BIO/TECHNOLOGY

JULY 1985 NATURE PUBLISHING VOLUME 3 NUMBER 7

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AND THEN THERE WERE TWO

by Arthur Klausner

Even as recently as a year ago, people spoke of the "Big Four" biotechnology companies—Genentech, Cetus, Biogen, and Genex. (Genetics Institute always seems to get slighted because it remains privately held.) Financial and scientific times have changed: The "Big Four" have dwindled to the "Big Three" or even the "Big Two." In the eyes of some analysts, Genentech and Cetus have risen above the rest.

Genentech is often thought of as the Cadillac of the biotech field, Cetus viewed as a Chevrolet. The burgundy Jaguar usually parked in front of Cetus headquarters—a car owned by Cetus president Robert A. Fildes and sporting "CETUS-1" plates—illustrates what Fildes thinks of Cadillacs. As for being an also-ran: Cetus is, in fact, the elder of the Big Two, founded in 1971, some five years before Genentech. True, Genentech's stock made Wall Street history in the fall of 1980 when its price rose from $35 to $80 per share on the day of its initial public offering. But few observers remember that when Cetus first tested the public waters just five months later, the firm raised more than three times as much money as Genentech ($120 million as compared to $38.5 million).

Cetus and Genentech have taken somewhat different scientific and business routes to position themselves atop the biotechnology field. Their similarities and contrasts both warrant examination by people trying to figure out how to make good in biotechnology.

Background

Genentech employs just over 700 people and occupies 350,000 square feet in four buildings in a South San Francisco, CA, industrial park. The view of San Francisco Bay is spectacular; the grounds, though small, are neatly kept. It is convenient to San Francisco International Airport and the university strongholds of Berkeley and Stanford. A small residential community calls South San Francisco home, but most of Genentech's staff resides some distance away. Says one employee, "When you live in the Bay Area, commuting is just a way of life."

Genentech's 74,000-square-foot manufacturing facility is the largest multi-product rDNA plant in the world. (Eli Lilly's Humulin® production plant is larger but is totally devoted to making the recombinant human insulin that Genentech pioneered.) Visitors are not allowed inside the plant; rather they peer into the huge room that has the 10-liter fermentors near the window and the more interesting equipment toward the rear. The company says the plant contains multiple 1,000-liter fermentors and at least one 10,000-liter bioreactor. Genentech will not disclose what it makes in the large fermentor. What it will say is that it has the capacity to satisfy the world's needs of human growth hormone and tissue-type plasminogen activator, two of the firm's most promising products. Genentech shipped some 250,000 vials of product for clinical trials last year. If the current pace keeps up, the company will top 350,000 vials this year.

Cetus's headquarters are on the other side of the San Francisco Bay, in Emeryville, CA. The company's California operations had been spread out with labs in Berkeley, Palo Alto, and two places in Emeryville. Now it has consolidated in one Emeryville cluster, though it has kept the Palo Alto diagnostic laboratories. Emeryville is older than South San Francisco and has more of a city flavor. "Emeryville is not beautiful," summarizes one of over 600 employees, "but it's practical."

All of Cetus's Emeryville buildings were converted from other uses, except for the pilot plant/manufacturing facility. According to Behzad Khosrovi, senior director of product and process development, "The key thing that separates us from even the best there are is that we are able to transfer the technology from bench to production extremely smoothly." The company is proud that only 11 months elapsed between initial

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Mammalian cells genetically engineered to express a herpes simplex virus envelope protein. The gene product is visualized by immunofluorescence after labeling with human anti-herpes simplex virus antibodies.

expression of interleukin-2 and approval for clinical trials. Now, the company reports, it could probably supply the world's needs of IL-2.

The Business Plans

Genentech's focus and direction have changed little since its inception. When venture capitalist Robert A. Swanson founded the company along with Herbert W. Boyer of the University of California (San Francisco), he dreamed of a $1 billion pharmaceutical house. That vision still drives the company. When Genentech brought in G. Kirk Raab as president and chief executive officer, it got his experience as CEO of Abbott Laboratories (North Chicago, IL).

