Clustering Biotech: A Recipe for Success? Spatial Patterns of Growth of Biotechnology in Munich, Rhineland and Hamburg

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ABSTRACT. The dynamic growth of biotechnology in Germany in recent years has an obviously spatial pattern. Some regions show a substantial potential for start-ups and young firms of this new industry whereas others lag behind. The paper is discussing this unequal spatial development elaborating perspectives which derive from recent debates about regional innovation systems. The biotech regions Munich and Rhineland, both winner regions of the BioRegio Competition are described and compared with the situation in Hamburg where biotechnology is much less important. We analyze the degree and relevance of locally integrated input-output relations of innovation systems based on typologies of the wide range of firms within the biotechnological value chain and the forms of co-operation. Moreover, a qualitative estimate is given with respect to the significance of untraded relationships and regional knowledge spillovers. Factors favoring local integration are compared with those favoring input-output systems on a transatlantic scale. The paper discusses the question whether the biotech industries in the regions of Munich, Rhineland and Hamburg represent identifiable regional systems of innovation. Our findings show that the spatial concentration does not necessarily imply a close network of input-output relations within a cluster. Knowledge and technology transfer often happens on a international, mostly on the North Atlantic scale. The exchange of tacit knowledge, however, is facilitated by spatial proximity. This underlines the importance of untraded relations and "relational assets" in a region. Political and institutional support for building a "business community" can reduce barriers to launch risky commercialization processes.

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1. Introduction

The remarkable rise of biotechnology is marked by spatial concentrations. The wave of successful commercialization processes and intensified research and development resulted in a fast differentiation into many different technologies and applications. Of greatest economic importance are new pharmaceutical products as a result of the discovery of new active substances and new technologies such as genomics and gene therapy. These innovation processes are organized by public research centers as well as small biotech firms and big pharmaceutical multinationals.

Regional motors of an economic use of biotechnological knowledge can be found in the U.S., especially in the Bay Area and the Boston region. But biotechnology has been a very dynamic industry in Germany, too. According to the latest market observation the number of companies increased from about 150 in 1996 to 279 in early 2000. Most of the European start-ups in this sector, the highest share of specialized biotechnology firms and the second highest number of employees are located in Germany (Schitag and Ernst & Young, 1998; Ernst & Young, 1999; 2000). In Germany, biotechnology companies are agglomerated in a few regions such as Munich, the upper Rhine, Heidelberg and Mannheim, Frankfurt, the middle Rhine, and Berlin.

The BioRegio Competition is often mentioned in order to explain the recent dynamics. In order to promote the commercialization process of biotechnology the Federal Ministry of Education, Science, Research and Technology (BMBF) proposed this competition in 1995 and asked regions to compete against each other using

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regional concepts of biotechnological specialization (BMBF, 1996). In November 1999 the BMBF extended this strategy, launching the BioProfile Competition (BMBF, 1999, 2000).

These initiatives reinforced the promotion of applied research and commercialization on a state level by encouraging regional actors and resources. The development of biotechnology concentrated in a few regions and the major role of globally active pharmaceutical companies underlines the challenge of understanding the spatial dimension of the organization of biotechnological input-output systems. This contribution[1] analyzes the degree and relevance of locally integrated input-output relations based on typologies of biotech firms and their forms of co-operation. The paper evaluates the question whether this industry is organized in identifiable regional systems of innovation (as defined by Cooke, 1998; Howells, 1999). It argues that a dynamic comprehension of scales of innovation systems needs to be developed in order to reveal the spatially and organizationally highly selective concentration processes of technology and knowledge production in biotechnology.

2. Regional innovation systems and the selective globalization of technology

The unequal spatial development, regional differentiation and new scales of production and innovation systems are important characteristics of the world economy. The existing literature on the regional variation of technological change and economic competitiveness offers a wide range of explanatory concepts. These explanatory concepts were discussed in debates on new industrial regions and technology districts, national and regional innovation systems and the path dependency of technological and regional developments.

Regional specialization and "techno-globalism"

The discussions on "flexible specialization" (Piore and Sabel, 1984), "new industrial spaces" (Scott, 1988; Saxenian, 1994), "technology districts" (Storper, 1992), "input-output systems" (Storper and Harrison, 1991) and various forms of "industrial districts" (Markusen, 1996) delivered new insights into the remarkable growth of certain regionally integrated industrial districts and new industrial regions. Yet it is obvious that the "new" as well as many 'mature' industrial regions go through a process of successful renewal linked with a strong restructuring of the dominant industry (Gray and Parker, 1998). Further criticism was referred to the underestimation of multinational companies, the concentration of capital and oligopolistic conditions (among others Amin and Robins, 1990; Martinelli and Schoenberger, 1991; Amin, 1992; Amin and Thrift, 1994; Harrison, 1994). Sternberg (1995, p. 165) emphasized the importance of international R&D cooperations causing remarkable disadvantages to locally oriented companies. He also emphasized the internationalization dynamics of industrial districts during the maturing process.

An analysis of the development of biotechnology show the limits of the approaches mentioned above. Parallel to the spatial concentration of biotech firms in a few regions there is a tendency towards the creation of global innovation relations. The multinational pharmaceutical corporations acquire biotechnological know-how on a global level and tie innovation networks on new scales (Drews, 1998). Access to and control of technology became a central factor in international competition. Despite a great variety the processes of "*techno-globalism*" (Archibugi and Michie, 1997) are going on spatially and organizationally extremely selective (Chesnais, 1997; Ruigrok and van Tulder, 1995; Zeller, 2001a).

Innovation systems and their fuzzy spatialorganization

Spatially-oriented innovation research offers important insights for the investigation of innovation systems in biotechnology. The concepts of interactive learning processes focus on the relation of different actors and complex forms of interaction (Kline and Rosenberg, 1986; Lundvall, 1988; Feldman, 1994). In general, innovation can be understood as the search for and the discovery, experimentation, development, imitation, and adoption of new products and production processes as well as of new organizational forms. Therefore it is a fundamentally uncertain process to solve problems linking private with public

knowledge (Dosi, 1988, p. 222). In this sense innovations comprise a broad field of social and economic institutions and connections in a region making up the technological infrastructure. This infrastructure promotes knowledge transfer, helps to solve problems, reduces the costs of innovations and creates innovation capacities or core competences of certain technologies and industrial sectors (Lundvall, 1988).

