The Role of Small Firms in U.S. Biotechnology Clusters

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ABSTRACT. The biotechnology industry poses a particular challenge to analysis because its origins were poorly understood or even noticed at the time. The purpose of this paper is to examine and make sense of recent developments in the U.S. biotechnology industry. The pioneers and subsequent followers in biotechnology came from other fields. They altered their career trajectories in sciences like genetics and medical research to enter an unknown and undefined field, which only subsequently became labeled as biotechnology. Those regions exhibiting the greatest success in developing biotechnology clusters also possessed the greatest ability to unleash the potential commercialization latent in those scientists. To generate a successful regional cluster, the existence of world class scientific talent is a necessary condition. However, it is not a sufficient condition. The ancillary or complementary factors must also be available to translate this knowledge into a commercialized product. The complementary factors include the presence of venture capital and other forms of finance, the existence of an entrepreneurial culture, and transparent and minimal regulations fostering the start-up and growth processes.

1. Introduction

The purpose of this paper is to examine and make sense of recent developments in the U.S. biotechnology industry. This paper tries to understand how the American biotechnology industry has evolved, with a particular emphasis on the role of public policy. The biotechnology industry poses a particular challenge to analysis because its origins were poorly understood or even noticed at the time. The pioneers and subsequent followers in biotechnology came from other fields. They altered their career trajectories in sciences like genetics and medical research to enter an unknown and undefined field, which only subsequently became labeled as biotechnology. Those regions exhibiting the greatest success in developing biotechnology clusters also possessed the greatest ability to unleash the potential commercialization latent in those scientists.

2. Definitions

The terms *biotechnology* and *biotech industry* are typically used in a casual and imprecise manner. To provide more precision and a common understanding it is important that the following concepts have a more exact definition:[1]

- *Biotechnology*
  A group of techniques and technologies that apply the principles of genetics, immunology and molecular, cellular and structural biology to the discovery and development of novel products.
- *Biotechnology Industry*
  The industry is composed of around 5,000 private companies that apply various biotechnologies to develop commercially viable products. The biotech industry is typically an input in the health care, food and agriculture, industrial processes, and environmental cleanup industries.
- *Pharmaceutical Industry*
  This industry is composed of around one hundred private companies whose products involve the design, discovery, development and marketing of new agents for the prevention, treatment and cure of disease. Pharmaceutical firms have a heavy reliance on scientific research. The industry may be evolving towards a new name – the biopharmaceutical industry – which reflects the heavy reliance of pharmaceutical companies on biotechnology.

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- *Medical Research*
  This refers to science-based inquiry, both basic and applied, where the goal is the improvement in health and the eradication or mitigation of disease and disability.

3. Formation and development of regionally based biotech industry

The United States biotechnology industry has grown considerably over the past fifteen years. In 1992 there were 1,358 patent applications by U.S. companies in the United States. By 1997, patent applications were up to 3,014. Between 1990 and 1999, private investment in the biopharmaceutical industry has grown from $10 billion to $24 billion. While the biotechnology industry in the United States has exploded over the past fifteen years, this growth has not been neutral with respect to geographic location. The U.S. biotechnology industry has been regionally concentrated in just a handful of geographic locations. The strongest presence of biotechnology companies has been in California, which accounts for around one-quarter of the biotechnology companies. Massachusetts accounts for the second highest share of biotechnology companies. Nearly one-tenth of American biotech firms are located in Massachusetts. A third tier of states accounts for about five percent of the biotechnology firms, including New Jersey, Maryland, North Carolina and Texas, each with a share of around five percent of U.S. biotechnology companies. In fact, even within these states, the location of the biotechnology industry is geographically concentrated within a very small region. In California, one-fifth of the biotechnology firms is located in the East Bay area, 15% in San Francisco, 18 percent in Santa Clara, 22 percent in Los Angeles, 18 percent in San Diego, and 4 percent in Sacramento (Blakely et al., 1993).

There are strong reasons both why the biotechnology industry remains geographically concentrated in just a few regions, and why these specific regions have emerged as the main *Standort* for the U.S. biotechnology industry. The most important input in the biotechnology industry is specialized knowledge. In most cases, only a few scientists have the potential to acquire this knowledge. In addition, the scientists possessing that knowledge must also have the information about a potential commercial market for viable products resulting from that knowledge. They also must be willing to act on that knowledge by commercializing that knowledge through a biotechnology enterprise. To commercialize requires start-up capital as well as managerial capabilities. For all of these factors to come together has been impossible with the exception of just a few select regions.

