# Ingredients in the Early Development of the U.S. Biotechnology Industry

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ABSTRACT. This paper explores the ingredients that stimulated the development of the biotechnology industry in the US and contrasts conditions with those in Europe. It examines relationships between established firms and new start-ups; the financing and managerial environment and the organizational environment, whereby firms were able to set up networks of alliances. Its main findings are that: 1) The funding of the medical science research base has been substantially more generous in the U.S. than Europe. It is the funding of the science base rather than of the biotechnology industry directly that has provided the foundations for start-ups to be created out of the science base. 2) It has been easier for U.S. academics to found start-ups, close to their research establishment, and to retain their academic posts and status as well as be involved in a commercial enterprise. In Europe, the scientific/academic and commercial worlds have a wider divide. 3) Start-ups have been concentrated in the therapeutics and agricultural fields, with strong scientific research inputs into their commercialization, in contrast to other sectors where downstream processing innovations have been more important, which have been undertaken in-house by the large incumbent companies. 4) Financing and managerial conditions have been significantly easier in the U.S. for start-ups, in terms of access to venture capital specialising in high technology, ability to use the stock market to raise capital, and access to people able to forge links between scientists and entrepreneurs, and to introduce managerial expertise into new companies. 5) There has been a greater facility in the U.S. than in Europe for alliances to be formed between incumbent companies and indigenous U.S. start-ups; European start-ups have not found similar backing from European incumbent companies.

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## Introduction

This paper explores particular themes around the biotechnology industry, its genesis and development in the U.S. It is interested in the origins of the industry, why its birth was so clearly located in California, and what the ingredients were in the environment that allowed such an industry to flourish where it did. The evolution of the biotechnology industry is important for two principal reasons: it is a prototype for commercialization of scientific ideas and suggests lessons for the mechanisms involved in transferring science into industry. It is also a clear example of U.S. superiority over Europe in the development of a novel industry based on new start-ups in alliance with large incumbent companies. The relationship between the different types of company, the extent to which the new technologies displaced the older i.e. were competence destroying or enhancing, the interaction between the small start-ups and the various financial institutions and agents were all ingredients in the fertile brew that was the biotechnology industry in geographical concentrations in the U.S. It so clearly was a product of particular geographical environments within relatively close confines that this geographical clustering aspect has been a dominant part of the literature on the growth of this industry. But it also throws up the importance of national environments in structuring the dynamics of local technology clusters and suggests that it is not purely the immediately local environment that is significant, although clearly for the major linkages between scientific research bases and new start-ups it is extremely important. Other wider, national features of the environment also shape the innovation system such as access to finance for small companies via the stock market and via venture capital; access to man-

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agerial expertise via venture capital; relationships with the large companies in particular sectors, important both for their financial backing but also for providing a market for the products of start-ups. Disentangling which of those features are very local and which transcend localness but are constrained by the national environment is one of the questions that this paper explores.

The paper is divided into five sections. Section 1 gives a brief *Early History of the Biotechnology Industry* in the U.S., with emphasis on why the industry took root on the west coast of the U.S. We give a preliminary view of the U.S. industry in 1991 looking at numbers of companies in different states, which industrial sectors those firms were concentrated in, in terms of numbers of firms and employment, and whether they were in small or large firms.

Section 2 *Characteristics of Firms and Innovation* looks at the role of established firms and their attitudes towards new biotechnology enterprises and at the different characteristics of new entrants and incumbent "user" firms. It examines various aspects of their differences. Why were the new entrants mainly focused on particular sectors – therapeutics, diagnostics, new equipment – and much less so in agro-chemicals, energy or food sectors. We look at the importance of scientific research in the science base to biotechnology innovation in these different industrial sectors as opposed to innovations in processing or downstream activities. We also examine the evolution of equipment technologies by new entrant companies and their role as a critical sector in the provision of specialist services, and their place in the development process.

Section 3 *The Financing and Managerial Environment* examines the role of investors, in particular venture capital entrepreneurs in the U.S. who played a prominent role in getting scientists and managers together and cementing the foundations of new biotechnology enterprises. Who were the founders of new enterprises and where did they come from and how did the mix of people change during the 1980s as the industry established itself? This section also looks at the role of the stock market and the Initial Public Offering in raising capital for enterprises and in providing incentives to entrepreneurial scientists to attempt to commercialise scientific innovations. This widens out into a discussion of financing constraints in general, and the advantages of the U.S. market-led environment with its stock market experience of technology companies. We contrast this with less favourable financing environments.

