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The billion mice – rivalry and collaboration in a rising technological arena

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

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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 corporate strategies of two companies involved in the innovation process 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 shows how during the period of the stock market boom in the late 1990s two technologies were commercialized and first drug candidates based on these technologies were developed. 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

After the presentation of the major phases of the emergence and early transformation of the technology which allows to produce human monoclonal antibodies with transgenic mice in the paper *The expectations on mice – rivalry and collaboration in an emerging technological arena* this paper focuses on the diffusion and application of the technology.

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 commercialization 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, 2008a). 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 empirical analysis in the second section presents the rivalrous race between two companies striving to obtain a competitive lead in commercializing the technology and developing drug candidates based on this technology. The analysis emphasizes the collaborative networks of the involved companies, their financing methods and their property rights strategies. The third section presents the beginning product commercialization since 2006. The concluding fourth section puts 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. Business take off and technology commercialization (1997–2006)

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. This phase is presented in the companion paper *The expectations on mice – rivalry and collaboration in an emerging technological arena*.

This paper focuses on the second phase of technology commercialization and diffusion which was launched by a cross-licensing agreement in 1997and 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 cross-licensing agreement between Abgenix and GenPharm in 1997 reduced the legal uncertainty just at a moment of rising expectations for monoclonal antibodies. In the same year, Genentech and IDEC successfully launched *Rituxan,* the first monoclonal antibody against cancer. Genentech's *Herceptin*, a monoclonal antibody against breast cancer was in a stage of advanced and successful clinical trials. Thus the general context turned out to be much more favorable for monoclonal antibodies than in the previous years. Both Abgenix and Medarex profited considerably from the upswing of the stock markets and the new economy bubble in the late 1990s and raised several hundreds of millions of dollars with stock market and convertible debt offerings. The acquisition of GenPharma provided Medarex with the opportunity to reinvent the company and focus on a new technological path. Spinning off Abgenix allowed Cell Genesys to profit from continuously selling a large part of its shares of Abgenix (Tab. 9).

Both companies aimed to become leaders in the discovery, development and commercialization of antibody-based drugs. They hoped to build a diversified product portfolio based on their technologies, including a mix of internally developed drug candidates. In this second phase of take-off and commercialization, the technological arena completely changed. The technology strategies of both companies will be presented here first, then the question of how Medarex and Abgenix financed their corporate growth will be examined. Both companies succeeded in entering into lucrative collaboration agreements with large pharmaceutical corporations, and the stock market boom until 2001 allowed both to raise several hundreds of millions of US dollars on stock market offerings.

Technological evolution

After the acquisition of GenPharm in 1997, Medarex shifted its focus from murine and humanized bispecific monoclonal antibodies towards human monoclonal antibodies. The *HuMAb-Mouse* technology increasingly became the core technology and business of Medarex. It continued the

collaborations already signed by GenPharm and entered into numerous further agreements with pharmaceutical and biotechnology firms interested in utilizing the *HuMAb-Mouse* technology to generate human monoclonal antibodies.

Medarex continued to acquire a range of complementing technologies and the related intellectual property rights. An important element in Medarex's strategy was to acquire intellectual property around a particular target or method of drug usage. *"And a lot of companies, I don't think, have been as aggressive at acquiring patents around targets as we have been for the last ten years. That's the reason why we have got such a big portfolio of these"* (Interview Sep. 2006).

Additionally, Medarex entered into various cross- and in-licensing agreements to enhance its technology portfolio. A key step in this strategy was the strategic technology alliance with Kirin, the pharmaceutical division of Japan-based Kirin Brewery, announced on January 10, 2000 (effective from September 4, 2002). Both companies aimed to improve their transgenic mice. Medarex's advantage was its large portfolio of fundamental patents around transgenic mice generating human antibodies (Medarex, 2001: 4f; 2003a: 12). Kirin was appointed the exclusive distributor of Medarex's *HuMAb-Mouse* technology in Asia, and Medarex was appointed the exclusive distributor of Kirin's *Transchromosomic Mouse* outside of Asia. Kirin's new *Transchromosomic-Mice* (*TC Mice*) are genetically engineered mice containing 100% of the human genes for making antibodies. In the *TC Mice*, the mouse genes relating to antibodies have been functionally replaced by the entire human chromosomal loci responsible for making human antibodies. Kirin agreed to pay Medarex $12 million in up-front fees, plus potential additional payments over the term of the alliance. In addition, Medarex and Kirin agreed to exchange broad licenses, subject to license, milestone and royalty payments, for in-house use of each other's technology for the development of human-antibody therapeutic products. The partners also initiated a research collaboration to combine their proprietary technologies. They anticipated that this alliance could generate milestone payments from third parties to the partners in excess of $250 million (Medarex, 2000b). Thus, the alliance had both geographical commercialization and strong technology aspects.

On 5 December 2000, Medarex presented its expanded fully integrated human-antibody technology platform at an Antibody Engineering Conference in San Diego. With the *UltiMAb (Human Antibody Development System)* platform, Medarex assembled a unique family of genetically engineered mice for creating the entire spectrum of high-affinity, fully human antibodies. Medarex and Kirin crossbred their transgenic mice and the unique traits of the *HuMAb-Mouse* and *TC Mouse* to create a new mouse, called *KM Mouse (Kirin Medarex Mouse)*, which combines the characteristics of both mice strains. The *KM Mouse* retained the capability to produce all human antibody isotypes with an immune response that Medarex believed was previously unseen in any human antibody producing mouse system (Medarex, 2000c; 2007: 15).

At the same conference, Medarex's technology partner, Biosite Discovery, also presented its phage display technology to make human monoclonal antibodies, which was integrated into the *UltiMAb* system. Medarex presented itself as the company offering the broadest range of human antibody discovery and development tools in the industry. According to Nils Lonberg, *"the UltiMAb technology can generate the entire spectrum of human antibodies"* (Medarex, 2000c). Out of Medarex's 34 antibodies in clinical trials in September 2006, probably 30 of them were from the original *HuMAb*

technology. Four products were under development using Kirin's technology. However, it was expected that more antibodies would be stemming from the integrated Kirin technology (Interview Sep. 2006; Medarex, 2007: 15).

To further enhance its ability to create monoclonal antibodies from genomics research, Medarex had also coupled the *UltiMAb Human Antibody Development System* with other technologies, such as the *Ultra-Potent Toxin* (*UPT*) technology for creating antibody immunoconjugates. Medarex planned to create a platform for generating cytotoxic drugs that specifically targeted various cancers (Medarex, 2007: 19). The company acquired this technology, which allowed certain toxins to be linked to monoclonal antibodies, from Corixa in May 2002. It also purchased two other technology programs and three monoclonal antibody targets. At the same time, Medarex provided Corixa with a license to use the *UPTs* with certain monoclonal antibodies in exchange for milestone payments and royalties. Corixa received $21 million, payable at Medarex's option in cash or shares of Medarex stock. In connection with this transaction, approximately 30 Corixa scientists, including highly experienced antibody-toxin experts working in South San Francisco, joined Medarex's California-based research and development group. In the first period, this team continued to work in its location because Medarex subleased from Corixa the corresponding laboratory and office space (Medarex, 2002). This stresses how spatial proximity can be indispensable to learning processes in social contexts such as shared project teams (Zeller, 2002; Moodysson, et al., 2007). The company leaders hoped to start clinical trials of products based on this technology in 2008 (Interview Sep. 2006).

Abgenix's strategy was entirely based on the commercialization of the *XenoMouse* technology, mainly by out-licensing human monoclonal antibodies. Abgenix reinforced its property rights and business substantially when in December 1999, Japan Tobacco changed its biotechnology-related strategies and sold the rights to the *XenoMouse* technology back to Abgenix (Interview Oct. 2006). This newly strengthened intellectual-property position helped Abgenix enter into very attractive collaboration agreements with pharmaceutical and biotechnology firms.