Biotechnology is a new industry that is knowledge-based and is predominantly produced by new start-ups and small firms. The relative small scale of most biotechnology firms may be attributable to the diseconomies of scale inherent in the "bureaucratic process which inhibits both innovative activity and the speed with which new inventions move through the corporate system towards the market" (Link and Rees, 1990, p. 25). Zucker et al. (1994, p. 1) provide considerable evidence suggesting that the timing and location of new biotechnology firms is "primarily explained by the presence at a particular time and place of scientists who are actively contributing to the basic science." More specifically, they find that firms are likely to locate in geographic areas where scientists who have published articles on gene sequencing are located.

The early evolution of the biotechnology industry took place in California, and in particular in the San Francisco bay area. This is because the key ingredients identified above were the most prevalent in this region. As Prevezer (1997) explains, there was a strong presence of venture capital already in Silicon Valley, as a result of the boom in high-technology industries such as semiconductors and computers. This also meant the existence of a very entrepreneurial culture. There was expertise in starting and growing high-technology companies, high job mobility, and strong networks. This was also the location of a number of the country's most important universities and government research laboratories.

The two most significant discoveries fuelling the biotechnology industry occurred in the early 1970s, when Cohen and Boyer at Stanford University developed the recombinant DNA technique, and Kohler and Milstein's production of monoclonal antibodies in Cambridge, U.K. The pioneering biotechnology companies, such as Cetus, Genetech and Hybritech, were located in

California near the top scientific centers, and Biogen was located in the Boston area to take advantage of the top scientists at Harvard and MIT. According to Prevezer (1997), the San Francisco bay area became the focal point for the incipient biotechnology industry, relying heavily upon scientific knowledge at the University of California at San Francisco (UCSF), Stanford, and CalTech. While the subsequent explosion of the biotechnology industry has remained concentrated in these regions, other regions combining the demanding requirements of scientific knowledge and a strong and vigorous entrepreneurial culture have emerged in Dallas, Texas, Research Triangle (North Carolina), and in Maryland (between Baltimore and Washington, D.C.).

4. Linkages & cooperation

Linkages and cooperation are particularly important in the biotechnology industry. These linkages occur between entrepreneurial firms, between the scientists involved with the firms, between the firms and universities, and between corporations and biotech firms.

Strategic alliances between large corporations and biotechnology companies have been particularly important for biotech companies specializing in therapeutics. This is because the costs of developing a new drug, complying with the various layers of regulation, manufacturing the product, and then marketing the product, have required a level of finance that far exceeds the budgets of most small firms. Cullen and Dibner (1993) estimate that the cost of bringing a therapeutic drug from basic research to the market is around $250 million. At the same time, the average budget for research and development of a biotech firm is $12.5 million. To close this gap, biotech firms have engaged in a broad range of marketing and licensing agreements. Under these agreements, the biotech firm provides access to cutting-edge technology in exchange of an infusion of capital from their corporate partners.

In documenting the evolution of strategic alliances in biotechnology, Cullen and Dibner (1993, p. 18) conclude that, "The primary strategic goal of small and medium-sized biotechnological companies was to develop products to be marketed by their partners and their primary concern was finding and developing alliances." The obvious advantages of such strategic alliances are that they enable a small, new company to concentrate on its core mission – moving from basic research to commercialization through technological innovation. The strategic alliances also enable the biotech company to reduce financial risks as well as operating costs. In addition, the biotech firm is able to better offset the major liabilities associated with biotech start-ups – acquiring manufacturing capabilities, marketing and sales.

5. The role of established firms towards biotech enterprises

Established firms are generally quite positive and supportive towards biotechnology firms. This is because of the strong complementary nature of biotechnology firms and established firms, particularly in the pharmaceutical industry. There are a number of reasons why such a complementary relationship has evolved between established and biotechnology firms. The first is that the former have recognized that it may be a more efficient structure to engage in an arms length market relationship to obtain new biotechnology products than to produce them internally. The market exchange is apparently more efficient than the internal transaction. The reason for this involves agency problems in doing research that is highly uncertain and asymmetric. In addition, the exposure to legal liabilities resulting from biotechnology research is reduced when that research is done by a small firm with limited assets rather than in a large corporation with massive assets.

Sharp (1999) identifies three main phases in the relationship of established firm and biotechnology companies. The first phase involved the formation and incipiency of the biotechnology industry. Sharp (1999, p. 137) reports that "most of the established pharmaceutical companies were uncertain what to make of the new technology and especially of the hype surrounding its development that grew with the small-firm sector in the U.S." This uncertainty combined with a considerable degree of skepticism resulted in most established pharmaceutical companies distancing themselves from the fledgling biotechnology industry in this initial phase. At the same time, Sharp points out that most established companies invested in sufficient scientific expertise to enable them to keep abreast of developments in biotechnology and monitor the industry.

