The Dynamics of California's Biotechnology Industry

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Foreword

After the great success and then faltering of Silicon Valley's information technologies sector during the 1990s, much has been made of the potential for the biotechnology industry to become California's "next big thing." The state is certainly well positioned to benefit from whatever growth might result from firms using cellular and molecular processes to produce goods and provide services. Nearly 40 percent of all public biotech companies in the nation are in California, and the state is also home to more than 40 percent of all employment in the sector. Close to half of all venture capital spent in the industry goes to California firms, and nearly half of all research and development spending in the sector occurs in California. Another significant factor is Proposition 71—state support of stem cell research—which passed by a large margin in the November 2004 election. Over the next ten years, the proposition promises to target $300 million per year to stem cell research in California—more than the National Institutes of Health spent in the whole country on stem cell research in 2003.

In this report, Junfu Zhang and Nikesh Patel cast considerable light on the nature of the biotech industry. One of their significant findings is that despite California's dominance in biotech, the sector is not likely to be a powerful engine of economic growth in the state. First, nationwide, the biotech industry involves fewer than 200,000 employees, and the industry's total revenues were less than $40 billion in 2003—small numbers compared to the size and scale of the information technology sector. Second, this industry has an insatiable appetite for new ideas and for venture capital to support the development of those ideas, but experience has shown that there is a long road to profitability and that only the most highly trained and educated scientists are likely to be involved in this work. Over 40 percent of 618 venture-backed firm founders in California were university professors. The authors point out that during the heyday of venture capital growth in Silicon Valley, start-ups of venture-backed biotech firms remained more or less at their historical average. Their conclusion is that biotech is one sector where good ideas are harder to come by than the money to support work on those ideas.

The authors found that even with biotech's modest potential for contributions to the economy, there is intense competition from other states to attract California firms. Everything from tax breaks and state funding of research to the development of science parks and incubators has been tried to recruit California's biotech businesses. It is bewildering that the sector has received so much attention, considering that, to date, very few firms have produced a commercially viable product with the prospect of long-term profitability.

California, nonetheless, seems to be a safe haven for the biotech industry. The authors found that throughout the 1990s, the state actually gained more jobs from firms moving into the state than it lost from those moving out. The largest firms in the industry have their major manufacturing facilities in California, and there is already some evidence of "clustering" in such areas as South San Francisco, Vacaville, and Thousand Oaks.

The authors were just completing this report when Californians passed Proposition 71. For many, it seems, stem cell research is not about economic development, because this is a small sector involving few employees; rather, it is about the hope that miracle cures will result from this research. To a great extent, the conclusion reached by Zhang and Patel about public policy toward the whole biotech sector is that it, too, is all about miracles. Given the huge flood of money about to pour into the sector for stem cell research alone, it appears that California is well positioned to be in the miracle business for many years to come.

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Summary

California—the birthplace of the U.S. biotech industry—houses a significant share of the industry. After the burst of the Internet bubble, we frequently hear that the biotech industry will be the "next big thing" that revives California's high-tech economy. The governor's office organized a series of bioscience summits to facilitate conversation among businessmen, capitalists, and researchers in this area. In the meantime, several bills related to the biotech industry are being circulated in the state legislature. Even California's "fourth branch of government," the initiative process, has become involved: In November 2004, California voters passed Proposition 71, pledging $3 billion for stem cell research over ten years. All of these reasons suggest the need for a study that will inform policy debate and discussion relating this industry.

Biotechnology refers to techniques that are used to genetically modify living organisms to produce marketable products. In the early 1970s, Stanford geneticist Stanley Cohen and University of California, San Francisco, biochemist Herbert Boyer invented the technique of recombining strands of DNA in desirable patterns to modify an organism. This recombinant DNA technology became the foundation of the biotechnology industry.

In 1976, Boyer teamed up with venture capitalist Robert Swanson, and together they founded Genentech in South San Francisco, which marked the inception of the biotech industry. The birth of Genentech occurred in the same year that Apple Computer was incorporated. At the same time that Apple was initiating a personal computer revolution, many people also envisioned a biotech revolution. Over the years, the biotech industry has experienced both highs and lows and has yet to reach its anticipated potential. Today, the relative size of the biotech industry remains small, whether we measure it by total employment, total revenue, or market capitalization. However, no one would deny its potential. With the growing number of biotech firms with drugs in

clinical trials, and with the plan of the commissioner of the Food and Drug Administration to reduce the time it takes to get a new drug approved for the market, there is extensive room for this industry to grow.

Similar to the information technology (IT) industries, the biotech industry is knowledge-intensive and attracts a great deal of venture capital investment. Yet it is important to recognize that there are many differences between the biotech and IT industries. The biotech industry is substantially more knowledge-intensive and relies more on academic research as a source of innovation and entrepreneurship. It takes biotech start-ups many more years to reach the stage of profitability. In the IT industries, the increasingly higher performance of integrated circuits has been driving growth on every front; yet in biotech, there is no such fundamental technological advancement to guarantee rapid growth. Also, in the IT industries, many products benefit from the network effect: The value of the product for a single customer rises as the number of the product's entire user base expands. This is why many IT firms can achieve exponential growth for many years. In contrast, such network effects rarely exist in the biotech industry. Although also widely applicable, biotech is not an "enabling technology" like information technology that lays the foundation for other industries and promotes growth in many other sectors. As a result, it is likely that biotech will change the economy less dramatically and at a slower pace than information technology.

The biotech industry relies heavily on venture capital investment. A biotech firm usually needs a large amount of capital and takes years to develop a product. On the one hand, the business is highly risky; on the other hand, it pays handsomely if a firm can successfully develop a marketable product. For these reasons, the biotech industry is attractive to venture capitalists. Although venture capital activities in the 1990s are remembered primarily for the Internet revolution, the biotech industry managed to attract 6.4 percent of the total U.S. venture capital investment and 7.7 percent of California's total. During the years before the Internet caught attention and after the bursting of the Internet bubble, biotech's share of the total venture capital investment in the nation was as high as 20 percent—far above the share of the biotech industry in the economy. Although venture capital is absolutely necessary for the development of biotech, it is not sufficient for creating a strong biotech economy. We find that despite increasing venture capital funds in the late 1990s, the formation of biotech firms remained steady, suggesting that money alone cannot promote the biotech industry. Quality research is at least an equally important ingredient for developing the industry.

Scientific research, indeed, drives the biotech industry. This was true when the industry was born. Industry leaders such as Amgen, Biogen, Calgene, Chiron, Genentech, and Hybritech were all founded or cofounded by prominent professors. As previous research has documented, "star scientists," those with an outstanding record of publications in the area of genetic research, are a significant factor in determining the location and timing of firm founding in the biotech industry. We find that academic research remains just as important for today's biotech industry. Our data show that scientists working at universities or research institutes have founded close to half of venture-backed biotech start-ups—firms with the greatest growth potential. This fraction is much higher than that in any other industry. Overall, about two-thirds of these professorial entrepreneurs chose to remain in the same state to start their biotech firms. In California, the fraction is even higher: Eighty-two percent of California's professorial entrepreneurs started their biotech firms in California. Thus, venture-backed biotech start-ups often represent technology transfers from academic institutions to the industry, and such transfers often take place locally.

Job creation in the biotech industry hinges on firm creation. Biotech firms generally take longer to develop marketable products, and they grow at a slower pace than those in the IT industries. Also, the biotech industry is relatively small. For these reasons, most growth in biotech employment depends on the formation of new business rather than the expansion of existing firms. Our data show that more than half of the job growth in biotech is attributable to new firms.

California faces competition from many other states in the growing biotech economy. The Biotechnology Industry Organization (2004) reported that almost all states in the nation have policies to promote their own biotech economy. These policies include strategic planning for the biotech industry, offering tax incentives to biotech companies, providing seed capital to biotech start-ups, funding biomedical research, and building research parks and incubators to facilitate entrepreneurship.

In addition, many states are willing to offer ad hoc incentive packages to attract California's biotech businesses, because recruiting existing companies from biotech centers is often easier than creating new ones. For example, when California's biotech leaders Genentech and IDEC decided to build their manufacturing plants, enticing offers from all over the country tried to persuade them to locate their manufacturing facilities elsewhere. State and local governments had to tender counteroffers to keep the plants in California.

It is often reported in the media that biotech firms are leaving California or deciding to expand elsewhere. Such stories, together with increasingly intense competition from other states, have created a serious concern in California as to whether the Golden State can retain its share of the U.S. biotech economy. Our data show that California has indeed lost biotech business to other states: More biotech establishments have moved to other states than have moved into California. However, this net loss of businesses has had a limited effect on the state economy, because the scale of the loss has been relatively small and the state has incurred no net job loss. For example, only 52 biotech establishments moved out of California during 1990–2001, eliminating 815 jobs. During the same period, 45 establishments moved into California, adding 1,739 jobs to the California economy—more than enough to offset what California lost. In addition, among the 52 establishments that left California, 36 were alive in 2001 and together offered 840 jobs. In contrast, 27 out of the 45 establishments that moved into California survived in 2001, employing a total of 2,993 people—more than three times as many as what California lost to other states. Thus, the overall effect of business relocation is not necessarily negative. More importantly, our data suggest that business relocation in California's biotech industry should not be a big concern, because relative to the entire industry, the effects of business relocation on state employment are so small that they are negligible.

Case studies also suggest that although California is a high-cost state in which to do business, it is not in an entirely disadvantageous position to compete for biotech manufacturing and related services. The industry is already concentrated in California, and many firms prefer to locate manufacturing close to research and development operations. California's strength in research, as well as the agglomeration economies created by its existing large biotech industry, has certainly helped to retain a large proportion of biotech manufacturing within the state.

Despite the fierce competition from other states and the high cost of doing businesses in California, our study suggests that California is by no means losing its edge in the biotech industry. In particular, the concern over losing biotech businesses to other states finds little empirical support. This makes us wonder whether the current discussion of the state's biotech industry has overemphasized the cost and neglected the benefit of starting and locating businesses in California. Obviously, high cost should not be a problem if it is balanced by high benefit. Indeed, the high cost of living and doing business in California may stem from California's unique advantages, ranging from a hospitable climate to a long tradition of innovation and a generally thriving economy. If many people prefer to live in California and if many businesses are founded in this state, their competition over the space and resources will naturally bid up the cost in the state. In that case, one should never expect California to become a low-cost state. And the right way to deal with the high cost is to keep the benefit high to offset the cost. Thinking in this way, we realize that maintaining California's edge in the biotech industry requires further strengthening California's advantages.

In the area of biotech, California enjoys many advantages. California's industry has always led and continues to lead the entire nation. This head start creates first-mover advantages that build momentum in creating dynamic industrial clusters. The state's strong research capacity, long tradition of venture capital investment, and high-quality labor pool already provide the necessary ingredients for a successful biotech economy. California's largest advantage in biotech is its world-renowned universities. As long as California's universities continue to conduct pioneering research in biological, medical, and chemical sciences, the Golden State's lead in the biotech industry is likely to continue.

State and local governments can play a big role in helping the biotech industry. Although California's lead in biotech has little to do with intentional policy promotions, the state has implemented policies to facilitate its growth. For example, California has supported biotech research through the Industry-University Collaborative Research Program, provided venture capital through CalPERS, and improved the labor force for its biotech industry through its higher education system.

Most recently, in November 2004, California voters passed Proposition 71, pledging to spend $3 billion on stem cell research over the next ten years. This initiative clearly stated that one of its goals is to "advance the biotech industry in California to world leadership, as an economic engine for California's future." The amount of financial support that Proposition 71 promised is extraordinary. By current standards, it dwarfs any country's investment in stem cell research, including the entire U.S. federal support for such research. Having recognized the possibility that Proposition 71 will tilt the playing field of stem cell research in favor of California, many states immediately started to consider countermeasures. However, no other state can possibly afford the amount of resources that California has pledged. Proposition 71 will likely attract talents throughout the world to California to conduct biotech research. Given the strong venture capital industry and risk-taking culture in California, any commercializable research findings will soon catch the attention of venture capitalists and find their way into the industry. It is widely expected that California's biotech industry will benefit a great deal from Proposition 71.

Our study suggests that California should continue to give strong support to biomedical research and encourage the commercialization of research findings and business formation. The recent passage of Proposition 71 represents an important move in the right direction. However, stem cell research is only a narrow subfield of biomedical research. Other promising research areas should also be emphasized, although many such areas are not as demanding on state resources because federal support is relatively abundant.

To keep biotech manufacturing in California, the state should consciously take advantage of its abundant biotech resources. No other state has so much biotech R&D capacity and so many biotech products in the pipeline. Biotech manufacturing plants benefit from proximity to R&D and shared labor pool and infrastructure. The state government should try to maximize such benefits for biotech manufacturers by building manufacturing clusters to host manufacturing branches for several companies. Those benefits will make California attractive to biotech manufacturing plants in spite of the high operating cost in the state. Vacaville in Northern California, where Genentech, Chiron, and Alza have manufacturing facilities, is a model of manufacturing clusters that can be cloned elsewhere.

Contents

Figures

Tables

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1. Introduction

Although venture capital investment in the high-tech sector has plummeted since the burst of the Internet bubble in 2001, investors still find the biotech industry attractive. In 2002, U.S. biotech firms raised $2.79 billion in venture capital, accounting for 14.4 percent of all venture capital investment in the United States—up from 4.4 percent in 2000 and the highest proportion of total venture capital in seven years. This proportion rose even further, to 19.9 percent in 2003.[1] In Silicon Valley, biotech is generally expected to be one of the growth engines that pulls the region out of its recent economic decline (Henton, Walesh, and Brown, 2001). Others similarly argue that biomedicine will play a major role in the economy of the entire state (California Healthcare Institute, 2002).

Meanwhile, more than 100 state and local economic development agencies in the United States (and still more around the world) have made it a priority to establish life science clusters to take advantage of biotechnology's potential to enhance their regional economies. These regions not only look to California for lessons and ideas but also seek to recruit the state's talents and companies. To counter this competition and further expand California's life science industries, Governor Gray Davis launched a life science initiative in his 2003 State of the State speech. He promised three things: (1) to increase the number of qualified lab technicians, (2) to work with the University of California (UC) to simplify the transfer of technology, and (3) to increase access to venture capital and federal grants. The governor's office organized a series of life science summits in the state: The San Francisco Bay Area hosted the first summit in December 2002, and three more followed in San Diego (May 2003), the Los Angeles region (June 2003), and the

[1]The latest venture capital industry statistics are available at VentureOne's website, http://www.ventureone.com/.

Central Valley (September 2003). By reaching out to industry leaders and decisionmakers, the state government has tried to identify strategies to retain and attract life science companies, investment, and research in California. Additional efforts may be expected from Governor Schwarzenegger's administration.

The governor's life science initiative was a continuation of California's supportive policy. Indeed, the California state government has long recognized the potential of biotech and has aggressively promoted its research and commercialization through legislation and government programs. Some of the most recent support of the industry is reflected in the following:

- SB 2065 by Senator Jim Costa created the Food Biotechnology Task Force to examine the issues surrounding biotechnology and the introduction of biotechnology products (signed by Governor Davis on September 24, 2000).
- In December 2000, state government committed $25 million annually for four years to establish the California Institute for Bioengineering, Biotechnology, and Quantitative Biomedicine at the University of California, San Francisco.
- SB 327 by Senator Jack Scott implemented the $250,000 that was included in the 2001–2002 Budget Act for the development of a Pasadena Bioscience Innovation and Training Center (signed by Governor Davis on October 1, 2001).
- In March 2002, Governor Davis signed a $200,000 contract with Los Angeles County to develop a biotech research park near the University of Southern California's Health Sciences campus in Los Angeles.
- SB 253 by Senator Deborah Ortiz put California on record as supporting the cloning of stem cells by permitting its research (signed by Governor Davis on September 23, 2002).

Twelve bills currently circulating in the state legislature also aim to promote the biotech industry, including, for example:

- AB 234, introduced by Assembly Member Ellen Corbett, proposes to allow operating losses incurred by biotech or biopharmaceutical companies to be carried over for 20 years.
- AB 743, authored by Assembly Member Gene Mullin, provides that any unused operating losses incurred by a corporation that are attributable to the development or marketing of any biomedical product in California may be transferred to any other corporation that continues to develop and market that product.
- SB 778, drafted by Senator Deborah Ortiz, authorizes the state to issue bonds to finance a specific biomedical research and development program.

Voters are directly involved as well in policies affecting the biotech industry. Most recently, on November 2, 2004, California residents approved Proposition 71 by a margin of 59 percent to 41 percent. This measure promises to spend an average of $295 million each year on stem cell research and research facilities over a ten-year period, funded by state bonds. Stem cell research is recognized as a vital and promising research area that receives insufficient federal funding, and thus California voters decided to use state resources to support it.

The amount of financial support that Proposition 71 has promised is unprecedented. The U.S. government expenditure on stem cell research was only $215.5 million last year, far less than what California is going to spend. Similarly, no other countries have invested so much in this area. In the rest of United States, Proposition 71 immediately sparked an interstate race to retain top researchers and biotech companies. Many states have realized that they have no choice but to also make a significant commitment to stem cell research. However, it is unlikely that they can afford comparable support. Thus, Proposition 71 will almost surely tilt the playing field in favor of California. It has the potential to make the state a magnet for bioscientists and a training center for coming generations of bioscientists. The commercialization of their research will certainly benefit California's biotech industry. Indeed, Proposition 71 made it an explicit goal to "advance the biotech industry in California to world leadership, as an economic engine for California's future."

All of these legislative activities are motivated by the assumption that the biotech industry will be a significant source of economic growth. Yet it remains unclear how large the overall industry might come to be and what strategies might help secure a large share of it. Answering such questions requires a clear understanding of the biotech industry. Thus, a careful study of this industry—one of the major life science industries—is much needed to inform policy debate and the formulation of state and local policies.

The Biotechnology Industry: A Definition

Under its simplest definition, the term "biotechnology" refers to the use of living organisms to develop products or run a process. In this sense, biotechnology has a long history. As early as 6,000 years ago, humans in various regions of the world learned to produce beer, bread, and wine through fermentation—a process in which bacteria, yeasts, or molds are used to generate carbon dioxide gas and alcohol. The same techniques were later used to manufacture cheese, vinegar, and yogurt.

Yet today, this term almost always refers to modern biotechnology—techniques used to genetically modify living organisms to produce marketable products.[2] Over the first half of the 20th century, scientists made a series of important breakthroughs that led to the discovery of the critical role of DNA (deoxyribonucleic acid) in reproduction. In 1953, biologists James Watson and Francis Crick proposed the double helix structure of DNA. Twenty years later, scientists successfully transferred DNA from one life form into another for the first time. In 1973, Stanford geneticist Stanley Cohen and University of California, San Francisco, biochemist Herbert Boyer managed to recombine segments of DNA in desired configurations and insert them into bacterial cells, which could then act as manufacturing plants for specific proteins. This

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[2]See, for example, Borem, Santos, and Bowen (2003); Robbins-Roth (2001); or Wolff (2001) for an introduction to biotechnology and the industry geared toward nonspecialists.

recombinant DNA technology launched the modern-day biotechnology industry.

The biotechnology industry is a collection of firms that use cellular and molecular processes, particularly the recombinant DNA technology, to produce goods or provide services. Included in this definition are biopharmaceutical companies that specialize in genetic research, the development of genetically engineered therapeutic proteins and antibodies, and the manufacturing of such biotech drugs and vaccines; companies that develop or produce genetically modified agricultural products; and companies that apply genetic engineering techniques to industrial production and environmental management. Excluded from this definition are pharmaceutical companies that primarily engage in the manufacturing and marketing of traditional drugs, such as chemical compounds developed through “trial and error”; companies that produce medical devices; and companies that provide ancillary services to biotech companies.

More specifically, the biotech industry includes companies that are involved in the practices described below.

Biotechnology Research

Although most scientific exploration is conducted in universities, the industrial sector continues to pursue its own research because of its immediate market applications and large economic potential. Biotech firms have entered the following fields of research:

- Genomics: the study of the structure and function of genes to discover their role in an organism’s growth, health, disease, resistance to disease, etc.[3]
- Proteomics: the study of the structure, function, and interactions of proteins to discover their role in an organism’s growth, health, disease, resistance to disease, etc.

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[3]In April 2000, Celera Genomics, a two-year-old biotech start-up based in Rockville, Maryland, announced the completion of the human genome sequencing, ahead of the internationally funded Human Genome Project.

- Bioinformatics: the application of computer technology to the creation, collection, storage, and efficient use of the fast-growing data in biotechnology.
- Pharming: the production of pharmaceuticals (or intermediate chemicals used to manufacture pharmaceuticals) in genetically engineered agronomic plants.

Biotech Drugs and Therapeutic Approaches

The advancement of modern biotechnology has created a wide range of innovative drugs and novel approaches to improve human health. Some of the most promising innovations include:

- Therapeutic proteins: Therapeutic proteins are naturally occurring proteins that are produced as drugs to treat patients. Some of them replace or supplement a protein in the body that is deficient or defective. Others signal the body to initiate or cease a biological function to cure a disease.
- Monoclonal antibodies: These replicate the body's natural defense agents and are employed to attack only the infectious agents with no (or significantly reduced) side effects.
- Gene therapy: Gene therapy treats human disease that could be caused by an absent or defective gene with a functioning gene, so that the human body can produce the correct enzyme or protein and consequently cure the disease by eliminating its root cause.
- Stem cell therapy: Stem cells have no specific function and have the potential to develop into specialized cells; they can be transplanted into the human body to repair damaged or diseased body parts.
- Personalized medicine: A population of patients showing identical disease phenotype may have distinct genetic profiles. A deep understanding of the human genome and disease biology will enable the development of diagnostic and therapeutic products that target smaller patient subpopulations, thereby offering the right treatment to the right patients.

Agricultural Biotech

Genetic engineering produces new plants and animals with desired characteristics. For example:

- Roundup-ready crops, including canola, corn, cotton, and soybeans, that tolerate over-the-top applications of Roundup® herbicide during the growing season for better weed control.
- Insect-protected crops, such as corn, cotton, and potatoes, enhanced with a gene that provides natural protection against certain pests.
- Disease-resistant crops, such as bananas resistant to fungal disease and corn hybrids tolerant to the gray leaf spot disease.
- Genetically modified tomatoes that have superior color, taste, and texture and a long shelf life.
- Bovine growth hormone, a natural hormone that induces cows to produce milk; the injection of a genetically engineered copy of this hormone could increase milk production by 10–15 percent.

Agricultural technology promises to improve agricultural production and boost food supply throughout the world. However, environmental concerns and heated policy debates over health concerns follow every step of development in this area.

Industrial Biotech

Biotechnology has also opened opportunities beyond the world of agriculture, medicine, and health care. Some of the industries most likely to benefit are:

- Energy: Biotechnology helps develop industrial enzymes that convert biomass to energy. Biofuels, such as ethanol made from starch and biodiesel made from vegetable oil, provide renewable energy, reduce pollution, and improve the sustainability of the economy.
- Environmental technology: Genetically engineered bacteria and enzymes could help clean up oil spills and toxins or improve techniques for waste management.

- Special materials: Genetic codes of spiders and silkworms can be deciphered, making it possible to produce incredibly strong fibers. Genetically engineered plants are able to produce plastic within their stem structures that biodegrades in months.

Most researchers and writers do not hesitate to provide a clear definition of the biotech industry, but it is extremely difficult to maintain a static definition when conducting empirical studies because the biotech industry is defined by an underlying technology that cuts across many traditional boundaries. As a result, the collection and organization of data at most institutions and government agencies make it difficult to define a specific segment of the economy as "biotech." In addition, neither the traditional Standard Industrial Classification (SIC) system nor the more recent North American Industry Classification System (NAICS) delineates a specific portion of the economy as the biotech industry. Thus, empirical researchers have little choice but to develop their own definitions, sometimes needing to compromise their precise definition given the constraints of available data. This study, which will use various sources of data and a changing empirical definition of the biotech industry, is no exception. We will always be explicit about the specific data source under examination and will use caution in interpreting the results with this limitation in mind.

The U.S. Biotech Industry

In his 2004 State of the Union address, President Bush declared, "much of our job growth will be found in high-skill fields like health care and biotechnology."[4] Table 1.1 summarizes biotech industry statistics for the United States over the past decade. Clearly, the biotech industry is growing fast. In a mere ten years, biotech revenues grew by 250 percent and total employment increased by 93 percent. Other measures present a similar picture. Biotech capitalization, $45 billion in 1994, quickly shot up to $353.5 billion in 2000. Even after the 2000 stock market correction, market capitalization totaled $206 billion in 2003. Another sign of growth in this industry is the number of market

[4]See http://www.whitehouse.gov/news/releases/2004/01/20040120-7.html.

Table 1.1

Growth of the U.S. Biotech Industry, 1994–2003

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Revenue ($ billions)	11.2	12.7	14.6	17.4	20.2	22.3	26.7	28.5	29.6	39.2
Research and development (R&D) expenditure ($ billions)	7.0	7.7	7.9	9.0	10.6	10.7	14.2	15.7	20.5	17.9
No. of companies	1,311	1,308	1,287	1,274	1,311	1,273	1,379	1,457	1,466	1,473
No. of public companies	265	260	294	317	316	300	339	342	318	314
Market capitalization ($ billions)	45	41	52	83	93	137.9	353.5	330.8	225	206
No. of employees (thousands)	103	108	118	141	155	162	174	191	195	198

SOURCE: Ernst & Young's annual biotechnology industry reports (1995–2004), compiled by the Biotechnology Industry Organization, available at http://www.bio.org/speeches/pubs/er/statistics.asp.

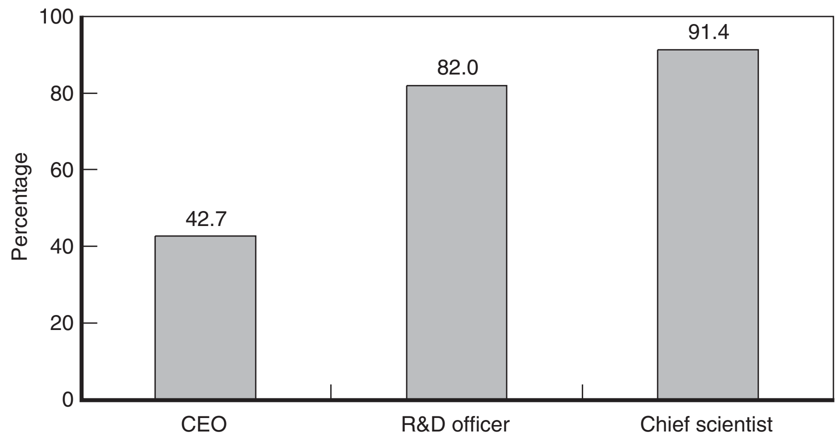
approvals. From 1982 to 1992, 31 biotech drugs and vaccines were approved. From 1993 to 2002, 203 were approved. In 2002 alone, the Food and Drug Administration (FDA) approved 36 biotech drugs and vaccines.

Although the rapid growth in biotech is undeniable, it still remains a relatively small, incipient industry. To put the industry into perspective, we need only to compare its statistics with leaders in the technology sector. The biotech industry's 2002 revenues were about equal to Microsoft's 2002 revenue; its 2003 revenues were only 44 percent of IBM's 2003 revenue. The biotech industry's 2002 market capitalization was $225 billion; in the same year, Intel's and Cisco's combined market value was $319.5 billion. Even after a sharp decline in the value of information technology stocks, Intel's and Cisco's combined value in 2003 was about equal to that of the entire biotech industry. And in terms of jobs, Hewlett-Packard and IBM had a combined U.S. employment of 212,000, 7 percent higher than the total U.S. biotech employment in 2003. Although it remains a relatively small share of the high-tech economy, improving technology, a growing number of drugs on the market, and an increasing number of drugs in the pipeline ensure that this industry is poised for substantial growth.

