Biotechnology on the Auction Block

In a difficult financial climate, more small biotech firms may be acquired by the big boys. Are takeovers good or bad for scientists who work in biotechnology companies?

THE ANNOUNCEMENT earlier this month that Swiss pharmaceutical giant Hoffmann–La Roche had made a deal to buy 60% of Genentech sent a shock wave through the ranks of scientists at the San Francisco company. For 14 years Genentech had been a role model among biotech firms: fiercely independent and nurturing a creative atmosphere in which cutting-edge science could be applied to commercial problems. Now, with a few strokes of a pen, that independence was gone. Genentech had become one more appendage of a multinational mammoth.

What will the consequences be for the scientists who work at Genentech? Will there be more pressure to steer research in commercially profitable directions? Will the atmosphere of creative energy and risk-taking that attracted the best and the brightest disappear? Answers to these questions have implications that go far beyond Genentech. At least half a dozen start-ups in the same independent mold have already been gobbled up, heightening the career concerns of entrepreneurial-minded researchers. And many analysts of the industry predict that in the current, difficult financial climate an increasing number of biotech firms will face the choice of being acquired or folding their tents.

Perhaps the best way to get a sense of what might happen at Genentech is to look at what has happened at some other biotech companies that have gone on the block in recent years. Insiders' views of what has happened at Oncogen in Seattle, DNAX Research Institute in Palo Alto, and Hybritech in San Diego suggest that the results can vary greatly, depending on the circumstances of the biotech firm and the style of the acquisitor. In some cases, it would seem, the transition is pretty rocky: the entrepreneurial climate evaporates, lines of research are trimmed, and once loyal employees take to their heels. In other cases the move may actually be healthy for research, as an infusion of cash liberates the biotech firm from the need to make a quick buck and actually turns scientific work in more basic directions.

Consider one of the rockiest cases: Eli Lilly & Company's 1986 acquistion of Hybritech. The San Diego company was founded on the basis of monoclonal antibody technology in 1978; the transition from independent firm to subsidiary was painful. Part of the reason may be that the company was relatively old (by the standards of the biotech industry) when it was acquired and, also somewhat unusual among biotech start-ups, it had already become fairly diversified. Furthermore, it was not doing well. All of these things may have convinced management at Lilly that a firm hand was needed.

And that's just what the company got: To bring the company's expenses in line and make it profitable, Lilly trimmed fat, discontinued some lines of research, and reassigned employees to new projects. "Lilly took a company that was just breaking even, and they made it into a business," says Howard Birndorf who is widely experienced in the world of San Diego biotech. (Birndorf, one of Hybritech's founders, has been involved in a total of five San Diego biotechnology start-ups and is currently president of a young biotech company called Ligand Pharmaceuticals.)

Birndorf acknowledges Lilly's methods didn't necessarily make for harmonious labor relations. Although Lilly stuck to a no-layoff policy, scores of Hybritech people quit, many blaming "culture shock" or a loss of the entrepreneurial independence for which the company was founded.

Not surprisingly, many of those who left Hybritech were willing to talk about the experience only on the condition that their names not be used. One of them, an employee who sought out the entrepreneurial environment again (this time at a fledgling San Diego biotech company) said: "People had difficulty with the change in philosophy. There was a distinct change in how structured the environment was."

One incident that particularly stuck in the craw of Hybritech's young scientist-managers was an effort to re-educate them to Lilly's way of doing things. It smacked a bit of being sent to the woodshed: "It was kind of like a teenager being brought to task by dad. Some of us were sent to Lilly management school, to teach us manners. It was obvious—we *were* kids. But some of the reasons Hybritech got where it was was because we were kids. Kids are great at enthusiasm, but they're not always so great at execution."

But it's possible to see that same experience in a different way. Gary David, a research scientist at Hybritech who was the company's third employee and continues to work there, says Lilly was just what Hybritech needed. "In the early stages of a biotech company, it's a research and development organization. . . . Eventually you get to a point where you're beginning to address a market. But the type of people who are experienced in R&D aren't necessarily the same type of people who are best to put together and run a mature manufacturing entity."