Section 4 *The Organizational Environment* looks at the role of networks of alliances formed between key biotechnology companies and a variety of established companies, especially in the area of drug development. It examines the pivotal role of alliances with incumbent companies and compares the ease of alliance-making in the U.S. with the difficulties that start-ups in the U.K. experienced. It raises the question of why there have been relatively few start-ups in Europe and the absence of any symbiosis between start-up and incumbent company within various European countries.

Section 5 *Lessons for Policy* concludes by asking what lessons might be learned for the development of the European biotechnology industry and policies relating to it.

## 1. The early history of the biotechnology industry in the U.S.

The genesis of the biotechnology industry was in California. The biotechnology industry inherited a great deal from the earlier development of computing in California. Several of the ingredients for successfully developing technology companies were there: a pool of scientifically aware venture capitalists, eager to back scientists with commercial ideas, a pool of highly skilled mobile labour and good communications networks, facilitating the spread of ideas. The linkages established between the Stanford Research Institute and the Industrial Park served as a model of the transfer of ideas from the universities into commercial companies. However whereas in the genesis of computing the important information flows were between engineers in companies, Swann et al. (1998) and others (Zucker et al., 1994; Audretsch and Stephan, 1996) have argued that for biotechnology it was the strength of the science base and linkages with key scientists in the science base that mattered most. Giesecke (2000) has framed this as research and innovation not being "just the realm of the firm any more but takes place in the interrelationship between the actors of the triple helix: academia, state and industry" (p. 206).

The funding that the science base received which formed the basis for the new technologies was an extremely significant factor in the development of the new industry. This fact has been well documented (Orsenigo, 1989; Kenney, 1986; Sharp, 1985). The largest part of the molecular biology research which formed the backbone of genetic engineering was funded by the National Institutes of Health and within that by the National Cancer Institute (Orsenigo, 1989). Following U.S. medical research policy funding increased in particular into cancer-related areas of research and the NIH's Viral Oncology Program grew substantially during the 1970s, which was molecular biology research leading to developments in the understanding of DNA. "The campaigns undertaken by NIH to find cures for diseases such as cancer have also turned out to be projects that prepared commodities to the point at which they were ready for commercialization by industry (Kenney, 1986, p. 241). In 1983 64 per cent of university research and development funding came from the federal government, amounting to $5,387 million, and another 8 per cent from state and local government of $653 million (National Science Foundation, 1985). As Kenney (1986, p. 35) put it "The all-pervasive federal research monies are the baseline of support for university research and will continue to be of primary importance. The American research system has been and is, quite simply, based on federal (that is, public) funding. NIH and NSF (National Science Funding) funding allowed the development of an enormous medical research base in the United States and made possible the construction of numerous laboratories and even entire research complexes (Kenney, 1986, p. 18)".

In comparison with any country in Europe, the funding of the medical science base in particular has been substantially more generous in the U.S. and this created the critical mass of research necessary to launch the biotechnology industry. For example expenditure in the U.K. on biotechnology by the U.K. Research Councils amounted to £81 million in 1988–1989 (NEDO, National Economic Development Office, 1991, p. 58). Expenditure in support of the biological sciences by the University Grants Committee in 1985–1986 was £60 million and the Department of Trade and Industry spent about £6 million on biotechnology in 1988. A NEDO survey (1991) estimated that around £49 million was spent on research and development expenditure in companies in biotechnology in 1988 rising to around £58 million in 1989. These amounts are dwarfed by U.S. expenditures in similar areas.[1] Similarly Giesecke (2000) reports some figures on federal R&D expenditure in Germany for biomedical and biotechnology research from 1974–1995 which increased from DM48 million to over DM430 million.[2] However the point that Giesecke makes in relation to the German case is that the U.S. industry has not relied on direct government support for the industry whereas the perception is that the German industry has been more reliant on directed federal funds into biotechnology research. The U.S. government's support for the science base formed the bedrock for the strength in scientific research but its approach was not directed specifically towards the creation of a biotechnology industry. In fact some of the relevant research strengths were developed in areas which were the product of the NIH campaign against cancer.

The story of the start of the industry is now relatively well-established (Orsenigo, 1989; Hall, 1987; Teitelman, 1989). However we will briefly bring out some of the main features, which serve as illustrations for other biotechnology communities being founded. The industry was founded through two scientific breakthroughs which were brought together and commercialised. Those were the discovery of the recombinant DNA technique by Cohen and Boyer in 1973 at Stanford and the University of California at San Franscisco (UCSF) and Kohler and Milstein's discovery of monoclonal antibodies at Cambridge (U.K.) in 1975.

