CAN SMEs Survive? Static vs Dynamic Externalities in the French Biotechnology Industry

By

Lynn K. Mytelka & Julie Pellegrin*

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France ranks third among European countries in the development of a biotechnology industry (Ernst & Young:2000b,6). Many of its firms are small,young (OECD:2001b) and lack competitiveness compared to their American rivals (Sharp: 1995). Historically they have tended to under-exploit their public sector research base in biotechnology[1], in large part because of weak mechanisms for the transfer of technology from public research organisations to the small and medium-sized enterprise (SMEs) sector (Vavakova:2001a) coupled with both legal and financial obstacles to the creation of spin-offs (Senker & Sharp:1997). This is now changing as a result of significant new public sector investment in biotechnology programmes and the creation of a 'Nouveau Marche' in 1996, followed by the law on innovation of 1999 (Vavakova:2001b) and the national competitions that opened new financing opportunitites for start-ups. Towards the end of the 1990s, these policies stimulated an upsurge in new start-ups with 88 created in the last three years of the decade alone (Table 1) Most of these have located in only a few of France's regions.

Table 1
The Creation of New Biotechnology Firms in France

Years	Total	Percent of Total	Annual Average
< 1980	37	14.3	4
1980-90	48	18.5	5
1991-93	49	19.0	17
1994-96	37	14.3	12
1997-99	88	33.9	24
Total	259	100.0	

Source: "Societes de biotech:Le dynamisme est aux commandes" Pharmaceutiques, November 2000, No. 81, pp.53-57, p.53.

* Director of UNU/INTECH and Post-doctoral fellow at UNU/INTECH respectively.

[1] If scientific potential is measured, as in the French national survey in 2000, by comparing the share of publications in the life sciences emanating from within a region and the share of researchers in the life sciences located in a given region to the number of enterprises in biotechnology in the region, the gaps are quite remarkable. Over forty percent of the publications and nearly 40% of the researchers in the life sciences are located in the Ile-de-France region where 29% of the biotechnology firms are to be found. Rhone-Alpes, which is France's second largest region and provided 10% of the publications and 9% of the researchers in this field, had 8 percent of the enterprises. The reverse was true in Alsace and Midi-Pyrennees each of which accounts for roughly five percent of the researchers but 9 and 7 percent of the biotechnology firms respectively. (France:2000).

Clustering of this sort is not unusual for biotechnology firms. In North America, for example, the prime area of concentration is California which accounts for 29.7% of US biotechnology firms. Alone the San Francisco Bay area accounts for 14% of the biotechnology firms in the US (Ernst & Young:2000a,31). Within Europe, Cambridge has the largest concentration of firms in the UK and accounts for approximately 25% of the total or some 70 firms (Segal Quince Wickstead:2000b,4). The Ile de France region is closest to the Cambridge biotechnology cluster in size. Nearly 30 percent of the biotechnology firms in France are located there (France:2000). Smaller clusters on the periphery of France, however, have also emerged and a number of these are growing[2].

This paper presents preliminary results from a study of 19 SMEs[3] in the biotechnology industry and their relationship to five local clusters in three French regions: Alsace, Province-Cote d'Azur (PACA) and Midi-Pyrennees(MP). These are located around cities of Strasbourg, Marseille, Nimes, Montpellier and Toulouse. Generally they also include a 'technopole' anchored by a major university campus and/or public sector research institution with a spatially designated area created to house new start-ups (incubators, nurseries).

The project initially set out to assess the relative importance to the SME of proximity, as measured by the number and nature of their local and long distance partnerships. The findings were counterintuitive in many respects and to some extent might even be seen as contradictory. Three of these stand out in particular: the relatively short independent life span of biotechnology SMEs, the relatively large number of long-distance partnerships they maintain and the increasing role of regional actors in the financing of new biotechnology start-ups and of the clusters themselves, in the life cycle of these firms. These findings have led us to question the traditional arguments for clustering based on the importance of static externalities and local linkages and to emphasize instead the role that clustering plays in the transfer of 'new' knowledge and in the 'renewal' of the SME sector though not necessarily in supporting the survival of any given SME.