Some Biotech Takeovers

Company	Founded	Acquired by	Date	Price	Employees	PhDs + MDs
DNAX	1980	Schering-Plough Corp.	1982	$29 M	150	77
Hybritech	1978	Eli Lilly & Company	1986	$375 M	800	(unavail.)
Oncogen	1983	Bristol-Meyers Company	1986	(unavail.)	209	63
Genentech	1976	Roche Holding Ltd. (60%)	1990	$2.1 B	1770	296
GenProbe	1983	Chugai Pharmaceuticals	1989	$110 M	166	24

Compared to the Hybritech tales, the post-takeover environments at Oncogen and at DNAX seem to have been quite different. Initially, there appear to have been the same fears among the scientists at those companies: apprehension over the loss of the risk-taking, entrepreneurial spirit that was often what drew young scientists to such ventures in the first place. But other themes come up as well, and these are more hopeful.

Few scientists seem to have left either of the two firms. And one reason is that at those companies acquisition seems—almost paradoxically—to have brought a lessening of commercial pressures. Whereas while they were independent, the small firms had

to think in terms of short-range profit, after they were acquired they appear to have gained the freedom to consider more fundamental scientific questions.

Perhaps the most startling case is that of DNAX—because its scientist founders were actually pushed toward more basic research by the new owners of the company. DNAX was started up in 1980 by three Stanford professors, who intended to carry out research in immunology. To develop products that came out of the work, the three founders planned to seek joint ventures with large pharmaceutical companies. The initial strategy—to focus on engineered antibodies—was just getting off the ground (DNAX was barely a year old, with a dozen Ph.D. scientists) when a purchase offer came from Schering-Plough.

"Schering's main interest was cytokines and immune regulation," says Kevin Moore, one of DNAX's original scientists. "That sat quite well with most of the staff, because they viewed it as a much more front-running and interesting area"—closer, that is, to the cutting edge of basic research.

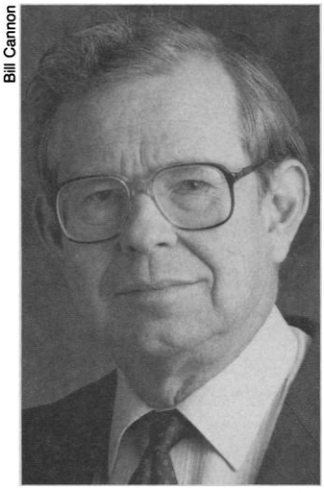
Stanford biologist Charles Yanofsky, a DNAX founder, says the Schering offer was a relief from the constraints of the marketplace. "It took off some of the pressure to develop a product quickly to survive. Schering was willing to be long range in its investment with DNAX."

That long-range attitude has brought with it considerable scientific freedom, Moore says. Indeed, although academic scientists often seem skeptical of the research atmosphere at commercial concerns, Moore argues that in some sense he and his colleagues at DNAX now have more freedom than academic workers do.

"Whenever the issue of academic freedom is mentioned in a self-righteous manner, I've always said, 'Look, you guys only have freedom to do what you can get money to work on. We essentially can work on what we choose, in a much freer way than you can.' The areas we choose to work on are chosen by DNAX. Schering never says no."

Part of that freedom, Moore says, is the ability to change research directions in midstream without going through the laborious process of getting new grant money. For example, Moore says, several years ago he began a research project aimed at studying the receptors on T cells that bind to antibodies. The research was basic, rather than applied: "It wasn't really yet clear what the product was going to be," Moore recalls. Nevertheless, Schering was supportive.

But research doesn't always turn out as planned. In the midst of the T cell work, the lab made an interesting discovery about an immune-system growth factor. Moore was eager to pursue that new—and entirely different—research direction. So he simply put the receptor work on the shelf. "We had that degree of freedom you wouldn't necessarily have if you were operating on a 3- or 5-year grant to study [the receptor]," Moore says.



Bill Cannon

Mixed bag. *Karl Erik Hellstrom of Oncogen describes advantages and drawbacks of acquisition.*

DNAX's director of molecular biology, Frank Lee, says that Schering has made a strong effort to preserve the productive scientific atmosphere there. DNAX scientists are free to publish and present their work at meetings—once the company's patent attorney has made sure no patents need to be filed. But there are no delays involved in that decision, according to Lee, because the company has an in-house patent attorney who attends all research meetings and is aware from an early stage of any work that is likely to lead to a potential patent.