Although the basic breakthroughs in recombination had been achieved, the process of turning science into usable technology was just beginning in the late 1970s. There are four lessons to be drawn from the early history of this industry, when the science was first moved into the commercial world. First it involved competition between research teams in the basic science: between teams on the west and east coasts of the U.S., around UCSF, the City of Hope and CalTech on the west coast and around Harvard on the east coast. Second, it involved collaboration between different aspects of the science: between recombinant research teams and insulin research teams at UCSF. Third, the commercial potential of the science drew in the interest and financial support of large pharmaceutical companies, Eli Lilly and Novo, which were interested in finding new methods of making insulin for the diabetic market. And fourth, it involved the creation of new companies in the process of commercializing the science, such as Genentech. The distances between the scientists in the research base and those in the early companies was very small, with linkages between them.

The creation of Genentech and Biogen illustrates the type of cooperation within companies that occurred between the scientists and more commercial people. Genentech was founded in 1976 out of an alliance between venture capitalists Robert Swanson from Kleiner Perkins, and Boyer at UCSF, drawing on the skills of team of scientists from City of Hope, CalTech and laboratories at UCSF. The entrepreneurial Swanson founded this company, based on research strengths and attractive to academic scientists, but with commercial backing and links with the financial community and a large pharmaceutical company, in the shape of Eli Lilly. A similar commercial prototype was created on the east coast in 1978 as Biogen, with Walter Gilbert from Harvard and the backing of Novo, Lilly's competitor in insulin (Teitelman, 1989). These early companies in the 1970s, such as Cetus (California), Genentech (California), Biogen (Massachusetts) or Hybritech (California), were all based near important research centres and were started by prominent scientists from those universities. In particular the area around San Franscisco and the research based at the University of California at San Francisco (UCSF), Stanford, City of Hope and CalTech were important focal points for these start-ups.

The U.S. prototype companies, which do not exist in the same way in Continental Europe and do only to a much lesser degree in the U.K., are the product of several other institutional features of the U.S. academia-industry environment. Technology transfer was facilitated during the 1980s, starting with the Bayh-Dole Act to 1980 to give incentives to universitites to commercialize their research. It was possible for U.S. academics to found companies whilst retaining their positions as scientist; they stayed in contact with the science base and thus information flowed between the two environments easily.[3] This is in marked contrast to the much starker divisions between academic and industrial environments in Continental Europe, with few incentives for academics to commercialize their research (Giesecke, 2000). Even in the U.K. where start-ups have been spawned, the difficulties of straddling both environments and the stigma of failure which harms careers is well attested (Prevezer and Shohet, 1996). Giesecke charts similar obstacles and insulation of academic researchers from commercial life in Germany.

Clearly closeness to the science base was not the only significant factor in the founding of new companies. One can note that Cambridge, U.K., spawned one of the main scientific techniques and yet failed then, in the early 1980s, to commercialise it. The U.K. government berated itself for years for the failure of U.K. institutions to patent the method of making monoclonal antibodies. In sections 2 and 3 we look at the financing and organizational environments that led the industry to develop in the U.S.

## 2. Characteristics of firms and innovation

In this section we look at the relationship between large established firms in the particular "user" industrial sectors and the small dedicated biotechnology firms. One of the distinctive features of biotechnology, as compared with computing for example, is that the main users of biotechnology were confined to industrial sectors and established firms within those sectors.

In computing sectors of the industry divided most naturally into the different technologies within the industry: components, hardware, software peripherals, systems etc. These technologies were interdependent in creating the end product. End markets for computing were spread across the economy, not confined to the industrial sector but encompassing the financial and domestic users. The biotechnology industry was structured differently, which has had implications for the way it permeates the economy. There has been considerable similarity, in the early days of the biotechnology industry at least, between the technologies used by the different sectors. Biotechnology companies have specialized instead in terms of the applications of the technologies to a particular industrial sector: for instance therapeutics and diagnostics firms were broadly within the pharmaceutical industry; agricultural and chemical firms saw their technologies as applying to the agro-chemical industry; new enzymes or food ingredients looked to the food processing industry. These divisions were not completely clear-cut. Diagnostic firms' products and technologies were used not just by the healthcare industry but also by water and food testing services; the research tools and equipment sectors supplied both industrial and research establishments; and environmental applications were a largely new sector without an existing industrial base to address. Nevertheless the broad distinction from the computing industry applied: biotechnology firms saw their market as the large established firms within existing industrial sectors and hence were dependent to a large extent on their relationships with large incumbent firms within their chosen sector. Links were therefore vertically forward to particular user firms in each industrial sector, rather than between sectors where technological interdependence was low. Sectors have developed more rapidly where those vertical links have been strong, than in sectors where they were weaker.

