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The expectations on mice – rivalry and collaboration in an emerging technological arena

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Christian Zeller

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Universität Bern, Institute of Geography, Economic Geography and Regional Studies
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The expectations on mice – rivalry and collaboration in an emerging technological arena

Christian Zeller
Geographisches Institut der Universität Bern
Hallerstrasse 12
CH-3012 Bern
Phone +-31-631 8556
Fax. +41-31-631 85 11
zeller@giub.unibe.ch

Abstract. Therapeutic products follow a very complex innovation path, from their discovery phase to preclinical and clinical development, to manufacturing and approval for the market. This paper analyzes the innovation paths of two major methods of generating monoclonal antibodies from transgenic mice. It reveals who the key actors were and how the economic and institutional constraints for developing this technology shaped the innovation paths.

The conceptual framework used here combines the technological systems approach and the multi-level perspective. Particular focus is on the numerous contradictory relations that occur in the creation of a technology, such as tensions between different collaborative and rival actors. Such conflictual relations are an outcome of institutional conditions and specific forms of industrial organization. In this sense, the actors involved in the development of the technology for generating monoclonal antibodies from transgenic mice are considered as elements of a technological innovation arena. It is argued that industrial organization, institutional conditions and financial constraints profoundly shape business and innovation strategies, and consequently the overall innovation process.

The empirical analysis herein reconstructs a technology's innovation path, from its origins up to the recent launch of a therapeutic product. The paper also shows how the initial concept passes from relatively protected niches to biotechnology companies which develop the technology and launch the commercialization and diffusion processes. The intellectual property-rights regime and corporate financing decisively influence innovation paths as well. Whereas academic institutes and small biotech firms conduct the innovation process until completion of a technology, large biotech and pharmaceutical companies play an increasingly crucial role in its commercialization and product creation.

Keywords: monoclonal antibodies, biotechnology, technological system, innovation trajectory, intellectual property

1. Introduction

The generation of monoclonal antibodies has become one of the key biotechnologies of recent times. Together with recombinant DNA technology and Polymerase Chain Reaction, the creation of monoclonal antibodies contributed to the emergence of further biotechnologies, new markets and a new industry: the biotechnology industry. The emerging biotechnology firms were the first to enter the drug industry after World War II. Because of the increased diversity of technologies, large pharmaceutical companies are no longer able to pursue the different discovery technologies in-house. Therefore, they enter into collaborations with biotechnology firms for acquiring specific technologies, drug targets and drug candidates.

The first generation of monoclonal antibodies generated by hybridoma technology had murine protein sequences. That is why the human body recognized them as foreign and the immune response led to inactivation of the monoclonal antibody. The challenge of immunogenicity was addressed by different technologies, such as chimerization and humanization, to increase the amount of human protein sequences. Further advances were achieved with phage display technology and with the creation of transgenic mice, both producing human monoclonal antibodies.

The subject of this paper is the evolution and diffusion of the technology of generating human antibodies through transgenic mice possessing a human immune system. Transgenic mice have in fact become a considerable source of human monoclonal antibodies. Currently, there are approximately forty-six projects in clinical trials, six of them in phase-three clinical trials (Medarex, 2007: 1; Abgenix, 2006: 6). In September 2006, the first drug based on this technology was approved by the FDA. It is expected that a considerable number more will be approved in the coming years.

The key questions of this paper are: How was the innovation path of this technology organized? Who were the key actors and what were the economic and institutional constraints for its development? As in the technological systems approach (Carlsson, et al., 2002b; Carlsson, et al., 2002a) and the multi-level perspective (Geels, 2002;2004), the object of analysis here is the evolution of a specific technological field. But instead of emphasizing the systemic relationships within a technological system, I rather focus on the numerous contradictory relations that occur in the creation of a technology, such as the tensions between different collaborative and rival actors, between technological breakthroughs and institutional orders, between industrial organization and technological dynamics and between the fundamentally social nature of technology generation and its private appropriation. Therefore, I consider the actors involved in the development of the technology for generating monoclonal antibodies from transgenic mice as players in a technological innovation arena. This arena is shaped by a specific technological regime and related technological trajectories (Nelson and Winter, 1982; Malerba and Oresnigo, 1993; Malerba and Orsenigo, 1996).

I argue that industrial organization and institutional conditions profoundly shape business and innovation strategies, and consequently the overall innovation process. Industrial organization characterized by selective, vertical disintegration largely defines maneuvering room for small biotechnology firms. The financing opportunities and constraints as well as the intellectual property rights regime are key elements of the institutional environment. The chosen financing methods are conditioned by the macro-economic regime and situation. Financial market conditions, opportunities

for intellectual property rights, second public offerings and partnering play a crucial role in shaping a firm's technological and business strategies for innovation processes and the constitution of an innovation arena (Zeller, 2008b). The intellectual property rights regime (IPR) partially defines the rules of the game. Corporate innovation strategies, corporate rivalry and collaborations are conditioned by the IPR regime and the concrete landscape of property monopolies (Coriat and Orsi, 2002; Coriat, et al., 2003; Orsi and Coriat, 2005;2006). Firms design their competitive and innovation strategies in order to maximize their intellectual property position. They use intellectual property offensively as a weapon against their competitors and rivals, enforcing claims against them or questioning rival claims. Property claims are an important means for the valuation of a company by financial firms and they are a lever for corporate financing (Robbins-Roth, 2000).

This paper will show how a new technology passes from relatively protected niches (Geels, 2002;2004) through a process of transformation and diffusion to the application stage. In such institutionally protected niches, geographical proximity is useful but not decisive. The spatial proximity of key actors favors informal exchange of knowledge and perceptions as well as the crystallization of a techno-business community in an innovation arena. However, technology integration and combination through corporate collaborations are driven by corporate business and technology strategies, which hardly depend on spatial conditions.

In 2006, almost twenty years after the first research efforts were made to generate monoclonal antibodies from transgenic mice, its first therapeutic application was introduced to the market. The contradictory path of such a technology can be illuminated only by analyzing it over a long period and considering cognitive, economic and institutional dimensions. A historical reconstruction and in-depth case analysis provides the basic data for interpretation. Additionally, it must be considered that the importance of technological breakthroughs often can be understood only after their applications are successfully introduced to the market.

This paper's organization is as follows: The second section summarizes the evolution of the monoclonal antibody technology and situates the transgenic mice technology. The third section formulates a conceptual framework derived from a critical assessment of the concept of technological innovation systems and the multi-level perspective. The empirical analysis in the fourth section presents the evolution of transgenic mice technology and the rivalrous race between two companies striving to obtain a competitive lead. The analysis emphasizes the cognitive evolution of the technology, the collaborative networks of the involved companies, their financing methods and their property rights strategies. The fifth section presents a preliminary conclusion. The concluding section of the companion paper *The billion mice – rivalry and collaboration in a rising technological arena* will put the insight into a broader context and critically assesses the current institutional conditions.

The empirical data is based on company reports, media releases and interviews. In September and October 2006 I interviewed 21 researchers and business executives who were involved in the innovation process of monoclonal antibodies, including human antibodies generated from transgenic mice. I am grateful to all interviewees.

2. Monoclonal antibodies in drug discovery

In the course of the molecular biology revolution of the early 1970s, various new technologies in the fields of genetic engineering and cell fusion emerged. The creation of recombinant DNA organisms in 1973 and of monoclonal antibodies by hybridoma technique in 1975, as well as the Polymerase Chain Reaction invented in 1983, were sources of numerous further biotechnologies and applications. New markets and products emerged. The new technologies also had far-reaching effects on the industrial organization of the drug industry. The emerging biotechnology firms were the first to enter the drug industry since World War II.

Antibodies are a broad spectrum of proteins normally found in the blood and generated by the immune systems of vertebrates in response to invading antigens. Antibodies are produced by some of the immune system's B-cells (lymphocytes) and recognize a specific antigen. Each B-cell produces only one kind of antibody. Thus, different B-cells produce structurally different antibodies that bind to different parts (epitopes) of the antigen. Such a natural mixture of antibodies found in serum consists of polyclonal antibodies. Humans have millions of different antibodies with different variable regions (Fig. 1) circulating in their blood. For example, certain antibodies seek out and attach to viruses, bacteria and diseased cells; by marking them they make them susceptible to destruction by the human immune system. But the polyclonal nature of the immune response to any antigen and the difficulty of purifying and manufacturing a single antibody impeded the process of developing antibodies into therapeutic agents for a long time (Reff, 2006: 566ff).

An antibody, or immunoglobulin, consists of two large, identical polypeptides called the heavy chains, and two smaller, identical polypeptides called the light chains (Fig. 1). The so-called variable region of the antibody in both the heavy and light chains is the part of each antibody that creates its unique binding specificity to antigens, such as bacteria, virally infected cells, or tumor cells. The rest of the antibody molecule is made up of a series of domains that are relatively constant in sequence, the so-called constant regions. They can interact with multiple proteins in an animal or human and are responsible for triggering host effector functions, such as lysis (cell death) or phagocytosis (engulfing material by the cell membrane) (Winter, 1989: 540; Reff, 2006: 566).

