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Abstract. The paper presents an in-depth analysis of the innovation biography and geography of a commercially successful monoclonal antibody and related technologies. At present, out of about 100 recombinant therapeutics on the market, 21 are monoclonal antibodies. The analysis is based on a conceptual framework that combines elements from sectoral innovation systems and technological systems approaches as well as debates on different knowledge bases. This detailed analysis of one therapeutic agent reveals the participants in the entire innovation process and their locations. Pharmacetical drugs follow a very complex innovation path, from basic research on disease mechanisms, to discovery of the drug candidate, to preclinical and clinical development, manufacturing and approval for market. The paper shows the structure of resource, knowledge and value flows over the course of the entire innovation process, from basic discovery up to the commercialization of the drug. The more the innovation process progresses, the more it is shaped by financial and commercial considerations.

Keywords: monoclonal antibodies, biotechnology, innovation systems, knowledge, intellectual property

1. Introduction

Much geographical research undertaken on innovation processes in biotechnology suffers from three shortcomings. First, a focus within predefined spatial demarcations, such as regional clusters or regional innovation systems, frequently hinders a broader spatial perspective on the relevant relations between actors in innovation processes. Second, the power relations between these actors, who are often very different, are ignored. Third, the factor of time is poorly conceptualized, especially in regard to the changing configurations of industrial organization, changes in the broader institutional context and changes in the constellation of actors in an innovation process. This article takes another approach. It focuses on the innovation path of one single drug, from its early conception to its manufacture and sale. It is *Rituxan* (rituximab), a drug against a specific form of cancer and one of the most successful monoclonal antibodies. Therapeutic products like *Rituxan* pass a very complex innovation path, from discovery, to preclinical and clinical development, to manufacturing and approval for market. A path-centered approach, without predefined spatial demarcations, is better suited to truly understanding the flows of knowledge, money and other resources as well as the power hierarchies in innovation processes.

A vast multiplication and differentiation of technologies and approaches occurred in biotechnology in the 1970s based on some fundmental discoveries. This molecular biology revolution, together with far-reaching macro-societal and institutional changes and the emergence of biotechnology firms provoked major changes in the pharmaceutical industry. The innovation process in the pharmaceutical industry has since become so complex and manifold that even large pharmaceutical companies are no longer solely able to exert important technological renewals and search processes for new active substances. Therefore, since the 1980s they have developed new strategies to acquire new drug targets, active substances and technologies through collaborations with smaller biotech firms and academic research institutes. One of the key technologies which emerged in the mid-1970s was the creation of monoclonal antibodies from hybridoma cells. This technology gave rise to considerable expectations for creating new diagnostic tools and drugs. However, it took more than twenty years before monoclonal antibodies were successfully commercialized as therapeutic agents. Currently there are 21 monoclonal antibodies as therapeutic agents on the market. In total, there are around 100 marketed recombinant therapeutics.

On the meso-level, this analysis combines elements from the sectoral innovation systems (Malerba, 2002) and technological systems (Carlsson, et al., 2002a) approaches. On the micro-level, to analyze the innovation trajectory of one product, I turn to concepts better suited to understanding different types and bases of knowledge, such as the cyclical recombination of explicit and tacit knowledge (Nonaka and Takeuchi, 1995; Nonaka and Toyama, 2002) as well as the distinction between analytical and synthetic knowledge (Asheim and Gertler, 2004; Moodysson, et al., 2008).

Large, oligopolistic pharmaceutical companies and biotech companies are connected by dense flows of financial means, knowledge and technologies between themselves and publicly funded research institutes and financial companies. Thus, the pharmaceutical and biotechnology industries are inseparably connected in a common industrial system, which I call the pharma-biotech-complex (Zeller, 2008c).

Thus, the central question is, how are the crucial innovation processes for the development of specific therapeutic products in the pharma-biotech-complex organized? In response, I will examine which actors (individuals and organizations) contributed to the innovation processes, the ways they contributed, as well as why and where the major work was undertaken.

The analysis of each innovation process must be embedded in the broader context of industrial organization as well as of institutional and social change. Based on previous research on the pharma-biotech-complex, this paper first argues that the spatial innovation biography of a drug is shaped mostly by large pharmaceutical companies, which also profit the most from the innovation processes (Zeller, 2004;2008c). However, in early stages, the innovation processes are still more science-driven because of the prevailing scientific culture and logic. In contrast, advanced stages are largely market- and even finance-driven. Large transnational companies, relying on their capital endowment and marketing power, structure the innovation processes and the global networks. In fact, the institutional context of the bio-tech industry changed over the period of *Rituxan's* innovation path. After major institutional changes in the 1980s, the biotechnology industry was increasingly driven by the hunt for intellectual property monopolies and royalty-staking strategies (Zeller, 2008b).

Second, the paper delineates how the spatiality of innovation processes is also determined by the way the involved actors produce, exchange and absorb knowledge. In most cases, the generation and exchange of explicit and analytical knowledge is not delimited by spatial restrictions. However, crucial stages of the innovation trajectory depend on very dense exchange of ideas and perceptions between key actors, including tacit knowledge and synthetic knowledge. These stages tend to happen in very close spatial and/or organizational proximity.

The paper is organized as follows. The next section presents a framework for the analysis of the innovation paths of therapeutic agents using a critical appraisal of sectoral systems of innovation, technological systems and debates on different types of knowledge. The third section presents major steps in the innovation process of a key technology and the characteristics of monoclonal antibodies. Then, in the fourth section, a detailed analysis and interpretation of the innovation path of rituximab provides an exact picture of the key actors involved, their hierarchical relations and the spatiality of these relations. The conclusion puts the spatial innovation biography into the context of the industrial organization's evolution and the broader macro-economic and institutional changes.

2. Innovation systems and innovation biography

There is a diverse literature explaining the spatial concentration of innovative activities and the competitiveness of firms concentrated in clusters or embedded in regional and national innovation systems. In contrast, the innovation processes themselves are the major concern of this paper. The focus is the division of labor among the key actors contributing to the innovation process of therapeutic agents, a process which can last about a quarter of a century, including the generation of required basic knowledge. The analytical framework for this study of the spatial innovation biography of rituximab borrows from three, partly related bodies of literature.

The first strand of literature comprises the debates on innovation systems and their insights on systemic conditions that favor knowledge creation processes and mutual learning among actors in an innovation system. Innovation systems are conceptualized as integrated within a broader institutional and cultural framework. Various collaborating actors together form an innovation system: companies and their employees who create and transform knowledge and technologies; firms, which react to the demand on markets; trade organizations, labor unions and other associations can also be important in shaping specific contexts. What's crucial is the knowledge base which is mainly formed by publicly funded research institutes, but also by collaborating firms. Each innovation system is characterized by its "rules of the game," which are an outcome of the institutions, but also of the broader societal, economic, political and cultural relations. The extended range of influence of financial markets, the extension of property rights, especially intellectual property monopolies and the modified role of publicly funded research have been important institutional changes in the biotechnology sector (Zeller, 2008b). Innovation systems approaches were originally applied on the national level, but soon after on the regional level as well. The approach of sectoral innovation systems analyzes the changing industrial organization, explicitly taking into account the specific *technological regimes,* which include specific combinations of opportunity and appropriation conditions, degrees of technological-knowledge cumulativeness, and characteristic knowledge bases in specific industry sectors (Malerba and Oresnigo, 1993: 47ff; Malerba, 2002; Malerba and Orsenigo, 2002; Malerba, 2004; McKelvey, et al., 2004).

The innovation processes in the pharma-biotech-complex are largely shaped by its power relations. Due to the enormous differentiation of drug discovery technologies and in order to minimize their own risk, large pharmaceuticals systematically observe technological development on a global scale and acquire promising substances and technologies. At the same time, the out-licensing of drug candidates and technologies is an important source of income for biotech firms and even universities. Biotech companies often transform and develop basic knowledge generated in publicly financed institutes. They then can either develop promising projects together with pharmaceuticals or out-license. Even without internalizing the entire value chain, 'big pharma' is able to steer production systems and innovation processes considerably. A pyramid of value acquisition has emerged (Zeller, 2008c).

An analysis of the spatial innovation biography of specific products needs an approach more suitable to micro-level analysis. Thus, the concept of technological systems, proposed to analyze the evolution of specific technologies or products (Carlsson, et al., 2002a; Carlsson and Stankiewicz, 1991; Stankiewicz, 2002) is the second reference here. 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).

However, the systems approach (cf. Carlsson, et al., 2002b: 234; Edquist, 2005: 187) is not necessarily appropriate for analyzing the spatial innovation biography of a specific drug, for several reasons. First, the entire innovation path normally lasts about two decades and can be interrupted several times. Thus, the constellations of involved actors as well as institutional and economic conditions change considerably over the entire process. Second, the overall innovation process is largely unplanned, with involved actors pursuing their specific and often rival goals within limited time frames. The firms

involved in the innovation process of a drug apply strategies which, depending on market conditions and institutional contexts, can include all kinds of relations, from hard rivalry to collaborative partnering. Finally, the innovation systems literature tends not to sufficiently integrate power relations, capital and financial constraints and incentives which are promoted or diminished by the broader institutional context.

This paper considers the innovation process leading to one product – in this case *Rituxan* (rituximab) – as part of a much broader technological innovation arena formed by the collaborating and rivaling actors who created monoclonal antibodies for therapeutic purposes (cf. Zeller, 2008a). 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

The third discussion concerns the knowledge problem. Often, codified and explicit knowledge are distinguished from tacit and uncodified knowledge (Nelson and Winter, 1982; Feldman, 2000; Gertler, 2003). The transfer of codified knowledge in most cases does not raise major technical or organizational problems, but probably legal ones. However, its understanding and application depends on tacit knowledge (Nightingale, 1998). Thus, the production, dissemination, appropriation and application not only of tacit knowledge, but even of explicit knowledge (though to a much lesser extent), depend on the involved actors' specific social and institutional contexts and competences. Such contexts are not easily transferable in space.

An organization continuously transforms explicit and tacit knowledge. Nonaka and colleagues suggested a dialectical understanding of process that consists of cyclical knowledge transformation, including socialization, externalization, combination and internalization (Nonaka and Takeuchi, 1995; Nonaka and Toyama, 2002). This perspective seems more appropriate, as it correctly emphasizes the permanent tension between individual and collective knowledge generation. Recently, a distinction between predominantly analytical and synthetic knowledge bases in industries was suggested to better analyze the role of different knowledge bases, depending on the type of industry and the stage of the innovation process (Asheim and Gertler, 2004; Moodysson, et al., 2008). Indeed, such a distinction may be helpful for this purpose. However, I would argue that each knowledge creation process, by including the generation of analytical and synthetic knowledge, consists of analyzing and synthesizing existing bodies of knowledge.

So to unify these elements, I suggest that the creation, transfer and absorption of knowledge includes at least four major dialectical processes, involving the tensions between individual and collective knowledge, between tacit and explicit knowledge, between analytic and synthetic knowledge, and between context-bound and context-detached knowledge. These processes overlap and thus are not clearly separable.

Whereas the creation and exchange of tacit and synthesized knowledge tend to be more bound to social contexts than explicit and analytical knowledge, the transfer and sharing of knowledge – thus socialization – between individuals and then between organizations depend on the degree of spatial and organizational proximity (Zeller, 2004), respectively functional and relational proximity (Moodysson and Jonsson, 2007). Depending on the concrete problems which need to be solved within

a long-lasting innovation process and the organizational and institutional context, one or another type of knowledge creation – or dialectical tension – predominates.

The path of any given medicine, from its conception to its market introduction, is long and very often full of obstacles. Many different actors contribute to the highly complex innovation and value-creation process in the pharma-biotech complex. It is not unusual for the research and development process to take more than ten years. If we include basic research on disease mechanisms and basic technological discoveries, the span is much longer. Due to increased competition, pharmaceutical companies have made great efforts in the last few years to accelerate this process, especially the development stage. In order to reduce time and costs, many activities are increasingly carried out simultaneously. The development process of therapeutics, from the discovery of drug targets and active substances to the market phase, passes through a number of steps, independently of whether its active substance is produced by chemical synthesis or by biotechnological procedures (Fig. 1).

This case study on the spatial innovation biography of one monoclonal antibody first focuses on the individuals and organizations who contributed to the entire innovation process of rituximab and how and where they pursued their work. Then the relations and flow of resources (money, knowledge, technologies) between the key actors involved are examined, followed by an investigation of the extent to which company size and strategies, market structure, ownership and power relations shape specific processes of the entire innovation path.

