The (Failed) Development of a Biotechnology Cluster: The Case of Lombardy

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ABSTRACT. This paper discusses the development of the biotechnology industry in an Italian region, Lombardy. It asks why significant innovative activities in biotechnology did not emerge in what might have been considered at the outset a promising area for the growth of this industry and why in very recent years some timid symptoms of dynamism seem to be appearing. After an overview of the patterns of the development of biotechnology in Italy, the specific case of Lombardy, is described. Then, the paper discusses what kind of factors might explain the lagging behind of the Italian (and more generally, European) biotechnology industry vis-à-vis the United States.

1. Introduction

This paper discusses the development of the biotechnology industry in an Italian region, Lombardy. It asks why significant innovative activities in biotechnology did not emerge in what might have been considered at the outset a promising area for the growth of this industry and why in very recent years some timid symptoms of dynamism seem to be appearing.

This paper is a case study about a failure, rather than a success story. As such, it is quite difficult to draw firm conclusions. In a sense, the problem is over-determined. There are too many possible candidate variables that might explain why innovative activities in biotechnology did not take off and available data do not allow any serious statistical test.

As a consequence, the paper is largely speculative. However, I shall try to make some steps forward in turning speculation into an appreciative account, based on a theory-driven interpretation of the determinants of the patterns of innovative activities in specific geographical areas.

After an overview of the patterns of development of biotechnology in Italy (Section 2), the specific case of Lombardy will be described (Section 3). Then, I shall briefly discuss what kind of factors might explain the lagging behind of the Italian (and more generally, European) biotechnology industry vis-à-vis the United States (Section 4).

2. The background: the development of biotechnology in Italy

In Italy, as in other European countries, innovative activities in biotechnology lagged significantly behind the U.S.A. and proceeded along different lines. Structural weaknesses in the industrial base, in the research system and at the institutional level hindered the development of biotechnology.

The most striking difference, of course, is the virtual absence of the phenomenon of the specialized biotechnology start ups, even as compared to other European countries. No reliable figure is available of the number of new biotechnology firms in Italy, but a rough estimate would suggest that they are around less than two dozens. Moreover, the few Italian start-ups do not resemble the American prototype under many respects. Basically, most of them are not involved in drug research or development but are instead either intermediaries commercializing products developed elsewhere, or in the provision of instrumentation and/or reagents. Finally, some of these companies (especially the most significant ones) have been founded as spin-offs of larger pharma-

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ceutical companies undergoing processes of restructuring rather than as University spin-offs.

However, the major distinctive feature of the Italian case is the delay with which innovative activities got started and the limited size and scope of such efforts, even within the large chemical and pharmaceutical (and agro-food) companies. Even today, Italy has to be considered a background country in biotechnology. Just to give a rough idea, it is worth noting that the number of Italian patent applications to the European Patent Office totals to only 163 in the whole period from 1978 until 1996.

In the absence of extensive new firm founding, most of the innovations in biotechnology in Italy – as in other countries of mainland Europe – occurred within established firms and public research centers. Indeed, the main actors in the development of biotechnology in Italy were the large chemical firms and the beginning of research activities, as well as the emergence of public policy, was contextual to the formation of a "biotechnology lobby", stimulating the interest of industry and above all of the government. By the early eighties, the two largest Italian chemical groups – ENI and Montedison – had already started some small research activities and had considered the possibility of some more systematic effort. However, such plans resulted only in the establishment of two small research agreements with Italian academic laboratories. Besides ENI and Montedison, only a handful of medium-sized pharmaceutical companies engaged in innovative activities, whereas the absence of any research tradition in the food industry and in agriculture prevented any significant effort in these directions.

A biotechnology lobby, however, gathered and organized aorund the chemical industry. Scientists were the first to perceive the potentialities of biotechnology and took an active role in eliciting both industrial and public interest in the new emerging techniques. Yet, they had traditionally only few linkages with industry and their pressure achieved some results only when they succeeded in involving the Association of the Chemical Industry (Federchimica). Federchimica was perhaps the single most influential institution in the development of Italian biotechnology. In 1986, it published the first major report on biotechnology and from then on it lobbied for getting public support. Subsequently, Federchimica spun off other initiatives, particularly the Italian Biotechnology Industrial Association, although its main result was to elicit and contribute to design government intervention.

The weakness of government support is a further distinguishing feature of the Italian case. Before 1986, public support to biotechnology was very small and uncoordinated. It flowed mainly to universities through the National Research Council's (CNR) "Finalized Projects", but research funding was small and it was spread over many diverse and very general projects, without any clearly defined priority. Industry was only marginally involved in these projects. Industrial research was funded through the two existing schemes supporting applied research, but again no specific priority was attributed to biotechnology.

Like in most countries, the Italian government agencies knew very little about biotechnology and, given the uncertainty surrounding its future developments, they were not able to devise any specific policy. Differently from other experiences, though, the Italian administrative apparatus lacked also the experience, the competencies and the structures for dealing with the problems of formulation and implementation of a set of policies in high-tech industries (Orsenigo, 1989). Thus the existence of biotechnology was not even perceived until the mid 1980s, under the pressure of the biotechnology lobby and of the example from other countries. Participation in the international research projects and the debates about patent legislation and DNA-research guidelines made the Italian government agencies realize that Italy was lagging behind in its support to biotechnology.

As a consequence, attempts to coordinate interventions and to devise a coherent strategy started only in the second half of the 80s, when a National Committee for Biotechnology was established at the Ministry for Scientific and Technological Research. The Committee comprised the scientists and the industrialists of the original biotechnology lobby and eventually designed the National Plan for Biotechnology, which was passed by the Parliament in 1987.