The second phase began in the mid-1980s, when the period of watching and waiting ended. The established pharmaceutical firms recognized that, in fact, biotechnology had a valuable market potential. While strategies pursued by the established enterprises varied, most devised and implemented a strategic biotechnology policy. One common strategy that all companies pursued was to invest heavily to develop an in-house competence in biotechnology. How this was done varied considerably from one company to another. In some companies, scientific teams were assembled. Other pharmaceutical companies acquired such competence through the acquisition of biotechnology firms or, in some cases through mergers. Another strategy was to engage in external linkages with biotechnology companies. As Cullen and Dibner (1993) document, strategic alliance between biotechnology firms and established enterprises exploded in the mid-1980s.

The third phase, which started around a decade ago involves the commercialization of biotechnology products. The first successful biotechnology products reached the market in the early 1990s. As Juergen Drews, head of R&D at Hoffman LaRoche observed in 1993, "While there are some redundancies among the 150 or so novel proteins in development, about 100 represent truly novel substances that have no precedent in medical therapy. Not all of these proteins will reach the market, but it is fair to assume that their attrition rate will be lower than that for small chemical entities because they should cause few unmanageable toxicological problems. A conservative estimate would expect 30–40 of the recombinant proteins now under development to become successfully marketed products over the next 5–6 years. This means that an average of 5–8 novel proteins should become available each year. If we assume an average sales volume for the forthcoming recombinant proteins equal to the average revenues generated by today's recombinant drugs, the portfolio of recombinant proteins now in clinical trials should amount to $10–$20 billion".

In this third phase, the large established companies take the new biotechnology products developed by biotechnology companies and convert them into large-scale marketed products. For example, Intron A was developed by Biogen but marketed by Schering-Plough, resulting in $572 million of sales in 1993. Humulin was developed by Genetech but marketed by Eli Lilly, for $560 million of sales in 1993. Engerix-B was developed by Genetech but marketed by SmithKline Beecham for $480 million. RecombiNAK HB was developed by Chiron but marketed by Merck for $245 million.

In addition, this third phase has experienced a shift by the established companies from the broad learning strategies of phase two and increasingly towards a more focused approach, targeting specific technologies. For example, Ciba Geigy reduced its portfolio of interests in biopharmaceuticals in 1989 in order to focus on the development of just several targeted products. Ciba Geigy subsequently increased its investment in those targeted areas and engaged in a number of research and licensing agreements with biotechnology companies. Similarly, Bayer reduced its biotechnology research in agro-chemicals while concentrating its focus on pharmaceuticals. Hoffman LaRoche similarly pulled out of agrobiotechnology to concentrate its focus on pharmaceuticals.

6. Investor attitudes

Investors come from established companies, venture capital and initial public offerings. A unique feature of biotechnology is that biotechnology firms have no commercial product on which to draw revenues for a substantial time period. This makes evaluating their success or whether to invest in them or not especially complicated. In addition, the science and research upon which they are based is typically so complicated and advanced that only a limited number of experts can hope to evaluate them. The high degree of uncertainty combined with asymmetric knowledge that is prohibitively costly to transact means that investing in biotechnology is different from investing in most other industries.

Since the biotechnology companies typically have no commercial products or production upon which they can be evaluated, potential investors focus instead on the major input of the biotechnology process, which involves the scientific team.

In terms of *bait* to the investment community, biotechnology firms, in the early stages of development, miss no opportunity to signal the abilities of their scientists as well as the science they are doing. It is not uncommon for prospectuses to read like proposals to the National Institutes of Health (NIH). Stephan and Everhart (1998) have shown the importance of scientific reputation at the time a biotechnology company goes public. Based on a sample of 45 firms, they find that the more substantial the reputation of the university-based scientific affiliates, the greater are the proceeds raised from the initial public offering (IPO).

7. Positioning profile of bioregion in global economy

The focus of a region's biotechnology industry generally reflects the scientific strengths at the knowledge source as well as the focus of complementary industries. For example, California's biotechnology industry is largely focused on human-diagnostic and therapeutic products (Blakely et al., 1993). By contrast, considerably less activity in biotechnology is devoted towards agriculture, or plant and animal, and biotechnology suppliers. This reflects that the emphasis on research as product of biotechnology is more pronounced in California than elsewhere inthe United States. It also reflects the relatively weak influence of pharmaceutical companies in California. Most of the pharmaceutical companies are located in New Jersey and New York. The pharmaceutical companies tend to rely on biotechnology companies also located in those regions for new products and innovations. In addition, the presence of the United States Food and Drug Administration (USFDA) on the East Coast has resulted in the location of testing facilities in New York and New Jersey.

The Biotech Industry Research Group reports that, as the result of a massive survey of biotechnology firms located in California, the most important factor determining location is the availability of qualified workers in the geographic area. The relative importance of the presence of this factor varies somewhat across fields. It is relatively more important in therapeutics and agritech, and relatively less important in diagnostics and for suppliers. The second most important factor in shaping location is the proximity of research universities and other research organizations. The third most important factor is the cost of industrial space. The fourth most important fact is county and city regulations. The fifth most important factor is taxes. The sixth most important fact is wage rates, followed by proximity of major suppliers, proximity to venture capital and financial institutions.