There is an important methodological argument for establishing a spatial innovation biography. A product or commodity embodies all social and economic relations which preclude and enable the innovation and production process of that product. Such a biography details the generation of the basic scientific knowledge, the identification of a drug target, the creation the monoclonal antibody itself, the trajectory of its development, the clinical studies, the up-scaling processes, the manufacturing, the commercialization and the extension of its application for the treatment of additional diseases. An analysis of the entire innovation path and related technological trajectories and business strategies provides valuable information about the geography of innovation processes that cannot be disclosed otherwise. Power hierarchies, flows of resources and values can especially be analyzed this way. The innovation biography encompasses the changing conditions over time. While approaches that look at global production networks (Henderson, et al., 2002), global commodity chains (Gereffi, et al., 2005) and sectoral innovation systems investigate a given configuration in a relatively short period of time, the innovation biography presented here attempts to grasp the entire process, from early discovery up to commercialization of a drug. However, the post-reconstruction of an innovation path also raises methodological challenges. When interviewees reconstruct the processes in which they were involved, they tend to overestimate results and success and to underestimate or even omit failures. Thus, information from interviews and involved firms needs to be carefully scrutinized.

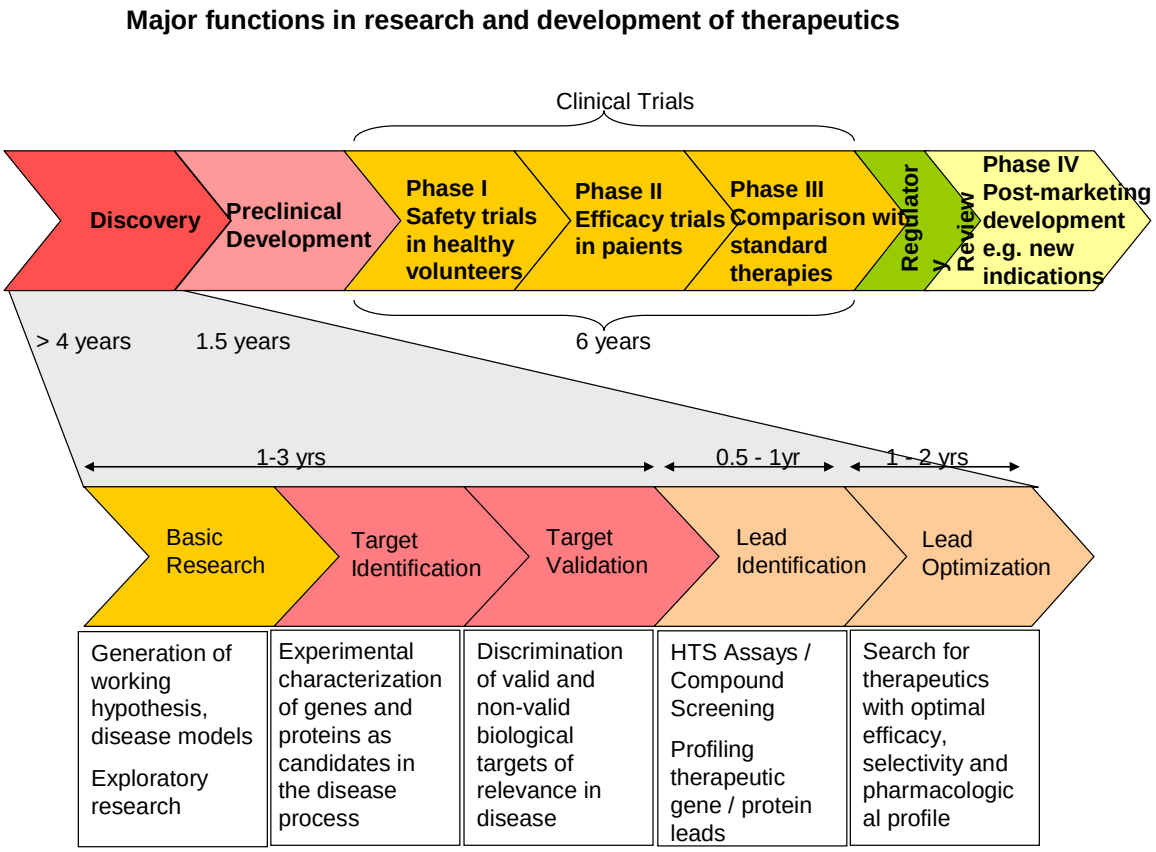

Fig. 1: Major functions in research and development of therapeutics

3. The evolution of a key technology

Three fundamental inventions

Over the course of the molecular biology revolution in the early 1970s, various new technologies in the field of genetic engineering and cell fusion emerged (Swanson, 1986; Robbins-Roth, 2000; Nobelprize, 2007; Genome News Network, 2007). Based on three fundamental inventions, biotechnologies multiplied into almost innumberable further technologies and applications. As a consequence, new markets and products emerged.

Paul Berg from Stanford University, Palo Alto, assembled the first DNA molecules that combined genes from different organisms. He inserted viral DNA into bacterial DNA. For his fundamental studies of the biochemistry of recombinant-DNA, Berg was awarded the Nobel Price in chemistry in 1980. Using restriction enzymes (jointly discovered in 1970 by the Swiss scientist Werner Arber and his American colleagues Hamilton Smith and Daniel Nathans), Stanley Cohen from University of California, San Francisco, and Herbert Boyer from Stanford University transferred DNA from one live organism to another, creating the first recombinant DNA organism in 1973. Some years later, in 1976,

venture capitalist Robert Swanson convinced Herbert Boyer to found the company Genentech to commercialize this technology. Together with Rita Levi-Montalcini, Cohen won the 1986 Nobel Prize in Medicine for their earlier work discovering cell growth factors in the late 1950s.

The second fundamental invention was the creation of monoclonal antibodies by the Argentinean Cesar Milstein and the German George Köhler, working together in Cambridge in 1975. Before and after his sabbatical in Cambridge, Köhler worked at the Basle Institute of Immunology, which was funded by the large pharmaceutical company F. Hoffmann-La Roche. Together with the Dane Niels Kaj Jerne, who had worked on theoretical conceptions of antibodies at the Basle Institute for Immunology, Köhler and Milstein were awarded the Nobel Prize in Physiology or Medicine in 1984.

The third important technology was the invention of the Polymerase Chain Reaction by Kary Mullis and his colleagues working at Cetus Corporation in Emeryville, near Oakland, California, in 1983. PCR is a method by which a few fragments of DNA can be duplicated into millions in a couple of hours. For his invention Mullis was awarded the Nobel Prize in Chemistry in 1993. This technology revolutionized medical diagnostics. It became a widespread basic tool in molecular biology. It is also used in criminology to analyze small fragments of DNA (for an excellent ethnography study on "making PCR" see Rabinow, 1996).

Monoclonal antibodies

Breakthroughs and their limits

Antibodies are a broad spectrum of proteins normally found in the blood generated by the immune systems of vertebrates in response to invading antigens. An antibody or immunoglobulin consists of two large, identical polypeptides, called the heavy chains, and two smaller, identical polypeptides, called the light chains (fig. 2). 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. This binding specificity is the property of the antibody that allows it to recognize and bind to specific antigens such as bacteria, virally infected cells, or tumor cells. The other part of the antibody molecule, the so-called constant region, can interact with multiple proteins in an animal or human. 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, but different B-cells will produce structurally different antibodies that bind to different parts (epitopes) of the antigen. This natural mixture of antibodies found in serum consists of polyclonal antibodies. Humans have millions of different antibodies with different variable regions circulating in their blood. But it is exactly the polyclonal nature of the immune response to any antigen and the difficulty of purifying or manufacturing a single antibody that impeded the development of antibodies into therapeutic agents for a long time (Reff, 2006: 566ff).

Georges Köhler and César Milstein, working together at the Laboratory of Molecular Biology of the Medical Research Council in Cambridge, UK, developed the path-breaking hybridoma technique to create monoclonal antibodies, and published their basic discovery in *Nature* in 1975 (Köhler and Milstein, 1975). First they removed B-cells from the spleen of a mouse that had been challenged several times with the antigen of interest. Then they fused these B cells, which produce a single antibody, with myeloma tumor cells (myeloma is a B-cell cancer) that 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. Monoclonal antibodies have specificity to a particular antigene. They are identical because they all are derived from the same cell line. Because of the immortal nature of the hybridoma, they can be produced indefinitely and developed into drug candidates.

Already Köhler and Milstein thought that the high antigen specificity and affinity of monoclonal antibodies would make them very suitable for human drug development. Soon, monoclonal antibodies were expected to be “magic bullets” in cancer therapy and in the treatment of autoimmune diseases (Fjermedal, 1984). Despite the rapid spread and important improvements in the technique to make monoclonal antibodies, the basic hybridoma technique remained fundamentally the same until the mid-1980s. The production of monoclonal antibodies was still dominated by artisanal methods (Mackenzie, et al., 1988: 156f).

But there was a decisive problem -- the murine properties of the monoclonal antibodies provoked an immune response. The human body recognizes murine antibodies as foreign. Therefore murine monoclonal antibodies provoke the emergence of antibodies to them (human anti-mouse antibodies, HAMA). This response leads to inactivation of the monoclonal antibody.

Another challenge was cost-effective manufacturing. Hybridomas do not produce enough monoclonal antibodies for cost-effective therapy. Moreover, antibodies are very large molecules compared with chemical, small molecule pharmaceuticals. Because of their molecular weight and their complexity they cannot be chemically synthesized in a cost-effective manner. Therefore, before monoclonal antibodies really could become successful therapeutic agents, two branches of scientific research had to come together. First, the recently developed recombinant DNA technology was needed to make the mouse antibodies more like human antibodies. And second, the high-level expression of recombinant proteins in complex mammalian cells was necessary to manufacture large amounts antibodies (Reff, 2006: 569).

In 1984, nine years after the generation of the hybridoma technique, the first successful experiments to make chimeric antibodies were reported. Three different groups published their chimerization results in 1984 and 1985. One group was composed of researchers from Columbia University, New York; Stanford University, Palo Alto, California; and Becton-Dickinson Monoclonal Center, Mountain View, California (Morrison, et al., 1984). A second team involved Michael Neuberger, Terrence Rabbitts and colleagues from the MRC Laboratory of Molecular Biology and the MRC Clinical Research Centre (Neuberger, et al., 1985). The third group, with Gabrielle Boulianne, Nobumichi Hozumi, and Marc Shulman worked in Toronto at the Department of Medical Biophysics of the University of Toronto, the Ontario Cancer Institute and the Wellesley Hospital (Boulianne, et al., 1984). Further groups of researchers working on chimerization included Research Development Corporation of Japan and the two U.S. biotech firms, Centocor and Ingene (Crawley, 1995: 320).

The approaches were similar. The emergence of recombinant DNA techniques allowed the transplantation of variable domains from rodent antibodies in place of the corresponding domains of a human antibody. The teams created mouse-human antibody molecules of defined antigen-binding specificity by taking the variable-region genes of a mouse antibody-producing myeloma cell line (with known antigen-binding specificity) and joining them to human immunoglobulin constant-region genes (which allow complementary immunological interaction with the body). These techniques also enabled to improve affinity of the antibodies (Winter, 1989: 540; Dübel, 2007: 5). The chimeric

monoclonal antibodies created for the first time 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. Greg Winter and his team working at the MRC Laboratory of Molecular Biology in Cambridge, UK, pioneered the techniques to humanize monoclonal antibodies (Jones, et al., 1986). In their groundbreaking process, 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), remain 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. Chimerization and humanization help reduce or remove the reactions that many monoclonal antibodies caused in some patients (Riechmann, et al., 1988). Chimeric and humanized monoclonal antibodies maintain the specificity of the murine antibody and at the same time possess human-effector functions, because the constant region of the antibody is human. In the 1990s, technologies to generate even human monoclonal antibodies were developed. Bacterial viruses that present the variable regions of human antibodies (phage display technology) and transgenic mice with human-antibody genes are the most important of these methods (Taubes, 2002; Lonberg, 2005). The innovation path of the technology for creating human monoclonal antibodies from transgenic mice is presented in another article (Zeller, 2008a).