The plan was aimed at supporting applied research in different fields (especially biomedical research), while support to basic research and industry-university collaboration was provided through new programs launched by the CNR. Other initiatives were taken to stimulate research conducted in the public research centres like ENEA (Ente Nazionale per le Energie Alternative) and the CNR. In the following years other programs were launched by the CNR, by the Ministry of University and Scientific and Technological Research (MURST), the Ministry of Agriculture, etc. It is very difficult to evaluate the effective size of the financial resources devoted to the support of (basic and applied) research and to the promotion of industry-university collaboration, let alone the impact of these projects. An extremely rough estimate would suggest that in the period from 1987 to 1996 the total funding amounted to a figure around L. 1,000–1,200 billion. An analysis of the National Research Plans on biotechnology launched by the Ministry of University and Scientific and Technological Research in the period from 1989 to 1997 suggests, however, that only a small group of universities and an even smaller group of companies were involved in these projects, with a very limited scientific output (only one patent extended outside Italy) and little interaction between universities and the companies (Cancogni, 1998).

In addition to these initiatives, the development of biotechnology in Italy was characterized by the mushrooming of local collaborative initiatives between public and private agents at the local level, through the establishment of science parks, research consortia, venture capital funds, etc. Quite limited as a whole the scope and the impact of these efforts however remained.

Thus, despite these efforts, very few firms engaged in significant research activities and their innovativeness was far lower than that of the major European competitors. Very few firms account for a large proportion of biotechnology patents, and innovation in biotechnology rests essentially on the activities of a small group of large/medium-sized established companies. Consequently, the Italian performance as a whole remains far behind that of Germany, France, U.K., Switzerland, but also of Sweden and Denmark (Table I).

Another indicator of the scarce involvement of Italian industry in biotechnology is given by the participation in the National Association for the Development of Biotechnology (Assobiotec), the trade association created within the Chemical Industrial Association in 1986.

TABLE I
Major biotechnology innovators in Italy

Institution	Number of EPO patent[a]	% of total Italian patents[b]
1978–1990		
Eniricerche	12	25.0%
Sclavo	7	14.6%
Farmitalia Carlo Erba	6	12.5%
1990–1996		
Eniricerche	16	14.7%
Biocine	10	9.2%
Pharmacia & AMP Upjohn	9	8.3%
Consiglio Nazionale delle Ricerche	9	8.3%

[a] Patent applications at the European Patent Office.
[b] *Source*: Own calculation of the EPO-CESPRI Database (Center on the Processes of Innovation and Internationalization, Bocconi University, Milan, Italy).

As Table II shows, the total number of participating firms is quite small and in recent years it has been declining. It is obvious that not all the firms involved in biotechnology participate in the Association, and over the last few years divergences within the Association have induced some companies to retire their membership. On the other hand, very few of these companies actually perform research, but they are mainly involved in the commercialization of products and services generated elsewhere.[1]

In the 1980s, the main actors were the two large Italian chemical groups, ENI (Ente Nazionale Idrocarburi) and Montedison. As far as Montedison is concerned, research capabilities in biotechnology were present in the laboratories of Farmitalia-Carlo Erba, its pharmaceutical subsidiaries and the largest and more prestigious Italian pharmaceutical company at the time and in the central laboratories of the group (Istituto di Ricerche Donegani). In the late 1980s, Montedison expanded its biotechnology research by acquisitions (mainly the Spanish company Antibioticos) and by the development of a network of collaborations with domestic universities and American laboratories and specialized biotechnology firms.

TABLE II
Number of companies affiliated to ASSOBIOTEC

Year	Number of companies
1987	39
1988	45
1989	51
1990	55
1991	58
1992	58
1993	57
1994	50
1995	46
1996	40
1997	38
1998	36
1999	38

Source: Own research on Assobiotec data.

As for ENI, a significant biotechnology group was created within EniRicerche (the research labs of the group). Moreover, ENI owned Sclavo, a medium-sized company located in Siena, considered to be among the world leaders in vaccine production.

Finally, a subsidiary of the Fiat group, Sorin, active in the production of medical devices, started research on the development of diagnostic kits based on the use of monoclonal antibodies and assays.

Since the beginning of the nineties, however, even these initiatives were drastically downsized. The Italian chemical and pharmaceutical industries underwent a deep crisis. The Italian chemical and pharmaceutical companies were already structurally weak, small on international standards and their commitment to innovative activities was certainly not comparable to that of their international competitors. The tendencies towards an increasing concentration on the world market led to a wave of acquisitions of the major Italian chemical and pharmaceutical companies. Now, more that 70% of total pharmaceutical sales on the Italian market are generated by foreign-owned firms and by subsidiaries of large multinationals. Moreover, a series of scandals linked to the diffusion of a bribery system in the processes of determing the prices of drugs, severely hit the industry in the early nineties. Finally, cost containment policies by the government implied a further shock on the profits and on the strategies of the pharmaceutical companies operating in Italy.

As a consequence, investments in biotechnology R&D were drastically reduced. For example, the pharmaceutical division of Montedison – Farmitalia Carlo Erba – was eventually acquired by Pharmacia and its research activities were subject to substantial processes of restructuring. Similarly Sclavo (now called Biocine), after a series of break-ups and vicissitudes, was acquired by Chiron. Many research projects were discontinued and – given the overall weakness of Italian research capabilities – only few initiatives were launched or maintained by the foreign research headquarters to compensate the decrease of domestic investments. In general, industrial research is extremely weak, with only few exceptions.

3. The development of biotechnology in Lombardy

The history of the development of biotechnology in Lombardy coincides to a very large extent with the history of Italian biotechnology as a whole. Indeed, since its inception, innovative activities in this area have been strongly concentrated in a few regions, Lombardy being by far the single most important center, followed by Tuscany and – in the nineties – by Latium. Lombardy accounts for almost half of (43.9%) the patents applied for to the European Patent Office in the period from 1979 to 1996 and its contribution has been only slightly declining in the period after 1996 (falling to 39.4%). All in all, Lombardy, Latium and Tuscany contribute to around 80% of total Italian patenting activities[2] and over the past few years the overall degree of spatial concentration of innovative activities in biotechnology has changed very little.[3]

The agglomeration of innovative activities in Lombardy – and more specifically the area around Milan – might be simply explained by the fact that Milan had the strongest concentration of research laboratories, both academic and industrial, and it was by far the major financial center of Italy.

