Clustering, Long Distance Partnerships and the SME: A Study of the French Biotechnology Sector

By

Lynn K. Mytelka[1]

Abstract

This paper examines the relationship between clustering and long distance partnering from the perspective of evolutionary economics and the innovation systems literature. Specifically, it brings into this framework business and management approaches and regional economic theories to analyze the preference for co-location in clusters and the extensiveness and degree of complementarity or substitutability between long distance and local partnerships pursued by small and medium-sized enterprises (SMEs) in the biotechnology sector. The study covers the partnering activity of 25 dedicated biotechnology SMEs located within six clusters on the periphery of France.

Keywords: cluster, innovation system, SME, biotechnology, France, knowledge flows, R&D partnerships

1. Introduction

Since the 1970s both inter-firm and university-enterprise research and development (R&D) partnerships have been regarded as new and promising directions for firms in a world of rapid technological change. Several bodies of literature have dealt with these collaborative partnerships. Theorists from an evolutionary economics perspective emphasize the importance of interaction between clients and suppliers and between agents involved in research and those in production as a stimulus to a process of innovation (Freeman:1992, Nelson & Winter:1982; Lundvall:1988). Their focus is on learning and knowledge flows as the glue that binds together this network of economic agents who, along with the institutions and policies that influence their behaviour and performance, constitute an innovation system (Nelson:1993; Lundvall,1992).

Innovation systems by definition involve a process of continuous innovation, bringing new products, new processes and new forms or organization into economic

[1] This paper grows out of a research project undertaken in collaboration with Julie Pellegin. A first paper on the biotechnology sector was presented in Aarlborg at the Druid meeting in June 2001 (Mytelka & Pellegrin:2001). A second deals comparatively with both biotechnology and information and communications technology firms (Mytelka & Pellegrin:2002 forthcoming). I wish to thank the Social Sciences and Humanities council of Canada for financial support in undertaking this project, Pier Paolo Saviotti and Paulo Guerreri for their very useful comments and Yannis Caloghirou and his colleagues for access to the database on participation in European programmes from which the first set of firms for this study were drawn.

use. As imperfect information is an integral part of this process, adaptive behaviour through the interaction of economic agents and of policymakers is essential (Metcalfe: 1997). Innovation systems are thus most often conceptualised in geographical and policy terms at either the national or local levels but attention to sector-based innovation systems has also emerged, particularly in the biotechnology and pharmaceutical sectors (Malerba & Orsenigo:1996; Malerba: 1999; Pyka & Saviotti:2001).

More recently, the openness of national innovation systems to flows of knowledge from elsewhere through, for example, labour mobility, foreign direct investment and a variety of long distance partnerships has come to be recognized. Cantwell & Piscitello: 2000; Mytelka: 2000). Few studies, however, have systematically explored the relative importance of local and long distance partnerships, the types of agents that engage in them or their purpose. Instead, even when working from an innovation systems or evolutionary economics approach, each of these types of partnering activity has been dealt with separately by two discrete bodies of literature.

Local linkages, especially trust-based partnerships, have been the preserve of regional economists and geographers who have traditionally stressed the role of proximity in facilitating the informal knowledge flows that stimulate innovation in clusters whether these are based on high tech or traditional industries (Saxenian: 1994, Storper: 1995; Maskell: 2001). In the transformation of both types of industries, the growing complexity of the technological competences required and hence the need for a wider knowledge base than most firms can support in-house has been emphasized. (Mytelka & Farinelli:2000; Smith:2000). Local public sector research, it was thus argued, would benefit private sector innovation and indeed, strong evidence of positive externalities for innovation in private firms was found in a recent study of knowledge flows at the local (departmental) level in France (Autant-Bernard:2001).

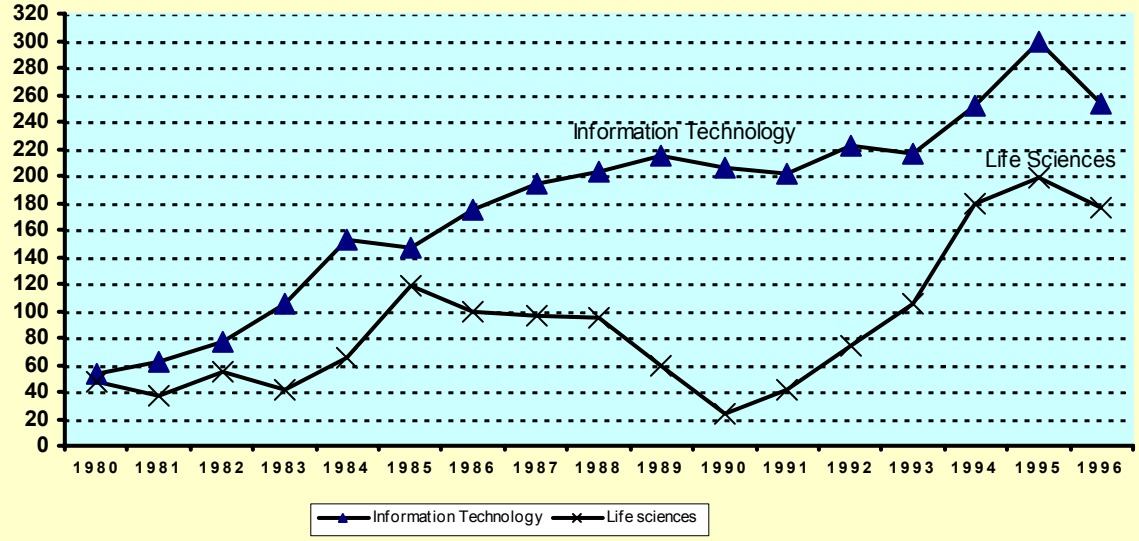
Proximity and the opportunity to create linkages to universities and research institutions that it affords, is thought to be especially important in the science-intensive sectors and where new start-ups and SMEs are concerned. This is arguably one of the underlying strengths in the development of biotechnology in the Cambridge area (Segal Quince Wicksteed:2000; UK:1999) and information technology in Silicon Valley. The phenomenal development of these two clusters thus motivated the creation of science parks and technopoles elsewhere across the United States and Europe. By 2001, for example, there were 44 registered 'technopoles' in France (Vavakova:2001).