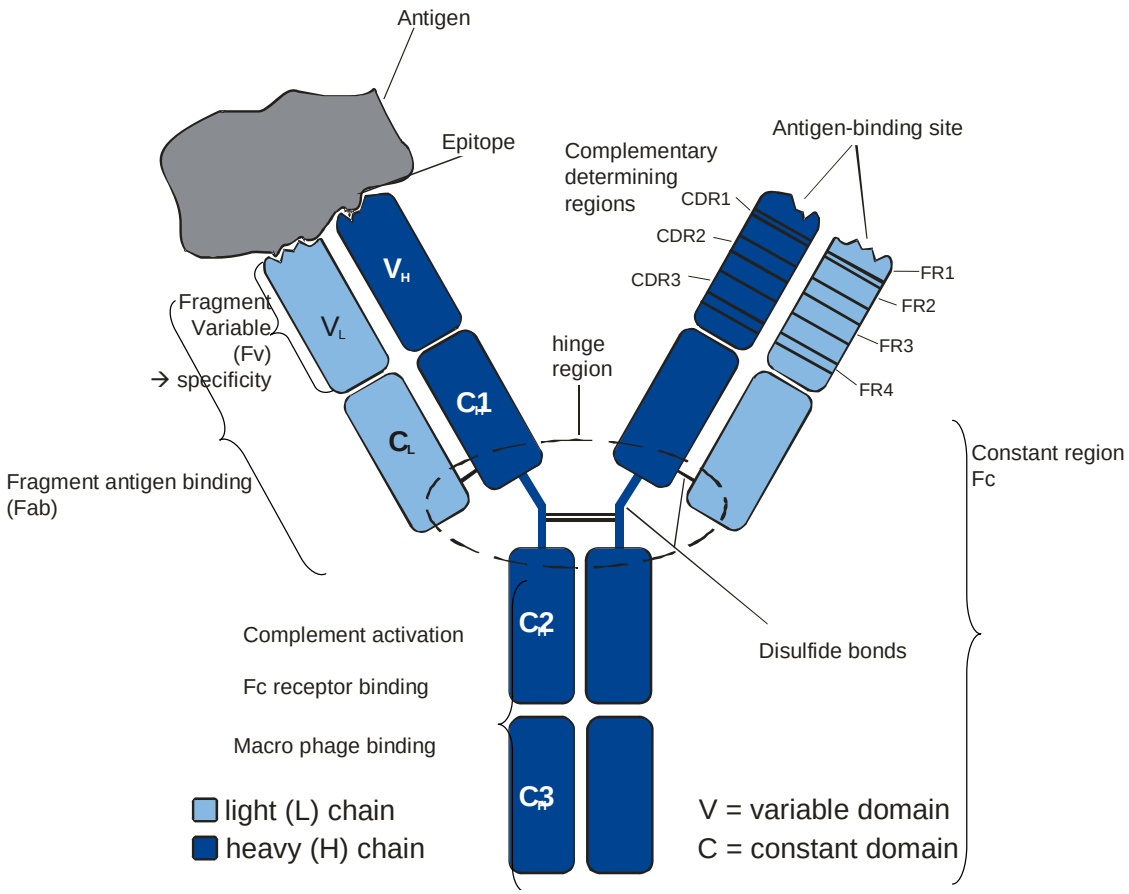

Fig. 1 The structure of antibodies

The invention of the groundbreaking hybridoma technique to create monoclonal antibodies by Georges Köhler and César Milstein in 1974, working together at the Laboratory of Molecular Biology of the Medical Research Council in Cambridge, UK, was a first step toward solving the problems of specificity (high specificity means it binds to only the one particular kind of antigen it is targeted against) and binding quality, or affinity to an antigen (high affinity means it binds tightly so it can neutralize the antigen) (Köhler and Milstein, 1975). They removed B-cells from the spleen of a mouse that had been challenged several times with the targeted antigen. They fused these B cells, which produce a single antibody, with myeloma tumor cells (myeloma is a B-cell cancer), which can grow indefinitely in culture and have lost the ability to produce antibodies. The result was a hybridoma, an immortal cell line that produced a single antibody. Next, antibodies of the required specificity were found by screening. Monoclonal antibodies have specificity to a particular anti-gene. They are identical because they are all derived from the same cell line. Because of the immortal nature of the hybridoma, they can be produced indefinitely (Winter, 1989: 538). Early on Köhler and Milstein thought that the high antigen specificity and affinity of monoclonal antibodies would make them very suitable for human drug development. With the new technology it became possible to distinguish between normal and cancer cells on the basis of reactivity to individual monoclonal antibodies, and thereby to identify molecular targets.

Köhler and Milstein did not patent their invention, which they published in *Nature* (Kohler and Milstein, 1975). They worked in the spirit of open science and were not aware of the consequences of not patenting their breakthrough invention. This was crucial to the further innovation path of monoclonal antibodies. The basic technology was accessible to subsequent scientists. Knowledge and

technology was completely free and spread rapidly to numerous laboratories in the world. That promoted a wave of progress in diagnostics and immunology laboratories. Many scientists founded their own companies to participate in the commercialization of the technological advances. High expectations for the development of cures against cancer and other diseases arose and many companies were launched in the 1980s which tried to turn this breakthrough into marketable drugs.

However, therapeutic applications proved more problematic. There were three major challenges: The human body recognizes murine monoclonal antibodies as foreign. Therefore, murine antibodies provoke the emergence of antibodies to them (human anti-mouse antibodies, HAMA). This immune response leads to inactivation of the monoclonal antibody. It can also cause significant toxicities with subsequent administrations of mouse antibodies. Second, the rodent monoclonal antibodies were often poor at triggering human effector functions. Moreover, the antigen-binding site had to be improved by "affinity maturation" (Dübel, 2007b: 5; 2007a: 723). The third problem was cost-effective manufacturing Hybridomas do not produce enough monoclonal antibodies for cost-effective therapy.

From the mid-1980s until the mid-1990s, scientists re-engineered subsequent generations of monoclonal antibodies to address these immunogenic complications. Different research teams created chimeric monoclonal antibodies with reduced murine and increased human protein sequences. However, the first chimeric monoclonal antibodies created in 1984 and 1985 still had approximately 33% murine protein sequences. Only a few years later, between 1986 and 1990, British and U.S. researchers developed a more sophisticated "humanization" method, resulting in approximately 90% human monoclonal antibodies. Instead of making chimeric antibodies, only the minimum essential parts of the variable domains required to transfer the antigen-binding specificity, the so-called complementary determining regions (CDR), were murine (Winter, 1989). But the resulting "CDR-grafted" antibodies often have diminished antigen-binding properties (affinity). Subsequent engineering to improve affinity can take several months.

Between 1988 and 1991 an approach emerged for creating human monoclonal antibodies through the establishment of phage libraries. Phages are virus-like agents that infect bacteria. Phage libraries are large pools of potential binding sites for a particular antigen. The panning of the library of phage antibodies against an immobilized target enables selection of a single phage specifically binding to this particular antigen. The vast excess of non-binding phage antibodies are washed away. The bound antibody phages are amplified by infection of Echerichia coli (clonal amplification of single phages). Phage-display antibodies also need additional engineering to improve binding affinity to the target.

Advances in making transgenic animals opened a further possibility for creating human monoclonal antibodies. Different teams of researchers achieved major breakthroughs in generating transgenic mice, which produce completely human monoclonal antibodies when they are immunized. In the first half of the 1990s, after a key invention made at MRC in Cambridge, UK, in 1988, this technology was advanced mainly by two groups of researchers from two rival companies, both located in the San Francisco Bay Area: GenPharm, located in Mountain View, and the Foster City-based Cell Genesys. The innovation trajectory of this technology from this key juncture is the subject of this paper.

GenPharm and Cell Genesys, and respectively their acquirer and spin-off companies Medarex and Abgenix, emphasize a number of this method's technical advantages (Lonberg, 2005: 1122; Abgenix,

2006: 11) and the attractive property rights situation. Customers are not forced to pay additional royalties to other parties because the entire process is owned by either Abgenix or Medarex. In contrast, phage-display-derived monoclonal antibodies in particular are situated in a highly complex intellectual property landscape. Several companies own specific phage technologies. Licenses for the patented antibodies may require paying license fees and substantial royalties to different owners of specific property rights.

Both Gen Pharm and Cell Genesys competed in a race for technological and economic advances in the area of monoclonal antibodies from transgenic mice. Property rights played a crucial role in the corporate strategies of both companies. Both used property rights in an offensive way to strengthen their own competitive position at the direct expense of their rival.

3. Technological trajectories and technological arenas

Based on recent contributions on sectoral innovation and technological systems as well as a multilevel perspective, this section summarizes a conceptual framework for analyzing the evolution of a technological field. The concept of technological systems was proposed to analyze the evolution of specific technologies or products (Carlsson, et al., 2002a; Carlsson and Stankiewicz, 1991; Stankiewicz, 2002). Broadly defined, a technological system is a *"network of agents interacting in a specific economic / industrial area under a particular institutional infrastructure and involved in the generation, diffusion and utilization of technology"* (Carlsson and Stankiewicz, 1991). A technological system is conceptualized in terms of knowledge and competence flows rather than flows of ordinary goods and services. Technological systems consist of dynamic knowledge and competence networks (Carlsson, et al., 2002a: 10ff).

The perception of systems raises some problems. Systems are made up of components, relationships, and attributes. When a system is understood as a set of interrelated components whose function is to work toward a common objective (Carlsson, et al., 2002b: 234; Edquist, 2005: 187), the question is, to what extent are different actors in a technological field really working toward a common objective, considering their specific roles and interests? Can an innovation system which evolved in a largely unplanned or even spontaneous manner (Edquist, 2004) really have specific functions, such as generating, diffusing and utilizing technology?

In a capitalist market economy, firms pursue the goal of making profits and improving their competitive position by selling products or services. They do this by applying strategies which, depending on market conditions and institutional contexts, can include all kinds of relations, from hard rivalry to collaborative partnering. On the other hand, the goal of governments and economic promotion organizations is to improve the competitive and technological position of their region or country. In so far as the different actors succeed in applying policies and pursuing economic strategies which enable them to form strong and coherent relations for a common objective, the notion of an innovation system is justified. However, in most cases there is no organic whole or unity. Components do not pursue common objectives, neither on a national, regional nor sectoral level, nor in a specific technological field. Moreover, often a technology evolves over time and space under different

institutional conditions, with actors pursuing different goals. The innovation systems literature tends not to sufficiently integrate analysis of power relations, capital and financial constraints and incentives promoted or diminished by the broader institutional context.

Therefore, I suggest viewing the tensions and contradictions between different collaborating and rivaling actors, between technological breakthroughs and institutional orders, between established technologies and emerging technologies, between industrial organization and technological dynamics and between the fundamentally social nature of technology generation and its private appropriation as decisive forces for understanding the path of innovation processes. Such contradictions provoke configurations of actors and technologies to form new configurations which remain stable for only a limited time, until new tensions and contradictions destabilize them.

In this sense, the paper considers the technological field of generating human monoclonal antibodies from transgenic mice as a technological innovation arena. This arena encompasses individual actors such as entrepreneurs, researchers and financiers as well as organizations such as biotechnology firms, pharmaceutical firms, clinics, financial firms and political authorities. Some of them consciously contribute to the development of the technology; others pursue only partial interests or are purely interested in financial returns. However, even those actors who actively promote a technological development can act as collaborators as well as competitors or rivals pursuing their specific goals of profit-making or social recognition (Fig. 2).