Our data taken from Dibner (1991) include both large and small firms, with differences in composition of small and large companies between sectors (see Table I). Diagnostics and waste companies were mainly small; therapeutics, agricultural and equipment companies were a mix of small start-ups and large pharmaceutical, agrochemical and equipment manufacturers. The food, energy and chemical sectors were dominated by large multinational companies, with very few start-ups by the early 1990s.

We can distinguish between new entrant companies and large incumbent industrial users in terms of their characterstics. The Dedicated Biotechnology Firms (DBFs) were far more reliant on their local environment and linkages in order to have access to their three key inputs – labour, tools and knowledge. They were "extrovert" firms, making use of and absorbing the maximum possible from their local environments. They needed to locate in a nourishing atmosphere, with the right mix and variety of ingredients. Incumbent user firms have tended by contrast to be much larger, more mature and further on in their lifecycles, being more insular by constitution, less open to the outside innovative influences of their local environments. They have had much larger and more developed downstream operations, which have complemented the skills of the new biotechnology firms. They have tended to rely on the scientific and processing expertise within their own firms rather than looking to skills in the local environment. Sharp (1991), Orsenigo (1989) and others have characterised the new genetic engineering technologies as a new technological trajectory or regime which was competence destroying for the incumbent companies in altering the methods for doing research, opening the way

TABLE I
Classification of firms by sector and size

| | Number of firms, small and large | Employment in firms of which | |
|---|---|---|---|
| | | Small firm | Small and large |
| All companies | 849 | 742 | 1850.7 |
| Therapeutics | 293 | 265 | 624.5 |
| Diagnostics | 158 | 151 | 84.5 |
| Equipment | 186 | 156 | 189.5 |
| Agriculture | 107 | 87 | 444.3 |
| Chemicals | 52 | 41 | 369.4 |
| Food | 10 | 7 | 37.0 |
| Waste | 30 | 28 | 42.1 |
| Energy | 11 | 7 | 65.3 |

*Source:* Dibner, 1991.

to new entry whilst creating a need for the incumbent firm to develop new skills in-house and have access to new capabilities via alliances with the DBFs.

Why were new entrant companies concentrated in particular sectors? This relates to the importance of the science base as a source of innovation in those particular sectors. The importance of scientific research in the science base to biotechnology innovation differed between industrial sectors of application. Dibner looked at the ratios of the importance of scientific activity to business activity in a sample of firms, dividing the industry into three broad sectors of therapeutics, diagnostics and agricultural biotechnology and looking at small, medium and large companies. He found that the sector therapeutics had the highest scientific to business ratio and agricultural biotechnology the lowest. Smaller newer firms tended to have higher scientific to business ratios than larger older ones. (Dibner, *Bio/Technology*, 1988). Across a wider spectrum of sectors, scientific research was more important for innovation and value-added in therapeutics, diagnostics and agricultural companies, than for chemicals, food processing or energy, and for the former sectors it has been important for companies to locate near the sources of that innovation, in the science base. In the latter three sectors, innovations in processing or other downstream activities such as marketing assumed a larger role in the creation of profit.

There was a difference between industrial sectors in terms of how much innovation was done by new companies specializing in new technologies or on the other hand was developed in-house within existing companies. The healthcare area has seen the greatest degree of specialist companies, building on research, providing services, licensing new technologies or selling products to the user pharmaceutical companies. Biotechnology research has been in increasingly specialized niches with new entrants created on the basis of a new research discovery. Orsenigo et al. (forthcoming) find a mapping between the evolution of scientific/technological knowledge in pharmaceutical research and the structure and evolution of the organizational forms in innovative activities that accompany it.

Healthcare users such as hospitals have been important with many new technologies for the diagnostic market, such as diagnostic probes, being initiated and developed by hospitals (*Genetic Engineering News*, June 1992). There has also been specialization in research activity with the growth of contract research organizations, undertaking contract research, conducting trials and managing clinical data, providing a service to the therapeutics companies, making use of the generic nature of clinical trials in different disease areas.