Section one situates this paper at the intersection of three bodies of literature, which have increasingly found a haven within the emerging school of evolutionary economics. These include the literature related to the process of innovation, to the role of clustering and to industrial dynamics. Section two describes the firms in our survey and presents a number of stylized facts concerning their life cycle paying particular attention to the origins of their founders, their financiers and their knowledge base. Section three analyzes their long distance and local partnerships and concludes by reconceptualizing the role of clusters in light of these findings.

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[2] A recently published survey of biotechnology firms revealed that the share of new enterprises going to the Auvergne, Loire, Rhone-Alpes and Midi Pyrennees regions exceeds their current share in total biotechnology firms across all regions. (France:2000).

[3] Twenty firms were intervieweed and one was subsequently reclassified outside of the biotechnology industry. The project also undertook interviews with 20 SMEs in information and communications technology. These will be reported upon at a later date.

1. Learning, Innovation and Linkages

Over the past several decades, production has become more knowledge-intensive and the range of knowledge inputs has extend beyond research and development (R&D) to include training, improvements in product design and quality, modifications to production processes that bring costs down, increase efficiency and ensure environmental sustainability, changes in organizational routines, creativity in marketing, and enhanced capacity to manage a wide variety of linkages and collaborative relationships with competitors, suppliers, clients, financing institutions, research and productivity centers. The latter skill is particularly important in stimulating innovation which is now widely believed to be an interactive process in which enterprises, in interaction with each other and supported by institutions and organizations, such as industry associations, universities, productivity centers, standard setting bodies, information gathering and analysis services, banking and other financing mechanisms, play a key role in bringing new products, processes and forms of organization into economic use (Lundvall:1988,.1992; Nelson:1993).

Much of this knowledge is tacit, embodied within the firm and in clusters of firms and related supplier and service industries (Brusco: 1982, Lundvall: 1992). As global competition intensified and became more innovation-based, attention was increasingly drawn to the relationship between such spatial clusters and innovation systems (Mytelka:2000; Mytelka & Farinelli: 2000). The latter lays emphasis on the interactive process in which enterprises in interaction with each other and supported by institutions[4] and organizations –such as industry associations, R&D, innovation and productivity centers, standard setting bodies, university and vocational training centers, information gathering and analysis services and banking and other financing mechanisms—play a key role in bringing new products, new processes and new forms of organization into economic use (Nelson & Winter:1982, Freeman & Perez:1988, Lundvall:1988; Kline & Rosenberg:1986).

Since Alfred Marshall's pioneering work on Italian industrial districts (1890), clustering is believed to offer unique opportunities for small and medium-sized enterprises to engage in the wide array of domestic linkages between users and producers and between the knowledge producing sector (universities and R&D institutes) and the goods and services producing sectors of an economy that stimulate learning and innovation Agglomerations such as these, for example, are said to generate **positive externalities** through the availability of skilled labor, of certain kinds of infrastructure, of innovation-generating informal exchanges and learning made possible through the adoption of conventions. Stable **vertical relationships** between users and producers can reduce the costs related to information and communication, the risks associated with the introduction of new products and the time needed to move an innovation from the laboratory or design table to market). **Horizontal collaboration** between same- sector small and medium-sized enterprises can also yield **'collective efficiencies'** in the form of reduced transaction costs,

[4] Formal definitions of "institutions" stress the "persistent and connected set of rules, formal and informal, that prescribe behavioral roles, constrain activity and shape expectations…they…give order to expectations and allow actors to coordinate under conditions of uncertainty" (Storper: 1998,24).

accelerated innovation through more rapid problem- solving and greater market access[5].

Despite its diversity in disciplinary and theoretical perspectives, much of this literature assigns particular importance to clustering in the survivability and growth of SMEs. For the most part this stems from two fundamental and yet somewhat static advantages of proximity: externalities of various sorts and linkages. When these are not present, there is a sense of disappointment. Schmitz (2000,334), for example, argues that cooperation amongst SMEs in a cluster is particularly critical in times of crisis, yet his study shows considerable variation across clusters. Nachum and Keeble (2001,5) point out that while "…linkages among firms based in proximity to each other are vital for their competitiveness… [these] are insufficient by themselves to gain access to expertise and knowledge which are increasingly shaped on a global basis". Looking specifically at US biotechnology firms, Audretsch and Stephan would agree. Fully two thirds of the links that the firms in their study maintained with university-based scientists, were non-local. They thus concluded that "…the proponents of the new growth economics may have overemphasized the importance of geographic linkages in facilitating knowledge spillovers" (Audretsch & Stephan:1994,23).