Following Dosi (1988, p. 222) and Feldman (1994, pp. 22–27) we examine the importance of a regional integration of innovation systems by means of a few features:

- The existence of external economies of scale and scope, especially the pooling of specialized labor market and other factors of production (Krugmann, 1991).
- The clustering of innovations is related to the existence of R&D-institutions of universities and firms in a region as main centers of knowledge creation (see Feldman, 1994, p. 18; Feldman and Florida, 1994, p. 214). The location of research institutions is playing a significant role for the development of a regional innovation system (personal contacts, spin-offs, research cooperation, learning by doing, specialized labor market). These are indispensible prerequisites for the development of biotech clusters. In this respect information spillovers are of particular importance. On the other hand it is by no means sure that regions disposing of a good science base will develop into biotech regions (Storper, 1997, p. 16).
- A reduction of insecurity may enable research-based companies to start different forms of cooperation, exchange information and build innovative networks (Saxenian, 1994). It is primarily the insecurity in connection with the development and use of new technologies that offers an incentive to firms to agglomerate (Lundvall, 1988, p. 355). In the case of biotechnology risk management may be very important.
- The increasing *complexity* of innovations suggests that related industries and specialized business-oriented services are important sources of information and input. The concept of interactive innovation presupposes a lot of information, a variety of decisions and possibilities of different actors coming together to facilitate commercialization (*learning by interacting*).
- Aspects of knowledge are "*tacit*". They cannot be codified and transferred with blueprints and instructions. Such knowledge needs to be acquired by concrete practice and direct social contacts (Nelson and Winter, 1982; Howells, 1998). Therefore *experimentation* in the form of *learning by doing* and *learning by using* gains a particular importance. "*Tacit knowledge*" which cannot be completely codified and transferred facilitates the clustering of innovations. Necessary expertise can come from related industries, customers and suppliers. Audretsch and Stephan distinguish knowledge and information and assume that the costs of transmitting information are invariant to distance but the costs of transmitting knowledge and in particular tacit knowledge increase along with distance (Audretsch and Stephan, 1996, p. 2).
- Technological change is not only a reaction to changes of market conditions but is also influenced by technologies already used. Technological progress is only possible for firms, organizations and countries on the basis of the technological level already achieved. In this sense technological change must be understood as having a cumulative nature.

These factors let us expect that the spatially concentrated firms develop close relations. Studies on the biotech industry, however, suggest that there is a close cooperation among biotech firms and with big pharmaceutical companies, but not in a regional context. In view of the many transatlantic cooperation agreements between European pharmaceutical companies and U.S. biotech firms it is not astonishing that an international technology transfer in the field of biotechnology is of particular importance (see among others Pisano, 1991; Dibner and Bulluck, 1992; Valle and Gambardella, 1993; Sharp et al., 1994; Dolata, 1996; Powell, 1996; Cavalla, 1997). The central problem of technology transfer within and between multinational companies and the cooperation with partners is how tacit or uncodified knowledge can be transferred (Howells, 1998).

In view of the extremely unequal geographical distribution of innovative activities the question of the spatial and organizational unit and of the scales of innovation processes arises. The *evolutionary economists* focus on the dynamics of national innovation systems (among others Lundvall, 1988; 1992b; Freeman, 1995). The internal organization of firms, the relations between firms, the role of the public sector, the institutional setting of the financial sector as well as the intensity and organization of R&D are considered to be the key elements of national innovation systems (Lundvall, 1992a, pp. 4–5). They are a set of institutions whose interactions determine the innovative performance of firms (Nelson and Rosenberg, 1993, pp. 4–5).

Howells (1999, p. 72) transfers this approach to the regional level. The regional governance structures, the long-term development of regional industrial specialization and core/periphery differences in the industrial structure and innovative performance are the most important dimensions characterizing regional innovation systems. Indeed, a company is confronted with very different geographical levels of its own innovation systems. Moreover, the geographical layers of national, subnational, regional and local innovation systems overlapping sectoral layers or sectoral systems of innovation need to be considered. As debates on "new industrial spaces" and "flexible specialization" show regional innovation systems have their own specific internal logic. They are important arenas of localized learning and of exchange of tacit knowledge. The impact of globalization will not entail a direct erosion of regional innovation systems, it will rather lead to an additional spatial unequality (Howells, 1999, p. 87).

Path dependency of technological and regional development

The differences between biotech regions raise questions of the evolutionary dynamics. Evolutionary economics not primarily interested in spatial and regional questions provided an approach helping to understand technological development paths (Nelson and Winter, 1982; Dosi et al., 1988) with special consideration of history, routines, environmental influences and institutions. The concept of a path dependency is based on the assumption of positive cumulative mechanisms facilitating or impeding technological options. Strong effects of the persistence of an industrial structure are opposing the fundamental change of locational conditions (Lundvall, 1988, p. 356). In this sense local technological changes can be understood as an evolutionary path where every step forward moves in a direction which cannot be reversed and future options are limited (Nelson and Winter, 1982; Storper and Walker, 1989, p. 113).

In the context of regional and industrial development paths the question is whether new industrial sectors primarily develop in new growth regions or in mature industrial regions. The analysis of the pharmaceutical and biotech industry provides a contradictory picture. The biotech industry is located in proximity to leading university research institutions in the regions of Boston, San Francisco and San Diego, but also in New Jersey where a strong pharmaceutical industry exists. Remarkably, activities of biotechnological production are more important in New Jersey than in the research-based "new spaces" in California. Also "mature" regions can hold their position in international competition because of the expertise related to the industrial activities (Gray and Parker, 1998).

To clarify the question of path dependency Storper (1997) integrated different approaches in the context of his new heterodox paradigm such as the Californian "new industrial spaces" and the "evolutionary economics" to a "holy trinity" of organization, region and technology whose interaction must be enlightened. In his plea for a new concept of regional innovation systems Cooke (1998, p. 15) relies on similar bases and attaches importance to the regional variations of governance structures. Therefore it is of particular interest how regional governments finance policy and at the same time provide a specific identity to the competing regions. The collective order of a region is determined by mutual trust within an "economic community".

Besides material assets relational assets which are shaped by uncodified knowledge and untraded interdependencies play a crucial role. Storper (1997, p. 28) interprets the economic process as "conversation and coordination" and the subjects

of the process not as factors but as reflexive human actors. In this sense he understands regional economies as "stocks of relational assets".

Material and relational assets are intertwined. Without "soft" communication there will be no "hard" cooperation, without an infrastructure of research institutions and research firms beyond a critical threshold there is no diversity of interaction and no knowledge spillover. A technology core region can establish itself because it provides a productive basis to the non-cosmopolitan knowledge. But non-cosmopolitan knowledge does not necessarily need spatial proximity. It can also be settled in a technological or organizational space such as a big multinational corporation and therefore go beyond territorial spaces. Yet regular human interaction is necessary in an interpretative and personal community (Storper, 1997, p. 70).

With regard to an understanding of the dynamics of biotechnology these approaches can be summarized in the following assumption: Biotechnology tends to develop spatially agglomerated but not necessarily regionally intertwined. Regional innovation relations are overlapped or even structured by interweavings on larger scales. Knowledge inputs, however, may be embodied in human, institutional and facility form. These types of resources are relatively immobile and place-specific. Therefore they facilitate a regional specialization and represent the starting points of specific regional pathways.