Abgenix focused on improving the *XenoMouse* approach. In December 2001, Abgenix reported the launch of new versions of *XenoMouse* mice that produce fully human monoclonal antibodies containing both lambda and kappa light chains. By introducing the complete lambda light chain locus, the Abgenix team extended an earlier breakthrough by Marianne Brüggemann of the Babraham Institute in Cambridge, UK. Already on March 29, 1994, Cell Genesys had licensed the lambda light chain and also obtained certain related materials from the MRC, Cambridge (U.S. patent 5,545,807). Abgenix was able to equip the *XenoMouse* animals with approximately 80% of the human heavy chain antibody genes and a majority of the human light chain genes (Abgenix, 2001; 2006: 10, 117).

In the years 2000 and 2001, the high stock market capitalization helped Abgenix to acquire some additional technologies (tab. 2). The SLAM technology acquired in November 2000 through a takeover of ImmGenics was expected to speed up the selection process of appropriate monoclonal antibodies. Almost at the same time, Abgenix acquired the company IntraImmune to obtain its technologies for allowing antibodies to gain access to intracellular targets. It was expected that such intrabodies would increase the number of potential drug targets. One year later, Abgenix acquired Hesed Biomed with its Catalytic Antibody Technology, which enabled the production of a new class of therapeutic antibodies. Abgenix integrated these technologies into the *XenoMax* platform, which

should allow researchers to rapidly scan the majority of the immune repertoire of an immunized XenoMouse animal and to identify B-cells that produce antibodies with the desired functional properties (Abgenix, 2001). Apparently, however, most of these acquisitions had no strategic impact and were not really successful. In 2005, Abgenix depreciated its engagement in the SLAM technology.

Collaborations as means of funding and knowledge transfer

Because product sales were still far in future, Abgenix and Medarex generated revenue by out-licensing their technologies to corporate partners. Such collaborative agreements triggered needed upfront and milestone payments. By offering research and manufacturing services for cash, they could generate additional, but relatively modest, revenues. By tracing the flow of technologies and money between the partners we can distinguish six types of corporate collaborations (cf. Abgenix, 2006: 17; Medarex, 2007: 12ff).

Out-licensing: Abgenix and Medarex licensed their *XenoMouse*, respectively *HuMab Mouse* / *UltiMAb*, technology to corporate partners. A collaborative partner usually identified a specific disease target it wanted to treat with an antibody. Abgenix and Medarex then sold exclusive access rights to their technologies to develop and commercialize antibodies for that specific target only. Some collaborating firms used the *XenoMouse* or *HuMab Mouse* / *UltiMAb* systems in their own facilities, in other cases Abgenix or Medarex generated antibodies to the chosen targets on behalf of the partner firm. A collaborator paid an upfront research fee and a license fee, agreed to a series of milestone payments as the development program reached specified progress points (e.g., initiation of clinical trials) and a royalty on sales once the drug was successfully commercialized. Typically, fees before commercialization ranged from $7 to $10 million per approved antibody, and royalty rates from 4%–6%. In the case of broader and multi-year collaborations, the in-licensing pharmaceutical company often also acquired a small percentage of equity. In some cases, collaborating firms reimbursed Abgenix or Medarex for research and development activities conducted on their behalf. Generally, the in-licensing partners were responsible for all costs of product development, manufacturing and commercialization of any products.

After 2000, both companies started to generate revenue by pursuing the early stages of drug development based on their in-house technologies. Then, normally after phase I clinical trials, they sold off the rights to develop and market the drug and received royalties on its sales. A variant of such a late-stage deal can be a joint development, including joint marketing and sharing costs with a collaboration partner.

Joint development: Over the course of the "genomics revolution," Agenix and Medarex began to enter into various kinds of co-development collaborations after 1999, mostly with small biotechnology firms focused on generating knowledge about new potential drug targets. Typically, a collaborator provided one or more target antigen(s), and Abgenix or Medarex committed to generate and develop antibodies against the antigen(s) using their *XenoMouse* technology, respectively *UltiMAb Human Antibody Development System*. The partnering firms typically agreed to share the costs of clinical development and manufacturing equally, as well as revenues, expenses and profits from product sales.

Access to drug targets: Each drug candidate needs to be directed to a specific drug target. Abgenix's and Medarex's strategy depended on gaining access to antigen drug targets, either through contractual arrangements with academic researchers and companies involved in the identification of targets or from publicly available scientific sources. Access to potential drug targets was mainly gained through in-licensing agreements. Often, co-development agreements also included the provision of potential drug targets.

Technology in-licensing and technology acquisition: Companies continuously try to enhance their core competencies and technological capabilities. Abgenix and to a larger extent Medarex in-licensed and acquired new technologies which were expected to be complementary to their existing technology portfolio. In some cases, entire companies were acquired for this purpose.

Joint research: In a few cases, partnering companies agree to jointly pursue specific research projects and share the expenditures. The obtained rights can be jointly used and commercialized. In some cases, one company undertakes research efforts as a service for the collaborating firm.

The tables 1 and 2 list and typologize most of the collaborations entered by both companies. Only a few representative and strategically important deals will be presented in more detail in order to illustrate the architecture of money, technology and knowledge flows. After the acquisition of GenPharm, Medarex increasingly focused on human monoclonal antibodies. Since 1998, Medarex has started numerous partnerships with large pharmaceutical and biotech companies. The type of collaboration Medarex entered reflects how business climates and "interesting" technologies changed over time.

In the first period after the acquisition of GenPharm and Medarex's reinvention, the company focused on efforts to out-license its *HuMAb-Mouse* technology to pharmaceutical and biotechnology companies. It offered to let potential corporate partners utilize the technology under their own control or to in-license human monoclonal antibodies produced by Medarex using its *HuMab-Mouse* technology. These deals, signed with firms such as Centocor, Eli Lilly, Schering AG, Novartis, Immunex, Bristol-Myers Squibb and Novo Nordisk, permitted Medarex to receive relatively early upfront payments and licensing fees.

Medarex sought to commercialize monoclonal antibodies derived from the *HuMAb* system in collaboration with European firms. But the first drug candidates had just entered into clinical trials a short time before. The company could sell nothing but access to its technology. In order to better contact European research and clinical networks and to profit from the friendly financial situation (including the promise of public funding), Medarex launched a spin-off firm in Copenhagen in March 1999. It shared the risk with BankInvest Biomedical Development Venture Fund, and together they formed Genmab. Initially, Medarex contributed a license to its *HuMAb* technology for producing antibodies to particular targets in exchange for 44% of Genmab's share capital (Medarex, 2000a: 10; 2001: 13). In August 2000, Medarex granted Genmab the right to make Medarex's transgenic mouse technologies for multi-target genomics partnerships available to certain pharmaceutical and biotechnology companies headquartered in Europe. This agreement expired in August 2005. For each year of its five-year existence, Medarex received $2 million from Genmab. After Genmab's IPO in

October 2000, Medarex continuously reduced its ownership interest to approximately 11% by February 2007 (Medarex, 2007: 17).

Medarex eagerly acquired or in-licensed new technologies which could be combined with its *HuMAb* technology. In order to enhance its technological capabilities, Medarex signed several cross-licensing and in-licensing partnerships, while by far the most strategically important was the agreement signed in December 1999 with the Japanese firm Kirin Pharmaceuticals (Medarex, 2000a: 6, 28). The numerous co-development partnerships between 2000 and 2003 mirrored the hopes to find a large amount of new potential drug targets generated by the "genomics revolution." These speculations were massively driven by the speculative stock market bubble of this period. When this wave calmed down, Medarex combined its out-licensing activity with more co-development partnerships entered into with smaller and more-focused biotechnology firms. Such co-development agreements typically meant that the partner firm contributed a specific technology or knowledge about drug targets and Medarex offered its *HuMAb /UltiMAb* systems. In a few cases, only rights to drug targets were in-licensed.

Based on successful clinical phase I and II trials and on its promising technology, Medarex could enter into two lucrative broad and strategic alliances with Pfizer and Bristol-Myers Squibb. In September 2004, Medarex agreed on a series of contracts with Pfizer. The first agreement amended existing collaborative research, license and royalty agreements with Pfizer to provide for the discovery and development of up to 50 antibody products over ten years. The second and third agreements represented sub-licenses and cross-licenses of certain patents and patent applications to Pfizer. In the fourth agreement, Pfizer acquired Medarex stock for an aggregate prize of $30 million. Pfizer also made an initial cash payment to Medarex of $80 million. Under the agreement, Medarex utilizes its *UltiMAb* Human Antibody Development System to generate product candidates for targets identified by Pfizer. Pfizer was assigned full responsibility for the worldwide development and commercialization of any products generated by the collaboration. Medarex acquired the potential to receive research funding, license fees and milestone payments, if certain milestones were met, exceeding $400 million if all 50 products obtained regulatory approval, as well as double-digit royalties on any commercial sales of the products (Medarex, 2004; 2007: 14).