Key Characteristics of the Biotech Industry

Biotech is sometimes misperceived as just another high-tech industry like the computer, semiconductor, and software industries. The chief executive officer (CEO) of a leading biotech company claimed to investors in 2000 that "genomics is now where the computer industry was in the 1970s." A popular book on biotech investment has an introduction entitled "biotechnology's PC paradigm" (Wolff, 2001). However, we must recognize that the biotech industry differs from information technology (IT) industries in many ways, as described below.

The biotech industry is extremely knowledge-intensive. Forty-seven percent of venture-backed biotech firm founders were university professors, scientists at research institutes, or newly minted Ph.D.s (see Chapter 6 for more detail). This is in contrast to founders of IT industries, most of whom are engineers. As shown in Figure 1.1, more

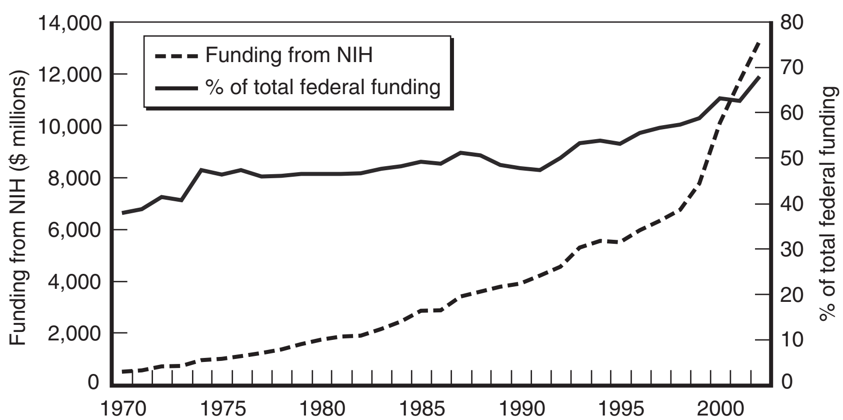


SOURCE: Authors' calculations from the Bioability data.

Figure 1.1—Percentage of Biotech Executives Who Hold Doctoral Degrees, 2003

than 40 percent of the CEOs in the U.S. biotech industry hold doctoral degrees. More than 80 percent of biotech R&D officers hold doctoral degrees, and the percentage is even higher for chief scientists in biotech firms.

Academic research and federal funding are particularly important for growth in the biotech industry. The biotech industry, far more than IT industries, relies on research universities as a source of technological innovation. As the UC annual reports on technology transfer show, most top-earning UC inventions are in biotech. Hepatitis-B vaccine (UC San Francisco), a process for gene splicing (UC San Francisco), human growth hormone (UC San Francisco), intracranial aneurysms treatment (UC Los Angeles), and interstitial cystitis therapy (UC San Diego) consistently top the list, often accounting for more than 70 percent of the total technology licensing revenue. Even after two important patents expired in recent years, life science inventions still earn the lion's share of UC's total royalty income. This is not an isolated case; it is a nationwide phenomenon. The Association of University Technology Managers (AUTM) conducts an annual survey of university technology licensing. The association found that approximately 80 percent of the gross license income received by U.S. universities is derived from inventions relating to life sciences. This is predictable, because for many decades the federal government has spent a large amount of money on R&D in life sciences. Figure 1.2 shows the trend in university research funding by the National Institutes of Health (NIH) over the past three decades. For many years, NIH has been the principal source of federal funding for American universities. In nominal terms, NIH grants for universities increased 20 times between 1970 and 2000. Its recent trend is comparable to the rapid growth of R&D spending in the biotech industry, as seen in Table 1.1. Funding from NIH constituted 38 percent of total federal funding in 1970, increasing to 68 percent in 2002. University researchers have carried out a great deal of research in life sciences and, as a result, universities hold a large share of life science patents. Rosenberg and Nelson (1994) show that in 1990, universities owned 18.1 percent of "genetic engineering" patents, the highest university share among 54 patent classes. In terms of number of university patents, organic compounds, bio-affecting and body-treating drugs, and molecular biology and microbiology topped the list. Obviously, the commercialization of such university inventions is a major source of growth for the biotech industry. Thus, it is important for policymakers to address the issue of technology transfer from universities to the industry.



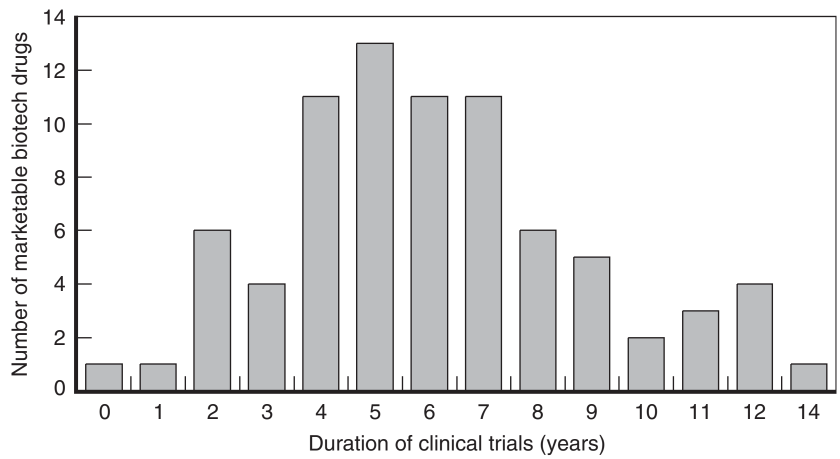
SOURCE: National Science Foundation.

Figure 1.2—NIH Funding for Universities, 1970–2002

Firm-level spinoffs are rare in the biotech industry. In the IT industries, it is common (at least in California) for engineers to leave established firms to found new enterprises. For example, an incomplete list of entrepreneurs in Silicon Valley who received venture capital during 1992–2001 shows that 117 had worked for Hewlett-Packard and 101 had worked for Sun Microsystems. These entrepreneurs founded 99 venture-backed Hewlett-Packard spinoffs and 79 venture-backed Sun Microsystems spinoffs (Zhang, 2003). This represents a major mechanism by which the IT industries expanded for more than three decades. However, it is an unlikely scenario in the biotech industry. As we see in Chapter 4, relatively few biotech firms trace their origin to leading biotech or pharmaceutical companies, partly because only highly specialized scientists grasp biotechnology, and patent law protects almost every piece of it. Another possible explanation is that biotechnology has fewer applications than information technologies.

Biotech firms are exposed to high risks. Many biotech firms' major activities involve R&D, which by its very nature is risky. As of December 2002, 72 biotech firms were included in the NASDAQ Biotech Index. Their median founding year was 1990, and by 2002, their average age was 12.6 years. Yet, even among these most successful biotech firms, only 12 were making a profit in 2002. Only 25 had enough total revenue to cover R&D expenditure and 31 spent more than 200 percent of total revenue on R&D.

In addition, most biotech firms are developing medicinal products subject to FDA regulation, which involves a lengthy and uncertain process. Recap.com, a biotech information company, maintains a database on clinical trials, which shows how risky the process is. As of August 4, 2003, the database included 3,465 clinical trials, among which 313 drugs reached the marketing stage and 659 trials were terminated; the remainder are still in various procedural stages. For those trials that generated marketable drugs, the database recorded the start date and completion date in 79 cases. As Figure 1.3 shows, the median duration of successful clinical trials is six years, the same as the average. The longest trial took 14 years. All of these risks explain why biotech stocks are among the most volatile.



SOURCE: Authors' calculations based on data from http://www.recap.com.

Figure 1.3—Duration of Clinical Trials of Biotech Drugs

There is no network effect in the markets for biotech products. Many companies in the computer industry experienced explosive growth because of the increasing returns created by the network effect. That is, the more customers who use a product, the more valuable the product becomes for a single user. For example, the more people who already use Microsoft Word software, the more likely new customers will prefer it because they want to share compatibility with others. This feature of information technology enables many leading firms to grow at an accelerated pace. It is not uncommon for a successful IT company to have 1,000 employees by age ten, but it is unlikely for a biotech firm to achieve this kind of job growth, because most biotech products do not benefit from the network effect: My biotech drug will not become more effective if more people take it.

There is no equivalent to Moore's Law applicable in the biotech industry. In the mid-1960s, Intel cofounder Gordon Moore observed an exponential growth in the number of transistors per integrated circuit and predicted that the number of transistors on a microprocessor would double approximately every 18 months. It has been dubbed "Moore's Law" and has proven remarkably accurate. Moore's Law implies a steep decline in the cost of information processing, which is really the ultimate driving force behind the rapid growth of IT industries over the past four decades. In fact, Moore's Law has even accelerated the growth in certain areas of the biotech industry, particularly in bioinformatics and genomics, where increasingly cheaper computing power continuously improves the efficiency of biological data mining. However, there is no such fundamental progress in biotech like Moore's Law that could continuously push growth on every front. Growth of the biotech industry will likely be more linear and less explosive.

The biotech industry has a smaller effect on other sectors of the economy. The advancement of information technology not only created a fast-growing high-tech sector but also greatly enhanced productivity in other sectors, creating a multiplier effect on the whole economy. The U.S. economy has recently experienced a significant increase in productivity growth, which is generally believed to be a consequence of the proliferation of computer and information technology (Jorgenson, 2001). The biotech industry is unlikely to have such a large effect on the overall economy. It is worth noting that an individual investor who expects high returns from a single company need not care about this difference, but a policymaker who cares about social welfare must recognize it.

Policymakers need to recognize these different features of the biotech industry in the process of developing policies for this industry.

Overview of This Study

This study avoids the controversial ethical issues surrounding the application of biotechnology and focuses instead on its economic aspects.[5] In particular, we will use various sources of data to investigate the unique features of California's biotech industry. Our objective is to portray the dynamics of this fast-growing industry and to provide information to policymakers on how to foster growth in this area.

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[5]This does not mean to imply that ethical issues can be completely separated from economic ones. For example, ethical concerns may prevent scientists from conducting research in certain areas or prohibit entrepreneurs from commercializing certain biotechnologies, which surely has economic consequences. Also, it is undeniable that ethical concerns must be taken into account when formulating public policies.

Chapter 2 provides a general overview of California's biotech industry, offering a profile of California's three biotech centers and analyzing their strengths and weaknesses.

Venture capital has always been a major source of capital finance for the biotech industry. Chapter 3 uses VentureOne data[6] to describe the trend of venture capital investment in this industry.

Chapter 4 uses the VentureOne data to study venture-backed biotech start-up founders. It will identify the people who take the most advanced technological innovation to the market.

Chapter 5 uses the National Establishment Time Series (NETS) database to describe firm formation, growth, and mortality in California's biotech industry. The analysis of these industry dynamics helps to illustrate the process of industry growth and job creation.

Chapter 6 uses the NETS data and other data sources to investigate business relocation and related issues in California's biotech industry. It will address in particular the concern that California may lose its edge in the biotech industry given the fierce competition from other states.

Chapter 7 summarizes the major findings and discusses related policies and the implications of this study.

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[6]A unique data source assembled by VentureOne.com has tracked venture capital in the industry since 1992.

2. California's Biotech Industry

This chapter documents the importance of California's biotech industry and its three biotech clusters. As mentioned in Chapter 1, the biotech industry still represents a relatively small fraction of the U.S. economy. This is also true in California. Using a very broad definition of biotech that includes not only biopharmaceuticals but also related academic research and laboratory services, the California Healthcare Institute (CHI) estimated a total employment of 119,000 in 2000 (California Healthcare Institute, 2002).[1] This amounts to 0.7 percent of California's total employment. However, California's biotech industry accounts for a large proportion of the U.S. biotech economy.

California's Share of the Biotech Industry

As the birthplace of biotech, California has garnered a significant share of the U.S. biotech industry. A 2002 U.S. Department of Commerce survey reported that of the 3,000 broadly defined biotech companies surveyed nationwide, 26 percent were in California, with human health as their primary focus.[2]

A recent Brookings report identified nine biotech centers in the nation, three of which are in California—in the San Francisco Bay Area, the Los Angeles region, and the San Diego region (Cortright and Mayer, 2002). As of January 26, 2004, 40 of 129 companies in the NASDAQ Biotechnology Index were in California. Together, they account for 44.8 percent of the index value.

Table 2.1 presents California's share of the U.S. biotech economy. Compared to California's 13.4 percent share of the U.S. Gross Domestic Product (GDP), the state's share of the U.S. biotech industry is much

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[1] CHI's estimates also included the medical device and wholesale trade industries. We excluded such industries resulting in the number 119,000.

[2] See http://www.technology.gov/reports/Biotechnology/CD120a_0310.pdf.

Table 2.1

California's Share of the U.S. Biotech Industry

	United States	California	% of United States
GDP/gross state product	$10.17 trillion	$1.36 trillion	13.4
Biotech revenue	$25.3 billion	$13.5 billion	53
Biotech R&D spending	$11.5 billion	$5.4 billion	47
No. of biotech companies	1,457	410	28
No. of biotech public companies	342	129	38
No. employed in biotech	141,000	60,000	43
Biotech venture capital (1992–2001)	$21.8 billion	$9.99 billion	45.8

SOURCES: Ernst & Young (2002); Industry-University Collaborative Research Program (IUCRP) (2003); and authors' calculations.

larger. Close to 40 percent of publicly owned biotech companies are in California. The state generates 53 percent of U.S. biotech revenues and accounts for 47 percent of national R&D spending on biotech. More than 40 percent of U.S. biotech employment is in California. From 1992 to 2001, the biotech industry raised nearly $22 billion (in 1996 dollars) of venture capital, 46 percent of which was invested in California.

The 41 California companies in the NASDAQ/AMEX biotechnology indexes together generated $11.67 billion in annual revenues in 2002. Not surprisingly, the 13 companies on this list that have a biotech drug on the market account for 83.6 percent of those 2002 revenues. Similarly, these 13 companies accounted for 65.8 percent of the total R&D expenditures in 2002. The remaining companies continue to focus on R&D, and many already have drugs in clinical trials. As the number of biotech companies that market drugs continues to grow, the biotechnology industry in California is bound to have a substantial effect on the state's economy.

Table 2.2 uses Quarterly Census of Employment and Wages (QCEW, or ES-202) data to compare California's biotech manufacturing with the U.S. total. Although the table includes research sector data, we could not separate biotech research from physical and

Table 2.2

Biotech Manufacturing in the United States and California, 2002

NAICS Code	Industry Title	No. of Establishments: United States	No. of Establishments: California	Employment: United States	Employment: California	Total Annual Pay ($ thousands): United States	Total Annual Pay ($ thousands): California	Average Annual Pay ($): United States	Average Annual Pay ($): California
325411	Medicinal and botanical manufacturing	395	86	23,529	2,904	1,619,370	134,874	68,824	46,444
325412	Pharmaceutical preparation manufacturing	1,441	209	230,436	27,928	17,512,814	2,340,487	75,999	83,804
325413	In-vitro diagnostic substance manufacturing	298	69	13,606	4,093	797,398	247,120	58,606	60,376
325414	Other biological product manufacturing	402	77	25,608	5,068	1,520,124	278,095	59,361	54,873
325411–4	All biotech manufacturing	2,536	441	293,179	39,993	21,449,706	3,000,576	73,162	75,028
31–33	All manufacturing	386,863	52,566	15,209,192	1,633,985	670,676,772	83,099,115	44,097	50,857
541710	Physical, engineering, and biological research	15,507	2,812	462,198	83,335	33,381,300	6,735,492	72,223	80,824

SOURCES: U.S. Bureau of Labor Statistics (http://www.bls.gov/cew/home.htm); California Employment Development Department (http://www.calmis.cahwnet.gov/file/es202/cew-select.htm).

engineering research. Table 2.2 shows that in terms of employment, California manufacturing industries represent 10.7 percent of the U.S. total, whereas in biotech manufacturing, California's 13.6 percent proportion is only slightly higher. That is, California's dominance in biotech primarily results from its large share of the U.S. biotech research. This also suggests that there is a large amount of room for expansion in California's biotech manufacturing.

Table 2.2 also shows that manufacturing jobs in biotech are much better paid than the average manufacturing job. In the United States, an average manufacturing worker earns $44,097 a year, whereas in biotech, a manufacturing job is paid $73,162 a year, 66 percent higher. In California, a manufacturing job in biotech pays 48 percent more. This higher wage rate reflects the knowledge-intensive nature of the biotech industry and the need to hire better-educated workers. Given that California is a high-cost state, this kind of job is exactly what California needs.

California's Biotech Centers

As noted above, California's biotech industry is concentrated in three centers: the San Francisco Bay Area, the Los Angeles region, and the San Diego region.

A Renowned History

California has a long tradition of entrepreneurship and innovation, usually conveyed in the context of Silicon Valley. Although biotechnology is not discussed as often as the IT industry, California's spirit of innovation is equally extraordinary and important in the development of the biotech industry.

The San Francisco Bay Area has produced many pioneers in the industry. By the mid-1970s, with Silicon Valley already well-established in the South Bay, the entire Bay Area became a fast-growing technology center. At the same time, the venture capital industry was taking root in the area. It was then that venture capitalist Robert Swanson initiated a meeting with UC San Francisco biochemist Herbert Boyer to discuss the idea of commercializing the recombinant DNA technology that Boyer helped invent. That meeting in 1976 led to the birth of the first biotech company in the world, Genentech ("genetic engineering technology"), the same year that Apple Computer incorporated. By 1978, Genentech scientists had cloned human insulin, and in the following year, they cloned the human growth hormone. In 1980, Genentech's initial public offering (IPO) was a great success, with one front-page headline reporting, "Genentech Jolts Wall Street." The stock price climbed from $35 to $89, settling at $71.25 at the end of the first trading day. In 1982, Genentech put the first recombinant DNA drug, human insulin, on the market. Over the years, Genentech has remained an industry leader.[3]

Genentech's success inspired many Bay Area scientists to follow suit. In 1980, UC Davis professor Raymond Valentine and entrepreneur Norman Doldfarb founded Calgene in Davis, specializing in the application of genetic engineering techniques in agriculture. In 1990, Calgene conducted the first successful field trial of a genetically engineered cotton plant designed to withstand the use of the herbicide Bromoxynil. (The same year, San Jose–based GenPharm International Inc. created the first transgenic dairy cow, which produced human milk proteins for infant formula.) In 1994, Calgene received FDA approval of the *Flavr Savr* tomato, the world's first biotech food that was claimed to taste better and stay fresh longer.

In 1981, UC San Francisco biochemists William Rutter and Pablo Valenzuela and UC Berkeley biochemist Edward Penhoet founded Chiron in Emeryville. In 1984, Chiron announced the first cloning and sequencing of the entire human immunodeficiency virus (HIV) genome. Two years later, the FDA granted Chiron a license for the first recombinant vaccine (for hepatitis).

The Cetus Corporation, founded by UC Berkeley postdoctoral fellow molecular biologist Ronald Cape in 1971 in Berkeley, was also involved in genetic engineering. In 1980, Kary Mullis and his colleagues at Cetus invented the polymerase chain reaction (better known as PCR) technique that enables scientists to produce billions of copies of a DNA molecule in only a few hours. PCR is such an important invention that

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[3]In 1990, Genentech agreed to a $2.1 billion takeover by the Swiss-based multinational pharmaceutical company Roche Holding Ltd.

it has been referred to as "the most revolutionary new technique in molecular biology in the 1980s." In 1981, Cetus completed its IPO, which, at the time, was the largest in U.S. history with $107 million in net proceeds. In the summer of 1991, Cetus sold its patent of the PCR technology to Hoffman–La Roche for $300 million and agreed to be acquired by Chiron. Two years later, the invention of PCR won Kary Mullis a Nobel prize in chemistry.

The presence of Silicon Valley in the Bay Area provided a unique opportunity for biotechnology to merge with information technology. In the late 1980s, UC Berkeley postdoctoral fellow, and later a research scientist at the Affymax Research Institute in Palo Alto, Stephen Fodor, came up with the idea that semiconductor manufacturing techniques could be used to build vast amounts of biological data on a glass chip, which would facilitate the analysis of complex genetic information. Using this idea, Fodor founded Affymetrix in Santa Clara. Today, Affymetrix's GeneChip technology provides a widely used platform for analyzing the relationship between genes and human health.

Amgen dominates the biotech industry in the Los Angeles region. Amgen was originally founded as Applied Molecular Genetics in 1980 by UCLA molecular biologist Winston Salser and venture capitalists Sam Wohlstadter and William Bowes. Although both venture capitalists were from San Francisco, the firm was located in Thousand Oaks, about 30 miles north of Los Angeles, to make it easily accessible from the UC campuses in Los Angeles and Santa Barbara and from the California Institute of Technology. In 1983, Amgen developed a recombinant protein that stimulates the production of red blood cells, which was launched as Epogen in 1989 for the treatment of anemia. In only ten years, Epogen became the world's sixth-best-selling drug, with 1999 sales of $1.8 billion. In 1991, Amgen launched Neupogen, a recombinant protein that stimulates the production of infection-fighting white blood cells. By 2001, the sales of Neupogen reached $1.3 billion.

With two blockbuster biotech drugs, Amgen soon became the largest biotech firm in the world, crossing over into the status of large pharmaceutical companies. In 2002, Amgen acquired Immunex, then the number-four biotech company, based in Seattle, making Amgen the

20th largest pharmaceutical company in the world, with global sales of $4.99 billion in 2002.

The formation of a biotech cluster in San Diego over the past three decades is one of the most admired success stories of regional economic development in the United States. In the late 1950s, when San Diego was known as a military town, no one could have anticipated its ascendancy as a biotech center. Yet a series of developments brought an army of first-rate scientists to San Diego. In 1956, one of the leading defense and aerospace companies, General Dynamics, opened a research lab in San Diego, which employed 3,000 people by the mid-1970s. The University of California opened its San Diego campus in 1960, which instantly attracted a top-quality research faculty. Immediately after, the Scripps Clinic and Research Foundation opened its research institute in San Diego, which would grow into "the world's largest, private non-profit biomedical research facility." In 1963, the Salk Institute for Biological Studies was established nearby. The two institutes are both world-renowned in the field of biology and would later become important sources of technology and entrepreneurs for San Diego's biotech industry.[4]

In 1978, two UC San Diego scientists, Ivor Royston and Howard Birndorf, founded San Diego's first biotech firm, Hybritech. Interestingly, the initial $300,000 capital also came from Kleiner Perkins Caufield & Byers, the same Bay Area venture capital firm that funded Genentech two years before. Hybritech went public in 1981 and grew into an 800-employee firm in 1986, before it was acquired by Eli Lilly. The culture of Hybritech did not fit well within the larger culture of Eli Lilly. As a result, some of Hybritech's original leaders chose to leave and start again. Hybritech alumni founded many other biotech firms in the San Diego region, including Gensia Laboratories, Ligand Pharmaceuticals, IDEC, Dura Pharmaceuticals, and Nanogen. These founders both planted and spread the seeds of the biotech industry in the area.

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[4]The Scripps Institute today houses 287 faculty members and nearly 800 postdoctoral fellows, with three Nobel laureates in its faculty. Five scientists trained at the Salk Institute have won Nobel prizes, and four of its current resident faculty members are Nobel laureates. See the history of these institutes at their websites: http://www.scripps.edu/ and http://www.salk.edu/about/.

San Diego's "world's finest climate" and high quality of life undoubtedly helped to attract talent from all over the world. In addition, its success also benefited from supportive city government and research institutions that foster entrepreneurship. Both the General Dynamics lab and the Salk Institute were built on land grants from the city of San Diego. In 1985, UC San Diego even founded a high-tech business networking organization, CONNECT, to support entrepreneurial activities in the San Diego region by "catalyzing, accelerating, and supporting the growth of the most promising technology and life sciences businesses." As the organization's website claims, "CONNECT is widely regarded as the nation's most successful regional program linking high-technology and life science entrepreneurs with the resources they need for success: technology, money, markets, management, partners, and support services."

Profile of California's Biotech Centers

We define California's three biotech centers as follows:

- San Francisco Bay Area—Alameda, Contra Costa, Marin, Napa, San Francisco, San Mateo, Santa Clara, Santa Cruz, Solano, and Sonoma Counties.
- Los Angeles region—Los Angeles, Orange, Riverside, San Bernardino, and Ventura Counties.
- San Diego region—San Diego County.

Table 2.3 summarizes the characteristics of the three biotech centers. The San Diego region, although much smaller in terms of population and geography, has the largest share of life science employment. San Diego's 25,290 life science workers account for more than 2 percent of the area's total employment; in the Bay Area, the share is about 1 percent, and the Los Angeles region's share is less than 1 percent.

Although the Los Angeles region has the largest total employment in the broadly defined life science industry, it has fewer biotech firms. The Bioability directory, a database of biotech companies, includes 257 biotech firms in the Bay Area, 209 in San Diego County, and only 98 in the Los Angeles region. Measured by the Biotechnology Industry

Table 2.3

Characteristics of California Biotech Centers

	San Francisco Bay Area	Los Angeles Region	San Diego Region
Population, 2000[a]	7,039,362	16,373,645	2,813,833
Total employment, 2001[b]	3,587,479	6,845,170	1,218,982
Life science employment, 2001[c]	39,025	54,674	25,290
Biotech employment, 2002[d]	28,303	18,049	14,989
No. of biotech firms[e]	257	98	205
BIO member companies[f]	139	24	58
NASDAQ/AMEX Biotech Index member companies[g]	27	3	11
No. of IPOs, 1998–2002[h]	36	2	15
No. of biotech alliances[i]	807	218	291
Total venture capital investment, 1992–2001 ($ billions)[j]	106.71	17.57	10.57
No. of venture capital firms[j]	256	45	14
Biotech venture capital investment, 1992–2001 ($ millions)[j]	6,493.62	356.11	3,370.64
No. of biotech patents, 1995–1999[k]	2,847	970	1,242
No. of research universities[l]	9	22	5
Total university research expenditures ($ millions, 2001)[l]	1,545.28	1,629.76	615.29
University expenditures on life sciences ($ millions, 2001)[l]	963.27	966.68	296.97
National Academy membership, 2002[l]	532	221	91
No. of life scientists, 2002[b]	6,300	5,650	3,830
No. of biological science postdoctoral fellows, 2000[m]	1,116	834	331
No. of biological science Ph.D. students, 2000[m]	1,482	2,084	425
No. of biological science doctorates awarded, 2002[m]	223	251	77
No. of NIH awards, 2002[n]	2,213	1,926	1,549
NIH funding, 2002 ($ millions)[n]	860.70	746.87	937.27

Table 2.3 (continued)

SOURCES:

[a]Census 2000.

[b]Bureau of Labor Statistics.

[c]National Establishment Time Series.

[d]Bioability and InfoUSA.

[e]Bioability.

[f]Biotechnology Industry Organization (http://www.bio.org).

[g]NASDAQ Biotech Index and AMEX Biotech Index.

[h]Ipo.com.

[i]Recap.com.

[j]VentureOne.com.

[k]U.S. Patent and Trademark Office.

[l]TheCenter at the University of Florida (http://thecenter.ufl.edu).

[m]National Science Foundation (http://www.nsf.gov).

[n]The National Institutes of Health (http://www.nih.gov).

Organization (BIO) member companies or the NASDAQ/AMEX biotechnology index companies, the Bay Area also has the most industry leaders, with the San Diego region once again outperforming the Los Angeles region. Similarly, from 1998 to 2002, the Bay Area cluster witnessed 32 IPOs, the San Diego region 15, and the Los Angeles region only two.