Cetus's history has been a little rockier. "Five years ago we were much more broadly focused, as compared to having broad capabilities," reports Jeffrey S. Price, Cetus's director of R&D. In 1982 the company cut back on its scientific staff in an effort to consolidate R&D. Fildes, who had previously been president of Biogen (Cambridge, MA) and had also worked for Glaxo and Bristol-Myers, stepped in as president at the beginning of 1983. Described by one staff member as "our own Winston Churchill," London-born Fildes eliminated self-funding of industrial projects and focused the company on cancer and viral infections. Cetus reports that three-quarters of its funds are devoted to health care, with most of this directed toward cancer.

"Fildes went over to Cetus and tried to make it what he wanted Biogen to be," says Steven Zimmer, an analyst for F. Eberstadt (New York, NY). "Certainly Cetus has come a long way from where it was three years ago, in great part due to the direction of Bob Fildes."

Have Cetus and Genentech assembled the necessary executive staffs to guide them through the treacherous process of developing new therapeutics? "I think they both have solid upper management," says Peter F. Drake, biomedical technology analyst at Kidder, Peabody & Co. (New York, NY). "I think the area that both companies have that is still unknown is real marketing and market research capacity."

Both firms realize that there is a dichotomy between their business and scientific personnel. Company dress codes, for example, vary greatly with position: lab workers are the most casual, but even upper management doesn't always wear business suits. Raab says that following his stint at Abbott, he was somewhat hesitant the first time he ventured into the office without a tie. (He compromised on a turtleneck.)

At Genentech laboratories and offices are purposely kept close together to promote interaction. Every Friday afternoon, a different department sponsors company-wide get-togethers called "Ho-Hos"—a Silicon Valley social ritual. Turnout varies based on menu (baked potatoes and toppings was a big winner), but employees really do show up. And a technician or secretary might very well find himself or herself talking to Raab or Swanson while waiting on line for a beer refill. To celebrate Genentech's ninth anniversary this year, Raab and Swanson dressed up like the Blues Brothers and performed "I'm a Soul Man," among other songs. The "Bob and Raab Show" is a hit at Genentech.

Cetus sponsors yearly scientific and business retreats to hash out corporate direction. The conclaves also give managers a time to get to know each other better and to quibble over wine (only Californian, of course).

Information drives markets, and well-managed public relations have been an integral part of Genentech's business strategy since the company's formation—if the average investor-on-the-street has heard of only one biotech company, it will be Genentech. "Stocks are *sold*; they are not *bought*," points out one stockbroker, and Genentech has sold its stock better than anyone in the field. Now, however, it can afford to be choosy—reporters and financial analysts will

generally find their questions answered by the public relations staff rather than management. Cetus, perhaps in a position to have to try harder, makes its executives more freely available for interviews. This policy, however, has prompted at least one observer to wonder whether such availability might not detract from their other duties.

The Projects

Genentech and Cetus both stress human health care. (See their respective product portfolios below.) "Each company is concentrating on products that treat serious, end-stage diseases and are administered by physicians in the hospital environment," summarizes James E. Rurka, vice president for marketing and commercial development at Cetus. The two firms, however, have surprisingly little overlap in the specific projects they have chosen to emphasize. "I think that if both companies could simultaneously make a choice, they would not want to work on the same targets," says Cetus's Price. "The only thing that would drive us to be working on the same things would be if it emerged over the next three to five years that there was only a limited spectrum of potential therapeutic products." And he doesn't think this likely.

On the interferon front, Genentech has licensed its alpha and beta varieties to Hoffmann-La Roche (Nutley, NJ), and is developing gamma itself. Roche has emphasized the alpha variety, but has done little with beta. Cetus, however, has focused on beta interferon through its agreement with Triton Biosciences (Alameda, CA), a subsidiary of Shell Oil. Alpha and beta interferon eventually may compete with each other: their activities seem to overlap as much as 80 percent. Roche-Genentech has been sponsoring clinical trials on alpha interferon for more than a year longer than has Triton-Cetus for beta, but Cetus says those trials are no