8. Institutional barriers impeding regional development of biotech clusters

A number of regions have tried to develop a biotechnology industry. Many of these attempts have not proven successful; only a handful of regions in the United States have successfully developed a biotechnology industry. For example, the region around Hanover, New Hampshire tried to develop a biotechnology cluster and failed. Atlanta, Georgia has been unable to develop a biotechnology industry. Only recently (1999) have there been signs of an emerging biotechnology industry.

One of the greatest impediments to developing biotechnology is the existence of institutional barriers. Perhaps the most imposing constraint has been an absence of scientific talent in a region. If no cluster of scientific talent is present, either at universities, government research laboratories, or private firms, then it is not likely that a biotechnology industry can be developed. The major reason why the biotechnology industry is so geographically concentrated is that the best scientific talent is also geographically clustered in just a few regions (Audretsch and Stephan, 1996).

However, the presence of a critical mass of excellence in science is a necessary but not sufficient condition for the development of biotechnology. There are numerous examples of clusters of scientific talent in the relevant fields where there is still an absence of biotechnology activity. This is attributable to the presence of other formidable institutional constraints.

For example, Dartmouth College, including the medical center, is the home of a large number of scientists involved in biomedical research. A project to develop a biotechnology cluster failed.

One of the reasons given why this attempt failed is that while the scientific talent was present, there is no base of large companies in the relevant areas, and no existence of an entrepreneurial culture.

In contrast, Atlanta not only has a very strong presence of biomedical researchers in Atlanta, which is the home of Emory University, with one of the top medical schools in the country, and the Center for Disease Control (CDC), but also is rich in private industry. The inability of Atlanta to translate the scientific knowledge into a biotechnology industry may reflect the absence of venture capital and perhaps the fact that the industry has had a tradition of large corporations such as Coca Cola but a relatively absence of high-tech entrepreneurship. This would suggest two other important institutional barriers to developing a biotechnology industry – the availability of finance and venture capital, which tend to be regional and not national, and the presence of an entrepreneurial culture, which is also a regional phenomenon. Venture capital and other forms of informal finance are local because the venture capitalist needs to monitor and interact with the company. The success of the company is highly dependent upon this interaction. Thus, geographic proximity between the venture capitalist and the biotechnology firm is essential for commercial success.

The presence of an entrepreneurial culture is important because this creates the opportunities for a scientist to change his career trajectory and shift it away from research to commercialization. In studying Silicon Valley, Saxenian (1990, pp. 96–97) emphasizes that it is the existence of such an entrepreneurial culture that provides individuals the information and support needed to become entrepreneurs themselves: "It is not simply the concentration of skilled labor, suppliers and information that distinguish the region. A variety of regional institutions – including Stanford University, several trade associations and local business organizations, and a myriad of specialized consulting, market research, public relations and venture capital firms – provide technical, financial, and networking services which the region's enterprises often cannot afford individually. These networks defy sectoral barriers. Individuals move from established firms to startups. And they continue to meet at trade shows, industry conferences, and the scores of seminars, talks and social activities organized by local business organizations and trade associations. In these forums, relationships are easily formed and maintained, technical and market information is exchanged, business contacts are established, and new enterprises are conceived. . . . This decentralized and fluid environment also promotes the diffusion of intangible technological capabilities and understandings."

A fourth type of institutional constraint to the development of a regional biotechnology cluster is the high cost of regulation. Blakely et al. (1993, p. 23) document the high concern that biotechnology firms have for regulation, "Predictable application of regulations concerning environmental and public health and the use of land are crucial to the location of biotechnology firms. Companies must be assured that their development activities will not be hindered by inconsistent applications of regulations."

9. Regional & global networks

Audretsch and Stephan (1996, 1999) document the strong linkages that exist among biotechnology scientists and between universities and biotech firms. These linkages are crucial because biotechnology companies are strongly defined by their scientists. Many of these scientists, particularly senior scientists with strong reputations, do not work for the biotechnology company full time, but instead are members of university faculties. For example, Audretsch and Stephan (1999) show that, of 101 founders of new biotechnology firms in the early 1990s, nearly half (50) are from universities. Of these fifty, 35 remain associated with their universities on a part-time basis, while the remaining 15 founders left the university to work full-time for their biotech firm.

These university-based scientists fulfill a variety of roles within biotechnology companies. Some are founders, others serve as members of scientific advisory boards (SABs), while still others serve as directors. The degree of knowledge provided by university-based scientists varies according to the role played by the scientist. Scientific founders seek out venture capitalists in order to transform technical knowledge into economic knowledge. Scientific advisors provide links between scientific founders and other researchers doing work in the area. They, along with founders, also provide the possibility of outsourcing research into university laboratories staffed by graduate students and post-docs. The concept of scientific advisory boards also provides the firm the option of having, at minimal cost, a full roster of the key players doing research in the firm's area of expertise.