This paper does not proceed from the assumption that all clusters are innovation systems. Looking solely within the cluster, several factors help to account for this. Amongst these are the size of the cluster, the configuration of actors within it, their competences, their habits and practices with regard to learning, collaboration and investment and the extensiveness and nature of their linkages Transformation of clusters into innovation systems, moreover, is not an automatic process. (Mytelka:2000; Mytelka & Farinelli:2001). When, where and how this takes place can thus be regarded as contingent.

In a globalized world economy, moreover, cluster dynamics must be taken in conjunction with industrial dynamics. The later play a critical role in shaping the opportunities for learning and innovation and in constraining the survival of start-ups and SMEs (Mytelka:2000). Firm size, notably the "appropriability advantages of large firms over small ones" (Nelson and Winter:1982,279), the pace of technological change and the nature of competition within the industry each tend to render the existence of SMES more precarious and may be reinforcing.. Malerba and Orsenigo thus raise the question of whether, within the context of technological regimes characterized by different combinations "of opportunity and appropriability conditions, degrees of cumulativeness of technological knowledge and characteristics of the relevant knowledge base" (1996:60), the coexistence of larger and small firms may only be possible during periods in which a new technology is emerging.

Biotechnology in the 1970s and early 1980s clearly fit this characterization. It occupied a field of knowledge that older firms had not mastered. A window of opportunity thus existed for the emergence and growth of new biotechnology firms, as in Schumpeter's classic model of 'creative destruction' (Mark I). Biotechnology, moreover, enjoyed wide application opportunities and difficulties in patenting life

[5] This paragraph draws on a considerable body of literature. See for example, Marshall :1890; Brusco: 1986; Freeman: 1988, 1992; Lundvall:1988, 1992; Maskell:1996, Maskell & Malmberg:1999; Nelson: 1993; Schmitz:1997,:2000; Storper:1995.

forms in this earlier period, limited possibilities for knowledge appropriation. Again this favoured the creation of new firms The rate of new firm creation in this period, however, slowed down considerably towards the middle of the 1980s as the high cost of product development, notably clinical testing of biopharmaceuticals and the slow pace of commercialisation led to a drop in venture capital investments in this emerging technology and an increase in vertical integration.(Malerba & Orsenigo:1996,77-78) [6] This period corresponds more closely to the Schumpeterian phase of concentration associated with the hypothesis concerning the link between size and innovation (Mark II). Even then,

> despite the sweeping nature of the molecular revolution, incumbent pharmaceuticals companies have not been swept away by new entrants…the relationships between incumbents and entrants has entailed not only competition, but also cooperation…and perhaps most importantly, the revolution did not create a monolithic new paradigm of technical development, but instead created two quite distinct trajectories of development that have only recently been combined: the use of biotechnology [genetic engineering] as a tool for the production of proteins whose therapeutic properties were already well understood, and the use of biotechnology [genetics and molecular biology] as a tool in the search for entirely new[7] therapies. (Henderson,Osenigo & Pisano:2000,267-8).

As we shall see, the biotechnology industry, thus, continues to evolve and so, too, does the position of SMEs within it. Choice sets available to the firm "…are not known and given." (Nelson & Winter:1982,279) and new regional drivers appear to be making an appearance. The following two sections approach the interrelationship between clustering, innovation sytems and industrial dynamics from this more dynamic and evolutionary perspective.

2. The Survey

To identify SMEs that were involved in long distance partnering and yet had ample opportunity to develop local partnerships, access was obtained to a data base composed of all European firms that were partners in the biotechnology programmes of the EU (Biomed 1 & 2) and Eureka from their inception through the late 1990s. From this group of firms, those that were co-located in specific 'technopolitan' region as identified by the French Association of Technopoles (France Technopoles: 1999/2000) were selected. Given the small number of French biotechnology firms in the 1980s and 1990s this did not provide a sufficiently large data set for analytical purposes. To these firms, therefore, were added other firms localized within the same

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[6] The Genentech story is typical of this period . "In 1987, Genentech introduced the first important product of genetic engineering on the market: the tissue plasminogen activator (tpa). Genentech's product was initially an enormous commercial success and the product was sold at very high prices. Shortly thereafter, however, similar new products chararcterized by higher quality and lower prices were launched by competing companies. Genentech's efforts to get to the market first and to sustain all the commercialization of the product on its own left the company in a difficult financial situation, ultimately leading to its acquisition by HLR" [Hoffman-LaRoche]. Malerba & Orsenigo:1996,78-79.