Only a few months later, on November 8, 2004, Medarex agreed on a broad collaboration and co-promotion as well as a related securities purchase agreement with Bristol-Myers Squibb (BMS). The global development and commercialization collaboration agreement became effective in January 2005. Both firms granted the other certain intellectual property licenses and product rights enabling collaboration in the research and development of certain therapeutic antibody-based therapies against cancer and other diseases. BMS and Medarex agreed to jointly develop ipilimumab (MDX-010), a fully human antibody investigational product targeting the CTLA-4 receptor, which was currently in phase III clinical development for the treatment of metastatic melanoma. Medarex granted BMS a license to commercialize ipilimumab, its most advanced drug candidate. Both companies committed to an initial multi-year budget of approximately $192 million to fund the development of ipilimumab, whereas BMS was to pay 65% of all development costs and Medarex the remaining 35%. Medarex received an initial cash payment of $50 million, of which $25 million was for a purchase of Medarex's common stock by Bristol-Myers Squibb. Medarex could receive up to $205 million from BMS if all regulatory milestones were met, plus up to an additional $275 million in sales-related milestones, plus either co-marketing rights or royalties on product sales (Medarex, 2005; 2007: 12). Such late-stage

deals can be interesting for both partners. The pharmaceutical company minimizes the risk of failure because the project is already in an advanced stage. The biotechnology firm, on the other hand, can demand much higher compensation amounts. However, the biotech company remains dependent on the successful commercialization of the drug by the pharmaceutical company.

As of February 1, 2007, Medarex reported more than 45 partnerships with pharmaceutical and biotechnology companies to jointly develop and commercialize products or to enable other companies to use Medarex's *UltiMAb Human Antibody Development System*. In more than two dozen of these collaborations, Medarex plans to jointly develop and commercialize human antibody products. It also entered into approximately two dozen licensing partnerships with various partners (Medarex, 2007: 12ff).

Abgenix concluded numerous contractual agreements with pharmaceutical, biotechnology and genomics companies to develop and commercialize products or to enable other companies to use the *XenoMouse* technology in the development of their products. Abgenix did not participate in the development or marketing of these product candidates. Six of Abgenix's licensing partners have advanced twelve antibodies into clinical trials: Abgenix has generated five antibodies for Pfizer, Amgen has selected three candidates and Chiron, CuraGen, Human Genome Science and Agensys has each brought one drug candidate to clinical trials (Abgenix, 2006: 6).

In addition, Abgenix entered into co-development agreements for the joint development of antibody product candidates with a variety of companies, including Microscience Limited, Dendreon Corporation, Chugai Pharmaceuticals Co., Ltd., Sosei Co., Ltd. and U3 Pharma AG. The partners typically share the costs of development and commercialization as well as any profits (Abgenix, 2006: 6, 17).

Decisive for the future of Abgenix and the *XenoMouse* technology was the collaboration Abgenix went into for the co-development of ABX-EGF, later named panitumumab, with the biotechnology firm Immunex in 2000. Subsequently in July 2002, Immunex was acquired by the largest biotech firm, Amgen, and the agreement was amended in October 2003. Amgen received decision-making authority for development and commercialization activities, and Abgenix had the right to co-promote panitumumab in the United States, which it opted for in 2005. Under the joint development and commercialization agreement, Abgenix was obligated to pay 50% of the worldwide development and commercialization costs and was entitled to receive 50% of any profits from sales of panitumumab worldwide. Under a separate agreement, Abgenix took responsibility for manufacturing clinical and commercial supplies for the first five years after commercial launch. The costs also were to be equally shared (Abgenix, 2006: 16).

The broadest collaboration Abgenix entered into was the strategic alliance it made with AstraZeneca on October 16, 2003, for the development of antibody therapeutics to treat certain types of cancer. Abgenix conducted early-stage preclinical research on behalf of AstraZeneca and received an opportunity to co-develop products with AstraZeneca, as well as to conduct preclinical and clinical research and manufacture for the development of product candidates chosen by AstraZeneca. The collaboration involved the development of antibodies against up to 36 targets to be exclusively commercialized by AstraZeneca. Abgenix was offered the chance to receive milestone payments of up

to $51 million per candidate and royalties on future product sales. It received the right to select and develop up to 18 antibodies, which the companies could elect to further co-develop on an equal cost- and profit-sharing basis. AstraZeneca made a $100 million investment in Abgenix securities (Abgenix, 2003b; 2006: 16f).

Since 2001, Abgenix has increasingly entered into collaborations to obtain access to new drug targets (e.g. CuraGen). This reflects new knowledge created by the genomics breakthroughs in 2000 and the hope to find better drug targets to which therapeutic monoclonal antibodies could be directed. Thus, Abgenix increasingly combined the strategies of license sales for *XenoMouse*-based antibodies and drug-target in-licensing, inducing a complicated flow of knowledge, property rights and money between the involved firms. In about the same timeframe, Abgenix increasingly initiated co-development deals as well, mostly with smaller firms. Under such agreements, both partners mutually exchanged licensing rights and shared development costs as well as potential profits from product sales.

Tab. 1: Medarex's collaboration agreements

Date	Partner	Technology out-licensing	Joint development	Access to targets	Technology in-licensing	Technology acquisition	Joint research
May 1998	Schering AG	X					
May 1998	EluSys, Inc.	X					
May 1998	ErythroMed, New York	X					
June 1998	Bristol-Myers Squibb, Princeton, NJ	X					
July 1998	FibroGen, South San Francisco	X					
Sep. 1998	medac GmbH, Hamburg	X					
Nov. 1998	Novartis Pharma AG, Basel	X					
Jan. 1999	Immunex Corporation, Seattle	X					
Feb. 1999	Leukosite, Cambridge, MA	X	(X) option				
March 1999	Genmab A/S	X					X
Feb. 2000							
Aug. 2000		X					
June 2001			X				
Aug. 1999	Gilead Sciences, Foster City, CA			X			
Aug. 1999	Eos Biotechnology, South San Francisco	X	X				
Feb. 2000		X	X				
Jan. 2003	(acq. by PDL)		X				
Sep. 1999	Amgen, Inc. Thousand Oaks, CA	X					
Dec. 2002	Amgen, Inc.,	X					
Dec. 1999	Immuno-Designed Molecules (IDM), Paris	X			X		
June 2002			X				
Dec. 1999	Kirin Brewery Co., Ltd., Japan	X			X		X
March 2000	Raven Biotechnologies, San Carlos, CA	X					
March 2000	Regeneron Pharmaceutical, Tarrytown, NY		X		X		
April 2000	Coulter Pharmaceutical (acq. By Corixa), S. Francisco	X					
May 2000	Centocor (Johnson&Johnson), Malvern, PA	X					
June 2000	MedImmune, Inc.	X					
Jan. 2003		X					
June 2000	Corixa Corporation, Seattle	X	X	X			
June 2000	Biosite Diagnostics Incorporated				X		
Aug. 2000	Athersys, Inc., Cleveland	(X) option	X				
Sep. 2000	Oxford GlycoSciences plc, Oxford	X	X				
Jan 2002		X	X				
Oct. 2000	ZymoGenetics, Inc.	X					
Nov. 2000	Eli Lilly & Company, Indianapolis	X					
Jan. 2001	Eli Lilly and Biosite	X					
Nov. 2000	Epigen, Millbrook, NY		X				
Dec. 2000	Genmab: Gemini Genomics, Cambridge		X				
Jan. 2001	Novo Nordisk A/S	X					
Jan. 2001	B. Twelve, Inc., Toronto (Kyoto	X					