In addition to providing knowledge to newly formed biotechnology companies, university-based scientists also provide a signal of firm quality to the scientific and financial communities. An effective way to recruit young scientists is to have a scientific advisory board composed of the leading scientists in the field. George B. Rathman, president and Chief Executive Officer of Amgen, attributes much of the company's success to an SAB of "great credibility" whose "members were willing to share the task of interviewing the candidates for scientific positions." Rathman goes on to say that the young scientists that Amgen recruited would not have come "without the knowledge that an outstanding scientific advisory board took Amgen seriously" (Burrill, 1987, p. 77).

Certain roles, such as being a founder of a biotechnology firm, are more likely to dictate geographic proximity between the firm and the scientist than are other roles that scientists play. This is because the transmission of the knowledge specific to the scientist and firm dictates geographic proximity. Presumably scientists start new biotechnology companies because their knowledge is not transferable to other firms for the expected economic value of that knowledge. If this were not the case there would be no incentive to start a new and independent company. Because the firm is knowledge-based, the cost of transferring that knowledge will tend to be the lowest when the firm is located close to the university where the new knowledge is being produced. In addition, the cost of monitoring the firm will tend to be minimized if the new biotechnology startup is located close to the founder.

By contrast, the role of scientific advisor to a biotechnology company does not require constant monitoring or even necessarily specialized knowledge. Thus, the inputs of scientific advisors are less likely to be geographically constrained. Furthermore, geographic proximity of all major researchers in a particular scientific field is unlikely given the opportunity cost that universities face in buying into a single research agenda. Thus, if firms are to have access to the technical knowledge embodied in the top scientists in a field, they will be forced to establish links with researchers outside of their geographic area. Scientists whose primary function is to signal quality are also less likely to bet local than are scientists who provide essential knowledge to the firm. Their quality signal is produced by lending prestige to a venture they have presumably reviewed – a task that can be accomplished with credibility from a distance.

To identify the links between knowledge sources, the incentives confronting individual scientists, and where the knowledge is commercialized, Audretsch and Stephan (1996) rely upon a data base collected from the prospectuses of biotechnology companies that prepared an initial public offering (IPO) in the United States between March 1990 and November 1992. This includes a total of 54 firms affiliated with 445 university-based scientists were identified during this time period. By carefully reading the prospectuses, it was possible to identify the names of university-based scientists affiliated with each firm, the role that each scientist plays in the firm, and the name and location of their home institutions. Universities and firms were then grouped into regions, which are generally larger than a single city but considerably smaller than a state. Certain areas, for example, metropolitan New York, cross several state lines.

Only 138 of the 445 links observed between scientists and biotechnology companies are local in that the scientist and firm are located in the same region. This suggests that geographic proximity does not play an important role for links between biotechnology companies and scientists in general. However, the geographic link between the scientist and the founder is influenced by the particular role played by the scientist in working with the firm. Most strikingly, 57.8 percent of the scientist-firm links were local when the scientist was a founder of the firm; 42.1 percent were non-local. By contrast, when the scientist served as a member on the SAB, only 31.8 percent of the links were local, while 68.2 percent were non-local.

This disparity suggests that the nature of the knowledge transmitted between the university and the biotechnology firm may be different between scientists serving as founders and those serving on a SAB. Presumably it is the difference in the nature and quality of the knowledge being transferred from the university to the company that dictates a higher propensity for local proximity in the case of the founders, but not for SAB members.

10. Innovation strategies of biotech firms

Biotechnology firms have pursued a broad spectrum of innovation strategies. The diversity of innovation strategies reflects heterogeneity of fields, backgrounds and goals. Still, several key innovation strategies have emerged in the biotechnology industry. One successful strategy has been to develop and exploit close links with university researchers. Such close links provide access to state-of-the art research and knowledge, as well as a source of potential employees. Another important strategy involves marketing. A successful marketing agreement with a large pharmaceutical company can result in the ability for a small biotechnology company to extend its product to a mass-market. Biotechnology companies are generally successful when they devote their resources and competence to their core product – research – and rely on other third-party firms for clinical testing and marketing.

11. Characteristics of newly founded regional biotech enterprises

The biotechnology industry is composed of nearly 1,300 companies that use various biotechnologies to develop products for use in health care, food and agriculture, industrial processes, and environmental cleanup. Most of these companies are very small. Two-thirds of them have fewer than 50 employees. All but twenty of these companies are "unencumbered by revenues" (Rosenberg, 1999). As Rosenberg (1999, p. 69) observes, "The biotechnology industry is a very entrepreneurial industry, but one with relatively few commercial successes."