Milan was traditionally one of the major centers of academic research in medicine and in biology. Whilst other universities had perhaps the best research teams and the more advanced "schools", yet in Milan you could find a very strong concentration of units and researchers in different disciplines.

The large majority of the chemical and pharmaceutical industry were located traditionally in Lombardy, and especially their headquarters and their research labs.[4] In general, Lombardy shows a consistently and very strong technological specialization in chemicals and pharmaceutical, whichever indicator is used (R&D expenditures, patents, number of researchers, etc.).

At the beginning of the nineties, Lombardy hosted 49% of the Italian firms active in biotechnology, 36.3% of the researchers in industry and 42.6% of the research laboratories. Similarly, Lombardy attracted 29% of the public funds made available by the National research Council's "Finalized Project" on Biotechnology. It is also worth noting that, more than three quarters and around 60% of all the collaborations among firms – both at the national and international level – and universities in biotechnology involved companies (universities) located in Lombardy (Orsenigo, 1991).

Against this background, a series of initiatives was taken to further develop biotechnology research and commercial activities, primarily by the creation of science parks or – more generally – aggregations of academic and industrial researchers to promote collaborative research and act as incubators for academic spin-offs.

The first initiative was the so-called "Biopolo", a consortium of a few pharmaceutical companies and academics of the Faculties of Biology, Chemistry and Agricultural Sciences, with the participation – under various headings – of the local authorities. The Biopolo was an offspring of the original "biotechnology lobby" and was promoted and stimulated by a group of professors of the State University of Milan since the late eighties. Its main area of interest was the applications of biotechnology to the agrofood industry and environment.

In practice, the Biopolo took off very slowly, as a consequence of the scandals in the pharmaceutical industry, political meddling and academic politics. Its main activity consisted in supporting the creation of the specific field denominated "biotechnology" within the Faculty of Sciences in the State Milan University and collaboration between university and industry was essentially focussed on teaching activities and training. Only recently, with the creation of the 2nd State University of Milan in 1998 – resulting from the splitting of the previous institution – the Biopolo has started operating in a more systematic way. With the creation of the 2nd University, in fact, a Faculty of Biotechnology was started which is beginning to act as a center of aggregation for research.

A second initiative, the S. Raffaele Science Park, was more successful. The Science Park was launched in 1993 under the impulse of the boss of the S. Raffaele hospital, a private institution created and managed by a charismatic (and highly controversial) priest/entrepreneur, Don Luigi Verzè. The San Raffaele Hospital was conceived and developed putting a high priority on research – particularly on biotechnology and in general on molecular biology – and it quickly became a leading scientific center in the biomedical area in Italy, with solid relationships with the international community and high quality standards and reputation. Around the S. Raffaele Hospital, DIBIT (Department of Biological and Technological Research) and subsequently the S. Raffaele Science Park, were formed, initially without any public funding. Now, the Science Park hosts 63 research units, including also laboratories of the National Research Council, of the Polytechnic of Milan, and since last year the new University "Vita e Salute" (another initiative of Don Verzè, with Faculties of Medicine and Psychology and conceived as a highly prestigious and selective institution). A number of important international pharmaceutical companies and a couple of new start-ups (which are not yet completely operative, though) participate to the S. Raffaele Science Park, with specialized laboratories in a large variety of research areas. Moreover, the S. Raffaele Science Park hosts also a number of laboratories funded by initiatives like Telethon and by other private foundations.

Although the S. Raffaele Science Park has among its main objectives the promotion and the assistance to spin-offs, with the provision of various types of services (scientific, technological, logistical financial and administrative services), no really important result has been achieved so far in this area.

Actually, the most important and notable examples of new biotechnology companies in Lombardy are not university spin-offs, but industrial spin-offs, born out the processes of restructuring large pharmaceutical companies.

One of these cases was Lepetit, leader in antibiotics research and production. After being acquired by Marion Merrel Dow, its laboratories had become one the major research centers in this field. After a series of vicissitudes, however, Lepetit was finally acquired by HMR (Hoechst-Marion-Roussel) and the lab was closed. At this stage, a group of researchers took the initiative to launch a new company, Biosearch Italia, trying to maintain and exploit the accumulated know-how. With the support of venture capitalists (3i Investor in Industry), the new company was founded with the aim of being quoted in the newly created "Nuovo Mercato" (the equivalent of the Neuer Markt or the Nouveau Marché) within the year 2000. Its main research lines are focussed on antibiotics, but new areas have also been opened in anti-tumorals and genomics, in collaboration with the former parent company, now Aventis.

A similar story is that of Newron. Here, once again, a group of researchers from Pharmacia & Upjohn (formerly Farmitalia – Carlo Erba) of the R&D labs near Milan decided to continue their research with funding from 3i in the area of the central nervous system after the closure of their lab. Initially, they are hosted by Biosearch Italy, renting some spaces and services by them. Newron is expected to be quoted on the Nuovo Mercato in about three years.

NovusPharma is a further example, being born from the restructuring processes of the Boehringer Mannheim branch operating in the area of oncology. After the acquisition from Hoffman La Roche, the labs were closed. In this case, three European venture capital firms (the Italian branch of 3i, Atlas Ventures (NL) and Sofinnova (F)) support the initiative of some researchers to create their own company. NovusPharma has already developed collaborations with the National Institute on Tumours, the European Institute of Oncology and the Faculty of Biotechnology of the 2nd University of Milan and maintains an agreement with Roche. NovusPharma has ambitious growth targets and quotation on the Stock Exchange is expected in two years.