We also find that biotech companies in NASDAQ/AMEX indexes from the Bay Area spent more than twice as much on R&D in 2002 than companies in the Los Angeles region and four times as much as companies in the San Diego region. Bay Area companies spent a total of $2.6 billion on R&D, whereas Los Angeles region companies spent $1.1 billion and San Diego region companies spent $626 million. However, the Los Angeles region, which has the largest biotech company, Amgen, generated the most sales with $5.8 billion, compared to $4.7 billion in the San Francisco Bay Area and only $1.2 billion in the San Diego region.

Because of both the risks and the potential for growth associated with biotech firms, the biotech industry relies heavily on venture capital to fund its start-ups. The Bay Area undoubtedly enjoys a great advantage along this dimension because of its access to abundant local capital. As mentioned above, the formation of the Bay Area's industry leader, Genentech, was actually initiated by a venture capitalist. Pioneering firms in the San Diego and Los Angeles regions, such as Hybritech and Amgen, were also funded by the Bay Area's venture capitalists. In recent years, venture capital investment has become more active in both the Los Angeles and San Diego regions. In fact, both areas are easily among the top ten regions in the country in terms of available venture capital. Still, they are both far behind the Bay Area in that respect. During 1992–2001, venture capital investment in the Bay Area totaled $106.7 billion, six times the total investment in the Los Angeles region and ten times that in the San Diego region.

In terms of the number of venture capital firms, the Bay Area's advantage is even more obvious. According to VentureOne (2001), 256 venture capital firms have headquarters or offices in the San Francisco Bay Area; only 45 and 14 such firms have a presence in the Los Angeles and San Diego regions, respectively. As is well known, venture capital firms are most likely to invest in start-ups within driving distance so that they can closely monitor the performance of such firms and provide assistance whenever necessary (see, for example, Sorenson and Stuart, 2001). Thus, it is much easier for the Bay Area's entrepreneurs to access capital and for the area's life scientists to commercialize their inventions.

The San Francisco Bay Area holds more biotech patents than the other two regions combined. As Jaffe, Trajtenberg, and Henderson (1993) show, knowledge spillovers through patent citation are primarily a local phenomenon. That is, use of patents is more likely to occur in the same metropolitan area as the cited patents. In this sense, the Bay Area will naturally benefit from its large number of local inventions.

The Los Angeles region has 22 universities, the San Francisco Bay Area has nine, and San Diego has five. However, research quality matters much more than the quantity of universities. In terms of university spending on life sciences research, the Bay Area and the Los Angeles region are almost equal, whereas the San Diego region remains far behind. However, the San Diego region's world-renowned research institutes, such as the Salk Institute and the Scripps Research

Institute—which are not counted in university spending—make up for some of the difference. If we look at the total grants from the National Institutes of Health to these regions, the San Diego cluster impressively outperforms the other two regions.

In terms of advanced training at the doctoral and postdoctoral levels, the San Diego region trails the other two regions. But again, the San Diego region's numbers are underestimated because its research institutes are not included in the comparison. Also, the San Diego region can easily recruit talent from universities in the Los Angeles region.

Cortright and Mayer (2002) characterize biotech centers using various data sources at the Consolidated Metropolitan Statistical Area (CMSA) level. Their nationwide study enables us to compare California biotech centers with other regions in the United States. Table 2.4 summarizes the national rankings of California's biotech centers using various measures. Overall, California's three regions are consistently ranked among the top ten. The San Francisco Bay Area leads the entire

Table 2.4

National Rankings of California's Biotech Centers

	San Francisco–Oakland–San Jose CMSA	Los Angeles–Riverside–Orange County CMSA	San Diego MSA[a]
Biotech companies, 2001	1	7	4
Companies with 100+ employees, 2001	1	6	4
Publicly traded biotech companies, 2001	1	4	4
Venture capital for biopharmaceuticals, 1995–2001	1	8	3
Biotechnology-related patents, 1975–1999	2	8	7
NIH funding, 2000	4	7	5
NIH research funding to medical schools, 2000	4	6	9

SOURCE: Cortright and Mayer (2002).

[a]Metropolitan Statistical Area.

country in the number and size of its biotech companies and in biotech venture capital investment. The Los Angeles region seems to have room for improvement, given its strength in research and abundance of venture capital. In terms of NIH funding, the Boston, New York–North New Jersey, and Washington-Baltimore areas lead the country. To a great extent, the leading position of California's biotech economy hinges on venture capital and the continual influx of federal R&D money for bioscience research.

A recent study by the U.S. Department of Commerce showed that California continues to generate a large share of new biotech firms. Thirty-eight percent of firms established between 1997 and 2001 located in California, increasing the number of biotech companies by 45 percent.[5] North Carolina, with its smaller base, is the only area that had higher growth, increasing its base by 52.5 percent.

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[5]U.S. Department of Commerce (2003).

3. Venture Capital and the Biotech Industry

Although many new firms in biotech are backed by venture capital, no existing studies focus on firm formation from this perspective. In this chapter, we document the intensity of entrepreneurial activities by looking at venture capital deals in the biotech industry over the past decade. In particular, we study the trend of firm formation and venture capital raised by new firms. Chapter 4 focuses on venture-backed entrepreneurs, especially academics, in the biotech industry.

The VentureOne dataset used in this analysis and described below covers all industries in the United States and has two advantages. First, the data allow us to compare California's biotech industry with other biotech centers as well as with the national average. Second, the data make it possible to compare the biotech industry with other high-tech industries. For these reasons, we freely extend our investigation to other regions and other industries for the sake of comparison, with the hope that a deeper understanding of the unique features of California's biotech industry will better inform policy discussions in this area.

Money is oxygen for businesses; this is particularly true for biotech companies. New firms usually spend millions of dollars on R&D before they have any products to deliver. For those start-ups whose products are subject to FDA approval, the development process can easily take years. On the other hand, the enormous health care market is already established. The United States spends about $1.55 trillion—14.9 percent of its GDP—on health care, of which 10.5 percent goes to purchase prescription drugs.[1] Thus, once a biotech firm has a "blockbuster" product on the market, it makes big profits. This is exactly the type of investment opportunity that venture capitalists like to pursue.

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[1]U.S. Department of Health and Human Services (2004).

Economists have shown that an entrepreneur's decision to start a business is affected by a "liquidity constraint" (Holtz-Eakin, Joulfaian, and Rosen, 1994). That is, potential entrepreneurs may surrender their intention to start a firm if they lack sufficient capital. Given that biotech firms are extremely capital-intensive, the liquidity constraint may be even more deterring.

From the earliest days of the biotech industry, venture capital has alleviated the liquidity constraint. In 1975, a rookie venture capitalist at Kleiner-Perkins, Robert Swanson, teamed up with Professor Herbert Boyer to found Genentech, the world's first biotechnology company. The founding team of Genentech typifies the combination of venture capitalists and academic researchers in this industry. Kenney (1986) documents that other early start-ups in the biotech industry followed the same pattern. For example, Genex, Advanced Genetic Sciences, Hybritech, Integrated Genetics, and Amgen were each founded by a team consisting of university professors and venture capitalists. Kenney argues that it was the availability of venture capital that created the freestanding biotech industry in the United States, whereas in Europe and Asia, biotech did not become a separate industry because of the weaker financial support for potential entrepreneurs.

The VentureOne Data

VentureOne—a leading venture capital research company—provided the data we use in our analysis of venture capital. VentureOne claims to have "the most comprehensive database on venture-backed companies." Our data cover venture capital deals completed from the first quarter of 1992 through the fourth quarter of 2001. They include 29,277 rounds of financing involving 11,029 firms.[2] Among these firms, 83.5 percent were founded in or after 1990.

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[2]A firm is included in the VentureOne database only if it is "venture-backed"—i.e., it received investment from venture capital firms. However, not every round of finance in the database is venture capital investment. For example, if a venture-backed firm entered the stock market through an IPO, the round of IPO is also included in the database. In some other cases, the database also captured bank loans to venture-backed firms. We exclude such rounds in calculating various venture capital statistics.

VentureOne categorizes venture-backed firms into 16 "industry segments." We regard the "biopharmaceuticals" segment as the biotech industry, which consists primarily of four groups of firms:

- Biotechnology companies: Conduct genetic research in such areas as genomics, proteomics, gene therapy, and bioinformatics.
- Drug discovery companies: Conduct research to develop new drugs.
- Drug delivery companies: Develop novel systems to deliver medicines directly to the diseased area in the human body.
- Pharmaceutical companies: Manufacture and sell medicinal drugs.

In general, traditional pharmaceutical companies that develop chemical compounds without applying gene technology are not considered biotech firms. Although the "biopharmaceuticals" industry segment may include some such firms, we are unable to exclude them. Given that almost all the firms in the dataset were founded after 1980 and a vast majority after 1990, we believe the inclusion of such traditional firms is rare. Similarly, because genetic engineering is also applied to improve crops and develop special materials, some firms in other industry segments such as "agriculture" and "special materials" may qualify as biotech firms. However, because we have no systematic method for separating out biotech firms from those industries and because those segments are much smaller, we decided to focus on biopharmaceutical firms only. Using this definition, the biotech industry completed 2,140 rounds of financing and involved 689 companies. We know the exact founding date of 665 companies, of which 79.1 percent were founded in or after 1990.

The VentureOne data include detailed information about venture-backed start-ups. Firm-level variables include the start year, address, industry, employment, current business status, current ownership status, and so on.

VentureOne also provides a separate dataset containing information about start-up founders. An "EntityID" variable allows us to match the firm data with the founder data. Brief biographical information on founders is available, which enables us to engage in some elementary studies of entrepreneurs in Chapter 4. Unfortunately, the founder information is not complete. Among the 689 biotech firms, 351 have founder information, which is matched to 626 individual founders.

Venture Capital in the Biotech Industry

The 1990s saw a great surge in information technology, characterized by the commercialization of the Internet. This development is reflected in the venture capital industry. As Table 3.1 shows, telecommunications, customer/business services (mostly e-commerce), software, and information services captured most venture

Table 3.1

Real Venture Capital Raised, by Industry, 1992–2001

	United States		California		
Industry	Venture Capital Raised ($ millions)[a]	% of Total	Venture Capital Raised ($ millions)[a]	% of Total	% of U.S. Total
Communication	49,502.21	23.31	18,447.98	19.70	37.27
Consumer/business services	41,240.49	19.42	17,802.22	19.01	43.17
Software	40,917.17	19.27	20,343.99	21.72	49.72
Information services	19,687.36	9.27	9,041.66	9.65	45.92
Biopharmaceutical	**13,606.89**	**6.41**	**5,908.42**	**6.31**	**43.42**
Retailing	9,242.43	4.35	4,111.54	4.39	44.49
Medical devices	8,903.98	4.19	4,995.81	5.33	56.11
Semiconductor	8,330.73	3.93	6,224.56	6.65	74.72
Electronics	6,608.62	3.11	3,524.01	3.76	53.32
Health care	4,607.45	2.17	609.22	0.65	13.22
Medical information services	5,669.59	2.67	1,544.93	1.65	27.25
Consumer/business products	2,111.29	0.99	665.34	0.71	31.51
Advance/special material and chemical	641.62	0.30	308.83	0.33	48.13
Energy	580.15	0.27	41.40	0.04	7.14
Agriculture	209.05	0.10	36.40	0.04	17.41
Other	463.30	0.22	49.19	0.05	10.62
Total	212,322.3	100	93,655.5	100	44.11

SOURCE: Authors' calculations from the VentureOne database.

NOTE: Totals may not sum exactly because of rounding.

[a]In 1996 dollars.

capital financing during the 1990s. Together, these four industries consumed more than 70 percent of all venture capital raised during 1992–2001. Measured in 1996 dollars, the biotech industry represents the fifth most heavily financed industry in the United States. It raised $13.6 billion over the decade, which amounts to 6.4 percent of the total venture capital investment in the United States. In California, the biotech industry represents a similar share, 6.31 percent of the total.

During 1992–2001, more than half of venture capital investment took place in California and Massachusetts, followed by New York, Texas, Washington, and Colorado, as shown in Table 3.2. California

Table 3.2

Top Ten States, by Real Venture Capital Raised, 1992–2001

State	Venture Capital Raised ($ millions)[a]	% of U.S. Total	No. of Deals
Total Venture Capital Investment			
California	93,655.50	44.11	9,856
Massachusetts	22,196.60	10.45	2,612
New York	11,129.79	5.24	1,179
Texas	12,008.25	5.66	1,145
Washington	6,881.90	3.24	787
Colorado	8,468.45	3.99	703
Virginia	5,632.51	2.65	673
Pennsylvania	5,466.01	2.57	657
Georgia	4,563.52	2.15	602
New Jersey	5,197.80	2.45	501
Venture Capital Investment in Biotech			
California	5,908.42	43.42	673
Massachusetts	2,386.78	17.54	297
Pennsylvania	706.99	5.20	99
North Carolina	594.51	4.37	83
Washington	607.86	4.47	65
New Jersey	470.90	3.46	57
Maryland	357.82	2.63	54
Texas	358.31	2.63	52
Colorado	436.07	3.20	45
Minnesota	121.91	0.90	29

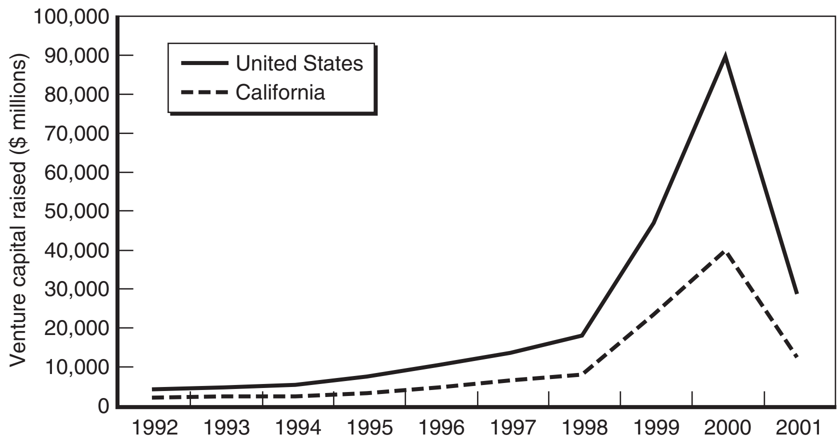
SOURCE: Authors' calculations from the VentureOne database.

[a]In 1996 dollars.

alone received $93.7 billion of venture capital, accounting for 44 percent of the U.S. total. Massachusetts placed a distant second, raising $22.2 billion, or 10.5 percent of the U.S. total. In the biotech industry, California and Massachusetts are even more overrepresented. Together, they account for more than 60 percent of the venture capital invested in biotech, and California alone absorbed 43 percent of the total. The San Francisco Bay Area, the Boston region, and the San Diego region are the most heavily invested biotech clusters.

Figure 3.1 traces the nominal amount of venture capital invested in the United States and California over the ten years from 1992 to 2001. The trends show accelerating growth in the 1990s followed by a severe crash. Between 1992 and 1994, venture capital investment in the United States first increased from $3.49 billion to $3.95 billion and then jumped to $4.72 billion. Compared to what happened later, these 13.2 percent and 19.4 percent increases seem modest. From 1994 to 1996, venture capital investment first experienced a 44.7 percent increase, followed by another 44.4 percent growth. During these two years, venture capital investment jumped from $4.72 billion to $9.86 billion, stimulated by the Internet revolution. In 1997 and 1998, venture capital investment maintained its momentum, registering annual growth of 31.5 percent and 34.4 percent, respectively. In 1998, the U.S. total reached $17.4 billion. The following two years can only be described as mania: Venture capital investment increased first by 166 percent, and then by 92 percent, totaling $88.90 billion by 2000. In nominal dollars, venture capital investment in 2000 was 24 times greater than in 1992. This increase even dwarfed the Internet bubble seen in the NASDAQ Index. The bursting of that bubble is also reflected in venture capital investment. In 2001, total investment crashed down to $27.98 billion, a 69 percent decline. In spite of this large decline, the year 2001 still represents the third most heavily invested year in venture capital history.

As shown in the figure, venture capital investment in California paralleled the national trend. California's yearly total venture capital investment constituted more than 40 percent of the U.S. total, except in 1994 and 1995. California's share ranged from 37 percent in 1995 to 49 percent in 1999.

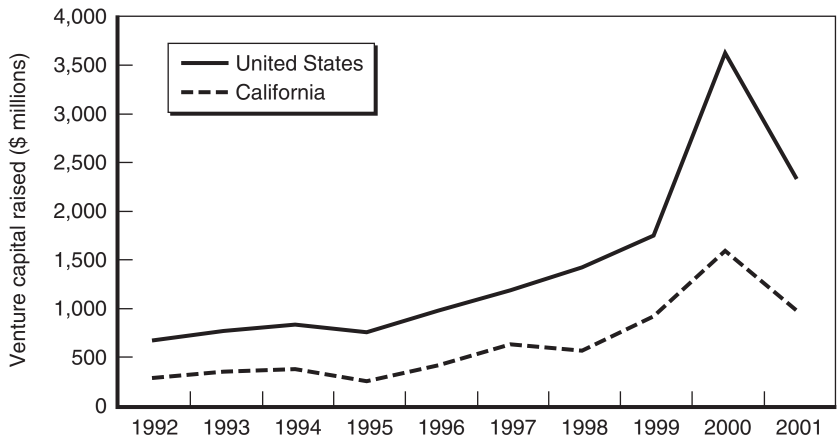


SOURCE: Authors' calculations from the VentureOne database.

Figure 3.1—Total Venture Capital Raised, 1992–2001

Figure 3.2 depicts the trends of venture capital invested in the biotech industry in the United States and California. Here we also see accelerated growth in the 1990s followed by a severe crash, although the trends are not as smooth as the U.S. and California totals in Figure 3.1. In 1993 and 1994, venture capital investment in U.S. biotech experienced annual growth of 15.6 percent and 8.8 percent. Yet in 1995, the U.S. total declined by 9.5 percent. This is the year the Internet picked up momentum and apparently competed with biotech for venture funds. The biotech industry quickly reclaimed lost ground with a 30.2 percent annual growth rate in 1996. It continued to grow at around a 20 percent annual rate for three years, and shot up in 2000 with a 109 percent increase. In 2001, total investment fell 36 percent, not as much as venture capital overall, making 2001 the second-best year in biotech venture capital history. In 2000, U.S. venture capital investment in biotech totaled $3.60 billion dollars, 5.6 times the 1992 total.

In the biotech industry, California's share of the U.S. total is typically very high but varies over the years. In 1997 and 1999, biotech venture capital in California accounted for more than half of the U.S.

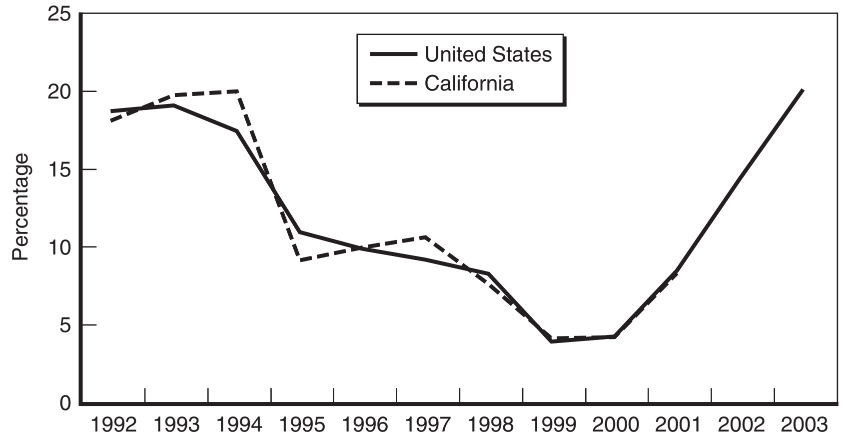


SOURCE: Authors' calculations from the VentureOne database.

Figure 3.2—Venture Capital Raised in the Biotechnology Industry, 1992–2001

total, at 52 percent in both years. Only in 1995 did California's share in biotech venture capital dip below one-third of the U.S. total, hitting 30.4 percent. The year 1995 was not a particularly bad year for venture capital funding, because the total amount of venture capital investment in California increased by 40 percent from 1994. However, that year marked the beginning of the Internet revolution, which, as noted above, might have drained venture capital away from the biotech industry.

Although Table 3.1 shows that only 6.4 percent of U.S. venture capital investment and 7.7 percent of California's venture capital went to biotech during 1992–2001, those numbers are somewhat misleading, since the percentages vary significantly from year to year. As Figure 3.3 shows, biotech received much larger proportions of the total venture capital in the early 1990s. In 1992, 17.8 percent of California's venture capital and 18.3 percent of the U.S. total were invested in biotech. During that time, biotech was one of the hottest areas for risk-seeking investors, who fueled a biotech boom in the early 1990s. In 1994, biotech still received 19.6 percent of the California total and 17.1 percent of the U.S. venture capital total. It was only after 1995, when the enormous potential of the Internet was recognized, that biotech

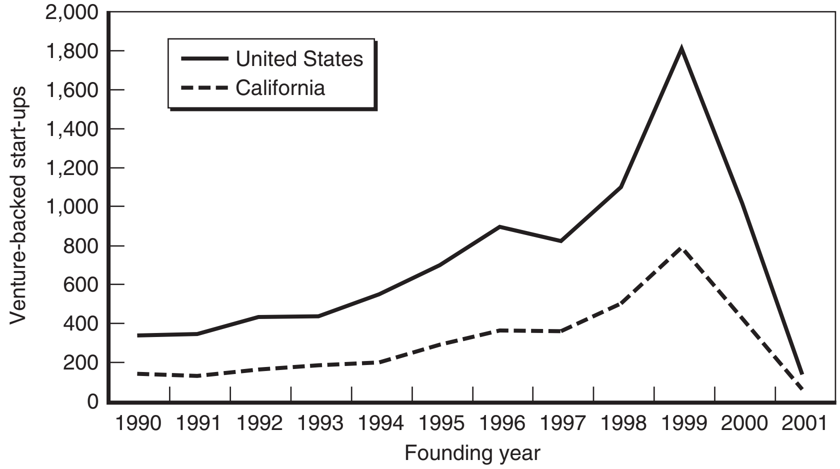


SOURCE: Authors' calculations from the VentureOne database.

Figure 3.3—Percentage of Total Venture Capital Invested in Biotech, 1992–2003

began to lose its appeal to venture capitalists. The percentage of venture capital allocated to biotech hit its lowest point in 1999, when only 3.9 percent of California's venture capital and 3.7 percent of the U.S. total went to the industry. From then on, as investment opportunities in Internet-related industries dried up, biotech reclaimed its share of venture capital investment. In 2002, 14.2 percent of the U.S. total was invested in biotech. The proportion shot up further to 19.9 percent in 2003, the highest percentage in the past 12 years. Although we do not have data for California for the last two most recent years, the share likely increased at a comparable level to the U.S. total, because California has closely followed the national trend in recent years.

Figure 3.4 presents the number of venture-backed start-ups in all industries by founding year. It shows that the trend in entrepreneurship parallels the trend in venture capital investment (Figure 3.1). Clearly, the total number of firms founded in all industries increased steadily in the 1990s before the burst of the Internet bubble. The trend peaked in 1999, a year earlier than the peak of venture capital investment, because, on average, start-ups complete their first round of financing more than a year after they are founded. We observe similar trends when examining the top



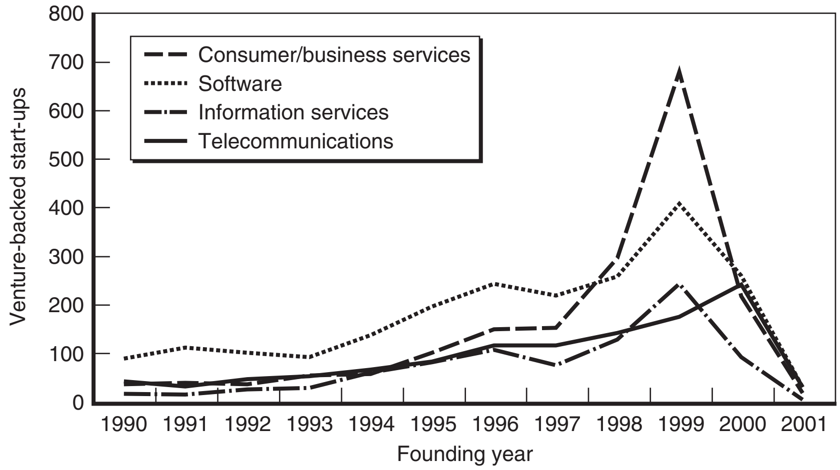
SOURCE: Authors' calculations from the VentureOne database.

Figure 3.4—Venture-Backed Start-Ups, All Industries, 1990–2001

four venture capital funded industries separately—telecommunications, consumer/business services, software, and information services (Figure 3.5).

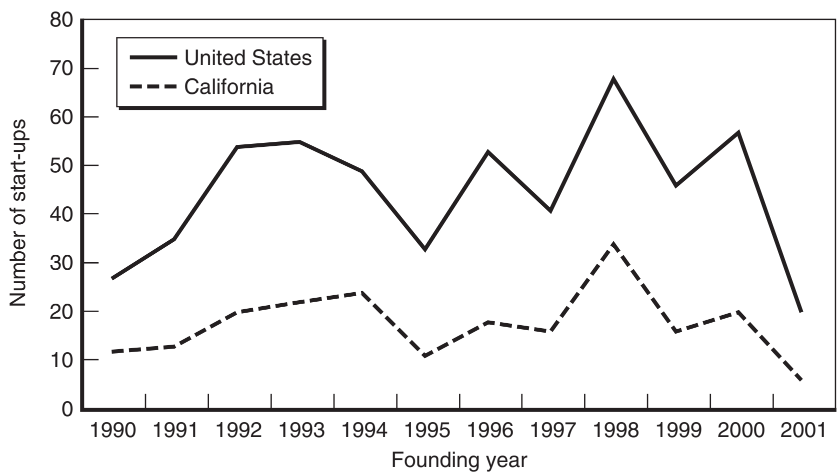
Figure 3.6 shows the number of biotech start-ups backed by venture capital in each year. A striking difference between the biotech industry and other industries is that entrepreneurship in the biotech industry does not exhibit a clear upward trend. The number of biotech firms founded in each year fluctuated a great deal over this period. In Figure 3.4, we see that the total number of venture-backed start-ups in all industries shot up from 417 in 1992 to 1,795 in 1999, a 330 percent increase. However, only 45 biotech firms were founded in 1999, compared to 53 in 1992. Similarly, as shown in Figure 3.7, there is no clear upward trend in biotech entrepreneurship in the three major biotech clusters in California. Figure 3.7 also includes the trend of firm formation in Boston, the largest biotech center outside California. Again, no clear upward trend is detected.

Figures 3.8 and 3.9 tell a more complete story about why there was no significant increase in the number of firms founded in the biotech



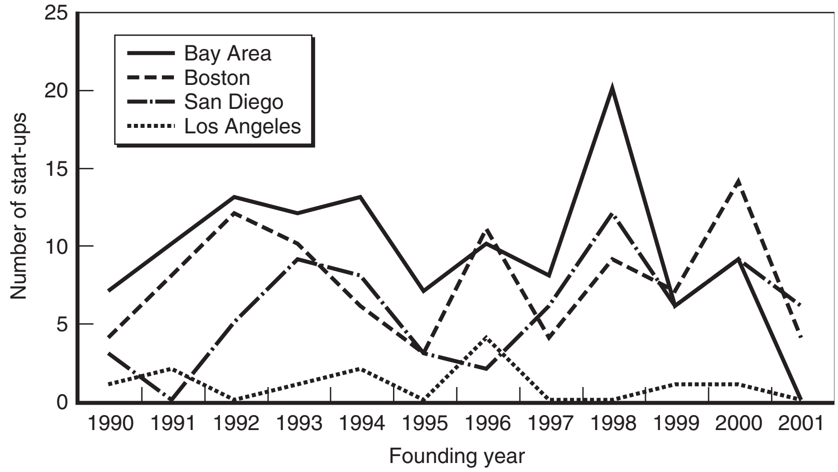
SOURCE: Authors' calculations from the VentureOne database.