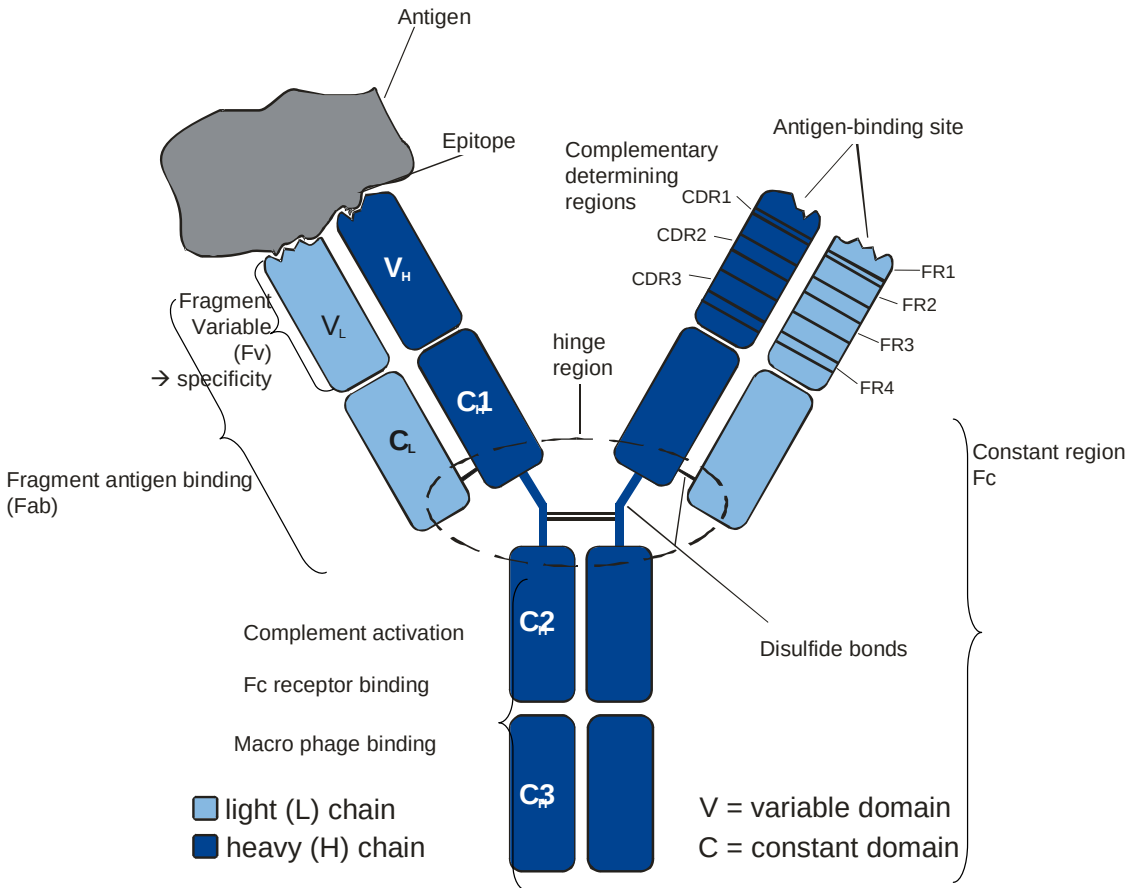

Fig. 2: The structure of antibodies

Antibodies on the market

In April 2007 there were around 100 drugs on the market produced by genetic engineering methods, 21 of which were monoclonal antibodies (tab. 3), and approximately 400 monoclonal antibodies were under development. The huge majority of active substances among the roughly 100 marketed recombinant therapeutics have their origin in the U.S., although basic scientific and technological knowledge had been created in Europe.

The unresolved problems of immunogenicity and cost-effective manufacturing cooled the excitement of the late 1970s and resulted in very careful or even pessimistic approaches on the part of financial organizations and large pharmaceuticals until the late 1980s and early 1990s. Almost all first-generation monoclonal antibodies failed during clinical trials. There was only one exception.

The first monoclonal antibody, named *Orthoclone*, was approved in 1986, 11 years after the invention of the basic technology to generate hybridoma cells. *Orthoclone* was primarily used in kidney transplantation to help prevent transplant rejection. However, some patients had severe reactions. Although this drug is still on the market, it was not very successful commercially. After the FDA declined to approve *Centotoxin*, a monoclonal antibody-based drug for the treatment of septic shock developed by Centocor (Malvern, Pennsylvania), and edobacomab, a product candidate from the Berkeley-based Xoma in 1992, Wall Street and large pharmaceutical corporations dissociated themselves from antibodies for a few years (Robbins-Roth, 2000: 54f; Taubes, 2002; Reichert and Dewitz, 2006: 191). The first chimeric monoclonal antibody approved by the FDA in 1994 was *Reopro* (Abciximab), again developed by Centocor. This antibody also had a disappointing performance. It in fact took 22 years to launch the first really successful monoclonal antibody against a specific type of cancer. This was the chimeric *Rituxan* (rituximab), which is a relatively effective treatment for non-Hodgkins lymphoma. *Rituxan's* immunogetic effects were reduced by chimerization. The properties of monoclonal antibodies make them suitable for developing therapies for the treatment of autoimmune diseases and cancer (4th column in table 1).

Table 1 shows that almost each monoclonal antibody on the market is a result of the combined work of many different actors. Almost in each case, the discoverer of the drug target, the inventor of the monoclonal antibody, the developer, the producer and the marketer came from different organizations. Thus each drug is result of socialized work. However, capital's answer is to privatize the most interesting aspects of the work. Decisive for the innovation processes today and the entire technological evolution is the fact that intellectual property monopolies cover almost every single aspect in this field, resulting in complex royalty cascades. Each firm which markets an antibody is forced to pay considerable amounts of royalties to the holders of specific but decisive patents. The 5th column lists some firms which receive royalties based on their ownership of strategic intellectual property.

There were three reasons for the delayed progress of monoclonal antibodies: First, the human body rejected the murine antibodies. Second, a method for cost effectively manufacturing large quantities needed to be developed. And third, the large transnational pharmaceutical corporations and institutional investors feared the economic risk of the new technology and avoided costly and risky development activities (Interview Nadler).

Tab. 1: 21 monoclonal Antibodies approved for therapeutic use until December 2007

First app.	Product	Company(s)	Description	Indication	Entities Receiving Royalties
6/86	Orthoclone OKT3 (muromanab-CD3)	Ortho Biotech (J&J)	Murine MAb to CD3 receptor	Reversal of acute kidney transplant rejection	-----
12/94	ReoPro (abciximab)	Centocor (J&J); Lilly	Chimeric MAb fragment to GPIIb/IIIa platelet receptor	Prevention of blood clots	Celltech
11/97	Rituxan (rituximab)	IDEC Pharmaceuticals (Biogen Idec); Genentech; Roche	Pan-B chimeric MAb that targets CD20 antigen on B cell surface	Low-grade or follicular CD20-positive B-cell non-Hodgkin's lymphoma	Celltech
12/97	Zenapax (daclizumab)	Protein Design Labs, Roche	Humanized MAb (SMART Anti-TAC) that binds to the interleukin-2 receptor (CD25) on activated T cells	Prevention of acute kidney transplant rejection	Celltech
5/98	Simulect (baxiliximab)	Novartis	Chimeric MAb that targets the CD25 antigen (IL-2 receptor alpha chain) on activated T cells	Prevention of acute organ rejection in renal transplant	Celltech
6/98	Synagis (palivizumab)	MedImmune; Abbott Laboratories	Humanized MAb that binds to the F (fusion) protein on surface of respiratory syncytial virus (RSV)	Prevention of serious lower respiratory tract disease	Protein Design Labs; Celltech; Genentech; Centocor
8/98	Remicade (infliximab)	Centocor (J&J); Schering-Plough	Chimeric MAb to tumor necrosis factor-alpha	Moderate-to-severe Crohn's disease	Genentech, Celltech
9/98	Herceptin (trastuzumab)	Genentech; Roche	Humanized MAb to epidermal growth factor receptor 2 (HER2/ErbB2)	HER-2 over-expressing metastatic breast cancer	Protein Design Labs; Celltech
5/00	Mylotarg (gemtuzumab ozogamicin)	Wyeth; Celltech Group	Humanized anti-CD33 MAb, conjugated with calicheamicin (chemotherapy)	Relapsed acute myeloid leukemia	Protein Design Labs

5/01	Campath (alemtuzumab)	Genzyme (Ilex Oncology); Berlex Laboratories (Schering AG)	Humanized MAb to CD52 antigen on T and B cells	B-cell chronic lymphocyticleukemia (B-CLL)	Cambridge University; BTG
2/02	Zevalin (ibritumomab tiuxetan)	IDEC Pharmaceuticals (Biogen Idec); Schering AG	Murine MAb that targets CD20 antigen on B cell surface, conjugated to yttrium-90 (used in conjunction with Rituxan	Low grade or follicular, relapsed or refractory, CD20-positive, B-cell non-Hodgkin's lymphoma	GSK (Corixa)
12/02	Humira (adalimumab)	Cambridge Antibody Technology; Abbott Laboratories (Knoll/BASF)	Fully human MAb to tumor necrosis factor-alpha (generated by phage display)	Moderate-to-severe rheumatoid arthritis in adults who had inadequate responses to DMARDS (subcutaneous)	CAT; MRC, Scripps and Stratagene (through CAT); Genentech
6/03	Bexxar (tositumomab)	Corixa (Coulter Pharmaceutical); GlaxoSmithKline	Murine MAb to CD20 antigen on B cells, conjugated to I-131, used in conjunction with the non-radioactive antibody	Patients with CD20-positive non-Hodgkin's lymphoma	University of Michigan
6/03	Xolair (omalizumab)	Genentech; Tanox; Novartis Pharmaceuticals	Humanized anti-IgE MAb	Moderate to severe persistent allergic asthma	Protein Design Labs
10/03	Raptiva (efalizumab)	Genentech; Xoma; Serono	Humanized MAb targeted to T cells (anti CD11a); reversibly blocks activation, reactivation and trafficking of T cells	Chronic moderate to severe plaque psoriasis	Protein Design Labs
2/04	Avastin (bevacizumab)	Genentech	Humanized MAb to vascular endothelial growth factor (VEGF)	First-line- or previously untreated-metastatic cancer of the colon or rectum	Protein Design Labs
2/04	Erbitux (cetuximab)	ImClone Systems; Bristol-Myers Squibb	IgG1 chimeric MAb to the epidermal growth factor receptor (EGFR)	Single use and combination therapy for treating EGFR-expressing, metastatic colorectal cancer	Genentech
11/04	Tysabri	Biogen Idec; Elan	Humanized MAb to alpha-4-beta-1 integrin; selective adhesion	Relapsing multiple sclerosis	Protein Design Labs

			molecule inhibitor		
06/06	Lucentis (ranibizumab)	Genentech, Novartis	Humanized antibody fragment that binds to and inhibits VEGF-A, which plays ciritical role in angiogenesis	Wet age-related macular degeneration	Protein Design Labs, Xoma
09/06	Vectibix (panitumumab)	Abgenix (Amgen)	Fully human MAb that targets the epidermal growth factor receptor (EGFr) (generated by transgenic mice)	Metastatic colorectal cancer in patients who have failed standard chemotherapy	
03/07	Soliris	Alexion Pharmaceuticals	Humanized antibody that is directed against complement protein C5 targeting and reducing hemolysis .	Paroxysmal nocturnal hemoglobinuria (PNH)	Protein Design Labs filed patent infringement

Sources: (Van Brunt, 2005; Reff, 2006) Van Brunt 2007

4. The spatial innovation biography of *Rituxan* (rituximab)

This section presents an analysis of the innovation path of rituximab, one of the commercially most successful monoclonal antibodies. Rituximab was the first therapeutic monoclonal antibody approved for the treatment of cancer in the United States. Later, other indications were added. Rituximab was developed by San Diego-based IDEC Pharmaceuticals and initially approved by the U.S. Food and Drug Administration (FDA) in November 1997 for the treatment of patients with B-cell non-Hodgkin's lymphoma (NHL) that was refractory to chemotherapy regimes. The drug's mode of action is to bind to the CD20 antigen on surfaces of normal and malignant B cells (CD means cluster of differentiation of cell surface molecules). It then destroys B cells by inducing one or more of three immune-cell-killing mechanisms. Stem cells (B-cell progenitors) in bone marrow lack the CD20 antigen, allowing healthy B cells to regenerate after treatment and return to normal levels within several months (Borman, 2005). Under the trade name *Rituxan*, the drug is sold by Genentech and IDEC in the U.S., and under the name *MabThera* by Roche in the rest of the world except Japan, where Roche-affiliate Chugai co-markets it together with Zenyaku Kogyo under the name *Rituxan*. Since its approval and introduction to the market, *Rituxan* has truly experienced an explosion of sales, which climbed up to 4 billion USD in 2006 (tab. 3).

The trajectory of the substance of this drug has spanned about 28 years. Its history is long and complicated, and at the beginning it was not obvious that the owners and marketers would earn huge profits with this product. The spatial innovation biography of rituximab shows that the drug is the result of the adaptation and combination of many different knowledge bases and technologies by specific actors in specific moments and under specific conditions. Its innovation trajectory is the result of planned and unplanned processes which were brought together. A characterization of the decisive technology inputs for rituximab and the contexts of their combination at the innovation trajectory's most crucial moments follows.