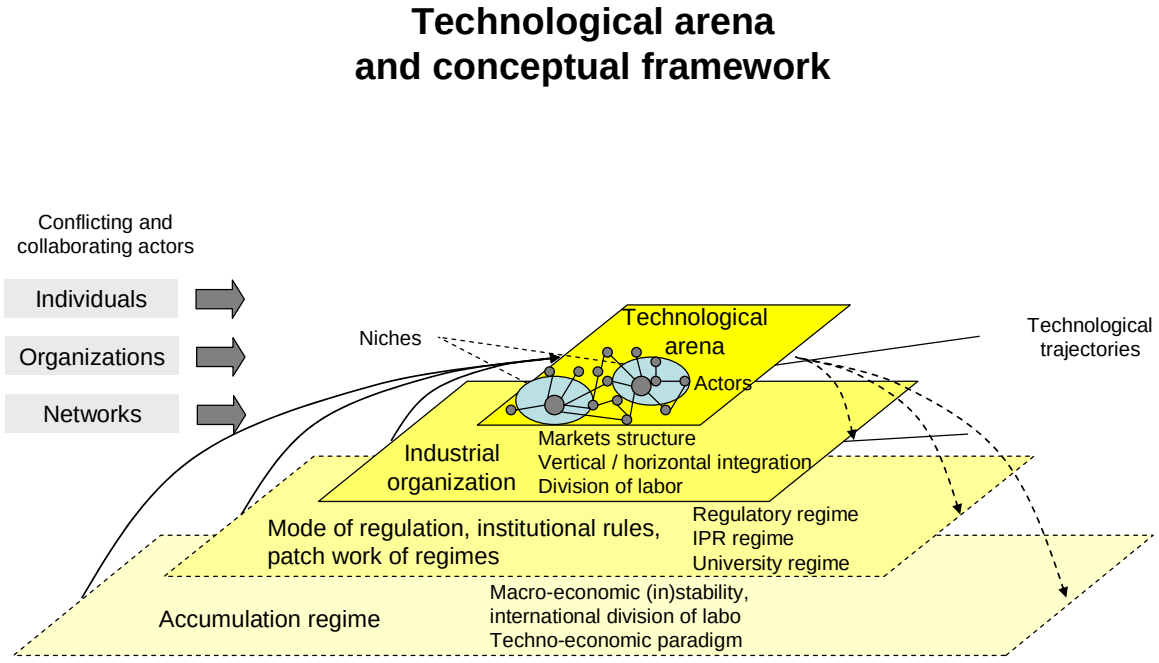

Fig. 2: Technological arena and influencing dimensions

A *technological innovation arena* is composed by clustering technologies to form a new set of technological possibilities (cf. Carlsson, et al., 2002a: 14). This *cognitive dimension*, the evolution of technologies and the accumulation of know-how through learning, adaptation and combination in the field of monoclonal antibody technologies generated by transgenic mice will be analyzed based on scientific publications, company media releases, patents and patent trails. More difficult to understand

is the transfer and appropriation of implicit or tacit knowledge, which can only partly be reconstructed by interviewing key actors.

The coordination between the different actors involved in the creation of a technology can be interpreted as the outcome of organizational and cognitive routines which together form a *technological regime* (Nelson and Winter, 1982: 258). Specific problem-solving methods and market perceptions can be shared by the researcher or engineering community in an industry sector. The selective and cumulative nature of innovative activities serves to channel technological opportunities for further innovations and research efforts into certain directions, or *technological trajectories* (Dosi, 1982: 152; 1988a: 225; 1988b: 1128). However, *technological trajectories* are not only influenced by researchers and engineers, but also by users, political authorities, societal groups, suppliers, financial organization, etc. The activities of these groups are guided by power relations and informal and formal rules (cf. Geels, 2002: 1260). The approach of sectoral innovation systems analyzes changing industrial organization, explicitly taking into account the specific *technological regimes* in an industry sector. Here the notion of *technological regime* concerns specific combinations of opportunity and appropriability conditions, degrees of cumulativeness of technological knowledge and characteristic knowledge bases in specific industries (Malerba and Oresnigo, 1993: 47ff; Malerba, 2002; Malerba and Orsenigo, 2002; Malerba, 2004; McKelvey, et al., 2004).

The *organizational dimension* involves interactions in the network of actors engaged in the creation of these technologies. They are spread across companies, universities, public bureaucracies and industry organizations in various countries (Carlsson, et al., 2002a: 15). The way in which actors in a technological innovation arena collaborate and compete also depends on the type of prevailing *industrial organization.* The organizational structure in the pharma-biotech-complex (Zeller, 2008b) is made up of large pharmaceutical companies running big research and development centers and organizing the commercialization of drugs; biotechnology firms focusing on the discovery of new substances and developing new technologies in specific technological fields; publicly financed research organizations; and universities undertaking indispensable basic research and financial organizations. The specific market and power relations between the different actors in this complex influence the innovation processes and the way new technologies emerge, how they are diffused and commercialized. This organizational dimension will be empirically shown by investigating the role of research institutes, firms and key individuals.

The different actors' behavior and strategies in a technological arena are also influenced by the *broader institutional and economic context.* Formal, cognitive and normative rules that guide the activities of actors and social groups embedded in organizations and networks in a technological innovation arena can be summarized with the notion *socio-technical regimes*. Actors include users, political authorities, societal groups, suppliers, scientists and financial organizations. Socio-technical regimes form a semi-coherent set of rules carried out by different social groups and promote certain stability in the existing system. This results in technological trajectories at the sectoral level. Thus, innovation processes which do not directly contradict a regime are usually of an incremental nature (Geels, 2002: 1260; 2004: 905; Geels, 2005: 367).

It is important to consider the geographically varied institutional conditions and changes which happened over the course of time. The intellectual property rights regime, the university regime –

which connected to a shifted role of universities and publicly funded research organizations, also modified R&D financing mechanisms – the corporate governance and corporate financing regimes all considerably changed since the late 1970s. Altogether, they have condensed into mutually complementing and reinforcing *institutional complementarities* (Coriat, 2002; Orsi, 2002; Coriat, et al., 2003: 240; Zeller, 2008b). These changes have transformed the economic "rules of the game."

The broader *economic dimension* is closely interconnected with the institutional dimension and defines the commercialization of new technological possibilities. The complementary institutional changes are closely linked with the emergence of a finance-dominated accumulation regime (Zeller, 2008b). The rising importance of concentrated placement capital together with changes in macro-economic configuration resulted in new methods of financing innovative activities, especially through venture capital and other financial market-based funds (Zeller, 2008c). The finance-driven model of innovation linked to institutional changes, and the move from 'open science' to 'patent intensive' science changed the behavior of actors such as firms, public research organizations or employees in a technological system (Coriat and Orsi, 2002; Coriat, et al., 2003; Orsi and Coriat, 2005). Transnational corporations' marketing power and capital resources are the decisive elements which permit them to acquire new knowledge and new technologies. Geels used the notion of *sociotechnical landscape* to summarize structural trends and conditions, such as the material and spatial arrangements of cities and infrastructures, as well the environment on a macro-level, such as macro-economic and societal conditions, political development, cultural patterns, migration movements ecological pressures, oil prices and wars. This landscape is an external context for the interactions of actors involved in technology creation, transformation, diffusion and application (Geels, 2002; Geels, 2005: 367). The economic dimension of a technological path on a micro-level can be analyzed empirically by examining the financing methods of firms, corporate collaborations, acquisitions and mergers, and product sales. Licensing agreements represent money flows and the commercialization of knowledge-based enclosed property rights.

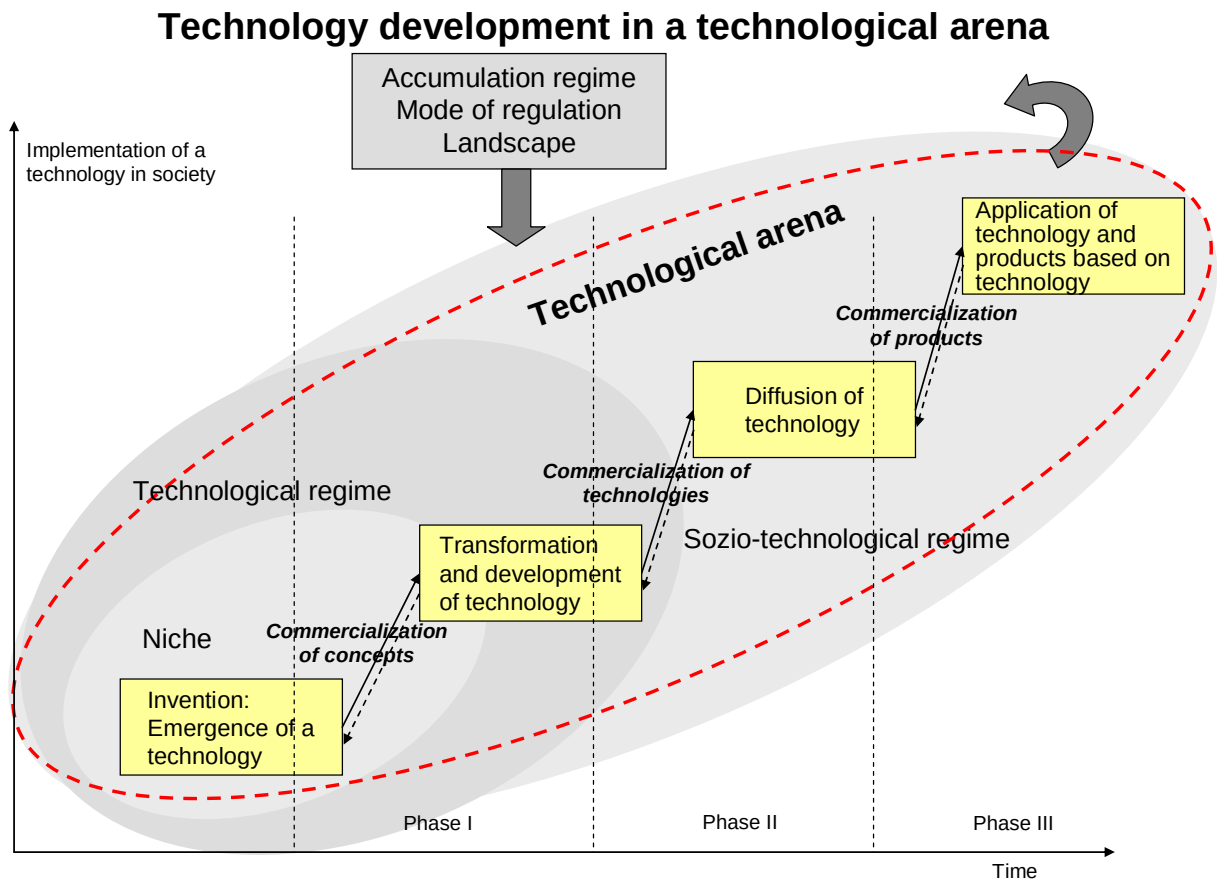

Fig. 3: Technology evolution in a technological arena

Over the course of their evolution, innovation processes are exposed to different actor constellations and economic constraints in such a technological innovation arena (Fig. 3). Radical inventions need *niches* which act as 'incubation rooms' for radical novelties, shielding them from mainstream market selection. Radically new technologies still show relatively low technical and economic performance. Niches also provide space to build the social networks which support innovations. Protection of subsidies is often provided by public authorities or as strategic investments within companies. Niches can offer 'proto-markets' for technologies as long as final products cannot be offered or demand is not yet present. Such *technological niches* on the micro-level are the locus for radical innovations (Geels, 2002: 1261; 2004: 912; Geels, 2005: 366). The spatial proximity of key actors in such technological niches favors informal exchange of knowledge and perceptions as well as the crystallization of a techno-business community in an innovation arena.