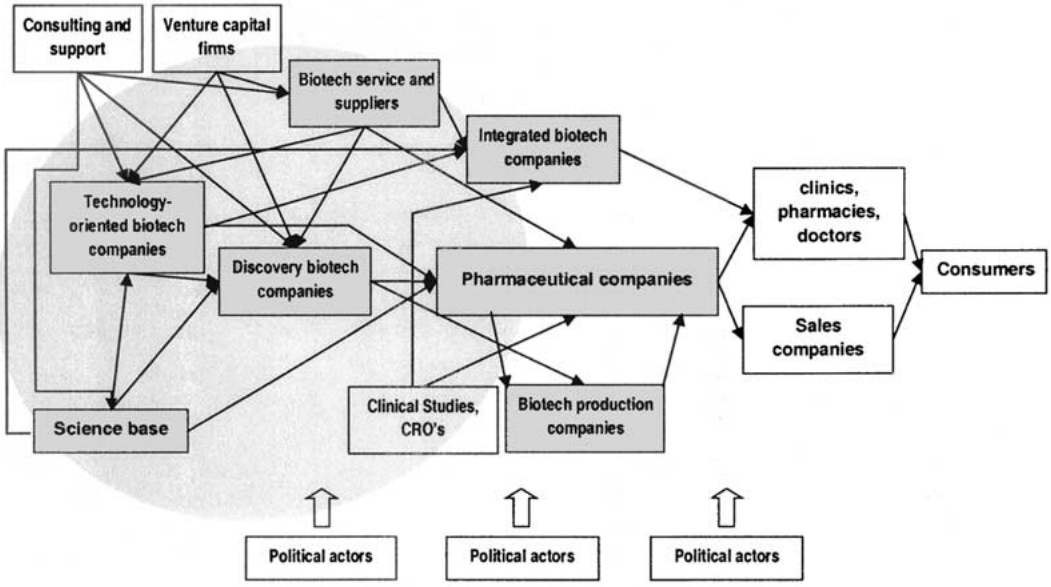
Because of obvious spatial concentrations of biotech firms we examine whether the analyzed agglomerations are examples of "regional worlds of innovation" in the sense of Storper's approach (Storper, 1997, p. 42, Figure 2.2). This contribution discusses the embeddedness and network integration of important biotechnological actors into their social, political and economic environment, created by competitors, clients, suppliers, consultants as well as economic and political institutions. The development process of therapeutics from the discovery of active substances to the market is illustrated in Figure 3. Value creating activities within one firm or a network of firms are characterized by research, development, production and commercialization of a product. In the context of biotechnology quite distinct transactions can represent input-output relations such as

- a sequence of activities to produce knowledge, a technology, a product or a service within a firm and between firms;
- the purchase of raw materials, intermediate products, production means and services necessary for the value creating process;
- the licensing of patent rights;
- services to analyze substances.

Different actors pursuing more or less distinct interests contribute to the emergence of specific innovative conditions in regions. The companies organize sections of the value chain and at the same time they are part of these regional conditions. We can distinguish several groups of actors which either hold a key role in biotechnological input-output systems or play an important part providing a supportive business, political and legal environment: biotech firms, supplier firms, user industries and institutions, institutions of basic research as science base, commercialization actors and political actors. Assuming that complexity and openness towards innovation processes cannot be depicted in quantified models we have decided to base our research on qualitative interviews (Schoenberger, 1991; Healey and Rawlinson, 1993; Markusen, 1994).

3. Munich, Rhineland and Hamburg: Specific Development Paths

On the federal state level three political measures profoundly shaped the development of biotechnology in Germany. First, the establishment of the gene centers in Berlin, Heidelberg, Cologne and Munich between 1984 and 1989 initiated by the Ministry of Research and Education as well as the orientation of an increasing number of university hospitals towards molecular biological activities. Second, the first passing of the genetic engineering law in 1990 and its renewal in 1993. Third, the BioRegio Competition organized by the BMBF (Federal Ministry for Education, Science, Research and Technology) in 1996 (BMBF, 1996; Winnacker, 1998). The BioRegio Competition focused on the promotion of biotechnology on a regional level. Since then the regions have increasingly been invited to reinforce their efforts in biotechnology and to develop their specific profile. Indeed Munich, Rhineland and



Source: Christian Zeller.

Figure 1. Firms and other actors in input-output systems of pharmaceutical biotechnology.

Heidelberg/Mannheim, the winner regions of the competition, developed different kinds and institutions of biotechnology. The BioProfile Competition launched in November 1999 extends this approach and together with BioFuture and BioChance represents a further biotech promotion package in the course of the program "Biotechnology 2000" (BEO, 1998; BMBF, 1999; 2000; BioRegio Initiative, 1999).

Munich: Research-based development

In the course of the "Zukunftsoffensive Bayern" (a future offensive for Bavaria) the state government launched several biotechnology promotion programs financed by an enormous privatization of public assets. The location of Martinsried near Munich gained particular attention in the sense of a regionalized technology policy under the label of "strengthening of the strong". The focus on the location of the Munich metropolitan area was to increase its attractiveness for new biotech firms and venture capital firms and to induce a multiplier effect following the example of the biotech clusters in the U.S.A.

The setting up of important institutions of basic research such as the gene center, the Max-Planck-Institute for Biochemistry and other centers preceded the commercial promotion of biotechnology. In the early nineties the formation of expertise was initiated in order to push the economic development of biotechnology and genetic engineering. Particular emphasis was laid to regional networking and cooperation. Important steps towards the creation of a spatial crystallization of biotechnological research were the Biotech Innovation and of Start-up Center Martinsried (IZB), the Max-Planck-Institute for Biochemistry, the Clinic Großhadern, the gene center, and the shifting of a large part of the natural sciences faculties of the university such as chemistry, pharmacy, biology, medicine and physics to Großhadern (which is located in the near vicinity of Martinsried).

The IZB built in 1994 and extended afterwards is of particular importance. It offers laboratory space for start-up companies, other useful internal and external infrastructure and facilitates formal cooperation and informal networking activities. Bio^{M} AG is a direct result of the BioRegio Initiative and was founded in 1997 to support the biotech region of Munich. Bio^{M} AG raises and

offers seed capital and coordinates grants of the BMBF. Bio^{M} AG offers help to start-up projects by individual business planning and management, helps to organize contacts with cooperation partners and gives advice in questions concerning patents and licensing.

Institutions active in molecular biological basic research are decisive starting points favoring a spatial concentration of biotech firms. Universities and research institutions build the foundations of the science base (Kenney, 1986). In Munich the Max-Planck-Institute for Biochemistry, the gene center and the Ludwig-Maximilian University (LMU) are among the most important institutions. They have formed a substantial basis for several firms founded after 1993. The regional science base is extended by two Fraunhofer-Institutes, GSF-Neuherberge, additional Max Planck-Institutes and the Technical University of Munich. The technology and knowledge transfer between the research institutes and the business sector is organized by means of direct cooperation, patent licensing and personal relationships with the companies within and outside the region. Companies such as MediGene, Connex, Domed, BayKG, Micromet, Microgen, Pulsion and Switch are spin-offs from the LMU, Morphosys, Toplab and Sugen Inc. (U.S.A.) are spin-offs from the Max-Planck-Institute.

