CHAPTER 2 UNIVERSITY-INDUSTRY RELATIONS IN THE U.S. BIOTECHNOLOGY[1]

2.1. Introduction

What follows summarizes a number of the developments in the structure of innovation in the western pharmaceutical industry and in related S&T policies, which are mainly based on Matthew Bullock's ideas[2]. It aims to provide a framework for understanding the role now played in western economies by small biotech firms. The new relationships that have grown up between the major pharmaceutical companies, academic institutes and small biotech firms are complex and their pattern of development has been hardly well understood. It is expected, with a better understanding of such a phenomenon, to have some policy implications.

This structure can be abstracted as Figure 2.1 depicted below. It shows that, the demand for more efficient technological innovation, pulled by the industry, and the supply of scientific research for innovation associated with molecular biology, pushed by the academia, have promoted the emergence of a market for enabling technologies in the biotechnology industry, for example, genomics, proteomics, combinatorial chemistry, high-throughput screening, and bioinformatics… and so on. Therefore there is a close relationship between academia and industry in the development of biotechnology.

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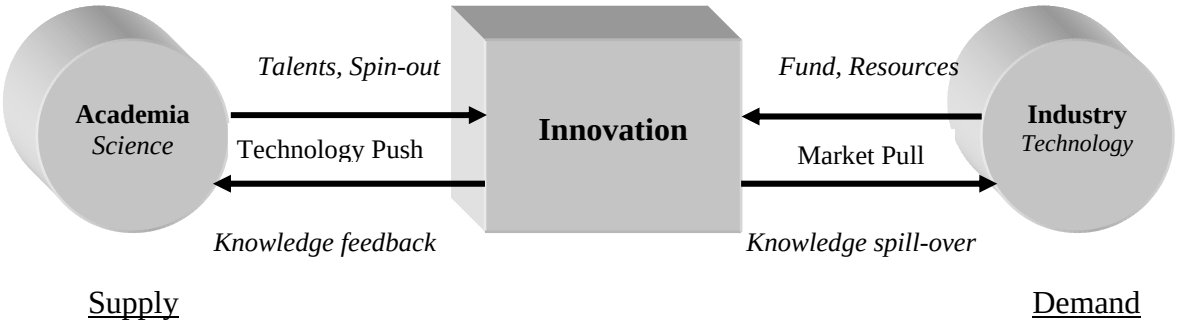
[1] The major contribution of the dissertation is the application of the framework of ***National Innovation Systems*** to an analysis of Taiwan's biotechnology industry by employing a large-scale survey, which is motivated by this chapter.

[2] In 1999 April, I visited the science parks in Cambridge, and interviewed Matthew Bullock, one of the founders of Cambridge Science Park. During the 1970s Barclays Bank in Cambridge, under the leadership of Mr. Bullock, had been very active in supporting small new technology based firms in the region. In the early 1980s he had visited universities, science parks and sources of venture firms in the U.S, to explore the University-Industry Relations in the U.S. Biotechnology.

Figure 2.1: University-Industry Relations in a Knowledge-based Economy



2.2. The "Market Pull" of Innovation

-- Pressures on Innovation in the Pharmaceutical Industry

Over the past several decades, the pharmaceutical industry has successively adapted to advances in frontier technologies and has exploited new sources of scientific knowledge. However, technological progress in drug discovery is very costly [3] and the industry now faces some difficulties in sustaining its rapid development.

One of the major challenges confronting the pharmaceutical industry is that all major governments are trying to reform their healthcare systems and to reduce healthcare expenditure. This is occurring at a time when the demand for better healthcare services, the expectation of improved quality of life by patients and the availability of new technologies are pushing healthcare budgets to their limits. Added to this is the political pressure of an ageing population, which would like to live longer and healthier lives, but cannot afford to pay more for age-related medication. Therefore, these multiple pressures to moderate the rate of growth in sales have led to a much more competitive climate in pharmaceutical industry than before.

[3] World pharmaceutical market was approximately $300 billion in 1997 and R&D expenditures were $40 billion, of which drug discovery was $10 billion (Smith, 1997). World pharmaceutical market is

In this climate the pharmaceutical companies have increasingly sought to concentrate their development efforts on producing "blockbuster" drugs, each with sales of over $1 billion a year, and have dropped programs that are unlikely to find a market of this size. It is only really in this way that they expect to be able to amortize the very high costs of development and approval and to earn the high profits necessary to support this research.

There were signs, however, that their success rate at discovering these "blockbuster" compounds had been declining and this had added substantially to the pressure on their research activities to produce promising drug leads. In response to this worrying trend, the top 20 companies had more than doubled their research expenditures in nominal terms over the period from 1990 to 1997. If this pattern remained unchanged for the period from 1998 to 2005, according to PriceWaterhouseCoopers research (1998), R&D costs per company would rise from an average $1.2 billion to around $2.5 billion a year by the year 2005 - a spending that was potentially enough for each to produce between 26 and 37 new drugs over the same period. If, given different scenario, the top 20 companies pegged their R&D expenditures to revenues, with an annual growth rate of 7%, they would expect to spend an average $1.9 billion a year by 2005. This would then potentially enable each to produce between 22 and 31 drugs over the same period.