When an innovation approaches the stage of an early concept's commercialization, it passes through a *transformation* and modification process. But emerging technologies and rising new technological fields and systems enter into conflict with existing forms of industrial organization and *sociotechnical regimes*. A successful new technology thus proceeds through a *diffusion* stage. This involves a gradual establishment of the new technology within the industry and the prevailing socio-technical regimes. In a fourth stage, products based on the emerging technology are commercialized and applied. This requires a corresponding transformation of the socio-technical regime. In most cases, large pharmaceutical companies control the mass markets of therapeutic products. However, it is not unheard of for new emerging technology-based companies in specific markets to conquer significant marketing positions. When fundamentally radical innovations with far-reaching societal effects gain

broad acceptance, in the long term they can even contribute to a destabilization of the *socio-technical landscape* (Geels, 2005: 367).

4. Technology transfer and transformation, and rivalry 1988–1997

The entire evolution of the technological arena of generating monoclonal antibodies with transgenic mice and the characterization of its key actors can best be presented by distinguishing four phases: The first phase, 1988–1997, saw technology transfer from academic research institutes to the business area as well as technology transformation in applied research. The second part of this phase was shaped by a sharp rivalry between the two firms developing the transgenic antibody technology. This rivalry blocked the innovation process. The second phase of technology commercialization and diffusion was launched by a cross-licensing agreement in 1997, which enabled a business take-off and consolidation. The third phase began in 2006 with the commercialization of the first monoclonal antibody generated from transgenic mice. The second and third phase are presented in the companion paper *The billion mice – rivalry and collaboration in a rising technological arena.*

The four analytical dimensions presented in the previous section strongly interact with one another. Therefore, in the empirical presentation they cannot clearly be distinguished. However, after discussion of each phase in the innovation process, an interim conclusion will summarize the main analytical lessons of the investigated innovation path. The technological arena will be delimited by the actors contributing to the development of the technology of monoclonal antibody generation through transgenic mice. However, in a broader sense, the entire technological field of monoclonal antibodies and its key actors could be considered as such an arena (Zeller, 2008a).

Already in 1985, researchers (Alt, et al., 1985) suggested that transgenic animals could be used for generating monoclonal antibodies with human sequence. In 1989, a research group led by Michael Neuberger, working at the Medical Research Council's Laboratory of Molecular Biology in collaboration with Marianne Brüggemann at the AFRC Babraham Institute, both in Cambridge (U.K.) created transgenic mice with human antibody genes and first reported the expression of a repertoire of human heavy chains and the generation of a trans-gene encoded immune response in these mice (Brüggemann, et al., 1989). Based on this breakthrough, researchers assumed that after immunization of the mice, the application of hybridoma technology would lead to the creation of rodent hybridomas that secreted human antibodies.

Almost concurrently, methods for introducing specific modifications into the mouse germ line were invented by different research teams at the University of Utah in Salt Lake City, the Whitehead Institute in Cambridge (Mass.) and Columbia University in New York. These were important steps toward generating a mouse that possessed diverse human heavy- and light-chain antibody repertoires capable of facilitating a true secondary immune response through high-affinity human monoclonal antibodies, in the presence of disrupted mouse heavy- and k light-chain genes (Lonberg, 2005: 1117).

Two companies and their researchers launched a ferocious race for developing transgenic mice with a human immune system, capable of producing human antibodies. Both GenPharm International and Cell Genesys were founded near each other in 1988/89 in the San Francisco Bay Area by former employees of South San Francisco-based Genentech. Both were venture-capital-driven firms. In each case, the basic goal was to commercialize pioneering technological insights created in universities and public research organizations. Both firms' strategies included first, to out-license technology to collaborative partners. and second, to internally develop technology and drugs based on these new breakthroughs.

The foundations of GenPharm's *HuMab* Technology

Genpharm International started in November 1988 as a merger between two different groups. One group began at Genencor, a company which had spun out of Genentech in 1982. This group was planning to build a company around transgenic animals, specifically transgenic cows that secreted recombinant proteins into their milk. The scientific founder, Herman de Boer, already had been a senior scientist with Genentech. In 1988, De Boer and his group established a company called Genfarm BV, headquartered in Leiden, Holland, de Boers home country. It received seed funding from Genencor and established an early relationship with Leiden University. The other group was also initiated in 1988, but by venture capitalists Sam Colella and Kevin Kinsella (founder of Avalon Ventures) and some other venture capitalists. They had recognized transgenic technology as a promising investment, recruited a scientific advisory board and started a company called Chimera Biotech, Inc., based in South San Francisco. These two groups merged in November 1988, and as a result, GenPharm International became a holding company for the two separate entities GenPharm U.S., Inc. and GenPharm Europe B.V. Jonathan MacQuitty became CEO and Sam Colella, from Institutional Venture Partner, became the chairman of the board of GenPharm International. Previously, MacQuitty had held business positions at Genencor and Genentech. Key investors in GenPharm were Abingworth and Avalon Ventures. GenPharm International first shared office space inside Genencor in South San Francisco, which owned 15% of the company. In early 1990, Genpharm International moved to nearby Mountain View (Carlsen, 1989; Foster and Higuera, 2001; Interview Sep. 2006).

The operations in Leiden specialized in transgenic dairy cattle for production of specific proteins, whereas the Mountain View-based part of the company focused on transgenic laboratory mice and rats for use as models in toxicology, immunology and other medical research and drug-discovery applications as well as for the production of human monoclonal antibodies. The laboratory animal models business brought GenPharm early cash earnings. GenePharming B.V., the renamed corporate branch in the Netherlands, had a major breakthrough in August 1991, when the world's first transgenic dairy calf was born. GenPharm International operated internationally from the beginning, as the founders expected easier access to European funding and talent this way. Remarkably, transgenic monoclonal antibodies were not yet mentioned in the first public announcements. The new firm considered transgenic animals as a platform technology to be used in different applications.

Soon after GenPharm's foundation, Nils Lonberg became the key scientific person. In 1990, he agreed to join GenPharm as a Senior Scientist and was asked to create a transgenic mouse secreting human monoclonal antibodies. Lonberg possessed a Ph.D. in biochemistry and molecular biology from

Harvard University and had worked as a post-doctoral researcher at Memorial Sloan-Kettering Cancer Center in New York City, where he had learned transgenic mice technologies. Prior to this he had been at Biogen in Cambridge, MA. He was promoted to GenPharm's Director of Molecular Biology in 1994, and was in touch with researchers from Frank Constantini's lab at Columbia University. Constantini was a pioneer in the filed of transgenic mice and was also a member of GenPharm's scientific board. His team already had been creating transgenic mice secreting antibodies with human immunoglobulin genes and was collaborating with Genetics Institute. Finally, GenPharm bought the rights to this project. In August 1990, Lonberg filed two patent applications for a rudimentary mouse (U.S. Ser. No. 07/574,748, filed Aug. 29, and No. 07/575,962, filed Aug. 31, 1990). The Sloan Kettering team including Lonberg published its first results on making an antibody with a human heavy chain in September 1990 (Blumberg, et al., 1990; Interview Sep. 2006) (see fig. 4).

Already in June 1989, GenPharm had entered into an exclusive licensing agreement with the University of Utah for the so-called gene-targeting technology, which uses a naturally occurring process of genetic recombination called homologous recombination. Homologous recombination can be utilized as a molecular biology technique for introducing genetic changes into organism. In homologous recombination, a piece of DNA can be exchanged with a homologous recombinant one. This process had been well recognized in yeast already in the late 1970s. But it had not been possible to re-create in mammals until the late 1980s. Gene targeting allows precise modifications to be made in the mammalian genome. It is a method for inserting genes where scientists want them in an animal's DNA. The corresponding patents (U.S. No. 5,464,764 and 5,487,992) had been filed by Professor Mario Capecchi (awarded the Nobel Prize in medicine in 2007) and Kirk Thomas from the University of Utah, Salt Lake City, on August 22, 1989 and issued November 7, 1995 by the United States Patent and Trademark Office (PTO). Capecchi was one of GenPharm's founding scientific advisors and a pioneer in creating transgenic mice. The patent covered methods and materials for using this technology in mouse embryonic stem cells. The original experimental work underlying the patent was published in November 1988 in the journal *Nature* (Mansour, et al., 1988; Hamilton, et al., 1990; GenPharm, 1995b).

On December 17, 1991, Nils Lonberg and other GenPharm researchers reported generating the world's first transgenic mice containing sequences of functional, human immunoglobulin genes that correctly recombine to provide a broad range of antibodies. This was a major breakthrough. But GenPharm was still not certain the mouse development program could be completed (GenPharm, 1991).

One and half years later, on June 8, 1993, the company reported new advances. GenPharm's research team, led by Ted Choi, was the first to inactivate ("knock out") the antibody genes of mice. The new technique allowed the transfer of very large segments of human DNA into mice. These transgenic mice contain a human heavy chain immunoglobulin gene fragment cloned in a yeast artificial chromosome. GenPharm's researchers also integrated techniques developed at the Massachusetts Institute of Technology by GenPharm's scientific advisor Rudolf Jaenisch This work was reported in the same month in the journal *Nature Genetics* (Choi, et al., 1993; GenPharm, 1993b). The GenPharm researchers succeeded in introducing pieces of DNA containing human immune genes using a bacterial-plasmid vector injected into fertilized single-cell mice embryos. These mice produce functional B-lymphocytes that, provoked by an antigen expressed human antibody subunits, could be

used to generate human monoclonal antibodies (Alper, 1993). This was the origin of the *HuMAb Mouse*, which possesses a human immune system.