4. Discussion: factors explaining the (slow) development of biotechnology in Italy and the case of Lombardy

To a large extent, explanations of the feeble development of biotechnology in Italy, of the clustering of innovative activities in Lombardy and in few other areas and of the specific evolution of the industry in Lombardy tend to coincide. I would also advance the hypothesis that the Italian case is just an extreme instantiation of the a general European experience.

To deal with these questions, however, it must be distinguished between two different issues. First, why was it possible that biotechnology was pioneered in the United States by small, newly founded firms, whereas in Europe largely by established firms? Secondly, why did large established European companies generally react slower in comparison to their American counterparts in adopting biotechnology – more precisely molecular biology?

4.1. *Factors hindering the development of new* biotechnology *companies*

It is now widely recognized that in the United States a combination of factors made it possible for small, newly founded firms to take advantage of the opportunities created by biotechnology. These factors included a strong scientific, technological and industrial base, mechanisms that favoured the communication and transfer of knowledge between academia and the industry, a favorable financial climate, strong intellectual property protection and finally a regulatory climate that did not restrict genetic experimentation. In Europe (although to a lesser extent in the U.K.) many of these factors were not available, and the development of biotechnology occurred at a slower speed and in different forms.

Let us quickly examine the role of these factors in the case of Europe and Italy in particular.

4.1.1. *Strength of the local scientific base*

It is widely recognized that the very strong state of American academic molecular biology played an important role in both facilitating the wave of startups that characterized the eighties (Sharp, 1985; Orsenigo, 1989; Zucker et al., 1998a). The strength of the local science base may also be responsible within Europe for the relative British advantage and the relative German and French delay. There seems to be no doubt about the superiority of the American and British scientific systems in the field of molecular biology, and it is tempting to suggest that the strength of the local science base provides an easy explanation for regional differences in the speed with which biotechnology developed.

In Italy, it is widely acknowledged that the level and the scope of basic research in molecular biology was not very high. Indeed, some research groups conducting state-of-the-art research were present in the early eighties, especially in fields like immunology. Naples and Pavia were particularly important in this respect. In Naples, IIGB (International Institute of Genetics and Biophysics), which was directed for a few years during the 1960s by James Watson, was an internationally renowned research center that spun off successive generations of high quality researchers and clusters of research groups spread all over Italy. Similarly, Pavia constituted another pole of excellence, where Italian studies in genetics were practically born thanks to the work of Buzzati Traverso and where subsequently an important National Research Council group was created and developed. Milan and Rome had also some excellent research groups, whereas Genua had a tradition of research in immunology and IST (Institute for Research on Tumours), a spin-off of the National Institute for Cancer Reasearch) was created. Padua, finally, had developed instead significant competencies in the field of the chemistry of proteins.

Other research initiatives were developed within public research centres (like the CNR's groups or ENEA)[5] and by private institutions. For example, the Italian Association for Cancer Research (mainly a funding agency) introduced a new, competitive approach to the funding of scientific research in Italy. The National Institute for Cancer Research and its offspring IST (Institute for Research on Tumors in Genoa) operated at the frontier of knowledge in experimental oncology and in immunology and had a dense network of relationships with American and British laboratories. Moreover, they have started a systematic attempt since the mid-eighties to slow down the brain-drain-process that was hitting the domestic research system by recruiting expatriated Italian researchers. The Mario Negri Institute for Pharmacological Research, which was initially located in Bergamo and then opened up various branches in other locations, was another center of excellence in research.

In sum, while some good research centers existed, yet on the whole Italian research in molecular biology and in other disciplines relevant to biotechnology was lagging behind most of the major European countries. Above all, research was concentrated in few heterogeneous clusters, with little communication and coordination except personal and informal relationships among the individual researchers. Over the years, the level and the scope of basic research have significantly improved, thanks also to the activities and the international contacts of a younger generation of researchers who studied and worked initially in the U.S.A. and other countries, but they still lag significantly behind the main European countries in terms of absolute amounts of funding, organizational efficiency and overall quality of the research.

The strength of the local knowledge base goes also a long way to account for the agglomeration of innovative activities biotechnology in few clusters in Italy. However, some qualifications are needed. First, as we have seen, Milan did not necessarily have the best scientific research in absolute terms compared to other Italian locations. Second, centers which had poles of excellence in scientific research did not become important biotechnology clusters, e.g. Naples. This would suggest, at this stage, that not only the absolute quality of science, but also the existence of critical thresholds in the "quantity" of good science were necessary conditions for the emergence of clusters.

4.1.2. *Industry-university relations*

An explanation based only on the strength of the local scientific base might seem unsatisfying to the degree that academic science is rapidly published and thus, in principle, rapidly available across regions and across the world. I shall come back to this point in some more length in Section 5. For the time being, is sufficient it to say that even in this extreme case of a science-based technology in the early years of the industry the exploitation of "biotechnology" required the mastery of a considerable body of tacit knowledge that could not be easily acquired from literature (Audretsch and Stephan, 1996; Zucker et al., 1998a; Pisano, 1991; Orsenigo, 1989).[6]

Thus, it has often been suggested that the flexibility of the American academic system, the high mobility characteristic of the scientific labor market and, in general, the social, institutional and legal context that made it relatively straightforward for leading academic scientists to become deeply involved with commercial firms were also major factors in the health of the new industry.

The willingness to exploit the results of academic research commercially also distinguishes the U.S. environment from Europe. This willingness has been strengthened since the late 1970s and the passage of the Bayh-Dole Act, and the resulting role of universities as seedbeds of entrepreneurship has also been extremely important in the take-off of the biotechnology industry.

In contrast links between the academy and industry – particularly the ability to freely exchange personnel – appear to have been much weaker in Europe. Indeed, the efforts of several European governments were targeted precisely towards the strengthening of industry-university collaboration.

Thus, one observes a mushrooming of initiatives all across Europe aiming at establishing stronger links between industry and universities and to encourage a more entrepreneurial attitude of the universities. Policies have practically been targeted mainly to the set-up of specific organizational devices to manage the technology transfer, like science and technology parks or other agencies for technology transfer. These initiatives have taken a wide variety of forms and show a mixed record in their performance.