Basic research: creation of hybridomas and discovery of a drug target

The technique invented by Köhler and Milstein to create hybridoma cells through cell fusion of a tumor cell and a lymphocyte cell (Köhler and Milstein, 1975) was the first key discovery. But a prerequisite to creating a therapeutic agent is the identification of a drug target. George and Freda Stevenson, working at the University of Southampton in 1975, laid the groundwork for this step in their work with B-cells. Each healthy B-cell expresses a unique "marker" protein on its surface, which it uses for binding antigens. When B-lymphocytes detect a foreign substance in the body, they respond by dividing and churning out the same protein over and over again. This then binds to the antigen, tagging the invader for destruction. In B-cell lymphoma, one cell divides endlessly, but without a purpose. The Stevensons discovered that in each individual patient, all malignant B-cells displayed the same "marker" protein, which could be used as a target (*The Economist*, 2002).

Applied research and discovery: first trials

After these basic inventions and discoveries, a long and contradictory period of applied research in medical research institutes followed. The challenge consisted in finding suitable drug targets and efficient antibodies which were safe and not rejected by the human immune system.

Lee Nadler, a 33-old hematologist and oncologist at the Dana Farber Cancer Institute of the Harvard Medical School in Boston, and his team played a crucial role in the innovation process that led to rituximab 10 years later. In 1980, he discovered the antigen CD20, a cancer-associated receptor only found on B cells (antibody-producing immune cells), and derived an antibody to the antigen (Garber, 2002). With his former classmate Phil Stashenko, who had learned the monoclonal antibody technology in Milstein's lab earlier, Nadler developed a large number of antibodies, including one they called B1. This antibody bound to CD20 and was expected to destroy the cancer B cells (Borman, 2005; Nadler, et al., 1980).

Nadler was the first person to administer a (mouse-based) monoclonal antibody to lymphoma patients. The results were promising. He and his colleagues demonstrated the safety and negligible toxicity of monoclonal antibody infusions in such patients (Nadler, et al., 1980). The patients experienced a response to the treatment; but the action mechanism of the antibody was not clear.

> "We had this antibody that was clearly B-cell specific, but we didn't understand the function of the B1 protein. And because we didn't know, to be quite honest, we did two things at that point: We tried to figure out what it did, and we tried to figure out if we could use the antibody for treatment." Lee Nadler quoted in Tuma (2003).

Moreover, because of the antibody's murine properties, much more research was needed. Nadler and his colleagues could not convince any pharmaceutical company to enter the field and finance further research. The pharmaceuticals considered the potential market for monoclonal antibodies against B-cell lymphoma to be too small. Not one company wanted to take the risk of advancing the technology. Lee Nadler remarked:

> I tried to convince many, many, many pharmaceutical firms between '82 and '84 that pan B-cell antibodies would run. … B-cell lymphoma with 30 to 40000 new cases a year would never be a market. Lymphoma would never be a market. Antibodies, you know, they figured, a few thousand dollars a dose, 40,000. And they all told me the same thing. If the drug couldn't make 300 million dollars, they weren't interested. So they rejected antibodies. And to be honest, in those early days, it was impossible, impossible to get any of the large pharmaceutical companies interested in antibodies. (Lee Nadler, Interview, October 20, 2006)

Nadler's department sold the rights on the B1 monoclonal antibody to Coulter Corporation in 1984. This antibody later became the backbone of a drug called *Bexxar*, developed by Coulter Pharmaceuticals, which in 2001 became a part of Corixa Corporation, a Seattle-based biotechnology company.

Two groups of researchers continued working with the B1 antibody in the early 1990s. University of Michigan hematologist Mark Kaminski and radiologist Richard Wahl conjugated Nadler's antibody to a radioactive substance (I-131) and created the antibody that later became *Bexxar*. Another team including Oliver Press and Fred Appelbaum at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle further focused on antibodies directed against lineage-specific "pan B" antigens, particularly the CD20 molecule. In 1985, they reported their first clinical trial using

monoclonal anti-CD20 antibodies and documented the safety and promise of this approach (Press, 2000). Press also worked with very high doses of radiation delivered by radioactive iodine that was attached to B1 following bone marrow transplantation (Tuma, 2003). Both Press and Kaminiski published their preliminary results in the *New England Journal of Medicine* in 1993. Kaminski collaborated with Coulter Pharmaceutical, which entered into a development and co-marketing agreement with SmithKlineBeecham in 1998 (Tuma, 2003; Interview, 20 Oct. 2006). Later, Corixa sold the worldwide marketing rights for *Bexxar* to GlaxoSmithKline in 2004 (GlaxoWellcome acquired SmithKline Beecham in 2000). Finally, GlaxoSmithKline took over Corixa in 2005 (GSK, 2004;2005).

Another group, headed by Ronald Levy and Richard Miller at Stanford University, worked in a similar field but pursued a different approach. Levy and his group wanted to create patient-specific antibodies, called anti-idiotypic monoclonal antibodies, that recognize the tumor-specific portion of the surface immunoglobulin molecule present on malignant B lymphocytes. The Stanford group learned the hybridoma technology from Leonard Herzenberg, who had been on sabbatical in Köhler's and Milstein's lab in Cambridge. But Levy reported that prior to this, they had received the malignant cell line that Köhler and Milstein had used and were already experimenting with hybridomas (Interview, 28 Sep. 2006).

Ron Levy tested an antibody specific to the B-cell lymphoma receptor in the tumor of a particular patient in 1981. His group published this experiment in 1982. The authors showed that treatment of B-cell lymphoma with a tumor- and patient-specific anti-idiotypic antibody was efficacious. The antibody effectively attacked the tumor, and the patient became free of disease and survived. Therefore, Levy and his team were the first to successfully treat human lymphoma with a monoclonal antibody. The patient's miraculous recovery marked the first successful use of antibodies against cancer. Further research showed that this customized approach produced similarly good results about 10% of the time, and established the principle of monoclonal antibody therapeutics. Despite their early successes, anti-idiotypic antibodies have not been widely adopted or commercially developed because of the logistic, financial, and temporal constraints inherent in producing and purifying patient-specific antibodies. The need to scale up and refine the process of locating the antibody, produce it in sufficient quantities and gain FDA approval did not present a promising enough business opportunity to attract significant investment (Miller, et al., 1982; Committee on Science, 1999; Volkers, 1999).

Founding of IDEC Pharmaceuticals

Interest for monoclonal antibodies grew in the mid-1980s. The prospect of antibodies boosted funding for biotech start-ups and helped Ronald Levy and Richard Miller to co-found Biotherapy Systems in Mountain View near Stanford University in 1985. Biotherapy Systems pursued the goal of developing and commercializing anti-idiotypic antibodies for the treatment of non-Hodgkin's lymphoma.

In the same year, Ivor Royston – a former fellow of Levy at Stanford and co-founder of the monoclonal-antibody pioneering firm Hybritech in 1978 – co-founded the biotech firm IDEC in San Diego. IDEC also made anti-idiotypic antibodies. Venture capital firms pressured the two firms to merge, which they did in 1986. The merged IDEC Pharmaceuticals moved its major facilities to San

Diego. IDEC created custom anti-idiotypic antibodies for about 50 individual patients to fight their B-cell receptors. *"But it became economically unfeasible. We realized it was economically unfeasible to make a new antibody for each person."* (Interview, 28 Sep. 2006).

In December 1986, William H. Rastetter, who came from Genentech, South San Francisco, and previously had been an associate professor at the Massachusetts Institute of Technology, was appointed Chief Executive Officer. In 1990, Nabil Hanna, who had been working at the National Cancer Institute and SmithKline&French Laboratories (which later became SmithKlineBeecham and afterwards GlaxoSmithKline), was appointed head of research. Neither Rastetter nor Hanna believed that patient-specific therapies would be commercially successful, although at the time IDEC was already in the middle of phase 2 trials with a panel of 17 anti-ID monoclonal antibodies. Also at this time (1990), IDEC was still a company of only 60 people. Interestingly, the initial public offering (IPO) IDEC launched in September 1991 at a value of 47.2 million USD was made on the promise of anti-idiotypic antibodies. Marked by their experiences in a successful biotech firm, respectively in a large pharmaceutical firm, Rastetter and Hanna pursued a more pragmatic and conventional business perspective. It was mainly Hanna who chose to focus IDEC on pan-B monoclonal antibodies that would recognize most B-cell tumors as well as the normal B cells. Hanna and the IDEC executives chose the CD20 antigen out of various cell-surface antigens because this one seemed to be the most scientifically promising and most technically feasible target. However, the first mention of IDEC's engagement in developing "pan-B" antibodies was in the 1992 annual report, after the company received clearance from the FDA to initiate human testing in early 1993. This choice was not made without tension. The northern California group around Ronald Levy pushed for the customized antibody business, and the more generic approach was driven by the southern group. Levy still thinks that making anti-idiotypic or a panel of quasi-custom antibodies represents a better plan scientifically (IDEC, 1992: 2; 1993: 3; Reff, 2006: 573; Interview, 28 Sep. 2006; Interview, 11 Oct. 2006).

Also in 1991, IDEC agreed to collaborate with Zenyaku Kogyo, Japan, for developing an anti-CD20 antibody (which was probably already rituximab). Zenyaku Kogyo in return paid $7.5 USD for a minority equity position and $2 million for licensing product rights for cancer and autoimmune therapeutic applications (IDEC, 1992: 2, 23.).

Engineering a chimeric antibody and a manufacturing method

To generate the anti-CD20 monoclonal antibody for the treatment of non-Hodgkins's lymphoma, two basic problems needed to be resolved. First, the human response against mouse antibodies required more human-like antibodies to be engineered. The successful creation of chimeric and humanized antibodies was an answer to this challenge. Second, hybridoma cells cannot be manufactured on a large scale because they do not produce enough antibodies for cost-effective therapy. This problem was resolved by using recombinant DNA technology in living, complex mammalian cells. Therefore, it was necessary to link up two branches of scientific research – the recombinant technology required to make the mouse antibodies more human-like, and the high-level expression of recombinant proteins in complex mammalian cells (Reff, 2006: 569) (fig 4).

Mitchell Reff, hired in 1990, played a key role in creating a procedure for expressing monoclonal antibodies in mammalian cells. He came from the large pharmaceutical company SmithKline Beecham (formed in 1989 by a merger between Smith Kline Beckman and Beecham). With the arrival of Reff to IDEC in 1990, a small group of researchers began building DNA molecules as antibody-expression vectors that would express antibodies when introduced into mammalian cells. These expression vectors were originally developed by Reff and colleagues at Smith Kline & French Laboratories, one of the predecessor firms of SmithKline Beecham (Reff, 2006: 569). IDEC licensed this method. Reff and his team eventually engineered 19 additional cloning steps to obtain the modular expression vectors used to make rituximab. Two different mammalian cells were used to express monoclonal antibodies at that time. A mouse myeloma cell (SP2/0) and a Chinese hamster ovary (CHO) cell in which many other recombinant proteins had been expressed There were intense contradictory scientific debates about which cell to use to manufacture the anti-CD20 antibody. Finally, IDEC opted for the hamster cell in May 1992 because of enhanced productivity. This CHO cell line was a mutant cell line already produced by Larry Chasin at Columbia University, New York, in 1986. It had been modified using a method already applied at Smith Kline. A molecular biologist, Roland Newman, brought this cell line to IDEC in 1988. Based on Reff's experience at SmithKline, the IDEC team adapted it into a serum-free media, and growth was carried out in suspension culture (Reff, 2006: 570f).

In order to create a monoclonal antibody to CD20, IDEC's Alice Cox and Darrell Anderson began immunizing mice with a human B-cell line in August 1990. In an experiment in January 1991, Anderson identified the only hybridoma that recognized CD20. It was a mouse monoclonal antibody of the immunoglobulin (IgG) subtype. From this mouse antibody, Reff and his team constructed the chimeric antibody which became rituximab.[1] The group genetically engineered human constant regions into the original mouse-based version of the antibody. In this way, the team succeeded in decreasing its immunogenicity and enabling it to mobilize immune-system cytotoxic mechanisms (Borman, 2005; Reff, 2006: 574). Roland Newman and his IDEC group isolated the variable domains of this mouse monoclonal antibody by polymerase chain reaction (PCR) and incorporated them into the IDEC antibody-expression vectors. The PCR technology had been developed only a few years earlier and it soon became a key tool in biotechnology laboratories. The team with Tom Evans and Gary Thelan produced the first quantities of the chimeric antibody generated from a CHO cell in hollow fiber reactors at IDEC's Mountain View site in spring 1992 (Reff, 2006: 574; Interview, 11 Oct. 2006).