Some months later, in October 1993, Lonberg gave a presentation at the BioWorld industry conference where he reported for the first time on a mouse that produced fully human antibodies with high affinities to a target. On October 22, at a biotech industry meeting at Laguna Niguel, GenPharm received the 1993 "Best Scientific Achiever" Award for its transgenic mouse system for generating completely human monoclonal antibodies (GenPharm, 1993c; Foster and Higuera, 2001: 15, 32; Stix, 2001; Weintraub, 2006).

The technology's development and the company's therapeutic product development program were still in an early phase. As for other biotechnology companies, it was obvious that it would take a number of years, if ever, before GenPharm would earn any revenues from product sales or royalties. GenPharm's business model was to fund its operations from four different sources. Through collaboration agreements with pharmaceutical and biotechnology firms, GenPharm hoped to receive support fees in exchange for sales access to initial research and development results and royalties, in the case of successful product development. Government research grants were a source of non-dilutive dollars. Equity investments from both financial companies and collaborative partners were a third important source, and GenPharm generated immediate revenues through sales of transgenic mouse models.

GenPharm International, Inc. started in 1988 with a $600,000 Series A and B venture capital investment and a $400,000 investment from the biotech company Genencor. The first investors were all from California (Carlsen, 1989; Foster and Higuera, 2001: 4, 28). On August 4, 1989, a Series C venture capital financing of over $6 million took place, with placements from different venture capital firms (Foster and Higuera, 2001: 8f). Then one year later, in July 1990, GenPharm raised an additional $4.1 million from a group of European investors, thanks mainly to the promising perspectives of its Netherlands-based subsidiary GenePharming B.V. (Atlas Ventures, 1990).

GenPharm's scientific advances helped obtain grants (e.g., from the NIH in May 1991) and convince investors to place their money in the firm's equity (Tab. 1). In November 1991, GenPharm was approached by two investment bankers who wanted to launch an initial public offering. The biotech sector had been performing well during this period, and there was a very favorable cycle for financing biotech companies. However, company executives decided that it was premature for an IPO and preferred a mezzanine financing round, which indeed was successfully closed in January 1992, raising $12 million (GenPharm, 1992a; Foster and Higuera, 2001: 11).

In view of the still favorable context, GenPharm began preparing for an IPO in February 1992 (GenPharm, 1992b), as the IPO window still seemed open for young biotech firms. But on April 16, 1992, the company announced a decision to postpone the IPO indefinitely, because the overall situation had completely changed, Centocor (Malvern, Pennsylvania), a major biotechnology company, had failed with an antibody product in phase III clinical trials (nebacumab, *Centoxin*). In the same period, Xoma Corporation (Berkeley, California) also failed with its antibody drug in phase III (edobacomab, Xomen-E5). As a result, Centocor's stock price dropped and dragged the biotechnology sector with it, especially firms focused on monoclonal antibodies (Robbins-Roth, 2000: 54f; Foster and Higuera, 2001: 14; Reichert and Dewitz, 2006: 191).

GenPharm depended on fresh capital inflow and had to open up new sources of capital. But in the context of an overall downturn in the biotech sector, additional funding was nearly impossible. This financial challenge emerged just when GenPharm had inactivated mouse antibody genes and was close to inserting the required human DNA in a mouse, although the researchers were not yet certain if this technique would work. But it was potentially more valuable than the transgenic cow business and the production of transgenic animal models. Despite the risk of running out of money, GenPharm decided to continue all three activities (Foster and Higuera, 2001: 15). Indeed, in June 1993, GenPharm reported considerable scientific progress in transferring a human antibody gene to transgenic mice (GenPharm, 1993b). The different research grants awarded between August 1992 and January 1994 did not resolve the financial shortage. A collaboration with Eli Lilly and Co. in October 1992, extended in August 1993, was decisive for financing the company's research activities in the field of monoclonal antibodies, as was an attractive agreement with Eisai Co., Ltd., in June 1993, renewed in December 1995 (Tab. 2) (GenPharm, 1993a;1995b; Foster and Higuera, 2001: 30f).

Based on its scientific advances and increased recognition through large pharmaceutical companies, GenPharm decided to file for another IPO in January 1994. Rival firm Cell Genesys had successfully completed its IPO already in January 1993 and a second offering in November 1993. GenPharm's executives believed that a public stock offering would provide the financial basis to launch clinical trials of antibody drugs and to set up manufacturing facilities. However, on February 1, 1994, a few days before GenPharm had prepared its filing for an IPO, Cell Genesys filed a lawsuit in state court in Santa Clara against GenPharm. It charged GenPharm with stealing a trade secret for inactivating a mouse gene. GenPharm immediately denied every accusation, but was forced once more to withdraw its filing for an IPO (GenPharm, 1994b; Foster and Higuera, 2001: 16f).

Tab. 1 GenPharm's financing history

Date	Amount	Investors
1988	$600,000 (Series A and B)	Institutional Venture Partners (IVP); Fairfield Venture; Avalon Ventures; Genencor
Aug. 1989	$6 million (Series C)	IVP; Fairfield Ventures; Delphi BioVentures; Kleiner, Perkins, Caufield & Byers; Merill Pickaard, Anderson & Eyre
30 July 1990	$4.1 million (Series D)	A group of European investors, including: Abingworth Management (UK), Atlas Ventures (NL); Charterhouse Venture Fund (UK); Euroventures (NL)
May 1991	$100,000	Two phase 1 Small Business Innovation Research grants by the National Institutes of Health (NIH).
Dec. 1991	$12 million (Mezzanine)	New Enterprise Associates (NEA); Paine Webber Development Corporation; Sed Ventures; Glynn Ventures; Ronald Family Trust; and nine previous venture capitalists.
4 March 1992		GenPharm files registration statement with SEC relating to an Initial Public Offering
16 April 1992		GenPharm announced to postpone the IPO indefinitely.
18 Aug. 1992	$500,00	One phase 2 Small Business Innovation Research grant by the NIH.
Sep. 1992	Undisclosed amount	Equity investment from Eli Lilly as part of a collaboration agreement.
17 March 1993	$5.3 million	Advanced Technology Program grant by the national Institute of Standards and Technology for extending the technology "Yeast Artifical Chromosomes" (YAC) to insert large genes into transgenic animal models.
10 May 1993	Purchase of $2.0 million of GenPharm stock	Collagen Corporation purchased $2.0 million of preferred stock in GenPharm as part of a collaboration agreement.
June 1993	Payments up to $25	Eisi Co., Ltd. agreed to make research and milestone payments up to $25

	million	million.
3 Aug. 1993	Undisclosed amount	Additional equity investment form Eli Lilly as part of phase II of the collaboration.
19 Aug. 1993	$900,000 approximately	Two 2-year phase II SBIR grants by NIH.
Jan. 1994	$1,000,000 approx.	Fourth phase II SBIR grants by NIH.
24 Jan. 1994	$3.1 million	Grant from the National Institute of Standards and Technology for supporting the program for *in vivo* modeling of human disease in transgenic immunodeficient animal model system.
24 March 1994	$11.5 million loan	Loan for GenePharming form The Netherlands Ministery of Economic Affairs.
April 1994		GenPharm announces to cancel the IPO.
28 June 1994	$3 million	Japanese investors, including: Techno Venture., Ltd; Nichimen Corporation; Kokusai Finance Co., Ltd; Daiwa Business Investment Co., Ltd.; and Fujigin Capital Company.
27 Oct. 1994	$1.6 million	Additional equity investment from Collagen Corporation
March 1997	Payments up to $57 million	Centocor, Inc. agreed to make research and benchmark payments up to 57$ million as part of a collaboration agreements.
March 1997	Up to $37.5 million	Cross-licensing and settlement agreement wit Cell Genesys, its subsidiary Abgenix, and Japan Tobacco.
6 May 1997	Issuance of stocks, no proceeds	Acquisition of GenPharm International by Medarex, Inc. for $65 million in Medarex stock. Medarex issued 3.5 million shares in 1997 and announce the issue of further share by the end of 1998 when GenPharm has receive specific patent license fees. In addition Medarex expects to receive cash of $33 million by the end of 1998 through a combination of GenPharm's cash and certain patent license fees and related payments from third parties

Tab. 2: GenPharm's collaborations and licensing agreements in the field of transgenic mice technology

Date	Partner	Subject
Sep.1989	University of Utah Research Foundation	GenPharm licenses homologous recombination technology developed by a research team at the University of Utah.
April 1990	Stanford University	Worldwide license granting GenPharm the rights to use the hematopoietic stem cell technology
Dec. 1990	LIDAK Pharmaceuticals, San Diego	Joint development of animal models
Jan. 1991	DNX Inc., Princeton	Exchange of licenses: DNX's microinjection technology and GenPharm's homologous recombination technology
March 1991	MIT and Whitehead Institute, Boston	GenPharm gains an exclusive worldwide license for mice lacking a class of antigenic proteins responsible for rejection of tissue transplants.
Sep. 1992	Eli Lilly and Company	Joint development of human monoclonal antibodies for treating certain cancers. The antibodies will be generated form GenPharm's transgenic mice strains. These antibodies will be used against Lilly's drug targets. GenPharm received immediate equity payments and an offer of milestone payments and royalties on resulting products.
June 1993	Eisai Co., Ltd.	GenPharm develops and initially manufactures an antibody product. Eisai makes milestone payments up to $25 million. Eisai received exclusive marketing rights for Asia
Aug. 1993	Eli Lilly and Company	Extension of previous collaboration.
Aug. 1994	Mollegaard Breeding and Research Centre (Ejby, Denmark)	Mollegard became exclusive distributor of GenPharm transgenic rat models in Europe.
March 1995	Nichimen Corporation, Japan	Nichimen became exclusive distributor of GenPharm transgenic animal models in Japan.

Dec. 1995	Eisai Co., Ltd.	Renewal of existing agreement
Sep. 30, 1996	Geron Corporation	GenPharm sub-outlicensed several technologies for genetically modifying primate primordial stem cells prior to their transplantation as a potential treatment for age-related diseases to Geron.
Dec. 1996	LeukoSite, Inc.	Collaboration in the area of immunology and inflammation, on human antibodies against IL-8.
March 1997	Centocor, Inc.	Development of completely human antibodies to several unnamed antigens based on HuMAb-Mouse strain. Research and benchmark payments could total $57 million.