However, even this would put an enormous strain on their research operations, since it would represent a four- to six-fold increase in the number of new drugs emerging from the R&D pipelines of the top 20 companies, a level of productivity that had been hardly conceivable. Moreover, even if the top 20 companies succeeded in handling such a large output, the returns they yielded might still fall far short of what they had previously delivered. Many financial analysts have been questioning whether the big pharmaceutical companies could continue to deliver double-digit sales growth for the future and maintain as high operating profit margins as before. Thus, if they were to maintain as high profitability as 20% (and to honor public commitments given by their CEO's to investors about maintaining sales and profits growth), the major pharmaceutical companies would need to dramatically

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$492 billion in 2003.

improve their R&D productivity by an order of at least 300-400%, or to ensure that every drug they developed is a "blockbuster" of more than $1 billion[4].

Therefore, the most critical factor determining survival and success of the pharmaceutical industry is its ability to provide novel and economically feasible medicines to meet those unmet medical needs. But the question is, how can the major pharmaceutical companies achieve this dramatic increase in both the number and quality of the drugs without commensurately large increases in discovery resources?

2.3. The "Technology Push" of Innovation -- The Application of Automation and Information Technology

Traditional drug R&D process is quite lengthy[5], costly[6] and risky[7]. Thanks to the development of robotics and computing technologies, they have supported searches for a new and modular approach to drug discovery, which allows for the more rapid, thorough, and efficient identification of drug leads. In particular, the emergence of biotechnology in the 1970s has started to offer an alternative to the core technology base of the traditional pharmaceutical industry in organic chemistry[8]. The previous trial-and-error approach[9] to drug discovery and development has been

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[4] In 2003, the sales of the top 10 "blockbusters" are $48.3 billion, accounting for approximately 10% of world pharmaceutical market.

[5] According to the homepages of Eli Lilly and Pharmacia & Upjohn (1998), average length of time from discovery to finished product was 10-15 years. It takes 12 years on average in 2003.

[6] According to the homepages of Eli Lilly and Pharmacia & Upjohn (1998), average cost to discover and develop a new drug was $350-500 million. According to Smith (1997), the average cost per drug, including failures, was estimated around $600 million. It costs $850 million on average in 2003.

[7] According to Smith (1997), it had to screen from 5,000 chemical compounds, on the average, to get a New Chemical Entity (NCE) to market.

[8] Molecular biology and genetic engineering have displaced traditional "chemical" capabilities for drug discovery. Chemical capabilities were "sunk" in the corporate tradition and "culture" of large pharmaceutical companies (Gambardella, 1995).

[9] The traditional drug discovery process was to choose a disease that affected a significant population, and then to define a model of the disease, and then to manually produce chemical compounds as potential drug leads from the chemists' shelves, and then to screen of potential targets from the leads. A new drug might be successfully developed through such laborious trial and error, although the understanding of the causes of biological interaction on the disease was often primitive (Powell, 1996). Therefore, the drug innovation rarely followed directly from the discovery of a general principle, and the nature of drug research was highly empirical, so it requires large R&D investment (Schwartzman

increasingly supplemented by the targeted genetic engineering approach of the biotechnology industry. With a better understanding of biologically causal mechanisms, biotechnology can provide more focused targets, and then can be used to design drugs to affect the biological interaction. Therefore, the new drug discovery approach has gradually turned drug discovery process from a chemical to a biological basis, and it can reduce the uncertainty of drug discovery and thus can rationalize the R&D process[10].

As Drews (1995) said, traditional pharmaceutical industry dominated drug R&D by chemistry in the 20th century, whereas the principle of genetic information and biotechnology will dominate drug discovery in the 21st century. This may still be the pharmaceutical industry, but only a pharmaceutical industry which has succeeded in progressing towards the new horizons of science, biotechnology. Stefan Ryser of International BioMedicine Investments points out that in 1996 and 1997, 10% of pharmaceutical product launches were attributable to the biotechnology industry, whereas in 1998 this had become 25%. Therefore, there are now more biotech firms offering products, and more and more of the research-based pipeline gap is beginning to be filled by biotech firms (Table A.2, Appendix 1).

The new drug discovery approach[11] basically centers around the following key technologies[12]:

(1) *Genomics and Proteomics*, which identify potential new drug targets and pathways[13];

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and Cognato, 1996).

[10] According to Smith (1997), new drug discovery approach can screen more chemical compounds (estimated 1,000,000 chemical compounds), and get better leads (estimated 200 leads), so it can reduce the cost more than $100 million per drug to get an NCE to market.

[11] See Figure 1.1 "Biotechnology: Life Science Based Technology Scope" in Chapter 1 for new drug discovery approach.

[12] According to Archer (1997), underlying three enabling technologies above and linking them together is the application of automation and information technology (*Informatics*).

[13] Genomics is in the process of providing us with the sequences and the chromosomal location of approximately 100,000 genes. A few thousand genes code for secreted proteins and a fraction of

(2) *Combinatorial Chemistry*, which provides a large number of diverse compounds as potential drug leads[14];
(3) *High-Throughput Screening*, which enables accurate, high speed screening of potential targets[15].

Teams of scientists specializing in these and other emerging technologies (say, *Drug Delivery Systems*, *Gene Therapy* / *Gene Targeting*, etc.), developed initially in the academia arena, have subsequently been active in setting up new biotech firms, usually in close proximity to the original research institution where the ideas were developed.