In order to understand biotechnology enterprises, it is essential to understand the scientists that start these enterprises. This is because the biotechnology firms are an extension of the scientific knowledge and competence embodied in those firms.

Audretsch and Stephan (1999) use a data base drawn from the prospectuses of 60 firms that made an initial public offering (IPO) in biotechnology during the period March 1990 to November 1992 to examine the sources and incentives for commercializing new knowledge. Prospectuses for the offerings were carefully read in order to identify the scientific founders of the new firms. In cases where it proved difficult to identify founders from the prospectuses, telephone calls were made to the firm. In addition, firm histories were checked and confirmed in *BioScan*. Founders having a Ph.D. or a M.D. were coded as scientific founders for the purposes of this research. In addition, several individuals who did not have a doctorate but were engaged in research were included as scientific founders. All told, we were able to identify 101 scientific founders for 52 firms making an initial public offering during this period.

Biographical information was also collected from the prospectuses and was supplemented by entries from standard reference works such as *American Men and Women of Science*. Four types of job experience were identified – academic experience (which includes positions at hospitals, research foundations and the government); experience with pharmaceutical companies; training experiences (as a student, post-doc, or resident), and "other" experience. This information was used to distinguish among five distinct career trajectories followed prior to the founding of the company:

1. The *academic trajectory* describes scientists who had spent all of their time since completing their training employed in the academic research sector;
2. The *pharmaceutical trajectory* describes those scientists whose careers subsequent to receiving training had been entirely spent working in the drug industry;
3. The *mixed trajectory* describes scientists who had worked in both the pharmaceutical industry and the academic research sector;
4. The *student trajectory* describes individuals

who went directly from a training position to founding a biotechnology firm; and
5. The *other trajectory*, which includes scientists who have been employed by non-pharmaceutical firms.

Additional biographical information coded was ascertained concerning date of birth and educational background. Citation counts to first-authored published scientific articles were measured using the 1991 *Science Citation Index* produced by ISI and are used here as an indicator of scientific reputation.

Summary data, presented in Table I, show that fifty percent of the scientific founders' careers followed an academic trajectory; slightly more than 25 percent a pharmaceutical trajectory. Half of this latter group had established their careers exclusively with large pharmaceutical companies such as SmithKline and Beckman; half had come from smaller pharmaceutical firms, some of which, like Amgen, were a first generation biotech firm. Table I also indicates that approximately an eighth of the founders had a mixed career in the sense that prior to founding the firm they had held positions in both a pharmaceutical company as well as a university or non-profit research organization. A handful of founders moved directly from a training position such as a residency or post-doctorate appointment to the startup firm, thereby short-circuiting the traditional trajectories from pharmaceutical firms and/or academe. The career trajectory of the remaining scientists was either indeterminate or followed another type of path.

The employment status of the founders with the biotechnology company was also determined. Note that 59 of the 101 scientific founders were working full time with the new firm at the time of the public offering; 41 were working part time, and almost all (35) of these had followed an academic trajectory. This means that 70 percent of the academic founders maintain full-time employment with their academic institutions, serving as consultants or members of the Scientific Advisory Boards to the startup firms. Only 15 of the academic founders had moved to full-time employment with the firm by the time the IPO was made. By contrast, all 28 scientists whose careers had been exclusively in the pharmaceutical sector held full-time positions with the firm at the time of the IPO; 9 of the 13 whose careers followed a mixed trajectory were full time.

The evidence from Table I supports the hypothesis that the incentive structure varies considerably between the pharmaceutical founders and the academic founders. Those founders coming from universities and non-profit research organizations have the option of eating their cake and having it too, by maintaining formal contacts with their previous employer, often in a full-time position. Even those from the academic sector who are full time with the new firm are often able to maintain some connection with the non-profit sector as

TABLE I
The age and citation record of biotechnology founders

		Birth date			Citations		
	N	M	SD	N_{known}	M	SD	N_{known}
All scientific founders	101	1943.18	10.20	96	92.13	171.05	99
All academic founders	50	1940.55	10.06	49	149.32	226.51	49
Part time	35	1938.79	10.29	34	172.71	259.03	35
Full time	15	1945.06	8.54	15	72.21	78.70	15
All drug founders	28	1945.61	9.20	28	29.71	46.28	28
Small	14	1945.93	9.84	14	30.30	57.40	14
Big	12	1947.00	7.67	12	34.00	34.41	14
Mixed career	13	1943.80	8.76	13	62.69	57.56	13
Student career	6	1957.00	3.54	5	58.17	83.72	6
All full time	57	1945.64	9.61	57	46.59	60.69	57
All part time	40	1939.42	10.03	37	159.30	245.52	37

Source: Audretsch and Stephan (1999).

adjunct or clinical faculty. By contrast, those scientists who have a career path in pharmaceuticals take full-time positions with the company, at least by the time the company goes public.