	Biopharma)						
Feb. 2001	Seattle Genetics, Inc.		X				
Feb. 2001	Immusol, Inc., San Diego		X				
March 2001	Schering-Plough Corporation	X					
April 2001	Northwest Biotherapeutics, Inc.		X	X			
Dec. 2002			X	X			
April 2001	NeuroTherapeutics, Inc., Vancouver		X				
May 2001	NovImmune, S.A., Geneva	X	(X) option				
June 2001	deCODE genetics, Inc.		X				
June 2001	Sangamo BioSciences, Richmond, CA		X				
Jan 2002			X		X		
July 2001	Epicyte Pharmaceuticals, Inc., San Diego		X				
July 2001	Human Genome Sciences, Rockville, Md.	X					
Aug. 2001	Genesto S/A, Kopenhagen	X					
Oct. 2001	Incyte Genomics, Inc., Palo Alto		X				
Nov. 2001	m-phasys GmbH, Tübingen, Germany		X				
Nov. 2001	Ambit Biosciences Corp., San Diego		X				
Jan. 2002	Tularik, S.San Francisco (acq by Amgen).	X	X				
Jan. 2002	ZYCOS, Inc., Lexington, Mass.		X				
May 2002	Corixa (former Coulter), Seattle	X		X	X		(X personnel)
July 2002	Abbott Laboratories, Inc.	X					
Jan. 2003		X					
Nov. 2002	Cytos Biotechnology AG		X	X			
April 2005			X	X			
Dec. 2002	Schering AG	X					
Jan. 2003	Ability Biomedical Corp., Vancouver		X				
June 2004						X	
Jan. 2003	diaDexus, Inc., South San Francisco	X	X				
Sep. 2004			X	X			
Feb. 2003	Ferric Technologies, Inc., Atlanta	X					
March 2003	Oncomab (PRIMABiomed), Australia		X				
April 2003	Pfizer, Inc.	X					
Sep. 2004	Pfizer, Inc.	X	X	X			
April 2003	Diatos SA, Paris	X	(X) option				
Oct. 2003	Trillium Therapeutics, Toronto		X				
Oct. 2003	Diversa, San Diego, CA		X				
Oct. 2003	BioWa, Princeton, NJ (Kyowa Hakko				X		
May 2005	Kogyo)				X		
Oct. 2003	Avalon Pharmaceuticals, Germantown, MD		X				
Dec. 2003	Cyto Pulse, Hanover, MD				X		
Sep. 2004	Cell Genesys, South San Francisco		X				
Nov. 2004	MedImmune, Inc., Gaithersburg, MD	X	X				
Jan. 2005	Bristol-Myers Squibb, Princeton, NJ	X	X				
May 2005	Ono, Osaka, Japan		X				
March 2006			X				
June 2005	Boehringer Ingelheim, Ingelheim, D	X					
Sep. 2005	ImClone Systems, Inc.	X					
Oct. 2005	Celldex (Medarex) acquires Lorantis			(X)	(X)		
Jan. 2006	PharmAthene, Annapolis, MD	X					
früher							
Feb. 2006	Organon, Inc. (Akzo Nobel), Oss, NL	X					
May 2007			X				
May 2006	Oxford Genome Sciences		X	X			
June 2006	Celera Genomics, Rockville, MD		X	X			
June 2006	Euroscreen s.a., Bruxelles			X			
Aug. 2006	GenPat77 Pharmacogenetics, Berlin		X	X			
Nov. 2006	PacMab Limited, Sydney		X				
Jan. 2007	Compugen, Ltd. Israel	X	X				
May 2007	Mitsubishi Pharma, Japan		X				

Pure clinical trials agreements are not included
Source: (Medarex, 2001: 7; 2003a: 11) and media releases from Medarex 1997–2007

Tab. 2: Abgenix's collaboration agreements

Date	Partner	Technology out-licensing	Joint development	Access to targets	Technology in-licensing	Technology acquisition	Joint research
July 1996	Cell Genesys (restructured Xenotech partnership)						
31 Mar 1997	CV Cancer Center, Dr. Ronald Billing			X			
17 July 1997	Neugenesis						X
31 Dec. 1997	Pfizer	X					
2 Feb. 1998	Schering-Plough Research Institute	X					
21 April 1998	Genentech, South San Francisco, Calif.	X					
23 June 1998	Genentech	X					
15 July 1998	Millenium BioTherapeutics, Cambridge,	X					
15 Oct. 1998	Mass.	X					
26 Oct. 1998	Pfizer	X					
16 Dec. 1998	Research Corporation Technologies	X					
7 Jan 1999	AVI BioPharma	X					
27 Jan 1999	Genentech	X					
Feb. 1999	Santen Pharmaceutical				X?		
26 March 1999	BASF	X					
27 April 1999	Amgen	X					
30 June 1999	Japan Tobacco		X				
13 July 1999	US Army, Fort Detrick, Maryland	X					
13 Oct. 1999	US Army, Fort Detrick, Maryland	X					
2 Nov. 1999	Pfizer	X					
1 Dec. 1999	Chiron, Emeryville, Calif.	X					
1 Dec. 1999	Human Genome Sciences	X					
9 Dec. 1999	CuraGen	X					
21 Dec. 1999	Japan Tobacco					X	
Jan. 2000	Neuralab	X?					
10 Jan. 2000	Elan	X					
13 Jan 2000	Gilatech	X					
28 Feb. 2000	Pfizer	X					
6 Mar 2000	Millenium	X					
21 Mar 2000	Corixa	X					
2 May 2000	Genzyme Transgenics				X		
19 May 2000	SmithKline Beecham	X					
22 May 2000	Abbott Laboratories	X					
May 2000	GTC Biotherapeutics				X		
12 July 2000	Lexicon Genetics	X					
26 July 2000	Immunex		X				
9 Aug. 2000	SangStat		X				
6 Sep. 2000	ImmunoGen				X		
3 Oct. 2000	Pfizer	X					
6 Nov. 2000	ImmGenics, Canada					X	
14 Nov. 2000	IntraImmune, Inc.					X	
13 Nov. 2001	Hesed Biomed					X	
28 Nov. 2000	CuraGen		X				
28 Nov. 2000	Immunex		X				
3 Jan. 2000	Lexicon Genetics				X service		
8 Jan. 2001	Dyax						X
9 Jan. 2001	Pfizer (extension)	X					
9 Jan. 2001	Amgen (extension)	X					
31Jan. 2001	Lexicon Genetics				X antigens		
5. Feb. 2001	Celltech	X					
27 March 2001	Diabetogen Biosciences		X		X		
16 April 2002		X	X		X		
28 March 2001	Cytogen and Progenics Pharmaceuticals	X success			X		
30 March 2001	Chiron	X					
May 2001	InforMax				X		
7 June 2001	Centocor (expansion)	X					
13 June 2001	Biogen	X					
29 June 2001	MDS Proteomics				X		
14 Aug. 2001	Agensys	X					
2 Nov. 2001	Gilatech				X		
Nov. 2001	Hesed Biomed					X	
Dec. 2001	Automated Cell						X service
26 Nov. 2001	Duke University				X		
April 2002	Ardais						X service
8 May 2002	Ilex Oncology	X	X				
14 May 2002	Corvas International		X				
12 June 2002	U3 Pharma		X				X
7 Jan. 2003	Morphotek				X		

10 Jan. 2003	CuraGen (manufacturing)				
3 Feb. 2003	Chugai	X	X		
31 March 2003	Sosei		X		
7 May 2003	Microscience	X			
12 May 2003	Human Genome Sciences	X	X		X
15 Oct. 2003	Amgen (modification)	X	X		
17 Oct. 2003	AstraZeneca	X	X		
June 2004	Strand Genomics				?
15 Mar 2005	Genentech	X			
Dec. 2005	Amgen (acquisition of Abgenix for cash)				

Sources: media releases of Abgenix, (Life Science Analytics, 2005), Recombinant Capital Database

Stock market-based financing

Stock offering, convertible debts and collaborations were the key elements of **Medarex's** financing strategy. Due to its acquisition of GenPharm and its *HuMAb-Mouse* technology, Medarex could attract dozens of partnerships with large pharmaceutical and biotech companies since 1998. These collaborations were crucial to organizing a continuous income flow. Medarex was already a public company when it acquired GenPharm. Therefore, compared to Abgenix, Medarex's strategy relied more on corporate partnerships than on stock offerings. However, a highly successful, $388 million stock offering in March 2000 was crucial to the subsequent period, just before the stock market downturn. This enabled Medarex to build a new research facility (Weintraub, 2006).