In the Munich region the pharmaceuticals and diagnostics company Boehringer Mannheim played an important role. Since 1946 Boehringer Mannheim has been running important biotechnological production facilities in Tutzing and in Penzberg since 1972 (Fischer, 1991). The company had more than 2000 employees at both sites just before the acquisition by the Swiss pharmaceutical giant Hoffmann-La Roche in 1997. In Penzberg Hoffmann-La Roche now disposes of the largest biotechnological research and production site in Germany. Already before the take-over by Hoffmann-La Roche Boehringer Mannheim had invested DM 1.5 billion into the modernization of the sites in Penzberg and Tutzing. Since then Hoffmann-La Roche has integrated the research center in Penzberg into its global research networks and has extended it in a massive way. It is now one of six "centers of excellence" of the pharmaceuticals division with global responsibility for the therapeutic area of oncology. Within the diagnostics division the site is responsible for research, development and production in the fields of "Molecular Biochemicals" and "Heterogeneous Immunoassays". The reinforcement of the site in Penzberg employing about 2500 staff members at present emphasizes the fact that Hoffmann-La Roche appreciates the resources and quality of research and is making any effort to be in touch with the biotechnological potential in the Munich region (Humer, 1999; Hoffmann-La Roche Magazin, 2000, p. 6). Boehringer Mannheim signed a broad range of agreements with universities and research institutes in the region. As the most important employer in biotechnology Hoffmann-La Roche shapes the labor market and contributes to the emergence of specialists with different qualifications. Hoffmann-La Roche is the most important pharmaceutical multinational corporation in the region. In the mid-nineties Hoechst Marion Roussel built a small genomics research center in Martinsried in the direct neighborhood of the well-known biotech company MediGene. Moreover, the multinationals SKW Trostberg, Wacker Chemie, Baxter, Fresenius, Serono and Amgen are present in the region.

Firms in the areas of finance, law and consultancy are of great importance in creating an appropriate biotech-friendly business climate in a region. We summarize these actors under the term of commercialization actors. There are many institutions supporting the financing of biotech companies. International venture capital firms such as ATLAS Venture GmbH, Techno Venture Management Gesellschaft mbH (TVM), Apax Partners & Co. and the Life Sciences Ventures GmbH which settled in Munich in the nineties. Of great importance are also investment firms such as Bayerische Kapital Risikobeteiligungsgesellschaft mbH and the Bay BG, both supported by the federal state of Bavaria. Procuring venture capital is a central instrument of the Bavarian technology policy. Although venture capital firms rarely base their investments on geographical criteria their strong presence influences the orientation of biotech firms. In view of the huge risks VC-firms invest only in companies providing a credible perspective of an initial public offering within a few years (Kulicke and Muller, 1994). Patent attorneys are another group of indispens-

able commercialization actors. Because Munich is the location of the German and European Patent Agencies a broad range of specialized knowledge can be found there. This facilitates the organization of the legal protection of intellectual property necessary for the commercialization process.

Rhineland: Industry induced biotechnology

The building of a gene center in Cologne was also the starting-point of the accumulation of biotechnological competences in Rhineland though the political and economic formation process of biotechnology differs from that in Munich. The BioRegio Rhineland developed from the BioRegio Competition and comprises locations in Aachen, Bonn, Cologne, Bergisch-Gladbach, Düsseldorf, Erkrath, Hilden and Wuppertal. The BioGenTec NRW, founded in 1994 is the central promotion organization in North Rhine-Westphalia developed from a local biotech promotion initiative in Cologne launched in 1991. In the course of the BioRegio Competition the BioGenTec expanded and became the central turntable and motor of the BioRegio Rhineland. It coordinates more specific networks such as the Biotech Competence Network, the Biotech Consulting and Coaching Network as well as the Biotech Capital Network Rhineland and the Bayer-Biotech Investmentfund. A further task consists in the promotion of public acceptance of biotechnology financed up to 90 percent by public means. Promoting biotechnology North Rhine-Westphalia and the BioGenTec want to press ahead with the structural change of the region. The industrial base is understood to be an advantage for the creation of an integrated biotech sector from research to production. The know-how and potential of a specialized workforce in connection with the research and production sites of the chemical and pharmaceutical industry are potentials which can be used. Indeed, successful firms such as Qiagen, Miltenyi and Rhein Biotech focus on activities which also comprise important production steps either of devices and instruments or of pharmaceutical active substances. A diversified biotechnology structure and integrated value chains are expected to be of advantage to a stable growth of the sector. Although there were initiatives for a spatial concentration of biotechnology in Rhineland, i.e. the Pharma-Zentrum Köln-Mühlheim and the Rechtsrheinische Technologie- und Gründerzentrum Köln, research sites as well as firms are spread over the BioRegio Rhineland.

The gene center Cologne, the Institute of Genetics of the University of Cologne, the Max-Planck-Institute for Cultivation Research, the Center of Molecular Medicine in Cologne, the Heinrich-Heine University in Düsseldorf, the Jülich Research Center and the Technical University in Aachen are the major generators of biotechnological knowledge in Rhineland.

The multinational Bayer disposes of locations in Leverkusen, Dormagen, Uerdingen and Elberfeld with about 43,000 employees. The manufacturing of pharmaceutical active ingredients is located primarily at the Wuppertal-Elberfeld site (3,400 employees). The largest pharmaceutical research center of the company is also located here. After a cautious period Bayer intends to extend the site in Wuppertal and build a second production site for recombinant pharmaceuticals in addition to the location in Berkeley. Since the acquisition of the pharmaceutical company Nattermann in Cologne in 1988 the French multinational Rhône-Poulenc was also among the most important pharmaceutical producers in the region. The former site of Nattermann in the north of Cologne became the headquarters as well as the research and development site of the German subsidiary. In 2000 the site counted 550 employees (Rhône Poulenc merged with Hoechst to Aventis in 1999). Besides these big multinationals some mid-size pharmaceutical companies such as Grünenthal, MCM Klosterfrau, Schwarz Pharma and Madaus AG make up the regional labor market and knowledge base (Stadt Köln, 1999; Aventis, 2000).

Like the structure of the biotech companies the financing landscape is quite diversified in Rhineland. Five regional capital investment associations as subsidiaries of local savings banks united as BTK-network and provided DM 70 million. Bayer AG complemented the BTK-network financing the Bayer Biotech Capital Fund endowed with DM 20 million in 1997. The BioGenTec holds a central position within the BTK financing network. It supports company start-ups and proposes companies to be financed. The technology program of the Ministry of

Economy, Technology and Transportation includes so-called "lost grants". The particular role of the regional savings banks in Rhineland is also an expression of the broad promotion strategy. The biotech promotion in Rhineland combines the goals of the technology policy with ambitions of regional economic development.

Hamburg: Modest biotech development

The BioInitiative Nord launched as a common project of Hamburg and Schleswig-Holstein was prompted by the BioRegio Competition. The promotion activities concentrate on biomedicine building on the application-oriented research potential in the region such as the Bernhard Nocht Institute for Tropical Diseases, the Heinrich Pette Institute for Experimental Virology and Immunology at the University of Hamburg, the University Hospital of Eppendorf, the Institute for Hormone and Reproduction Medicine at the University of Hamburg and various institutes at the universities of Kiel and Lübeck. In 1997 the BioInitiative Office as part of the technology transfer office of the Technical University Hamburg-Harburg took over the coordination of the biotech promotion. The successful company Evotec BioSystems was considered to be a crystallization point of a developing biotech landscape.