There are other differences between those scientists coming from an academic trajectory and those scientists coming from a pharmaceutical trajectory. The most notable is the difference in age at the time the public offering was made. On average, those coming from universities were born approximately five years earlier than those coming from the pharmaceutical sector, a difference which is statistically significant at the 95 percent level of confidence. As would be expected, we also find that those following the academic trajectory have significantly more citations than those coming from a pharmaceutical trajectory.

Of perhaps even greater interest are the differences between the part-time academics and the full-time academics. Academic founders who remain full-time with their institution, working but only part-time for the new firm, were, for example, born more than six years earlier than academic founders who leave their institution to go full time with the firm were. The part-timers are not only older; they are also more eminent, having significantly more citations than academics that go full time with the firm. This suggests that eminence gives these scientists the luxury of hedging their bets; both the firm and their research institution welcome a chance to claim them as affiliates. And, although we have not yet measured the incidence, such individuals often serve as directors and members of Scientific Advisory Boards of additional start-up firms. The full-timers, by contrast, have developed sufficient human capital to be recognized as experts but lack the luster to hold "dual" citizenship. In terms of both citation counts and date of birth they are remarkably similar to their fellow founders who followed a pharmaceutical trajectory.

These preliminary observations suggest that the incentive structure depends upon the career trajectory that the scientist has followed as well as upon whether the scientist has established sufficient eminence to be able to sustain multiple roles. Scientists working in incumbent pharmaceutical firms face the well-known problem of deciding whether to remain with the incumbent firm or start a new firm. Furthermore, the goal of an incumbent firm to capture their economic knowledge seldom permits a scientist to establish a reputation based solely on publication. Instead, their scientific reputations are typically established in terms of the products they helped to develop and are known primarily to "insiders" in the industry. Scientists in academe, however, face a different incentive structure. They live in a world where publications are essential for the establishment of reputation. Early in their careers they invest heavily in human capital in order to build a reputation. In the later stages of their career, scientists may trade or cash in on this reputation for economic returns. A variety of avenues are available to do this, including the establishment of a new firm.

The data suggest that this *cashing out* pattern is determined in part by eminence. As noted, a number of academic founders have established sufficiently strong reputations as to be able to eat their cake and have it too. They maintain their full-time jobs in academe, while seeking part-time opportunities to gain economically from their knowledge and scientific reputation. The economic returns are tied to the shares they own in the startup companies. A subset of academic scientists, however, go full time with the firm. They, too, hold stock in the firm. But, their rewards are more immediate in terms of the salaries paid to executives in the companies. And, while they have established solid reputations, they are considerably less cited than those academic founders who maintain full-time positions in academe. Although this may be a result of age (they are, after all, about five years younger), it is more likely a characteristic that age cannot alter. Science, as numerous researchers have established, is noteworthy for persistent inequality which age merely amplifies.

12. National biotech promotion programs

There is, in fact, no official program for promoting biotechnology at the federal, or national, level. This, however, does not imply an absence of programs that *de facto* promote biotechnology. Because scientific research and knowledge plays such an important role in biotechnology, policies promoting the underlying scientific research also promote biotechnology. Much of this scientific research has been funded by a national agency, the

National Institutes of Health (NIH). As Penhoet (1999, p. 41) founder and former CEO of Chron observes, "The history of biotechnology to date has involved the commercialization of technologies that were funded almost entirely by the National Institutes of Health (NIH). Partnership, therefore, has been a major theme of the biotechnology story – partnership between government, industry, and universities. Much of the technology commercialized by industry was developed in the university setting using NIH grants."

Rosenberg (1999) concludes that the role of advocacy of research organizations has fueled the rapid growth of the NIH: "Effective lobbying from the Association of American Medical Colleges, Research America, Funded-First, disease groups, and others, have been responsible for the growth in support for federally-funded medical R&D over the past 30 years, and the past 10 years especially." In 1990, the NIH budget was $8 billion; in 1999 it is $14.6 billion, with projected strong growth. This is essentially a doubling of NIH funding within a decade, and there are indications that the Congress will double the budget of NIH again over the next five years.

The NIH has steadily expanded its support of biotechnology startups. For example, in 1998, NIH and private companies entered into 166 cooperative research and development agreements (Cards), which allow for the sharing of compounds and other research materials and results, as well as for the exchange of funds. This is the largest number ever of Cards between NIH and the private sector.