Non-health sectors have not witnessed such specialization within research activities. The impact of biotechnology on the chemicals and food industries has been far-reaching affecting a range of substances used by the industries – amino acids, enzymes, oils and lipids, biopolymers, catalysts and dyes for uses in feed, detergents, dietary uses, thickeners. The role of bioprocessing technologies has been particularly important in these areas and there has been a greater reliance on new instruments such as bioreactors and biosensors which are designed to cope with the problems involved when scaling up activities from small-scale research procedures to commercial quantities. In food processing the introduction of new technologies has had to be more cautious due to fears of genetic modification and reluctance to change food consumption patterns. They have been more reliant on bioprocessing innovations, more likely to be developed in-house by applied scientists and engineers within companies than by independent specialists in the science base. An example of this has been the development of the automated membrane affinity separation system developed in-house by NY Gene Corporation (*Genetic Engineering News*, April 1990).

The evolution of equipment technologies by new entrant companies and their role as provider of specialist services has been shown[4] to have played a key part in the development process. The move from scientific research-scale activities to industrial-scale commercialization could not have been done without the development of a whole new range of instruments which automated procedures and created more sensitive machines with which to work. These changed procedures, from being done by expensive postdoctoral researchers taking considerable time to do them, to automated procedures done by sequencers and synthesisers much more cheaply and on a larger scale within industry. In 1980 it took one postdoc one week to add one nucleotide to a growing nucleotide chain. By 1985 the average time for a base addition was ten minutes and the operator did not need to understand anything about chemistry.

The technologies developed for these purposes included new separations and purifying technologies, and bioreactors and biosensors for growing and monitoring the growth of biological materials. The evolution of such instruments and analysis technologies has been done both by specialist start-up companies in particular niche markets, by established older equipment companies, and by companies adapting equipment in-house to their own specialist needs. The separations segment for example has been dominated by a relatively small number of large companies such as Millipore, Pharmacia, Applied Biosystems or Du Pont. Similarly the electrophoresis apparatus and reagents part of separations has been dominated by large companies such as Beckman Instruments or Corning Medical. Alongside these there have been many specialist small companies producing purity reagents, enzymes, tissue cultures and DNA probes with applications across diagnostics, food and water industries.

To summarise, new instruments have been close both to the research end of the spectrum and to downstream processing, developing facilities to mass-produce cell cultures and products, with start-ups being founded in response to these demands; but parts of the sector have continued to be dominated by larger established companies.

## 3. The financing and managerial environment

This section looks at the role of the venture capital entrepreneurs in the U.S. who played a prominent part in getting scientists and managers together and stimulating the foundation of new companies. We look in detail at where the founders of companies came from, and how the mix of people involved in the new enterprises changed during the 1980s as the industry became more established.

The venture capitalists played a key role in the creation of the industry, in helping form links between scientists and entrepreneurs. These venture capitalists were entrepreneurial yet were open to the language of scientific or technological advance. Such people came in a variety of guises. Venture capitalists such as Robert Swanson and Brook Byers of Kleiner Perkins Caulfield and Byers were important in the foundation of Genentech. Swanson was its first chief executive, and KPCB had investments in Genentech, Athena Neurosciences and Glycomed. Byers was president of Hybritech, IDEC, Insite Vision and Progenex and was involved with eighteen companies. Table II gives some examples of key individuals involved in creating the biotechnology industry in the U.S.

Dibner has established that the process of biotechnology company creation shifted during the 1980s, as the industry became established and was

TABLE II
Key individuals in brokering the early biotechnology industry in the U.S.

| Name | Name or type of institution to which individual belonged | Connection with firms |
|---|---|---|
| Robert Swanson | Venture capitalists | Genentech, Athena Neurosciences, Glycomed |
| Brook Byers | Kleiner Perkins Caulfield and Byers | Hybritech, IDEC, Insite Vision, Progenex |
| Peter Drake | Vector Securities | |
| Stephen Burrill | Ernst and Young | |
| Bruce Mackler | Association of Biotech Companies | |
| Joseph Perpich | Grants and Programmes at Howard Hughes Medical Institute | |
| James Watson | Office of Human Genome Research at NIH Cold Spring Harbor Laboratory | |

*Source:* Prevezer, 1998 in: Swann et al., 1998, pp. 166–167.

able to attract, and required more experienced managers. Looking at the background of the founders of new biotechnology companies, he discovered several features. Companies were founded by up to 6 people, on average by 3. The academic/industrial mix of those people changed during the 1980s. In the later 1970s over half of the founders came from universitites. By the mid-1980s this proportion had dropped to a fifth and the proportion of founders from industry rose from a quarter in the late 1970s to two-thirds by the mid-1980s.