Most of the new enabling technologies of drug discovery belong to biotechnology [16]. But biotech is a "competence-destroying innovation" in Schumpeterian terms because it is built on a new science base that differs significantly from the knowledge base of the traditional pharmaceutical industry (organic chemistry and its clinical applications). Furthermore, biotechnology industry is such an R&D-intensive sector noted for rapid technological development, where research breakthroughs are so broadly distributed that no single firm can internalize all the necessary capabilities (Powell, 1996).

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those may be eligible to become therapeutics in their own right. Many of the other intra-cellular or matrix proteins will qualify as targets for drug therapy (Drews, 1995).

[14] Combinatorial Chemistry could generate large numbers of structural analogues and derivatives around certain prototypes that have been designed rationally or were found by chance (Drews, 1995).

[15] Screening is the process of applying libraries of compounds to an assay to identify which compounds affect a selected target. High-Throughput Screening (HTS) employs robotics to perform compound preparation, dilution and distribution, assay operation, and signal detection, so high volumes of data generated in the process are stored and analysed by sophisticated information management system. Normally, HTSs are on the order of 2,000 compounds a day (Hambrecht & Quist, 1998).

[16] Aggregate net present value (NPV) of all of the biotech firms, which specialised in either "biological target" or "chemical lead", is estimated $7.5 billion in 1997, where Genomics companies account for approximately $5 billion, and Combinatorial Chemistry companies account for $500 million (Smith, 1997).

2.4. Emerging Patterns of Drug Innovation[17]

What, then, is the innovation strategy of a pharmaceutical company in relation to these new developments? Is a new pattern of drug innovation starting to emerge? This appears to be the case. Based on the annual reports and the homepages on web sites of the top 20 pharmaceutical companies, it could be found that a high degree of interest in biotechnology, which they pursue an active search for collaboration opportunities with the small biotech-related organizations. Indeed, it appears that most of the large pharmaceutical companies have already forged strategic research alliances with the small biotech firms or academic institutes.

According to Andersen Consulting (1998), the major companies that they surveyed had allocated on average 20% of their discovery budgets to external alliances by the year 2000 - up from 4% in 1994, and some had been entering into mission-driven partnerships with academia and with biotech firms. Establishing a broad reach through strategic alliances would have been an important element of success in drug R&D.

In principle, there are three possible forms of strategic alliances.

(1) Research collaboration

Academic institutes or universities can provide ideas and concepts rather than potential development compounds or mature products. Collaborations with them might be very useful during the exploratory phase of drug discovery or in connection with technology transfer although they will rarely directly result in the delivery of drug candidates. Academic institutes, in their pursuit of basic research, and pharmaceutical companies, in their pursuit of new drugs, might achieve their respective goals by collaborating in a complementary way[18] (Drews, 1995).

[17] It will be further explored in details by the following two sections, 2.5 and 2.6.

[18] The general principles of "*science*" enable particular applications of "*technology*" to develop products at relatively low incremental cost, while the demand of innovation motivates the finding in

However, the goal of "*science*" (basic research) of university and that of "*technology*" (applied research) of industry sometimes contradict each other, because the former seeks to add to the stock of public knowledge through public disclosure[19] while the latter pursues the rents resulting from the possession of particular knowledge[20] (Schwartzman and Cognato, 1996; Lackie, 15 April 1999).

By contrast, small research-based biotech firms, set up by scientists or academic staffs from the universities, can both gain access to "*science*" easily and keep "*technology*" secret on collaborators' request. They are able to carry out research projects on a bespoke contract basis and thus to transfer the technologies from the academia laboratory to industry. Therefore, they can supply new ideas, compounds, therapies, and applied research outcomes while pharmaceutical companies can provide complementary research capabilities and assets. Cooperation between big pharmaceutical companies and such small biotech firms has become an increasingly important pattern of drug innovation (Drews, 1995; Gambardella, 1995; Powell, 1996; Ledley, 12 April 1999).

(2) Research services outsourcing

According to the investigation of Hambrecht & Quist LLC (1998) and Powell (1996), outsourcing to specialist biotech firms of drug discovery services, such as screening and compound preparation, has become an integral component in many pharmaceutical companies' business strategy. With the fact of high uncertainty in drug discovery and development process, it is untenable to create and maintain ever larger R&D spending in-house. Outsourcing of research services provides a solution by turning fixed costs (including overhead and equipment investment) into more manageable variable costs. Besides, through outsourcing, companies can also access a broad spectrum of expertise and technologies that they lack.

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basic research (Schwartzman and Cognato, 1996).

[19] Universities usually encourage the scientists to publish their ideas. Publication places knowledge in the public domain, which becomes *non-excludable* in terms of public goods.

[20] In the viewpoint of commercial firms, the know-how bestows rents only so long as it remains secret. Patents do not encourage quick dissemination (*excludable*).

(3) Acquisition

Based on the research of Drews (1995), there had been between 10 and 20 new drugs, potential $1 billion "blockbusters", from the activities of the biotechnology industry per year by 2000. Biotech firms have represented an important source for new drugs. Either acquiring compounds from these firms or taking over some of these firms has been to make a significant contribution towards the establishment of new drug development capacity in the pharmaceutical industry (Senker and Sharp, 1997; Galambos and Sturchio, 1998).