GENENTECH (PUBLIC) PRODUCT PORTFOLIO

	PRODUCT	STATUS	PARTNER(S)	COMMENTS
THERAPEUTICS	Human Insulin (Humulin®)	Market	Eli Lilly	First genetically engineered therapeutic; on the market since 1982
	Human Growth Hormone (Protropin®)	Pending FDA approval	GCP, Kabi Vitrum	For treatment of hypopituitary dwarfism; other indications possible
	Alpha Interferon (Roferon®)	Pending FDA approval	Hoffmann-La Roche	Roche also has rights to Genentech's beta interferon
	Gamma Interferon	Phase II clinicals	GCP, Boehringer Ingelheim, Toray, Daiichi-Seiyaku	Treatment of cancer, viral, and parasitic diseases
	Tissue-Type Plasminogen Activator	Phase II clinicals	GCP II, Boehringer Ingelheim, Mitsubishi Chemical, Kyowa Hakko	First indication being tested with this clot dissolver is myocardial infarction
	Tumor Necrosis Factors	Preclinicals	GCP III, Boehringer Ingelheim, Fujisawa Pharmaceutical	One of Genentech's high-priority projects
	Factor VIII	Development	Speywood Labs, Cutter Labs	The largest protein ever cloned
	Human Serum Albumin	Development	Mitsubishi Chemical	Not a high-priority project
	Herpes I and II Vaccine	Animal studies	None	Subunit vaccine
	Hepatitis B Vaccine	Development	None	Has cloned and expressed hepatitis B surface antigen protein
DIAGNOSTICS	HTLV-III Virus Diagnostic Kit	Development	Travenol Laboratories	Development through Travenol-Genentech Diagnostics joint venture; also working on cancer diagnostics
INSTRUMENTS	TiterCalc™	Market	Hewlett Packard	Automated microtitration instrument developed by HP Genenchem joint venture
AGRICULTURE	Bovine Interferon (Interceptor®)	Animal trials	None	Protection against bovine shipping fever; had been funded by Granada R&D Ventures
	Bovine and Porcine Growth Hormones	Animal trials	Monsanto	Studies have shown that bovine growth hormone improves milk production efficiency 10–15%
	Foot-and-Mouth Disease Vaccine	Animal trials	Bayer	Subunit vaccine under development at Plum Island
INDUSTRIAL	Flavor Age® Enzyme	Large-scale commercial trials	A. E. Staley and Corning Glass Works	Enzyme blend for use in cheese processing; being developed by Genencor joint venture

Note: GCP = Genentech Clinical Partners

longer a full year ahead of their own. Scott R. King, an analyst for Montgomery Securities (San Francisco, CA), echoes Genentech's view when he says that gamma seems so far like the most promising interferon. Cetus, not unexpectedly, is most enthusiastic over the early clinical results of beta.

The one product the two companies have in common is tumor necrosis factor. Both have recently cloned and expressed TNF, an agent that seems to kill some tumor cells by disrupting their cell membranes. Both firms maintain that progress on TNF, while a high priority, should not be taken as indicative of the companies' relative strengths. "We will do our damnedest to be in the clinic first," says Genentech's vice president of research, David W. Martin. "But it will be our 'damnedest' without neglecting our other projects."

Raab adds that Genentech's development and marketing agreements for TNF with West Germany's Boehringer Ingelheim International GmbH and Japan's Fujisawa Pharmaceutical should give it an edge. "I don't have any doubt that we're ahead of Cetus," he says.

Like all anticancer therapeutics, most of Cetus's are drugs in search of diseases. Cetus estimates that the U.S. market for cancer therapeutics and diagnostics is $400 million per year