Long distance partnerships, for the most part, are studied by those working from a business and management perspective (Granstrand et. al:1992; Hagedoorn:1995; Hood and Young: 2000). While there is an acknowledged tendency for firms in biotechnology and information and communications technology (ICT) to cluster, data collected by these researchers show that firms in these two sectors are also active in longer distance inter-firm partnerships. During the 1980s and into the 1990s inter-firm R&D partnerships rose steeply from roughly 200 agreements in 1980 to a high of nearly 700 agreements in 1995 (Figure 1). Uncertainty and the need for flexibility provided much of the impetus for this dramatic increase in strategic

partnering activity. Uncertainty resulted from the rapid pace of innovation, the erosion of frontiers between industries and the discontinuities in what were previously incremental technological trajectories.[2] Combined with the globalisation of innovation-based competition, earlier strategies of vertical integration and cartelisation designed to reduce the uncertainties, risks and costs associated with investments in scale and knowledge production became less effective. Flexibility was thus enhanced relative to mergers and acquisitions in this period (Mytelka & Delapierre:1999). In most data bases the 'life sciences' as the biopharmaceutical and bio-agriculture sectors were briefly called in the 1990s,[3] were thus second only to information and communications technology in the number of R&D partnerships formed each year.[4]

Figure One

Number of inter-firm technology agreements in Information Technology and Life Sciences (1980-96)



Source: Merit / UNCTAD Database

[2] Digitial switching in the communications industry, for example, is not an incremental extension of earlier electro-mechanical switching technology, nor are compact discs based on laser technology derive logically from earlier phonograph records.

[3] Prior to the revolution in molecular biology, the pharmaceutical industry was largely chemical based and little in the nature of the underlying research gave rise to congruence in the interests of seed companies and pharmaceutical firms. During the 1990s this led to a number of mergers and then demergers across industry boundaries.

[4] Data provided by Thomson Financial data services from their stategic partnering data base,for example, also showed that biotechnology came second to information and communications technology and well ahead of energy and automobiles in all years from 1994 to 1999. The exception to this generalization is in the research joint venture database compiled by Nick Vonortas from among RJVs registered in the United states over the years 1985-1995. Biotechnology, even when combined with pharmaceutical RJVs came well behind such sectors as environment, advanced materials and energy (Vonortas :1997).

In addition to the broad underlying changes that stimulated the growth of strategic partnering in other sectors, firms in biopharmaceuticals had still other reasons for forming R&D partnerships. The reluctance of large pharmaceutical firms to invest in a significantly different knowledge-base –biological as opposed to chemical-- and one with a potentially long time horizon, initially led large pharmaceutical firms to play a game of watchful waiting. As small dedicated biotechnology firms faced not only the high cost of research but the heavy investments needed for product development, clinical testing[5] and marketing, partnerships between large pharmaceutical firms and small dedicated biotechnology firms were highly beneficial to both parties in the early phase of the biotechnology sector's life cycle. But as the large diversified firms acquired the necessary competences in the new scientific areas required by biotechnology, the extensiveness of such partnering activity would likely to diminish (Saviotti: 2001).

Moreover, in a maturing innovative biotechnology environment, as Schumpeter and Chandler lead us to expect, not only the volume but also the type of partnerships would likely change. The 1990s fit this picture. Biotechnology was established, the first products were on the market, larger firms had overcome their reluctance to move into unchartered waters and had developed competences in-house, which could now be enhanced through mergers and acquisitions. The search for scale economies and market reach, moreover, were propelling large pharmaceutical, chemical and seed companies into mega-mergers amongst themselves (Mytelka & Delapierre: 1999). M&As involving smaller biotechnology firms also increased, reflecting the growing need "…to reach critical mass and develop activities which are integrated horizontally (within a particular pathology or application) or vertically (development of own products)". (Ernst & Young:2001,13).

Along with the rise in M&As in the latter half of the 1990s, non-equity biotechnology partnerships remained robust with an average of nearly 500 new partnerships formed each year. (Hagedoorn:2001). The nodal importance of large science-based firms, however, had changed. This is reflected in the relative intensity of partnering by small and large firms in this sector. By the end of the decade, "…the alliance intensity of large firms exceed(ed) the intensity found for small firms" (Hagedoorn & Roijakkers: 2001,23).

For Hagedoorn and Roijakkers, however, a small firm is one with up to 500 employees. Expectations might be different for firms with less than 50 employees and even if competitive conditions were conducive to mergers and acquisitions and large pharmaceutical firms had acquired the necessary biological competences, the uncertainties, risks and costs of research in biotechnology still create a need for flexibility and thus for partnering. But does the literature suggest that the truly small firms –new start-ups and spin-offs, for example—with few employees, nearly all of whom are engaged in research, would be likely candidates for long-distance strategic partnering. Or should we rather accept the argument advanced in the regional and evolutionary economics literature that interaction with proximate agents is particularly important for SMEs. And if we do, what kind of partners would they seek-- other small dedicated biotechnology firms (DBFs), large firms or universities and research

[5] Clinical testing and marketing, moreover, were activities in which the large, integrated pharmaceutical companies had acquired considerable experience.

institutes? And lastly, what might be the objectives of such partnerships? Would SMEs in the early phase of their life cycle, as some of the literature suggests, primarily seek alliances for financing purposes, particularly to support product development and the movement of products to market? If these were indeed the needs of small biotechnology firms, would they be met through long distance or local partnerships? Would more established biotechnology firms, those at a later phase in their life cycle, share the same partnering objectives and partner preferences? Would location thus continue to matter and if so, for what reasons.

This project set out to assess the relative importance to the SME of proximity, as measured by the extent and nature of their local and long distance partnerships. It presents results from a study of 25 SMEs in the biotechnology sector located in six clusters in five French regions: Alsace, Province-Cote d'Azur (PACA), Rhone-Alpes, Languedoc-Roussillon and Midi-Pyrennees(MP). The clusters are located around the provincial cities of Strasbourg, Marseille, Lyon, Nimes, Montpellier and Toulouse. Generally these clusters 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).