As a result of such efforts, Lee says, a climate has been created in which the DNAX scientific staff have remained happy. Only two have left, he notes, and in each case the lure was chairmanship of an academic department in the scientist's home country (Canada and Japan, respectively).

At Oncogen, acquisition seems to have brought greater freedom to do basic research—but not without costs. In 1986 the young Seattle-based company specializing in cancer diagnostics and therapeutics was purchased with its sister company, Genetic Systems, by Bristol-Myers. One of the scientists at Oncogen when it was acquired was Karl Erik Hellstrom, who left Seattle's Fred Hutchinson Cancer Research Center to join the biotech firm in 1983.

Hellstrom's work focuses on antitumor antibodies. He makes clear that, on the whole, Bristol-Myers has been a benevolent owner. "Very few things have changed and by far most have changed for the better." Specifically, he says, there is greater security of funding for research—and little direction from above. "We can control our research, and that's wonderful."

Yet Hellstrom acknowledges that there are certain costs in a takeover. One thing that is lost, he concedes, is the level of entrepreneurial excitement, the sense that "we will sink or swim, depending on how good we are."

Another difficulty, Hellstrom says, is the fact that products based on Oncogen research must wait with other Bristol-Myers products for development and clinical trials: "In a way, one has to wait in line. For example, Bristol-Myers Squibb gives a lot of resources [now] to work on the anti-AIDS drug, ddI. That means a lot of resources go to that. If one wants to have an antibody as quickly as possible, we feel that it takes a longer time. . . . When we were in an academic setting, we more or less could make an antibody on the lab bench and inject it into patients next week. It was simpler, because an academic situation doesn't have to live up to the guidelines that a big company has."

George Todaro, Oncogen's president, who left the National Institutes of Health in 1983 to found the company, feels the tradeoff is worth it. "There is no question that there is a frustration on the part of scientists about the lengthy process of getting drugs approved. I tell them it would go even slower if we were doing it entirely by ourselves. . . . [That frustration] reflects, in part, naivete on the part of scientists about how difficult it is to get a new drug approved."

In general, Todaro thinks, acquisition has helped rather than harmed Oncogen. Indeed, he notes that in some ways Oncogen has influenced the people from Bristol-Myers rather than the other way around. "The atmosphere here is a rather relaxed, West Coast, younger atmosphere." When the management types from Bristol-Myers first arrived on the scene in Seattle, he says, they were known to the Oncogen scientists as "the suits." But today the "suits" have been converted, he adds. Asked if they wear tennis shoes, a symbol of the biotech youth culture made famous at Genentech, he replied: "It's open-toed sandals."

MIT Nominee Withdraws

As this issue of *Science* went to press, the Massachusetts Institute of Technology announced that Phillip A. Sharp has withdrawn as a candidate to be president of the university in order to continue his research and teaching (see p. 912).

In fact, Todaro says, the relationship with Bristol-Myers is so relaxed that the parent company doesn't necessarily have to know about every detail of Oncogen's research. "We're doing stuff on Alzheimer's disease," he said, adding "I don't know if they [Bristol] know about it. I don't even ask them. If it pans out, I will tell them. If it doesn't, a few people will have spent a year or two doing something that may lead nowhere. We've got an idea, we'll try it."

What lessons can be drawn from all of this for Genentech—and other companies that may be taken over in the future? The first is that takeovers aren't all bad. There is clearly an added dimension of security that may, in some instances, be quite good for research—even turning it toward more basic questions than it was possible to consider when the firm was independent.

Beyond that the picture is cloudy. Clearly, the emotional atmosphere that prevails after a takeover will depend heavily on the management style of the new owners and on the financial health of the subsidiary. But whether the post-takeover atmosphere is rosy or gloomy, in all these cases there does seem to be at least one common thread—a loss of the risky, entrepreneurial elation that drove the initial undertaking.

Indeed, there are those who fear that that process is already under way at Genentech. And they aren't all outsiders. One is David Martin, who, until he resigned from Genentech last November, was the longtime vice president of research and a person many feel was responsible for much of the risk-imbued creative atmosphere at Genentech.

Now a consultant to the firm, Martin says: "My concern . . . is that the people who have been responsible for the quality of science are going to feel this is no longer risky enough, no longer a challenge, and are going to leave anyway. Genentech has a group of remarkably talented risk-seekers. . . . The more risky something is, the more the adrenaline flows, and the more effective they are."