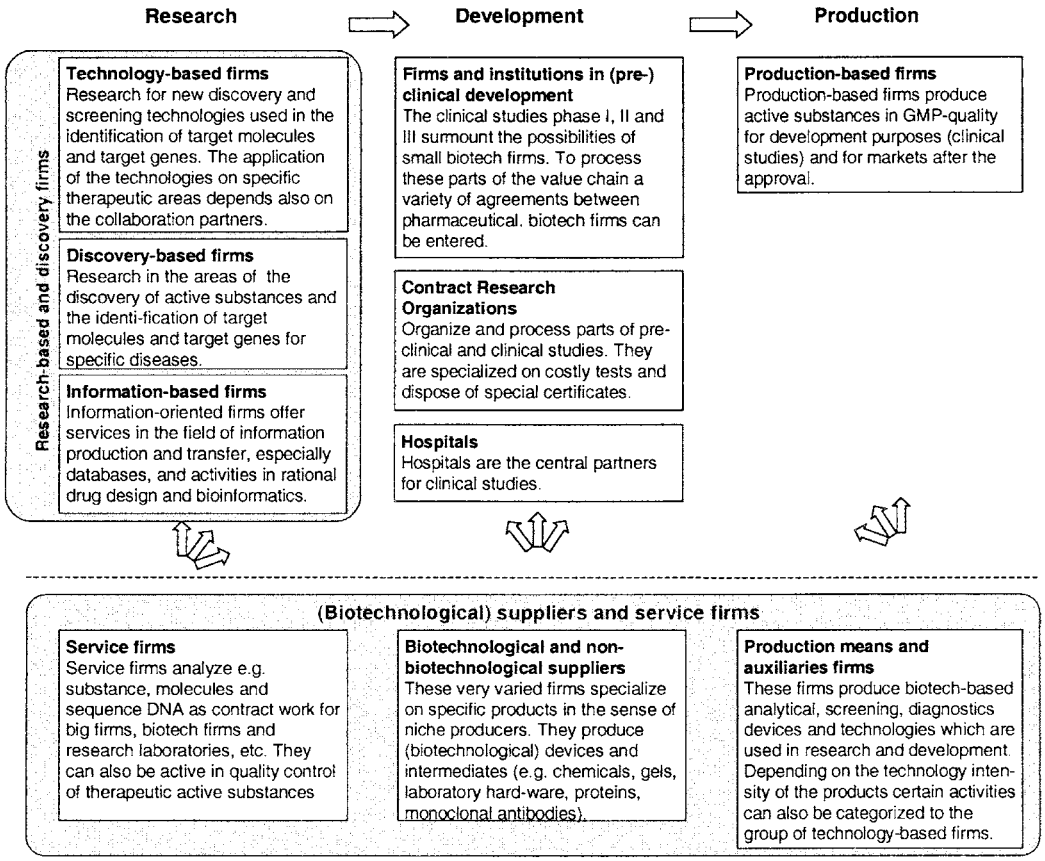
In addition to Evotec BioSystems GmbH founded in 1993 and Sequenom founded by a professor from Hamburg in Boston in 1994 located a subsidiary in Hamburg a year later, about twelve new biotech firms have been founded in the Hamburg, Lübeck and Kiel region since 1996. Probably the most interesting firm is CellTec GmbH which develops methods and active substances based on somatic gene therapy. However, compared to Munich and Rhineland the development of biotechnology and the impulses by the BioRegio Competition are very modest in Hamburg. Motivated by the recent general dynamics of biotechnology and new growth expectations the BioAgency AG was founded by the director of the Institute for Hormone and Reproduction, a co-founder of Evotec and the Hamburg Chamber of Commerce in early 2000 in order to reinforce the promotional activities. Similar to Bio^{M} AG in Munich BioAgency provides seed capital and competent support to new start-up companies. Although there is no significant agglomeration of biotech firms in Hamburg, Evotec AG belongs to the most successful biotech companies in Germany. In mid-2000 the number of employees amounted to more than 240 an the company is pursuing a very ambitious and aggressive international growth strategy (see below). This shows that a dynamic regionally integrated growth and a successful expansion of firms are different and not necessarily linked phenomena of the biotech industry.

Biotech companies: Divers and highly specialized

The patterns of input-output relations are primarily an outcome of the function of the different companies and of other actors in the whole innovation system. Based on the principal activities in the value creating process of therapeutics and diagnostics we can elaborate a typology which takes the core competence of the firm as a central distinguishing feature (Figure 2). This typology of firms allows a better understanding of the typical cooperation agreements which are legal forms of input-output relations. Cooperation agreements always represent specific forms of division of labor. An understanding of the spatial pattern also allows us to grasp the spatial organization of a part of the externalized input-output relations. This method enables us to describe the spatial integration of major actors in a biotech cluster.

Our research shows that the large majority of the firms in Munich is active in the fields of diagnostics and therapeutics while the spectrum of companies in Rhineland is much more diversified. In entire North Rhine-Westphalia of 44 identified core biotech firms only 25% were active in therapeutics and 7% in diagnostics (Prognos, 1997, p. 32). The first biotech companies in Rhineland were founded already in the mid-eighties, earlier than in Munich. Indeed the setting up of Qiagen, the biggest company of the sector took place in 1985. Rhein Biotech emerged in the same year. Miltenyi BioTec started its business in 1989. All three companies are bigger than the most successful companies in Munich.

An analysis of both biotech regions by means of the presented typology shows that more companies in Munich are involved in the discovery



Source: Christian Zeller.

Figure 2. Typology of biotech companies.

of pharmaceutical active substances than in Rhineland. On the other hand Qiagen and Miltenyi in Rhineland, two companies specializing on the production of laboratory instruments, were able to establish on an international level. The firm strategy determines also the spatial organization of input-output relations. Many companies in Munich are dependent on venture capital and therefore adopt an early transatlantic or triadic perspective whereas in Rhineland with a different financing situation the growth strategy must not necessarily be based on venture capital.

Biotechnology as a result of regional conditions

By founding the gene centers, by improving the regulatory conditions and by organizing the BioRegio Competition the federal policy set important general conditions. Various institutions developed a specific biotech promotion policy in the individual federal states and contributed to further the initiatives of a federal government. The BioRegio Competition resulted in an important impetus for biotechnology by founding numerous companies and by establishing networks with other actors. This was the result of a specific German kind of a national technology policy deriving from a deeply rooted federalism that contributed to the breakthrough of new forms in the commercialization of technological innovations. Although political actors in both regions are willing to realize concepts for building "incubator" institutions (Blakely and Nishikawa, 1992), the different development of biotechnology in the regions points out a path dependency. Therefore a connection between the regional economic struc-

ture, the related governance pattern and the specific form of biotechnology can be noticed.

After World War II during a period of catching up-modernization high tech industry settled in the Munich region fostering a positive climate for biotechnology as well. Young firms, institutions of biotech promotion and commercialization actors can profit from a business culture and knowledge whose basis was created by high tech industries (aerospace, electronics and computer) in the decades before. This knowledge, in a sense of a Bavarian "governance spillover", has been successfully turned into the promotion of a biotechnology pathway, especially into successful institutions assisting the commercialization process. Moreover, this knowledge is responsible for creating a friendly public "climate" for biotechnology. The establishment of an innovation and start-up center in Martinsried and of the Bio^{M} AG as effective institutions of biotechnology promotion are an expression of the Bavarian economic and technology policy aimed at making Munich a leading biotechnology location in Europe. The biotech clusters near San Francisco, Boston and Cambridge serve as models.