In the case of Italy, the structure and standards governing the academic system did certainly not favour the entrepreneurial exploitation of university-based research. Interactions between industry and university had been traditionally weak and in any case largely informal and based on personal – rather than institutional – relations.

I shall discuss this issue in some more depth in Section 4.2.2. It may be sufficient to say here that this state of affairs has changed very slowly over the years and only recently symptoms of the diffusion of a different attitude have started to emerge. In a survey carried out in 1994 among the academic researchers participating in the National Plan for Biotechnology – a program launched by the Ministry of University and Scientific and Technological Research (MURST) to sustain biotechnology research and industry-university collaboration, a large fraction of the respondents to the questionnaire were willing to engage more directly in the commercial exploitation of their research. However, administrative rules and the lack of appropriate organizational structures within the universities were quoted as the main factor hindering such developments (Cesaroni et al., 1995). A more recent study on industry-university relations in Italy (Orsenigo and Cancogni, 1999) confirmed that, despite a renewed dynamism in this field, only few universities have developed any systematic organizational structure to deal with the relationship to industry and with the commercial exploitation of scientific research. More than 60% of universities do not even have standard contract typologies, let alone dedicated technology transfer offices.

Thus, the traditional separation between academia and industry and the organizational deficiencies within universities made it very difficult to commercialize academic research. However, it has to be stressed that, given the weakness of scientific research in general, the absence of appropriate "transfer mechanisms" appears to have played a relatively minor role so far. To put it provocatively, transfer mechanisms are largely irrelevant if there is nothing to be transferred. Moreover, as it will be discussed in detail in section 4.2.2, the development of organizational structures supporting technology transfer appears to be largely dependent on the existence of a strong research base.

4.1.3. *Access to capital*

It is commonly believed that the lack of venture capital restricted the start-up activity of biotechnology firms outside the U.S. Obviously, venture capital played an enormous role in fueling the growth of the new biotechnology based firms (or NBFs). However, at least in Europe, there seem to be many other sources of funds (usually through government programs) available for the prospective start-ups. In addition, the results of several surveys suggest that financial constraints did not constitute the main obstacle for the founding of new biotechnology firms in Europe (Senker, 1998). In addition, although venture capital played a critical role in the founding of U.S. biotechnology firms, collaborations between the new firms and the larger established firms provided a potentially even more important source of capital. This raises the question: Why could not prospective European start-ups turn to established pharmaceutical firms as a source of capital? A speculative but plausible answer would suggest that European companies tended to collaborate relatively more with U.S. biotechnology firms.[7] Even in the absence of other institutional barriers to entrepreneurial ventures, start-ups in Europe might have been crowded out by the large number of U.S. based firms anxious to trade non-U.S. marketing rights for capital (Henderson et al., 1999). Given the number of U.S. NBFs in search of capital, European firms interested in commercializing biotechnology had little incentive to invest in local biotechnology firms.

As a partial support to this interpretation, several initiatives were attempted by both domestic and foreign investors to launch venture capital funds in Italy in the 90s, with little success so far. These funds, if anything, ended up investing in new biotechnology companies outside Italy. Conversely, some of the few experiences of successful Italian NBFs have been funded by foreign venture capital firms. Thus, the failed development of venture capital in Italy seems to depend less on the lack of investors and funds than on the paucity of supply of promising start ups based on solid scientific research.

4.1.4. *Intellectual property rights*

It is widely acknowledged that the establishment of clearly defined property rights also played a major role in making possible the explosion of new firm foundings in the U.S., since the new firms, by definition, had few complementary assets that would have enabled them to appropriate returns from the new science in the absence of strong patent rights (Teece, 1986).

In the U.S.A., a very tight appropriability regime in the biotechnology industry emerged quite quickly. In 1980, the Congress approved the so-called Bayh-Dole Act, which gave universities (and other non-profit institutions, as well as small businesses) the right to retain the property rights to inventions deriving from federally-funded research.[8] In 1980, the U.S. Supreme Court ruled in favor of granting patent protection to living things (Diamond v. Chakrabarty), and in the same year the second reformulation of the Cohen and Boyer patent for the rDNA process was approved. In the subsequent years, a number of patents were granted establishing the right for very broad claims (Merges and Nelson, 1994). Finally, a one-year-grace-period was introduced for filing a patent after the publication of the invention.

In Italy, as in Europe as a whole, the grace period introduced in the U.S.A. is not available: any discovery that has been published is not patentable. Moreover, the interpretation has prevailed that naturally occurring entities, whether cloned or uncloned, cannot be patented. As a consequence, the scope for broad claims on patents is greatly reduced and usually process rather than product patents are granted. A draft directive from the Commission that attempted to strengthen the protection offered to biotechnology was approved by the European Parliament only in 1998, and an earlier version was rejected in 1994. Still, considerable controversy surrounds this issue.

While it is clear that stronger intellectual property protection is not unambiguously advantageous, it is however highly plausible that at least in the early days of the industry the U.S. reaped an advantage from its relatively stronger regime.

4.1.5. *A regulatory climate that did not restrict genetic experimentation*

Although public opposition to genetic engineering was a significant phenomenon in the U.S.A. in the earliest years of the industry, it has quickly became less important and in general the regulatory climate in the U.S. has been a favorable one. In contrast opposition to genetic engineering research by the "Green" parties is often quoted as an important factor hindering the development of biotechnology, especially in Germany and in other Northern European countries, and public opposition to biotechnology is said to have been a factor behind the decision of some companies to establish research laboratories in the U.S.A. In Italy, opposition was not, however, an important factor, at least until 1999 when systematic opposition to genetically modified food started to develop among consumers.