Figure 3.5—Venture-Backed Start-Ups, by Industry, 1990–2001



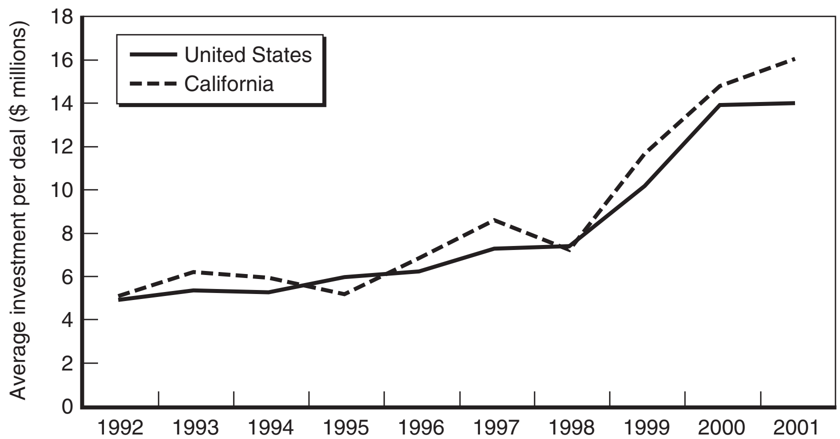
SOURCE: Authors' calculations from the VentureOne database.

Figure 3.6—Venture-Backed Biotech Start-Ups, 1990–2001



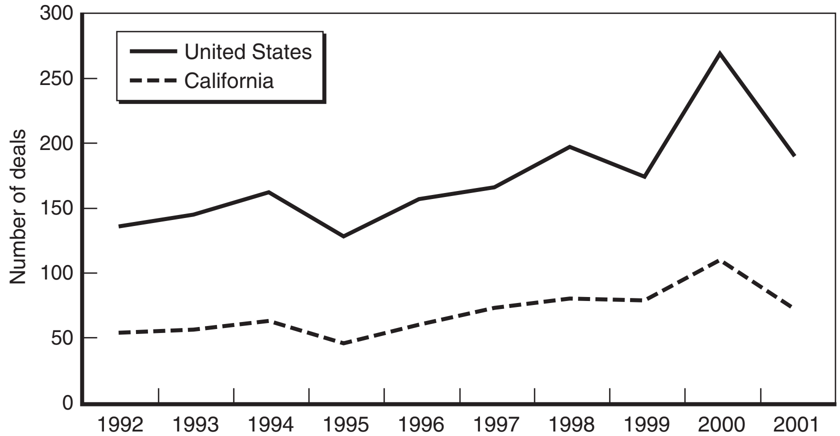
SOURCE: Authors' calculations from the VentureOne database.

Figure 3.7—Venture-Backed Biotech Start-Ups, by Region, 1990–2001



SOURCE: Authors' calculations from the VentureOne database.

Figure 3.8—Average Venture Capital Investment per Deal Raised by Biotech Firms, 1992–2001



SOURCE: Authors' calculations from the VentureOne database.

Figure 3.9—Number of Venture Capital Deals Completed for Biotech Firms, 1992–2001

industry during the venture capital boom. As more venture capital investment was available to biotech start-ups, each round of financing represented a larger amount of money. The average amount of venture capital raised per deal by biotech firms was $7.26 million in 1998, but this figure jumped to $13.79 million in 2000. In fact, before 2000, the trend of the average amount of venture capital raised per deal in biotech (Figure 3.8) almost perfectly mirrored the trend of total venture capital raised by this industry (Figure 3.2). At the same time, the number of deals closed in 2000 also increased, which means that more existing firms got refinanced quickly. From 1992 to 1999, between 120 and 200 rounds of financing were completed each year in the biotech industry. The year 1999 saw 172 deals, but by 2000, that number jumped to 267. Thus, the biotech industry, despite the infusion of venture capital, did not produce significantly more firms as did other industries but instead provided more funds to each firm and more rounds of financing to existing firms.

Overall, the data show that stimulated by the commercialization of Internet technology, a large amount of venture capital was invested in the late 1990s. This abundance of venture capital benefited the biotech industry, resulting in a parallel surge of venture capital in biotech, although the relative share of venture capital investment in biotech shrank significantly during the years of the Internet boom. However, the increase in venture capital did not cause a significant increase in the number of biotech start-ups founded over the period. Instead, each biotech firm received more money in each round of financing, and more existing firms got refinanced. This situation of "too much money chasing too few ideas" suggests that the availability of venture capital is not a binding constraint on entrepreneurship in biotech. Previous studies have explained the important role of star scientists—those with groundbreaking discoveries—in firm formation in the biotech industry. Thus, a natural hypothesis is that founding a biotech firm is primarily determined by whether there is a new marketable technology in genetic engineering.

Characteristics of Venture-Backed Biotech Firms

This section summarizes the characteristics of venture-backed biotech firms and compares them with the overall sample of venture-backed firms. We focus on firms founded in the 1990s because relatively few older firms were captured by the VentureOne data.

Biotech firms obtain their first round of financing more quickly than the average venture-backed firm. On average, it takes a biotech start-up 13.5 months to get its first round of venture capital in place; the overall average for start-ups in all industries is 16.6 months. In California, the difference is smaller: 11.2 months versus 13 months (Figure 3.10).[3]

Biotech firms also obtain more rounds of venture capital investment. On average, they completed 2.8 rounds of financing compared to an overall average of 2.4. In California, an average biotech firm completed three rounds of financing compared to an overall of 2.5 (Figure 3.11).[4]

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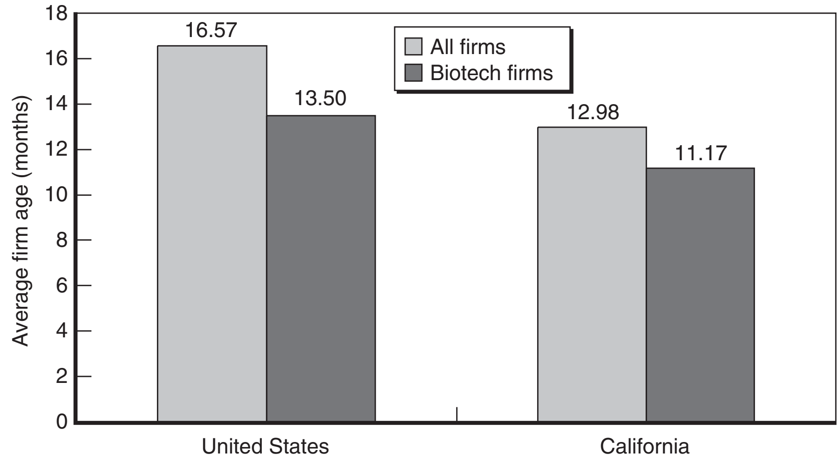
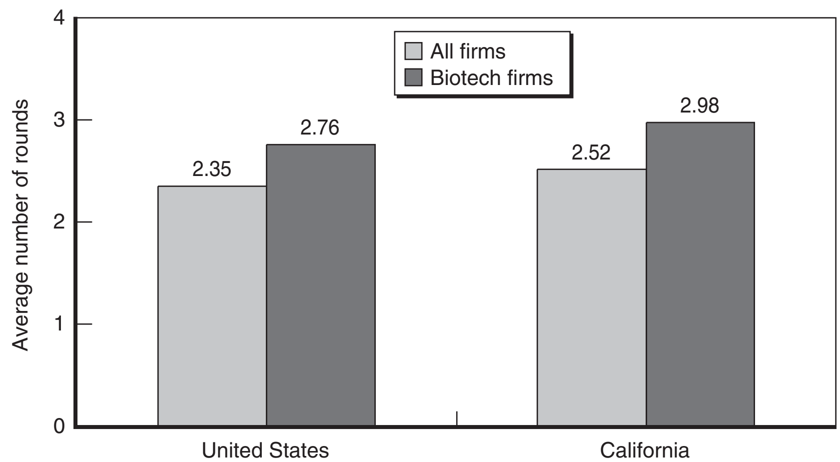
[3]We conducted a one-sided t-test to compare the means of the two samples. For the nation, the difference is statistically significant at the 1 percent level, whereas for California, the difference is significant only at the 10 percent level.

[4]Both differences are statistically significant at the 1 percent level.



SOURCE: Authors' calculations from the VentureOne database.

Figure 3.10—Average Firm Age at Closing Date of First Round of Venture Capital

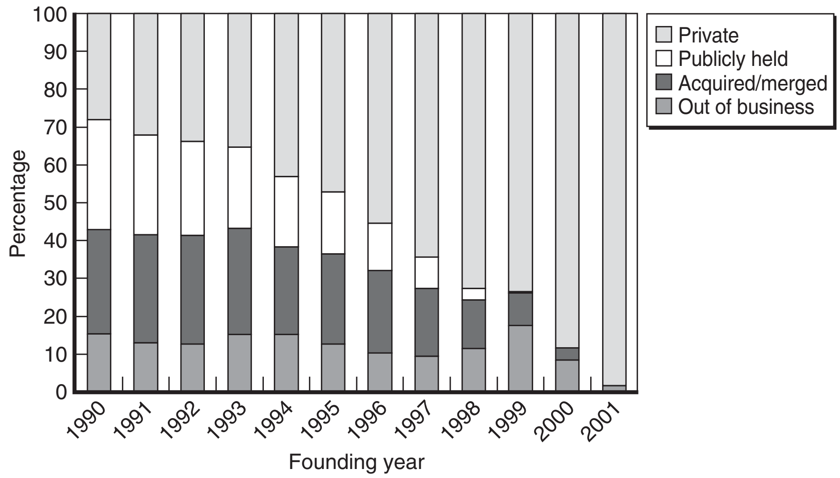


SOURCE: Authors' calculations from the VentureOne database.

Figure 3.11—Average Rounds of Venture Capital per Firm

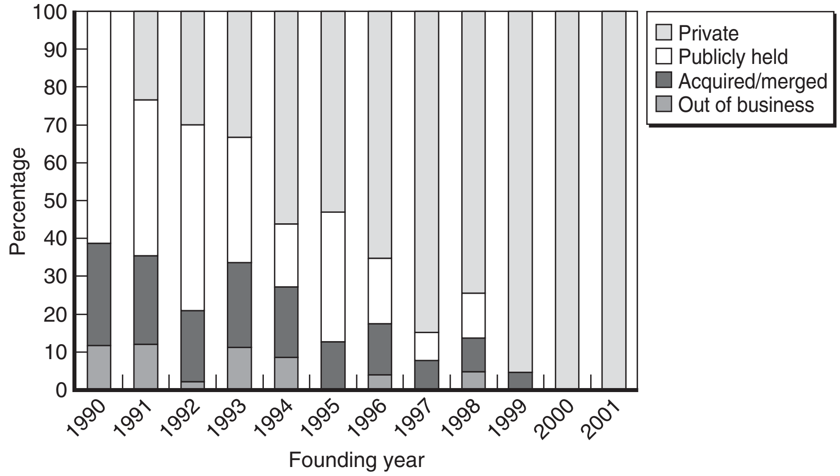
Compared to the national average, California firms (both biotech firms and all firms) receive venture capital more quickly and more often. These observations reflect the fact that California firms enjoy easier access to venture capital, which likely gives them some first-mover advantages.

Figure 3.12 and 3.13 illustrate the ownership status of all firms and biotech firms, respectively, by founding year. Naturally, firms founded earlier are more likely to be publicly held, more likely to be acquired or merged, more likely to go out of business, and less likely to remain privately owned. In the whole sample, between 10 and 20 percent of venture-backed firms go out of business, which is considerably less than the failure rates often presented in the media. It seems that if firms can survive the first three years, their risk of mortality drops substantially. The mortality rate of the 1999 cohort is particularly high, probably because firms founded around this time were too generously funded and not strictly screened. By the fourth quarter of 2001, 17.4 percent of the start-ups in that cohort had gone out of business.



SOURCE: Authors' calculations from the VentureOne database.

Figure 3.12—Ownership Status of All Venture-Backed Firms in the United States, 2001



SOURCE: Authors' calculations from the VentureOne database.

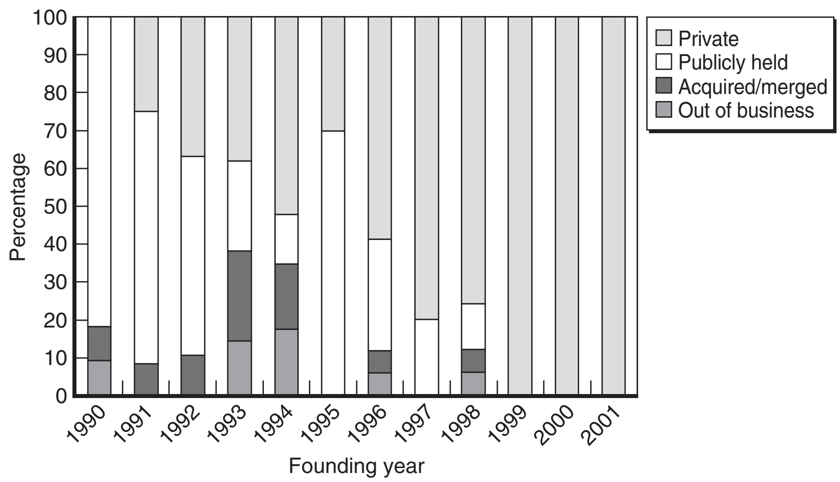
Figure 3.13—Ownership Status of Venture-Backed Biotech Firms in the United States, 2001

As firms become older, more and more go public as well. Yet, IPO is not the only way venture capitalists liquidize their investments. A more frequently observed change of ownership is through merger and acquisition. In the whole sample, start-ups that are acquired or merged outnumber those that go public in every cohort. Although firms are less likely to remain private as they grow older, by the end of 2001, one-third of the firms founded in 1992 were still privately owned.

The biotech industry behaves like other industries in the sense that firms in older cohorts are more likely to be publicly held, to be acquired or merged, and to be out of business. On the other hand, biotech firms also exhibit some distinct features. Specifically, relatively more biotech firms go public than are acquired or merged, and very few remain private in the long run. By the end of 2001, no biotech firm founded in 1990 remained privately owned, probably because private biotech companies cannot raise enough capital to survive that long.

The mortality rate differs significantly between different cohorts as well. Although the 1999 cohort in the whole dataset has the highest mortality rate, none of the 45 biotech firms founded in 1999 went out of business. On average, biotech start-ups seem less likely to go out of business. Several reasons may explain this lower mortality rate in the biotech industry: (1) Biotech firms go through a stricter review process at venture capital firms, and hence bad business plans are more likely to be screened out early; (2) biotech products take a longer time to develop, and hence it takes many more years to realize a failure; (3) the abundance of capital during the Internet boom resulted in imprudent investments, which mainly affected Internet-related industries rather than the biotech industry.

Figure 3.14 shows the ownership status of California's venture-backed biotech firms. Since this is a much smaller subset of firms (a total of 200 firms over 11 cohorts), the ownership outcomes vary drastically from one cohort to another. It is impressive that none of the firms founded in 1991 and 1992 had gone out of business by 2001. Yet the 1993 and 1994 cohorts performed remarkably poorly. A considerably larger share of them either went out of business or lost independence through merger and acquisition.



SOURCE: Authors' calculations from the VentureOne database.

Figure 3.14—Ownership Status of Venture-Backed Biotech Firms in California, 2001

Table 3.3 describes the business status of venture-backed firms in 2001. For start-ups that were still privately held, the business status was their current business status as of the fourth quarter of 2001. For those that were acquired by other firms or went through an IPO, the "current business status" variable refers to their status at the time of these events, because VentureOne stops tracking them once a merger/acquisition or IPO occurs. The overwhelming majority of the venture-backed firms are in the high-tech sector and thus involved in risky businesses. About 70 percent of one-year-old firms were developing or testing their products;

Table 3.3

Business Status of Venture-Backed Firms Founded Since 1990

	Profitable	Shipping Product	Clinical/ Beta Trial	Product Development	Start-Up	Total
U.S. Overall						
Out of business	22	787	62	163	26	1,060
Private/independent	381	3,483	455	792	46	5,157
Acquired/merged	125	999	74	169	8	1,375
Publicly held	141	540	59	58	0	798
U.S. total	669	5,809	650	1,182	80	8,390
U.S. Biotech						
Out of business	0	4	0	18	1	23
Private/independent	3	51	96	166	6	322
Acquired/merged	2	13	15	36	2	68
Publicly held	5	23	47	38	0	113
U.S. biotech total	10	91	158	258	9	526
California Overall						
Out of business	4	334	40	82	9	469
Private/independent	93	1,284	231	373	19	2,000
Acquired/merged	32	442	38	80	4	596
Publicly held	45	264	26	30	0	365
California total	174	2,324	335	565	32	3,432
California Biotech						
Out of business	0	2	0	8	1	11
Private/independent	2	15	43	59	0	119
Acquired/merged	0	2	5	8	1	16
Publicly held	2	11	19	22	0	54
California biotech total	4	30	67	97	2	200

SOURCE: Authors' calculations from the VentureOne database.

the fraction is lower but close to 50 percent for the two-year-olds. Older firms are more likely to have a product to deliver. But, across cohorts, including those founded in 1990, more than 10 percent of the firms had no product by 2001. Older firms are also more likely to make a profit but, overall, less than 8 percent of the firms had ever made any profit. Even among the 1990 cohort—the oldest ones in the current sample—fewer than one-third were profitable. This unprofitable outlook over a long horizon is precisely why venture capitalists rather than conventional financial institutions backed these firms.

Biotech is probably an even more risky business than other high-tech industries because of its lengthy product development timeline. As Table 3.3 confirms, more than 70 percent of all the biotech firms founded since 1990 were still developing or testing their products. Within the whole biotech industry, only ten out of 526 firms founded since 1990 were profitable. This suggests that most venture capital invested in biotech firms is spent on R&D rather than production.

The 200 California biotech firms tell a similar story. Only four of them registered any profit, and thus R&D is the major activity of these start-ups. However, as Table 3.3 shows, venture-backed biotech firms, although far from profitable, are also less likely to go out of business in the short run. They tend to survive a longer period of time without making any profit, clearly a unique feature of the biotech industry.

Table 3.4 presents the size distribution of venture-backed firms in 2001. Once a firm goes out of business, is acquired, or completes an IPO, VentureOne stops updating its employment data. We have excluded such firms from the calculation. Biotech firms tend to be smaller than those in other industries in terms of employment size. Over 80 percent of biotech firms in the United States that received venture capital during 1992–2001 had no more than 50 employees in the fourth quarter of 2001; that number was 57.8 percent for start-ups in all industries. In California, this difference is smaller: 71.1 percent of biotech firms and 57.9 percent of all firms had no more than 50 employees. In both California and the nation as a whole, no venture-backed biotech start-ups had more than 250 employees, although quite a few firms in other industries surpassed this mark.

Table 3.4

Size Distribution of Venture-Backed Firms, 2001

No. of Employees	All Firms	% of Total	Biotech Firms	% of Total
United States				
0–5	187	3.81	43	13.96
6–20	967	19.69	101	32.79
21–50	1,685	34.32	104	33.77
51–100	1,063	21.65	48	15.58
101–250	726	14.79	12	3.90
251–500	165	3.36	0	0
500+	117	2.38	0	0
Total	4,910	100	308	100
California				
0–5	60	3.16	11	9.65
6–20	341	17.99	35	30.70
21–50	697	36.76	35	30.70
51–100	440	23.21	25	21.93
101–250	291	15.35	8	7.02
251–500	45	2.37	0	0
500+	22	1.16	0	0
Total	1,896	100	114	100

SOURCE: Authors' calculations from the VentureOne database.

Table 3.5 shows average employment levels of venture-backed firms founded in or after 1990. For privately held firms, these are their average sizes in the fourth quarter of 2001. For other firms, these numbers reflect their average employment at the time of bankruptcy, merger/acquisition, or IPO. In each category, biotech firms are at least 50 percent smaller than the overall average, a clear indicator that firms grow slower in the biotech industry. This implies that rapid growth in this industry relies more on the growth of the total number of firms than on the growth of existing firms. That is, firm formation is the most important source of growth.

Table 3.5

Average Employment Level of Venture-Backed Firms, 2001

Ownership Status	Number of Firms	Average Employment
U.S. Overall		
Out of business	939	78.31
Private/independent	4,804	130.69
Acquired/merged	1,231	93.08
Publicly held	790	298.26
U.S. Biotech		
Out of business	63	30.97
Private/independent	301	32.50
Acquired/merged	63	30.97
Publicly held	113	95.22
California Overall		
Out of business	420	53.60
Private/independent	1,866	171.61
Acquired/merged	543	77.56
Publicly held	364	188.88
California Biotech		
Out of business	10	16.20
Private/independent	111	40.35
Acquired/merged	14	33.21
Publicly held	54	122.81

SOURCE: Authors' calculations from the VentureOne database.

Conclusion

Using a unique dataset, we have documented venture capital investment and firm formation in the biotech industry during the past decade. We present our major findings below.

First, the commercialization of the Internet technology caused a big surge in venture capital investment during the late 1990s. The biotech industry benefited from this abundance of venture capital because a great deal of the capital was invested in biotech firms.

Second, the sudden increase of venture capital investment facilitated entrepreneurial activities in many industries. A much greater number of venture-backed start-ups were founded during the late 1990s in Internet-related industries such as telecommunications, e-commerce, software, and information services.

Third, in contrast to those industries noted above, we find that the biotech industry did not experience a similar upward trend in entrepreneurship. The venture capital invested in the U.S. biotech industry in 2000 is almost five times as much as it was in 1995; and California's total increased sevenfold over the same period. Yet, the birthrate of biotech start-ups appeared relatively insensitive to that increase. This pattern of firm formation is also incompatible with continuously growing NIH support to "Small Business Innovation Research," which increased at an average annual rate of 16.5 percent during 1991–2001. These findings suggest that the availability of capital is not a binding constraint on biotech entrepreneurship.

Since the collapse of the Internet bubble, many people, including industry analysts and policymakers, have envisioned the biotech industry as stimulating the high-tech sector in the coming decade. In the meantime, many regions have resolved to build and foster their own biotech centers. Our findings suggest that although venture capital investment is a key ingredient of the biotech industry, it alone cannot create a strong biotech economy. And thus, simply pouring money into the industry is not likely to make it grow significantly faster. Other measures, especially strong support to biotech research in academic institutions and streamlined transfer of technology to the industry, are necessary.

4. Venture-Backed Biotech Entrepreneurs

Schumpeter (1934) teaches us the distinct roles of an entrepreneur and a capitalist. The entrepreneur translates a new technology into a marketable innovation, which may include a new product, production technique, or distribution method. The capitalist provides the resources to the new firm. Either role could involve several individuals. For example, venture capitalists often invest together in a start-up, and we frequently see two or more entrepreneurs cofound a single firm.

The biotech industry is both knowledge- and capital-intensive, and two unique features characterize its entrepreneurial activities. First, the formation of biotech firms, both in timing and location, is often influenced by the inventors of new technologies, who in many cases are academic researchers. Second, venture capital firms, rather than conventional financial institutions such as commercial banks, typically support biotech start-ups. This is because a new firm in biotech is usually a very risky enterprise demanding a high level of R&D investment and providing no guarantee of profit for a long period of time. On the other hand, once a biotech firm has a "blockbuster" product on the market, it enjoys a very high profit margin. This is exactly the type of investment opportunities that venture capitalists pursue.

A few early studies of entrepreneurship in the biotech industry revealed the important role of academic researchers, especially star scientists. Kenney (1986) documented the involvement of academic researchers in the early years of the biotech industry. He called the biotech industry a "university-industrial complex." Zucker, Darby, and Brewer (1998) presented evidence suggesting that the timing and location of new biotech firms are mainly explained by the presence of scientists who are actively contributing to basic science. More specifically, they pointed out that new biotech firms tend to locate close to scientists who have published genetic sequence discoveries. Audretsch and Stephan (1996) identified 445 academic researchers associated with 54 firms that prepared an IPO during 1990–1994. They found that university-based scientists are heavily involved in biotech firms, either as founders or as scientific advisors. In particular, they noted that founders have a substantial influence over the location of the firms whereas advisors have less influence.

Other high-tech industries, such as the semiconductor industry, also rely on university-based research as a major source of technological innovation. However, university professors have never played an equally important role in founding new firms as in biotech. New firms in the semiconductor industries are mostly spun off from pioneer firms such as Fairchild and Intel (Kenney and Von Berg, 1999). This naturally leads to the question of whether the biotech industry is influenced more by early biotech firm spinoffs or by academic researchers.

Biotech Firm Founders

In Chapter 3, we saw that although venture capital investment surged in the late 1990s, the birthrate of biotech firms remained steady and did not follow the same growth patterns as other industries. As a result, we here examine the biographical information of biotech firm founders in hopes of explaining how entrepreneurial activities and patterns differ in the biotech industry.

Studies of the semiconductor, the personal computer, and the Internet sectors in Silicon Valley find clear patterns of firm-level spinoffs. That is, employees of established companies tend to found their own start-ups. For example, Kenney and Von Berg (1999) point out that most of the semiconductor firms in Silicon Valley trace their origins back to Fairchild. The personal computer industry and the recent Internet revolution are also characterized by layers of spinoffs from such established companies as Hewlett-Packard and Apple Computer. It is fair to say that once the transistor invented at Bell Labs was commercialized, the industry had the ability to carry the technology to higher levels without much direct involvement from the academic community. Does the biotech industry also spin off start-ups and follow similar patterns?

In our sample, 351 biotech firms have founder information, which is then matched to 626 entrepreneurs. By examining firm founders' biographical information, we determined each founder's career path. As shown in Table 4.1, 43.1 percent of biotech firm founders were university-based professors or researchers; another 2.6 percent undertook research at nonprofit institutes. By adding new Ph.D. students to these two groups, we found that 292 (or 46.7%) of the 626 entrepreneurs had engaged in nonprofit research. These 292 individuals founded or cofounded 203 (or 58.2%) of the 351 biotech firms for which founder information is available. Given that 92.6 percent of those firms with founder information were started in or after 1990, we argue that the important role of academic researchers in founding biotech firms continued through the 1990s.

Table 4.2 shows the proportion of academic entrepreneurs in all industries. Among the 10,530 venture-backed entrepreneurs whose background information is available, 903 (or 8.6%) are associated with universities. Nearly 90 percent of the academic entrepreneurs specialize in engineering or life sciences (medical sciences, bioscience, and chemistry). The biotech industry clearly stands out. With only 618

Table 4.1

Career Path of Biotech Firm Founders, 1992–2001

Career	No.	% of Total
Professor/researcher in university	270	43.13
Scientist in research institute	16	2.56
Newly minted Ph.D.	6	0.96
Scientist in for-profit sector	74	11.82
Venture capitalist	44	7.03
Other	216	34.50
Total	626	100

SOURCE: Authors' calculations from the VentureOne database.

Table 4.2

Venture-Backed Entrepreneurs, by Industry, 1992–2001

Industry	No. of Entrepreneurs in Sample	No. of Academic Entrepreneurs	% of Academic Entrepreneurs in Each Industry
Advance/special material and chemical	39	11	28.21
Agriculture	11	0	0
Biopharmaceutical	618[a]	270	43.69
Communication	1,442	91	6.31
Consumer/business products	71	10	14.08
Consumer/business services	2,467	79	3.20
Electronics	279	20	7.17
Energy	12	2	16.67
Health care	138	7	5.07
Information services	1,159	41	3.54
Medical devices	347	54	15.56
Medical information services	302	51	16.89
Retailing	228	3	1.32
Semiconductor	442	43	9.73
Software	2,966	220	7.42
Other	9	1	11.11
Total	10,530	903	8.58

SOURCE: Authors' calculations from the VentureOne database.