CETUS (PUBLIC) PRODUCT PORTFOLIO

	PRODUCT	STATUS	PARTNER(S)	COMMENTS
THERAPEUTICS	Beta-Interferon (Betaseron™)	Phase II clinicals	Triton Biosciences	Testing on cancer, hepatitis, common cold, genital warts, and others
	Interleukin-2	Phase II clinicals	CHLP	Testing IL-2 mutein on leukemias, lymphomas, solid tumors, and AIDS
	Tumor Necrosis Factor	Preclinical testing	CHLP	Testing of TNF mutein on humans to begin this year
	Colony Stimulating Factor	Basic research	CHLP	Goal is to clone and express CSF this year
	Breast Cancer Immunotoxin	Preclinical testing	CHLP	Monoclonal antibody attached to genetically engineered ricin toxin A-chain
	Monoclonal Antibody Anti-Infectives	Preclinical testing	CHLP	For use against hospital-acquired infections
DIAGNOSTICS	Prostate Cancer Test	Late development	CHLP	Now has permission to market one of its two monoclonal antibody-based tests
	Colon Cancer Test	Development	CHLP	Monoclonal antibody test
	Breast Cancer Imaging	Evaluation and testing	CHLP	Uses radioactively labeled monoclonal antibodies
	Cetus™ CMV IHA Kit	Market	CHLP	Qualitative and quantitative cytomegalovirus serology tests
	Chlamydia/Gonorrhea Tests	Development	CHLP	DNA probe-based diagnostics
	Bacterial Diarrhea Test	Basic research	CHLP	DNA probe test for salmonella
	Sickle Cell Genetic Screening Test	Development	CHLP	DNA probe test; marketing expected to begin this year
	Tissue-Typing Test	Development	CHLP	DNA probe test; marketing expected to begin this year
INSTRUMENTS	Pro/Pette™ System	Market	None	Automated pipetting system; attachments also available
	Pro/Group™	Development	None	Automated pipetting for blood bank uses; expects to begin marketing this year
AGRICULTURE	Genetically Improved Plants	Basic research	W. R. Grace	Awaiting government approval to field test a disease-resistant, engineered tobacco
	Microbial Crop Treatments	Field trials	W. R. Grace	In third year of field testing
	LitterGuard™ Vaccine	Market	Norden Laboratories division of SmithKline	Cetus makes two of the four antigens in this vaccine against porcine scours
	Lymphokines for Shipping Fever	Animal trials	W. R. Grace	Interleukin-2 being tested on cattle
INDUSTRIAL	Food and Food Additives	Basic research	Nabisco Brands	Development through Nabisco/Cetus Food Biotechnology Research Partnership
	Wood Derivatives	Basic research	Weyerhaeuser	Products not expected before 1990

Note: CHLP = Cetus Healthcare Limited Partnership

and that the figure will top $2 billion by 1995. The company has opted for a high-risk, high-return approach. Industry observers agree that interleukins and interferons will eventually be used to fight some cancers and other diseases. But the jury is still out on which—if any—will be the really big winners. Cetus's interleukin-2 (IL-2) and beta interferon are both in phase II clinical trials. The firm is sponsoring preclinicals for recombinant tumor necrosis factor and for human monoclonal antibody-based anti-infectives against hospital-acquired infections.

In March of 1984, Cetus became the first company to receive FDA permission to test IL-2 in patients with cancer and acquired immune deficiency syndrome. It is also testing IL-2 in combination with other cytotoxic and antiviral agents, interferons, and adoptive immunotherapy. Cetus received a U.S. patent on its IL-2 this spring and hopes to put the product on the market by 1988.

If one product line strays from Cetus's focus, it is instruments. Although the Pro/Pette™ automated micropipettor accounted for $2.4 million in sales last year, some analysts believe that Cetus will either have to find a marketing and development partner for further instrumentation, or drop this program. Says Rurka, "At this point it's a major strategic point of discussion as to where to move beyond Pro/Group™ [the automated pipettor for blood bank uses]. The decision is made a little bit easier inasmuch as the instrumentation group is profit-making." Genentech has already made a similar decision: it formed a joint venture with Hewlett-Packard to develop instrumentation.

There is a fine line between "lack of focus" (undesirable) and "diversity" (desirable because it spreads risks), but Genentech's therapeutics program is both less focused and more diverse than Cetus's. Most analysts view this as an advantage: "When you compare the two companies, you see a broader range of possibilities at Genentech," says Zimmer.

In addition to the lymphokines, Genentech's recombinant human insulin—made and marketed by Eli Lilly (Indianapolis, IN)—is the first and only genetically engineered therapeutic on the market. Lilly sold an estimated $25–30 million worth of Humulin last year.

Genentech HGH will be the second genetically engineered therapeutic to win FDA approval for sale in the U.S. At least Genentech has been predicting this for a number of years now. Last September the FDA asked Genentech to provide clinical data on a larger sample of children suffering from hypopituitary dwarfism. The company intends to supply such information this summer.

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The effects of tumor necrosis factor *in vitro*. *Left*: Live, human cervical cancer cells grown in culture. *Right*: After treatment with TNF, the cell walls are disrupted and the cells die.