[7] In some cases this also involved tools that speeded the discovery of new 'small molecules' (combinatorial chemistry) for the production of synthetic drugs.

five clusters and identified through data published in *L'Usine Nouvelle* and other specialized publications or provided by local and regional authorities. This enabled us to expand the number of firms in the survey to a total of 20 SMEs one of which was subsequently reclassified out of the biotechnology industry. Our group of firms roughly corresponds to the pattern of growth in the French biotechnology industry to 1990. It, however, underestimates the group of firms in the period 1990 through 1996 and over represents those in the most recent period. Of the 19 firms covered in this study, five (26.3%) were created prior to 1990, 4 (21%) between 1990 and 1997 and ten (53%)in the period 1998-2000.

These firms can be described in generational terms. First generation firms, those created between 1974 and 1992 are quite different in a number of respects from those created after 1995 and several of the former were progenitors of 'second generation' firms. We have distinguished these spin-offs from other new start-ups whose founders had not previously apprenticed in a biotechnology firm, as this will later be shown to have relevance in reconceptualizing the role that clustering plays in the sustainability and growth of the industry as opposed to the survival of any given firm within it.

First generation firms also have significantly different patterns of initial financing from second generation firms. (Table 2). First generation firms relied more on national public and private capital and only one of the seven had a regional public financing partner. Among the second generation firms, in contrast, eleven of the 12 firms had some sort of regional financing. Eight of the 12 had public regional financing partners and 7 of the 12 had regional private capital investors. Of the three spin offs located in the Marseille technopole of Luminy one had regional public funds and two regional private funds. All three of the second generation firms located in Nimes, had local financing. The spin-off and one of the start-ups had both public and private local financing and the other new start up had regional private investors. Of the two new start ups in Montpellier, one had a regional public investor as did the only new start-up in Strasbourg. All three of the second generation firms in Toulouse had regional public funds and of these, the one spin-off also had private local investment.

Table 2
Generational Differences in Financing and Ownership among firms in the survey
In numbers of enterprises

			Initial Sources of Financing					
	Firms	Takeover	Own funds	Regional		National		Int'l
Generation				Public	Pvt	Public	Pvt	
First[a]	7	5	1	1	0	1	3	1
Spin offs[b]	5	0	1	3	4	1	4	2
Start ups[c]	7	0	4	5	3	3	3	2
Total	19	5	6	9	7	5	10	5

(a) Of these 2 were created in the 1970s, 3 in the 1980s, one in 1990 and one in 1992.
(b) Of the spin offs from first generation firms, one was created in 1985, 2 in 1998 and 2 in 1999.
(c) Of the new start ups, one was created in 1995, 5 in 1999 and 1 in 2000.

Of the 12 second generation firms, 9 also had some form of national financing. The point here, however, is not whether second generation firms continued to benefit from national or foreign investment but rather the major role that regional investors began to play in the second half of the 1990s.

Table 2 also reveals another distinguishing feature of first generation firms –the age- relatedness of takeovers. Five of the seven 'first generation' firms have been the object of takeovers with the average time from establishment to takeover of between six and eight years. Of these five, three were obliged to seek new partners when original shareholders changed their strategies. One was the object of takeover by a minority shareholder and the second by an unaffiliated firm. In both of these cases financial weaknesses had made growth difficult. Of the remaining two firms, financial difficulties also emerged, but one faught takeovers, went bankrupt and managed to climb out of debt but has stagnated ever since and the other avoided takeover through infusions of venture capital but at the expense of instability in management. Even without a change in shareholder strategy, all of these firms had begun to face problems that related to their financial structure relative to their need for financing either to expand the knowledge base or to overcome growth problems associated with the existing strategy of the firm, notably its choice between focus and diversification.