2. The Survey

The Ile de France region centred on Paris is France's pre-eminent region and accounts for between one third and one half[6], of the country's 'technological potential' and its biotechnology firms. (OST:2000). Of France's 21 other regions, Rhone-Alpes, PACA, Alsace, Languedoc-Roussillon and Midi-Pyrennees account for a further third. Each has become home to a vibrant cluster of biotechnology firms. Located on the periphery of France, cluster externalities, local linkages and knowledge flows are more easily identified than in the more dispersed Ile de France region with its many distinct centres of intensive interactivity located in proximity to different university centres, research institutes and technopoles[7].

To identify SMEs that were involved in long distance partnering and yet had ample opportunity to develop local partnerships, access was obtained to a database 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[8]. From this group of firms, those that were co-located in specific 'technopolitan' regions 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 five clusters and identified through data published in *L'Usine Nouvelle* and other

[6] This depends upon the indicator used. Of the 71,609 researchers in public sector institutions in 1996, Ile de France, for example, accounted for 32.7%, Rhones-Alpes for 10.6%, PACA for 8.7%, Midi-Pyrenees for 7.1%; Languedoc-Rousillon for 5.5% and Alsace for 3.3% (OST:2000,168) . In terms of biotechnology –related publications, Ile de France accounted for only 25.5% of the French total in 1997, a decline of ten percentage points since 1985 as other regions became important biotechnology centres (OST:2000,XIV).

[7] The Genepole created in 1998 at Evry in the southern part of the Ile de France region is perhaps the best known of the biotechnology-based technopoles in this region.

[8] For a description of this data base see Caloghiou et al:2001.

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 26 SMEs one of which was subsequently reclassified out of the biotechnology industry.

French firms and to some extent French public sector research institutes were slow to enter the field of biotechnology (Republique Francaises:1993). From a survey of biotechnology firms undertaken by the French Ministry of Research in mid-2000 (Table 1) and the data on firms collected for this study, two broad periods in the evolution of the biotechnology sector can be distinguished. A first generation of biotechnology firms was slowly created over the 1970s,1980s and to the mid-1990s. A second generation of biotechnology firms emerged following major changes in the legal and physical support structures and the financing that stimulated a rapid growth in new start-ups and spin-offs in the second half of the 1990s. These policy changes included a significant increase in new public sector investment in biotechnology programmes from the mid-1990s onward, the creation of a 'Nouveau March'[9] in 1996, the 1999 Innovation Law and the national competitions that opened new financing opportunities for start-ups. Thus, of the 255 biotechnology firms identified in the French government's survey, 36 were created prior to 1980, 84 between 1980 and 1990 and 135 over the 1990s with 100 of these established in the 1997-1999 period alone.

Table 1
Distribution of Biotechnology Firms :1970-2000

Years	French Government Survey	Data Set in this Study
<1980	14%	8 %
1980-1990	33%	20 %
1991-2000	53 %*	72 %
Number of Firms	259	25

*The overall French survey covered the years 1991-1999 only.
Source for the French Survey:"Sociétés de biotech: Le dynamisme est aux commandes" *Pharmaceutiques*,No.81, (Nov. 2000), p.53.

3. Inter- Generational Differences among French Biotechnology Firms

Among the 25 firms interviewed in this study, these rough trends are also evident with 8% of the firms established before 1980, 20% in the period 1980-1990 and 72 percent from 1991-2000. The inclusion of firms that started up in the year 2000 thus further emphasizes the rapid growth in second-generation biotechnology firms. Of the 25 firms in this study only 8 date to the pre-1995 period and are classified as first generation firms. Seventeen of the firms belong to the second generation[10].

[9] The French equivalent of the Nasdaq.
[10] A list of the firms interviewed for this study is contained in Apprendix 1.

First generation firms, share a number of characteristics that distinguish them from those created in the latter half of the 1990s. Three of these are briefly examined here because of their potential impact on the clustering and partnering behaviour of these firms. These include inter-generational differences in the firm's origins, pattern of specialization and ownership structure.

First and second generation firms differ substantially in their origins. Six (75%) of the first generation firms classified themselves as spin-offs from universities or public sector research institutes, one was created as a subsidiary or joint venture and only one was an independent start-up. In contrast, among second-generation firms the number of spin-offs was much lower, 4 of the 17 firms (24%), two were either subsidiaries or joint ventures and 11 (65%) were independent start-ups. Clearly the impact of changes in policy and the development of financial mechanisms to support new start-ups can be seen in these figures.

But there is some evidence to suggest that the substantial increase in the number of independent start-ups among second-generation firms can be traced back to the apprenticeship of their founders in biotechnology firms, something that was not possible for first generation companies. One of the founders of Transgene, a pioneering French biotechnology firm established in 1979, for example, subsequently founded Appligene (now Qbiogene) and then created the second-generation firm, Proteus. A founder and two other employees of Immunotech, another of France's early biotechnology firms, went on to create second generation firms – Trophos, Innate Pharma, and Ipsogen. Similarly the founder of Kappa Biotech came from Biovector Therapeutics, a first generation firm established in 1989.

Differences in specialization across generations are also pronounced. As might be expected given the evolution of the agro-business and pharmaceutical industries and the technological trajectory in biotechnology, first generation firms are heavily concentrated in the area of diagnostics based on monoclonal antibodies (MABs), a field in which none of the second generation firms are active (Table 2) and secondarily involved in drug delivery.

Table 2
Changing Areas of Specialization in First and Second Generation Firms
(Numbers of firms)

Generation	Diagnostics	Drug discovery	Drug Delivery	Detection	Genomics	Services	Total
First	4[a] (50%)	1	3[b]	0	0	0[a]	8
Second	0	7[c] (41%)	3[c]	3[c]	3[c]	1[c]	17

[a] Two of these firms also provide services
[b] One of these firms is also involved in drug discovery
[c] All of the three firms in detection, two of those in genomics, one each in delivery and discovery also provide services.

In contrast, second generation firms are more involved in diagnostic techniques based on genomics and have moved into the newer field of detection, which largely focuses on contaminants in food products, an area of considerable contemporary concern. The largest single specialization among second generation firms, however, is drug discovery. Forty-one percent of the second-generation firms are active here. In addition and primarily as a means to finance their research, 8 of the 17 second generation firms (47%) also provide services, whereas only two of the 8 first generation firms (25%) are service providers.