Medarex surfed on the new economy and genomics wave (fig. 1). The exploding market capitalization compelled *Forbes* magazine to include Medarex in its 32nd edition of the Forbes 500 list. Medarex was ranked as one of the top 500 U.S. companies in market value. In addition, Medarex was featured in the Forbes 500 Market Value Winners timeline spanning 70 years, 1930-1999. Medarex was noted as the "Biggest One-Year Mover" based on its market value increase during 1999 (*Forbes*, April 17, 2000). Based on these financial inflows and on the perspective of advancing its drug candidates in clinical trials, Medarex – like Abgenix – expanded its clinical department in 2001.

After the stock market downturn, the issuance of convertible debt notes to institutional buyers became the favourite financing tool. Such notes bear a fixed interest and are convertible into shares. Despite completing a $175 million offering of convertible notes in 2001, due to the expected financial needs and the uncertain financial landscape, Medarex decided not to realize a planned manufacturing facility in 2002. However, the company could keep a comfortable cash situation. Medarex ended 2002 with cash, cash equivalents and marketable securities of $350 million, compared to approximately $467 million at the end of 2001 (Medarex, 2003b).

Still accumulating losses, Medarex was forced to issue further convertible debts. It successfully raised $275 million gross in 2003 und 2004. The broad and strategic alliance entered into with Pfizer in September 2004 quickly brought in $110 million, and can ultimately reward Medarex even with $400 million in total. The late-stage collaboration with BMS in January 2005 to jointly develop ipilimumab (MDX-010) provided initial cash payment of $50 million.

The ongoing upswing on the stock markets and the financial community's friendly valuation Medarex's monoclonal antibody strategy opened a new window to a further successful stock offering in April 2006, bringing in $111.6 million. Finally, Medarex sold approximately 2.5 million shares of the Copenhagen-based former spin-off and subsidiary Genmab and received approximately $150 million. This sale reduced Medarex's equity ownership in Genmab to 10.8% (Medarex, 2007: 17).

Abgenix focused its financing strategy on the stock market even more so than Medarex (fig. 2). During its first two years until July 1998, Abgenix continued to operate as a Cell Genesys subsidiary. The IPO on July 2, 1998, opened Abgenix to a broader financial public and reduced Cell Genesys's ownership to 42%. The IPO reward of about $20 million net was not particularly successful. The follow-on offering in March 1999, which brought about $45 million net, was more thriving. Then, from the autumn of 1999 until autumn 2000, a real stream of cash inflow followed. Abgenix rode the explosion of stock prices over the course of the new economy bubble. It succeeded in raising about $800 million through various stock offerings until November 2000 (tab. 4). Profiting from a sharp increase in its own share prices and market capitalization, Abgenix even became a Nasdaq-100 company in 2000.

By re-acquiring its *XenoMouse* technology in December 1999 from Japan Tobacco, Abgenix reinforced its property rights substantially. This also helped the company to become higher valued by the financial community and to complete a highly successful secondary stock offering, earning approximately $450 million net on February 11 and March 1, 2000. Due to this strong financial position, in April 2000 R. Scott Greer, President and CEO of Abgenix, could describe the company as *"well positioned to ride the antibody wave"* (Dolan, 2001: 1).

But in 2001 the financial climate began to change. Further public offerings of stocks became impossible. Therefore, Abgenix offered in total $250 convertible subordinated notes, due in 2007. The notes were convertible into common stock in the company at a conversion price of $27.58 per share and accrued interest at an annual rate of 3.5 percent.

During this period and in the following years, corporate collaborations again became more important as a means of corporate financing. Corporate deals with large pharmaceutical corporations tended to be broader and more comprehensive than in the previous period of relatively focused out-licensing agreements. For instance, the agreements with Pfizer and Amgen were extended several times. And the strategic alliance entered into with AstraZeneca in October 2003 included a $100 million equity investment in Abgenix by AstraZeneca and could potentially reach a value of several hundred million U.S. dollars in milestone and license payments. Instead of offering stocks to the public, Abgenix received considerable equity investment from corporate collaboration partners.

Former mother company **Cell Genesys also** profited very well from Abgenix's high stock market valuation. Continuously selling Abgenix shares in November 1998, and primarily during the stock market bubble of 2000, Cell Genesys earned more than $250 million. In December 1999, even the acquisition of Cell Genesys by Boston-based Genzyme failed because Cell Genesys's 19% of Abgenix (worth about $130 million when the merger with Genzyme was announced on October 18) nearly tripled in value to about $370 million on December 21st. That exceeded what Genzyme was able to pay for all of Cell Genesys (Cell Genesys, 1999), These earnings declined during the stock market downturn. After the stock market recovery, Cell Genesys repeatedly sold Abgenix shares, earning approximately $82 million from 2002 to 2005. Finally, the acquisition of Abgenix by Amgen in spring 2006 refueled Cell Genesys's cash holdings with about $62.68 million. Thus, spinning off the *XenoMouse* business and still keeping a considerable amount of Abgenix shares was successful from a financial point of view (see tab. 5).

Tab. 3: Medarex's financing history after its acquisition of GenPharm International

Date	Amount	Type of transaction
12 Jan. 1998	$7.5 million	Medarex receives $7.5 million payment from Xenotech, L.P. trtriggered by the issuance of a European patent on Medarex's HuMAb-Mouse(TM) technology.
22 Jan. 1998	no proceeds	Approximately 1.8 million of the 3.5 million shares issued during 1997 in connection with its acquisition of GenPharm International, Inc. were sold by GenPharm shareholders.
5 Aug. 1998	no proceeds	BCC Acquisition I LLC tendered and accepted for purchase the rights of former GenPharm shareholders to receive $25,122,670 of shares of Medarex common stock. Through these transactions, BCC has acquired 15.8% of Medarex's shares. In addition, Fred Craves, Ph.D., a principal of Bay City Capital LLC, has joined the Medarex Board of Directors.
24 Nov. 1998	$ 7.5 million	Medarex received a $7.5 million payment from Xenotech, L.P. This represents the balance of the amounts due from the Xenotech Group under a Cross-License Agreement under which $16 million has already been received by Medarex this year. This agreement provides the Xenotech Group with a license to this patent and to certain other patents relating to certain transgenic mouse technology.
3 / 7 March 2000	$388 million net	Follow-On Public Offering including an overallotment totaling 2,399,204 shares at $172.00, with net proceeds of approximately $388 million. The shares were offered by an underwriting group with Morgan Stanley Dean Witter, Chase H&Q, Dain Rauscher Wessels, and Warburg Dillon Read LLC as representatives.
12 Sep. 2000	no proceeds	Two-for-one split of the Company's outstanding shares of common stock. The stock split entitled each shareholder of record at the close of business on September 27, 2000, to receive one additional share of common stock for every share of common stock held. The number of outstanding shares of common stock increased from 36.0 to approximately 72.1 million and the number of authorized shares of common stock increased from 100 to 200 million.
26 June 2001	$169 million net	Completing a $175 million 4.5% convertible subordinated note offering, which raised approximately $169 million in net proceeds;
18 / 22 July 2003	$125 million	Private placement of $100 million + 25 million aggregate principal amount of 4.25% Convertible Senior Notes due 2010 to qualified institutional buyers. The Notes will bear interest at 4.25% per annum and will be initially convertible at the option of the holder into shares of Medarex Common Stock at the rate of 148.8261 shares per each $1,000 principal amount of Notes, which is equivalent to an initial conversion price of approximately $6.72 per share
28 April 2004	$150 million	Private place of $150 million aggregate principal amount of 2.25% Convertible Senior Notes due 2011 to qualified institutional buyers. The Notes will bear interest at 2.25% per annum and will be initially convertible at the option of the holder into shares of Medarex Common Stock at the rate of 72.9129 shares per each $1,000 principal amount of Notes, which is equivalent to an initial conversion price of approximately $13.72 per share. This private placement served to refinance 4.50% convertible subordinated notes due 2006.
4 Oct. 2004	$7.2 million	Medarex received two grants from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), to support its research and development of MDX-1303, a fully human antibody being developed for use against human anthrax infection. If all performance milestones are met, the grants may total approximately $7.2 million over the next three years.
14 Jan 2005	no proceeds, payment	Redemption of 4.25% Convertible Senior Notes Due August 15, 2010. Notes could be converted into shares. Medarex made payments of $12.5 million in cash in case of fractional shares.
7 April 2006	$111.6 million net	Public offering of 10 million shares of newly issued common stock at $11.75 per share. Medarex expects the net proceeds from the offering to be approximately $111.6 million. Goldman, Sachs & Co. acted as the sole book-running manager, J.P. Morgan Securities Inc. acted as the joint lead manager of the offering. Janney Montgomery Scott LLC served as a co-manager.
20 Feb. 2007	$150 million	Medarex sold approximately 2.5 million shares of Genmab A/S which stock is traded on the Copenhagen Stock Exchange. Medarex expected to receive approximately $150 million (USD) in net proceeds from the sale. The sale of Genmab shares reduced Medarex's equity ownership in Genmab to approximately 11%.

