

Lessons from the Past

Some members of the biotech class of 1982-83 reflect on the startup experience

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CELEBRATING
A DECADE OF
EXCELLENCE

Experience is a funny thing—one never has it until after one needs it. Another's experience is a poor substitute, but better than nothing at all. What follows is the result of interviews with scientists who founded or co-founded biotech companies ten years ago—a distillation of hard-earned experience and of what drove these researchers to form companies, conquer obstacles, endure, and—in two cases—leave the companies they had founded to start all over again with new ventures.

Setting the stage

The first wave of biotechnology, the pioneer group, was a handful of companies founded in the seventies and the first years of the eighties—Cetus (Emeryville, CA), Genentech (S. San Francisco, CA), Biogen (Cambridge, MA), Centocor (Malvern, PA), Amgen (Thousand Oaks, CA), Chiron (Emeryville, CA), and others. In 1982 and 1983, as *BioTechnology* was conceived and launched, the second major assemblage of biotechnology companies emerged in the U.S. About 35 of them survive to this day.

The second biotech wave, the class of 1982-83, was led by founding and co-founding scientists energized and motivated by several seminal events: Genentech's successes in expressing somatostatin and developing a recombinant human insulin; its \$38-million public offering of 13 percent of its equity at \$35 per share; the electricity generated by the stock's dramatic first-day run-up; Cetus's sale, six months later, of 35 percent of its equity, which brought in \$120 million and gave the company an unprecedented market value of almost \$400 million.

These were heady times. The Reagan era was underway. Government-funded research institutions were encouraged to transfer their discoveries to the private sector. Genentech's link up with Eli Lilly (Indianapolis, IN) on the insulin project provided proof of the commercial value of recombinant DNA research.

That period of heightened expectations and of a rich flow of investment to biotechnology soon faded. The IPO market started turning sour in the fall of 1983, and the investing public's disenchantment with biotech issues intensified in 1984. The class of 1982-83 was the first to encounter feast-or-famine financing.

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Introducing the cast

The spokesmen for the class of 1982-83 are all talented scientists with strong entrepreneurial instincts.

Patrick C. Kung is vice chairman and scientific director of T Cell Sciences (Cambridge, MA), a company devoted to the discovery and development of treatments for diseases caused by the misregulation of the body's natural defense systems. Born in Nanjing, Republic of China, Kung got his graduate education in the U.S. and fulfilled his postdoctoral requirement in David Baltimore's lab at MIT. After a short stint with Du Pont (Wilmington, DE), in 1978, he joined Johnson & Johnson's Ortho Pharmaceutical Corporation (Raritan, NJ) as senior research fellow. During his three years there, Kung was co-discoverer of the OKT (Ortho Kung T Cell) monoclonal antibody series. In 1986, the FDA approved OKT3 for treating renal transplant rejection. Kung moved to Centocor in 1982 as vice president of research and began the earliest work on what, many years later, would become Centoxin. In December, 1983, a year after Centocor's \$21-million IPO, he left to start T Cell Sciences. In 1991 Kung shared the Pharmaceutical Manufacturers' Association Discoverers Award in recognition of his work on OKT.

Roberto Crea is president and CEO of Creagen (Cambridge, MA), a company he organized to exploit proprietary and gene technologies for the design, synthesis, and development of a new generation of engineered proteins. Crea, a native of Reggio Calabria in southern Italy, did his graduate work at the University of Pavia and the University of Leiden. He was one of the first three scientists hired by Genentech in May, 1977. As director of DNA chemistry, he spearheaded the DNA synthesis that led to development of human growth hormone and human insulin. He left Genentech in November, 1981 and formed Creative BioMolecules (Hopkinton, MA) the following year. His co-founders were Charles Cohen, about whom I'll say more in a minute, and Fred Graves, who, shortly thereafter, left to head Codon (S. San Francisco, CA) and, later, Berlex Biosciences (S. San Francisco, CA; created by the merger of Triton Biosciences and Codon). Crea served as senior vice president, chief scientific officer, and director of Creative BioMolecules until February, 1990, when he left to start yet another company. After investigating the potential of protein engineering for environmental applications, Crea chose another route offering greater challenge and greater prospective returns, and founded Creagen (Cambridge, MA) in December, 1991.

Charles Cohen is chairman, CEO, and chief scientific officer of Creative BioMolecules. The company

pursues the discovery and development of proprietary protein-based products for regenerating and repairing human tissues. The company's products in development are based on two classes of naturally occurring signaling proteins that initiate and regulate the cellular events of tissue and organ formulation. After completing his graduate education at New York University Medical School and serving as a research fellow in the University of Virginia's department of biophysics and biochemistry, Cohen became manager of biochemical development at Waters Associates (Milford, MA), the Millipore subsidiary, while they were trying to find their niche in what is now known as the "biotechnology revolution." His job put him in contact with scientists in the first-wave biotech companies—including his co-founders at Creative BioMolecules.