Lastly, the current ownership structure of first generation firms also sets these apart from second generation DBFs. Seven of the 8 were created as independent companies. Only one , Imedex[11], was a subsidiary but it emancipated itself over the 1980s. All of these independent firms, however, depended upon corporate shareholders and/or venture capital firms as a source of finance. As these investors changed strategies or became wary of investments in biotechnology or financial weaknesses made growth difficult, all but two of the first generation independent firms, Biovector Therapeutics and Anda Biologicals, were acquired or merged with other firms (Table 3). Although M&A have risen dramatically in the biotechnology sector over the 1990s, none of the second generation firms have, as yet, been the object of a takeover. Two second generation firms, however, were created as subsidiaries or joint ventures of larger firms, Rhobio[12] and HLA-G.[13]

Table 3
Mergers and Acquisitions involving First Generation Firms

Firms taken over	Date of establishme	Date of 1st Takeover	Nationality of takeover firm	Date of 2nd Takeover	Nationality of takeover firm	Date of 3rd Takeover	Nationality of takeover firm
Immunotech	1982	1995	Non-European	1997	Non-European		
Biocytex	1990	1996	French				
Mycos	1992	1998	European				
Transgene	1979	1990	French	1990-94	French		
Q BIOgene	1985	1993	Non-European	1999	Non-European	2000	Non-European
Imedex	1986	2000	French				

[11] Originally created as a research subsidiary of Pasteur Merieux, they became independent in 1997 and were subsequently acquired by a French firm.
[12] Rhobio was created as a joint venture between Rhone-Poulenc, now Aventis, and Biogemma, itself the research arm of a group of seed companies (Limagrain, Pau-Euralis,Unigrains and Sofiproteol.
[13] HLA-G, a subsidiary of Parteurop Development linked to Pasteur Merieux Connaught

.

4. Locating in a Cluster/Locating in a Technopole

All of the firms in this survey are located in a cluster, though two of these do not have all of their activities in that cluster. Kappa Biotechnology has established its production facilities in Montauban but maintains its research activities in the Hall G. Durand, an incubator located at INSA on the campus of the University of Toulouse[14]. Similarly, HLA-G's research activities are pursued at the Hopital St. Louis in Paris while its headquarters are in Lyon[15]. What accounts for this high propensity to agglomerate?

This section distinguishes between simply locating in a cluster, that is a geographical area, in this case centred upon a number of provincial cities, in which clients and suppliers, research and other actors engaged in business- support activities and services have co-located and the decision to locate in a structured space within the cluster. Four of these have been differentiated.

The research or research and support -oriented technopole is a specially designed and prepared space located either on the campus of a university or in proximity to a public sector research institution. Research-oriented technopoles such as Luminy on the campus of the University of Marseille or the Hall G. Durand at the University of Toulouse provide laboratory space and access to critical and expensive equipment. They often incubate spin-offs for a time, but space is a constraint on remaining in such a facility.

Support-oriented structures or industrial parks are sites that provide business-support services and/or the necessary infrastructure. Unlike industrial parks, support-oriented structures such as the Parc Georges Besse in Nimes and Cap Alpha in Montpellier provide incubators and other infrastructure to new start-ups along with a variety of supporting services, such as assistance in drawing up a business plan or in securing financing. No research institutions, however, are located within the geographical space of the support-oriented structures.

Mixed research and support technopoles are found less frequently but more of these are now being created. Illkirch, in the Strasbourg cluster is quite close to the university campus and is the only mixed technopole in which firms in this survey are currently located. The new Rockefeller technology park which is planned for Lyon, will combine the academic environment, accompanying business services, hospitals, incubators that small biotechnology firms require along with the advantages of an industrial park sought by larger pharmaceutical companies. One of the firms currently located in Novacite, an industrial park in Lyon has plans to move to this mixed technopole once it is built.

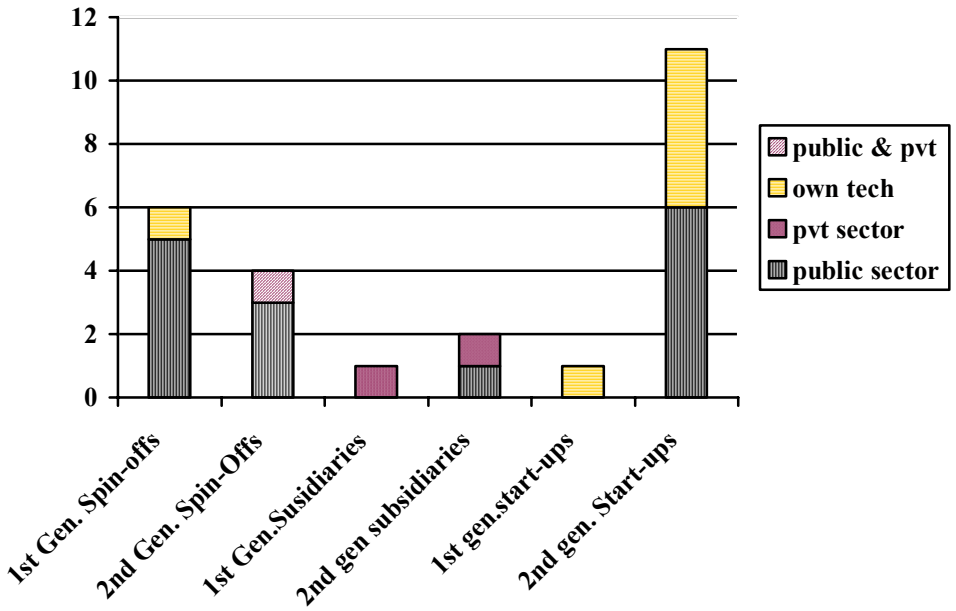
The literature on biotechnology would lead us to expect that co-location in a cluster, particularly one anchored by universities and research institutions specialized

[14] Interview, Kappa Biotech S.A.,Toulouse, 05/03/01.
[15] Interview, HLA-G, Lyon,11/06/01.

in biotechnology, would be particularly attractive to small biotechnology firms, and the evidence from this and other studies would appear to overwhelmingly support this hypothesis. But there is more to locating in a cluster than simply a preference for co-location. The decision to locate in the particular cluster where these firms were established at their origin and where they have chosen to remain must still be explained. Two factors appear to have shaped these decisions: the firm's origin and its initial source of technology.