Tab. 4: Abgenix's financing history after spin-off from Cell Genesys

Date	Amount	Type of transaction
23 Dec. 1997	$20 million	Private placement: 3.1 million new shares of Series B Convertible Preferred Stock had been issued at $6.50 per share to a group of new investors lead by the Omega funds and including Mehta and Isaly; Lombard Odier; New York liefe; Forward Ventures; and SE Banken. Then Abgenix had 7.8 million shares outstanding. Cell Genesys did not sell any of its Abgenix shares in the offering and stilled owned approximately 56% of the outstanding shares.
2 July 1998	$20 million	Completion of Abgenix' IPO: 2,500,00 shares at a price of $8.00 per share providing. This offering reduced Cell Genesys' ownership of Abgenix to 42%.
30 July 1998	$ 3 million gross	Sale of 375,000 shares at $8 per share pursuant to the exercise of the underwriters' over-allotment option.
20 Nov. 1998	no proceeds	Cell Genesys reduced its ownership on Abgenix to 30%.
4 March 1999	$45 million gross	Sale of 3,000,000 shares of Common Stock in a public offering at a price of $15.00 per share.
7 April 1999	$3.12 million gross	Sale of 208,000 shares of its Common Stock at $15.00 per share pursuant to the exercise of the underwriters' over-allotment option.
15 Nov. 1999	$75 million	Abgenix entered into definitive purchase agreements for the sale of 1.8 million shares of newly issued Common Stock to selected institutional and other accredited investors. The purchase price is $42.00 per share.
11 Feb. 2000	$453.6 million gross	Abgenix sells 2,160,000 newly issued shares at a price of $ 210.
1 March 2000	$6.8 million gross	Abgenix sells additional 324,000 shares at a price of $210 pursuant to the exercise of the underwriters' over-allotment option.
1 March 2000	two-for-one split	Abgenix, Inc. announces a two-for-one split of the Company's outstanding shares of common stock. The stock split was effected in the form of a stock dividend and entitled each stockholder of record at the close of business on March 16, 2000, to receive one share of Common Stock for every share of common stock held.
8 June 2000	two-for-one split	Abgenix, Inc. announces a two-for-one split of the Company's outstanding shares of common stock. The stock split was effected in the form of a stock dividend and entitled each stockholder of record at the close of business on June 19, 2000, to receive one share of common stock for every share of common stock held.
1 Nov. 2000	$230 million gross	Abgenix sells 3,300,000 shares as part of a private placement at a price of $70 per share.
27 Feb 2002	$200 - 250 +3.5% interest	Abgenix, Inc announced that it has priced its previously announced private placement of $200 million aggregate principal amount of its Convertible Subordinated Notes due 2007. In addition, the company granted the initial purchasers of the notes an over-allotment option for up to an additional $50 million principal amount of notes. The notes will be convertible into common stock of the company at a conversion price of $27.58 per share and will accrue interest at an annual rate of 3.5 percent.
17 March 2004	$250	Abgenix, Inc. announced that it has filed with the U.S. Securities and Exchange Commission to periodically sell up to $250 million in debt securities, preferred and common stock, and warrants.
17 March 2005		Abgenix, Inc. announced that it has filed a resale registration statement on Form S-3 with the U.S. Securities and Exchange Commission covering its 1.75 % Convertible Senior Notes due December 2011 and the common stock issuable upon conversion of the notes. The notes were issued in a private placement in December 2004. Abgenix did not issue any new securities and did not receive any proceeds from the resale of securities under this registration statement.

Tab. 5: Cell Genesys's earnings through the sale of Abgenix shares

Date	Amount	Type of transaction
20 Nov. 1998	$9.5 million	Private sale of approximately 1.1 million shares of Abgenix to Zesiger Capital Group. Cell Genesys reduced its ownership on Abgenix to 30%.
11 Feb. 2000	($176.4 million brut)	Cell Genesys sells 840,000 shares of Abgenix at a prize of $210 per share. Cell
16 Feb. 2000	$168 million net	Genesis retains 12.5% ownership of Abgenix.
1 March 2000	$25 million net	Cell Gensys sells additional 126,000 shares of Agenix stock at a price of $210. Cell Genesys retains 12% ownership of Abgenix which on 29 February 2000 had a market value of $781 million.
1 Nov 2000	$52.5 million brut	Cell Genesys sells 750,000 shares of Abgenix as part of a private placement at a price of $70 per share. Cell Genesys retains 10.5% ownership of Abgenix.
2000	$239.660 million	
2001	-	no sale of Abgenix shares
2002	$2.246 million	Cell Genesys holds 9 million shares of Abgenix at the end of 2002
2003	$12.638 million	Cell Genesys holds 8.7 million shares of Abgenix at the end of 2003.
2004	$12.16 million	Cell Genesys holds 6.6 million shares of Abgenix at the end of 2004.
2005	$55.123 million	
2006	$62.677 million	Amgen acquires Abgenix for $2.2 million. Cell Genesys sells its …. Remaining shares at a stock price of $

Riding the antibody wave and the stock market wave

Here now is a summary of the major findings of this stage of technology commerzialization and diffusion in respect to the technological, organizational, institutional and economic dimension. Both companies' activities in the period after 1997 were mainly characterized by the commercialization of the *HuMAb* and *XenoMouse* technologies and by efforts to develop therapeutic monoclonal antibodies based on them. In parallel, both Medarex and Abgenix tried to enrich their technology portfolio by acquiring new technologies from other firms. In this regard Medarex, notably by buying access to Kirin's *TC-Mouse*, was more active and successful than Abgenix,

Both companies were able to surf the new economy wave and to use high expectations for monoclonal antibodies (caused by FDA approvals of promising antibodies in 1997 and 1998) to raise enormous amounts of cash and enter rewarding collaboration agreements with larger firms. However, Abgenix and Medarex have never made profits in their history. Abgenix had an accumulated deficit of $959.2 million in 2005. In the same year, the last of its independent existence before being acquired by Amgen, Abgenix had incurred net losses of $207 million (Abgenix, 2006: 25). Rival Medarex had an accumulated deficit of approximately $963.7 million until 2006. In that year alone, it recorded net losses of $181.7 million (Medarex, 2007: 31). Thus, the amounts both companies raised on the stock markets and what they earned by entering collaborative agreements were burned up by their corporate activities. This constellation was only possible in the context of the new economy wave and symbiotic relationships with large pharmaceuticals, which suffer from an innovation deficit and are desperately seeking new technologies, drug targets and drug candidates (Zeller, 2008b).

The financial and technological promises of the late 1990s left a certain disenchantment in their wake. Therefore, it was not surprising when in December 2005 Abgenix's shareholders preferred to sell the company to Amgen. Indeed, Amgen acquired only panitumumab and the *XenoMouse* technology, not the entire company. Amgen laid off almost a quarter of Abgenix's personnel. Thus exactly at the moment when Abgenix's first drug candidate, pantiumumab, had good chances of approval by the

FDA, a much stronger player in the biotech business acquired this promising option for potential profits. Today, the future perspectives of the *XenoMouse* technology depend much more on Amgen's financial and business considerations than on the pure characteristics of the technology.

