be financial drought for the next 2 years," says Rothberg, "but we're financially ready to go through this desert."

Narrowing vision?

The trek could be harsh, and biotech executives are trying to focus ever more intently on commercial objectives. This narrowing concerns some researchers, such as Andrej Sali of Rockefeller University in New York City, one of the co-founders of SGX. The molecular physicist says that the shortsighted view of investors is likely to stifle the power of genomics. The pressure to deliver high stock market values is creating a "regression to the mean," he says: "Genomics companies all are trying to be like mini-Mercks and -Pfizers." Sali believes they will lose their uniqueness and competitive edge. What's more, Sali fears that genomics information might be sequestered from academia.

But others do not see information hoarding as a long-term problem. Pointing to Celera's promise to release human genome data eventually, endocrinologist Kenneth Gabbay of Baylor College of Medicine in Houston, Texas, says, "ultimately, these things will all see the light of day."

Burley also tries to assuage academics. Some knowledge emerges when a drug reaches the market; patentable information will likely come out upon patent approval; and information that has little commercial value might be posted immediately on a database or published. SGX is posting the coordinates of many of its structures into public protein databases operated by Rutgers University. "I have a strong commitment to SGX making some of its noncompetitive information public," says Burley, who chairs the scientific advisory board for the university's Protein Data Bank.

NHGRI's Nussbaum says government funders are looking at the future of genomics and how it should be steered to benefit biology. He is organizing a conference to be held 7 to 9 October near Washington, D.C., to discuss how the research community might harvest the low-hanging genomics fruit. One role for scientists in academia, Nussbaum says, is to go after more risky, "off-the-wall" ideas and technologies. As a rule, researchers are freer to explore novel genes "simply for the sake of understanding them"—which can lead to unexpected findings. "It's not a question of whether biotech will interact with academia," Gabbay says. "They have to. And they do."

There will be many opportunities for partnership, says Nussbaum. Shimkets of CuraGen agrees: "People got confused about genomics because of the stock market and the hype," he says. "I thinks genomics will be successful but not in the ridiculous time frame that impatient investors had thought."

–TRISHA GURA

Trisha Gura is a Knight Science Journalism Fellow at MIT.

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