The foundations of Cell Genesys's XenoMouse technology

Foster City-based Cell Genesys also began operating in 1989. In July 1990, the new company completed its first round of venture capital financing, raising over $7 million. Together with earlier seed funding, this round brought the total amount raised to approximately $8 million. Investors included the Mayfield Fund; Robertson Stephens & Co.; U.S. Venture Partners; Interwest Partners; and Stanford University. The business plan for the company was designed in the offices of Mayfield, where company founders began work on the project and started looking for a facility (Interview Oct. 2006).

Cell Genesys's research department was led by Aya Jakobovits, who together with two other scientists were the first employees to start company. She had done her PhD at the Weizmann Institute of Science, Rehovot, Israel, and her postdoctoral work on mouse embryonic stem cells at the University of California, San Francisco (UCSF) together with Gail Martin and Michael Bishop, and had also collaborated with Harold Varmus. She gained experience in molecular biology at Genentech, where she had worked three years prior to joining Cell Genesys.

Like the GenPharm scientists, the founders of Cell Genesys also intended to exploit the gene-targeting technology that is based on homologous recombination and enables genetic modifications in mammalian cells by replacing, activating or inactivating selected genes within cells (Cell Genesys, 1990a; Hamilton, et al., 1990; Sherwin, 1994) (see fig. 4). Cell Genesys acquired an exclusive, worldwide license for the gene targeting technology based on homologous recombination (U.S. patents 5,416,260 and 5,413,923) developed at the University of North Carolina by one of its scientific advisors, Oliver Smithies, in 1990 (TSI, 1992). The company specified three areas of product and technology development, all based on homologous recombination: the manufacture of important therapeutic proteins, the production of completely human monoclonal antibodies and the development of "universal donor cell" transplant products as an application of gene and cell therapy (Cell Genesys, 1990b). Jakobovits became a senior scientist in the company. She led the project from its conception in late 1989 to the creation of the proprietary *XenoMouse* strains. Company cofounder ***Raju Kucherlapati*** was another key person. He was Professor and Chairman of the Department of Molecular Genetics at the Albert Einstein College of Medicine at the Yeshiva University, New York from July 1989 to September 2001, and he contributed decisively to the concept of the *XenoMouse* technology.

The project required the fusion of many different types of expertise. The team consisted of researchers from different areas, such as molecular biologists, specialists on embryos and mice, immunologists and cellular biologists. It was relatively small, ranging from 20 to 25 people and brought different people together developing the *XenoMouse* technology (Interview Oct. 2006).

On March 18, 1993, Cell Genesys reported that two research groups had created two different strains of mice (Cell Genesys, 1993d). One strain was genetically purged of its mouse immune system. In work described in March 1993, scientists successfully used gene targeting technology to eliminate the ability of certain mice to produce mouse-origin antibodies (Jakobovits, et al., 1993b). The other strain was endowed with a large piece of human DNA. The researchers used artificial chromosomes derived from yeast as a carrier to clone very large pieces of the human antibody machinery, from both heavy- and light-chain of antibodies, in order to put them into mouse embryonic stem cells, which were then used to permanently introduce human genetic information into the breeding characteristics of a strain of mouse. This gene transfer technique using yeast artificial chromosomes was applied to introduce an array of human antibody genes into mice in order to produce human monoclonal antibodies. It was presented in the journal *Nature* (Jakobovits, et al., 1993a). Later in 1993, these mice were bred together. The offspring of such transgenic mice, *the XenoMouse,* produced human antibodies following immunization (Leary, 1994; Cell Genesys, 1994c).

On **April 26 and 27, 1994**, one year after publication of the first scientific breakthroughs, both companies, Cell Genesys and Genpharm International, almost simultaneously reported that their research teams had successfully produced fully human monoclonal antibodies isolated from genetically engineered mice and then produced by hybridoma cells (GenPharm, 1994a; Cell Genesys, 1994c; Petit, 1994; Lonberg, 2005: 1117). The GenPharm group, led by Nils Lonberg, summarized its results leading to the *HuMAb Mouse* in the April 28th issue of *Nature* (Lonberg, et al., 1994). The Cell Genesys team, led by Aya Jakobovits, published their breakthroughs forming the *XenoMouse* in the May 1st issue of *Nature Genetics* (Green, et al., 1994). Both articles had been submitted within a week of eachother in December 1993. The race between the two firms to generate human-like monoclonal antibodies from transgenic mice became more difficult. These advances were published only two months after Cell Genesys's law suit against GenPharm, which had had to postpone its IPO.

Back in June 1991, to leverage its modest **financial resources,** Cell Genesys had entered into collaboration with JT Immunotech, a research unit of Japan Tobacco, Inc. This company offered Cell Genesys up to $30 million for a minority equity investment and funding support for company research and development. Cell Genesys was asked to complete the development of a new strain of mice capable of producing fully human monoclonal antibodies. Both partners formed a 50-50 joint venture called Xenotech to market human monoclonals from engineered transgenic mice. According to a media release, "with the extensive resources of Japan Tobacco and its affiliates," Stephen Sherman, president and CEO of Cell Genesys expected his company would "be able to explore a number of product opportunities and proceed as rapidly as possible towards commercialization" (Cell Genesys, 1991).

Japan Tobacco, Inc., committed the funding of $24 million until April 1993. With the joint venture, both companies Abgenix and JT Immunotech obtained the right to use the technology (Cell Genesys, 1993c; Chase, 1993). On January 6, 1994, Cell Genesys and JT Immunotech expanded the scope of

the joint venture by creating the Xenotech Division of Cell Genesys to carry out preclinical studies on human monoclonal antibody products. Cell Genesys received an additional $20 million for operating the Xenotech Division. Cell Genesys maintained options for exclusive North American product rights for those products developed through 1997, whereas the partner Japan Tobacco received the option for products in the same time frame for Japan, Taiwan and Korea (Cell Genesys, 1994d; Sherwin, 1994).

Already on March 17, 1992, only two weeks after GenPharm's first filing, Cell Genesys filed for an initial public offering of 3 million shares of common stock at a price of $11 to $13 a share (Cell Genesys, 1992a). Like GenPharm, because of the rapidly changing biotech financing landscape, Cell Genesys postponed its IPO. One year later, a new IPO window opened. After a successful private placement raising $9 million in October 1992, and on the wave of a biotech-friendly stock market constellation, Cell Genesys successfully completed its IPO in January 1993, raising $40.9 million after deduction of fees and commissions. In a successful follow-on offering in November 1993, Cell Genesys collected another $35.4 million net. The new cash enabled the firm to launch an extensive recruiting program for experienced personnel, mainly in management, and for product development (Cell Genesys, 1992b;1993e;1993a;1993c;1993b).

Cell Genesys's technology strategy was to develop quite varied applications, all based on homologous recombination and gene modification. In the first phases, it was not yet clear which application would be most successful. Besides an evaluation of its own technology portfolio, the company's strategy was also influenced by overall perceptions in the "biotech and pharma world." In the mid-1990s, the perspectives for monoclonal antibodies were not yet confirmed. However, several large pharmaceutical firms bet on cell and gene therapy (which has not been confirmed until today). In addition, already in July 1994 Cell Genesys's CEO Stephen Sherwin announced an increasing long-term focus in the cell therapy area (Sherwin, 1994).

This successful corporate funding strategy – first an attractive joint venture agreement which helped generating revenues in the early years, and then a successful IPO completion and follow-on offering – was decisive for further business and technological evolution in the coming years. Cell Genesys disposed of $85.7 million cash, cash equivalents and short-term investments at the end of 1993, up from $15.5 million at the end of 1992. Thus, Cell Genesys was in a very comfortable position to pursue its technology and product development program and to frontally attack rival GenPharm International with a law suit in early Februay 1994 (Cell Genesys, 1994b;1994a).

Tab. 3: Cell Genesys's financing history until the spin-off of Abgenix

Date	Amount	Investors
23 July 1990	$7 million first round	Mayfield Fund; Robertson Stephens & Co.; U.S. Venture Partners; Interwest Partners and Stanford University
12 June 1991	$30 million (later information $ 25 million)	Minority equity investment and funding for research and development by JT Immunotech (subsidiary of Japan Tabacco). Cell Genesys will complete the development of a new strain of mice capable of producing fully human monoclonal antibodies Additionally, Cell Genesys and JT Immunotech USA form a 50-50 joint venture called Xenotech.to develop and commercialize drugs based on human monoclonal antibodies.
17 March 1992	3 million stock at $11-13 each	Filing for an IPO at the SEC through Robertson, Stephens & Company; Oppenheimer & Co.; Daiwa Securities America, Inc.

8 Oct. 1992	$9 million	Private placement (total private equity funds raised to this date approximately $25 million). New investors include General Electric Investment Corp.; New York Life Insurance Co.; Frazier & Co. and Invemed Associates, Inc.
4 Jan. 1993	3 million stock at $9-11 per share	Filing for an IPO at the SEC through Robertson, Stephen & Company; Invemed Associates, Inc. and Oppenheimer & Company Inc.
26 Jan. 1993	4 million stock at $ 11 per share providing $40.9 million net	Successful IPO providing Cell Genesys $40.9 million net in cash.
9 Feb. 1993	$10 million	JT Immunotech USA will provide a second phase of research funding of approximately $10 million for research in the human monoclonal antibody field through June 1995. To date, Cell Genesys received approximately $11.4 million through the joint venture and expects to receive further funding.
April 1993		At the end of the first quarter, Cell Genesys had $54 million in cash. Since June 1991 Cell Genesys received $24 million from Jaban Tobacco.
1 Nov. 1993	2 million stock	Filing for a stock offering at the SEC through CS First Boston; Invemed Associates, Inc. and Oppenheimer & Co.
19 Nov. 1993	2 million share at $19 per share providing $35.4 million net	Successful stock offering providing Cell Genesys $35.4 million net in cash.
6 Jan. 1994	$20 million	JT Immunogech pays Cell Genesys $20 million for the creation of the Xentech Division of Cell Genesys to conduct ongoing preclinical research on behalf of Xenotech L.P., both companies' equally owned joint venture for the commercialization of fully human monoclonal antibody products. Xenotech granted options for exclusive marketing rights to Cell Genesys in North America and to Japan Tobacco in Japan, Taiwan and Korea. Xenotech. Xenotech will fund the new division of Cell Genesys with an estimated $40 million through 1997. This additional $20 million in net revenues would brig to$44 million the total amount of payment to Cell Genesys from the inception of the joint venture in June 1991 through 1997.
16 May 1995		Filing for a secondary stock offering. 1,475,002 shares are being sold by early venture capital investors. No proceeds for the Cell Genesys
24 May 1995		Cell Genesys completes secondary stock offering.
12 July 1995		Agreement with JT Immunotech USA Inc. for extension of research collaboration for human monoclonal antibodies for approximately two additional years. Up to this date, Cell Genesys had received approximately $27 million through its agreement with JT Immunotech.
	$ 150 million	Collaboration with Hoechst Marion Roussel
27 June 1996		Cell Genesys spins off its antibody business in a new company called Abgenix which receives the partnering rights with JT Immunotech and $10 million in cash from Cell Genesys.