Paradoxically, although Medarex has a broader and larger pipeline than Abgenix, but no such advanced drug candidate as pantiumumab, has been a less interesting takeover target. However, the possibility cannot be ruled out that Bristol-Myers Squibb or Pfizer will launch a bid for Medarex as soon as one or two of its advanced drug candidates are likely to be approved by the FDA. Such an acquisition would enable them to avoid the expensive milestone payments and royalties payable to Medarex. Moreover, they would take control over a promising technology.

Fig. 1: Development of Medarex's stocks
Source: http://finance.yahoo.com

Fig. 2: Development of Cell Genesys's stocks
Source: http://finance.yahoo.com

3. Product commercialization since 2006

Amgen's acquisition of Abgenix and the approval of *Vectibix* (panitumumab) by the FDA in September 2006 launched a third phase of the innovation process. After almost twenty years, when the first experiments generating human monoclonal antibodies from transgenic mice were started, the first therapeutic product based on such a technology was approved.

Almost all human monoclonal antibodies derived from transgenic mice currently in clinical trials are produced either with Abgenix's *XenoMouse* or Medarex's *UlitMAb* technologies. In early 2006, just before its acquisition by Amgen, Abgenix and its partners had fourteen antibodies generated with *XenoMouse* technology in clinical trails, or had regulatory applications submitted for such trials. In spring 2007 Medarex, together with its partners, even had 34 drugs generated from its *UlitMAb Antibody Development System* in the same stage of development (in spring 2005 it had 31 drug candidates). Out of Abgenix's fourteen drug candidates, two proprietary drug candidates and twelve antibody product candidates were developed by companies that had licensed Abgenix's technology. Medarex pursued three proprietary and six co-developing development programs, while the remaining 25 drug candidates were out-licensed to partner firms. Already six human monoclonal antibodies were in phase III clinical trials. One of them was developed together with Bristol-Myers Squibb, two were developed by Centocor (a fully owned subsidiary of Johnson&Johnson), one by Genmab A/S and Merck Serono, one by Genmab and GlaxoSmithKline, and one by Genmab alone (Abgenix, 2006: 3; Medarex, 2007: 1).

As of summer 2007, only one therapeutic product based on transgenic mice technology had been approved by the FDA. It is *Vectibix* (panitumumab), derived from the *XenoMouse* technology. **Abgenix** was pursuing four clinical studies programs in 1998 when it launched its IPO. It had begun the most promising and most advanced program in late 1997 when it launched a phase I clinical trials with ABX-IL8, its lead product for inflammation (Cancer Weekly, 1997). However, it canceled development of its anti-IL8 monoclonal antibody on March 15, 2002. Two other of the initial projects also failed. Only one of the initial development programs was still ongoing in spring 2006.

One year after its IPO launch, Abgenix began the clinical development of panitumumab, previously called ABX-EGF, a human antibody that targets the epidermal growth factors receptor (EGFr), which is over-expressed in a variety of cancers one year after its IPO. It is based on its advanced version of the *Xenomouse* technology. The company started a phase I clinical trial in July 1999, examining the product's safety in patients with a variety of advanced cancers. In order to share the costs and the risk, Abgenix entered into a 50-50 co-development collaboration with Seattle-based Immunex to develop panitumumab for the treatment of EGFr-positive cancers in July 2000. Immunex was bigger, financially more powerful and already more experienced in drug development and clinical trials than Abgenix. A number of phase II studies were initiated in 2001 and 2002. In January 2002, Abgenix and Immunex initiated a phase II clinical trial of ABX-EGF in patients with colorectal cancer (Abgenix, 1999;2002;2006).

In 2002, Immunex was acquired by biotech giant Amgen (Thousand Oaks, CA). Amgen continued the development collaboration and phase III trials of panitumumab for the treatment of colorectal cancer with Abgenix. In August 2003, during this late stage of the development of panitumumab, Amgen changed the terms of the agreement and increased its control over the program (Abgenix, 2003a). Finally, the FDA approved panitumumab under the marketing name of *Vectibix* for the treatment of colorectal cancer in September 2006.

However, at this moment, Abgenix had already ceased to exist as an independent firm. On December 14, 2005, collaboration partner Amgen launched the acquisition of Abgenix and offered to pay $22.5 a share, or $2.2 billion total in cash, a 54% premium over the last closing price of $14.65. After shareholder and regulatory approval, this acquisition was completed in March 2006. It provided Amgen full ownership of the anti-cancer drug *Vectibix* and of Abgenix's promising technology and product portfolio. Moreover, by acquiring Abgenix, Amgen avoided paying royalties to Abgenix for commercializing *Vectibix.* Amgen expected that panitumumab had the potential to be a blockbuster drug, with $2 billion or more in worldwide sales. Abgenix's former 100,000-square-foot manufacturing plant in Fremont. CA, continued to produce panitumumab. Nevertheless, Amgen laid off 83 former employees.

The most advanced drug candidate of Medarex is ipilimumab (previously named MDX-010). This is a fully human antibody that targets the cytotoxic T-lymphocyte antigen 4 immune receptor. This receptor has been shown to diminish or down-regulate the immune response to tumors or infectious agents. By using a fully human antibody to block the activity of this immune receptor, Medarex believes that patients' immune systems may be able to mount a stronger immune response against foreign pathogens and cancers. In order to have enough active substance material of ipilimumab for clinical supply, Medarex entered into a clinical manufacturing agreement with Lonza Biologics in September 2003 (Medarex, 2007: 21). In January 2005, Medarex began collaborating with Bristol-Myers Squibb to develop and potentially commercialize ipilimumab for melanoma and any additional disease indications. In summer 2007, the partners were undertaking several phase III and phase II clinical trials for various treatments. They expect the drug could be approved in 2008 (Medarex, 2007: 7ff).

The approval of *vectibix* and Amgen's acquisition of Abgenix marks an important step toward maturation in the technological arena. This first, although late, confirmation of the technology provoked numerous speculations, especially among competitors, potential acquirers of Medarex and of course among financial organizations looking for profitable places to place their liquid money. These recent events mark the beginning of a new stage in the innovation arena, with large pharmaceutical and biotech companies enforcing their capital power as well as their development and marketing capacities. They take over the further commercialization of the outcomes of the technology of monoclonal antibodies derived from transgenic mice.

4. Conclusions

This reconstruction of the innovation paths of the two major methods of generating human monoclonal antibodies from transgenic mice is based on a dynamic comprehension of a technological arena. This approach permits us to understand how the key actors shape and drive specific innovation processes. The analysis of the innovation path of this technology can be summed up in four conclusions regarding the technological, organizational, institutional and economic dimension of the technological arena (Tab. 5).

Tab. 6: Dimensions of technological evolution in a technological arena

	Phase I	Phase II	Phase III
Cognitive dimension	Transfer from academic niche to business area. Development and completion of technology	Commercialization of technology, biotech learns early clinical trials	Commercialization of technology and products, experience in clinical trials
Organizational dimension	Academic-business collaborations.	Out-licensing agreements from biotech to pharma. Technology agreements biotech-biotech	Out-licensing agreements from biotech to pharma. Technology agreements
Institutional dimension	Technology transfer based on intellectual property, entrepreneurial researchers and informal relations	Out-licensing based on intellectual property	Out-licensing based on intellectual property
Financial dimension	Grants, research collaborations, seed and venture capital	IPO, stock market, joint research and development, license fees	Joint development, license fees, royalties, sales

Knowledge transfer and technological evolution

Important components of both technologies, the *HuMAb Mouse* and the *XenoMouse*, originally stem from academic research organizations such the Medical Research Council's Laboratory of Molecular Biology in Cambridge, Stanford University, Columbia University and the University of Utah. These institutions can be interpreted as niches guaranteeing a financially protected area for conducting basic research.