4.2. *Factors hindering the adoption of biotechnology among large established firms*

A further important feature of the patterns of development of European biotechnology is the lagged response of many large established companies to adopt the new techniques as compared to American (and to some extent to British) companies. The relevance of this factor can hardly be underestimated. Given the low rate of creation of new start-ups, the development of biotechnology in Europe rested on the activities of large companies. The delay in the adoption of molecular biology within large corporations was therefore an essential factor explaining the European sluggishness. Moreover, in the absence of a vibrant research activity by large firms, new prospective start-ups lacked an essential source of survival and growth, through the establishment of collaborative agreements. As mentioned previously, in the absence of such competencies, large companies would turn to the American scientific and technological base to tap and absorb the new requisite competencies during their catching-up process. Thus, in Europe a vicious circle of the relative backwardness of large firms and low rate of formation of new startups was created.

4.2.1. *Firms' size, market structure and the competitive environment in Europe*

The rate of adoption of molecular biology by established companies varied widely across the world and across firms. Within Europe some large British and Swiss firms were able to adopt the technology rather quickly. Other firms having smaller research organizations, being more local in scope or more orientated towards the exploitation of well established research trajectories[9] found the transition more difficult (Henderson and Cockburn, 1994; Gambardella, 1995). Thus many of the smaller American companies and almost all of the established French, Italian, German and Japanese companies appear to have been slower to adopt the new technologies.

The relative strength of the local science base appears to be again an important part of the explanation. American and U.K. science was rather more advanced than mainland European: hence the slow diffusion of the new techniques to Continental European pharmaceutical firms. This explanation is not the whole story, though. For example, many Swiss companies established strong connections with the U.S. scientific system, suggesting that geographic proximity as such played a much less important role in the diffusion of molecular biology.

A second possible explanation is that diffusion was shaped by the relative size and structure of the various national pharmaceutical industries. The pre-existence of a strong pharmaceutical national industry, with some large internationalized companies, may have been a fundamental prerequisite for the rapid adoption of molecular biology. In many European countries (particularly in Italy), the industry was highly fragmented into relatively small companies engaged essentially in the marketing of licensed products and in the development of minor products for the domestic markets. Notice, however, that while size or global reach may have been a necessary condition, the delay of the largest German firms to adopt these techniques suggest that it was not sufficient. The largest German firms were undoubdtedly among the most internationalized and largest companies in the world.

Thus, the most plausible explanation is that other institutional variables were also important. A possible candidate is the stringency of the regulatory environment. There is now widespread recognition that the introduction of the Kefauver – Harris Amendments had a significant impact in inducing a deep transformation of the U.S. pharmaceutical industry, particularly through raising the cost and complexity of R&D. Partly as a result many U.S. firms were forced to upgrade their scientific capability.

Similarly, Thomas (1994) has suggested that the European country whose leading firms moved more rapidly to adopt the new techniques – Britain – also appears to have actively encouraged a "harsher" competitive environment. Ever since the 60s, the British system encouraged the entry of highly skilled foreign pharmaceutical firms, and a stringent regulatory environment also facilitated a more rapid trend towards the adoption by British companies of institutional practices typical of the American and Swiss companies: in particular, product strategies based on high-priced patented molecules, strong linkages with universities and aggressive marketing strategies focused on local doctors. The resulting change in the competitive environment in the home market induced British firms to pursue strategies aiming less to the fragmentation of innovative efforts into numerous minor products than to the concentration on few important products that could diffuse widely into the global market. By the 1970s, the ensuing transformations of British firms had led to their increasing expansion into the world markets.[10]

The diffusion of the new technologies varied, however, not only across *regions*, but also across *firms*. Most of the firms that rapidly adopted the new techniques were large multinational or global companies, with a strong presence, at least as research is concerned, in the U.S.A. and generally on the international markets. Zucker and Darby present some evidence that size alone is a reasonable predictor of adoption, at least in the U.S. (Darby and Zucker, 1995). Henderson (1994) and Henderson and Cockburn (1996) have shown that those firms that adopted faster and more efficiently molecular biology had also already adopted the techniques of "rational" drug discovery. By and large these were larger firms that had early developed a "taste" for science and were able to integrate the new knowledge within the firms. This was accomplished by a series of organizational changes directed towards building and sustaining tight links to the public research community, essentially through the successful adoption of particular, academic-like forms of organization of research (Cockburn et al., 1997; Henderson et al., 1999). Here other institutional factors appear to have been a necessary, albeit not a sufficient condition. First, it is likely that the Anglo-Saxon forms of corporate governance made it easier for companies to "hire and fire" personnel or rapidly cut non-performing assets, as compared to firms located in "stake holders" economies such as Germany. In addition to the problem of cutting established research competencies, European companies faced the risk of giving long-term employment to biologists before biology was proven to be successful over the long run.[11]

Second, as the adoption of the new techniques and of the associated academic-like forms of organization of research within companies was faster in companies that had early developed a "taste for science", it is tempting to suggest that the origin of the American advantage in the use of biotechnology within large corporations as well as in new biotechnology companies lies in the proximity and availability of first rate scientific research in universities and in the closer integration of industry and the academic community, as compared to other countries. One might also speculate that this was – at least to some extent – the result of a strong scientific base of the American medical culture and – relatedly – of the adoption of tight scientific procedures in clinical trials. Through this mechanism, American companies might have to develop earlier and stronger relationships with the biomedical community and with molecular biologists in particular. Segregation of the research system from both medical practice and close contact with commercial firms (as in France and possibly in Germany) has been highlighted as a major factor hindering the transition to molecular biology in these two countries (see for instance Thomas, 1994 and Henderson et al., 1999).