David M. Goldenberg is chairman of Immunomedics (Morris Plains, NJ), which applies proprietary technologies to the discovery and development of highly specific monoclonal antibodies designed to deliver radioisotopes, chemotherapeutic agents, or toxins to tumors or sites of infection. Goldenberg received his Sc.D. and M.D. degrees from German institutions in the mid-sixties, and then spent the next fifteen years in U.S. academia, teaching and following his research interests in pathology and oncology. For the last ten years of that period, he was professor and director of the division of experimental pathology at the University of Kentucky. He found then that the university had no interest in patenting and licensing his discoveries; by default, they reverted to him. Goldenberg was spurred to start Immunomedics in 1983 to commercialize his work. Goldenberg still manages to pursue outside research interests, and serve as chairman of the Garden State Cancer Institute, a non-profit research institution.

John Stephenson is president and CEO of Santa Cruz Biotechnology (Santa Cruz, CA), a company focused on exploring signal transduction. Stephenson is a Canadian who earned his Ph.D. and did his post-doctoral work at the University of Toronto. He then moved to the U.S. National Cancer Institute for thirteen years, attracting widespread interest for his research into the mechanisms of oncogenesis. Stephenson benefited from the Reagan-era privatization drive: When he decided to leave and start Oncogene Sciences (Manhasset, NY) in 1983, the National Institutes of Health (NIH) let him take along intellectual properties and five NIH scientists and technicians. Stephenson stayed with Oncogene Sciences as vice chairman and chief scientific officer until 1991, filling in as CEO at various times because of turnover in that office. In 1991, he opted for an entirely new slate, and founded Santa Cruz Biotechnology (Santa Cruz, CA).

Act I—Getting started

Each scientist gives a different account of how he decided to start his own company. One consciously laid out and followed an eight-year career plan that would give him the necessary skills. Another started a company in frustration because of academic and industry indifference to discoveries he though had significance. Another could see a niche opening up as

his zest for the big-company job he held faded. Still another became infected with the startup bug through contact with others in the industry. All were influenced in varying degrees by the success stories of biotech companies already in existence.

Patrick Kung was at a critical point in his life at the end of his post-doc. As he relates, "Both academic and industrial paths were available to me. I had a teaching opportunity, a professorship, and other similar opportunities, but I wanted to work in industry and learn about its complexities. In the back of my mind, I had the idea to start something of my own someday. I decided to work in a couple of places to see how things work. I started at Du Pont, and it was too big. I switched to J & J, and there I saw more. For the first time, I understood the road from the lab bench to the product. Although things moved faster, I found out the organization was still too big for me to learn a lot of things in a short time. Looking for a smaller company to join, I landed at Centocor, then an early-stage company, where I set up a research infrastructure. I was waiting for an opportunity to realize my dream and start something entirely from scratch. The opportunity came when a major discovery on T cell antigen receptors was made by Tak Mak in Canada. I saw a technology platform there on which to build a company."

Roberto Crea was directing DNA synthesis for Genentech. In the company's earliest days, this had been an exciting, pressure-cooker project. As Genentech moved on, however, it had become routine. So Crea began thinking about other things to do: "Initially, my idea was to set up a company to support other recently formed companies by doing DNA synthesis for them. I felt that by selling our capabilities in this area we could generate sufficient revenue to support internal R&D in recombinant technology, specifically, protein engineering. The idea in the first stage was to use DNA as a kind of software for the biotech industry."

For the first two years of its existence under this service charter, the company had two labs, East Coast and West Coast. During that time, Crea found that what had been a good idea at first was failing because biotech companies moved DNA synthesis in-house to keep complete control over a critical operation. Creative BioMolecules refocused and became a recombinant protein product firm. Operations were consolidated in Hopkinton, MA in 1985.

Charles Cohen had been working at Millipore (Bedford, MA) since 1977 and was one of the people charged with finding projects that wed Millipore's capabilities with opportunities emerging from the early biotech companies. Millipore wanted to develop automated equipment for gene synthesis, protein sequencing, and peptide synthesis, among other applications. In the course of making his investigations and placing prototype equipment at test sites, Cohen met many of the industry's leading scientists. With the brashness of youth—Cohen was about 31 years old then—he concluded, as he puts it, "Hey, if they can do it, I can do it." He was working with Roberto Crea on a gene machine for Genentech, and that relationship soon flowered into co-foundership.