Only two of the 12 second generation firms are reaching the critical six year mark and both have spontaneously evoked the problem of financing. These two firms have strong regional financing but also international partners[8]. One is relying on its overseas partner to substantially increase its capital in the firm though this would likely shift the 'centre of gravity' abroad. Another expressed a preference for an initial public offering rather than a takeover. With the emergence of the Nouveau Marche, this option is now open to the firm. It is also possible that the increased importance of regional finance may reduce the vulnerability of SMEs located within technopolitan regions or clusters to takeover in the future.

Generational differences are also evident in the origins of the founders of the firms in our survey (Table 3), though not in the source of their technology. Founders of first generation firms are overwhelmingly from the research sector, though two of the seven were established by researchers with experience in pharmaceutical firms, one French and one American. In the first instance, the founder left his firm to establish a start-up in a different region – the region of his technology partner, the Centre d'Immunologie located on the Luminy campus of the University of Marseille. He brought into the partnership a technique for blood-based diagnostics that he had developed in his previous firm. In the second case, the researcher remained in the region, Strasbourg, but struck out in an entirely new direction , founding a company to develop and manufacture kits to test for pregnancy Among second generation firms, five are spin-offs from first generation biotechnology firms and the founders had thus all apprenticed in first generation biotechnology firms.. Of these five, three were spin-offs in the wake of a takeover and all three remained in the region . None of the founders of these spin-offs left with technology from the former firm and all three returned to Luminy to exploit technology from the research sector there.

[8] Only four of the 12 second generation firms have international partners, the other two,however, are four years younger and were created only in 1999.

Similarly, in the fourth case, the individual left his firm of origin but remained in Toulouse and initially established the enterprise in the "Hall G. Durant' , a sort of incubator on the University of Toulouse campus. In the remaining case, an inter-regional move took place as the founder left Strasbourg for Nimes and settled into the Parc Georges Besse to pursue a strategy based on in-house research and development of intellectual property acquired through partnerships. Of the seven new startups the cycle of first generation firms appears to be repeating itself with, 5 of the 7 founders (71%) originating in the research sector and two from the business sector.

Table 3
Origins of the Founders and of the Technology

Generations (number of firms)	Origins of the Founders		Origin of the Technology	
	Research Sector	Business sector	Public sector	Private sector
First (7)	5	2*	6	(1)****
Spin-offs (5)	0	5**	5	1
Start-ups (7)	5	2***	7	0
Total	10	9	18	1

*The individual had been a researcher in the business sector
**Three of the five had been researchers in their previous firms.
***Both were initially researchers.
****Part of the technological package came from the private sector

Despite the importance of spin-offs from existing companies, new start-ups emerging from the research sector are likely to remain a potent force in the development of the French biotechology industry for sometime to come. This is illustrated by the overwhelming importance of public sector research as the knowledge base in both first and second generation firms irrespective of whether the founders came from the research or business sector. This will likely continue as a result of the stimulus provided by the availability of public funds for new start-ups including the national competition held annually by the Ministry of National Education Research and Technology (MINERT) for funds to create new companies. In 1999, awards of over a million francs each were given to 79 competitors judged to be within three to six months of being able to establish their firms and a further 165 candidates were awarded and average of 200,000FF each to finance the studies needed to create a new company. Of these 244 award winners, 60 of the firms (25%) were identifiably in biotechnology . Of the total nearly 40% were researchers in the public research sector. (Minert:1999). The second competition generated a further 59 potential biotechnology start-ups (Min. de la Recherche:2000).

Lastly, and of some importance for the thesis that the evolution of the industry globally helps to shape the opportunities and constraints on local choice sets, is the finding that generational differences are also evident in the product structure and orientation of the firms.Table 4 reveals that first generation firms, as might be expected given the evolution of the industry and it technological trajectory, are heavily concentrated in the area of diagnostics (57%), whereas 50% of the second generation firms are involved in the newer area, of drug discovery especially through genomic research.

Table 4
Changing Areas of Specialization Overtime in French Biotechnology SMEs
in numbers of firms

Generation	Diagnostics	Drug discovery	Drug Delivery	Detection*	Total
First	4	1	2	0	7
Second	2	6	2	2	12
Total	6	7	4	2	19

*Detection largely concerns the agricultural biotechnology sector and in particular contaminants in food products.