Curiously there was far less inter-generational difference in the source of technology than might be expected. As figure 2 illustrates, irrespective of generation, the ten firms that classified themselves as spin-offs from universities and research institutes tended to source their technology primarily from these public sector institutions. The three subsidiaries and joint ventures sourced mainly from their parent firm(s) and the twelve independent start-ups either brought their own technology into the new venture or sourced their technology from the public sector.

Figure Two
Source of Technology



Given the high percentage of independent start-ups that sourced their technology from public sector research institutions and universities, a closer look at this group and, in particular, at the origin of their founders is warranted. Many of these had apprenticed in a biotechnology or pharmaceutical firm, yet none had taken technology in the form of patents or licenses with them when they left. Time in a business environment, however, had an impact of another sort. It enabled them to acquire the tacit knowledge needed to start-up their own biotechnology firms. Four

sets of competences were particularly important[16]. These included knowledge of where to source technology and finance and of the networks needed to access these resources, knowledge about how to renew and expand their knowledge base and knowledge about how to manage a portfolio of partnerships. It is the first of these that helps to explain the importance of public sector research as a source of technology in second-generation independent biotechnology start-ups.

As to the choice of cluster, data from this survey show that irrespective of generation, all 10 spin offs from universities and public research institutions initially located in proximity to their 'mother laboratory' even when their technology did not entirely come from that source but rather was based on their 'own' work or was a combination that involved work at the 'mother laboratory' and either their own knowledge or technology licensed from a company. All three subsidiaries/joint ventures also located in proximity to their 'parent firm'. As to the independent start-ups, the pattern is somewhat more varied but strongly supports the role of 'parentage' and 'technology source' as major influences on the locational decisions of these firms. Whether as independent start-ups, spin-offs from educational or research institution or subsidiaries, second generation firms overwhelmingly sourced their technology, in whole or in part, from universities and public sector research institutes as shown in Figure 2 above and then tended to stay in proximity to these technology sources.

Within the cluster, Table 4 provides data on the extent to which these firms located in structured spaces at their origin and the extent to which this has changed overtime. Of the 25 firms in this study, 14 were originally located in a structured space. Of these 14 firms only 7 were in a research oriented or a research and support – oriented (mixed) technopole. All but one of these was a second-generation firm.

Table 4
Enterprise Location by Generation and by Type of Structured Space

Generation	originally in a structured space		Currently in a structured space		type of structured space			
	yes	no	yes	no	Research-oriented	Support-oriented	Mixed	Industrial park
First (n=8)	1	7	4	4	0	0	2	2
Second (n=17)	13	4	14	3	6	5	1	2
Total (n=25)	14	11	18	7	6	5	3	4

For firms created in the 1970s and early 1980s, the very concept of a technopole was quite new, although industrial parks had existed for some time. Given that biotechnology is a science-based sector, locating on or near to a campus was clearly an advantage, but new start-ups such as Transgene which emerged from the

[16] Interviews with Biocytex, Appligene/ Qbiogene, Kappa Biotech, Innate Pharma, Trophos and Ipsogen.

Institute for Cellular and Molecular Biology, a joint university/CNRS[17] laboratory headed by Professor Chambon were unable to remain on the campus where no facilities of this kind then existed. Immunotech, on the other hand, which emerged from the Centre for Immunology, a joint CNRS/Inserm laboratory on the campus of the University of Marseille at Luminy, were able to initially locate on the campus and to remain there for ten years. At that point, space considerations[18] obliged them to move into a new zone where some second-generation biotechnology firms are currently locating[19]. Even then, the move has resulted in reduced knowledge flows. A firm like theirs, they emphasized, must be in an environment that is scientifically dense. There is the library at Luminy and seminars all the time. But since they have moved out of Luminy, it has become more difficult for them to attend seminars there, even though it is only three kilometers away. As a result, they tend to be more selective and thus are not exposed to as wide an array of new ideas as before[20].

As might be expected, the vast majority of second-generation firms (77%) initially located within a structured space and 11 of the 13 are still in the same place. Of the four that had not, one subsequently moved to the 'support-oriented' Parc G. Besse and two others into industrial parks. As Table 4 illustrates, there is no preference for research-oriented or mixed research and support-oriented technopoles on the part of second-generation firms. Instead, as each of the clusters, provides opportunities for interaction with local university faculties and research institutes known for their excellence in biotechnology related work, second generation firms are looking to such structured spaces, less to gain access to research facilities once they move out of their laboratories of origin, than to provide business support services. Though technopoles and science parks have proliferated, it thus appears that second generation firms were not attracted to a cluster by the presence of a research-oriented 'technopole', though support-oriented structures and industrial parks seem to play a role in inducing them to remain there.

Table 5 provides additional evidence to support this argument. It present the responses to a question in which respondents were asked to provide as many reasons as they wished for their decision to locate or to stay in their cluster. These were subsequently regrouped under seven headings. Frequencies by generation were then tabulated. Sixty-eight percent of the firms gave 'infrastructure' are one of their reasons. This was mainly linked to the general availability of infrastructure in the cluster, transportation and communication, for example and to business support services. The second most frequent response was the opportunity to tap into new substantive knowledge and the third was the ability to participate in the information circulation of business-related information. A slightly higher percentage of second-generation firms (59%) gave knowledge-related reasons as the explanation for their decision to locate or remain in their cluster then did first generation firms (50%). The reverse was true of the frequency with which first generation firms cited 'information'

[17] Public sector research institutes in the regions that are heavily engaged in research on biotechnology include those belonging to the Centre National de Recherche Scientifique (CNRS) and to, the Institut national de la Sante et de la Recherche Medicale (INSERM)

[18] This is a particular problem in Luminy where a struggle pits environmentalists against further expansion into the adjacent national park and those desirous of staying on or close to the campus.

[19] Herve Brailly, CEO of Innate Pharma referred to it as part of a "Triangle d'Or" , a "Luminy Virtuel" (Interview,Innate Pharma, Marseille, 12/01/01)

[20] Interviews: Immunotech, Marseille, 19/12/01.

(50%) as a reason for locating or remaining in their cluster as compared with second-generation firms (35%) in a much earlier phase of their business life cycle.