[a]This total is different from the total in Table 4.1. Many entrepreneurs in the biotech industry are "serial entrepreneurs" who have founded more than one firm. To avoid double-counting, entrepreneurs in this table are categorized by the latest firm's industry. That creates the discrepancy.

entrepreneurs[1]— a total much smaller than the total number of entrepreneurs in the software, consumer/business services, communications, and information services industries—the biotech industry has the greatest number of academic entrepreneurs. Academic entrepreneurs account for 43.7 percent of biotech founders, far greater

[1]To avoid double-counting, some of those who have founded two or more firms are counted in other industries according to their latest firms.

than in any other industry. The advanced/special material and chemical industry[2] also has a very high proportion of founders from universities (28.2%), but the size of this industry is far smaller than biotech. Among the major industries with more than 100 entrepreneurs in the sample, medical devices and medical information services also have proportions of academic entrepreneurs far above average, with 15.6 and 16.9 percent, respectively. It appears that the entire life science sector depends heavily on university research.

We still see venture capitalists directly involved in founding biotech start-ups, but not as commonly as we did in the early years of the industry. Forty-four of the 626 entrepreneurs were at one time venture capitalists.

Table 4.3 shows the number of spinoffs at selected research institutions and major pharmaceutical and biopharmaceutical companies. When an employee leaves firm A and founds firm B, we call B a spinoff from A. Regional economies generally benefit from spinoffs, since they provide a channel for knowledge transfer and technology spillover. Other than Genentech—the pioneer in the industry—biopharmaceutical companies produced very few biotech firm founders. For example, Amgen, the industry leader, spun off only three biotech firms. An early industry leader, Hybritech, is famous for spawning new biotech firms in the San Diego region after it was acquired by Eli Lilly.[3] Yet our data, probably not capturing some firms founded in the 1980s, reveal only five Hybritech spinoffs.[4] None of the firm founders in our dataset can be traced back to the legendary biotech company Biogen. In contrast, the same VentureOne data show that in the information technology industries, such leaders as Hewlett-Packard and Sun Microsystems have produced 117 and 101 founders, respectively (Zhang, 2003).

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[2]Presumably, many start-ups in this category should also belong to a broadly defined biotech industry.

[3]Using a larger dataset, Stuart and Sorenson (2003) identified 13 Hybritech spinoffs.

[4]We also identified a medical device company founded by two former Hybritech employees.

Table 4.3

Biotech Spinoffs

Employer	No. of Employee Founders	No. of Spinoffs
University		
Stanford	25	20
UC Berkeley	15	12
UC San Francisco	13	11
UC San Diego	8	8
Caltech	7	6
Harvard	24	22
MIT	9	10
Duke	10	8
Yale	9	7
Research Institute		
NIH	8	8
Scripps	14	10
Pharmaceutical		
Abbott	4	5
Baxter	3	3
Bristol-Myers Squibb	9	6
Johnson & Johnson	2	2
Merck	11	9
Pfizer	3	3
Schering Plough	2	2
Biopharmaceutical		
Affymetrix	3	3
Alza	5	4
Amgen	4	3
Biogen	0	0
Chiron	3	3
Genentech	16	14
Genzyme	2	2
Hybritech	5	5
Ligand	3	3
Millennium	1	1

SOURCE: Authors' calculations from the VentureOne database.

Traditional pharmaceutical giants seem to be equally unimpressive in terms of spinning off biotech firms. Among the top ten pharmaceutical companies, Bristol-Myers Squibb and Merck significantly outperformed others. Overall, major universities dwarf the industry in spinning off biotech firms. In the San Francisco Bay Area, Stanford, UC Berkeley, and UC San Francisco are all major sources of biotech firm founders. Harvard and MIT play similar roles in the Boston region. In the San Diego region, the Scripps Institute produced 14 biotech firm founders, outshining even UC San Diego. Note that we are talking only about firm founders who were employed by universities, not individuals who simply graduated from them. Given that those universities also continuously provide a high-quality labor force for the industry, their importance cannot be exaggerated. Our observations here are only suggestive, because the venture capital data are not rich enough for more conclusive analysis.

We speculate below about possible reasons why the biotech sector heavily depends on nonprofit research institutions to generate new firms.

Marketability of Technology

History repeatedly teaches us that the individuals who make important technological breakthroughs or inventions may or may not harvest the wealth created by the technology. For example, Alfred Nobel and Thomas Edison benefited greatly from their inventions, whereas Vinton Cerf—the inventor of the Internet—and Tim Berners-Lee—the inventor of the World Wide Web—did not. An inventor typically benefits from the new technology only if it is easily marketable. If there is ready market demand for the technology, as in the case of Nobel's dynamite, the inventor will see the economic value immediately. Sometimes inventions are devised with the market demand in mind. However, if there is no immediate market value, as in the case of the personal computer and the Internet, the inventor may miss the opportunity to reap the economic benefits. In these situations, it usually takes one or several entrepreneurs to bring the technology to market, and it is the entrepreneurs who are financially rewarded. For example, personal computers hardly found buyers when the technology first became available. IBM, Hewlett-Packard, and DEC all missed the chance to be the first to mass-market personal computers, simply because they believed that only a few hobbyists would want them. It took Steve Jobs, not the inventor, to found a new firm, Apple, to establish the huge personal computer market. Entrepreneurs see the potential of a technology before others do, and they pursue their vision with great determination and energy. Obviously, a great entrepreneur requires a set of talents different from those of a great inventor.

In the case of biotechnology, its application in the health care industry became salient once Swanson and Boyer founded the first biotech firm. Biotechnology need not create its own demand; it serves the multibillion-dollar market that already exists for health care. Because the market demand is simply waiting for technological breakthroughs, it is likely that the inventors themselves (professors) will see the economic value of biotechnology. Although we say that the existing market demand for more effective drugs is large, biotechnology may also have other not-so-obvious applications. In such cases, discerning entrepreneurs, rather than university professors, are likely to bring these applications to fruition.

Diffusion of Technology

The personal computer industry has a long tradition of the "open system"—that is, an inventor freely disseminates a technology (especially software) so that others can create compatible products—and this network effect benefits the original inventor. Because of this network economy and the tradition of open systems, information technology is usually not well protected by patents. This promotes the diffusion of information technology and fosters the creation of spinoffs. If a company uses patent laws to protect every innovation, its employees cannot easily found start-ups using their inventions from the previous employer. As opposed to the more open tradition in the information technology industry, biotechnology is better protected, making it more difficult for potential spinoffs. The complexity and costs of biotechnology itself may also slow the diffusion process. All of these factors explain why firm-level spinoffs are not as common in the biotech industry as in the personal computer industry.

Asymmetric Information and Signaling

We have seen that most start-ups in biotech remain unprofitable over a long horizon. To some extent, this is due to a long approval process at the FDA for new drugs and new plants. Thus, investment in biotech is generally more risky. Related to this risk is an asymmetric information problem between entrepreneurs and investors. Entrepreneurs know more than investors about just how risky a proposed project might be. Moreover, it is extremely difficult for investors to acquire the knowledge to fully evaluate the blueprint of a biotech start-up. In this situation of asymmetric information, venture capitalists must base their investment decisions partly on their faith in the entrepreneurs. On the other side, entrepreneurs want to send signals to investors revealing the long-term value of their ideas. Naturally, a record of outstanding work in hard science will be the most convincing evidence that the entrepreneur knows the true value of the proposed idea and has the ability to implement it. At the same time, venture capitalists know that they will earn their money back by selling a start-up to the public through an IPO even before the firm becomes profitable. But how do they convince the public that a currently unprofitable start-up is valuable? Again, a star scientist will be a very important selling point. If this is how venture capitalists evaluate proposals of biotech start-ups, star scientists (mostly university professors) have a much better chance than others to pass the screening process.

Policy Incentives

State policymakers have long recognized the economic potential of biotechnology. According to a report released by the Biotechnology Industry Organization (2001), 41 states have implemented policies to stimulate the development of their biotech economy. The most commonly used policy tool is to provide incentives to university faculty members to commercialize academic research, including financial support, business development, and specialized biotechnology incubators and research parks.

For example, in Georgia, the Advanced Technology Development Center (ATDC) has a Faculty Research Commercialization Program that provides funding to university researchers who want to commercialize discoveries by starting companies. ATDC and the Georgia Research Alliance (GRA) together with research universities in the state have created several biotechnology incubators:

- The Center for Applied Genetics Technology at the University of Georgia provides offices and labs for start-up companies engaged in agricultural biotechnology and genomic research.
- EmTech Biotechnology Development Inc., jointly launched by Emory University, Georgia Tech, ATDC, and GRA, is dedicated to creating bioscience companies in Georgia. EmTech provides wet lab and business expertise to start-up companies.
- CollabTech at Georgia State University offers 7,000 square feet of space for companies that focus on biological and chemical applications.

These incubators aim to assist university researchers who intend to start biotech firms. Georgia also uses these institutions and facilities to attract eminent biotech scholars, expecting them to serve as both professors and entrepreneurs.[5]

Massachusetts is another example of a state that encourages entrepreneurship through university-based biotech incubators:

- Massachusetts Biotechnology Research Park, created in 1985 and located adjacent to the University of Massachusetts Medical Center, provides one million square feet of building space on 105 acres and houses more than a dozen biotech companies.
- BioSquare, a private research park affiliated with the Boston University School of Medicine and Boston Medical Center, provides over 400,000 square feet of building space on 16 acres.
- Tufts Science park, located on the campus of the Tufts University School of Veterinary Medicine, provides space for biotech R&D and pilot manufacturing.

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[5]Harper (2002).

- University Park at MIT, located on 27 acres next to MIT and created in 1983, was one of the first biomedical parks in the United States. It has 1.5 million square feet of first class office space, R&D facilities, a 210-room hotel, and a conference center.

Although California leads the U.S. biotech industry, the state government has not promoted the commercialization of biotechnologies as aggressively as many other states, partly because commercialization activities have been extensive without state intervention.

Star Scientists and Academic Entrepreneurship

People often use the phrase "ivory tower" to refer to universities, implying that researchers treat practical issues with impractical and often escapist attitudes. A traditional stereotype is that professors hardly care about the real world, and only those less devoted to science take the time to join the ranks of the business world. The development of the biotech industry confounds such perceptions.

Biotech start-ups are often founded by some of the best academic researchers. As noted above, the history of the biotech industry traces its roots back to Herbert Boyer, a first-rate professor at UC San Francisco and cofounder of Genentech. He first isolated an enzyme that could be used to cut strings of DNA into precise and "cohesive" segments that would carry the code for a predetermined protein. Around the same time, Stanley Cohen, then a professor at Stanford, developed a method of isolating and cloning genes carried by certain rings of DNA and inserting them into other cells. Boyer and Cohen brought together their techniques to recombine segments of DNA in desired configurations and insert the DNA in bacterial cells, which could then act as manufacturing plants for specific proteins. This work was not only a great scientific breakthrough but also set the foundation upon which the biotechnology industry developed. Even if one were to ignore his involvement in Genentech, Herbert Boyer would forever be remembered for his scientific contribution.[6]

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[6]In 1986, Boyer's collaborator, Stanley Cohen, won the Nobel prize for his contribution to the discovery of proteins called cell growth factors that directed the

Biogen, one of the industry leaders, provides another salient example that the biotech industry is closely related to first-rate researchers. In 1978, a group of internationally acclaimed scientists met in Geneva, Switzerland, to create a new biotechnology company. These scientists were leaders in genetic engineering and saw the potential of harnessing the power of human genes to develop novel therapeutics that improve the quality of people's lives. This initial meeting was the genesis of Biogen, which was originally incorporated in Europe and moved to Massachusetts in 1988. Two of these scientists would later receive Nobel prizes for their work: Walter Gilbert of Harvard won the 1980 Nobel prize in chemistry, and Phillip Sharp of MIT won the 1993 Nobel prize in medicine.

These are not isolated examples. A browsing of the Nobel prize's online archive (http://www.nobel.se/index.html) and a search through Google on the Internet yield a long list of Nobel laureates who founded or cofounded biotech firms (Table 4.4). One may wonder whether these scientists started businesses only to capitalize on their fame following their winning of the Nobel prize. Yet the founding year column in the table indicates that most of these scientists founded their firms before they won the prize, a sign that their founding behavior was not affected by the Nobel prize. Note that Table 4.4 includes only the prizewinners in the past decade and only in the two disciplines of chemistry and medicine. Although an incomplete list, it demonstrates rather convincingly that starting businesses in the biotech industry is a common practice among the best of scientists.

Empirical evidence shows that basic scientific research has profound effects on the development of the biotech industry. In particular, it is the star scientists who are most influential. In a decade-long research program, professors Lynne Zucker and Michael Darby at UC Los Angeles, together with their coauthors, conducted a comprehensive study of the relationship between top academic scientists and biotech firms (see, for example, Zucker, Darby, and Brewer, 1998; Zucker, Darby, and Armstrong, 2002; Zucker, Darby, and Torero, 2002). Zucker and

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growth of certain cells. In 1996, Boyer and Cohen were awarded the Lemelson-MIT prize, the world's largest single prize for invention and innovation, for their work on genetic engineering.

Table 4.4

Biotech Firms Founded by Nobel Laureates

Name	Affiliation	Nobel Prize	Firm Founded	Founding Year
H. Robert Horvitz	MIT	Medicine, 2002	NemaPharm (acquired by Sequana Therapeutics) and Idun Pharmaceuticals (merged with Apoptech)	1990, 1993
Leland Hartwell	Fred Hutchison Cancer Research Center	Medicine, 2001	Rosetta Inpharmatics (bought by Merck)	1996
K. Barry Sharpless	Scripps	Chemistry, 2001	Coelecanth (bought by Lexicon Genetics)	1996
Alan Heeger	UC Santa Barbara	Chemistry, 2000	Uniax Corporation (acquired by DuPont)	1990
Arvid Carlsson	Goteborg University, Sweden	Medicine, 2000	Carlsson Research	1998
Paul Greengard	Rockefeller University	Medicine, 2000	Intra-Cellular Therapies	2002
Eric Kandel	Columbia University	Medicine, 2000	Memory Pharmaceuticals	1998
John Pople	Northwestern University	Chemistry, 1998	Gaussian	1987
Ferid Murad	University of Texas, Houston	Medicine, 1998	Molecular Geriatrics Corp. (acquired by Hemoxymed)	1992
Stanley B. Prusiner	UC San Francisco	Medicine, 1997	InPro Biotechnology	2001
Richard E. Smalley	Rice University	Chemistry, 1996	Carbon Nanotechnologies	2000
Christiane Nüsslein-Volhard	Max Planck Institute, Germany	Medicine, 1995	ARTEMIS Pharmaceuticals GmbHn (acquired by Exelixis)	1997
Alfred G. Gilman	University of Texas, Dallas	Medicine, 1994	Regeneron Pharmaceuticals	1988
Michael Smith	University of British Columbia, Canada	Chemistry, 1993	Zymos (now ZymoGenetics)	1981
Phillip Sharp	MIT	Medicine, 1993	Biogen	1978

SOURCE: Authors' Internet search.

Darby identified more than 300 star bioscientists by examining their publications of genetic-sequence discovery articles. Their work shows that the location of star scientists predicts the location of firm entry into new biotechnologies, which is true in both the United States and Japan. Also, collaborations between top academic scientists and firm scientists have significant positive effects on a wide range of firm performance measures in biotechnology. These ties with top scientists also enable biotech firms to enter the IPO stage more quickly and increase the amount of their IPO proceeds. In addition, the higher the quality of an academic star scientist's research, the more likely that he or she will start to collaborate with firm scientists or move to biotech firms.

Zhang (2004) presents a detailed study of academic entrepreneurs using the entire VentureOne dataset. One particular question he asked is why some universities spin off more venture-backed firms than others. He conducted a multivariate analysis by regressing the number of university spinoffs on a set of university characteristics, including faculty quality (national academy membership, number of faculty awards), research expenditure (total research expenditure, research expenditure on science and engineering), advanced training (doctoral degrees awarded, number of postdoctoral appointees), and undergraduate quality (median SAT score, number of national merit/achievement scholars). In addition, he also included relevant explanatory variables such as local venture capital investment, private institution or not, located in California or not, located in Massachusetts or not, and so on. Not surprisingly, in a one-on-one regression, all the explanatory variables are positively correlated with the number of spinoffs. Yet, if all the explanatory variables are put into a single regression, only the "national academy membership" variable is positively and significantly related to the number of university spinoffs.[7] Other variables lost their explanatory power once pooled with the "national academy membership" variable. And the "national academy membership" variable remains so significant that it has a t-value close to 16. As with the Zucker et al. analyses, Zhang's empirical analysis suggests that it is the university's quality of

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[7]"Number of postdoctoral appointees" is the only other significant variable, but it has a negative coefficient.

research that really matters. It implies that only the most advanced research in universities will be commercialized with the support of venture capital. And again, this analysis points to the important role of star scientists in the development of technology sectors.

Location of Firms by Academic Founders

In this section, we focus on 296 entrepreneurs who are or were professors or researchers at universities or research institutes. For the sake of presentation, we will call them academic entrepreneurs. We want to study this group because it is easy to identify the location of the research institutions with which these entrepreneurs are associated. Since we also know the location of their firms, it is informative to compare the locations of academic institutions with the locations of biotech firms to see whether those entrepreneurs move when they start firms.

Table 4.5 summarizes the geographic distribution of academic entrepreneurs by academic association and business location, which is quite uneven. California's academic institutions spun off 89 academic entrepreneurs, nearly one-third of the U.S. total and more than twice as many as the number two state, Massachusetts. A majority of these 89 people, 73, or 82 percent, chose to locate their businesses in California, and 16 started biotech firms in other states.

Overall, 181 out of 282, or 64.2 percent, of the researchers associated with U.S. institutions chose to remain in the same state to start their businesses. But this percentage varies significantly from one state to another. For example, among the top five states, California, Massachusetts, and North Carolina produced the most academic entrepreneurs and all had around 80 percent retention rates. In contrast, Maryland had 13 academic entrepreneurs but only one of them chose to stay in Maryland, and New York lost seven out of 11 academic entrepreneurs.

A total of 118 academic entrepreneurs chose to locate their businesses in California, accounting for about 40 percent of the U.S. total. Among these entrepreneurs, 45 are associated with academic institutions outside California. Given that 16 researchers located their businesses in other states, California has a net gain of 29 academic

Table 4.5

Distribution of Academic Entrepreneurs

	By Academic Location				By Business Location		
State	Moved Out	Stayed	Total (a)	Net Gain (b) – (a)	Total (b)	Stayed	Moved In
California	16	73	89	29	118	73	45
Massachusetts	9	33	42	12	54	33	21
North Carolina	4	15	19	–2	17	15	2
Maryland	12	1	13	–8	5	1	4
New York	7	4	11	–7	4	4	0
Connecticut	4	6	10	–1	9	6	3
Illinois	4	6	10	–4	6	6	0
Texas	5	4	9	–1	8	4	4
Washington	3	4	7	2	9	4	5
Michigan	2	4	6	–1	5	4	1
Missouri	3	3	6	–3	3	3	0
Pennsylvania	1	5	6	3	9	5	4
Colorado	0	5	5	3	8	5	3
Georgia	2	3	5	0	5	3	2
Arkansas	4	0	4	–4	0	0	0
Rhode Island	0	4	4	0	4	4	0
Tennessee	4	0	4	–3	1	0	1
Utah	2	2	4	–2	2	2	0
Wisconsin	0	4	4	0	4	4	0
Alabama	2	1	3	2	5	1	4
New Jersey	3	0	3	1	4	0	4
Indiana	1	1	2	–1	1	1	0
Kentucky	2	0	2	–2	0	0	0
Ohio	1	1	2	1	3	1	2
Oklahoma	1	1	2	–1	1	1	0
Virginia	2	0	2	2	4	0	4
Washington, D.C.	1	0	1	–1	0	0	0
Florida	1	0	1	0	1	0	1
Iowa	1	0	1	1	2	0	2
Kansas	1	0	1	–1	0	0	0
Maine	1	0	1	–1	0	0	0
Minnesota	0	1	1	1	2	1	1
Oregon	1	0	1	–1	0	0	0
Vermont	1	0	1	–1	0	0	0
Arizona	0	0	0	1	1	0	1
New Mexico	0	0	0	1	1	0	1
Total	101	181	282	14[a]	296	181	115

SOURCE: Authors' calculations from the VentureOne database.

[a]Net gains do not add up to zero because 14 entrepreneurs are associated with foreign institutions.

entrepreneurs. Massachusetts is another big winner, with a net gain of 12 entrepreneurs. It is very likely that these two states benefited because of their existing large biotech clusters and the abundance of venture capital. This suggests that the agglomeration economies of biotech clusters work in favor of California and Massachusetts, which gives the most advanced biotech centers further advantages. Interestingly, among the next 17 states that produced more than three academic entrepreneurs, only three—Washington, Colorado, and Pennsylvania—registered positive net gains. These three states also have vibrant high-tech economies and active venture capital investment.

Table 4.6 shows the academic location for those who came to California to start their businesses in biotech and the business locations for those academic entrepreneurs who left California. California's biotech industry attracted academic entrepreneurs from all over the country and even from outside the United States. In fact, 20 percent of those who came to California, or nine out of 45, had conducted their research in foreign countries. In the entire sample, only 14 entrepreneurs with foreign affiliations moved to the United States, and two-thirds of them came to California. We do not know whether there were California-based researchers moving to other countries to start biotech firms, because our data cover only those who have venture-backed businesses in the United States. It is also interesting that California received six academic entrepreneurs from Massachusetts and had the same number moving in the opposite direction.

Conclusion

We have confirmed previous studies regarding the importance of academic researchers in founding biotech firms and found that this pattern continued in the 1990s. In our dataset, nearly 50 percent of the biotech firm founders did or still do conduct nonprofit scientific research. Leading universities and research institutes seem to spin off more biotech entrepreneurs than the industry itself. Thus, first-rate scientists are the key to building a biotech industrial sector.

Table 4.6

Academic Founders Moving Into or Out of California

Moving Into California		Moving Out of California	
Academic Location	No. of Entrepreneurs	Business Location	No. of Entrepreneurs
Foreign countries	9	Massachusetts	6
Maryland	6	Washington	3
Massachusetts	6	Connecticut	2
New York	4	Ohio	2
Arkansas	2	Iowa	1
Missouri	2	North Carolina	1
New Jersey	2	New Jersey	1
Alabama	1	Total	16
Connecticut	1		
Illinois	1		
Kansas	1		
Kentucky	1		
Michigan	1		
Ohio	1		
Tennessee	1		
Texas	1		
Utah	1		
Vermont	1		
Virginia	1		
Washington	1		
Washington, D.C.	1		
Total	45		

SOURCE: Authors' calculations from the VentureOne database.

The importance of academic researchers in founding biotech firms should stimulate local policymakers to recalculate the economic externalities that universities provide for regional economies. Previous studies show that researchers contributing to basic science heavily influence the founding of biotech start-ups, and their technological breakthroughs are usually accomplished within academia. We see this situation continuing and even strengthening in the 1990s. Given this fact, we should recognize that although scientists work at research universities and appear unrelated to the local economy, they can contribute a great deal to regional economic growth through technology transfer or business formation.

California has a strong venture capital industry, with an array of experienced capitalists alert to technological innovations. The state's innovation support services (venture capitalists, lawyers, accountants, consultants, bankers, etc.) are the strongest in the nation. Thus, commercialization is not California's major concern; the state needs innovations to commercialize. The state government could help by firmly supporting California's high-quality research universities, particularly efforts to attract and retain high-caliber bioscience researchers, and streamlining the process of technology transfer. Once scientific discoveries or inventions with economic potential emerge in California, it is likely that they will soon catch the attention of local venture capitalists. Such discoveries and inventions will quickly become the foundation of business plans. Thus, from the government's perspective, the key to maintaining California's lead in the biotech industry is to preserve the state's strength in bioscience research.

5. Formation, Growth, and Mortality of Biotech Firms in California

The economy is a dynamic system. At any point in time, new firms are formed; existing ones grow, shrink, merge, relocate, or spin off new ventures; and still others go out of business. In parallel fashion, jobs are continuously created and eliminated. Even simple demographic statistics of the population of businesses have important implications for policymaking in a dynamic economy. For example, economists have long been trying to determine the role of small businesses in job creation and technological innovation (Birch, 1987). From this perspective, a study of the economy or of any particular industry needs to highlight the evolution of a large population of corporations.

Chapters 3 and 4 consider only *venture-backed* biotech firms. This chapter examines the demographics of all of California's biotech firms, with an emphasis on their dynamics. In particular, we describe firm birth, growth, merger and acquisition, and mortality in California's biotech industry to better understand job creation and growth processes in the industry.

We use the NETS database developed by Walls and Associates. Our version of the NETS data merges 12 annual snapshots (1990–2001) of the U.S. economy, with raw data provided by the credit rating company Dun & Bradstreet (D&B). Firm-level information in the NETS data includes address, employment, industry, start year, death year, and so on. The NETS database is designed to cover the entire universe of U.S. corporations. Walls and Associates has made an extract available to PPIC, which covers all establishments in the biotech industry that ever resided in California (including those that had moved to other states) during these 12 years.

The NETS database uses SIC codes to categorize industries. Our version of the data contains up to eight-digit SIC codes, which classify the economy into very specific industry segments. However, as discussed in Chapter 1, biotechnology cuts across many traditional industry boundaries. To define the biotech industry using SIC codes, we can include only some of the industries in which biotechnology is most widely applied. We chose to include all of the pharmaceutical research and manufacturing but to exclude the agricultural and environmental industries because only a small proportion of firms in agricultural and environmental industries are biotech companies. Our approach will necessarily leave out some real biotech companies and bring in some others that are only somewhat related to biotech. However, this definition seems to be the best we can do with the data, and we interpret our results with this limitation in mind.

The basic unit of observation in the NETS data is an "establishment." An establishment is a single physical unit of business, which might be either a firm or a branch/subsidiary of a firm. In case of multiple-unit firms, the corporate family structure can be inferred from the unique identification numbering system used by D&B.

Some Descriptive Statistics

Our dataset contains 5,634 establishments. Excluding establishments that have already moved to other states, we find 5,582 California biotech establishments in the data. Table 5.1 shows the distribution of establishments over SIC industries. Note that less than a quarter of the establishments are engaged in manufacturing (SIC codes 2833–2836), whereas the remainder focus on research and development. The two largest industry segments are biological/medical laboratories and commercial biological research, each accounting for one-third of the whole industry.

Table 5.2 presents size distributions of California's biotech establishments alive in 2001. Business size is generally small in the biotech industry: For example, 44.3 percent of establishments had fewer than five employees and nearly 90 percent employed no more than 50

Table 5.1

Distribution of Biotech Establishments over SIC Industries, 1990–2001

SIC Code	Description	No. of Establishments	% of Total
	Manufacturing		
2833	Medicinal chemicals and botanical products	293	5.25
2834	Pharmaceutical preparations	739	13.24
2835	In-vitro and in-vivo diagnostic substances	144	2.58
2836	Biological products, except diagnostic substance	137	2.45
	Laboratories and Research		
8071[a]	Biological, medical laboratories	1,896	33.97
8731[b]	Commercial biological research	1,807	32.37
873301	Noncommercial biological research organization	566	10.14
Total		5,582	100

SOURCE: Authors' calculations from the NETS data.

[a]Includes only 807100 (medical laboratories) and 80710102 (biological laboratories).