The Small Business Innovation Research (SBIR) program is another federal policy that provides NIH funding of biotechnology firm (Audretsch et al., 1999). The United States Congress enacted the SBIR program in the early 1980s as a response to the loss of American competitiveness in global markets. Congress mandated each federal agency with allocating around four percent of its annual budget to funding innovative small firms as a mechanism for restoring American international competitiveness. A Phase I award provides an opportunity for a small business to establish the feasibility and technical merit of a proposed innovation. The duration of the award is s six months and can not exceed $70,000. A Phase II Award is granted to only the most promising of the Phase I projects based on scientific/technical merit, the expected value to the funding agency, company capability and commercial potential. The duration of the award is a maximum of 24 months and generally does not exceed $600,000. Approximately 40 percent of the Phase I Awards continue on to Phase II. A Phase III Award is for the infusion and use of a product into the commercial market. Private sector investment, in various forms, is typically present in Phase III.

Through the Small Business Innovation Research (SBIR) program, NIH awarded $266 million in grants to small firms for medical and biopharmaceutical research. It is expected that the SBIR program at NIH will exceed $300 million in 1999.

In addition to the NIH, the United States Department of Defense also uses the SBIR program to fund biotechnology firms. Between 1983 and 1997 there was more than $240 million in SBIR awards for biotechnology companies from the Department of Defense. Phase I accounted for $47 million and Phase II accounted for $194 million.

In addition, the Advanced Technology Program (ATP) funded by the U.S. Commerce Department awarded $29 million to small biotechnology companies in 1999. The ATP, like the SBIR, is expected to grow in the future.

There is compelling evidence that the SBIR program has had a positive impact on developing the U.S. biotechnology industry. The benefits have been documented (Audretsch et al., 2000) as:

- The survival and growth rates of SBIR recipients have exceeded those of firms not receiving SBIR funding.
- The SBIR induces scientists involved in biomedical research to change their career path. By applying the scientific knowledge to commercialization, these scientists shift their career trajectories away from basic research towards entrepreneurship.
- The SBIR awards provide a source of funding for scientists to launch start-up firms that otherwise would not have had access to alternative sources of funding.
- SBIR awards have a powerful demonstration effect. Scientists commercializing research

results by starting companies induce colleagues to consider applications and the commercial potential of their own research.

13. Regional biotech support programs

While the SBIR is a federally funded program, it also has a regional element. Many or most states have formed programs to assist firms in applying for SBIR grants. States sponsor seminars and hire agents who contact potential recipients of SBIR grants.

In addition, a number of states and cities have developed programs to try to develop a biotechnology cluster. Most of these efforts revolve around transferring the knowledge out of universities via new-firm start-ups. They typically revolve around technology transfer programs and technology parks. As Blakely et al. (1993, p. 12) point out, "State and regional policy makers are taking advantage of the lessons learned from the micro-electronics experience and applying them in recent attempts to revitalize the declining industrial areas with new technologies. Unlike traditional approaches to economic development that are aimed at luring high-technology firms from their established bases, states are becoming increasingly sophisticated in their approach to economic development through biotechnology." In particular, the traditional incentives and instruments used to promote economic development, such as low taxes, cheap land, low-cost labor, and subsidies, are not effective in developing biotechnology. In an assessment of the state's approach to economic development through biotechnology, the California State Senate Office of Research concluded, "The strategies that states are employing in the pursuit of biotechnology are a good deal more sophisticated and better funded than the past economic development strategies, which have been, more often than not, marketing efforts designed to encourage firms to locate new production facilities in their states" (Blakely et al., 1993, p. 12).

For example, the University-Industry Relations (UIR) program at the University of Wisconsin has resulted in the formation of a dynamic cluster of biotechnology companies in Madison, Wisconsin. The size of the grants is generally modest. In 1995, they ranged from \$2,500 to \$33,000. To date, the program has funded 39 biotechnology start-ups that have received subsequent private investment of \$10,723,200.

Similarly, South Carolina recently established the South Carolina Research Grant Program, with one goal being to develop a biotechnology industry. Faculty at the universities was encouraged to submit proposals for funding. Not only were the proposals meant to advance science, but also contribute to the economic development of South Carolina by inducing scientists to commercialize their knowledge via a biotechnology start-up.

14. Conclusions

Because the biotechnology industry in the United States is rapidly evolving it is difficult to make inferences about appropriate policy in the new century. What may have been effective when the industry was incipient may be less effective or even counterproductive today. Still, several major policy lessons emerge from the experience in the United States. First, the biotechnology industry is and remains a local phenomenon. The biotechnology industry not only clusters regionally, but there are only a handful of regions that have successfully generated a viable biotechnology industry. To generate a successful regional cluster, the existence of world class scientific talent is a necessary condition. However, it is not a sufficient condition. The ancillary or complementary factors must also be available to translate this knowledge into a commercialized product. The complementary factors include the presence of venture capital and other forms of finance, the existence of an entrepreneurial culture, and transparent and minimal regulations hindering the start-up and growth processes.

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Note

[1] These definitions follow those provided for by Rosenberg (1999) for the United States National Academy of Sciences.

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