3. Clusters, New Competences and Renewal

As might be expected in a science-based industry such as biotechnology, clusters are often anchored by a research-oriented 'technopole', a specially designated and prepared space located on the campus of a university or a site in proximity to a public sector research institution. In analyzing the physical location of the firms in our survey, however, it was necessary to distinguish the 'research oriented' technopole, such as Luminy, from 'support-oriented ' technopoles in which facilities and infrastructure are provided to new start-ups along with a variety of supporting services such as assistance in drawing up a business plan or in securing financing but no research institution is located within the geographical space of the technopole. Parc Georges Besse in Nimes and Cap Alpha in Montpellier are typical of the 'support-oriented' technopoles covered in this study. Mixed technopoles are found less frequently. In the case of Illkirch in the greater Strasbourg region, this is probably influenced by the development of BioValley, a conceptual space and network linking biotechnology firms in the adjacent regions of France, Switerland and Germany.(Table 5).

Table 5
Enterprise Location by Generation and by Type of Technopole

Generation	Outside the Technopole	Orientation of Technopole			Total
		Research	Support	mixed	
First	3	3	0	1	7
Second	0	7	4	1	12
Total	3	10	4	2	19

Of the 19 firms in this study, ten were initially located in research-oriented technopoles, two in mixed technopoles and four, all second generation firms, were located in support-oriented technopoles (Table 5). Even then, with the exception of Nimes, the cluster as a whole had strong university biotechnology research faculties

and/or Institutes that belong to the Centre National de Recherche Scientifique (CNRS), the Institut national de la Sante et de la Recherche Medicale (INSERM) or another national research institution. This applies, as well, to the three first generation firms that were not physically located within a technopole. All of these were situated in clusters with a strong biotechnology research base.

It is also important to note that all first and second generation firms which had initially located within technopoles, moved out only when faced with space constraints[9] and all relocated to sites within the cluster. Moreover, as we saw earlier, all three spin-offs from one such company moved back to the technopole of origin. Clearly, then, there is something that keeps graduates of the technopoles in the cluster, induces spin-offs to remain there and attracts new start-ups to these agglomerations. But what is that 'something'?

The cluster literature suggests that we look to externalities that reduce search and transaction costs as part of the 'glue' holding the cluster together. Yet the firms in our survey illustrate that the static advantages of infrastructure or a pool of skilled labour are no longer important once the start-up moves out of an incubator or ceases to share facilities with a laboratory there. Firms that have done so all emphasized in the interviews that they were paying the going rate for their facilities and only a few mentioned the cluster as an important source of skilled labour in the classic sense of this term. This is the critical point. It was not the 'skills' that mattered but the newness of them. Thus it was not simply the pool of trained scientists but rather the ability to access **degree candidates** or **newly minted Ph.Ds** for their closeness to the frontier of knowledge and the originality of their thinking. These special knowledge competences and not merely the skills that come from education and training are what research-oriented clusters provide.

The importance of newness emerges again from an analysis of the linkages that these firms have created. Both the cluster and the innovation literature emphasize the role of interactions as either the glue that binds the cluster together or as a means to stimulate innovation. These interactions can be proxied by partnerships involving joint research, joint development, input sourcing and relationships with clients.

Although most of the firms in our survey are physically proximate, this is only party reflected in their alliance patterns. If physical proximity were critical in the formation of partnerships, we would expect that firms that had purposely chosen to locate in a cluster, as the firms in our survey did, would mainly partner with other actors in the cluster. Through interviews in which the firms discussed the nature and importance of their partnerships, it was possible to assess the extensiveness of partnering activity by these firms and its directionality . Table 6 classifies these 19 firms into two categories, those with few alliances and those with many and within these two categories into firms with mainly local or mainly long distance partnerships.. By dividing the firms into first and second generation it was also possible to simulate the alliance pattern in biotechnology firms over time.

[9] This was particularly true in the Luminy technopole on the campus of the University of Marseille which is locked into a struggle with environmentalists over further expansion into a national park..