In contrast, the biotech firms in Rhineland start from the specific circumstances of an old industrialized area with an important chemical industry.[2] Therefore it is not surprising that the most successful enterprises in Rhineland focus less on the discovery process and the development of new pharmaceutical active substances but on the development of biotechnological devices and instruments which are broadly applicable in research laboratories (e.g. Qiagen, Miltenyi) or in specific biotechnological production processes (RheinBiotech). The new industry is characterized by a variety of application sectors and a relative spatial dispersion.

In view of the industrial change and of the massive downsizings in the chemical industry since the end of the eighties the political actors in Rhineland pursue goals in the direction of a regional and employment-oriented policy whereas in Munich priority lies in the development of a research-based technology region. The promotion policy in Rhineland proceeds from the assumption that a broad spectrum of biotechnological activities increases the regional coherence.

Hamburg cannot be considered as a biotech region. Structural change is much more based on other sectors for example media. Fast growing Evotec BioSystems AG incorporated a considerable part of the regional potential. Besides some specific reasons urbanization advantages of a great metropolitan area in general favored Evotec's location in Hamburg.

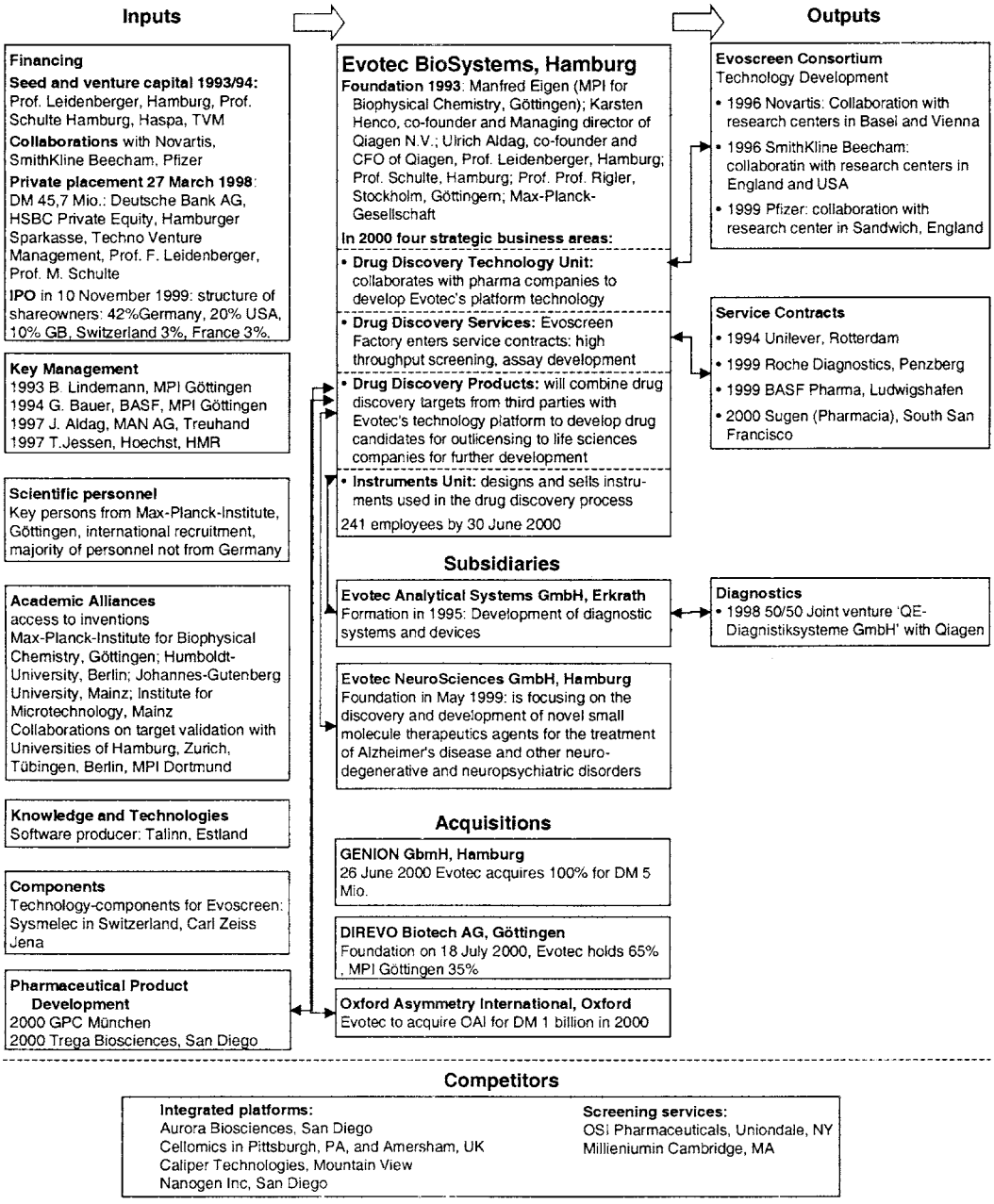
4. Spatial structure of input and output relations

Cooperations as a form of input-output-relations

The typology of cooperations leads to a better understanding of the major input-output-relations in and between companies and institutions. They can only be identified on the basis of a detailed knowledge of the firms and intensive interviews. The characterization of cooperations leads to a better understanding of the externalized input-output relations in the context of a whole innovation system. The internalized input-output relations remain hidden behind the "closed doors" of the firms. The expansion of the Hamburg-based Evotec Biosystems AG shows that innovation relations occur on many different levels. The regional level is only one of them. Qualified labor, early financing and personal networking among the company founders are of great importance (Evotec, 1999, 2000). Despite of their location within a biotech cluster the most advanced companies in Munich such as MediGene and MorphoSys developed similar patterns in their input-output relations (Oßenbrügge and Zeller, 2001).

An *innovation-oriented cooperation* is usually an exchange relationship lasting several months or years. Cooperation for the common development of a technology or a therapeutic active substance requires a high commitment and confidence in the exchange of information among the partners. Such agreements frequently consist of very distinct transactions over a longer period of time creating new knowledge from which both partners can profit. At the same time the innovation process involves great insecurity. Financial returns from the customers range from "*milestone payments*" to royalties and to extensive capital investment in the biotech firm.

Cooperation with producer services in biotech-



Source: Christian Zeller.

Figure 3. Input and output relations of Evotec BioSystems AG, Hamburg.

nology tends to be short-term although there are also long-term orders. The customer usually pays for a clearly defined work of the supplier. This kind of input-output-relation bears little insecurity. The agreement has the form of an order or a purchase. There are normally no significant capital interlockings.

Clinical studies are carried out in close cooperation with hospitals. In the course of the outsourcing of such studies a market for so-called

Contract Research Organizations (CRO) has evolved. "Late stage" biotech firms (such as MediGene), intending to develop their own therapeutics, are dependent on a close cooperation with partners in the field of clinical studies.

At present discovery- and technology-oriented biotech firms are normally not able to carry out up-scaling processes for the production or even the industrial manufacturing of active substances. As a result, a special market developed in this area. Some companies have focused on the *biotechnological production* of therapeutic active substances, for example Rentschler and Thomae (subsidiary of Boehringer Ingelheim). Also Düsseldorf-based Rhein Biotech pursues a growth strategy focused on specialized production processes. It is interesting to see that none of these firms is located in the Munich region.