David Goldenberg would have happily stayed in

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academia if his university had recognized the value of intellectual property and moved to patent his discoveries. When the rights reverted to him, he contacted every commercial entity he could think of to sell off the rights or establish a licensing agreement. Turned down at every juncture, he felt he had no choice but to start his own company. Today, he openly admits, "I was naïve. I had no idea how hard it would be. I knew I just had to do it."

Act II—Financing

How difficult was it in 1982-83 to find financing for a start-up? Easy for some; hard for others. Oncogene Science's Stephenson and T Cell Science's Kung raised seed financing in three months. Crea and Cohen took almost six months, about the norm, to acquire seed money for Creative BioMolecules. All three companies took what was becoming the traditional venture capital route for funding.

Cohen notes some differences between venture capital funding ten years ago and today: "Back then, it was all personal. Investors bet on the person, the scientist. Venture capital funds were smaller, less formal, and there were fewer firms around. Today, it seems the funds are managing vaster amounts of money. They've become more sophisticated and more process-oriented. Most of the personal element is gone." As testimony to the personal bonds that were forged back then, representatives of the seed financing providers still sit on the boards of all three companies.

At Immunomedics, Goldenberg had a different experience. Every venture capital firm he approached turned him down. Undaunted, he put up his own money in 1982 to start the company. He then went public the following year through a now-defunct small cap stock investment banking house, raising \$2.5 million, his real seed money. He continued to use this financing strategy over the years, relying on a periodic equity issues, usually in public offerings. The net result: he's been able to control the dilution in his portion of the company's equity. Other scientific founders in the class of 1982-83 relied on venture capital, and saw their proportionate share of equity diluted through successive rounds of venture investment. At last report, Goldenberg and his family owned 46.7 percent of Immunomedics' approximate 28 million shares outstanding.

This financing strategy worked for Goldenberg. Immunomedics leads this sample pack with 8 products currently in clinical trials. Oncogene Sciences has 3; T Cell Science, 4; Creative BioMolecules, 4. But other companies in the class of 1982-83 that used Goldenberg's financing approach have been chronically underfunded and, as a result, are nowhere near as advanced as their classmates.

Act III—Personal growth, company growth

As biotech companies in the class of 1982-83 grew, their emphases moved from discovery to development. The scientific founders faced new challenges. They had built their careers and reputations around hands-on discovery, but now they had become science managers, and stepped back from something they

loved. (That love is readily apparent. Kung describes the joy of discovery, "like finding water in an uncharted desert.")

Their new responsibilities required them to quickly climb a steep learning curve and master such management skills as hiring the right people with the right abilities for their company's newest phase of development—and then selling those new people on a shared company vision. As CEOs, they had to maintain their original scientific team's morales, while hunting outside for new hires, and then integrating new and old into smoothly functioning wholes. At the same time, as top managers, they had to master increasingly important budget and cost issues. Development is always more expensive than discovery. Along the way, they learned previously unsuspected verities, like Cohen's maxim that "formulation chemistry is as important as any other issue in developing a product."

The founders we spoke to had all made successful transitions. They view their companies now as blueprints for discovery and development. They use this image to explain an interesting feature of most U.S. biotech companies: the scientific side of the organization tends to be stable; the business side suffers considerable turnover. Kung, for example, says a company needs a promoter in the business role during the company's discovery phase, but needs a seasoned manager when it switches focus to development.

Only one founder, Goldenberg, would admit to being "obsessive-compulsive" about his company. And none would admit to being consumed by the venture, outrunning and burning out the business-side executive. But that seems to be the reality, and a big reason why these companies have grown. If you're thinking of starting a biotech company and your psychological profile doesn't fit this model, save yourself the trouble.

Confronting licensing opportunities is a key rite of passage of developing technology-based companies. It's fraught with peril. "If you can afford to do the clinical development yourself, you should do it," Cohen advises. If you do take a partner, "make sure that what you're licensing out is extremely important to your partner's plans," warns Goldenberg. And then, says Cohen, "be aware that people championing your cause at your licensee will transfer, overriding changes in strategic plans will occur, mergers can happen." And remember, says Stephenson, "if you're a partner in a program that dies, the stigma is never on your large corporate partner. It is always, without fail, seen as a negative reflection on your technology."

Finale

Crea, who's now done it twice, offers advice on starting a biotech company to today's prospective scientific founder: "Strive for a well-balanced company, first-class science, first-class management. Hire superstars: they'll take you to the next level. Have a platform, a well-balanced portfolio of programs to spread risk. Don't relinquish your responsibility: it's your vision, don't let anyone else tamper with it. Timing is critical, develop a sensitivity to timing in your market. Be prepared for total involvement and struggle."

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