4.2.2. *Industry-university relations and the structure of academic systems*

These observations lead us back to the question why relationships between science, universities and industry were stronger in the U.S.A. and in the U.K. than in most continental European countries. It is generally recognized that the absolute size and the higher degree of integration of the American research system as opposed to the fragmented collection of national systems in Europe constituted a fundamental difference. Moreover, molecular biology research in Europe was much less integrated with teaching. The relevance of the research-teaching nexus in favoring high-quality scientific research and its integration with industrial research can hardly be underrated. The diffusion of molecular biology into general training in many European countries is a relatively recent phenomenon as compared to the U.S.A. and it has only recently become a standard part of the curriculum of pharmacologists, pathologists and medical consultants (see Senker et al., 1998). Research tended to be confined into highly specialistic laboratories in universities and especially in public research centers, with little interaction with teaching, medical practice and a fortiori with industrial research.

But why does such a gap exist between academic institutions and industry in continental Europe, as compared to the U.S.A.? And why is it so difficult to fill this gap?

Comparative history and sociology of academic systems offers interesting insights for an understanding of the deep motivations of this situation and suggests that improvements may need far deeper changes in the structure and organization of universities than bureaucratic simplification and the introduction of incentives. This literature suggests the conjecture that one (certainly not exclusive) important determinant of the diverging attitude towards collaboration with industry of the continental European academic (and more generally, research) systems and the American (Anglo-Saxon) systems is to be found in their different deep structure and organization, particularly as it concerns the higher degree of integration of teaching and learning that has been characterizing the latter since the end of the last century (Ben-David, 1976; Clark, 1995; Braun, 1994).

These differences are expressed not only in the structure of curricula, but also in the organization of the universities. Specifically, in the U.S.A. (and in Great Britain) departments have long been the main organizational entities as opposed to the European institutes, dominated by a single professor and far less interdisciplinary in nature. Moreover, integration of teaching and learning has been achieved to a much larger extent in the U.S.A. than in Continental Europe by the sharp separation between undergraduate and postgraduate levels. The creation of research-oriented post-graduate studies entailed, in fact, a number of important consequences. In particular, postgraduate students are typically exposed and trained to the practice of scientific research within research teams composed by students and professors within departmental organizations. This arrangement does not only tend to free resources for scientific research, but also provides a fundamental experience in participating to and managing relatively complex organizations. In other words, it constitutes an essential source for the development of organizational capabilities. Moreover, graduate students joining the industrial world after the completion of their studies constitute an essential source of skilled demand for academic research.

The coupling between scientific and organizational capabilities constitutes an essential precondition for subsequent developments in industry-university relations. Indeed, the development of an entrepreneurial function within universities has not substituted the other more traditional functions. The entrepreneurial function rather appears to be strongly complementary to and integrated with the other functions, primarily teaching. The U.S. experience would seem to suggest, in this respect, that linkages with industry simply cannot develop without the constant mediation of teaching, that produces demand for relationships and it is an important source of absorptive capabilities within firms.

In continental Europe, the integration of teaching with research has progressed far less than in the U.S.A. (and to some extent than in the U.K.). Clearly, enormous differences in the educational systems, especially on the higher education level, exist across continental European countries and they certainly should not be overlooked. For example, in France, universities have never been the main center of both scientific research – which has been essentially conducted within the national laboratories and co-ordinated by the CNRS (National Center for Scientific Research) – and the education of the elites – monopolised by the system of the grandes écoles. In Germany, the "institute" – dominated by an individual professor – has been the main organisational unit co-ordinating teaching and research.[12]

Despite these enormous differences, the structure of the academic systems of many European countries shares some important common features, as compared to the Anglo-Saxon systems. Ph.Ds are a relatively recent innovation in many Continental European countries and they remain far less professionally orientated than in the U.S.A. Departmental structures are also relatively new and in many cases institutes continue to be a very important organisational entity. In general, research has tended to be far more removed from teaching than in the U.S.A. And in fact, in many Continental European countries, research has been separated from the universities to a large extent and concentrated in specialised institutions. At the cost of oversimplification, a model has been emerging in Europe based on high degrees of division of labour and specialisation between teaching and research institutions, whereas in the U.S.A. the dominant model has been an integrated one.

It is possible to speculate that this separation might have had negative effects on both the quality of research and on the ability of academic institutions to interact with industry. Integration of research and teaching and collaboration with industry has been relatively more developed and frequent in the case of engineering schools (the Continental European polytechnics) and in some selected disciplines in particular countries (chemistry in Germany). In the 1960–1970s, however, with the development of mass academic education, the scientific revolutions linked mainly to microelectronics and molecular biology (developed mainly in the U.S.A.) and the crisis of the traditional industries mainly connected with the polytechnics, in many cases industry-university interaction further weakened. To remedy this gap, a re-proposition of the "specialized model" has tended to spread in more recent years for the management of the interactions between research and industry and technology transfer. Different from the U.S. case, where universities have gradually extended their functions (an integrated model centered on universities), we observe the development of various types of specialised institutions for technology transfer in Continental Europe, acting as intermediaries between research and industry (the institutional specialisation model).

The presence of large-scale intermediary institutions, however, might in some cases have paradoxically increased the distance between university and industry, introducing an additional layer in the relationship instead of favouring the required organisational and integrative capabilities directly within forms and within academic institutions.

5. Conclusion

In this paper, I have argued that the sluggishness of the development of biotechnology in Italy was due to the lack of most of the basic preconditions for the take-off of innovative activities in this field, as it concerns the scientific and industrial base, the organizational structures linking science to industry, venture capital and intellectual property rights.

Innovative activities clustered, but did not take off, in those regions, primarily Lombardy, where at least some of these preconditions were partially present: concerning the availability of good science and a solid industrial base. But these conditions were not sufficiently developed. As a result, biotechnology did not take off.

These observations might have some implications for policies. Indeed, in recent years European biotechnology seems to have found a new dynamism and even in a backward case as the Italian one, especially in Lombardy, some interesting developments are taking place.