The group headed by Andrew Grant, process science engineer at IDEC, was successful at working with the CHO cell line, and this allowed IDEC to produce large amounts of antibodies for clinical trials. It was the first time that the people in charge of large-scale mammalian cell culture at IDEC had manufactured a product from the CHO cell line. Particularly challenging at the time was the relocation of IDEC's Mountain View operation 400 miles away to San Diego, which was to unify the company in a new facility. The manufacturing group had already built a commercial-scale, 1,750 liter

[1] Lee Nadler expresses another view of the story. "*I never patented it* [the anti-CD20 antibody]. *But they* [IDEC Pharmaceuticals] *did. And I know – you can publish – that they bought the antibody from Coulter, because I heard the stories. And they copied the antibody; they called it IDEC B1 … And so they didn't have to do this big R&D thing. Somebody suggested it – me. They bought an antibody and [made] an antibody to something that is known."* ((Interview, 20 Oct. 2006)

fermentation tank at its Torreyana Road site in San Diego to prepare the future launch of rituximab. Indeed, this was the facility rituximab was launched from in 1997.

The manufacture of recombinant protein from cell lines is still as much an art as a science. The large-scale manufacture of proteins in mammalian cells is delicate. Many companies suffered from the demise or delayed development of biopharmaceutical compounds (Reff, 2006: 574: 576f). This underlines the importance of experience embedded in working teams, especially when a synthesized knowledge base is required, as is the case in manufacturing.

IDEC expected to use its proprietary efficient gene expression system developed by Mitchell Reff and his team to produce each of its product candidates. To earn immediate cash revenue, the company out-licensed this production platform to other companies, such as Genentech, Chugai Pharmaceutical of Japan and Boehringer Ingelheim of Germany. Additionally, IDEC applied its gene expression technology on a contract basis to develop specific cell lines for other firms, such as F. Hoffmann-La Roche and Pharmacia&Upjohn, and entered manufacturing contracts with Merck, OraVax and Pharmacia & Upjohn (IDEC, 1996a: 16; 1997).

Development and clinical trials

In December 1991, IDEC formed two project teams to develop two promising drug candidates: the anti-CD20 antibody and a "primatized" (derived from macaque monkeys) anti-CD4 antibody. The second one did not progress rapidly and a modified form was still under consideration for additional clinical trials in 2005 (Reff, 2006: 575). Mitchell Reff led the project team for Rituximab at IDEC.[2] A year later, in December 1992, all necessary information was compiled to file an investigational new drug (IND) application to convince the FDA to allow testing of the novel drug in humans.

Only two years and four months passed between immunizing the mice with CD20 in August 1990 and filing the IND for rituximab in December 1992. This was a brief span. The small size of the organization and the direct involvement of key people in the project – i.e., close organizational and spatial proximity – facilitated the process and the internal exchange of experience and knowledge. This illustrates how knowledge is embodied in social relations.

At the end of 1992, IDEC hired Antonio Grillo-Lopez, a hematologist-oncologist, as chief medical officer and vice president of medical and regulatory affairs. He joined the rituximab development team. Previously he had worked at DuPont Merck Pharmaceutical Company and Warner Lambert's Parke Davis pharmaceutical division. His skill at designing and conducting clinical trials was crucial to the rapid development of rituximab. He managed the trials and also regulatory affairs during the approval process and maintained close contact with the FDA (Borman, 2005; Reff, 2006: 574, 578; Interview, 11 Oct. 2006).

[2] Additionally, IDEC also started developing two other pan-B monoclonal antibody candidates for the treatment of B-cell lymphoma. One was an yttrium-conjugated pan-B therapeutic agent and the other one an indium-conjugated pan-B tumor-imaging agent (IDEC, 1993: 3, 11). The first one later became the drug *Zevalin* (ibritumomab tiuxetan) approved by the FDA in 2004. The second one was abandoned in 1993 (IDEC, 1994: 18; 1995: 19).

As already mentioned in section 2, the general business context was not very favorable to monoclonal antibodies in the early 1990s, after the FDA rejected the approval of Centocor and Xoma Corporation's phase III monoclonal antibody-based drug candidates in spring 1992 (Robbins-Roth, 2000: 54f; Foster and Higuera, 2001: 14). In this period, the conventional wisdom on Wall Street was that antibodies just did not work. After IDEC executives decided to abandon the so-called "specifid" program that still comprised a panel of 15 anti-idiotypic monoclonals for individualized therapeutic purposes in 1993, already in phase 3 clinical trials, the rituximab project became the heart of the company. This agent was designed to be administered in all patients. After making this business decision, IDEC no longer had an advanced lead product. The response from the financial markets was negative, which dropped the company's market capitalization by extremes. This happened in a context of generally sinking biotech stocks. More than half of the people in the entire company were working on some aspect of rituximab's development during this period. This risky endeavor was an outcome of the specific financial and scientific circumstances (IDEC, 1994: 18; 1995: 19; *The Economist*, 2002; Robbins-Roth, 2000: 55; Reff, 2006: 578).

Rituximab's phase I/II single-dose safety study was conducted at Stanford University Medical Center together with Ronald Levy and completed in October 1994. These first clinical trials showed that antibodies to CD20 induce tumor cells to go through apoptosis (programmed cell death), and this was believed to contribute to rituximab's efficacy *in vivo* (Reff, 2006: 574; IDEC, 1994: 11; 1995: 2). However, it was a surprise, even for Levy, that normal B-cells could be attacked and depleted without provoking immune deficiency or infections (Interview, 28 Sep. 2006). Although the clinical data showed safety and efficacy with rituximab, it became clear that as a small company, IDEC could not continue the development process alone.

Threatened with bankruptcy, IDEC approached many large pharmaceutical and biotech companies to form a development partnership. But the companies were not interested, thinking the lymphoma market was too small to make such a collaboration profitable. However, because of the estimated small size of the lymphoma market, IDEC got "orphan drug" status, giving it regulatory and financial advantages in drug development (Reff, 2006: 576; Interview, 11 Oct. 2006). Finally, using Bill Rastetter's Genentech contacts and supported by Levy, IDEC convinced South San Francisco-based Genentech to enter a collaboration in March 1995. Genentech was much stronger than IDEC and applied its expertise to the development of rituximab. More importantly, Genentech financed the development costs and obtained the right to co-market *Rituxan* in the United States (IDEC, 1996a: 1, 6; Interview, 28 Sep. 2006). Genentech also had experience in developing monoclonal antibodies; after using them primarily as a research tool and hesitating a while, the company had started working on monoclonal antibodies in the late 1980s and had begun clinical trials with *Herceptin*, a monoclonal antibody directed to treat a form of breast cancer, in 1992 (Bazell, 1998; Kleid and Hughues, 2002; Interview, 6 Oct. 2006).

This collaboration was decisive for the success of the already ongoing clinical trials and the entire commercialization of rituximab. The agreement was to complete the clinical development and share the potential commercialization of rituximab for the treatment of non-Hodgkin's lymphoma. IDEC executives considered this relationship as the centerpiece of the commercialization strategy for rituximab. The agreement was that IDEC and Genentech would co-market *Rituxan* in the United States, with IDEC receiving a share of profits on sales. Genentech's strategic partner Hoffmann-La Roche was assigned to conduct further development and commercialization outside the U.S., except in

Japan where Zenyaku Kogyo Co. would be responsible for development, marketing and sales. The collaboration provided IDEC with financial support from Genentech that could reach $54 million in the form of equity investments, licensing fees and milestone payments. During 1995, IDEC received 14.1 million USD in total, pursuant to its collaboration with Genentech (IDEC, 1996a: 1, 6f, 19). Roche and Genentech had already agreed on a strategic partnership in 1989, including a 60% stake for Roche in Genentech's capital. This partnership provided Roche the option to develop and market Genentech products outside the U.S.

IDEC and Genentech started the Phase III, 166-patient, single-arm, pivotal trial for rituximab in April 1995 (indeed it was more like a phase 2 trial because it was not compared to another drug). The study was conducted at over 30 clinical sites and cancer institutes in the United States and Canada. The clinical results from this trial were reported at the American Society Meeting for Hematology in December 1996. The pivotal trial results were first published in 1997 (IDEC, 1996a: 6; Maloney, et al., 1997; Reff, 2006: 578).

Clinical development was expedited (three years), with the first patient entered in phase I/II trials in March 1993, and the last patient entered in phase III study in March 1996 (Grillo-López, 2000). The pre-clinical and clinical development process took only seven years from discovery to approval, which was extraordinarily rapid, especially for a small company developing its first successful drug. One reason was that the non-blinded, single-arm, pivotal trial only required 166 individuals, because the refractory low-grade non-Hodgkin's lymphoma was an orphan indication (Reff, 2006: 581). Another reason was the close connection between the different key actors within IDEC and between IDEC and the Ronald Levy group at Stanford, who conducted the first clinical trials (Interview, 28 Sep. 2006).

The FDA approved rituximab for marketing on November 26, 1997. The approval was based on clinical studies led by Mc Laughlin, Department of Hematology, University of Texas M.D. Anderson Cancer Center, Houston (McLaughlin, et al., 1998). Half a year later, in June 1998, rituximab was also approved in the European Union under the trade name *MabThera* (Genentech website) (IDEC / SEC, 2002: 2). In Japan, IDEC's partner Zenyaku Kogyo had been engaged in the focused development of antibody medical treatment since 1991. It received the development and distribution rights for *Rituxan* from Genentech in 1995. One year later, it completed a patient accrual for a phase 1 multi-dose clinical study of rituximab in Japan (IDEC / SEC, 1997: 12). Rituxan was approved in Japan in June 2001. Zenyaku Kogyo and Nippon Roche co-promoted the drug until Hoffmann-La Roche took over Chugai and merged its Japanese subsidiary with Chugai in 2003 (IDEC, 2002).

Manufacturing

The manufacturing of one specific drug cannot be understood outside the context of the entire manufacturing system of a company. Initially, IDEC produced the substance for the clinical studies and the very first marketing period at its La Jolla (San Diego) site. The 1995 agreement between IDEC and Genentech implied that IDEC would supply the product for the first two years of sales. For the long run, Genentech would assume the principal manufacturing responsibility for *Rituxan*. As part of the big development and marketing collaboration in 1995, IDEC licensed its gene expression technology to Genentech. This technology is also used in Genentech's manufacturing process for

Rituxan. The increasing amounts required a much more sophisticated manufacturing infrastructure. Therefore, Genentech took over all worldwide manufacturing responsibilities in September 1999 (IDEC, 2001: 39). Soon specialized subcontractors such as the Swiss firm Lonza Biologics were integrated into the manufacturing network. Currently, the manufacturing system of *Rituxan* / *MabThera* consists of three sites:

Genentech's original manufacturing facility is located together with its research and development site in South San Francisco. In 1985, Genentech started to produce growth hormones. The site now has a capacity of 96,000 liters (8 x 12,000-liter fermenters). It also produces *Rituxan,* and most of the other Genentech products (Genentech, 2006a). Genentech opened a production facility in Vacaville, California, in 1998 to manufacture *Rituxan* and later also *Herceptin* and *Avastin*, with a capacity of 144,000 liters (12 x 12,000-liter fermenters). In 2004, it started a large extension process at this manufacturing site, with an investment of approximately $600 million. When completed in 2009, it will be the world's largest cell-culture biotech plant, with an additional 200,000 liter capacity (Genentech, 2006b). In December 2003, Genentech and Lonza Biologics announced a manufacturing agreement under which Lonza Biologics would manufacture commercial quantities of *Rituxan* (Rituximab) for Genentech at its production facility in Portsmouth, New Hampshire (Genentech Media Release, 2003b). In 2005, Lonza received licensure to produce *Rituxan.* It was expected that Lonza would produce approximately 50% of Genentech's *Rituxan* bulk requirements for the next several years (Genentech Media Release, 2003a).

In 2004/05 BiogenIDEC opened a new manufacturing site in Oceanside, north of San Diego. Originally, IDEC had planned to manufacture *Rituxan* and *Zevalin* at this facility. However, following the merger of IDEC with Biogen in 2003, the merged company BiogenIDEC sold the site to Genentech for $408 million cash in June 2005, after *Tysabri*, a monoclonal antibody against multiple sclerosis, provoked mortal side effects in two patients and its sales were suspended. Now, Genentech manufactures *Avastin* there, another highly successful monoclonal antibody (Crabtree, 2006). Interestingly, Hoffmann-La Roche receives all of its *Rituxan* supply from Genentech, despite its marketing rights outside the U.S. (Genentech / SEC, 2006: 8). In contrast, Roche manufactures most of its other monoclonal antibodies marketed together with Genentech, such as *Herceptin* and *Avastin,* at its new plant in Penzberg, Germany, and at a new plant at its headquarters in Basel, Switzerland.