Cooperation with venture capital firms and patent attorneys can be very decisive in procuring capital and legal safety especially for those companies focused on value intensive and specialized products and technologies. These input-output relations are important components of the entire innovation system.

Cooperation with academic research institutions is an instrument of knowledge transfer and commercialization. The cooperation may have various forms reaching from licensing and the financing of grants for close cooperation partners in common research projects, depending on the object and conditions.

Market-oriented agreements can be very diverse. They can involve a sharing of the markets and/or a licensing of patent rights or a pharmaceutical company can acquire control over the development and marketing rights of a product which is based on an active substance discovered by a biotech firm. In addition we observed the tendency with biotech firms to sell marketing rights to each other in order to neutralize competition. In doing so entry barriers of new markets are reduced for the partners.

Spatial patterns of input-output relations

What are the spatial patterns of such input-output relations? An investigation of important inputs and output such as workforces, technology and knowledge, capital, devices, intermediate products and services helps to show the spatiali character of biotechnology. The following summarizing remarks are based on an investigation of key biotech firms in Munich, Rhineland and Hamburg.

A *highly qualified workforce* and the know-how of this workforce are decisive input factors for research-oriented firms. There are several factors which contributed to a critical mass of researchers in molecular biology and biotechnology especially in Munich. In particular the establishment of research institutes such as the Max Planck Institute, the gene center as well the longstanding existence of companies such as Boehringer Mannheim contributed to the development of a specialized workforce. Although highly qualified specialists can be recruited on a European or North Atlantic level, the existence of a specialized labor market is of particular importance to promote biotech companies. Service-oriented firms as well are dependant on qualified and specialized personnel but not to the same extent as the research-oriented firms.

All companies and institutions improve the qualification of their employees. Thus the general knowledge level is increased and a qualified workforce is created which may serve other firms when people change their jobs. Employees, firms and institutions contribute to the cumulative regional processes of learning by doing.

Knowledge and technologies are strategically the most important inputs for research-based biotech firms. Innovative firms obtain technological knowledge mainly from employees or cooperation partners. A very important input factor is the know-how related to the foundation and management of a company. An already existing team is a prerequisite of a start-up firm. This illustrates that mutual understanding and trust is a crucial factor in the early stage of a biotech company. Spatial proximity to the science base and similar companies facilitates the start-up process of biotech firms remarkably.

On the other hand the acquisition of technological knowledge by in-licensing of patents can happen almost everywhere. Firms focusing on research, technologies or highly specialized production processes such as Morphosys, MediGene, Genome Pharmaceuticals Corporation and Micromet in Munich, Qiagen, Artemis, Rhein Biotech in Rhineland and Evotec in Hamburg

acquired strategic technological inputs from Europe and North America. Moreover, technologies and substances are developed in the course of cooperation agreements with large pharmaceutical companies which normally acquire the rights to commercialize them. These agreements differ in economic and legal forms. The various levels of outputs and knowledge are often summarized in very complex contracts. The most advanced companies are focused on such specialized, high quality and complex technologies that the potentially interested partners must be found on a North Atlantic or Triad level.

Service-oriented firms such as Toplab or supplier firms such as Microcoat organize their input of technologies by purchasing or leasing them. The transfer of highly specialized knowledge by partners, consultants and patents is less relevant than with research-oriented firms. Likewise the production and output of technology and knowledge is less important.

Most research-oriented firms are based on venture *capital*. This is especially true of above-mentioned companies involved in a North Atlantic competition. From the mid-nineties the financing situation has improved remarkably and since that time important venture capital firms have been established in Munich. In addition, companies benefited from public grants of the federal states of Bavaria and North Rhine-Westphalia. Seed capital came from institutions in the regions, the BioRegio Initiative and the European Union. Companies pursuing an international strategy must secure international financing. Highly innovative firms pursue an international strategy at a very early stage. A partnership with well-known internationally active venture capital firms increases the confidence in the technologies and the product pipeline of a company, improving the chance to come to significant cooperation agreements with a pharmaceutical company which will last for several years.

Entering into cooperation agreements with pharmaceutical multinationals is a central strategic aim of research-based biotech firms. After the first period of financing based primarily on venture capital such agreements offer the basis to secure the existence of the company for several years. These companies assume that expansion is only possible according to the pattern of the U.S. companies a few years ago that means pursuing very aggressive and international financing strategies. Private placements and finally the initial public offerings on the stock markets are further components and stages in the financing strategy of a highly specialized research-based biotech company.

Less advanced companies and less internationally oriented firms in contrast are dependent on regional and national financial sources. The personality of the entrepreneur is extremely significant. To avoid dependency or guardianship from venture capitalists a company can deliberately rely on its own capital resources and classical forms of loan capital. In a similar way service-oriented firms in the field of laboratory services finance themselves by loans and own capital. Venture capital is less important because the expected profits are much smaller than those of successful research-oriented biotech firms. Finally, it can be concluded that the availability of seed capital, the existence of financing institutions and venture capital companies in the region can mainly be of great importance during the foundation of the companies.

Although it could be assumed that research-based companies share certain *means of production* with other companies we have found only a few examples of such cooperation in IZB and in the Max-Planck-Institute. The same is true of service-oriented firms and biotech supplier firms regarding the question of the procurement of devices and means of production. Equipment is purchased or leased. But the enormously high costs of such equipment such as for proteomics or mass spectrometrics require a very careful planning of the firm's expansion.

For research-based biotech firms, especially those focused on the development of technologies or bioinformatics, classical physical *intermediate products* are much less important than knowledge and technologies. The geographical origin is of no significance for the procurement of specialized biochemicals, monoclonal antibodies or other biological molecules. Inputs of specialized intermediate and auxiliary products have the character of mass products which can be purchased in many places whereas some intermediate products such

as biochemicals and reagents are important inputs of service firms and biotech suppliers firms. These products can be important outputs used in research and development processes in other biotech and pharmaceutical companies. Although we clearly discovered important transactions between companies in this field, a specific spatial context of these transactions cannot be identified.

Technology and discovery-oriented biotech firms normally procure analytical *services*, DNA-sequencing and other laboratory services from biotech and other companies specialized in these activities. Our research gives evidence for the assumption that spatial proximity to the customers can be very useful for service-oriented biotech firms. This allows a fast and exact handling of the specialized orders. Spatial proximity allows the intensification of the division of labor between clients and service firms though it is difficult to estimate its exact significance.

The exchange of input and outputs can take very different forms and shapes depending on conditions, business sectors and market structure. While input-output-systems of supporting firms like service and supplier firms are characterized by market exchange, relations between research-oriented biotech companies and pharmaceutical multinationals represent a great difference between hierarchies and markets. Depending on the complexity of the common project the cooperation agreements can combine almost all transaction forms such as licensing, purchase, capital investment, milestone payment, royalty and leasing. It is decisive that the cooperation agreements represent exchange relations which will last for several years. Already the enormous transaction expenditures to arrange such longstanding and complex contracts are signs for the importance of untraded relations of all the actors involved.