[b]Excludes 87310000 (commercial physical research), 87310203 (computer (hardware) development), 87310204 (engineering laboratory, except testing), 87310205 (industrial laboratory, except testing), 87310300 (natural resource research), 87310301 (energy research), and 87319901 (electronic research).

Table 5.2

Size Distribution of Biotech Establishments in California, 2001

No. of Employees	No. of Establishments	% of Total	Total No. of Employees	% of Total
0–4	1,426	44.31	3,213	2.55
5–9	605	18.80	3,855	3.06
10–19	429	13.33	5,516	4.38
20–50	393	12.21	12,185	9.69
51–100	177	5.50	13,151	10.45
101–250	112	3.48	18,094	14.38
251–500	41	1.27	14,312	11.38
501–1,000	18	0.56	15,000	11.92
1,001–2,500	12	0.37	20,611	16.38
2,500+	5	0.16	19,868	15.79
Total	3,218	100	125,805	100

SOURCE: Authors' calculations from the NETS data.

NOTE: Totals may not sum exactly because of rounding.

people. Establishments with more than 500 employees constituted only 1 percent of the industry. If we exclude those establishments set up by existing firms as branches, the size distribution is even more skewed: 47.1 percent of establishments had fewer than five employees and only 0.5 percent offered more than 500 jobs. However, if we look at total employment, establishments with more than 100 employees accounted for 70 percent of total biotech employment, although less than 6 percent of the establishments belong to such categories.

Table 5.3 compares total employment in the biotech industry in 1990 and 2001. On average, manufacturing establishments hire more people. Although manufacturing accounts for less than a quarter of the total establishments in the dataset, 45.9 percent of 2001 total employment was in manufacturing. In 1990, manufacturing jobs constituted an even higher percentage, representing 52.3 percent of the biotech workforce.

According to data released by the California Employment Development Department, the state had a total employment of

Table 5.3

Biotech Employment in SIC Industries, 1990 and 2001

SIC Code	Description	Employment	% of Total	Employment	% of Total
	Manufacturing				
2833	Medicinal chemicals and botanical products	5,145	5.52	4,127	3.28
2834	Pharmaceutical preparations	36,880	39.57	39,886	31.70
2835	In-vitro and in-vivo diagnostic substances	4,046	4.34	9,435	7.50
2836	Biological products, except diagnostic substance	2,674	2.87	4,292	3.41
	Laboratories and Research				
8071[a]	Biological, medical laboratories	16,071	17.25	18,453	14.67
8731[a]	Commercial biological research	24,079	25.84	37,999	30.20
873301	Noncommercial biological research organization	4,296	4.61	11,615	9.23
Total		93,191	100	125,807	100

SOURCE: Authors' calculations from the NETS data.

NOTE: Totals may not sum exactly because of rounding.

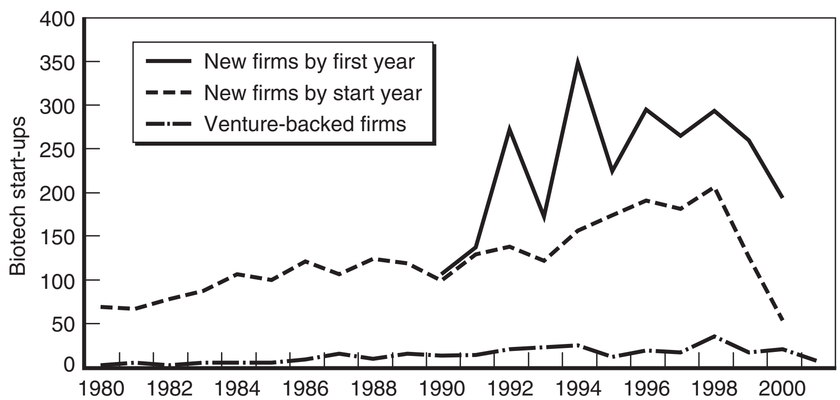
[a]As noted in Table 5.1, some industries under these four-digit SIC codes are excluded.

14,319,200 in 1990 and 16,260,100 in 2001.[1] Measured by the state's total employment, the biotech industry represented less than 1 percent of the state economy, a surprising statistic considering the amount of public attention given to this industry. However, biotech's 35 percent growth rate during this period was much faster than the 13.6 percent growth in the overall economy, which suggests its considerable growth potential.

Table 5.3 also shows that biological research, both commercial (SIC 8731) and noncommercial (SIC 8733), experienced a much faster growth rate than the biotech industry and the overall economy: 57.8 percent and 170 percent, respectively. In 1990, biological research accounted for only 30.5 percent of employment in biotech; in 2001, it represented 39.4 percent.

Firm Formation

Figure 5.1 plots the trend of new firm formation in California's biotech industry. In our calculations, we concentrated on new firms, excluding establishments that were set up as branches of existing firms. For most establishments in the NETS data, self-reported start year is available. These firms tend to be larger and stay in business for a longer



SOURCES: Authors' calculations from the NETS and VentureOne database.

Figure 5.1—Biotech Firm Formation in California, 1980–2001

[1] See http://www.calmis.cahwnet.gov/htmlfile/subject/lftable.htm.

time. Those establishments with an unknown start year are likely to be smaller firms that never hired more than five people and stayed in business for only a short while. For these firms, the best we can do is to use the first year these firms were captured by the NETS data as an approximation of their start year.[2] Obviously, if an establishment's start year is known and occurs after 1990, it is identical to its first year. Since the NETS data started in 1990, the series of new firms by first year also starts in 1990, but the series by start year goes back for many years.

The series of new firms by start year shows a fairly steady increase of firms founded in each year between 1980 and 1998. This trend peaked in 1998 and declined in the following two years. Using the same NETS data, we observe a similar trend in the whole high-tech sector in Silicon Valley (Zhang, 2003). It seems that the trend of firm formation lost its momentum long before California's most recent recession, which began in 2001. The trendline for first year start-ups was highly erratic in the early 1990s. The number of biotech firms founded in 1992 was double the number founded in 1990; after a sharp decline in 1993, the trend shot up again in 1994, leaving that year with the highest level of entrepreneurial activities in biotech. However, another severe decline followed immediately in 1995.

The trendline illustrating first year start-ups shows that new firm formation after 1994 never reached the 1994 level again. Yet a closer look at the data reveals that the "noise" in the early 1990s was mostly created by small ventures that were short-lived. This is why the start year series, which captured mostly larger firms, peaked much later in 1998. The early 1990s saw the creation of many biotech firms and thus was a period that might be considered a biotech boom. VentureOne data show that in the early 1990s, more than 20 percent of total venture capital investment flowed into biotech, although the industry's share of the technology sector was much smaller. Using Lexis-Nexis, a database of news stories, we searched the keyword "biotechnology" in the *San Francisco Chronicle* and the *Los Angeles Times*. Both papers published more biotech-related news in 1992 than in 1996. The early 1990s

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[2]Every establishment has a first year, but some of them did not report their start year. Thus, first year and start year series do not overlap.

biotech boom was clearly reflected in the media. However, the Internet boom in the second half of the 1990s distracted people's attention from biotech, which may partly explain why venture capital and entrepreneurial activities in biotech slowed down after 1995.

Figure 5.1 also plots the series of venture-backed new firms in California's biotech industry. Only firms that received venture capital after 1991 were captured in this series. Therefore, the numbers in the 1980s more than likely underestimate the number of firms created, since many of them may have died or stopped relying on venture capital by 1991. Notice that only a small fraction of the total firms founded in biotech ever receive venture capital.[3] From 1990 to 2001, between 4.5 and 11.3 percent of biotech start-ups obtained venture capital financing. Overall, in this period, 195 out of 2,544 (7.7%) biotech start-ups were backed by venture capital. Although this is a small overall percentage, it actually represents a fairly high percentage compared to most other technology firms, because although biotech start-ups are capital-intensive, risky, and unattractive to such traditional financial institutions as banks, they have the potential for tremendous profits and therefore are attractive to venture capitalists.

Firm Growth

We are able to track employment growth for biotech firms founded after 1990. Table 5.4 shows the average employment of each founding year cohort over the decade. These calculations are limited to biotech firms that were founded as independent firms and were not acquired by other firms. The employment of establishments set up as branches was included in the total for their headquarters. Note that our data capture only establishments in California: If a firm sets up a branch outside California, that branch's employment is not included in the table. Given that these firms are all young start-ups, such omissions should be rare and will not significantly bias our estimated employment size.

There is a great deal of variation among different cohorts, in both their initial employment size and their subsequent growth. For example,

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[3]This small fraction may partly result from the narrower definition of biotech firms used in the VentureOne data.

Table 5.4

Average Employment Growth of California's Biotech Firms, 1991–2001

Cohort	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
1990	8.52	7.03	7.04	8.35	8.74	9.14	11.21	12.26	13.01	13.72	15.33
	(18.40)	(11.27)	(11.27)	(14.13)	(14.11)	(14.65)	(17.93)	(20.00)	(20.90)	(24.85)	(28.00)
1991		9.23	9.17	10.16	11.49	10.50	13.71	16.06	17.80	19.66	23.50
		(25.38)	(25.55)	(26.14)	(28.19)	(15.31)	(25.46)	(29.32)	(33.04)	(35.28)	(46.73)
1992			8.68	8.70	9.84	11.28	11.82	13.72	16.71	21.78	24.99
			(18.20)	(18.69)	(19.86)	(22.29)	(23.64)	(27.66)	(34.95)	(46.91)	(55.81)
1993				6.02	6.34	6.89	8.21	9.10	10.75	12.90	15.50
				(8.52)	(9.30)	(10.11)	(12.66)	(14.39)	(19.72)	(23.42)	(26.03)
1994					6.70	5.83	6.38	6.87	10.83	12.57	13.45
					(18.71)	(7.50)	(7.91)	(8.79)	(33.53)	(31.14)	(31.99)
1995						7.56	7.08	8.38	9.19	11.82	13.25
						(16.36)	(13.30)	(15.67)	(13.78)	(25.19)	(28.88)
1996							6.01	6.38	6.63	12.80	9.67
							(9.40)	(9.84)	(9.34)	(72.44)	(15.24)
1997								5.99	6.42	7.66	11.45
								(8.89)	(10.23)	(11.70)	(22.70)
1998									5.83	6.79	8.45
									(8.15)	(10.11)	(11.96)
1999										6.25	6.78
										(13.84)	(14.92)
2000											7.80
											(21.40)

SOURCE: Authors' calculations from the NETS data.
NOTE: Standard deviations are in parentheses.

the 1990 cohort had an average employment size of nine in 1991. Apparently, those in the cohort were adversely affected by the economic downturn in the early 1990s, and so by 1993, their average employment size declined to seven. In 2001, this cohort had grown to an average of only 15 employees. In contrast, the 1992 cohort started with a similar size of nine; yet by 2001, that cohort had on average hired 25 people, significantly more than the 1990 cohort.

Table 5.4 again shows that average biotech start-ups are small: Their first year employment will likely be between five and ten people. Biotech start-ups take six to eight years to double employment size. However, the calculations in Table 5.4 did not take into account failed firms; only survivors are included. These numbers may exaggerate the growth of the biotech industry, because those that grow slowly are more likely to die and drop out of the database. It is also worth pointing out that the growth of employment is not likely to continue at this pace; the trajectory will necessarily level off as biotech firms mature.

An alternative way to examine firm growth is to look at the total employment of each cohort, taking into account that failing firms eliminate some jobs and surviving firms grow. Table 5.5 shows the total employment of each cohort of biotech firms in each year. The growth is much less dramatic than the average numbers indicated in Table 5.4. For example, the 1990 cohort of biotech firms experienced a serious cutback in jobs in 1992; not until 1997 did these firms hire more people than they did in 1991. As a result of some firms exiting the industry, their 2001 total employment was merely 14.3 percent higher than the 1991 total. In contrast, firms in the 1991 cohort experienced substantial growth, with their 2001 total employment over 47 percent higher. For some cohorts of biotech start-ups, such as those founded in 1994, the growth of the surviving firms were not even enough to cover the job losses incurred by failing ones in the first several years.

Overall, it seems that employment in biotech start-ups is not growing very fast. Thus, to a great extent, the expansion of the industry will rely on new firm formation.

Table 5.5
Total Employment Growth of California's Biotech Firms, 1991–2001

Cohort	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
1990	818	668	669	760	787	795	919	944	937	919	935
	(96)	(95)	(95)	(91)	(90)	(87)	(82)	(77)	(72)	(67)	(61)
1991		1,182	1,156	1,250	1,333	1,155	1,371	1,510	1,566	1,537	1,739
		(128)	(126)	(123)	(116)	(110)	(100)	(94)	(88)	(80)	(74)
1992			2,004	1,915	2,028	2,177	1,998	1,990	2,189	2,505	2,549
			(231)	(220)	(206)	(193)	(169)	(145)	(131)	(115)	(102)
1993				879	914	965	1,035	1,083	1,172	1,187	1,333
				(146)	(144)	(140)	(126)	(119)	(109)	(92)	(86)
1994					1,984	1,580	1,326	1,244	1,755	1,835	1,829
					(296)	(271)	(208)	(181)	(162)	(146)	(136)
1995						1,534	1,346	1,501	1,498	1,749	1,696
						(203)	(190)	(179)	(163)	(148)	(128)
1996							1,539	1,526	1,445	2,457	1,538
							(256)	(239)	(218)	(192)	(159)
1997								1,449	1,438	1,456	1,901
								(242)	(224)	(190)	(166)
1998									1,563	1,590	1,657
									(268)	(234)	(196)
1999										1,569	1,445
										(251)	(213)
2000											1,475
											(189)

SOURCE: Authors' calculations from the NETS data.
NOTE: Number of firms is in parentheses.

Firm Mortality

Firm death, more than anything, eliminates jobs and generates turbulence in the labor market. Figure 5.2 depicts the survival rates of California's biotech firms. During their first two years, biotech firm mortality rate was fairly low, with 96.7 percent surviving until age two. The survival rate then declines almost linearly with age. At age five, 77.4 percent of biotech firms are alive; by age ten, 51.5 percent are still in business.

Actually, the survival rates of biotech firms are fairly high. Using the same Dun & Bradstreet data that our NETS data are based on, Birch (1987) found that in the whole U.S. economy, about half of new firms were surviving in the fifth year and only 38 percent were still around at age ten. Using the same NETS data, Zhang (2003) documented that in Silicon Valley, only 42 percent of the technology firms in the service sector and 46 percent in the nonservice sector survived for more than ten years. Figure 5.2 suggests that California's biotech firms have lower mortality rates than firms in other sectors, at least in the first ten years. This is likely because biotech firms spend a substantial amount of time on research and development before any marketable product is created or approved. Thus, it takes longer than in other sectors to recognize a failed company.

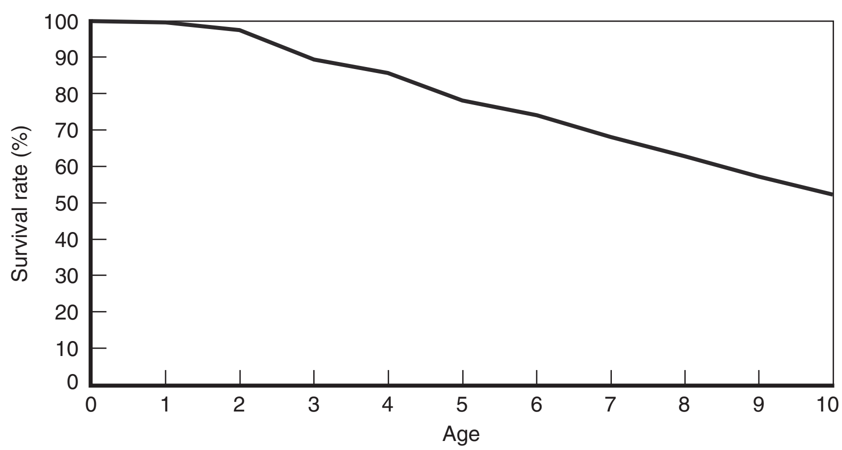

Figure 5.2—Survival Rate of Biotech Firms in California

California's biotech industry was hard-hit by the economic recession in the early 1990s, with the industry's employment declining. But from 1992 to 2001, the biotech industry experienced an impressive 52.5 percent job growth. There are several potential sources of growth: First, existing establishments may hire more people; second, establishments may relocate from other states to California and bring jobs with them; third, new firms may emerge to create jobs; and fourth, existing firms, either from California or out of state, may branch out or set up new establishments and create jobs.

Table 5.6 deconstructs the employment gains in biotech in the manner just described. It shows that total employment at establishments started before 1992 actually declined between 1992 and 2001, because

Table 5.6

Decomposition of Employment in Biotech, 1992 and 2001

	Biotech Manufacturing	Biotech R&D	Total
1992 total employment (1)	38,823	42,472	81,295
2001 employment at establishments started before 1992 (2)	39,713	35,861	75,574
2001 employment at establishments moving to California since 1992 (3)	92	199	291
2001 employment at establishments started as stand-alone firms in California since 1992 (4)	7,662	15,385	23,047
2001 employment at establishments started as branches/subsidiaries of California firms since 1992 (5)	4,034	11,879	15,913
2001 employment at establishments started as branches/subsidiaries of non-California firms since 1992 (6)	6,239	4,743	10,982
2001 total employment (2) + (3) + (4) + (5) + (6)	57,740	68,067	125,807

SOURCE: Authors' calculations from the NETS data.

many of these firms failed. This decline occurred primarily in the R&D sector; the manufacturing sector in fact increased its employment. The number of jobs provided by establishments relocating to California during this period is negligible. However, new firm formation contributed a great deal to job growth. Stand-alone firms founded since 1992 added more than 23,000 jobs to the 2001 total employment in biotech. The branching out of existing firms was equally important. Again, we see some differences between manufacturing and R&D. In manufacturing, new branches of non-California firms created more jobs than those of California firms during the decade; in R&D, the opposite is true: The branches of California firms substantially outperformed branches of non-California firms in job creation.

Table 5.7 translates the job numbers in Table 5.6 into proportions of job growth attributable to different sources. Overall, new firm formation and branching out of existing firms explain more than 100 percent of the job growth. Without those activities, total employment would have declined by 2001. New firms founded in this period account for about half of the job growth; the share is even higher in the area of biotech R&D.

Conclusion

Using a longitudinal database, we have studied the formation, growth, and mortality of California's biotech firms. We find that despite the 30-year history of the biotech industry and the continuous public attention surrounding it, the industry itself constitutes only a small proportion of the overall economy. An overwhelming majority of the biotech firms are small and hire no more than 50 people. Also, many of the biotech establishments are engaged in research and development activities. In fact, biotech R&D has provided as many jobs for California as biotech manufacturing. Biotech firms tend to have a lower-than-average mortality rate. It suggests that biotech is unlikely to create too much fluctuation in the labor market, as did the information technology industries. New firm formation accounts for a substantial amount of job growth in biotech. That is, job creation, to a great extent, is about firm creation.

Table 5.7

Decomposition of Job Growth in Biotech, 1992–2001
(in percent)

	Biotech Manufacturing	Biotech R&D	Total
Total job growth,1992–2001	18,917 (48.73%)	25,595 (60.26%)	44,548 (54.82%)
Growth at establishments started before 1992	4.70	–25.83	–12.76
Growth due to establishments moving to California since 1992	0.49	0.78	0.65
Growth due to establishments started as stand-alone firms in California since 1992	40.50	60.11	51.74
Growth due to establishments started as branches/subsidiaries of California firms since 1992	21.32	46.41	35.72
Growth due to establishments started as branches/subsidiaries of non-California firms since 1992	32.98	18.53	24.65
Total	100	100	100

SOURCE: Authors' calculations from the NETS data.

NOTE: Totals may not sum to 100 percent because of rounding.

A comparison of the dynamics in California's biotech industry with those in other industries would have generated more insights. However, data limitations at this stage prevent us from conducting such a study.

6. Can California Maintain Its Edge in Biotech?

There is no doubt that California's biotech industry is in the leading position. However, more and more states have realized the potential of the biotech economy and have started to compete for it. At the 2003 Biotechnology Industry Organization's annual meeting in Washington, D.C., nine governors and more than a dozen states recruited industry leaders by offering tax breaks, time with the governor, and the use of state university labs.[1] Some of these states sought to actively recruit promising biotech companies from California. Since the burst of the Internet bubble, other states (and even other countries) have sent delegations to California's technology centers to advertise their regional advantages and policy incentives, with the intention of luring California's businesses. As one entrepreneur vividly describes it, "the red carpets are out from many other states." Given the efforts of competing states and the high cost of doing business in California, it is becoming an increasingly urgent concern as to whether the Golden State is able to maintain its lead in biotechnology.

Biotech firms take several years to develop products and require a great deal of initial investment in research. DeVol (2000) cited a survey of executives at biotech, pharmaceutical, and medical device companies conducted by the management consulting firm A. T. Kearney and pointed out that start-ups and mature firms in biotech have different concerns. Start-ups require capital and focus on R&D. As a result, they want to be near venture capitalists and research institutions, which makes California attractive. But mature firms are more concerned with such sustainability factors as operating costs. Because the initial investments in this industry are extremely high, policymakers and academic

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[1]See www.govtech.net/news/news.php?id=59359.

researchers often wonder whether firms, once mature, maintain the majority of their operations in the state or decide to move elsewhere.

Pollak (2002) cautioned that California often has to compete with other states to attract and retain biotech businesses. State laws and regulations can add significant costs to the equation when companies choose locations for start-ups or expansion. Pollak noted that people in the industry and local government feel that California's regulatory climate makes it difficult for bioscience companies to locate or remain in California.

Two reports recently released by the California Healthcare Institute (2004a, 2004b) hold similar views. They claim, "[t]here is little to stop companies from leaving the state, taking their revenues, export dollars, and jobs with them. An outward migration of California's biomedical industry threatens to undermine the California biomedical industry's future success." And they believe that California biomedical manufacturing is in peril because "a majority of California's biomedical companies plan to expand manufacturing outside the state in the next two years."

In this chapter, we use the NETS data to study business relocation in California's biotech industry. The NETS data include a variable that tracks the address of each physical unit of business from 1990 to 2001 in the United States. With these data, we can determine how common business relocation is and the size of the effect on California's biotech industry. We then discuss related issues such as whether California's biotech firms flee the state by branching out, what actions other states have taken to promote their biotech economies, and what California has done.

Firm Relocation

In this analysis, it makes more sense to consider establishments rather than firms. An establishment is a single physical unit of business that could be a firm or a branch of a firm. For multiestablishment firms, it is possible to relocate part of the operation (such as manufacturing) and leave the rest of the firm (such as headquarters and R&D) where it is. Our analysis is able to capture such movements by working with establishment-level data.

Our extract of the NETS data covers only biotech firms that ever located in California. There are 5,634 establishments, 826 of which moved at least once.[2] Of the biotech firms founded in California, 14 percent (781 out of 5,589) moved during 1990–2001. As Table 6.1 shows, 93.3 percent of those that moved stayed within California; only 6.7 percent, or 52 establishments, moved out of the state.

Among the 729 establishments that moved within California, 208, or 28.5 percent, remained in the same city, and 566, or 77.6 percent, stayed in the same county. These statistics suggest that biotech firms do not often move and that those that do move tend to stay near their original location. Businesses moving to other states are rare cases.

Table 6.2 shows the top destination and origin states when biotech firms moved across the state boundary. When biotech firms moved out of California, they tended to go to other western states. In fact, four of the top five destination states are in the west or southwest, two of which are California's immediate neighbors. However, top origin states show a different pattern: Three of the top five origin states are East Coast states, and those three far outnumber others in terms of biotech jobs moving to California. Interestingly, these moving patterns are consistent with high-tech business relocation into and out of Silicon Valley (Zhang, 2003). Furthermore, the fact that California's firms tend to go to nearby western states corresponds to migration trends of the California population.

Table 6.1

Origin and Destination States of Moving Biotech Firms, 1990–2001

	Destination State: California	Destination State: Other
Origin State: California	729	52
Origin State: Other	45	—

SOURCE: Authors' calculations from the NETS data.

[2]For those that moved more than once, we have the origin and destination information for the last move.

Table 6.2

Top Destination and Origin States of Biotech Firms Moving in California, 1990–2001

State	Establishments Moved	Jobs Involved
Top Destination States		
California	729	18,693
Washington	7	107
Texas	6	49
Arizona	4	52
Oregon	4	35
Nevada	3	76
Top Origin States		
California	729	18,693
New Jersey	7	420
Washington	5	35
New York	4	457
Massachusetts	3	407
Ohio	3	21

SOURCE: Authors' calculations from the NETS data.

Although causing a great deal of concern within the state, the migration of biotech firms seems to have a small effect on California's biotech industry. Although we do see more firms leaving California than moving in, only 52 crossed the state border over this ten year period, which had a very limited effect on the labor market. Moreover, as Table 6.3 shows, although firms that moved out outnumbered those moving in, they took fewer jobs away than those brought in by incoming firms. Measured by the employment level at the time of relocation, the 52 establishments that moved out of California eliminated 815 jobs, yet the 45 establishments moving into California added 1,739 jobs to the California economy, more than enough to offset what California lost. In addition, among the 52 establishments that left California, 36 were alive in 2001 and together offered 840 jobs in 2001. In contrast, 27 out of 45 establishments that moved to California survived in 2001, employing a total of 2,993 people, more than three times as many as what California lost to other states.

Table 6.3

Employment at Biotech Firms Moving Out of or Into California, 1990–2001

	Moving from California to Other States		Moving from Other States to California	
	Establishments	Jobs	Establishments	Jobs
Total	52	815	45	1,739
Alive in 2001	36	840	27	2,993

SOURCE: Authors' calculations from the NETS data.

Figure 6.1 presents the distribution of biotech establishments that moved into or out of California by start year. Clearly, those moving to California during 1990–2001 tend to be younger than those moving out: 67.3 percent of those moving out were established before 1990, whereas only 42.2 percent of those moving in started before 1990. About one-quarter of the biotech establishments moving into California were established after 1994, whereas only 9.6 percent of those moving out were established in the same period.

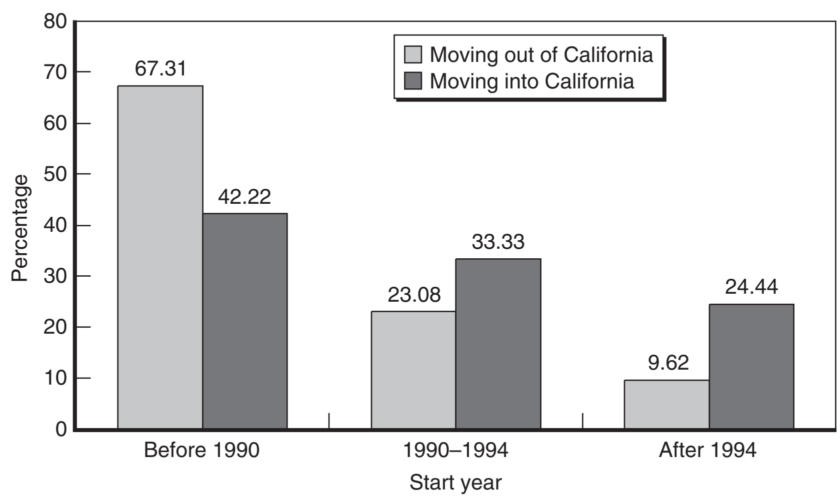

Figure 6.1—Distribution of Moving Establishments, by Start Year, 1990–2001

Overall, these numbers of relocating establishments and jobs are so small relative to the biotech industry that they are far from statistically meaningful. One message we can take from this is that business relocation in California's biotech industry has a very limited effect. Even if we view these numbers with some concern, they suggest nothing like the supposed flight of biotech businesses. In fact, these statistics show that California's biotech industry attracted younger firms with more jobs and higher growth potential. This confirms the general impression that the California economy provides an innovative environment that is particularly favorable to young start-ups and less attractive to mature firms. Previous work on Silicon Valley yielded similar findings (Zhang, 2003).