Table 6 summarizes the pattern of partnerships of these firms. It shows that nearly 50 percent of the firms (9 of the 19) mainly have local partners. But as one would expect, this is true only when the firms have few alliances and six of the seven firms who do, are second generation. What might also be anticipated is the way in which the extensiveness of partnering activity inevitably leads to a widening of the geographical spread of these alliances. Of the 11 firms that have many alliances, 9 mainly have partners at long distance. Of importance here is the large number of new start-ups that fall into this category. Normally we would expect to find that newer firms had fewer alliances and given their origins in the cluster would presumably partner locally. This was born out by the survey results

Table 6
Alliance Patterns by Generation

Generation	Few Alliances			Many Alliances		
	Mainly local	Mainly long distance	Total	Mainly local	Mainly long distance	Total
First	1	1	2	0	5	5
Second	6	0	6	2	4	6
Total	7	1	8	2	9	11

What is remarkable among second generation firms in this survey, most of which are barely two years old, is the speed with which they have moved to long distance partnering. While local linkages remain important to these firms, long distance partnerships came in quite quickly as a complement. It is thus not a question of either/or, but of both.

Why this is so becomes clearer from an analysis of their partners and partnerships. When the type of local partner is taken into consideration, in nearly all cases, it a local research institution[10] and not a firm, as the literature on the development of the biopharmaceutical industry would lead us to believe. But a substantial number of their long distance partners also come from the research, rather than the enterprise sector. This is somewhat unexpected as the literature on the dynamics in this industry, particularly the drug-related specializations within it, stresse the importance of alliances with large pharmaceutical firms as the means to reduce the high cost of clinical testing and to acquire the specialized skills needed to secure FDA certification.

The logic behind the close links to both the local and the long distance research sector, however, lies less in the market for goods than in the market for knowledge.. The competence based nature of these alliances emerges from a closer look at the reasons for partnering. All seven of the first generation firms gave joint development as one reason and six of the seven, some **85 percent, gave "access to technology"** and the need to reduce innovation time as two others. Even among second generation firms, fully **75 percent cited** "**access to technology",** along with joint development and the need to reduce the costs and risks of innovation as paramount. As Saviotti has argued, along the lines of Adam Smith's earlier

[10] We include here both university laboratories and local institutes of national research institutions.

observations concerning the division of labour within the firm , the characteristics of the learning process in this industry are such that the knowledge base of a firm limits its own extension. (Saviotti:1998). Quite early in the life cycle of SMEs in the biotechnology industry, therefore, widening the knowledge-base as the industry evolves becomes critical. Without exception, the firms in our survey emphasized that, this meant searching for the very best competences, irrespective of where they are found.

Even then survival of the firm as an independent actor is not assured. The gap between the firm's strategies and the evolution of the global industry creates new sets of choices to be managed. How they do so becomes critical but fraught with uncertainties as Nelson and Winter pointed out

> In an evolutionary theory of the sort that we develop, the nature of the "economic problem" is fundamentally different from that depicted in contemporary orthodox theory. The latter view choice sets as known and given. The economic problem is to pick the best possible production and distribution, given that set of alternatives….Although some choices may be clearly worse than others, there is no choice that is clearly best ex ante….Firms facing the same market signals respond differently, and more so if the signals are relatively novel." (Nelson & Winter:1982,276)

For SMEs in biotechnology, two sets of choices are particularly difficult to resolve. The first is the tension beween a strategy of specialization versus one of diversification. The second is the gap between their initial financial structure and their needs for financing either to expand the knowledge base or to overcome growth problems associated with the existing strategy of the firm. Choices here are shaped by both the availability of financing and the pace of technological change in the global industry. Driving the biotechnology industry over its short thirty year history have been a number of technological ruptures and several financing cycles. These have created new opportunities and constraints for the survivability of SMES. France is a latecomer to the industry. It is only within the past few years that regional funds, for example, have become available to finance new firms. Whether this will strengthen opportunities for the SMEs of today to survive and grow is still not evident.

What is clear, however, is the role that clusters are playing in the renewal of the industry as a whole. Underlying the ability of clusters to generate new knowledge and to stimulate the emergence of new generations of firms are a set of policies that have supported public sector research, decentralized initiative to the regional level and created new mechanisms to finance start ups. From an evolutionary perspective that emphasizes the tacitness of knowledge, the importance of clusters, then, is twofold: to generate the new and to renew.

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