A key feature in the creation of new companies has been the combining of scientific with entrepreneurial and managerial skills. This has either been done through particular individual scientists with entrepreneurial flair, or through the collaboration of scientists with managers. From the early days there have been key individuals who have been responsible for the foundation of several companies, specializing in recognising commercial potential in scientific ideas and creating companies on that basis. These individuals frequently came out of managerial positions in large established companies, being dissatisfied with the lack of innovation within those positions. Table III shows the career paths of a few of these founders of biotechnology companies. The challenge of breaking away from a large company and helping create a small new company appealed increasingly to managers from the established sectors, as the biotechnology industry itself became more established.

Another feature of the U.S. environment for the creation of new companies has been the role of the stock market for new companies and the initial public offering. Genentech's example in 1980 when it managed to raise substantial sums even before any products came on-stream and before any profits from sales could be expected, set the scene for other fledgling companies to use this route to raise capital and establish themselves in the public eye. The ability to make initial public offerings and open up the raising of capital to the wider public also gave venture capitalists and the founders of companies an exit route, an ability to sell on their share of the company should they wish to do so. This has greatly increased the incentive to become involved and invest in such companies in the first place.

The favourable experiences that young high technology companies have had both in raising

TABLE III
Examples of career paths of founders of biotechnology companies

| | | | | |
|---|---|---|---|---|
| Roberto Crea | Genentech 1977 | Creative BioMolecules 1981 with Charles Cohen and Fred Graves | Founder Creagen 1991 | |
| Fred Graves | Creative BioMolecules | Founder Codon | Founder Berlex Biosciences (merger between Codon & Titon Biosciences) | |
| Patrick King | MIT, Du Pont | Johnson and Johnson | Centor, 1982 | Founder T Cell Sciences 1986 |
| David Hale | Hybritech president (1983–1987) | Gensia president | Viagene president | |
| Ted Greene | Baxter Travenol, Hybritech co-founder | GenProbe co-founder | IDEC co-founder, Cytel | Amylin involved with Neurex, Vical |
| Henry Termeer | Baxter Travenol | Genzyme | | |
| Stephen Chubb | Baxter Travenol | Cytogen | | |
| James Glam | Baxter Travenol | Genetic Systems | | |
| Robert Carpenter | Baxter Travenol | Integrated Genetics | | |
| George Rathmann | Abbott | Amgen | | |
| G. Kirk Raab | G. D. Searle | Genentech | | |
| R. Fildes | Glaxo Bristol Myers | Cetus | Biogen | |

*Source:* Prevezer, 1998, pp. 164–167; Dibner, 1988.

capital and in finding the backing of venture capitalists, experienced in technology ventures, raises the question of whether such new firm foundations are possible in other country environments lacking such infrastructure, and how such skills and institutions can be created or substituted for, if the prospect for them to exist does not look promising. The U.K. has presented the next most favourable climate in this respect, but follows a good way behind the U.S. It has had the most flourishing population of venture capitalists outside the U.S., but these have been found to be highly biased in favour of "safer" lower technology ventures, rather than getting involved in high technology sectors. Data comparing venture capital investment in the U.S. and U.K. by the technology-related sector and non-technology the sector is revealing. Overall throughout the 1980s the proportion of venture capital excluding buyouts that was involved in technology-related businesses was between a third and a half that of the U.S. Of the medical and biotechnology-related investments, the comparison is the same, the proportion going to these ventures well under half of the amounts directed at these ventures in the U.S. These are much smaller proportions of an already much smaller absolute amount of investment. The overall pool of venture capital investment was roughly about 15–17% of that of the U.S., with funds in the US estimated at between $3000 million and $4000 million per year in the U.S. and at between $400 million and $900 million per year in the U.K. (Beecroft in Dimsdale and Prevezer, 1994). Interviews with venture capitalists in the U.K. involved with biotechnology established that even where the technological risk may have been acceptable, most projects were rejected by the venture capitalists on the grounds of business risk, as few biotechnologists wishing to set up companies in the U.K. possessed the requisite business skills (NEDO, 1991, p. 56). The U.K. and Continental Europe lacked the individuals who were crucial in setting up the industry in the U.S. (see Table II).