2.5. The Impact on the Overall Industry Structure

Having said that, it is important not to overstate the extent of the impact of biotech firms on the complete drug R&D process. The primary role in this new pattern of innovation is to provide initial drug targets in the earliest phases of discovery (pre-clinical stage), not to provide completely developed drugs[21]. A recent study of the interaction of small innovative biotech firms and large, established pharmaceutical companies in the US, based on empirical research by Gray and Parker (1998), gives a detailed insight into these new relationships.

According to Gray's and Parker's research, the new biotech firms were clustered around leading research universities in the Boston, San Francisco Bay, San Diego, Los Angeles and Seattle areas. They suggested that successful innovation in biotechnology requires a renewed link between research and production, and that biotechnology research also requires a large ensemble of specialized scientists, and thus tends to cluster around research universities. It is difficult, however, for these academic enterprises to perform the post-R&D functions, so most of the new biotech firms concentrate solely on the R&D activity. They are less likely to become fully integrated drug-producing companies (see Table 2.1).

[21] It averagely takes 100 months in the complete drug R&D process, where pre-clinical stage averagely accounts for only 18 months (Gambardella, 1995, pp.19). Well-established pharmaceutical

Table 2.1: The percentages of the 32 approved biotechnology products, each of whose function was undertaken in new biotechnology and traditional pharmaceutical sector respectively.

Sector	Function					
%	Research	Pilot Manufacturing	Advanced Manufacturing	High-Volume Manufacturing	Domestic Marketing	Foreign Marketing
Biotech	82	47	43	34	25	9
Pharmaceutical	18	53	57	66	75	81
Total	100	100	100	100	100	100

Source: Adapted from Gray and Parker (1998), "*Industrial change and regional development: the case of the US biotechnology and pharmaceutical industries*".

R&D budgets range from approximately 10% of revenues for the top 20 pharmaceutical companies to averagely 22% of revenues for the representative biotechnology firms (Table A.3, Appendix 1). Research is the primary focus of most biotech firms, and remains an important function in the traditional pharmaceutical companies as well. Most biotech firms have specialized in research, and a large fraction of their revenues is composed of research contracts for large pharmaceutical companies (Table A.4, Appendix 1). Noticeably, according to Gray and Parker, the firms in the new biotechnology regions carried out research on 82% of the 32 approved therapeutic products based on biotechnology in the United States, thus showing that these biotech firms have established a leading position in research on recent innovative drugs.

It is quite difficult, however, for those biotech firms who conduct research to control all of the post-R&D functions of developing, testing and manufacturing biotechnology-based drugs. Gray and Parker argued that because the science underlying biotechnology remains poorly understood, pilot manufacturing, where drugs are produced in relatively large batches for the first time, is hard to achieve. Scale-up issues often arise, as production in the laboratory is very different from that in the plant, so scaling up to commercial production is not yet a routine function for biotechnology-based drugs. Therefore, although the production process of chemically synthesized and biotechnology-based drugs are quite different from each other, traditional pharmaceutical companies, with their process engineering and skilled manufacturing workforce, can still capture most of the pilot production (53% of the

companies are still better at developing drugs at clinical stage (average 60 months) (Powell, 1996).

sample in the study of Gray and Parker, 1998).

Production usually shifts from the pilot plant to the commercial plant just before FDA approval, so that large volumes of the drugs are ready for the product launch. Commercial production consists of two parts: advanced manufacturing, a high value-added stage in which intermediate active ingredients are produced, and high-volume manufacturing, a low valued-added stage in which the drug is formulated and packaged in its final form (Gray and Parker, 1998).

Following the investigation mentioned above, we find that the traditional pharmaceutical sector still dominates both in advanced manufacturing (57%) and in high-volume manufacturing (66%). Therefore, it shows that the engineering expertise, as well as their filling and packaging know-how, acquired through manufacturing chemically based drugs, gives the large pharmaceutical companies a natural advantage when producing biologically based drugs (Gray and Parker, 1998).

Marketing drugs is also an extremely labor-intensive and expensive function. The marketing networks to distribute drugs across the country are quite difficult for the small biotech start-ups to create. Furthermore, the minimum scale needed to set up a global network of distribution channels poses significant entry barriers to new entrants, and this encourages many small biotech firms to license marketing rights to the large pharmaceutical companies. Therefore, only 9% of foreign marketing and only 25% of domestic marketing of biotechnology-based drugs was controlled by the firms in the new biotechnology regions (Gray and Parker, 1998).

In short, as Gambardella (1995) argued, large pharmaceutical companies have comparative advantages in large-scale development and commercialization of innovations, whereas small biotech firms are better suited for discovery research.

2.6. The Role of Strategic Alliances

Most of the biotech firms, clustered around universities and research institutions, have been set up by scientists. Consequently, they mainly focus on research, and their reputation is tied to their R&D prowess. As a result, they "contract out" many of the financial and managerial aspects of the business. Internally, they are prone to organize themselves flexibly into overlapping and interdisciplinary project teams to do research, so they usually are flat organizations with minimal hierarchy. Therefore, the biotech firms have permeable "boundaries", in which some of non-research functions are provided by either venture capitalists, law firms or well-established companies, and some of research projects are pursued jointly with external collaborators, say, large pharmaceutical companies (Powell, 1996).