And yet Martin may be lamenting something that would inevitably have passed. After all, institutions grow up and the spirit appropriate to adolescence is no longer appropriate in middle age.

As a former Genentech employee put it: "A company ages like a person. It gets more mature—bigger, older, fatter. You can accept it or not. When you accept it, you can age gracefully. Genentech fought it. It was sort of like a frat house where people never graduate, or like a guy who reaches 50 and wears gold chains and his shirt half unbuttoned—it's grotesque. They should have said, listen, things will just be different as we get older." ■ MARCIA BARINAGA

NIH Goes "Extra Mile" on Gallo

In an unprecedented move, the National Institutes of Health has turned to the National Academy of Sciences and the Institute of Medicine for help in conducting an internal review of recurrent allegations against AIDS scientist Robert C. Gallo. *Science* has learned that NIH has asked the two organizations to nominate a slate of scientists who have no connection to the AIDS controversy or to Gallo to oversee the institute's own review of events leading to the discovery of the AIDS virus.

For most of his 30-year career as one of the National Cancer Institute's stars, Gallo has been a lightning rod for controversy, never more so than during the past 6 years when he has been the target of relentless accusations, often couched in innuendo, that he stole the AIDS virus from a French group headed by Luc Montagnier.

The most recent salvo came in December when Representative John Dingell (D–MI), provoked by a 50,000-word article on Gallo in the *Chicago Tribune*, wrote NIH a letter that could not be ignored (*Science*, 5 January, p. 19). The NIH, Dingell said, has not done a good job of investigating allegations against its scientists in the past. What, if anything, he demanded to know, was NIH planning to do in light of the *Tribune* article by reporter John Crewdson.

Former NIH director James B. Wyngaarden, now a deputy director of the White House science office, is among those who urged NIH officials to turn to outside observers in the hope that their oversight will preclude accusations that NIH is not entirely objective in its review.

For his part, Gallo supports the decision to name outside advisers. "I welcome this," he told *Science*. "These allegations have been going on too long. I have done nothing wrong and I have no apprehension or anxiety about the review. And, I'm confident that the only chance I have is the help of independent colleagues." Gallo's notebooks, correspondence, and other records have been in the hands of both NIH and French lawyers ever since the dispute about credit erupted in 1984. "There's nothing that hasn't been looked at over and over," says Gallo.

The NIH's top officials initially dismissed the Crewdson article as a rehash of a controversy that they think was settled by an agreement between the United States and France dividing the credit for discovering the AIDS virus between Gallo and Montagnier. But Dingell's letter, and the implicit threat of congressional hearings, drove NIH to launch an official review nonetheless, to be conducted under the institutes' Office of Scientific Integrity and coordinated within the National Cancer Institute by Richard Adamson. That review has now begun and Adamson is said to be going over the Crewdson article line by line. (Adamson will not talk with the press, or with NIH colleagues, about the investigation until it is complete.)

Now, NIH leaders have concluded that a strictly internal inquiry will not be sufficient to satisfy either Dingell or the scientific community that this time all the facts are in and no notebook page has been left unexamined. Acting NIH director William Raub, along with Joseph E. Rall, director of intramural science, have asked Frank Press, president of the National Academy of Sciences, and Samuel O. Thier, president of the NAS's Institute of Medicine, to nominate a slate of qualified observers to verify the independence and thoroughness of the NIH's own investigation. According to the current scenario, a jury of peers would then be selected from the NAS-IOM panel by James O. Mason, the assistant secretary for health. "We decided to go the 'extra mile' for the NIH's sake and for Dr. Gallo's," Raub told *Science*.

Press and Thier have agreed to propose such a panel with the stipulation that Mason confine his selection to that list and agree not to add anyone recommended by the government, which can be said to have a stake in the outcome because it is a signatory to the U.S.–French agreement.

Press and Thier, in consultation with their executive committees, are in the process of identifying individuals who are scientifically qualified to review the case, unconnected to Gallo, and willing to agree in advance to take the time necessary to do the job. If Mason accepts the NAS-IOM terms, a panel of potential jurors could be lined up within a couple of weeks.

Even so, Raub estimates that it will be a matter of months before the review is complete. "We'll be asking their advice on both the strategy of our review and the substance of the conclusions. We'll need some running room to do a thorough job."

■ BARBARA J. CULLITON