Although analysts believe that HGH sales will be modest, health problems associated with the pituitary-derived product should help speed acceptance. Genentech has hired a national sales manager and has laid the foundations of its sales force. "We have tried very early on—in fact earlier than some people thought was logical—to think about marketing issues," says James M. Gower, Genentech's vice president of marketing. Gower says he will do little different the day after Protropin® is approved—that is if he can get any work done at all during the huge company celebration that will follow.

Genentech's tissue-type plasminogen activator (t-PA) has been making headlines for several years as a revolutionary blood clot dissolver. Now Genentech has moved into phase II trials with its recombinant agent produced from mammalian cells. More than 500 patients have been treated with the drug, and the company hopes to submit data to the FDA in the first part of next year. (It has stopped predicting dates for FDA approval after its sobering experiences with HGH.) The company is exploring the possiblility of adapting t-PA to automatic injectors developed by Survival Technology (Bethesda, MD). Eventually people with heart conditions might be able to self-inject t-PA.

On the agriculture side, Genentech has licensed its subunit vaccine against foot-and-mouth disease to West Germany's Bayer AG, and its work on animal growth hormones is sponsored by Monsanto (St. Louis, MO). Genentech's bovine interferon has been in field tests for over a year as a possible preventative against shipping fever in cattle. Granada Corp. (Houston, TX) had funded some of this work, but pulled out recently. Martin says Genentech could develop the product itself because there are a manageable number of feedlots where it would be useful. Raab, however, predicts that Genentech will soon find a new partner for bovine interferon.

The Science

Genentech is widely regarded as having the best science in biotechnology. "There's no question about it: they have great science," says Zimmer. "They have a lot of things going for them. The one thing they don't have going for them is humility. And that one day may shoot them in the hip." The caliber of science at Cetus is generally viewed as strong, but not on a par with Genentech. "I see Genentech as a leader," sums up one industry observer. "I see Cetus as more of a follower."

"I think that if you look at the 'firsts,'" says Martin, "Genentech most of the time is first. And if you look at who is second, it is not the same company every time."

One area where Genentech has the edge over Cetus is in its experience using different expression systems.

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COURTESY CETUS

The effects of tumor necrosis factor *in vivo*. *Left*: A mouse with a tumor on its shoulder. *Right*: After treatment with TNF, the tumor cells darken and die.

Cetus has been able to use genetically engineered *Escherichia coli* to produce its beta interferon, IL-2, and TNF. Although it does work with mammalian cell culture, Cetus has never found it necessary to scale up these processes past 10–20 liter explorations. "We don't need it today, and we probably won't need it tomorrow for the products that are already in clinicals," says Cetus's Price.

Genentech uses bacteria to produce its interferons, TNF, and growth hormone. Complications with t-PA, however, led to its manufacture via mammalian cell culture; factor VIII, because of its large size, will probably also have to be made this way. Martin notes that Genentech might opt to go to mammalian production earlier than some of its competitors: "I would not characterize our use of mammalian cells as a last resort."

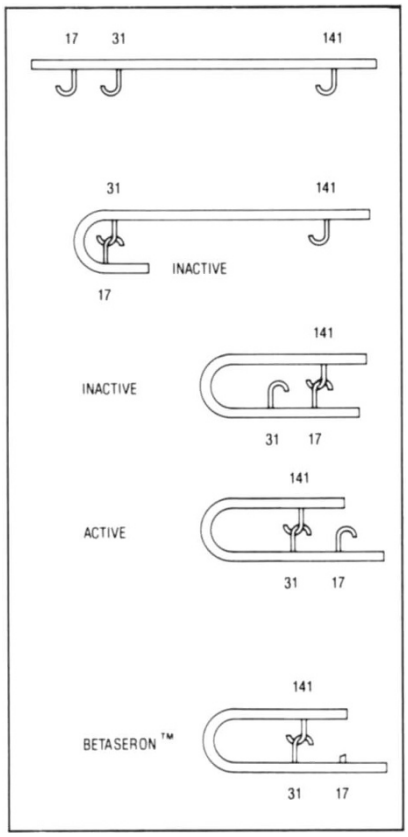
"I think their molecular biology group is still a bit stronger than ours," admits Thomas J. White, Cetus's vice president of research. But he points out that Cetus's production capacity was in place before Genentech's. "We had the capacity to go from start to finish for a product—to put it in a vial for clinicals—long before they did," says Cetus's Price. And he does not believe that any other biotech company can rival the downstream processing capabilities now in place at Cetus and Genentech.