Tab. 4: Cell Genesys's collaborations and licensing agreements in the field of transgenic mice technology (collaborations in other fields such as cell and gene therapy are not listed)

Date	Partner	Subject
1990	University of North Carolina	Cell Genesys acquires exclusive, worldwide license for a gene targeting technology developed by Oliver Smithies from the University of North Carolina.
12 June 1991	JT Immunotech, U.S. subsidiary of Japan Tobacco	Cell Genesys receives $30 million for a minority equity investment and funding support. Both partners establish a 50-50 joint venture, called Xenotech L.P., to develop and commercialize products based on human monoclonal antibodies.
25 June 1992	Dana-Farber Cancer Institute, Boston	Cell Genesys licenses exclusive worldwide rights to a cell adhesion molecule believed to be a drug target to treat inflammation and cancer with human monoclonal antibodies.
30 Sep. 1992	TSI Corporation, Worcester, Mass.	Cell Genesys sells license to TSI Corporation granting access to

		proprietary gene targeting technology originally developed by O. Smithies, University of North Carolina.
6 Jan. 1994	JT Immunotech, U.S. subsidiary of Japan Tobacco	JT Immunotech and Cell Genesys create the Xenotech Division of Cell Genesys to conduct ongoing preclinical research on behalf of Xenotech L.P. The Xenotech joint venture will fund the new Xenotech Division with an $40 million to conduct preclinical research through 1997 (net revenue ä20 million).
29 March 1994	Medical Research Council, Cambridge, UK;	Cell Genesys licensed the lambda light chain and also obtained certain related materials from the MRC.
May 1994	University of Columbia, NY Immgenics	Cell Genesys acquires license for SLAM technology.
12 July 1995	JT Immunotech USA, Inc., subsidiary of Japan Tobacco.	Extension of research collaboration for human monoclonal antibodies for approximately two additional years.
27 June 1996	Japan Tobacco	Cell Genesys spins off its antibody business in a new company called Abgenix which receives the partnering rights with JT Immunotech and $10 million in cash from Cell Genesys.

Sharpened rivalry and blocked innovation, 1994–1997

GenPharm was preparing an IPO in February 1994 when Cell Genesys – financially well equipped after going public – sued GenPharm. Cell Genesys accused its rival of industrial espionage, stealing a trade secret for inactivating a mouse gene and unlawfully filing patent applications covering this technology. Cell Genesys claimed that a consultant who worked for both companies, with whom Cell Genesys had an agreement to maintain confidentiality, passed details of Cell Genesys's research to GenPharm. Cell Genesys was seeking ownership of certain GenPharm patent applications and claiming millions of dollars in damages from the company

The consultant named in the case, genetics expert Frederick Alt, denied the charges, as did GenPharm (Cell Genesys, 1994a; GenPharm, 1994b). However, Cell Genesys emphasized that it had filed its original U.S. patent application in January 1990, six months before GenPharm (Coghlan, 1997). On the other hand, according to Nils Lonberg from GenPharm, *"They were clearly behind in terms of technology but clearly ahead in terms of money"* (Stix, 2001). Not surprisingly, Cell Genesys denied that it used lawsuits to catch up and claimed that its mouse technology was better than the GenPharm's (Stix, 2001).

Cell Genesys's lawsuit began a three-year-period of legal battles accompanied by business uncertainty and hindered innovative activity at GenPharm. This court case not only blocked GenPharm's IPO, but also limited its ability to raise additional funds and attract collaboration partners. GenPharm had 110 people and a significant monetary burn rate. By the end of 1994, GenPharm was running low on cash, was no longer able to sustain its various research projects, and tried to find a buyer. But the lawsuit deterred potential acquirers. A merger with Scotgen, a Scottish biotech firm focused on humanization of antibodies, failed in April 1995 because Scotgen ceased its operations.

On the other hand, the Netherlands-based subsidiary GenePharming recorded some success in entering various new collaboration agreements in 1994, and also received a loan worth approximately $11.5 million from the Netherlands Ministry of Economic Affairs in March 1994. Thus, the perspectives of the European subsidiary were not bad. In April 1995, GenPharm's board voted to spin off

GenePharming, which was renamed Pharming B.V. All of the GenPharm International shareholders received shares in the new company, in the same *pro rata* fashion as their ownership in GenPharm International. This way, GenPharm's investors saved their holdings before a potential devaluation (Foster and Higuera, 2001: 18f).. In this very difficult period, GenPharm earned some cash by extending its transgenic animals business and entering into commercialization agreements with partners in Japan and Europe, which sold transgenic animal models from GenPharm. It also managed mouse facilities for another firm in exchange for a small laboratory space (Stix, 2001). However, in August 1995, GenPharm sold its transgenic laboratory products division to Taconic Farms, Inc., in Germantown, New York. Despite the renewal of R&D collaboration with the Japanese pharmaceutical company Eisai Co., Ltd. in early December 1995, GenPharm's shareholers' equity had dropped to negative $2.1 million by the end of 1995 (GenPharm, 1995b; Foster and Higuera, 2001: 19). The company was on its knees--it fired everyone but a skeleton staff of about nine employees, relocated to smaller facilities and drastically reduced expenses. From this time on, GenPharm officially focused on its core business of generating high-affinity human antibodies using the *HuMab-Mouse* system. But practically, the company entered into a stage of hibernation and ceased activities (Interview Sep. 2006).

The legal battles continued. After GenPharm filed a cross-complaint on March 2, 1994 against Cell Genesys, it followed up with a second claim on February 9, 1996, alleging that Cell Genesys had violated the Sherman Antitrust Act when it filed an action against GenPharm in February 1994 (Cell Genesys, 1996c; *Applied Genetics News*, 1996). The uncertainty was extended further that February when Cell Genesys obtained a delay in the trial until 1997 (Foster and Higuera, 2001: 20).

Only when GenPharm obtained two U.S. patents for transgenic mice producing human antibodies (U.S. No. 5,545,806 and 5,569,825) in October 1996 did the situation begin to change, and the company achieved a superior intellectual-property position (GenPharm, 1995a). At this time, GenPharm launched a counter attack, suing Cell Genesys, respectively Abgenix, Inc. (the wholly owned subsidiary of Cell Genesys) for patent infringement. In January 1997, GenPharm was issued a further U.S. patent (5,591,669) relating to transgenic mice technology. The company immediately filed another patent infringement suit against Abgenix (GenPharm, 1997b).

Two weeks before the trial in early 1997, on January 14, 1997, Cell Genesys dropped its lawsuit, probably to avoid a trial (GenPharm, 1997c). At that point, the rival companies began to negotiate a cross-licensing agreement. The situation soon changed completely. Within one month, March 1997, the two rival companies designed a cross-licensing agreement, and GenPharma dismissed its remaining litigation. Under the agreement, both companies share a world-wide, royalty-free cross-license to all issued and related patent applications pertaining to the generation of fully human monoclonal antibodies in genetically modified strains of mice. With this agreement, each company could pursue its methods without fear of lawsuit from the other. Cell Genesys and its partners agreed to pay GenPharm up to $37.5 million which also had to pay its lawyers. In detail, Cell Genesys agreed to issue a note due September 30, 1998, for $15 million. Japan Tobacco agreed to make a cash payment within 15 days, and Xenotech (equal joint venture of Cell Genesys and Japan Tobacco) agreed to make two potential milestone payments of $7.5 million each, based on the future issuance of patents relating to human antibody technology in Europe, Japan and/or the United States (Cell Genesys, 1997). Interviewees deny that there were more intense contacts, exchange of personnel or

even collaboration between both companies, although of course the key protagonists of both companies knew each other. The agreement was restricted to a pure cross-licensing of intellectual property rights. It was a means to settle a dispute and enabled both companies to move forward (Interview Oct. 2006). It also lay the foundation for substantial money inflow and rapid growth for both companies in a period of growing expectations for monoclonal antibody-based therapies.

Already prior to the cross-licensing agreement, GenPharm began approaching several companies for partnering opportunities based on its improved intellectual property rights position. On March 3, 1997, it entered into a research and commercialization agreement with Centocor, Inc. Under the agreement, Contocor announced it would pay as much as $57 million in research and benchmark payments to GenPharm, depending its success in generating completely human antibodies to several unnamed antigens based on the *HuMAb-Mouse*. It also announced two equity investments. Should products result from the collaboration, Centocor agreed to pay royalties to GenPharm (GenPharm, 1997a).

In October 1997, a few months after the cross-licensing agreement, the moment finally arrived for venture capitalists to liquefy their shares in the company. They sold GenPharm for $62.2 million in stock to Medarex, an antibody company based in Annandale, New Jersey. Medarex, founded in 1987, was working with bispecific monoclonal antibodies (recognizing two different targets), a technology that was in-licensed from Darmouth College in the same year. It had sufficient cash and even manufacturing facilities for clinical trials. Through the transaction, Medarex obtained Genpharm's *HuMAb-Mouse* technology. This acquisition profoundly changed both companies. Lonberg became scientific director and senior vice president at Medarex and was the only remaining employee to have worked on the program since its inception. The merger proved quite successful over the following years. Increasing focus on the acquired *HuMab*-technology, Medarex later downgraded its not very exciting technology on bispecific monoclonal antibodies (Stix, 2001; Weintraub, 2006; Interview Sep. 2006).

Cell Genesys was in a much better financial situation than GenPharm. After its successful IPO in January and follow-on offering in November 1993, the company also profited from large pharmaceutical companies' high interest in cell and gene therapy in the mid-1990s (Robbins-Roth, 2000: 88). Already in October 1995, Cell Genesys formed a $160 million deal with Hoechst Marion Roussel, focused on experimental gene therapy against AIDS which significantly improved Cell Genesys' cash situation (Biotechnology Business News, 1996).

A few months later, Cell Genesys confirmed its emphasis on gene and cell therapy, at the time in vogue, with both ex vivo therapy with genetically engineered human immune cells and in vivo gene delivery technology. The company leaders expected to profit financially much more by spinning off Cell Genesis's antibody business and the *XenoMouse* technology. For this purpose, they launched a wholly-owned subsidiary called Abgenix, Inc., on June 27, 1996. The new company was based on the *XenoMouse* technology and exclusively focused on developing and commercializing Cell Genesys's human monoclonal antibodies for pharmaceutical applications. Cell Genesys contributed $10 million in cash and provided loan opportunities to the new company.