In contrast, traditional pharmaceutical companies found themselves gradually losing out in competition for drug discovery, which has been reshaped by biotechnology. This is because they are unable to recruit a work force with every kind of intellectual talents in such a new field, and also unable to keep equipping their laboratories with state-of-the-art equipments, and unable to create an internal environment that can be comparable to university or academic institutes as well. But, once a new drug, even based on biotechnology, is discovered, they are still better at delivering it to market than small biotech firms. That is, while biotechnology has had a notable influence on the discovery process, it has not really changed the type of assets that are needed for drug development and commercialization, which still require conspicuous financial, managerial, and organizational resources to conduct long and costly clinical trials, and extended distribution networks to sell the new products. These assets have been firmly owned by the established pharmaceutical companies but will not easily be built up for the biotech firms in a short period of time (Gambardella, 1995).

Therefore, large pharmaceutical companies are often looking for new products to supplement their own pipelines, whereas small biotech firms are usually searching for research funds, the ability to scale up production quickly, and global marketing capabilities. Both sectors also want to share risk and lower cost, so their so-called *Strategic Alliances*[22] typically revolve around joint R&D, product or technology licensing, or marketing rights, although the exact mix of partnerships and issues negotiated vary enormously. Therefore, deals may be struck among and between large pharmaceutical companies, small biotech firms, and academic institutes. According to the study of Gray and Parker (1998), in the United States, the majority of the pharmaceutical companies' agreements (69%) are negotiated with biotech firms rather than with other pharmaceutical companies. Likewise, the average biotech firm is more likely to be linked with a pharmaceutical company (49%) than with other biotech firms (34% of agreements). Besides, biotech firms are twice as likely to have agreements with public institutions, such as universities and the National Institute of Health, so we can regard these new firms as a bridge between academia and industry in terms of technology transfer.

From the viewpoint of pharmaceutical sector, the small biotech firms are more interested in R&D and tend to negotiate away some of manufacturing and marketing rights, and thus making themselves fully integrated firms is almost impossible. For well-established pharmaceutical companies, the resulting privileged access to the drug development experiences (required in launching extensive clinical trials), manufacturing capabilities, and marketing channels is a major source of competitive advantage in their own business environment. Scale economies allow the traditional pharmaceutical companies to maintain their position in the new biotechnology-based as well as the older chemically synthesized drug business. To minimize their costs of research and the time of drug development as well as to boost yield rates, large pharmaceutical companies are increasingly reorienting their own R&D efforts in the area of biotechnology to include a sophisticated network of access to the new

[22] Such arrangements were referred to as “deals” in 1980s, and then became “strategic alliances” and “agreements”, and eventually were called “partnerships”, “collaborations”, and “cooperation”, or in contractual language, technology and product swaps and co-promotions (Powell, 1996).

technologies through various kinds of research alliances with the small biotech firms (Powell, 1996; Gray and Parker, 1998; Galambos and Sturchio, 1998).

Drews (1992) predicted that the drug industry will polarize around two fundamental agents: giant multinational corporations with considerable abilities to manage large and complex organizations, and small innovative firms with sophisticated scientific expertise in selected areas, which will act as "suppliers of ideas, product opportunities and new technologies" (Gambardella, 1995). As Galambos and Sturchio (1998) found, a new pattern of innovation have emerged in the drug industry. Biotech-pharmaceutical collaboration now plays a significant role in drug R&D process and is likely to remain important for many years to come[23]. In other words, it is not a transitory phenomenon, but something prompted by a change in the technological paradigm (Gambardella, 1995). Given the improved biotech capabilities of the well-established pharmaceutical companies, it appears that they will continue to be dominant players in the global drug markets (Galambos and Sturchio, 1998).

2.7. Institutional Arrangements for the Cluster Centered on University

The following, mainly based on Bullock's observations and ideas, considers the critical elements of how the innovation comes from the small research-based firms, which were originally spawned from the university. It then describes how such an "innovation system" emerges, how it develops and how it affects the innovation strategy of big companies in knowledge-intensive sectors, particularly in biotech-related fields[24].

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[23] Galambos and Sturchio (1998) found that most leading pharmaceutical companies have established significant capabilities in the new field by the mid-1990s, but they are continuing to work with specialised biotech firms in order to innovate across a broad range of therapeutic categories. Senker and Sharp (1997) also observed that the research alliances between pharmaceutical companies and biotech firms have not vanished as biotechnology has matured and are more in evidence than they were in the early days of the commercialization of biotechnology.

[24] What follows is based on my interview with Bullock on 3 February 1999, 9 February 1999, 20

(1) Low Threshold Policies in the university

The science underlying biotechnology has its origins in university laboratories and research organizations. They played a critical role in biotech's emergence, not only as the places where scientists were educated but also as the sources of breakthrough discoveries and techniques that fostered scientific and technological innovation. Indeed, the science and technology of biotechnology are so intertwined that the distinction between basic and applied sciences has largely collapsed in biotech-related fields, and fundamental research in the biosciences has simultaneously become commercially relevant. Therefore, academic research is an essential contributor to the advance of biotechnology, but the commercialization of the science has been initiated by the biotech firms, mainly founded by the academia staffs or scientists from universities (Powell, 1996).