Cetus, through its strong agricultural joint venture with W.R. Grace (New York, NY) certainly has a lead in plant biotechnology. According to Martin, Genentech "has a little bit of plant activity on the inside, but we're not convinced that the time is ripe for us to jump in yet."

Cetus has diagnostic technology well covered too. The company's labs in Palo Alto, CA, specialize in diagnostics, and Cetus already has monoclonal antibody-based tests on the market. DNA probe-based kits should follow this year. According to Fildes, "The general view that I have is that Cetus as a biotechnology company is much broader based than Genentech in terms of its breadth of technical capability."

Martin stresses that Genentech's diagnostics joint venture with Travenol Labs has hybridoma expertise, and that Genentech has a strong in-house hybridoma group making monoclonals for research purposes. "To us," he says, "it's a very important technology, but it's a tool."

A major difference in the approaches of Cetus and Genentech is that Genentech strives to make products that are as close as possible to the natural agents. The FDA might look more favorably on such products, and the natural form could elicit fewer immunogenic reactions in patients—so, at least, the reasoning goes.



COURTESY CETUS

Recombinant beta interferon folds into three configurations, only one of which is active. Cetus researchers substituted a serine for the cysteine amino acid at site 17, thereby eliminating site 17's disulfide bonding capability. The resulting product can form only one bond and is active and stable.

Cetus's strategy is to develop muteins—altered forms of the natural product. These can have improved activity and stability, and give Cetus the opportunity to patent novel protein forms. In the case of beta interferon, Cetus found that three different structures of the product are possible due to cysteine-cysteine disulfide bridges (see illustration). Unfortunately, only one form is biologically active, so the original genetically engineered product had low biological activity. Cetus scientists modified the protein by replacing one cysteine amino acid with serine. This left only two cysteines that could form a bridge—only one configuration became possible, and biological activity increased. The company reports that it engineered a similar cysteine-to-serine shift for its IL-2 mutein. As for TNF, Cetus says its mutein involves a different manipulation, one that provides *added* biological activity rather than just restoring activity. "At this point, without knowing the 3-D structures, improving activity is really a hit-or-miss approach," says David F. Mark, manager of Cetus's lymphokine program. "We are applying this technology to every gene that we clone. It doesn't have to be a therapeutic product."

Analysts are split on the value of mutein technology. "I think it is a worthwhile strategy to follow if you're second in line. If you're not first, you have to use what options are available," says Zimmer. Others point out that modifying agents increases the number of products possible.

The Partners

Both Cetus and Genentech have

realized that they cannot follow all the promising research routes that they turn up. Their strategy to deal with this has been the same: joint ventures. Almost all of Cetus's agricultural projects are now part of its Agracetus joint venture with W.R. Grace. Under the year-old agreement, 51-percent owner Grace is paying Cetus $10 million in installments and has agreed to fund another $50 million in research. Cetus has contributed its Cetus Madison (Middleton, WI) subsidiary. Cetus president Fildes is president of the joint venture, but he may be succeeded by someone from Grace when products—improved crops, crop treatments, and animal health products—near the market.

Cetus also maintains a joint venture with Nabisco Brands (Parsippany, NJ) focusing on applying biotech to food and food processing, and Cetus is exploring making useful products from wood with Weyerhaeuser (Tacoma, WA). It has also worked on vitamin B_{12} with Roussel Uclaf (Paris) and ethanol biosynthesis with National Distillers and Chemical Corp. (New York, NY).

Genentech holds minority interests in three joint ventures. Genencor (equally owned with A.E. Staley and Corning Glass Works) focuses on industrial enzymes; Travenol-Genentech Diagnostics (with Travenol Laboratories) specializes in developing cancer diagnostics and is working on a blood test for acquired immune deficiency syndrome; and HP Genenchem (with Hewlett-Packard) works on instrumentation. "We didn't want to do too many things and not do them well," explains Genentech's treasurer, Shirley L. Clayton.