It is not possible to draw general conclusions about the geography of the manufacturing system in the case studied here. Of course, practical aspects, such the availability of facilities as well as the amounts and complexity of the biological material to be produced, are important elements the firms had to consider. Not surprisingly, manufacturing for clinical purposes occured in close proximity to research, engineering and development, all located at IDEC in La Jolla / San Diego. When the drug reached mass production for global markets, proximity lost relevance. Then, effective manufacturing in big production facilities became necessary. Because of the enormous capital intensity, the drug's manufacturing is still highly concentrated in very few facilities. Even the European market is supplied by the three sites in the U.S. Moreover, corporate alliances and mergers entered into for reasons other than manufacturing, such as the Genentech-Roche alliance and the takeover of IDEC by Biogen, decisively influenced the production system. Interestingly, a specialized third party manufacturer like Lonza Biologics can assume a considerable part of the entire manufacturing needs. By outsourcing specific manufacturing mandates, Genentech and Roche can concentrate their manufacturing infrastructure on other products and economize investments into fixed capital.

Sales and extension of application, new therapeutic areas

Surprisingly, the sales of *Rituxan / MabThera* exploded soon after its approval in 1997 and 1998. It now is a standard therapy in the initial treatment of aggressive lymphomas in combination chemotherapy. The success motivated IDEC and Genentech, together with partner Hoffmann-La Roche, to explore the further therapeutic potential of rituximab in various oncologic diseases and to expand the clinical trials.

Its remarkable and unexpected safety profile and efficacy in treating refractory low-grade follicular non-Hodgkin's lymphoma encouraged the increased usage of rituximab for other types of non-Hodgkin's lymphoma, other B-cell tumors with CD20 on their surface, and other indications where B-cell depletion may have a desirable effect (Reff, 2006: 579). Clinical studies were undertaken on the application of *Rituxan* to intermediate- and high-grade NHL, chronic lymphocytic leukaemia, multiple myeloma, immune thromobocytopenic purpura, autoimmune haemolytic anemia, IgM polyneuropathies, rheumatoid arthritis, lupus and other vasculitis syndromes, as well as many other malignant and non-malignant B-cell driven or MAb-dependent disorders (Grillo-Lopez, et al., 2001). The involved firms and their clinical collaborators conducted well over 150 clinical trials by the end of 2001 (IDEC, 2002: 18). In March 2002, the European Medicines Evaluation Agency, or EMEA, approved the use of rituximab in combination with standard chemotherapy, or CHOP, to treat patients with aggressive non-Hodgkin's lymphoma (IDEC / SEC, 2002: 2). Later the drug received approval for the treatment of further autoimmune disorders, such as multiple sclerosis. *Rituxan* / ***MabThera*** is also being used off-label at very high doses for treatment of chronic lymphocytic leukemia (CLL) and in combination with chemotherapy regimes. The off-label use is much larger even than that indicated in the FDA-approved use (Reff, 2006: 580). *Rituxan/MabThera* became a blockbuster drug, with sales of almost 4 billion USD in 2006. By 2005 it was the most successful monoclonal antibody and biotechnology-based drug ever (Van Brunt, 2007).

Table 2: Genentech's Rituxan / MabThera sales

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
IDEC revenue from Rituxan $ in millions (1)	9.3	53.8	93.2	132.8	251.4	385.8				811
Genentech (including IDEC) U.S. sales $ in millions	5.5	152.1	262.7	424.2	779	1,080.2	1,360.2	1,574.0	1,831.4	2,071
Genentech sales to collaborators $ in millions		10.4	16.7	19.9	39.6	82.7	128.9	137.2	157.9	181
Genentech sales total $ in millions	5.5	162.6	279.4	444.1	818.6	1,162.9	1,489.1	1,711.2	1,989.3	2,252
All (Genentech, Roche, Chugai) $ in millions		162.6	279.4	444.1	818.7	1,163	2,243	2,989	3,154 (3,341)	3,966

(1) Sales of IDEC Include copromotion profits generated from its joint business arrangement with Genentech, bulk Rituxan sales to Genentech, reimbursement from Genentech for IDEC's Rituxan sales force and development expenses and royalty income on sales of Rituxan outside the U.S.

Sources:
Raw 1: IDEC Annual Reports 1998: 30; 1999: 26, 48; 2000: 38: 2001: 3, 35; 2002: 36, 2006: globalsinsight.com
Raw 2, 3 and 4: Genentech: http://www.gene.com/gene/ir/financials/historical/rituxan.html, January 7, 2008,
Raw 5: http://www.i-s-b.org/business/rec_sales.htm; 2005: contractpharma.com/articles/2006/07/f-hoffmanla-roche.html; 2006: http://www.sigalsmag.com

Generic competition is not yet an issue in most countries. However, *Rituxan* is not protected by a patent in India. In April 2007, an Indian pharmaceutical firm named Reddy's launched its generic version, *Reditux*. Reddy's developed the product using a cloned antibody made for the Indian firm by a U.S. company. It sells the drug in India and charges about 50% less than *Rituxan's* price. Reddy's currently produces *Reditux* in a 200-liter fermentation tank at its site outside Hyderabad in central India. In October 2007, it completed construction of three more 200-liter tanks. The firm is working on a $30 million second facility that will include three 5,000 liter fermentation tanks for producing *Reditux* and other monoclonal antibodies (*The Economic Times*, 2007).

Corporate Strategies, institutional context and technological trajectories

The length of the entire innovation process of this drug was characteristically long, although in some periods the problems were resolved quite quickly and in others the hurdles seemed to be almost invincible. The rhythm of the innovation path of *Rituxan* was largely influenced by corporate strategies, financial interests and pressures in an evolving institutional context in different states.

Corporate strategies

Interestingly, the large pharmaceutical firm Hoffmann-La Roche played a certain indirect role in the earliest stages of monoclonal antibodies. Roche financed the Basle Institute of Immunology headed by Niels Kaj Jerne, who was awarded the Nobel Prize in 1984 for his pathbreaking theoretical work in the field of antibodies. The young researcher George Köhler had also worked there, both before and after a successful sabbatical at Milstein's lab in Cambridge. Roche quite quickly realized the value of monoclonal antibodies in the field of diagnostics, but made no significant effort to push forward Milstein's and Köhler's invention in therapeutic applications. Generally, the pharmaceutical industry was not interested in monoclonal antibodies during the 1980s.

It took more than fifteen years for large pharmaceutical firms to become really engaged in the field of monoclonal antibodies. Interestingly, Hoffmann-La Roche was again among the initiators. Already in 1989, Roche entered into a collaboration with the California biotech firm Protein Design Labs for the development of *Zenapax*, a monoclonal antibody against immune rejection following organ transplantation (PDL / SEC, 1997: 13). However, it was the success of *Rituxan* (soon followed by Genentech's *Herceptin*) which triggered a real wave of collaborations and investments in monoclonal antibodies in the mid-1990s (see also Zeller, 2008a).

IDEC itself undertook a highly risky course in 1992 when it decided to put all its resources into the development of rituximab. In 1991 non-Hodgkin's lymphoma treatment was still considered a small market, with perhaps less than 200 million USD in anticipated sales per year. Therefore, large pharmaceuticals were only rarely active in the same field (Reff, 2006: 575).

The capital raised at the IPO in 1991 was quickly burned. Since 1993-94 IDEC has increasingly

suffered from financial shortages. The annual 1994 report warned about the constraint to "reduce cash outflow," despite increasing development efforts (IDEC, 1995: 2).[3]

The successful and rapid development of rituximab occurred under specific circumstances: On the one hand, the anticipated market was small enough to repel competitors but could gain important federal regulatory and financial benefits with the orphan status. Plus, the drug had considerable off-label potential to fuel expansive growth. On the other hand, IDEC focused its resources on the rituximab project, abandoned other projects in its pipeline and risked financial ruin, which nearly happened just before Genentech accepted the partnership (Reff, 2006: 581).

The development and commercialization deal between IDEC and Genentech saved both companies. In the mid-1990s, IDEC urgently needed new financial infusion. The continuation of the clinical trials and even the entire company's existence were threatened. In a weaker position, IDEC was forced to license marketing rights and the majority of any potential future revenue stream to Genentech. Interestingly, it became clear some years later that this deal also was decisive in saving Genentech. Genentech's partnership with Roche entered a difficult period in the second part of the 1990s. One possible outcome was that Roche exercised its option to acquire the rest of Genentech's outstanding stocks. During this period Genentech shifted its focus from large recombinant proteins to monoclonal antibodies. In the same period it developed *Herceptin*, a monoclonal antibody directed against breast cancer. Based on the explosive sales of *Rituxan* and the resulting cash inflow (only shortly thereafter *Herceptin* was successfully launched), Genentech had good reason not to integrate into the Roche organization. Roche's role was focused on organizing clinical trials and sales. Due to its technological experience, global development organization and commercialization power – and basically, therefore, its capital stock – Roche was able to acquire a large portion of the potential future income from sales.

Because of the successful clinical trial, early market success of *Rituxan/MabThera* and extreme profit expectations, the stocks of IDEC Pharmaceuticals climbed to astonishing heights. The share price multiplied 36-fold within four and a half years, between the beginning of 1995 and the end of June 1999. After the approval of *Rituxan/MabThera* in November 1997, the stock price increased from about 30 USD to about 100 USD more than two years later (Robbins-Roth, 2000). The stock market explosion in the late 1990s was not only a result of *Rituxan's* success and the high expectations of the financial world. The trajection of the curve is typical for a biotech company highly driven by its search for stock market-based financing. However, the special phase of the "new economy bubble" ended in 2001 (Zeller, 2008b). Over the last few years the stock market has highly fluctuated.

IDEC Pharmaceuticals grew rapidly due to *Rituxan's* success; it,employed hundreds of new employees and launched an extensive expansion of its built infrastructure. In 2004 it moved into a new research and corporate campus consisting of office and lab space for over 1000 employees, located in La Jolla / San Diego. At the same time it also erected new manufacturing buildings for clinical and mass production purposes in Oceanside, about 30 miles north of its corporate headquarters in La Jolla (IDEC, 2003: 5). Meanwhile IDEC and the larger biotech firm Biogen (Cambridge, Massachusetts) merged. The rationale was to combine forces with the intention of rapidly building a fully integrated

[3] In the early 1990s, IDEC entered collaborations with SmithKline Beecham and Mitsubishi Chemical Corporation, both aimed at the research and development of "*primatized*" antibodies. Revenues in 1994 came primarily from these ongoing collaborations (IDEC, 1995: 18). This collaboration probably was not directly linked to the development of rituximab, but it provided important financial means for the survival of the company.

biotech and pharmaceutical corporation. However, recent product launches, such as the monoclonal antibodies *Zevalin* (IDEC) and *Tysabri* (Biogen), either failed or fell short of high expectations. Thus, the merger can also be seen as answer to the unsatisfactory development of both companies' stocks prices and disappointing results in further drug discovery activities. Because of the continuously unsatisfactory course of business, BiogenIDEC was even offering itself intensely as a takeover object for large pharmaceuticals in 2007. However, as of January 2008 there have been no serious offers.

Table 3: Key figures of IDEC Pharmaceuticals from 1990 to 2002 (1)

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Revenue	6.9	6.2	5.2	12.7	7.4	23.6	30.0	44.6	87.0	118.0	154.7	272.7	404.2				
R&D Exp.	10.4	10.9	14.5	18.7	21.2	22.5	26.8	32.4	31.5	42.8	68.9	86.3	93.6				
Net loss Net income	4.3	5.8	12.7	8.9	18.0	17.3	5.7	15.5	21.5	43.2	48.1	101.7	148.1				
Retained earnings / accumulated deficit	16.2	21.6	34.7	43.5	61.6	78.9	83.8	99.4	77.9	34.7	13.4	115.1	263.2				
Shareholder's equity	6.1	54.9	43.8	35.7	27.9	31.2	92.6	80.7	106.4	160.0	694.6	956.5	1,109.7				
Employees	60			137	136	164	185 (1) 268 (2)	339	365 (3)	407 (4)	493 (5)	650 692 (6)	995 (7)	3215 (8)	4266	3340	

(1) IPO was in 1991, IDEC and Biogen merged in 2003 to BiogenIdec.