One interpretation of this dynamism might be that policies might have begun to exert some impact. In many countries, measures have long been taken to introduce within Europe some (or parts of) of the typical American institutional features which have been crucial to the development of new biotechnology start-ups, like fostering venture capital, developing financial markets tailored for new high-risk companies, promoting the commercialization of academic research and the mobility between academia and commercial activities. The effects of policies seem to have been widely different across countries and regions. This, in turn, may be the outcome of different policy designs and/or of other structural conditions. In general, these seemed to be a minimum critical thresholds that policies have to overcome before they can have some impact and that in any case interventions aimed at modifying institutions and deeply ingrained forms of behaviour take time.

Thus changes in other structural conditions may have played an important role. A primary candidate is to be found in a general process of maturation and catching-up in the scientific, technological and organizational base of European biotechnology, mainly as it concerns basic research in universities and in large established companies. As it was argued in the paper, the strength and width of the knowledge base, both in universities and in industry, and its integration in efficient organizational forms, was and remains the single most important factor in explaining performance in biotechnology.[13] Thus, the increasing diffusion of molecular biology in the general training of doctors and in the medical practice, an increased integration of research and teaching, the widening and the increasing integration of the research base in Europe produces now state-of-art knowledge that can be exploited by NBFs, at least in specific niches, and by large corporations which are now in the position to express a qualified demand for such research and services.

It could also be noted that the take-off of the European start-ups has been taking place in conjunction with the emergence of new technological trajectories based on generic techniques. Certainly in Germany, but not in Italy, most new start-ups are indeed active in these areas (Casper, 1999). This may not have occurred purely by chance, because these techniques have characteristics that make them relatively easier to develop within the European technological and institutional environment. First, it is intriguing to think that these techniques represent sort of revenge of the old chemical-based research paradigm in pharmaceuticals. Their function is essentially to allow the fast screening of thousands of potentially promising compounds, as it happened – at an infinitely lower speed – at the times of "random screening" before the molecular biology revolution. To the extent that the "culture" of the European industry has remained more closely linked to the old paradigm, it should come as not too big a surprise that it is in these areas that new start-ups have more chances to be born and prosper.

Second, the new companies embodying competencies in these fields are profoundly different from the other types of NBF in nature. Precisely because they are based on generic, transversal techniques, their core competencies are less unstable and technical change is less destroying them. Moreover, they can interact with a large variety of different agents and in principle have a much larger market (Orsenigo et al., 2000). Similarly, lead times are much shorter, because sales are usually on a contract basis and immediate. As a consequence, their risk profile is also comparably lower and access to capital comparably easier (Casper, 1999).

To be sure, the gap with the U.S.A. is far from being filled. Moreover, the institutional structure of most European countries remains profoundly different from the American one. Thus, the future of the new European NBFs and of the patterns of evolution of the biotechnology industry remain to be seen. However, some tentative implications might be drawn from this case.

First, policies can and do have effects, especially if they overcome some critical threshold and if they are "integrated", i.e. they act simultaneously on all the relevant variables. Second, however, policies take time before exerting their effects. Third, the development of a strong research base and of strong technological competencies remains a crucial pre-condition for industrial dynamism and also for the efficacy of other policy initiatives aiming at inducing institutional and cultural changes: the creation of appropriate incentive mechanisms is clearly an important issue, but incentives without competencies may be totally ineffective or even dangerous.

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Notes

1 An independent survey on the Italian biotechnology industry carried out in 1989 showed that of the 134 companies identified by Federchimica as being involved in biotechnology research, only 20 actually do some ongoing research. The total R&D expenditure of these companies was estimated to be around L.200 billion, including expenditures not directly linked to research proper, like salaries paid to all the employees in specialized firms (Orsenigo, 1991).

2 The Tuscany clusters reflect the strong position of Siena, where there is considerable tradition in biomedical scientific research at the university and where Biocine (formerly Sclavo) is located. Conversely, Latium is the location of the headquarters of several multinational companies and thanks to public subsidies several research laboratories have been opened in Pomezia, just outside Rome.

3 In this perspective, the Italian case would seem to support the hypothesis that innovative activities (especially in new technologies) tend to exhibit strong tendencies towards the agglomeration in a few geographical areas and that spatial concentration tends to persist over long periods of time. In the present case, however, this observation might be simply the outcome of a small numbers problem and – more generally – of the absolute low level of innovative activities in this field in Italy. In other words, spatial concentration might result here not so much from the working of specific agglomeration

forces, but simply from the sporadic nature of innovative activities.

[4] Federchimica was located in Milan. Montedison had its headquarters in Milan and its main research laboratories (Istituto Donegani) were located in the neighborhood (although in a different region Piedmont). Similarly, the main research laboratories of ENI, EniRicerche were located just in the outskirts of Milan.

[5] ENEA was the Agency for research on nuclear technologies. Its mission changed several times after the decision to stop nuclear research in Italy and successively became an agency for research in alternative energy sources and a center for coordinating technology transfer.

[6] It is also worth mentioning at this stage that the transmission of this kind of tacit knowledge was probably facilitated by geographic proximity (Jaffe et al., 1993; Audretsch and Feldman, 1996; Swann et al., 1998). In the case of biotechnology, however, other authors have suggested that the U.S. start ups were not simply the result of geographic proximity (Zucker et al., 1998a, b).

[7] Indeed, most NBFs' strategies emphasized licensing product rights outside the U.S. to foreign partners. Thus to an even greater extent than many established U.S. pharmaceutical firms, European firms were well positioned as partners for U.S. NBFs.

[8] The 1984 the passage of public Law 98-620 expanded the rights of universities further.

[9] In short, those firms that had not adopted the techniques of "rational" or "guided" drug discovery.

[10] In many respects the Japanese experience also looks like that pursued in Europe outside Switzerland and the U.K.

[11] I owe this observation to an anonymous referee. A similar argument is suggested by Casper (1999).

[12] An extremely efficient intermediate level of teaching applied disciplines like engineering has been developed (the "Fachhochschulen"), which integrates teaching and practice, but largely overlooks fundamental research.

[13] Mahdi and Pavitt (1997) reach the same conclusion in a study on combinatorial chemistry.

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