At the same time, Cell Genesys and Japan Tobacco signed a new agreement. By this point, Cell Genesys had already received approximately $38 million in funding through its agreements with JT

Immunotech and Japan Tobacco. Cell Genesys assigned its partnership rights to Abgenix. Under the new agreement, Abgenix and Japan Tobacco were each able to use the transgenic technology to select and develop product candidates. For products developed separately, the corresponding company could obtain worldwide rights. Rights to jointly targeted products were licensed to Abgenix in North America, to Japan Tobacco in Japan, Taiwan and Korea, and co-exclusively to both elsewhere in the world. Abgenix's own portfolio included three product candidates: one anti-cancer and two anti-inflammation drugs. Forty Cell Genesys employees, including all who were primarily involved with the company's antibody program, started work with Abgenix. Aya Jabobovits was named scientific director of the new company (Cell Genesys, 1996a;1996b).

During this period, GenPharm was very much concerned with the survival of the firm. Therefore, technological advances were modest after the successful generation of human monoclonal antibodies with the transgenic *HuMAb Mouse* technology published on April 26 1994. On December 5, 1995, at a conference on antibody engineering in La Jolla (San Diego), GenPharm reported the addition of other human sequences into the mouse, along with extensive characterization of fully human IgG antibodies which it had generated, compared to the transgenic mouse that had been described one and half years earlier in *Nature* (Lonberg, et al., 1994). The resulting monoclonal antibodies had higher affinity levels. This technology improvement was published in the July 1996 issue of *Nature Biotechnology* (Fishwild, et al., 1996; GenPharm, 1995b;1996).

Also Cell Genesys, respectively Abgenix, was more occupied with refining the *Xenomouse*-technology than with further breakthroughs. In early February 1997, Jakobovits's team reported a further completion of its technology in *Nature Genetics* (Mendez, et al., 1997). The team successfully introduced a large, intact human DNA segment containing the majority of human antibody-producing genes into the *XenoMouse II* mice strain. The previous efforts of Cell Genesys and others had only included the introduction of smaller portions of human antibody genes. It was reported that the Abgenix team was the first to introduce the majority of the human genes – approximately 80% – that are responsible for diverse antibody production. The created transgenic mouse bore almost the complete complement of the human genes used in the production of immunoglobulin heavy chains and kappa light chains. Jakobovits reported that her team was *"able to reproduce an almost complete human antibody response in these mice and generate very high affinity, high specificity human antibodies to a wide variety of antigens, including human antigens"* (McCarthy, 1997).

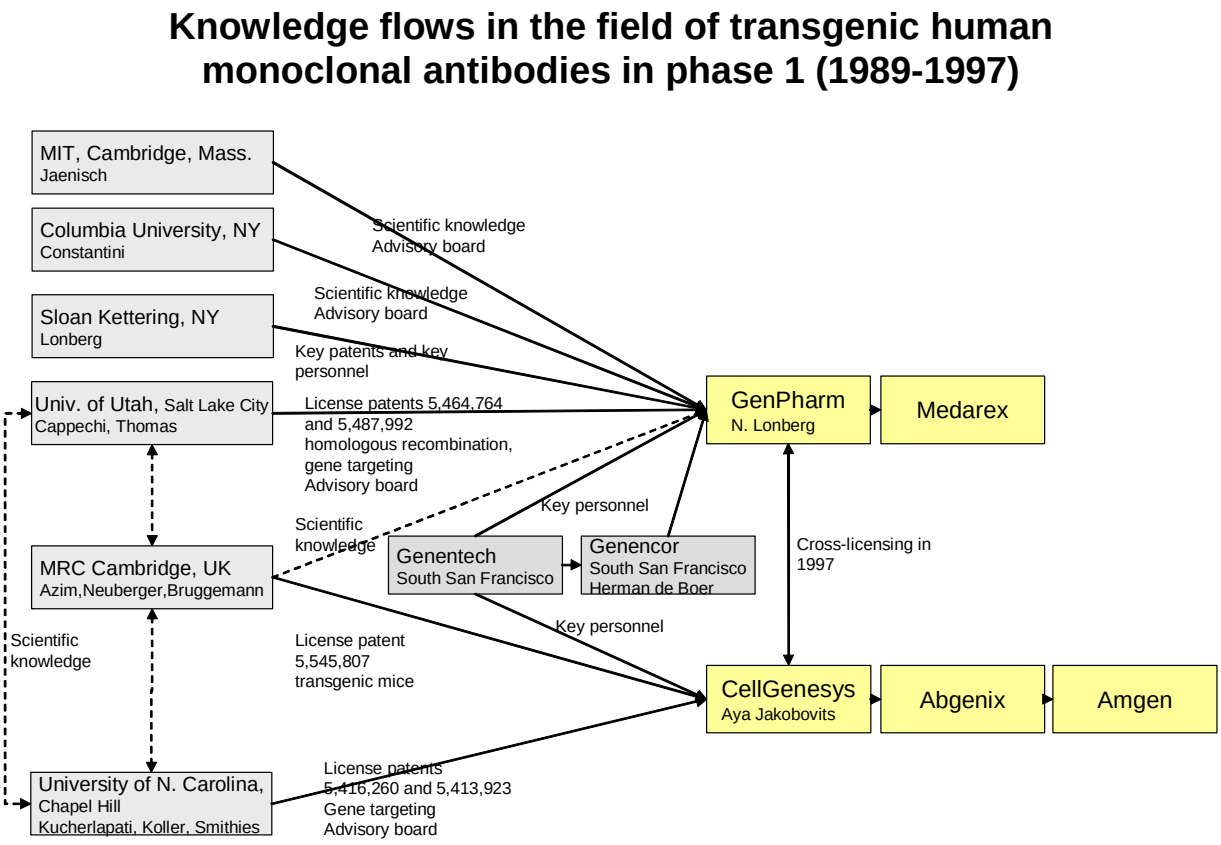

Fig. 4: Knowledge flows in the field of transgenic human monoclonal antibodies in phase 1 (1989-1997)

5. Preliminary conclusion: rivalry and collaboration in a technological arena

In this preliminary conclusion, the major characteristics of both innovation paths will be summarized and some lessons for understanding the dynamics of the innovation arena will be formulated. Despite the ferocious rivalry between Cell Genesys and GenPharm, there are important similarities in both their innovation processes. Both companies' technological advances were based on knowledge transferred from universities and public research organizations. The inventions made at the MRC and at the Babraham Institute in Cambridge, at the University of Utah, at MIT, and at Columbia University were decisive in the process (Fig. 4). These institutions acted as niches, providing a protected environment for basic research. Subsequently, Cell Genesys and GenPharm undertook the transformation of the original concepts into marketable technologies. Interestingly, former researchers from Genentech were involved in both companies' founding. In both cases, entrepreneurial scientists played a key role in starting the inventions' commercialization processes and the basic concepts.

The teams at Cell Genesys and GenPharm both created two different types of gene-modified mice. One had a disabled immune system and could not produce any of its own antibodies. The other bore the genes that are responsible for making human antibodies. Creating the first type of mice, the GenPharm team with Nils Lonberg and the Cell Genesys team with Aya Jakobovits both used a form

of genetic targeting to inactivate a portion of the immune system in certain strains of mice, in order to prevent their ability to generate mouse antibodies following immunization. To generate the second type of mice, they inserted genes used in human cells to make immunoglobulins, the building blocks of antibodies, into embryos of normal mice. Both companies created this transgenic mouse using specific gene transfer techniques involving yeast artificial chromosomes to insert large pieces of human DNA (antibody genes) into mice embryo cells. Each group used its own proprietary method. Afterwards, these mice were cross bred with mice whose own antibody-related genes had been knocked out. Both groups generated transgenic mouse lines that produce fully human antibodies in response to an immune challenge and which pass on the trait to their offspring. The B cells harvested after immunization can be immortalized by fusion with a myeloma cell line, as in traditional hybridoma technology. The hybridomas can be screened for specific antibodies (Alper, 1993; Brekke and Sandlie, 2002: 55; Fishwild, et al., 1996; Eisenstein, 2006: 757; Hust, et al., 2007: 47).

The Cell Genesys group was able to insert larger parts of human antibody-producing genes into mouse embryos, whereas the GenPharm team inserted smaller pieces of DNA using a more conventional injection method and receiving a smaller human antibody repertoire. A former key scientist from Abgenix argues that in those pieces of DNA, a lot of important information lies in between and neighboring the exchanged fragments.*"We always believed it took us maybe longer, but this is the right way to go…. I mean our strategy was really to go after the entire repertoire; it was a little bit longer. I think that the Medarex mice were available even earlier."* (Interview Oct. 2006). Also GenPharm emphasizes the very high affinity of the monoclonal antibodies generated by its *HuMAb*-system (Fishwild, et al., 1996; GenPharm, 1996). Both technologies, in transferring huge pieces of intact DNA from one species into the other, can be regarded as a breakthrough in molecular biology. They opened the way toward creating antibodies which are identical to human antibodies.

The property rights regime was crucial for defining institutional rules, in that the transfer of knowledge into the business area was based on intellectual property. Property rights were also crucial to both companies' strategies of impeding and braking their rival's commercialization efforts. Cell Genesys's law suit against GenPharm resulted in a standstill of almost two years for GenPharm's activities in the field of human antibodies. The court conflicts between 1994 and 1997 drastically impeded the entire innovation process. Thus, in understanding the evolution of innovation processes within a technological arena, conflicts and rivalries become as important as different forms of collaboration. And such company rivalry aided by institutional conditions can impede innovative activities. Hypothetically, collaboration between GenPharm and Cell Genesys could have improved the technological outcome and accelerated the innovation process. But such non-competitive collaboration is not favored by the broader institutional and economic framework.

The case study also underlines the importance of finance and business cycles. The financing strategy of a biotech company decisively frames its innovative activities and the future possibilities of technology commercialization. Fueled by its financially rewarding joint venture with Japan Tobacco and a relatively successful IPO, Cell Genesys was able to launch nearly fatal attacks against GenPharm. However, a funding strategy based on venture capital, an IPO and stock markets is very vulnerable. Stock market conjunctures can abruptly interrupt promising technological developments. Funding through collaborations with large pharmaceutical companies can provide more plannable conditions, at the price, however, of strong dependence of the partner's strategic choices.

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