Table 5
Reasons for Locating or Staying in a Cluster

Reasons[a]	First Generation (N=8)	Second Generation (N=17)	Total (N=25)
Infrastructure-related: access to transportation, communications, equipment and material, incubators, other facilities and services to business.	4 (50%)	13 (77%)	17
Finance-related: available funding, fiscal or other incentives offered.	1	6	7
Employment related: available pool of skilled labour, scientific competences, ability to change jobs easily because of the size of the cluster.	3	5	8
Knowledge-related: tap into the knowledge base of the university, availability of frontier researchers, newly minted PhDs, opportunities for learning about complementary research	4 (50%)	10 (59%)	14
Information-related: monitor the competition, circulation of information through social networks and informal contacts including with other firms on business-related problems.	4 (50%)	6 (35%)	10
Business Partner–Related: the presence of clients, suppliers, sub-contractors, partnerships with other firms.	2	4	6
Imagine/Reputation of the Cluster	1	2	3

(a) An additional 2 responses from first generation and 8 from second-generation firms dealt with life style or personal reasons mainly related to living in the South of France.

.

5. Long Distance and Local Partnerships

All firms in this study engage in partnerships with universities and research organizations. Twenty-one of the 25 firms also have inter-firm partnerships. In terms of the extensiveness of their partnering activity, nearly one third of the firms could be classified as having many partnerships with universities and research organizations as opposed to only a few. Inter-firm partnerships are far less intense. Only 24 percent of the firms could be classified as having many such partnerships. Are there inter-generational factors that account for these differences in the frequency of partnering activity? Normally we would expect to find that newer firms would have fewer alliances and given their origins in the cluster would presumably partner locally. To a large extent this was born out by the survey results

Table six summarizes the pattern of partnerships of these firms in generational terms. It shows no relationship between age of the firm (generation) and the extensiveness of partnering activity with universities and research institutes. Thus 37.5% of the first generation firms and 29.4% of the second-generation firms have many partnerships with the research sector. In contrast, the extensiveness of inter-firm partnering activity does appear to have some relationship to inter-generational differences. All first generation firms have at least some partnerships with other firms, but four of the second-generation start-ups and spin-offs have none at all and few second-generation firms have extensive partnering activity with other enterprises.

Table 6
Pattern of Partnerships by Generation
(frequencies)

	Universities and Research Institutes			Inter-firm		
First Generation	Volume	Proximate	Distant	Volume	Proximate	Distant
None	-	-	-	-	-	-
Some	5	2	3	5	0	5
Many	3	2	1	3	0	3
Total	**8**	**4**	**4**	**8**	**0**	**8**
Second Generation						
None	-	-	-	4	-	-
Some	12	10	2	10	5	5
Many	5	3	2	3	0	3
Total	**17**	**13**	**4**	**17**	**5**	**8**

Overwhelmingly these first generation firms have inter-firm relationships at long distance and many of these are with other SMEs. Although, over a third of the second generation inter-firm partnerships are with local firms, nearly two thirds are also at long distance and again, they are with other SMEs and not with the larger

firms that marked the earlier phase in the life cycle of this industry. This does not mean that large pharmaceutical companies are not among the client firms of the drug discovery or drug delivery DBFs in this survey, but rather that these are arms-length relationships or licensing agreements and not collaborative R&D partnerships. The logic behind the close links to both local and the long distance partners, for second generation firms thus lies less in the market for goods than in the market for knowledge. The competence-based nature of these partnerships emerges from a closer look at the reasons for partnering.

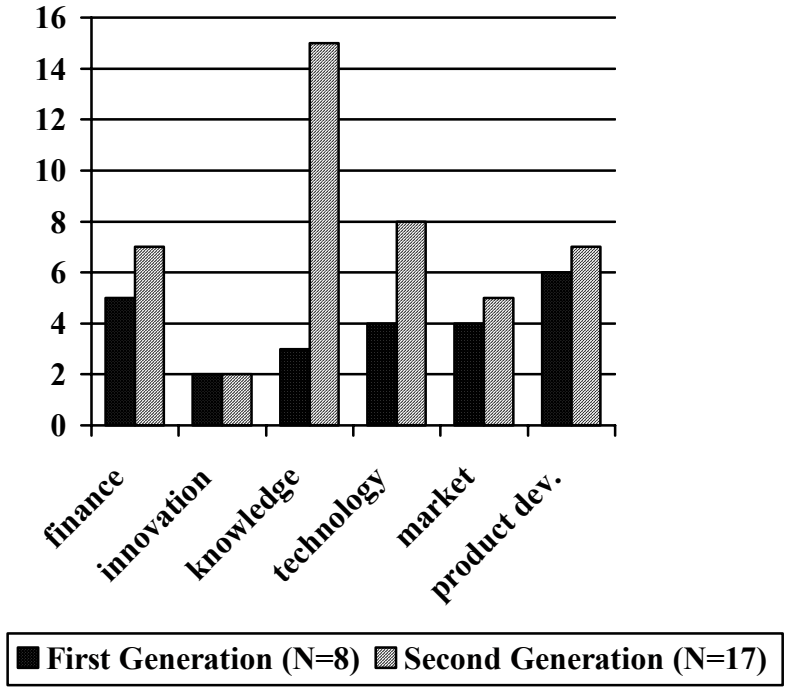
A matrix of possible partnering objectives was provided to respondents during the interview and they were requested to rate on a scale of 1 to 4 the most important objectives of their partnerships with universities and research institutions and with other firms in proximity and at long distance. The responses were regrouped into six categories.

- Finance-related: reduce costs of R&D, access expensive equipment
- Innovation-related: increase the speed of innovation, reduce time to market.
- Knowledge-related: access to knowledge, databases or technology through licensing or joint research.
- Technology-related: validation of a technology (clinical testing, for example), widen applications across sectors or end product users for a given technology.
- Market-related: access to or penetration of markets, reinforce client-supplier linkages.
- Product development: joint research on the development of a new product.

First generation firms are more heavily involved in inter-firm partnerships, which provide them with opportunities for joint product development. Seventy-five of the first generation firms gave this as an objective of partnering activity. Also very high on their list of partnering objectives was the need to reduce the costs and risks of R&D and product development. Financial considerations were thus cited by 5 of the 8 (62.5%) firms and 50% of the first generation firms also gave technology and market-related reasons for their partnering activity.