A major difference between the two companies is that Genentech has lined up marketing and development partners for almost all of its projects, while Cetus is working alone on everything except beta interferon. Genentech will serve the U.S. markets itself whenever possible with a relatively small marketing staff. Licensing out European and Japanese markets serves two purposes: it ensures a cash flow for Genentech and it allows clinical trials to take place all over the world. Genentech also has formed an equally owned joint venture, Genentech Canada, with Boehringer Ingelheim (Canada) Ltd. This collaboration will commercialize Genentech's products in Canada.

Cetus recently announced that it now is looking for Japanese and European partners. Any deals will probably involve joint ventures rather than straight licensing. "There is no lack of opportunity out there," says Fildes. "It's a matter of picking the partner that can best meet your needs. The easiest thing would be to license away your technology. But we're not in a hurry to do that." Cetus hopes that by waiting until its products are into development it will be able to command more lucrative collaborations.

The Financing

Cetus and Genentech excel at raising capital. They have both built huge financial reserves and operate at near break-even levels. Each has reached its state of financial security through somewhat different paths. Genentech raised $38.5 million in its initial public offering and $50 million more through another public offering earlier this year. It also recently sold $40 million in private placement interests to Boehringer Ingelheim. Cetus has used equity financing just once: it raised a whopping $120 million in its initial public offering.

Both firms have made good use of R&D limited partnerships. Genentech's three partnerships (Genentech Clinical Partners, Genentech Clinical Partners II, and Genentech Clinical Partners III) raised $55 million, $34 million, and $33 million, respectively. GCP is funding development of human growth hormone and gamma interferon; GCP II is sponsoring t-PA; and GCP III will fund R&D and clinical trials on TNF.

Again, Cetus opted for one such financing—a large one. Cetus Healthcare Limited Partnership (CHLP) raised $75 million to fund a "market basket" of the company's cancer therapeutic products. To this Cetus is adding $30 million of its own funds. In the risky arena of therapeutics, Cetus's arrangement has the advantage for investors of spreading out risk over a group of potentially successful products. Unfortunately, projects that fall under CHLP end up competing with each other for funding because $105 million is still not enough to develop all of them.

Genentech's one- or two-product RDLPs represent a different strategy: there is no hedging through product diversity. Genentech reports that it reduces risk to investors by using RDLPs to fund only late-stage development of products: the agents must be cloned and expressed, and biological activity of the recombinant form must be demonstrated in culture and animal tests. The strategy almost typifies Genentech's strong belief in itself: If you're sure that you're the best, why do you have to reduce risk to investors by putting more than one or two projects in an RDLP? Although one Wall Street analyst describes Genentech's partnership on the promising—but early-stage—anticancer agent TNF as "a crime" because there is still so much work to be done, the company had little trouble selling the idea to investors.

Genentech stock has done quite well in the past six months, rising from around $29 per share in October 1984 to $45 when it offered 1 million shares to the public last March. "I think the stock began to move when we announced the conclusion of GCP III," says Clayton. "People were impressed with that because it was done when the market was fairly bearish."

"Genentech is the only biotechnology company with a reputation that lets it raise money at will," summarizes Robert Kupor of Cable Howse & Ragan (Seattle, WA). Genentech has been profitable for six straight years and spent $55 million on R&D last year. Its net income for 1984 was $2.7 million on revenues of $69.8 million. Over 90 percent of recent revenues came from contracts. "Our plan," says Clayton, "is to phase out gradually on these contracts and have them replaced by sales." For now, however, partners have committed an estimated $100 million to Genentech for contract research. With more than $100 million in cash, the company can certainly fund a lot of its own R&D, though its policy is to reserve capital for capital expenditures.

Cetus posted profits of $1 million last year, compared to a loss of $4.7 million in 1983. The company spent some $31 million on R&D in 1984 and expects this figure to rise to $38 million this year. "Between the partnership, the Grace transaction, and the cash we have on hand today, we have access to close to $200 million," says treasurer R. Jefferson Works. "We're one of the best financed biotechnology companies." Cetus's policy is to balance R&D expenditures with revenues. It, like Genentech, plans to be around for a long time.

Most analysts agree. "I think that they are both going to make it," says Drake, "in part because they are not going head-to-head on the products side. They are almost competing away from each other."

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