(1) 31 March 1996, (2) 31 January 1997, (3) 31 January 1999 (4) 31 January 2000 , (5) 31 January 2001, (6) 31 January 2002, (7) 31. January 2003, (8) 20 Feb. 2004 (IDEC / SEC, 1997: 22)

IDEC: IDEC Annual Reports: 1993: 17; 1995: 3, 18; 1997: 20; 2001: 8; 2002: 7, 36

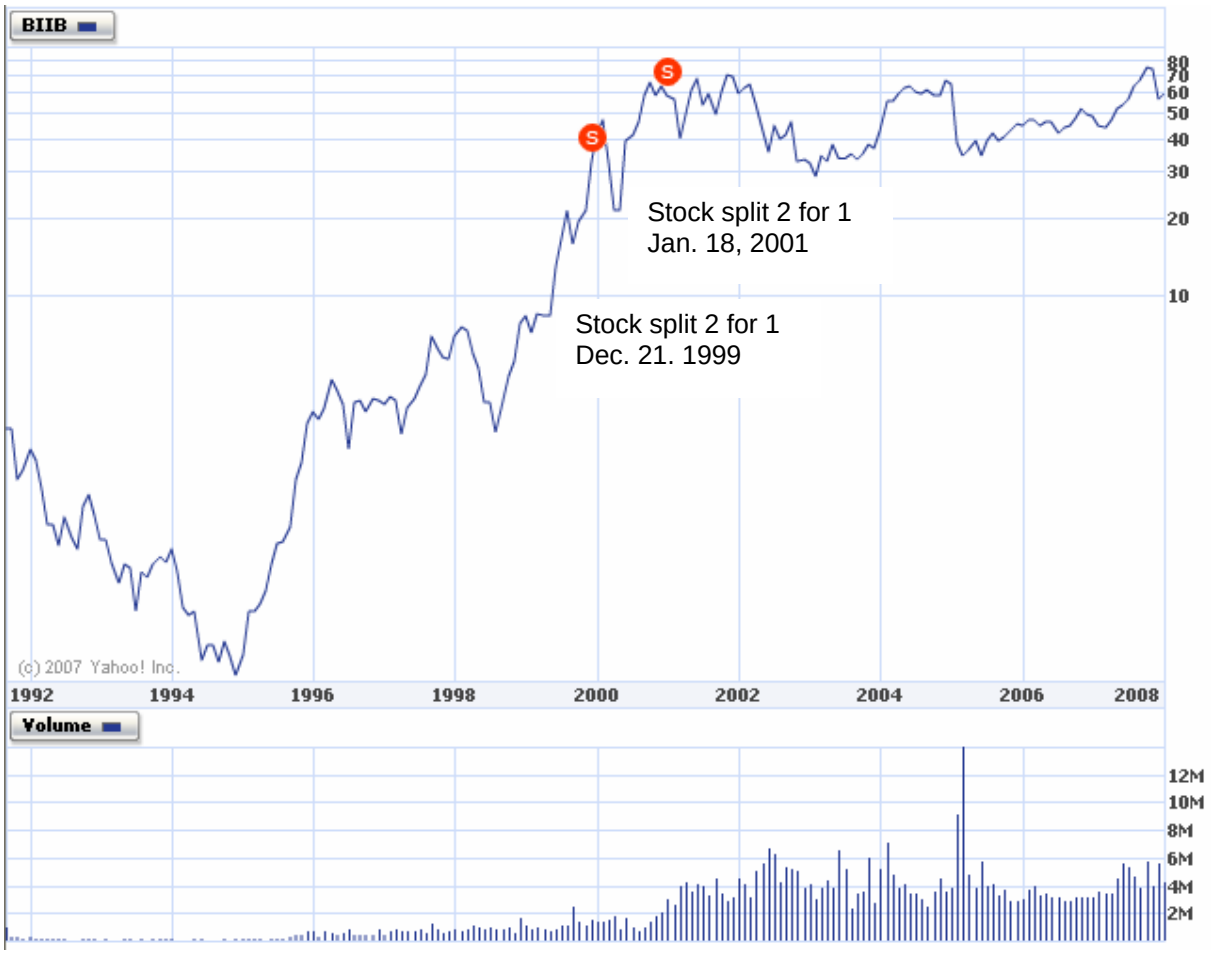

Figure 3: Development of IDEC's stock price

Source: http://finance.yahoo.com (download January 11, 2008)

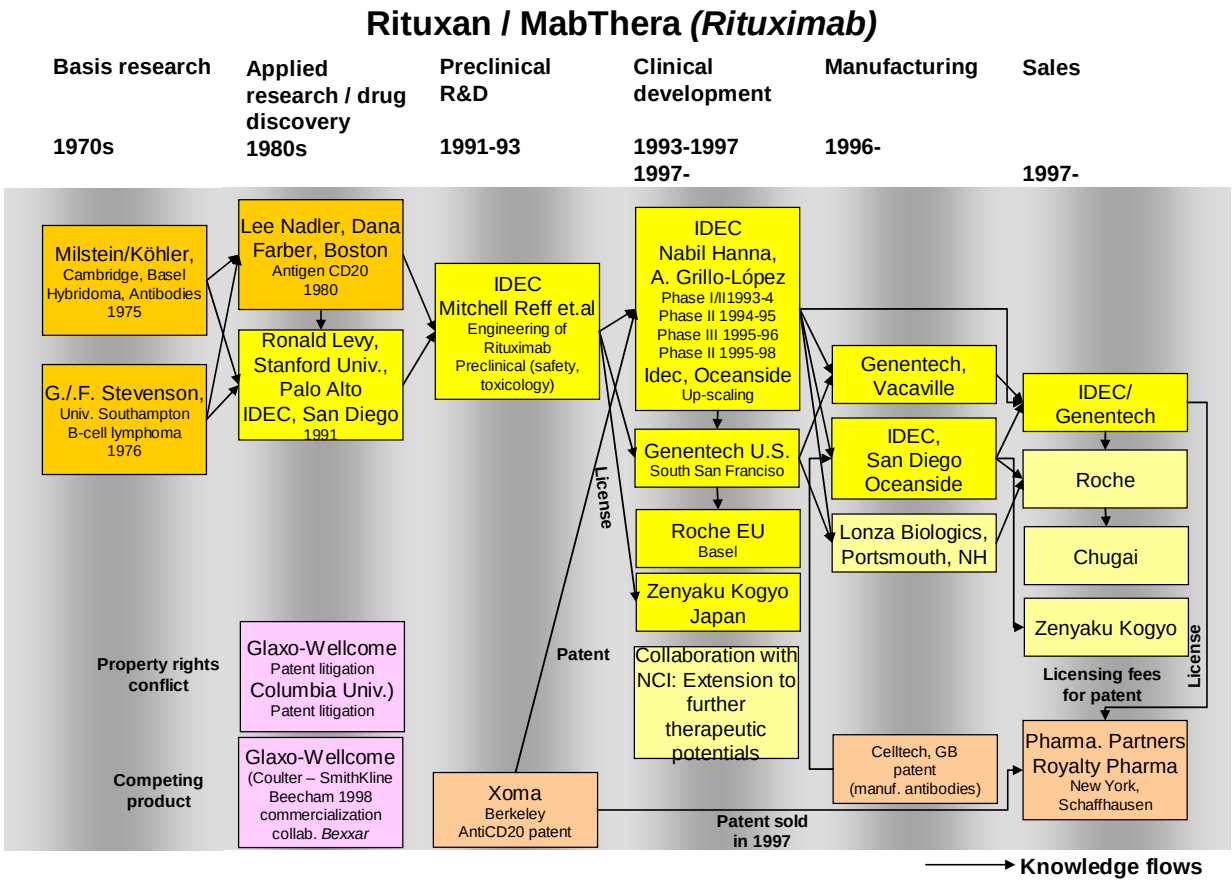

Figure 4: Innovation biography of Rituxan / MabThera

Table 4: Collaborations relevant for the innovation path of rituximab

Date	Company	Description of deal
1991/06	IDEC and Zenyaku Kogyo Co	▪ IDEC and Zenyaku entered into a product rights agreement and a stock purchase agreement under which IDEC granted Zenyaku a license to manufacture, use and sell certain products for cancer and autoimmune therapeutic applications.
1992/10	SmithKline Beecham	Primatized
1993/11	Mitsubishi Chemical Corporation	Primatized anti-B7 antibody
1994/12	Seikagaku Corporation	Primatized anti-CD23
1995/12	Eisai Co., Ltd.	Primatized anti-gp39
1997/01	Boehringer Ingelheim International GmbH	Licensing IDEC's gene expression technology
1996/03	Chugai Pharmaceutical Co., Ltd.	Licensing IDEC's gene expression technology
1995/03	IDEC and Genentech	▪ Co-marketing of rituxan in the US with IDEC receiving a share of sales. ▪ Co-marketing in Canada with Genentech or its sublicense with IDEC receiving royalties. ▪ Genentech licenses IDEC's expression technology and IDEC receiving royalties manufactured using IDEC's proprietary gene expression technology. ▪ Preferred stock purchase agreement providing for certain equity investments in IDEC by Genentech. ▪ Milestone payments.

		▪ Genentech assumed worldwide manufacturing obligations for Rituxan beginning in September 1999 ▪ IDEC may receive payments totaling $57,000,000, subject to the attainment of certain milestone events.
1995/03	Genentech and Roche	▪ Commercialization outside US in responsibility of Roche except Japan (where Zenyaku Kogyo Co. is responsible for development, marketing and sales. IDEC receives royalties on sales outside the U.S. and Canada.
1995/11	IDEC and Zenyaku Kogyo	▪ In November 1995, IDEC and Zenyaku terminated the product rights agreement from 1991and concurrently IDEC, Zenyaku and Genentech entered into a joint development, supply and license agreement where Zenyaku received exclusive rights to develop, market and sell IDEC-C2B8 in Japan which resulted in IDEC recognizing $2 million in license fees from Zenyaku. ▪ IDEC entered into a joint development, supply and license agreement with Zenyaku and Genentech, under which Zenyaku received exclusive rights to develop, market and sell Rituxan, and we receive royalties on sales of Rituxan in Japan.
1996/02	IDEC and Genentech	▪ Genentech exercised its option to extend collaboration on two radioconjugates also for the treatment of B-cell lymphomas
1996/05	Genentech and Xoma	▪ Xoma received a $3.0 million payment for an exclusive license to Genentech including a sublicense to IDEC, to intellectual property covering the use of chimeric IgG1 antibodies specific to the CD20 antigen on the surface of human B-cells. Xoma was entiteled to royalties on the sale of products employing the anti-CD20 technology that are sold in the US an in other countries where Xoma held relevant patents.
1996/05	IDEC and Genentech	Genentech grants IDEC a non-exclusive sublicense to use Xoma's patent related chimeric antibodies against CD20 antigen.
1997/12	Xoma and Pharmaceutical Partners	Xoma assignes the anti-CD20 antibody patents and royalty rights to Pharmaceutical Partners, LLC for $17.0 million.

Sources (IDEC, 1996a: 19)[IDEC / SEC, 1997 #1897: 16; Exhibit 13.3: 9](IDEC / SEC, 1997: [Xoma / SEC, 1997 #1898: 31; Xoma / SEC, 1998: 5, 30; IDEC, 1996b; IDEC / SEC, 2002 : 15)

Importance of intellectual property monopolies

Köhler and Milstein did not patent their pathbreaking hybridoma technique to create monoclonal antibodies,, 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, for basic technology was accessible to subsequent scientists. Knowledge and technology was free and rapidly spread to numerous laboratories in the world. That enabled a wave of progress in diagnostics and immunology laboratories. This situation encouraged many researchers in publicly funded institutes to transform monoclonal antibodies into effective therapies. 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 were aroused and many companies were launched in the 1980s to try and turn this breakthrough into marketable drugs.

Nadler did not patent his inventions either. At that time, the early 1980s, he and the responsible persons at the Dana Farber Cancer Institute thought targets and antibodies were not patentable (Interview, 20 Oct. 2006). In the period before and just after the implementation of the Bay Dole-Act in 1980, scientific culture was not yet shaped by the enclosure of intellectual property rights as much

as during the following period. Quickly, however – only a few years after Köhler and Milstein's basic invention – a real hunting race for intellectual property monopolies broke out. These monopolies multiplied and soon each aspect of monoclonal antibody technology was enclosed by patents. In fact, the Bay Dole-Act of 1980 considerably changed the institutional context in regard to intellectual property rights. In parallel to this, financial capital and institutional investors increasingly favored corporate strategies to hunt for intellectual property monopolies (Zeller, 2008b). As a consequence, subsequent users of enclosed knowledge were, and are, obliged to buy licenses and to pay royalties (Eichmann, 2005: 99ff; Zeller, 2007).

Table 5: Key patents of the trajectory of *Rituxan / MabThera*

Rituxan is approved for:

- The treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma, including retreatment and bulky disease;
- The first-line treatment of patients with diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma (or "DLBCL") in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens; and
- The first-line treatment of follicular, CD20-positive, B-cell non-Hodgkin's lymphoma in combination with CVP chemotherapy.
- The treatment of low-grade CD20-positive, B-cell non-Hodgkin's lymphoma in patients with stable disease or who achieve a partial or complete response following first-line treatment with CVP chemotherapy.
- Use in combination with methotrexate for reducing signs and symptoms in adult patients with moderately-to-severely active rheumatoid arthritis (or "RA") who have had an inadequate response to one or more tumor necrosis factor (or "TNF") antagonist therapies.