The university, consistent with the principles of academic freedom, has a gently supportive attitude towards its academic staffs' involvement of all kinds with industry by lowering the threshold to commercialization of academic know-how. It is for the individual academic to decide whether to exploit his invention commercially or not (Segal Quince & Partners, 1985; Bullock, 3 February 1999).

As part of this policy approach, the ownership of intellectual property should vest with the academia concerned unless the research contract specifies otherwise. Many universities, however, adopt a contrary stance, insisting that under their contracts of employment, their staffs assign their intellectual rights to the university. According to a report of a committee on patents set up by Oxford University and chaired by the eminent lawyer, Sir Patrick Neale QC (1980) found that these contracts were unenforceable and that the right of a typical university research project should be deemed to be vested in the academia staff and not the university. Bullock, consequently, argued that the university did not have any legal right for work done by its academic staffs for outside bodies (Bullock, 3 February 1999).

February 1999, and 13 March 1999 in Cambridge.

The university authorities also recognize that realistically it is impossible for them to exercise any effective control over how individual staffs spend their time, so the university has to take a relaxed and liberal attitude towards its academic staffs' spending time on outside work. Therefore, the contractual arrangements with its academic staff are very loosely specified and give a great deal of freedom to the individual, just so long as they carry out their specified teaching and formal research duties (Segal Quince & Partners, 1985).

Low threshold policy makes it easy for academic staffs or scientists to enter into commercial activity and to move increasingly in this direction if they wish while still maintaining their academic posts. In other words, the risks to income and lifestyle associated with the transition can be minimized. The academic has the opportunity to acquire substantial business experience and to test the water without fear of sacrificing his career before deciding to enter into commercial life (Segal Quince & Partners, 1985).

Many universities also set up university-industry liaison offices to support academics seeking to commercialize their work. These are generally helpful, although they need to be viewed as long term cost centers serving to assist, and not replace, scientific entrepreneurs in exploiting their ideas (Bullock, 3 February 1999)[25].

(2) Soft Company Model

The small academic start-up, or soft company termed by Bullock (1983), that emerges from a low threshold university environment follows a distinctive pattern of development. The first stage is where an academic engages in outside consultancy. This typically involves applying his highly specialized knowledge to specific needs of

[25] As for industrial liaison offices or technology transfer offices, Bullock argued that direct involvement of the scientific entrepreneur with the problems of the outside world was usually much more effective than mediated involvement. He found that there had been unfortunate examples of where such "bridges become bottlenecks", seeking to generate an income on their own behalves to justify their existence.

the client, say a big company, and the product is usually an advisory report. The next stage is for a reasonably standard analytical or design service, available on a custom-specific contract basis, to be developed out of the high-level consultancy work. Then the work leads naturally to identification of specific product opportunities or some enabling technologies. This phase involves design and production of a particular product or materialization of some know-how. As the consultancy work evolves, the trend is increasing standardization of the product or the know-how, finally reaching volume production for a non-specialist market -- what Bullock describes as the “hardening process” of a soft company.

The build-up of costs is more gradual because the soft company can use the resources of the university to start up with the minimum investment in overheads and equipment. Besides, soft company provides its consultancy or product under bespoke contract and thus contract price can primarily be based on an assessment of the incurred cost rather than externally determined market price, so the soft company has relative stable cash flow and thus it makes planning easier. The muddle-through periods that a soft company typically experiences can be reasonably well accommodated, allowing time for learning and for conflicting goals to be clarified and resolved. Knowledge of the market is gradually built up and the pace of hardening can be adjusted accordingly. The hardening process can even be halted or reversed if necessary, and the activity might continue in high-level bespoke consultancy only. At the other extreme, intermediate stages can be jumped and a soft company quickly becomes a hard company to make production into operation. Therefore, the low opportunity cost of entry into business and the flexibility with which the hardening process can be managed (Segal Quince & Partners, 1985).

This is especially evident in the bioscience fields, where the academias usually have no previous experience of industry, and besides the development period and the capital required is relatively long and substantial. As Galambos and Sturchio (1998) found, the scientific entrepreneurs who founded many of the early biotech firms frequently continue to hold university positions while they were getting their enterprises underway. Academic scientists used to play less important roles in the

ventures to which they had provided technical expertise. In biotechnology, however, they are often both inventors and entrepreneurs, line and staff, president as well as head of the labs.

(3) Component Technology Transfer

The ease with which soft companies can be formed will result in a large number of small companies, ready to supply relatively cheap but sophisticated consultancy reports or technical components or enabling technologies to resolve big companies' R&D problems. Therefore, big companies become increasingly alert to the effects which purchasing the components from the soft companies could have in enhancing the range and flexibility of their own products, or they become highly interested in having access to the enabling technologies to reinforce their innovation ability. As a result, once a soft company succeeds in producing a rather standardized product or offering a relatively mature technology, big companies will be willing to place a contract for its exclusive supply as a source of component or technology. It accordingly will lead to a pattern of big companies acquiring small but key technical suppliers as a means of assimilating new technology and of sustaining the pace of their own innovation. This pattern of integration can be described as "component technology transfer" and is becoming more marked among big pharmaceutical companies in biotechnology industry in the West (Bullock, 1983). By the mid-1990s, according to Galambos and Sturchio (1998), many pharmaceutical companies had built more elaborate contractual relations with biotech firms and sought through acquiring the biotech capabilities they needed[26].