An analysis of input-output relations of biotech firms shows that with respect to "hard" and traded interdependencies spatial proximity is not a decisive factor. But spatial proximity facilitates "soft" untraded interdependencies and tacit knowledge. The relevance of these factors depends on the business focus, growth strategy, market conditions and maturity of the firms.

5. Conclusion: Scales of innovation systems and untraded interdependencies

Spatial concentration and relational assets

Our research confirms the great importance of public research institutions. A science base strong in quality and quantity is a prerequisite for the spatial concentration of biotech firms. Moreover, adequate conditions are important for the transfer of knowledge into applicable and commercial know-how.

Interactive innovation relations exist on very different scales. Highly innovative and specialized biotech firms active in the discovery of pharmaceutical active substances and the development of new technologies usually enter into cooperation with big pharmaceutical corporations. Such innovation relations are mostly international or transatlantic. Biotech firms offering special services or biotech suppliers are more likely to be integrated in regional innovation relations.

The problems related to the transfer of knowledge as well as the accumulation and transmission of tacit knowledge are decisive factors favoring a spatial integration and specialization of biotech firms and institutions. This spatial integration can take various forms. The emergence of agglomerations of biotech firms as well as the creation of large "centers of excellence" by pharmaceutical companies are possibilities to take into account the importance of tacit knowledge. This does not exclude that common projects and a dense exchange of information and knowledge can be organized over long distances. This is most obvious in the numerous cooperation agreements between biotech firms and pharmaceutical multinationals. However, spatial concentration and accumulation favor "untraded interdependencies" and therefore reinforce regional innovation systems.

Spatial proximity facilitates the integration of specialized suppliers and service firms into the entire innovation system going along with the complexity of innovation processes. For a successful interaction among biotech firms, for service firms and commercialization actors such as technology transfer institutions, patent attorneys, venture capital firms and finance and consulting firms spatial proximity is often more

relevant than for input-output relations among biotech firms.

Significance of untraded dependencies and the significance of regional governance

An agglomeration of firms does not in any way conform with dense intra-regional exchange and interweaving relations. In addition to spatial agglomeration the "systemic" relationships are important to understand innovation systems (Cooke, 1998, p. 10f). To exchange "tacit knowledge" and "untraded interdependencies" spatial proximity is necessary, at least temporally. The significance of untraded relations may be illustrated by the following two examples:

Especially in the early stages of foundation of a company untraded and tacit knowledge can be of great importance. Entrepreneurs must have some knowledge about scientific, market, financing and management issues related to growth perspectives of their firms. A remarkable amount of this knowledge cannot be purchased. It has to be created within specific social contexts of the research community itself. This means that proximity and clustering favors the creation of such untraded dependencies which finally lead to relational assets in a specific region.

The second example emphasizes the cooperation between biotech firms and big pharmaceuticals. In this case, untradable relations are a condition to conclude a complex cooperation agreement. Both partners share the perception of the business perspectives, of the goals and the major milestones of a common project, they have to trust each other. Mutual understanding is necessary to achieve common goals in business activities. But this argument suggests that regional coexistence does not play a crucial role because most cooperations among biotech and pharmaceutical companies are on a North Atlantic scale.

Both examples illustrate different space concepts of firms. While for small and less specialized biotech companies proximity is relatively important to organize their crucial input and output relations, bigger, advanced and highly specialized companies which are focused on high value added technologies and products organize a "time-space-compression". For the latter group it is even necessary to manage operations beyond the regional and national scale.

The different developments in Munich, Rhineland and Hamburg can be interpreted as an expression of specific industrial and technological paths (Zeller, 2000b). The emergence of very specific biotech agglomerations in the regions of Munich and Rhineland as well as the strong political and institutional support of the "business communities" (Cooke, 1998) contributing to the reduction of entrance barriers and a risky commercialization process confirms only partially the existence of "*regional worlds of innovation*" (Storper, 1997). The regional processes are overlapped by powerful triadic or highly selective global processes. Yet the success of the Hamburg-based Evotec emphasizes that agglomeration or clustering are not a condition for a very dynamic growth of an individual corporation.

Regional specialization as a source of extra-profit for multinationals

Successful biotech firms, especially technology- and discovery-oriented firms, normally enter into cooperation with big pharmaceutical companies. This means that globally active companies based outside the regional structure give important incentives for the development of new products and technologies. In the fields of the discovery and development of new pharmaceutical substances regional actors are integrated in global networks which are shaped by powerful oligopolies. Therefore multinationals use the local competence without being forced to contribute to the development of regional assets to the same degree. Thus regional relational assets are an important factor for the re-organization of multinational companies because they allow the internalization of results from research and development activities conducted by external partners as oligopolistic rivals combine regional innovation systems (Zeller, 2001a) by a selective globalization of the use and production of technology.

Fuzzy scales of innovation systems

The results show that the spatial organization of innovation systems in biotechnology must be understood by a differentiated understanding of

the scales of input-output relations which go beyond the rhetoric of globalization and regionalization. Companies organize their input-output relations on very different scales. The tendencies and advantages of regional agglomeration are not equally relevant for all companies, functions and activities. The spatial organization of innovation systems can be shown only by a dynamic interpretation of scales.

- Classical agglomeration advantages exist due to the spatial concentration but they do not reveal the real interweaving in the industry. In contrast, untraded interdependencies and tacit knowledge are factors requiring, at least temporally, a spatial proximity. Innovation processes of highly specialized and advanced technologies normally happen on a North Atlantic as well as on smaller scales. For technologically advanced companies and those competing on a global scale regional and national contexts play a minor role. The scale of innovative activities depends on many different factors such as technological competition, market structure, opportunities for cooperation and capabilities of transferring tacit knowledge.
- The industrial capitals, many regulatory conditions, and political power relations continue to be constituted on a national level. In the context of a global competition national states implement national innovation policies in order to build and attract high value-added sectors in their sphere of influence. The BioRegio and BioProfile Competitions are an expression of these efforts of German technology policy. Organizing an institutionalized competition of the regions represents the specific German variety of a national biotechnology policy taking up deliberately the federalist context of Germany.
- Innovative biotech clusters are a result of an appropriate perception of regional actors with regard to the relations between global scientific and economic conditions and the potentials of a region. At the same time the understanding of the economic and social path dependency allows to identify better options for a future development. Therefore, the local social and cultural context permitting such perception is the sphere where untraded relations and tacit knowledge evolve and where we can identify evidence of a regional innovation system. But the regional scale in itself does not explain the dynamic within certain regions or within the biotechnological sector. Proximity is just one aspect of different and interacting scales of innovation.

Notes

[1] This article is an outcome of the research project *Spatial organization of innovation systems in the field of biotechnology* supported by the German Science Foundation (DFG).
[2] The importance of the chemical and pharmaceutical industry for the emergence of spatial biotech concentrations is controversial (Willoughby and Blakely, 1990; Willoughby, 1993; Gray and Parker, 1998). While the chemical industry in Rhineland plays a very important role and in Munich a subordinate one, the pharmaceutical industry is present in both regions but without being a dominant sector. In the Hamburg region there are only a few pharmaceutical companies and the chemical industry focuses on basic chemicals.

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