The contrast with second-generation firms is dramatic. Access to knowledge is the overwhelmingly most important objective of their partnering activity with 88% of the firms giving this as an objective. The second most frequent response was technology-related with only 47% of the second-generation firms citing this as an objective for partnering activity. Finance and product development are given by 41% of the firms.

Figure Three
Partnership Objectives



Following Adam Smith, Saviotti has argued that 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. Thus, although we might have expected that, in a study of long distance and local partnerships a relationship between the extensiveness of partnering activity and a widening of the geographical spread of these alliances would emerge, this is not the case. Looking across partner types we found that of the 8 firms that have many partnerships with universities and research institutes only three of these have most of their partners at long distance. All of the six firms that have extensively engaged in inter-firm partnering activity, however, have most of their partners at long distance. But so do the firms with fewer partnerships. The substantial inter-generation difference in the choice of partner types –universities and research institutions as opposed to enterprises-- is thus not matched by an inter-generational difference in the preference for long distance or local partners.

Conclusions:

This paper supports that of others in providing evidence for the strong tendency of firms in science-based industries to cluster. To say this, however, is not to explain the co-location preferences of such firms. Nor does the conventional view

of clustering enable us to understand the collaborative relationships that are established by these firms within their cluster. Lastly it does not prepare us for the roles that long distance partnering play in relation to these local partnerships.

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 **a continuous flow of new knowledge** in the form of seminars and degree candidates or newly minted PhDs 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.

Although these firms overwhelmingly located in cluster where such knowledge flows of this sort were present, the choice of specific cluster was far more dependent upon the origin of the firm as a spin-off from a university, research institute or enterprise within that cluster. Reinforcing this pattern amongst spin-offs and subsidiaries and shaping this pattern among independent start-ups was the source of technology. Continued partnership with the 'mother laboratory' and or 'parent firm' were thus powerful inducements to co-location in a cluster and although this relationship was attenuated over time, it was a factor in the decision of these firms to remain in this cluster even when their clients were at long distance.

What was also remarkable in this study was the speed with which second generation firms, most of which were barely two years old, moved to engage in relatively intense partnering activity and in partnerships at long distance. While local linkages remain important for these firms, long distance partnerships came in quite quickly as a complement. It is thus not a question of either/or, but of both.

The relatively low frequency of their linkages to large enterprises was, however, somewhat unexpected as the literature on the dynamics in this industry, particularly the drug-related specializations within it, stress 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. We also did not expect that financing would not appear as a critical component of their inter-firm partnerships but a factor of lesser importance.

Appendix 1
Firms in this Survey, Location and Date of Establishment

Firm	Date of Establishment	Location
First Generation		
Anda Biologicals	1974	Strasbourg
Transgene	1979	Strasbourg
Immunotech	1982	Marseille
Q Biogene (Appligene)	1985	Strasbourg
Imedex	1986	Lyon
Biovector Therapeutics	1989	Toulouse
Biocytex	1990	Marseille
Mycos	1992	Montpellier
Second Generation		
Syn:tem	1995	Nimes
Kappa Biotech	1995	Toulouse
Novotec	1997	Lyon
Proteus	1998	Nimes
Rhobio	1998	Lyon
HLA-G	1998	Lyon
TMI Europe	1998	Lyon
Trophos	1998	Marseille
Innate Pharma	1999	Marseille
Ipsogen	1999	Marseille
Probiotec	1999	Montpellier
Skuld - Tech	1999	Montpellier
Phylogene	1999	Nimes
Millegen	1999	Toulouse
EntoMed	1999	Strasbourg
GTP Technology	2000	Toulouse
ID Myk	2000	Lyon

Bibliography

Autant-Bernard, C. (2001) " Science and knowledge flows : evidence from the French case" Research *Policy*, 30 , pp. 1069-1078.

Caloghirou, Y., A. Tsakanikas & N.S. Vonortas (2001), "University-Industry Cooperation in the Context of the European Framework programmes" in *Journal of Technology Transfer*, Vol. 26, pp. 153-161.

Chandler, A. jr. [1990], *Scale and Scope, The Dynamics of Industrial Capitalism*, Cambridge, Mass. The Belknap Press and Harvard University Press.

Cantwell, J. & L. Piscitello (2000) "Agglomeration in the Technological Activities of MNCs in Europe: The Role of Spillovers and other Territorial Externalities" paper prepared for the EIBA Conference, Maastricht.

Cooke, P. (2001) "New Economy Innovation Systems :Biotechnology in Europe and the USA" in *Industry and Innovation,* Vol.8, No. 3, December, pp. 267-289.
Ernst and Young (2000a) *Convergence: The Biotechnology Industry Report*. Millenium edition.

_____(2000b) *Evolution : European Life Sciences Report 2000.*

_____ (2001) *Life Sciences in France-2001 "Where Creativity Meets Business".*

Faulkner, W. & J. Senger (1994) " Making sense of diversity : public-private sector research linkage in three technologies" *Research Policy*, 23, pp. 673-695.

Freeman, C. (1992) "Formal Scientific and Technical Institutions in the National Systems of Innovation" in B. A. Lundvall *National Systems of Innovation. Towards a Theory of Innovation and Interactive Learning,* U.K.: Pinter Publishers..

Gransrand, O., L. Hakanson & S. Sjolander (eds) (1992) *Technology Management and International Business: Internationalisation of R&D and Technology*. Chichester, John Wiley and Sons.

Hagedoorn, J. (2001) "Inter-firm R&D Partnerships – An Overview of Major Trends and Patterns Since 1960" *Research Policy*, forthcoming.

_____(1995) "Strategic Technology Partnering During the 1980s: Trends, Networks and Corporate Patterns in Non-Core Technologies", Research Policy, Vol. 24, pp. 207-31.

Hagedoorn, J. & N. Roijakkers (2001) "Small Entrepreneurial Firms and Large Companies in Inter-Firm R&D Networks –The International Biotechnology Industry" in M. Hitt, R.D. Ireland, S.M.Camp,k D. L. Sexton (eds), *Strategic Entrepreneurship creating a new mindset*, U.K.:Blackwell Publishing, pp. 223-252.

Henderson, R., L. Orsenigo & G. Pisano (2000) "The Pharmaceutical Industry and the Revolution in Molecular Biology: Interactions Among Scientific, Institutional and Organizational Change" in D. Mowery & R. Nelson (eds.) Sources of Industrial Leadership, U.K.: Cambrdige University Press, pp. 267-311.