Key research scientists and entrepreneurial scientists played essential roles in transferring academic knowledge into newly created biotechnology companies. Interestingly, in both cases only a few people were crucial to the continuity of the technology creation and the progress of the technological path. Whereas Nils Lonberg decisively contributed to the survival of GenPharm and the transfer of knowledge to Medarex, and still has a strategic key position in Medarex, Aya Jakobovits guaranteed the transformation from Cell Genesys to Abgenix. But she left the company in 2001. Probably the longer personal continuity of the scientific director and the longer existence of Medarex as an independent firm were helpful to its strategy of integrating and combining complementary technologies and pursuing a more active technology plan in this phase of the innovation path. This

underscores not only that knowledge and experience (and their transfer) are embodied by persons such as research scientists, entrepreneurial scientists and managers (cf. Zucker and Darby, 1996), but that key persons also help guarantee the continuity of a knowledge-producing social context within an organization. Tacit knowledge is exchanged in such social contexts. Cell Genesys/Abgenix and GenPharm were located almost in the same neighborhood. Thus, the early technology's transformation phase occurred in close spatial proximity. 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.

The innovation arena of monoclonal antibodies derived from transgenic mice is a result of the ambition to resolve the problem of immunogenicity provoked by murine monoclonal antibodies. Thus, problem-solving efforts and scientific breakthroughs channeled innovative activities and opened the possibility for the emergence of a new innovation arena. This *technological trajectory* led to a series of further technological challenges. GenPharm's and Cell Genesys's early efforts involved integrating and combining different knowledge bases which were expected to permit the creation transgenic mice with human antibody machinery. These efforts to internalize technological complementarities drove the early formation of collaborations between academic research organizations and other firms. This technological combination and fusion continued in the second phase as well, from 1997 to 2006. However, its procedure and range changed. Whereas in the first phase both companies focused on improving their core technology, in the second phase it was more about combining with neighboring technologies, such as phage display. In terms of resulting products, many expectations were not realized. From the four product development programs Abgenix launched in 1996, only one finally led to an approved drug in 2006 (panitumumab).

Collaborations and industrial organization

The combination of existing knowledge and technologies as well as the transfer of codified and commodified knowledge is shaped by corporate collaborations, which for their part are driven by business and technology strategies. Abgenix and Medarex chose their collaborative partners in most cases for financial reasons. Out-licensing their technology was a major lever for obtaining funding from financially stronger collaboration partners. Cross-licensing and in-licensing technologies were instrumental to gaining access to complementary technologies and drug targets.

Quantitative analysis of corporate networks is helpful to get an idea of the greater network pattern (cf. Gay and Dousset, 2005). This study clearly shows that it is important to distinguish the intensity of collaborations. Collaborations are formed to accomplish specific goals. Highly complex collaborations, such as the one Medarex arranged with Bristol Myers Squibb and Pfizer, or Abgenix's agreement with Immunex / Amgen and AstraZeneca, have more far-reaching effects on the evolution and diffusion of a technology than focused in- or out-licensing agreements do. Corporate collaborations not only influence the extension of a technological arena but also the direction of its evolution.

A new technology creates new opportunities for the entry and emergence of new firms in an industrial sector. However, our example shows that established firms are able to incorporate new technologies and to dominate the newly emerging technological field. This confirms Dosi's statement that the emergence of a new paradigm is often related to new "Schumpeterian" companies, while its establishment often also displays a process of oligopolistic stabilization (Dosi, 1982).

The innovation arena changed considerably in the second phase compared to the first. The power of large pharmaceuticals unfolded more evidently during the commercialization and diffusion of the technology than during the commercialization of the concepts before their realization. This also reflects some characteristics of the pharma-biotech-complex and the tendency toward a selective vertical disintegration (Zeller, 2008b). In the context of an innovation deficit in the pharmaceutical industry, the large pharmaceutical corporations are forced to acquire drug targets, substances and technologies (Drews and Ryser, 1996; Angell, 2004). Their financial and marketing power, broad knowledge base and manufacturing capabilities enable them to integrate and combine a broad range of technologies. The dynamic collaboration landscape reflects the permanently changing boundaries of an innovation arena. Thus, the meso-level of a technological arena is an appropriate level to understand technological evolution, but always in the context of the broader industrial and macroeconomic dynamics. In the case studied here, both companies' strategies were directly interrelated. In the setting of an almost duopolistic rivalry, the dynamics within the innovation arena can only be understood in a relational sense.

Property rights and institutional conditions

The behavior of collaborating and rivaling individuals and organizations within a changing innovation arena is influenced not only by industrial organization but also by institutional conditions. The presented analysis shows that over a long period, both companies were more engaged with legal fights, mutual disturbing and financial shortages than with advancing the innovative processes. In both cases, the key inventions happened in the period between 1989 and 1991. The ensuing period up to the cross-licensing agreement in 1997 was marked by destructive, rivalrous activities. Thus, a technological path is also an outcome of the conflicts within a technological arena. A favorable market context which drove the innovation and commercialization processes emerged only, on the one hand, after settlement of the patent dispute, the cross-licensing agreement and the acquisition of GenPharm by Medarex, and, on the other hand, after the spin-off of Abgenix and the subsequent capital inflow by a successful IPO. The stock market boom helped both companies to complete the *HuMAb* and *Xenomouse* technologies respectively, and to move their previously discovered monoclonal antibodies into clinical trials. For this they were forced to enter into collaborations with large pharmaceutical and biotechnology companies. Only after 1998 *"did we have a stable company environment and we were free of litigations, so that we could actually make partnerships"* (Interview Sep. 2006).

Both companies used the argument of a greater certainty of intellectual property rights, compared to other monoclonal antibodies technologies, to promote their technologies. Medarex declared it was not aware of any licenses required to create fully human antibodies using its *UltiMAb* technology platform to a target owned by the user except under patents currently owned or licensed by Medarex itself. In

contrast, in other areas of monoclonal antibodies, various entities hold patents that may cover the chimerization and humanization of monoclonal antibodies and the phage display technology (Medarex, 2007: 20). In all these fields, a complex landscape of intellectual property monopolies sets the conditions for corporate strategies. Companies even develop new humanization technologies in order to avoid occupied intellectual territories. The problematic of the property rights landscape and the hard rivalry between GenPharm and Cell Genesys underscore the importance of institutional conditions and broader economic contexts. Thus, on the one hand, the property rights regime favored a very specific form of knowledge and technology transfer from academia to the business world. On the other hand, this property rights regime could also set the conditions for ferocious rivalry and unproductive mutual blocking of innovative activities.

The power of finance: How the economic arena determines the cognitive arena:

Over the course of the technological arena's maturation period, large pharmaceutical and biotech companies increasingly took direct command over the further evolution and commercialization of the technology and related products. Because of GenPharm's weakened position, Medarex could acquire the *HuMAb* technology quite cheaply in 1997. Concurrently, in the context of the stock market boom, Cell Genesys succeeded in earning a huge amount of cash spinning off Abgenix with its *XenoMouse* technology. Then nine years later, as a result of its acquisition of Abgenix in April 2006, Amgen purchased the *XenoMouse* technology and gained access to patents, patent applications and inventions licensed to Abgenix from third parties. Amgen is a much more powerful player than Abgenix, and its strategic goals underlie other economic dynamics. Since the purchase by Amgen, the fate of the *XenoMouse* technology has been submitted to this company's strategic orientation in different biotechnology areas.

In general, it can be concluded that as the specific technology and the whole technological arena matured, power relations moved toward large corporations such as AstraZeneca (which gained access to different technologies for generating human monoclonal antibodies and became a leader in the entire technological field of monoclonal antibodies by acquiring advanced biotechnology firms), Amgen (through acquiring Immunex and Abgenix) or Johnson&Johnson (which acquired the strong antibody pioneer Centorcor in 1999 for $4.9 million).

The innovation process's reliance on the mood of the stock markets raises a fundamental question. Rivalry and dependence on stock markets forced firms to look after their cash as a first priority. The stock market does not seem to be the most efficient instrument for allocation of capital for research and development. While there was a shortage of money during a poor financing conjuncture from 1993 to 1995, there was an oversupply during the stock market boom from 1998 to 2001. The capital shortage meant that companies were forced to commit their resources to activities that were far from innovative. But the oversupply of capital during the new economy bubble encouraged companies to undertake speculative activities purely oriented toward financial gains, which again could disturb technological development.

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