(4) The Development of Network

Several of the leading biotech firms had collapsed or been acquired by other firms (Galambos and Sturchio, 1998). The growth of this acquisition routine is also important in stimulating the further development of a network of small research-based company entrepreneurs. This is due to the tendency for the scientific entrepreneurs to "recycle" themselves as they spin out to start again from the big companies that had

[26] It is called the *Hoffmann-La Roche* strategy in the study of Galambos and Sturchio (1998).

acquired their previous venture, as well as due to the growing financial, technical, management and marketing expertise required to develop young enterprises more rapidly. Thus there is a tendency for their second companies to skip the early stages and thus to become fully hardened more quickly. Therefore, the resilience of soft company model, the strong flow of potential entrepreneurs and a continuing source of new ideas from the university are central to the sustained expansion of this network and its expertise (Bullock, 1983).

In addition, Powell (1996) argued that the small research-based firms, particularly biotech firms, approach collaboration as a means of enhancing their capability for learning, so the firm would be willing to pursue multiple, related or overlapping cooperative opportunities to expand their competencies. Therefore, there are significant incidences of collaborations between the firms and thus numerous alliances within the network.

In short, the close relationship between the local firms around university as well as the close interaction between the university and the research-based firms make the network very dense and solid. Therefore, such a phenomenon can be self-sustaining and self-enforcing[27].

2.8. Innovation System

The development of the network can serve as an "innovation system" because it can provide fast access to new information, technological knowledge and research resources. Research alliance is an admission ticket to the "innovation system".

Bullock (20 February 1999) proposed that, one way of visualizing the development of this localized "innovation system" is as a pyramid, which is made up of biotech firms coming out from the university. There are great many tiny soft

[27] Such phenomenon first happened in the US, MIT and Stanford, and later in the UK, Cambridge and Oxford (Bullock, 1983; 3 February 1999). *Cambridge Phenomenon* was an example (Segal Quince & Partners, 1985).

start-ups at the bottom of the pyramid, and then a lot of small firms at the second level from the bottom, and then a number of bigger and harder ones above them, until at the top of the pyramid only a few well-established companies have worked their way through. The small firms can work up to the higher levels, but not all companies can keep growing, and only very few become very large and well established[28] - that is why this model is shaped like a pyramid (Figure 2.2). Some companies can not keep growing and so stay at the same level, while some slip back to the lower level or are acquired by other firms or even drop out from the pyramid altogether (Table 2.2). All the while, however, new soft start-ups from the university keep entering at the bottom and thereby broaden the base of the pyramid. In the real world, for example, Genentech is one of the few companies, which were initiated from soft start-ups and finally became large[29] (Table A.1, Appendix 1).

Table 2.2: Survival Index of U.S. Biotech Firms

	1999		2000		2001		2002	
	Number of firms	*% of total*	Number of firms	*% of total*	Number of firms	*% of total*	Number of firms	*% of total*
More than 5 years of cash	76	*25%*	148	*43%*	145	*43%*	79	*25%*
3-5 years of cash	29	*10%*	41	*12%*	37	*11%*	26	*8%*
2-3 years of cash	30	*10%*	29	*8%*	42	*12%*	37	*12%*
1-2 years of cash	59	*20%*	56	*16%*	59	*17%*	71	*22%*
Less than1 years of cash	107	*36%*	68	*20%*	59	*17%*	105	*33%*
Total public companies	**301**		**342**		**342**		**318**	

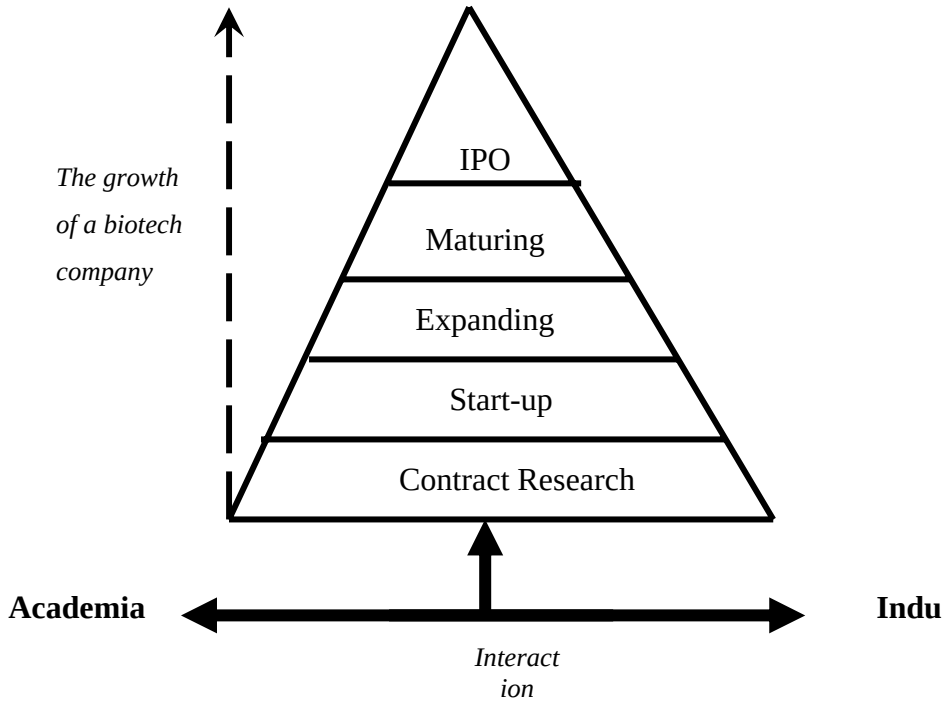
Source: Ernst & Young (2003), ***Resilience-Americas Biotechnology Report 2003.***