Relocation Through Expansion

We have shown that although more biotech establishments moved out of California than came in, the difference is small and the net effect on the state's economy is probably positive. However, we have been studying firm relocation by focusing on biotech establishments that physically moved. Firms may effectively "move out" of California in other ways. For example, a mature biotech firm may set up or acquire a manufacturing plant in some other state and start growing elsewhere. A top executive at a multiestablishment biotech firm in Southern California told us that every time his board members discuss a potential acquisition target outside California, they seriously consider the possibility of shifting some of their operations to the acquired firm to avoid some of the soaring costs incurred in California.

It is natural that firms might consider setting up their R&D and production operations in different locations to maximize profit. Indeed, California is not alone in facing this problem. Massachusetts, the second-largest state in the biotech industry, has similar worries. In a report issued by the Massachusetts Biotechnology Council and the Boston Consulting Group, the major concern is that top firms are choosing to locate manufacturing operations elsewhere. The report warns, "If the picture plays out, the state may end up creating a huge industry but not capturing much of the benefit."[3]

David L. Gollaher, president of the California Healthcare Institute, reiterates this, "Start off with the assumption that it is already very expensive to do business in San Diego. . . . Then add the housing and infrastructure problems. That means you have to pay people a lot to work here. But how much of a premium will the manufacturing sector be willing to pay?" (Somers, 2004).

It is a challenging task to systematically track firm growth and expansion at multiple locations all over the country. Conceptually, the NETS data we are using allow one to do that because the data do provide information about the family structure of multiestablishment firms. However, the extract of NETS data we have covers only firms that ever located in California and do not include branches set up by California firms in other states. So we cannot conduct a comprehensive empirical study of the expansion of mature California biotech firms in other states, but we certainly can learn some useful lessons from case studies.

In fact, there are not many mature biotech firms yet. For example, the San Diego region has long been famous for its biotech cluster. Yet very few biotech firms in San Diego have entered the stage of manufacturing and marketing biotech drugs. Many are engaged in R&D; some have been conducting clinical trials of their products and will be able to deliver them in the near future. In the entire country, only 28 companies, including quite a few big pharmaceutical companies, have biotech drugs or vaccines on the market.

However, it is likely that many of the biotech firms in California will become full-fledged biotech companies like Amgen, Chiron, and Genentech, which not only continuously develop new drugs through research but also manufacture and sell drugs on the market. As a biotech firm that focuses only on R&D grows into a pharmaceutical company, it has the potential to create many more jobs. Table 6.4 shows the typical employment structure of leading pharmaceutical companies. Both the manufacturing and marketing employees outnumber the R&D staff.

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[3]See http://www.massbiotech2010.org/pdf/Globe_biotech_12_11.pdf.

Table 6.4

Domestic Personnel of PhRMA-Member Companies, 1990–2000

Employment Function	1990	1995	1999	2000
Production, quality control	59,546	59,541	57,962	54,001
R&D	43,952	49,409	45,192	51,588
Marketing	56,014	55,348	81,296	86,226
Administration	21,915	28,810	22,499	29,448
Distribution and others	7,384	5,611	4,722	16,273
Uncategorized personnel[a]				9,797
Total	188,811	198,719	211,671	247,333

SOURCE: Pharmaceutical Research and Manufacturers of America (PhRMA), PhRMA Membership Survey, 2002.

[a]Some companies provided total employment but not function details.

This suggests that some biotech research companies are likely to generate much more employment once their drugs hit the market. But the question is whether such jobs will be created in California.

One common concern is whether California's biotech industry will become a big "think tank" and the manufacturing and marketing jobs created by the industry's research will be captured only by the big pharmaceutical companies on the East Coast, such as those in New Jersey and New York. This concern seems to be unfounded. Most of the existing manufacturing facilities at the big pharmaceutical companies could not be easily modified for the production of biotech drugs. There are two types of drugs: small-molecule drugs and big-molecule drugs. Most traditional drugs are small-molecule drugs, which are delivered to the disease area through the human digestion system or blood vessels because they can travel through the body without changing its function. Biotech drugs are mostly big-molecule proteins. This type of drug cannot travel through the human body and maintain its molecular structure. It must be delivered directly to the area affected by the disease. The production of small-molecule and big-molecule drugs involves different techniques. And this is why many early biotech drug manufacturers must build their own plants or contract out to other biotechnology companies such as Genentech instead of contracting out to existing pharmaceutical companies.

Yet there is another channel through which big pharmaceutical companies could benefit from the R&D activities of small biotech firms. Pharmaceutical companies have a great deal of money, and biotech firms, especially those still at the stage of drug development, are thirsty for cash. A typical biotech company that focuses on drug development spends millions on R&D each year and keeps losing millions for years. For example, the 28 California companies in the NASDAQ and AMEX Biotech Indexes that do not have a drug on the market together spent a total of $1.5 billion on R&D in 2002. Although many of them did generate some revenue by licensing out their technology, together they lost $1.2 billion that same year.

Take Amylin Pharmaceuticals as an example. It was founded in 1987 in San Diego and currently employs 500 people. Amylin develops diabetes drugs and already has two promising products waiting for FDA approval. Table 6.5 presents some of Amylin's financial data. As is evident, without a single product on the market, Amylin has been unable to cover its expenditures with its own revenue.

Amylin is not an unusual example. As Table 6.6 shows, the overall financial situation of 40 California firms included in the NASDAQ and AMEX Biotech Indexes in December 2003 tells a similar story:

Table 6.5

Selected Financial Data of Amylin Pharmaceuticals, 1998–2002
($ thousands)

	Year (Ended December 31)				
	1998	1999	2000	2001	2002
Revenue under collaborative agreements	16,236	—	—	—	13,395
Expenses:					
R&D	53,597	19,181	33,807	49,601	94,456
General and administrative	10,191	7,920	10,716	20,469	25,334
Net interest income (expense)	(3,546)	(3,463)	480	(1,902)	(3,392)
Net loss	(51,098)	(30,564)	(44,043)	(71,972)	(109,787)

SOURCE: Company website http://www.amylin.com.

Table 6.6

Financial Situation of 40 California Biotech Firms in the NASDAQ and AMEX Biotech Indexes, 2000–2002

	2000	2001	2002
Total revenue, $ millions	4,174.6	5,354.5	6,144.1
R&D expenditure, $ millions	3,727.6	2,824.3	3,263.0
R&D as a % of sales	89.29	52.75	53.11
Net income, $ millions	–835.3	–1,293.2	–1,438.4
No. of firms with profits	6	8	7

SOURCE: Data collected by the authors from company websites.

unimpressive sales, large expenditure on R&D, and a large amount of net loss.[4] Note that these are all the leaders in the biotech industry.

Big pharmaceutical companies are cash rich; small biotech firms are constantly in demand of R&D money. And because their research and business expertise are usually complementary, the situation is ripe for biotech firms to collaborate with pharmaceutical companies. In fact, organizations such as the former California Technology, Trade, and Commerce Agency and the Bay Area World Trade Center have organized networking events for biotech companies and big pharmaceutical companies around the world. In 2003, 15 California biotech companies participated in the California Biotechnology Trade Mission to BioSquare, a European partnership program in France. Companies were given, on average, 18 one-on-one meetings with potential European pharmaceutical partners. In fact, these 15 companies reported potential partnership deals of $400 million as a result of the contacts made at this mission. Organizers have also planned Biotechnology Trade Missions to other European countries.[5]

In a typical collaborative relationship, the big pharma provides the biotech firm with R&D money in exchange for access to the technology or the right of manufacturing and marketing the potential biotech

[4]Amgen's data are excluded from this calculation, because it is much larger than any other biotech firm, and its 2002 financial data include a $3 billion writeoff related to the acquisition of Immunex, which would have greatly distorted the overall picture here.

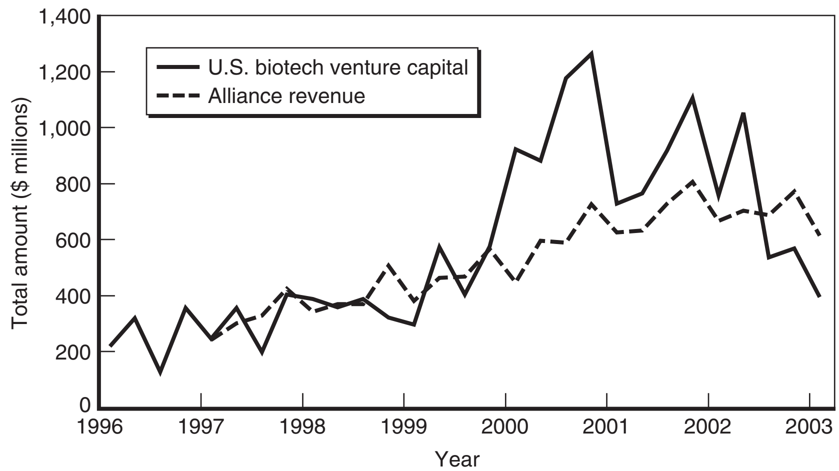
[5]See http://www.caltradereport.com/eWebPages/page-two-1057042450.html and http://www.bawtc.com/tradenews_details.asp?PartnerID=&ArticleID=59.

products. In Table 6.5, note that Amylin earned some revenue under "collaborative agreements." This is the money provided by its partners. For example, in September 2002, Amylin signed an agreement with Eli Lilly to collaborate on the development and commercialization of Exenatide, a promising new drug for the treatment of diabetes that was in the final stage of clinical trial. Under the agreement, Eli Lilly would first make some $80 million in nonrefundable payments to Amylin. Eli Lilly would also purchase $30 million of Amylin's common stock. Additionally, in the future, Eli Lilly would pay Amylin up to $85 million upon the achievement of certain development and product profile milestones of the new drug. Eli Lilly also agreed to make additional future contingent payments of up to $130 million upon global commercialization of the drug.[6]

In fact, alliance agreements between biotech firms and pharmaceutical companies are so common that they have become a major source of R&D money for many biotech firms (Koehler, 1996). Figure 6.2 plots the trend of biotech firms' alliance revenue in comparison to the total venture capital investment in biotech in the United States. Except in the peak years of the Internet bubble, alliance revenue followed a growth path similar to that of venture capital investment. Although venture capital investments typically precede alliance revenues for biotech firms, the total amounts from these two sources of finance are comparable. Because venture capital investment has plummeted since the burst of the bubble, alliance revenue may have surpassed it as a major source of R&D money for fledgling biotech firms.

Early research (e.g., Gray and Parker, 1998) suggested that although losing much of their preeminence in research and development to biotech firms, pharmaceutical companies have managed to capture a substantial amount of manufacturing and marketing. The extensive collaborative relationships between pharmaceutical companies and biotech start-ups undoubtedly provide a lever for the pharmaceutical giants to influence the decisions of biotech firms, which is likely to have implications for the geographic distribution of the manufacturing and marketing activities in the biotech industry and hence affects the

[6]See press release at http://www.amylin.com/Corporate/Partnerships.cfm.



SOURCES: http://www.ventureone.com/ and http://www.recap.com/.

Figure 6.2—Alliance Revenue and Venture Capital Investment in Biotech, 1996–2003

distribution of job creation in the industry. It is still too early to tell whether the clusters of biotech industry in the West will shake the dominance of the New York–New Jersey region in drug discovery and manufacturing.

We examined some of the larger companies in California that have biotech products on the market to get a general sense of their manufacturing practices. One thing is immediately clear: A number of companies, including such large firms as Gilead Sciences, Ligand Pharmaceuticals, Connectics Corp., and InterMune Pharmaceuticals, contract manufacturing of the majority of their drugs to partners. Some of these outsourced manufacturers are larger biotech companies in California, including Amgen and Genentech, but most are typically outside California and are larger pharmaceutical companies, including Roche and Pfizer. Genentech and Chiron manufacture the majority of their own drugs within California. In fact, both have significant presences in Vacaville, California. We found that Genentech manufactures nine of its 14 drugs in its South San Francisco plant while producing four in Vacaville and one in Spain.[7] Amgen, on the other hand, has several manufacturing plants, including large facilities in its Thousand Oaks headquarters as well as facilities in Colorado, Rhode Island, and Puerto Rico, where the company recently announced it was going to spend $800 million and employ 600 workers.[8] To date, 22 California companies have FDA-approved biotech drugs or vaccines. Among these companies, the early ones such as Alza, Amgen, Chiron, Genentech, Gilead, and IDEC all have manufacturing facilities in California. Some of them only later expanded out of California to the rest of United States and Europe. But this seems to be a natural process of expanding in lower-cost areas or close to customers, rather than preparing to move out of the state altogether. The number of biotech drugs currently in the clinical development pipeline continues to increase, and California companies own the largest share of these products (17.5%). As a result, preparing for sufficient manufacturing capacity and incentives within California will be important now, since the industry estimates that it takes up to five years to design, build, validate, and qualify new plants.

State Biotech Policies

It has been almost three decades since the inception of the biotech industry. Its rapid growth over these years has convinced regional governments that this industry will be a powerful growth engine for their economies and thus they are determined to grab a piece of the pie.

Almost all states have implemented policies to support their own biotech industries. In 2001, the Biotechnology Industry Organization published a comprehensive report that documented bioscience policies in 41 states. In 2004, an updated version of the report expanded the coverage to the whole country, because "40 states are targeting the biosciences for development and all 50 states have technology-based economic development initiatives that are available to bioscience

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[7]See http://www.gene.com/gene/news/kits/corporate/manufacturing.jsp.

[8]See http://wwwext.amgen.com/news/news03/pressRelease030320.pdf.

companies." This section draws heavily from these publications (Biotechnology Industry Organization, 2001, 2004).

The following are among the most commonly used state policies to promote the biotech industry.

Tax Incentives

Almost all states offer some sort of tax break for biotech firms. Most of the biotech start-ups focus exclusively on R&D, and even the most mature ones spend a large proportion of revenues on R&D. Thus, the most widely adopted tax policy that benefits biotech firms is the tax reduction for R&D expenditures.

Corporate income tax breaks would affect very few biotech firms because most of them have never made any profit. Thus, it is not an effective policy lever. In contrast, how to treat business losses has a great effect on the biotech industry. One type of tax incentive to biotech firms is to allow the carryover of net operating loss (NOL) for purposes of tax deduction. Specifically, in promoting the biotech industry, some states have recently extended the period of time allowed for the carryover. Thirty states in the nation allow net operating losses to be carried forward; in Idaho and West Virginia, losses can also be carried backward for two years.

However, because typical early-stage biotech firms keep losing a large amount of money for many years, NOL carryover may not be fully used in the short run. Thus, some states allow biotech firms to sell their unused operating losses to other taxpayers. By September 2004, seven states had adopted this policy, including Arkansas, Idaho, Louisiana, Massachusetts, New Jersey, New Mexico, and Pennsylvania. Connecticut, Hawaii, Iowa, and Minnesota even make tax credits refundable. For example, in Connecticut, early-stage biotech companies can exchange unused R&D tax credits with the state for cash equal to 65 percent of the credit value.

A few states use tax incentives to foster their local venture capital industry, which is presumably helpful for business formation in the biotech industry. States such as Florida, New York, and Texas give tax credits to insurance companies if they invest in certified capital companies. Others such as Arizona and South Carolina directly offer tax credits to venture capital firms. Residents in states such as Iowa, Kansas, and Oklahoma get tax credits for investments in qualified venture capital funds.

Biotech Strategic Planning

If many states missed the chances of developing their own "Silicon Valleys" during previous information technology booms, they have surely learned their lessons. Some states have become fully prepared for the long anticipated biotech booms by developing plans that explicitly identify biotech as a growth industry. Others have developed strategic plans for the whole technology sector that include biotech as an important element. The objectives of state-level strategic planning usually include specifying the common goal of developing a strong biotech economy, identifying specific industry niches suitable for the state, providing guidance for creating biotech clusters, and, more importantly, laying out recommendations to policymakers and industry leaders to prioritize actions. The most common recommendations in these strategic planning efforts are to build networks among regions, institutions, researchers, and businesses; form research alliances; attract talent; and provide funds to researchers and entrepreneurs.

State Biotech Specialists

Most states have staff members in charge of the technology sector. Given the unique features of the biotech industry and its growth potential, some states have appointed individuals with in-depth knowledge of the biotech industry to deal specifically with its needs. They generally act as liaison between the industry and state government, provide the industry with regulatory assistance, monitor the development of the industry, and seek to recruit biotech firms from other states or countries.

Tobacco Settlement Funds for Biotech

In November 1998, the five largest tobacco companies in the United States settled a long-standing lawsuit with states over the health care costs incurred as a result of the consumption of tobacco. The five companies agreed to make annual payments to the states in perpetuity, with total payments over the first 25 years estimated at $246 billion. Many states decided to use this money to support biomedical research. For example, Pennsylvania spends 25.6 percent of its tobacco settlement dollars on life science research; a quarter of Missouri's tobacco settlement dollars will go to a Life Sciences Trust Fund; Ohio uses its settlement money to support biotech research and commercialization through its Biomedical Research and Technology Transfer Trust Fund, which expected to receive a total of $77.6 million in fiscal years 2001–2004.

State Funds for Biotech

Many states make various funds available for the biotech industry's special needs. This may include funds for building modern biotech research labs and facilities or seed and venture capital for biotech start-ups. For example, Wisconsin invested $317 million on life science facilities at the University of Wisconsin–Madison; Texas decided to spend $385 million on life science research facilities on several campuses; Arizona approved $440 million to invest in research facilities with a goal of enhancing its bioscience research. Many states directly invest in or provide venture capital funds, but only a few exclusively target biotech start-ups. For example, Connecticut created a $5 million BioSeed Fund, and North Carolina used $10 million to help launch a North Carolina Bioscience Investment Fund.

Research Parks and Incubators

Many states have constructed research parks and incubators to house technology companies, including those in biotech. Some research parks and incubators even specialize in biotech. For example, at the Advanced Biotechnology Park at State University of New York's Downstate Medical Center, a 50,000 square-foot biotech incubator is under construction, with ImClone Systems as the anchor tenant. In Colorado, a 160-acre Colorado Bioscience Park Aurora is affiliated with the University of Colorado and provides emerging biotech companies with access to its medical center.

Table 6.7 summarizes biotech policies adopted by selected states. Although it is only a partial picture of California's competition, policymakers should be concerned about the challenges they face from

Table 6.7

Biotech Policies in Selected States

State	Tax Break[a]	Years of NOL Carryover	Bioscience Plan, Year Adopted	State Biotech Specialist	Tobacco $ for Biotech	State Biotech Funds	Biotech Research Park	State Incubator
Alabama	Y	5				Y		Y
Arizona	Y		2002			Y	Y	Y
Arkansas	Y[b]	5	2000		Y	Y		Y
California	Y	8				Y	Y	Y
Colorado	Y		2003		Y		Y	Y
Connecticut	Y[b]	20	1998[c]		Y	Y		Y
Delaware	Y	15	2002	Y		Y		
Florida	Y	20	1998, 2002		Y	Y		Y
Georgia	Y		2002	Y	Y	Y		Y
Hawaii	Y	20	1999		Y			
Idaho	Y	20 + 2 back						Y
Illinois	Y	12			Y	Y	Y	Y
Indiana	Y	20	2003					Y
Kansas	Y	10	2003[c]		Y			Y
Louisiana	Y	5	2000[c]	Y	Y	Y		Y
Maine	Y		2004[c]			Y	Y	Y
Maryland	Y		1991	Y	Y	Y	Y	Y
Massachusetts	Y	5	1993,[c] 2002[c]	Y	Y	Y	Y	Y
Michigan	Y		2000, 2002	Y	Y	Y		Y
Minnesota	Y	15	2001	Y	Y			Y
Missouri	Y		2000, 2003	Y	Y	Y		Y
New Jersey	Y[b]		2004		Y	Y	Y	Y

Table 6.7 (continued)

State	Tax Break[a]	Years of NOL Carryover	Bioscience Plan, Year Adopted	State Biotech Specialist	Tobacco $ for Biotech	State Biotech Funds	Biotech Research Park	State Incubator
New Mexico	Y	5	1999	Y	Y			
New York	Y	15				Y	Y	Y
North Carolina	Y	15	2004			Y	Y	Y
Ohio	Y	15	2002[c]	Y	Y	Y	Y	Y
Oklahoma	Y					Y	Y	
Oregon	Y	15	1999			Y		Y
Pennsylvania	Y	15			Y	Y	Y	Y
South Carolina	Y	15	2003[c]			Y		Y
Tennessee		15	2002				Y	Y
Texas	Y		2003		Y	Y	Y	Y
Utah	Y	5		Y	Y			
Vermont	Y		1996[c]			Y		
Virginia	Y		2003	Y		Y	Y	Y
Washington	Y		2004					Y
West Virginia	Y	20+2 back						
Wisconsin	Y	15			Y	Y		Y

SOURCE: Authors' summary based on Biotechnology Industry Organization (2001, 2004).

[a]Y indicates a policy adopted.

[b]Indicates tax breaks exclusively designed for the biotech industry.

[c]Indicates an overall technology development plan with bioscience as a major part.

other states. Notice that Massachusetts, California's major competitor, has taken action across the board.

Because these policies were adopted rather recently, little is known about their effectiveness in nurturing the biotech industry. However, some of the policies have been extensively studied in different contexts. For example, tax incentives have long been an important subject in the local economic development literature, and science parks and incubators have been studied in the technology transfer literature. Some of the findings in this related literature are worth noting here.

It is an enormous challenge to evaluate the effect of tax incentives on regional economies because of conceptual, measurement, and estimation difficulties. As a result, although there are hundreds of papers written in this area, researchers can provide little guidance to policymaking in regional economic development (Buss, 2001). In a comprehensive review of the literature, Wasylenko (1997) reports that 23 out of 38 interregional studies find a statistically significant effect of overall tax levels on aggregate economic statistics such as manufacturing employment or gross state product. Out of 34 studies that focused on business taxes, 24 find a statistically significant effect. However, the effect in general is insubstantial and thus is not economically significant. In terms of firm location decisions, survey studies tend to find that taxes have little or no effect. But some authors argue that tax may be a factor at certain stages of the location decision although not at all stages. Also, firms in different sectors are not equally responsive to tax incentives. For example, the location decision of manufacturing firms appears to be more sensitive to taxes (Buss, 2001).

Researchers in technology transfer find that science parks are often perceived as "enclaves of innovation," giving firms in the park the benefit of a certain image. Also, firms in science parks profit from cooperation with universities. Empirical evidence shows that firms in science parks have significantly higher survival rates, but in terms of employment growth, they are not significantly different (see, for example, Ferguson and Olofsson, 2004). Business incubators, although often established with the good faith of government officials and incubator managers, are found to be not very effective in job creation. However, as economic development tools, they are more cost-effective than business relocation programs designed to attract firms to a region (Hackett and Dilts, 2004).

According to many researchers, the limited effect of local development policies partly stems from the tendency that states adopt similar policies as the result of interregional competition. And the competition is nowhere more intense than in the biotech sector, which has implications for the effectiveness of state biotech policies. However, we must recognize that the biotech industry is growing rapidly and thus interregional competition is not necessarily a "zero-sum game." It is quite possible that it takes the universal support of the entire nation to fully realize the growth potential of this industry.

Recruiting Efforts by Competing States

The state policies listed above do not fully reveal the assistance and allowances that competing states are willing to offer to court biotech companies, including those in California. Such generous offers make it even more difficult, especially with California's rising costs, for the state to retain its successful biotech companies.

As an example, in 1994, the South San Francisco–based biotech pioneer, Genentech, planned to spend a quarter billion dollars on a new manufacturing plant. The company's first choice was to build the plant in Northern California because of its proximity to headquarters and research centers. Yet, as the company's spokesman said, "Cost pressures and regulatory constraints have expanded the search to outside California." Other states quickly offered a broad range of incentives. Genentech looked at approximately 50 sites in several states and Europe before deciding on the city of Vacaville, located in Solano County, 60 miles from its headquarters in South San Francisco.[9]

Genentech could have saved 20 to 30 percent of construction and operating costs if it had built the plant outside California. It took the state and the city of Vacaville a great deal of effort to keep the new plant in California. In searching for sites, Genentech initially hired a search

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[9]See, for example, Eckhouse (1994), "Genentech Sweeteners" (1994), "Genentech to Build Plant in Vacaville" (1994), Jacobs (1998), Lucas and Barnum (1994), Marsh (1998), and Sinton (1994).

firm and remained anonymous. Once such states as Virginia started approaching Genentech, officials with the California Trade and Commerce Agency figured out the identity of the anonymous company. They quickly came up with an enticing package. To stress the state's commitment, California's then-governor Pete Wilson phoned the president of Genentech and later met with him in the governor's office. In the end, the firm was swayed by the state's incentive package, including California's R&D tax credit—a state investment tax credit worth up to $6 million. Genentech would also receive a $3.2 million federal economic development grant, a $10 million state grant for retraining workers, a $4 million property tax rebate by the city of Vacaville and Solano County, a waiver of $1.8 million in permit fees and sewer costs, and a discounted long-term energy contract offered by Pacific Gas and Electric Company.[10]

San Diego's biotech champion, IDEC, had a similar experience.[11] IDEC was founded in 1985 to develop and commercialize "anti-idiotype monoclonal antibodies," a patient-specific, customized approach to treating non-Hodgkin's lymphoma. After a dozen years of research and development, in November 1997, IDEC had its first product, Rituxan, approved by the FDA. For the next several years, Genentech manufactured the drug for IDEC and shared in the profits. As early as 1998, IDEC was ready to spend more than $100 million on a manufacturing plant. Naturally, many other states courted IDEC in hopes of luring its manufacturing arm. Although IDEC did consider sites near its headquarters in the San Diego region, San Antonio, Texas, presented a quite competitive offer.

In almost every respect, San Antonio beat San Diego. San Antonio has lower labor rates, cheaper power and water, no state corporate

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[10]The state's and Vacaville's investment seems to have paid off. In April 2004, Genentech broke ground for the construction of a new plant in Vacaville. This $600 million expansion plan—which is expected to be completed in 2009—will double the size of Genentech's manufacturing facilities and its employment in Vacaville. By then, Genentech's manufacturing plant in Vacaville will become the largest biotech drug factory in the world.

[11]See, for example, Aryan (2000), Freeman and Kupper (2000), Jacobs (1998), Nowlin (1996, 1997), and Sherman (2000).

income tax, and a lower cost of living. To impress IDEC chairman William Rastetter, San Antonio's economic development representatives took him to a golf course "lined with million dollar homes" that cost only $200,000. Furthermore, San Antonio offered a 50-acre stretch of land virtually free ($1 per year) to IDEC if it built a plant there.

In 2000, after a three-year search, IDEC finally decided on Oceanside—a city north of San Diego and within an hour's drive from its headquarters in La Jolla. The proximity to IDEC's headquarters certainly gave Oceanside an advantage, but the deal was not free. To woo IDEC, Oceanside pledged to meet the company's requirement of 1.4 million gallons of water per day and also promised to build a $1.2 million brine line to carry the plant's wastewater. In addition, Oceanside agreed to forgo $30,000 in business license taxes, $1 million in equipment taxes, and $3.4 million in building and processing fees.

Another successful San Diego firm, Stratagene, made a choice in favor of Texas.[12] Stratagene, also headquartered in La Jolla, develops and manufactures lab testing kits and devices used by life science researchers. When the privately held firm began searching for a site to double its size, it first considered staying close to home. Yet it finally chose Colorado River, Texas, rather than San Diego for its new plant. Colorado River offered Stratagene a low-interest, tax-free loan of $9 million and a partial exemption of local property taxes over a period of ten years. San Diego did counteroffer a package of incentives, but it was not good enough to alter Stratagene's decision.