The process of new company creation has also been more expensive than in the U.S., and the business of making an initial public offering perceived to have been harder and more expensive in the U.K. than the U.S. (Beecroft, op. cit.). This is in part because the public market was less deep in the U.K., with less wealth and enthusiasm for private risky investment in the stock market (NEDO, 1991, p. 56). The climate in Continental Europe and Japan has hitherto been perceived to be more hostile still to the creation of new high technology ventures, which has been linked to different patterns of ownership and control of firms. The financing systems, being less market oriented and more geared towards bank support and involvement, have been seen as being more conservative in the type of backing they are prepared to give, favouring established companies rather than new ventures, although offering more favourable terms and involvement to those companies that they do back (Dimsdale and Prevezer, 1994).

## 4. The organizational environment

This section examines the role of networks, both of the more formal type of alliances, but also informal networks of communication between companies and universities in the local area. The fluidity and density of these networks is thought to have played a key role in the diffusion of ideas, technical expertise and commercial opportunities related to high technology areas. The history of having grown the computing industry in California was relevant to the establishment of biotechnology in the Bay area. The creation of fluid networks in computing in California is described by Saxenian (1994). She looked at what she called local industrial systems in the computing industry in California and Massachusetts and found a distinct contrast between them. Silicon Valley had a network-based local industrial system which promoted collective learning and flexible adjustment among specialist producers of a web of related technologies. The dense social networks and open labour markets, with high job mobility, encouraged start-ups and entrepreneurship. Companies competed intensely with one another, whilst learning from each other about changing markets and technologies through informal communication and collaborative practices. The relatively "flat" non-hierarchical nature of firms in the area encouraged horizontal communication among firm divisions and with outside suppliers and customers. Saxenian paints a vivid contrast between these sorts of networking firms in Silicon Valley in the nascent computing industry and firms on Route 128 in Massachusetts which were dominated by a small number of large corporations, which were more hierarchical and secretive, maintaining a culture of self-reliance rather than networking.

The type of companies in biotechnology were more similar in Massachusetts and California. The east coast also fostered small scientific companies, such as Biogen or Genetics Institute, under similar conditions to those in California with venture capital backing (Teitelman, 1989). However biotechnology probably benefited from the cultural networks on the west coast, linking together the science base and commercial community of other small firms, venture capital and large user companies. The ability to build informal networks through trade associations, personal ties, scientific conferences and venture capital was state-of-the-art in California. The process was self-reinforcing. Job mobility was high because it was relatively easy to find a new job in an area densely populated by different types of firm. The region's culture encouraged risk and accepted failure. Those who attempted to start a firm were held in high regard. The role of networking in building up the northern California cluster was recognised and copied in the south of the state, by the University of California at San Diego. It created the CONNECT network in 1985 as a university-private sector partnership to encourage local high technology entrepreneurs and put them in touch with relevant scientific, technical and managerial expertise.

The ethos of the early biotechnology firms such as Genentech, imitating in part the early computing firms, was one of openness and informality, encouraging an academic atmosphere in the hope of attracting high calibre research scientists and encouraging them to maintain their scientific links, to continue to publish papers, to attend conferences and maintain their status as academics if possible. Features such as informal dress and keeping firms open day and night to allow flexible working times were designed to imitate academic laboratories and be attractive to top research scientists (Teitelman, 1989).

Apart from informal networks of communication between scientists and commercial people within the locality, more formal networks of strategic alliances were also a critical feature of the thriving cluster. Inter-firm collaboration increased markedly during the 1980s in all high technology industries, and alliances between companies have been a prominent feature of the biotechnology industry. Hagedoorn and Schakenraad collected over 1,200 cases of inter-firm collaborative agreements in their MERIT-CATI databank, 90 per cent of which occurred during the 1980s, 60 per cent since 1985 (Hagedoorn and Schakenraad, 1990). In a sample of alliances collected by Dibner (1991) of U.S. companies between 1988 and 1991, of 374 alliances, 52 per cent were between two DBFs and just under half involved established user companies, almost all in alliance with DBFs.

These networks of alliances served various purposes: to bring together complementary assets between different types of companies, especially upstream research capabilities of DBFs with downstream processing and marketing capabilities of incumbent user companies (Dodgson, 1991); to learn about and absorb new technologies outside the core competencies of the incumbent user companies (Arora and Gambardella, 1993). "External linkages are . . . both a means of gaining fast access to knowledge and resources that cannot be secured internally and a test of internal expertise and learning capabilities" (Powell and Brantley, 1992). Symbiosis has existed both between the new entrants (DBFs) and incumbents and between DBFs specializing in different technologies. Alliances have also been formed for motives of strategic choice and due to technological competition (Barley et al., 1992). Prevezer and Toker (1996) related the different types of alliances to varying degrees of closeness or integration between the two firms, with distinct patterns of integration depending on the respective industrial sector, the size of the two firms and their nationality. These networks of alliances were also methods of coping with uncertain appropriability between firms (Levin et al., 1987) and difficulties in learning and absorbing the new technologies into organisational structures with well-established existing competencies and routines (Cohen and Levinthal, 1990).