[28] The evidence and the reason that very few biotech firms become fully integrated pharmaceutical companies are illustrated as above (see the context under the subtitle of "The Impact on the Overall Industry Structure" and "The Role of Strategic Alliances" respectively).

[29] 1997 sales of top biotechnology companies as follows. Amgen: $2,303 million; Chiron: $1,313 million; Genentech: $967 million; Genzyme: $536 million; Alza: $466 million. The total industry sales for biotech products were estimated to be $13 billion (Galambos and Sturchio 1998). The figure of the total sales is an impressive sum for a young field but still $10 billion less than the sales of pharmaceutical giant Merck, and it roughly equals to that of GlaxoWellcome.

Outside this local pyramid are the very large national and international companies and they keep in touch with those small firms. In the future one can envisage that these very large companies will look to obtain a growing proportion of their innovative products or enabling technologies from the small firms inside the pyramid and that the pyramid will come to play a role as a supporting "innovation system" for the largest companies. The large companies' interaction with the small companies will keep the system lively and at the same time enables the larger companies to maintain their own technological vitality and to survive in the more competitive environment. In short, we can use the term *Symbiosis* to characterize the relationship between the large well-established companies and the small research-based firms[30] (Bullock, 20 February 1999) (Figure 2.2).

Figure 2.2: Innovation System for Biotechnology



A "*market*" for new technological ideas arises when the large established pharmaceutical companies display increasing demand for innovation vitality, and meanwhile, the formation of many small research-based biotech firms can supply new

[30] Even within such an innovation system (pyramid) can also see symbiotic relationships between the small biotech firms (Powell, 1996).

technological ideas (Gambardella, 1995). However, it is not a real "*market*" in a strict sense but creates and promotes such network relationships (*symbiosis*) in the drug innovation, which lie halfway between "*market*" and "*hierarchy*"[31] (Senker and Sharp, 1997).

2.9. Technology Transfer from the Academia to the Industry

The interaction between the academia and the high-tech industry is increasingly close and extensive. This is occurring at a time when universities face relatively tighter budgets or less research funding, and big companies need new sources of innovation to ensure their technological vitality. The rapid development of technologies is reshaping university policy regarding the relations between academic staffs and commercial firms. A new identity has emerged - the academia *entrepreneur*. What would once have been regarded as inappropriate for a top scientist will be increasingly viewed not just as legitimate but as desirable under the knowledge-based economy (Powell, 1996).

From the university's point of view, the existence of this mass of small research-based firms around campus appears to provide a sort of flexible and permeable membrane between academic research and industry. Small soft start-ups are thus seen as spanning the gap between the research of the university and the operations of the big company. Indeed, industrial innovation is now much more as a continuous process of the interaction between large companies and small research-based firms rather than as a series of major occasional pushes undertaken by the giants of the industry, particularly in biotech-related sectors (Bullock, 1983, Figure 2.2).

2.10. Policy Implications

[31] In other words, the boundaries of the firms can not be well-defined. Powell goes further. "Networks can be complex: they involve neither the explicit criteria of the market nor the well organized routines of the hierarchy. A basic assumption of network relationships is that parties are mutually dependent upon resources controlled by another, and that there are gains to be held by pooling resources." (Senker and Sharp, 1997)

The anxiety of economic planners to encourage the growth of so-called bio-clusters as a critical part of the infrastructure for the development of biotechnology has led to intensive examination of the economies of California, Massachusetts. These analyses have however tended to focus on the "innovation systems" there as they now exist and too little attention has been paid to understanding how these systems had emerged and grown. In particular, many visitors have departed with the notion that the main features that they need to replicate are physical science parks and a community of venture capitalists - and are then surprised when there is an inadequate flow of new technology companies to create a self sustaining cluster. Science parks and venture capitalists are helpful, but not usually sufficient to initiate the change process itself: they amplify, but do not initiate developments (Bullock, 13 March 1999).

So, what are the policy implications to build up such an "innovation system" for biotechnology, which calls for a "blurring of the boundaries" between science (basic research) and technology (applied research)? The critical factors that set off the change process, based on Bullock's arguments mentioned above, are supportive university policies that encourage individual scientists to set up their own enterprises to exploit their research (*Low Threshold Policies*), the development of an initially low risk, but resilient growth path by the new enterprises, based around contract research rather than immediate new product development (*Soft Companies*), and the readiness of large companies to purchase elements of their research and development needs from these new specialist technology suppliers (*Component Technology Transfer*). On the basis of the resulting trade, the finance community could then invest in the new companies and further accelerate their growth and development (Bullock, 3 February 1999).