Hood, N. & S. Young (2000) *The Globalization of Multinational Enterprise Activity and Economic Development*. U.K. Macmillan.

Kline, S.J. & Rosenberg, N. (1986) "An Overview of Innovation" in National Academy of engineering, *The Positive Sum Strategy: Harnessing Technology for International Growth* , Washington, D.C.: The National Academy Press, 1986, pp. 275-305.

Lemarie, S. ,M-A De Looze, V. Mangematin (2000) « Strategies of European SMEs in biotechnology : The role of size, technology and market » Scientometrics, Vol. 47, No. 3, pp. 5411-560.

Lundvall, B.-A. (1988), "Innovation as an Interactive Process: From User-Producer Interaction to the National System of Innovation" in Giovanni Dosi, Christopher Freeman, Richard Nelson, Gerald Silverberg and Luc Soete , eds., *Technical change and Economic Theory*, Pinter Publishers, UK, pp. 349-369.

Malerba, F. (1999) "Sectoral Systems of Innovation and Production" paper presented at the DRUID meeting in Rebild, 9-12 June.

Malerba, F. & L. Orsenigo (1996) « The Dynamics and Evolution of Industries » *Industrial and Corporate Change*, Vol. 5, No. 1, pp. 51-88.

Marshall, A. (1890) *Principles of Economics* (reprinted London:Macmillan 1920) (8th edition).

Maskell, P. (2001) "Growth and the territorial configruration of economic activity", paper presented to the DRUID summer conference, Aalborg, 12-15 June.

Maskell, P. & A. Malmberg (1999) "Localised Learning and Industrial competitiveness" *Cambridge Journal of Economics*, Vol. 23, pp. 167-185.

Metcalife, S. (1997) " Technology systems and technology policy in an evolutionary framework", in D. Archibugi & J. Michie (eds.) Technology, Globalisation and Economic Performance, U.K.: Cambridge University Press , pp. 268-296.

MINERT (1999) Premier concours national d'aide a la creation d'enterprise de technologies innovantes (Paris : Ministere de l'Education Nationale, De La Recherche et De La Technologie, 1999).

Ministere de la Recherche (2000) *Deuxieme Concours National d'Aide a la Creation d'enterprises de Technologies Innovantes* (Paris : Ministere de la Recherche, septembre).

Mytelka, L.K. (2000) " Local Systems of Innovation in a Globalized World Economy" in *Industry and Innovation*, Vol. 7, No. 1, June, pp. 15-32.

Mytelka, L.K. & M. Delapierre (1999), "Strategic Partnerships and the rise of knowledge-based networked oligopolies"(with Michel Delapierre) in C. Cutler, V. Haufler & T. Porter (eds.) *Private Authority and International Affairs*, Binghamton: Suny University Press, pp. 129-149.

Mytelka, L.K. & F. Farinelli (2000), *Clusters, Innovations Systems and Sustained Competitiveness,* Maastricht: UNU/INTECH discussion paper #2005, October., (WWW.intech.unu.edu)

Mytelka,L.K. & J. Pellegrin (2001), " Can SMEs Survive ? Static vs Dynamic Externalities in the French biotechnology Industry" ,paper presented at the DRUID summer Conference, Allborg, June 12-15.

Mytelka, L.K. and J. Pellegrin (2002) "Clustering and the Life Cycle of SMEs in the French Biotechnology and Information Technology Sectors" forthcoming.

Nelson, R. (1988) "Institutions supporting technical change in the United states" in Giovanni Dosi, Christopher Freeman, Richard Nelson, Gerald Silverberg, and Luc Soete (eds.) *Technical Change and Economic Theor*y. U.K.: Pinter Publishers, pp.312-329.

Nelson, R.& S. Winter (1982) *An Evolutionary Theory of Economic Change*, Cambridge, Ma.:Harvard University Press.

Orsenigo, L., F. Pammolli & M. Rioccaboni (2001) "Technological change and network dynamics Lessons from the pharmaceutical industry" in *Research Policy*, Vol. 30, pp. 485-508.

OST (2000) *Science and Technologie Indicateurs edition 2000*, sous la direction de Remi Barre, Paris: Economica.

Pyka, A & P. Saviotti (2001) "Innovation Networks in the Biotechnology-Based Sectors" Grenoble: INRA.

Saviotti, P.P. (1998) "Industrial structure and the dynamics of knowledge generation in biotechnology" in J. Senker & R. van Vliet (eds.) *Biotechnology and Competitive Advantage: Europe's Firms and US Advantage.* U.K.: E. Elgar, pp. 19-43.

Saxenian, Annalee (1994) *Regional Advantage: Competition and Cooperation in Silicon Valley and Route 128* . Cambridge, Ma.: Harvard University Press.

Schumpter,J.A.(1934) *The Theory of Economic Development*. London:Oxford University Press.

Segal, Quince, Wicksteed (2000a) *The Cambridge Phenomenon Revisted: Part One*. Cambridge.

_____ (2000b) *The Cambridge Phenomenon Revisted: Part Two*. Cambridge.

Senker, J. & M. Sharp (1997), "Organizational learning in cooperative alliances:some case studies in biotechnology" in *Technology Analysis and Strategic Management*, Vol.9,no.1, pp. 35-51.

Smith, K. (1999) *Industrial structure, technology intensity and growth: issues for policy*, paper prepared for the DRUID conference on National Innovation systems, Industrial Dynamics and Innovation Policy, Rebild, Denmark, June 9-12.

Storper, M.. (1995) "The resurgence of regional economies, ten years later: the region as a nexus of untraded interdependencies." *European Urban and Regional Studies*, Vol. 3, No. 2, 191-221.

_____ (1999) *The Regional World Territorial Development in a global Economy.* New York: The Guilford press.

United Kingdom (1999) *Biotechnology Clusters,* Report of a team led by Lord Sainsburgy, Minister for Science (August)

Vavakova, B. (2001*) La Science de la Nation? Les paradoxes politiques de la logique economique* .Paris. Harmattan.

Vonortas, N. (1997) "Research Joint Ventures in the United States" *Research Policy,* Vol. 26, pp. 577-595.