It has been relatively easy for U.S. start-ups to form alliances with large incumbents in the U.S. Ernst & Young reports from the 1980s abound with examples of the different types of alliances in biotechnology that sprang up between small and large companies in the U.S. According to their survey, 74 per cent of responding companies in the U.S. market were involved in strategic alliances in 1989, with an industry-wide average of 10 alliances per company. (Ernst & Young, Biotech 89 Commercialization, 1988, p. 45). By contrast specialist small biotechnology companies in the U.K. have been at a disadvantage in the lack of opportunities for strategic alliances with large U.K. pharmaceutical companies (NEDO, 1991, p. 56). This has limited U.K. companies' sources of funds for development and made it difficult to tap into the managerial resources of large U.K. companies, the equivalent of which has been so important in the U.S. in setting up new companies (see Table III). In the U.S. access to managerial skills encouraged venture capital participation through the perceived reduction in business as well as technological risk.

## 5. The role of policy and lessons for Europe

1. The first lesson for Europe regarding the role of policy in the development of the US biotechnolgy industry concerns funding. The federal funding that formed the basis for this industry was the non-directional funding that went into the research base, funding basic research and not attempting to fund biotechnology research *per se*. Thus some scientific spin-offs came from research driven by seeking to cure cancer. It demonstrates that governments are not in a position to predict the source of commercial products in basic research. The European country that has emphasised direct funding of biotechnology most has been Germany, and with conspicuously little success. "Direct targeting by a government agency is, by definition, remote from the organization of research and development and cannot anticipate the innovative dynamic a specific technology – following its inherent logic of development – might take" (Giesecke, 2000, p. 216).

2. Direct linkages between the science base and start-ups and the ability for academics to found start-ups has been crucial in the genesis and development of this industry. Information flows needed to be as close and direct as possible. This links to Orsenigo's paper (see this volume) which points to the role of post-doctoral students in the U.S. moving between research centres and industry and being the natural mechanism by which tacit knowledge and expertise is transferred. Using third party intermediaries such as technology transfer offices, as has been done to some extent in the U.K. for example to make the linkages (see Shohet and Prevezer, 1996) is a poor substitute for the direct information flows that need to pass between the science base and industry.

3. The role of venture capitalists and other "brokers" interested in managing the formation of new companies has been well documented and recognised as playing a significant part in the early development of the U.S. industry. The pool of venture capital is deficient in Europe and more important the lack of involvement of venture capitalists, in terms of helping with and taking over the business side of company formation and finding appropriate managers, makes the task of founding a company by an academic much more difficult and more likely to fail.

4. There has also been a significant role for managers from established companies eager for the challenge of running a new start-up with managerial experience of their sector. The stigma of failure in Europe makes leaving the large established companies much harder and it is rightly perceived as being a much riskier and more expensive exercise, involving greater difficulty in returning to the large company or founding new spin-offs if this particular enterprise should fail. Looking at the career paths of U.S. managers, there is considerable mobility – they do not tend to stay with any one company for long and they become expert at founding companies or helping to start them.

5. There is a considerable facility in the U.S. where the industry has developed in forming networks of alliances especially with indigenous home-based companies. U.S. start-ups have had the advantage of the eagerness of U.S. incumbents to get involved with them, for a multiplicity of reasons, but principally in order to have access to these new technologies. The density of these networks involving a mixture of collaboration and competition with any one company having multiple alliances with other DBFs and incumbents appears to be well in advance of the density of similar networks in Europe. These networks are

created out of increasingly specialized niches which prevent direct competition and hence foster multiple linkages. European companies tend to be linked, as satellites, to the core U.S. networks. Being able to foster European centred networks of a similar density and complexity is probably part of the key to developing the European biotechnology industry.

## Notes

[1] At an extremely rough exchange rate of $1.7 = £1, this would put total U.K. public expenditure on biotechnology in the science base at around $250 million in 1988 compared with Kenney's estimate of around $6,000 million in 1983 in the U.S.

[2] Again at very a rough exchange rate of DM0.53 = $1 we get an estimate of $230 million federal funding on the German biotechnological science base in 1995.

[3] This is well documented in Zucker et al. (1994), Audretsch and Stephan (1996) and Giesecke (2000).

[4] See Swann et al., 1998.

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