As more and more California biotech firms have products ready for the market and enter the stage of manufacturing and marketing, the battle between states will only become fiercer. In the area of manufacturing, California's high cost of doing business makes it challenging to keep biotech firms. Yet it is not impossible. California has a clear advantage in that many firms are already established in the state. A 2002 Ernst & Young survey of biotech chief executives in the San Diego region found that many of the mature companies planning on manufacturing want their operations to be close to headquarters. Since

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[12]See, for example, Jacobs (1998), Janes (1997), Redding (1991), and Todd (1997).

California also offers a rich culture, benign weather, a high-quality labor pool, and top-notch research universities, the calculation does not immediately fall against the Golden State. Yet one thing is clear: The state will often face competing offers. To retain biotech firms, local and state government officials must work together to find solutions and must be prepared with proactive offers—because most of the time, an incentive package will be necessary to entice firms to stay.

Because California has three biotech centers and many biotech companies, it makes sense to foster smaller clusters in the periphery of those centers. Vacaville is a good example. Genentech's plant is not the only biotech facility in the city; Vacaville also houses Alza's manufacturing plant, Chiron's fermentation facilities, and the headquarters of Biosciences Technologies. In fact, Vacaville is already recognized as an emerging biotech cluster that naturally attracts the attention of other Bay Area biotech firms when they consider branching out. A cluster such as that in Vacaville is obviously more attractive to biotech firms than a location far from their headquarters and with no existing biotech industry (Prevezer, 1995).

This is a logical time for the state government to consider a few sites as candidates for manufacturing clusters. In late 2002, 371 biotech drugs were going through commercial tests, with 116 having reached Phase 3 clinical trials—the final stage before the FDA decides whether they are safe and effective enough for approval.[13] Undoubtedly, a good proportion of them will get approval and proceed to market. But, as noted above, constructing a manufacturing plant takes several years, and the big East Coast pharmaceutical facilities are not ideal for making big-molecule biotech drugs. Thus, a serious shortage in the manufacturing capacity of biotech drugs is projected in the coming decade. But given California's experience in biotech manufacturing, the state is in a position to develop competitive manufacturing centers.

California's Biotech Policies

It is fair to say that no state or local policies directly caused the inception of the biotech industry in California in the 1970s. If one has

[13]See Abate (2002).

to identify some factors that are crucial for giving the Golden State a head start in this industry, one should probably point to the state's entrepreneurial tradition and its strength in biological research. However, the California state government is undoubtedly among the earliest ones to recognize the potential of the industry and the role of state policies in fostering this industry's growth. As early as 1996, the California Research Bureau, upon the request of Assembly Member John Vasconcellos, conducted a comprehensive study of the industry and laid out a series of state policy options (Koehler, 1996). The state assembly has long formed a Select Committee on Biotechnology, whose members have closely followed the industry's development and tried to learn about its needs.

The state of California encourages universities and the industry to collaborate on biotech research. In 1996, then–UC president Richard Atkinson launched the Industry-University Cooperative Research Program (IUCRP). The state government soon joined the effort. Its basic idea is to allow UC researchers and California R&D companies to jointly conduct commercializable research at laboratories in the UC system. Researchers receive grants from the state and UC, and a matching fund is provided by participating companies. The program allows researchers to develop risky projects that are outside the priority areas supported by federal agencies. Participating companies benefit from access to a large talent pool and research facilities in the UC system, which allow them to tackle technical problems that cannot be easily handled in-house. Also, participating companies gain access to potential research findings in collaborative projects. IUCRP started as a single-field biotechnology program, but its success in fundraising soon led to its expansion in other technology areas. It now covers five sectors, two of which—biotechnology and information technology for life sciences—are directly related to California's biotech industry.

Since its inception, IUCRP has received $3 million from UC every year. The state funding steadily increased to $17 million a year by 2000, but the recent budget cut decreased the state's annual contribution to $14.5 million for fiscal year 2003–2004. The program has a one-to-one industry matching requirement demanding that every state dollar be matched by a dollar from private funds, which is consistently exceeded by industry contributions (Industry-University Cooperative Research Program, 2004).

Different from many other programs, IUCRP has a built-in evaluation team that studies the effect of UC research on the California economy. The team relies on surveys, interviews, case studies, and data analysis to measure the effect of IUCRP. Its recent survey reveals that a quarter of California's biotech companies are founded by UC scientists (Industry-University Cooperative Research Program, 2003).

The California state government has also directly supported and sponsored biomedical research. In December 2000, it announced the creation of the Institute for Bioengineering, Biotechnology and Quantitative Biomedical Research (QB3). Located on three UC campuses (Berkeley, San Francisco, and Santa Cruz), QB3 would receive $100 million from the state to build research facilities. It was expected to raise an additional $200 million primarily from private donors in the industry to match the state funds. QB3 provides a platform for scientists from multidisciplinary backgrounds to collaborate in quantitative biomedical research.

To encourage business formation and technology transfer, California constructed or planned several research parks or incubators that either are dedicated to biotechnology or include it as a major component. In the city of San Francisco, a biotech incubator built on the 43-acre UC San Francisco Mission Bay campus has just begun to take in tenants. A 185-acre University Research Park adjacent to the UC Irvine campus hosts quite a few biotech companies. Research parks at the planning stage include a 38-acre University Research Park on the UC Davis campus, a Biomedical Research Park close to the University of Southern California Medical Center, and a 1,000-acre San Diego Regional Technology Park. Some incubators are established with help from local governments. For example, the San Jose Bioscience Incubator and Innovation Center, which started operation in June 2004, was funded by the San Jose Redevelopment Agency with a $6.5 million investment. In the city of Alameda, the local government has raised more than $150 million to match a $6.4 million federal construction grant to build a biotech incubator at the former Alameda Naval Air Station.[14]

Although a large amount of private venture capital funds is already available to biotech start-ups in California, the state seeks to boost access to venture capital. In June 2000, the California Public Employees' Retirement System (CalPERS) established a $500 million California Biotechnology Fund. As the nation's largest public pension fund, CalPERS invests all over the globe. But, for the biotechnology fund, it explicitly expressed a preference for deals inside California. California-based venture capital funds, including Prospect Venture Partners, MPM Biotech Crossover Fund, Burrill Life Sciences Capital Partners, and the UC San Francisco's Seed Capital Fund, were among the earliest to receive investment from CalPERS. The Seed Capital Fund was particularly set up to create a biotechnology incubator at the UC San Francisco's Mission Bay campus.

A highly educated labor force is needed for the biotech industry, and the state of California meets this need with various special programs in its higher education system.

At the UC level, the University of California Biotechnology Research and Education Program (UC BREP) was established in 1985. UC BREP is an advanced training program that awards grants to fund outstanding research and graduate training in biotechnology-related disciplines. By 2002, UC BREP had allocated $22.4 million to 135 grants that supported 789 graduate students and postdoctoral fellows.

On California state university campuses, the California State University Program for Education and Research in Biotechnology (CSUPERB) was created in 1987. This is a multicampus, interdisciplinary training program that fosters workforce development. CSUPERB's main activities include developing biotech-related curriculum and special training programs; providing funds to hire instructors; supporting faculty and student research and travel to biotechnology-related conferences; acquiring, maintaining, and

[14]In October 2004, the federal government decided to terminate this grant because an audit showed that the money was improperly used to cover some of the incubator's operating costs. The fate of the incubator remains unclear as of this writing.

upgrading educational and research facilities; running biotechnology symposiums, short-courses, and workshops, etc. The program also encourages joint research with the industry and facilitates technology transfer.

California community colleges are also involved in biotechnology workforce development. In 1996, the California legislature amended the mission of community colleges to explicitly require that they contribute to economic growth through continuous workforce improvement (Education Code Section 66010.4.(a)(3)). And biotechnology was specified as one of the key areas that community colleges should help with labor training. The California Community College Biological Technologies Initiative was launched in 1997 to fulfill this requirement. During 1996–1998, state grants under this initiative helped establish biotechnology centers at six community colleges in different regions throughout the state. Each center is designated to serve its own region's need of a biotech workforce. The centers develop biotechnology curriculum, facilitate university-industry communication and collaboration, and run job placement and internship programs in biotech.

Partly spurred by actions from other competing states, the California state government has recently helped organize regional planning meetings for this sector. In his State of the State speech in January 2003, then–Governor Gray Davis launched the California Life Sciences Initiative. It promised that the state government would help train qualified laboratory technicians, streamline the process for technology transfer from research institutions to industry, and increase access to venture capital and federal grants. Under this initiative, the governor's office made an effort to reach out to researchers, industry leaders, and stakeholders to foster partnership and collaboration.

Four life science summits were held in the San Francisco Bay Area (December 2002), the San Diego region (May 2003), the Los Angeles region (June 2003), and the Central Valley (September 2003). Representatives from biotech companies, research institutions, government agencies, and other decisionmakers were drawn together to conduct regional strategic planning on issues related to biotechnology research, technology transfer, venture capital investment, and labor training. Recommendations from these summits were summarized in four regional Life Science Strategic Action Plans, and a statewide synthesis appeared as *Taking Action for Tomorrow: California Life Sciences Action Plan* (2004). These documents laid out detailed plans to improve the state's financial environment, reform governmental regulations, encourage technology commercialization and entrepreneurship, provide a qualified labor pool, resolve critical infrastructure needs, and facilitate life sciences community collaboration. Obviously, although the state has done a great deal in support of the biotech industry, a lot more is expected to be done.

California's most recent attempt to promote biotechnology was decided directly by voters. On November 2, 2004, the initiative measure Proposition 71 (officially known as the "California Stem Cell Research and Cures Act") passed by a statewide vote of 59 percent to 41 percent. It authorizes the state to provide an average of $295 million per year in bonds over ten years to fund stem cell research and medical research facilities in California. Stem cells could potentially turn into any other kind of cell in the human body, and scientists consider research in this area promising for finding cures for devastating diseases such as Alzheimer's and Parkinson's. In August 2001, President Bush announced a federal policy that allows federal funding for research on only 60 lines of embryonic stem cells that already existed by then. In contrast, the California law applies no such restrictions. In September 2002, with the passage of SB 253, California was the first state to grant permission to do embryonic stem cell research. And Proposition 71 takes an even further step.

What Proposition 71 promises is a large amount of money. In fact, even the federal support for stem cell research will be dwarfed by the $295 million a year guaranteed by Proposition 71. In 2003, the National Institutes of Health awarded $24.8 million to researchers over the entire nation for embryonic stem cell research. Research on adult stem cells, which is less controversial because it does not involve the destruction of human embryos, received $190.7 million in federal grants. Thus, for California stem cell researchers, Proposition 71 created a source of grants that is nothing less than another NIH.

Even by international standards, Proposition 71 is making a big push for stem cell research. The United Kingdom, Singapore, Israel, and

South Korea are often referred to as countries most supportive of stem cell research, but none have committed resources comparable to those promised in Proposition 71. When the British parliament approved embryonic stem cell research in December 2000, its effect was soon felt in California. In July 2001, Roger Pedersen—a leading stem cell researcher at UC San Francisco—relocated to the University of Cambridge, citing unfriendly U.S. policy and tremendous UK support as a reason. Proposition 71 could soon reverse the "brain circulation" in favor of California. In its biennial spending review in December 2002, the British government allocated £40 million (about $64 million then) to stem cell research over a two-year period (fiscal years 2004–2005 and 2005–2006), which is significantly less than California's planned spending.

The rest of the United States, more than other countries, is most likely to be affected by Proposition 71. Indeed, quite a few states have become alert to the possibility that their top researchers will be lured to California. A few of them, such as Wisconsin and New Jersey, promised new funding for stem cell research right after the passage of Proposition 71. Others are considering similar legislation to endorse such research. For example, on November 18, 2004, a bill that sought to legalize embryonic stem cell research was debated in the Illinois state senate but narrowly failed.

It is still too early to predict the full effect of Proposition 71 on California and the nation. Yet it is very likely that it will tilt the playing field for biomedical research in favor of California, because no other states can possibly afford a comparable amount of resources to support it. California will become a magnet for bioscientists, and a large proportion of the coming generation of bioscientists will emerge in the Golden State. Given California's long tradition of entrepreneurship and its strong venture capital industry, any commercializable research findings will soon find their way into the industry. Thus Proposition 71 will definitely help California maintain its lead in the biotech industry.

Conclusion

This chapter addresses the concern that the biotech industry may only bud in California but blossom, bear fruit, and ripen in other places.

During 1990–2001, more biotech establishments moved out of California than moved in. Yet it is not particularly worrisome because these activities involved only a tiny proportion of the biotech industry and did not hurt California's economy. Those establishments moving out tended to be older, offered fewer jobs, and had a poor growth potential. By 2001, the employment at the establishments that moved into the state was more than 70 percent higher than at those that left.

We also discuss two observations that cause concern. First, fledgling biotech firms rely heavily on pharmaceutical companies to provide R&D money, which increases the possibility that East Coast pharmaceutical companies could profit a great deal from the R&D at biotech firms and create jobs outside California. Second, many other states are competing for the biotech economy and are actively recruiting California's biotech firms. In the manufacturing area, California is particularly vulnerable because the state's high cost of doing business works against its competitiveness.

Overall, it seems that biotech companies prefer to be near their headquarters and high-quality research universities. However, cost pressures may eventually prevail and force firms to move manufacturing and marketing operations to low-cost regions. Nonetheless, thus far, California appears to have been able to retain key firms within the state and has not incurred much job loss because of firm relocation.

This finding implies that the benefit of founding and locating businesses in California must also be high enough to balance the high cost. Such benefits are most likely to have stemmed from California's large capacity of biomedical R&D, its strong venture capital industry, and the agglomeration economies generated by its biotech clusters. The recently passed Proposition 71 will further enhance California's strength in biomedical research, which will help the state to maintain its lead in the biotech industry.

To help maximize the benefit and offset the high operating cost of manufacturing plants, the state government could consider the possibility of developing smaller biotech manufacturing clusters outside the traditional R&D centers. State and local economic incentives are necessary to give the momentum to emerging clusters at the early stage. Once such small clusters reach their critical mass, the economy of scale derived from a shared labor pool, shared infrastructure, and knowledge spillovers is likely to balance California's high cost of doing business. Such clusters would be more attractive to existing biotech firms because of their proximity to their headquarters. To implement this policy, the state needs a biotech specialist in the state government to keep track of major developments in the industry and to coordinate state and local government policies affecting the biotech industry.

7. Summary and Policy Discussion

In this concluding chapter, we summarize the major findings of this report, discuss related policy issues, and offer suggestions to state policymakers for further cultivating and promoting California's biotech industry.

Major Findings

The biotech industry still represents only a small portion of the California economy, but it has a lot of upside potential. It has been almost 30 years since the birth of the biotech industry. Over the years, the media as well as the stock market have followed every important technological breakthrough with immense interest. Scholars in various disciplines have written about the industry's economic potential, speculated about the new world that biotechnology may create, and debated over its ethical and environmental concerns. Numerous books have popularized such notions as the "biotech revolution," the "biotech century," and "our posthuman future." This dramatic attention is partly the reason why so many regional development agencies throughout the United States have decided to jump on the biotech bandwagon.

As early as 1984, *Business Week* carried a cover story entitled "Biotech Comes of Age" (*Business Week*, January 23, 1984). Yet 20 years later, the relative size of the biotech industry remains very small. However, no one can deny its potential to transform health care. Given the growing number of biotech firms with drugs in clinical trials, and the FDA commissioner's plan to reduce the time it takes to get a new drug approved, there is extensive room for this industry to grow for years to come.

Moreover, biotech salaries are significantly higher than salaries in many other sectors of the economy, and a strong biotech economy could generate a multiplier effect on the rest of the local economy. In this sense, the importance of the biotech industry is likely much higher than the size of its direct employment suggests.

The biotech industry is substantially different from information technology industries. Like the IT industries, the biotech industry is knowledge-intensive and attracts a great deal of venture capital investment. However, it also has its own characteristics, which are likely to affect the way policymakers should approach it (Swann and Prevezer, 1996). Biotech is substantially more knowledge-intensive and relies heavily on R&D. Biotech firms do not expect profits for a long time and lose money for years before developing a marketable product. Also, there is no Moore's Law that predictably drives the growth of biotech on every front. Biotech benefits little from network effects, whereas increasing returns are common in IT industries. Moreover, biotech is not an "enabling technology" like IT, which promotes growth in many other sectors. As a result, it is likely that biotech will transform the economy less dramatically and at a slower pace than information technology.

Life science research is the most powerful engine of growth for the biotech industry. Scientific research is the powerful driver of the biotech industry. This was true at the time the industry was born and it remains true today. It has been well documented that scientists with an outstanding record of publications in the area of genetic research have a significant effect on where and when biotech firms are founded. A survey study also shows that one-quarter of California's biotech firms were started by UC scientists (Yarkin, 2000). Our data further show that in the whole country, scientists working at universities or nonprofit research organizations have founded close to half of venture-backed biotech start-ups—firms with the greatest growth potential. We find that despite increasing venture capital funds, the number of biotech firms founded remained steady, suggesting a technological constraint. Thus, money is necessary but not sufficient for creating a regional biotech economy: Research quality and star scientists are equally as important, if not more so. It is no coincidence that the San Francisco Bay Area, Boston, and San Diego have emerged as the country's top biotech centers, which has a lot to do with their high-quality universities and researchers specializing in the field.

Growth of the biotech industry hinges on firm creation. Biotech firms generally take longer to develop marketable products and grow at a slower pace than those in the IT industries. Also, the biotech industry is relatively small. For these reasons, rapid growth in biotech employment depends on firm creation. Our data show that more than half of the job growth in biotech is attributable to new firms.

Competition from other regions is intense, although the flight of biotech firms has not been a serious threat to California. The geographic distribution of the IT industries was primarily an outcome of market forces and had little to do with government intervention. However, the prosperity of technology centers such as Silicon Valley has inspired policymakers all over the country to fancy that they, too, could build their own Silicon Valley—or "Gene Valley" in the case of biotech. Consequently, state and local governments throughout the country are fully prepared to expend resources in anticipation of the biotech boom. Many state and local governments are proactive and offer incentives to lure biotech businesses. This creates intense competition for traditional biotech regions. Our data show that California indeed lost biotech businesses to other states because more biotech establishments moved to other states than moved in, but this had a limited effect on California's economy because the losses occurred on a relatively small scale and the state incurred no net job loss. A similar concern is that other states offer incentives to entice California biotech firms to set up branches in their states. Although California is undoubtedly a high-cost state in which to do business, it is not in an entirely disadvantageous position to compete for biotech manufacturing and related services. The industry is already concentrated here, and many firms prefer to locate manufacturing close to R&D operations. California's strength in research, as well as its existing larger share of the U.S. biotech industry, will continue to condition it as one of the most attractive places to form biotech companies.

Policy Suggestions

Compete with comparative advantages. Both our study (in Chapter 1) and others (e.g., DeVol et al., 2004a, 2004b) show that the biotech industry is still relatively small by many measures. It is really a bet on its future growth that caused many states to jump on the bandwagon of promoting the industry. And once the interstate competition started, it created its own momentum: It is now common for a state to cite other states' competing policies to justify its own supportive policies. Although our study has little to say about whether California should support the biotech industry, it does have implications about how to do it given that the state has already decided to do so.

Comprehensive biotech policy recommendations have been proposed in California. The California Research Bureau released two reports that each prescribes a complete menu of policy options to sustain the growth of California's biotech industry, ranging from state funding and incentives to workforce training programs (Koehler, 1996; Pollak, 2002). The more recent *Taking Action for Tomorrow: California Life Sciences Action Plan* (2004) also offered a wide range of policy recommendations. Although numerous policy approaches could help strengthen California's biotech industry, it is necessary to identify which options are likely to be most effective so that policymakers can prioritize their actions.

It is true that California is facing competition in the biotech sector. Policymakers throughout the country, eager to capture some of the economic potential of biotechnology, are willing to offer incentives and investments to foster their own biotech economies. To counter this challenge, California policymakers must recognize the state's weaknesses and strengths. Accordingly, there are two types of policy responses policymakers may consider: One is to fix the state's weaknesses, which may be difficult to overcome, and the other is to further develop California's strengths. Although current policy discussions pay much attention to the state's weaknesses, it is the balance of the two sides that matters.

California's most prominent disadvantage is the high cost of living and of doing business. The threat of these high costs is not limited to the biotech industry but applies to the whole state economy. High cost of living drives away talent, and high cost of doing business potentially endangers California's ability in business formation and retention. However, these costs, to some extent, reflect a healthy California economy. And they should be discussed in conjunction with potential benefits of founding or locating firms in California. Most likely, it is California's unique advantages, ranging from its pleasant climate to its culture of innovation, that have driven up the cost in the state. California's pleasant climate and diverse culture make it attractive to people; its tradition of innovation and entrepreneurship makes it a hotbed for new businesses. As a result, too many people and businesses compete for limited resources in California, which in turn pushes up the cost of living and doing business in the state. Given that, it is unlikely that California will ever become a low-cost state. Thus, policymakers must focus on further enhancing California's advantages, generating a high benefit to offset the high cost.

In the area of biotech, California enjoys many advantages. Some observers may argue that California was a latecomer in the IT industries, because Boston was once far ahead of Silicon Valley. However, in biotech, California was "in from the beginning" and continues to lead the entire country. This head start creates some first-mover advantages and enables the state to continues building momentum in creating dynamic industrial clusters. California's strong research capacity, its long tradition of venture capital investment, and its high-quality labor pool already provide the necessary ingredients for a successful biotech economy. The state's largest advantage in biotech is its world-renowned universities. As long as California's universities continue to conduct pioneering research in biological, medical, and chemical sciences, the Golden State's lead in the biotech industry is likely to continue, despite actions from other states. State and local governments need to facilitate the growth of the biotech industry by preserving and even strengthening these institutions.

In terms of the retention of biotech businesses in California, our research seeks to broaden the framework for policy discussions. It is true that some businesses are leaving California, but preventing them from moving should not dominate the issue. There are firms moving into California from other states that mitigate if not completely offset the negative effect of those moving out. Additionally, the formation of new firms makes the exit of other firms less worrisome. Policymakers must weigh the cost of creating new businesses against that of keeping businesses from exiting the state or attracting businesses from competing states. Given California's entrepreneurial tradition in technology industries, policies are likely to be more effective if they focus on the formation of biotech businesses and the commercialization of biomedical research.

Our study of the dynamics of California's biotech industry suggests that state policies should try to enhance California's strengths by giving strong support to biomedical research, facilitating its commercialization and business formation, and using economies of scale to keep biotech manufacturing from leaving the state. Thus, our study suggests three priorities for state policymakers.

Support biotech research. Both previous studies and our work (in Chapter 5) show that academic research is a major source of biotechnology for commercialization. One of California's advantages is its strong venture capital sector, in which risk-seeking investors are always alert to new opportunities created by scientific advancement. California's private sector has provided and continues to provide enough "Robert Swansons"—venture capitalists eager to support start-ups that commercialize technological innovations (as discussed in Chapter 4). The government should foster the incubation of more "Herbert Boyers" who invent or grasp new technologies. Specifically, the state government should continue to strongly support academic research in biosciences. Policymakers must remain wary of cutting research budgets in the UC system. California's delegation in Washington could help secure federal funding for biotech R&D.

The recently passed Proposition 71 created an opportunity for California to continue to lead the nation in biotech research. The Independent Citizen's Oversight Committee under Proposition 71 should not only use the money to strongly support stem cell research but should also direct some of the resources to the construction and upgrading of research facilities. The committee should also use the resources as a lever to recruit talent from throughout the world, including both distinguished scientists and the brightest doctoral and postdoctoral researchers. In both the IT and biotechnology industries, it has become evident that California tends to attract talented individuals and convert them into entrepreneurs. Being a high-cost state, this is an effective way to keep an industry growing because it is difficult to recruit businesses from other regions. As long as California can bring the most talented people to the state and maintain its innovative and entrepreneurial tradition, its strong biotech economy will likely continue to prosper.

Facilitate technology transfer to the industry. Our research shows clearly that a large proportion of new businesses in biotech results from the commercialization of public-funded research, as discussed in Chapter 5. State government could help streamline technology transfer from academic institutions to the industry through various channels. Incentives can be created to encourage technology transfer from universities to businesses. Both state and local governments can sponsor biotech incubators near major research institutions to help accelerate the process of commercialization of biotechnology through entrepreneurship among academics.

As discussed in Chapter 4, biotech start-ups often take many years to become profitable. It is a very risky business. One policy that would help technology transfer in this sector is to encourage research institutions to take start-up equity as royalty payment, which academic research has shown to be an important policy that helps start-up formation. Because of the natural excludability of complex biotechnology, inventors are often in the best position to commercialize it. However, they do not necessarily know how to do it. Technology transfer offices on university campuses could choose a more proactive strategy by approaching inventors and initiating the process of commercialization. They could also provide more assistance to inventors in the process of commercialization, such as running entrepreneurship workshops.

Technology transfer is a particularly relevant issue in the implementation of the recently passed Proposition 71. The effect of this initiative measure will, to a great extent, hinge on how its Independent Citizen's Oversight Committee handles technology transfer. The law clearly stated that its purposes are to benefit the California budget by "providing an opportunity for the state to benefit from royalties, patents, and licensing fees that result from the research," benefit the California economy by "creating projects, jobs, and therapies that will generate millions of dollars in new tax revenues," and "advance the biotech industry in California to world leadership." However, it is natural that stem cell research will be primarily conducted at universities and research labs. The realization of such economic benefits will occur only if technology invented in research institutions finds its way into industry in a timely manner.

Proposition 71 gives its oversight committee the authority to set the technology transfer policy. In this case, federal policy has a great lesson to offer. In 1980, the U.S. Congress passed the Bayh-Dole Act. It allows universities to own patents from research funded by federal support; the federal government retains the right of using the inventions but gives up the patent fees, which are shared between the university and the inventor. The Bayh-Dole Act has had a large positive effect on university patent and commercialization activities. While Proposition 71 will create an opportunity for the state government to benefit from technology licensing fees, it might be a better policy to give the opportunity to the universities as an incentive for commercialization. The state will probably benefit more from jobs created and tax revenue generated by a stronger biotech industry. On the other hand, in the cases for which the state directly supports R&D companies for stem cell research, fee charges for the research findings are appropriate.

Accommodate biotech manufacturing. Our research (in Chapter 6) finds no evidence that California is losing a significant share of biotech manufacturing to other states. Case studies of leading biotech firms such as Genentech and IDEC show that manufacturing often benefits from proximity to R&D. However, it is still a legitimate concern that more and more manufacturing plants will be located in other states or foreign countries because of California's cost disadvantage. One way to fight this tendency is to exploit agglomeration economies. Because of California's head start in the biotech industry, it is in a unique position to take advantage of economies of scale that hardly exist in other states. California state and local governments could coordinate policies and activities to develop biotech manufacturing clusters close to the research centers in the Bay Area, Los Angeles, and San Diego. Small clusters outside the research centers will pay less for their real estate, and shared infrastructure and labor pools, knowledge transfers, and interfirm collaborations will further help reduce cost and increase productivity.

The proximity to research centers facilitates regular communication between R&D and manufacturing groups, which will also boost productivity.

State government could establish an office or appoint someone in the administration to serve as a central liaison for the biotech industry. The office could develop short- and long-term plans to prepare for the industry's growth. In particular, it should develop methods for building a manufacturing base to host plants of several firms and create agglomeration economies. At the same time, it could educate policymakers and the public, coordinate local activities and partnerships, monitor the industry's progress, and respond to its needs and concerns.

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