Source: Genentech 2007

The royalty cascade linked to the innovation path of *Rituxan* rituximab illustrates the importance of royalty-hunting strategies. This innovation path also underscores the strong division of labor and the social character of the entire innovation process. Mitchell Reff developed a gene expression system partially based on techniques already developed in the late 1970s (Richard Axel et al. had developed a technique for inserting foreign DNA into a host cell to produce certain proteins) and in 1986 (Lawrence Chasin et al.) at Columbia University, New York. Thus over a period of several years, *Rituxan* manufacturer Genentech paid considerable amounts of royalties to Columbia University, which licensed the Axel patent to over thirty companies, including Genentech.. Columbia successfully extended the original patents issued in 1983, filing two other patents in 1993 and 1997. They all expired in August 2000. But in September 2000, the patent office even issued a fourth patent based on the same research and extending Columbia's monopoly until 2019. It is estimated that Columbia previously earned some $400 million in royalties between 1983 and 2002 due to these patents (anoymus, 2004: 592ff; Huggett, 2003; Wysocki Jr., 2004). However, in April and July 2003 Genentech and other biotech companies filed lawsuits against Columbia and challenged its monopoly. The parties reached a settlement after Columbia announced it would not sue the non-paying companies (Kerber, 2005). IDEC also licensed expression vectors from SmithKline Beecham, where Mitchell Reff had previously learned this technique. Thus until the related patent expired, IDEC and Genentech had to pay royalties to successor firm GlaxoSmithKline.

There were several other patent suits and litigations concerning *Rituxan*. GlaxoWellcome filed a suit in May 1999, maintaining that Genentech had infringed on four of its patents, and demanded Genetech

to pay a 12% royalty on sales of *Rituxan* and *Herceptin*. In 2001, Chiron Corporation also filed a suit, alleging Genentech's manufacturing process for *Rituxan* and *Herceptin* infringed on its property rights. These conflicts both were settled in 2003 confirming Genentech's patents (Waters, 2001; Jacobs, 2001). Another patent litigation and royalty conflict occurred between IDEC and Corixa over their anti-CD20 antibodies *Zevalin* and *Bexxar*. Both sides filed suits, asserting their respective property rights (Corixa, 2001). IDEC claimed that four of Corixa's *Bexxar* patents were unenforceable in September 2001. In October 2003, a judge ruled that Corixa cannot use four patents to block sales of IDEC's lymphoma drug *Zevalin* (San Diego Business Journal, 2003). After a court denied BiogenIDECs motion against Corixa's *Bexxar* patent in January 2004 Corixa, GlaxoSmithKline and BiogenIDEC settled the patent litigation and entered into a cross-licensing agreement covering both companies' radioactive-labeled anti-CD20 antibodies *Bexxar* and *Zevalin* and providing for BiogenIDEC to pay modest milestone and royalty payments on the sale of *Zevalin* to Corixa respectively GlaxoSmith Kline (Pihl-Carey, 2004).

The manufacturing path of *Rituxan* also hinges on the "Boss-Cabilly-controversy." Over a long period, there were two landmark patents broadly covering methods for making monoclonal antibodies, both issued in 1989: the "Boss" patent (US patent No. 4,816,397), owned by the British biotech company Celltech (acquired by Belgian-based UCB in 2004), and the "Cabilly" patent (US patent No. 4,816,567) of South San Francisco-based Genentech. During this time, a great many producers of monoclonal antibodies had to pay royalties either to Genentech or to Celltech. The manufacture of *Rituxan / MabThera* is partly based on Celltech's technology and property rights. After a long patent dispute and before expiration in March 2006, Genentech succeeded in obtaining a "new Cabilly" patent (US patent No. 6,331,415), which also covers the "Boss" patent field. If the new patent resists legal challenges, Genentech will hold a monopoly until 2018 and will therefore profit from an IP monopoly for 29 years (Teskin, 2003; Lorenzo, 2007). Any company wishing to use corresponding cell culture to make recombinant antibodies for use as human therapies needs to enter into a royalty agreement with Genentech (Van Brunt, 2005). Thus, in the case of *Rituxan*, with Genentech as major manufacturer, this is only a matter of internal accounting. Over the last few years, annual reports from Genentech (55% of which is owned by Hoffmann-La Roche) shows that it not only successfully launches new therapeutics, but is a successful royalty recipient (between 13% and 15% of total operating income from 1999 to 2006), particularly in the field of monoclonal antibodies.

The following example linked to *Rituxan* shows that intellectual property monopolies can also become independent and transform themselves into financial placements. The Berkeley-based biotech company Xoma was alreading working on an anti-CD20 monoclonal antibody in the late 1980s. Lacking immediate success, it abandoned this target and project. However, Xoma possessed a crucial patent which IDEC and Genentech needed to in-license in order to produce rituximab. But Xoma encountered acute financial troubles in 1997, and it sold patent rights and the connected rights to royalties on rituximab to Pharmaceutical Partners, a firm specialized in the patent business, for 17 million USD cash. Pharmaceutical Partners, a subsidiary firm of Switzerland-based Royalty Pharma, now rakes in the royalties from *Rituxan/MabThera* sales. In view of the skyrocketing sales of rituximab, this deal was extremely profitable for Royalty Pharma. For their part, Xoma, which had sold the property rights on royalties, was left empty-handed, apart from the above-mentioned 17 million USD (Xoma, 1998) (Robbins-Roth, 2000: 159, 216). This example is not an isolated case. Royalty Pharma arranged several similar and recently even much bigger deals (Royalty Pharma, 2005; Herman, 2006; Scannon, 2006).

Immaterial assets such as patents became a key indicator for the valuation of pharmaceutical and biotech companies on the stock markets. Intellectual property titles even attained the character of a security in such cases. For instance, Royalty Pharmaceutical does not pursue any industrial interests. Its interest is purely financial: making more money from money. Thus interest-bearing and rent-bearing capital merges. This situation developed in the context of concentrated financial capital's increasing power over corporate governance, which expresses itself in the increasing prominence of shareholder value (Lazonick and O'Sullivan, 2000) and far-reaching institutional changes that reinforce and extend intellectual property rights.

Combining technologies and knowledge bases, paradoxical outcomes

Rituximab's innovation biography reveals that each critical stage in the entire path is characterized by the fusion of two or three previously successful technological breakthroughs (Fig. 4). Levy and Nadler combined Köhler's and Milstein's hybridoma technology with recently created knowledge on malignant B-cells and lymphoma disease mechanisms. Reff from IDEC based his chimerization of the selected murine anti-CD 20 antibody on a chimerization method previously developed by Morrison and colleagues. The construction of the expression vector, which was needed to manufacture sufficient quantities of monoclonal antibodies, was based on the method developed by Reff and colleagues at Kline & French lab. The Chinese hamster ovary cell lines came from Columbia University. However, without Levy's vast experience in monoclonal antibodies and anti-idiotypic antibodies, IDEC would hardly have been able to advance the engineering and development of rituximab so quickly. The manufacturing method is also based on inventions made by the British biotech firm Celltech some years ago, which were enclosed in the "Boss patent" issued in 1989. Furthermore, IDEC would not have been able to conduct clinical trials without the experience of Genentech and Hoffmann-La Roche. Manufacturing for mass markets can only be assumed by experienced and well equipped firms. Finally, only a large pharmaceutical company like Hoffmann-La Roche could have launched the marketing of the drug on a global scale.

This clearly shows that the long-lasting innovation process of a drug is the result of socialized labor. Almost innumberable persons working in different contexts, some individually but most collectively in research teams, contribute to the entire innovation process. Nadler himself expressed this in simple way. *"I discovered the antibody and antigen, and Antonio and IDEC made it a drug"* (Borman, 2005).

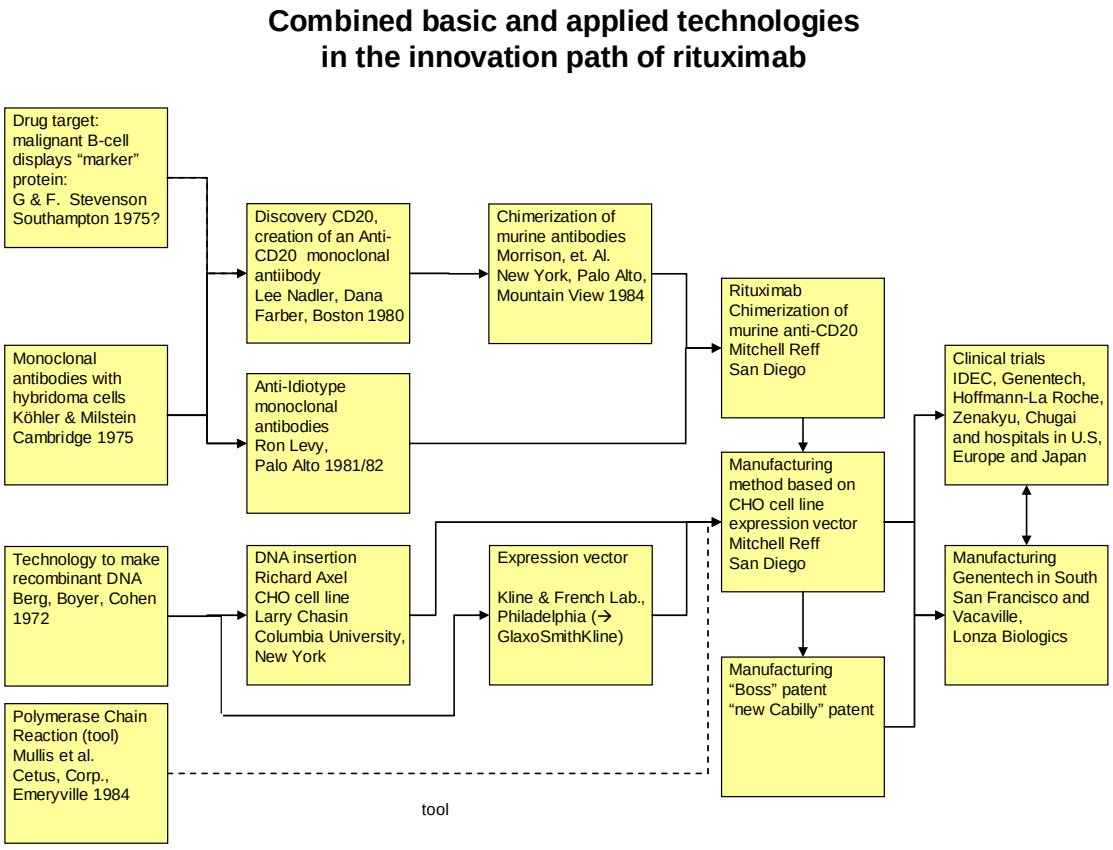

Figure 5: Combined basic and applied technologies in the innovation path of rituximab

The spatial innovation biography also provides insights on the types of generated and exchanged knowledge involved in this process. The distinctions between analytical and synthetic knowledge raises some problems. Even if we differentiate between the distinct stages of the innovation process, it is almost impossible to assign specific types of knowledge to specific innovation stages (Moodysson, et al., 2008). Each stage and even each specific activity in the entire innovation trajectory of a drug can only be undertaken if the actors are able to combine or better synthesize explicit and tacit knowledge bases. Of course, Nadler, Levy, Reff, Hanna, Grillo-Lopez and their teams made their discoveries and inventions by analyzing existing knowledge. These were analytical acts based on explicit knowledge codified in scientific publications and patents. The enhancement of their knowledge consisted in synthesizing this knowledge and sharing and creating new tacit knowledge through direct experience and experiments, as well as explicit knowledge through articulating and dialoging (Nonaka and Toyama, 2002). However, each individual person and team depended on intuition, mutual understanding and perceptions about possible working processes and outcomes that could only be created and shared within close and dense collective working relations, organized in spatial or at least in organizational proximity (Zeller, 2004). The first human trials conducted by Nadler's and Levy's teams, or Reff's group's idea of developing another manufacturing method, were only possible in the context of a dense exchange of experiences, perceptions and even hopes. This not only underlines the importance of tacit or uncodified knowledge, or experimental intuition, but it also reveals the highly socialized nature of discoveries, inventions and entire innovation processes. Each knowledge application and production happens embedded in specific social relations and contexts.

The key phases in the innovation trajectory of rituximab occured in close spatial proximity in the cities of (in order) Cambridge (to a minor extent Basel), Boston, Paolo Alto and San Diego, South San

Francisco, and again in Basel. The generation of basic scientific knowledge took place in publicly funded research organizations, with their specific social climate favoring path-breaking discoveries and inventions. Nadler and Levy recall close cooperative and conflictive relations with colleagues working in their environment. Later, the push toward the drug's application and commercialization also occured within a specific social context. IDEC Pharmaceuticals was in a very crucial period of corporate development when its executives decided to make a considerable and risky strategic move from the ideotypic antibodies to the development of an anti-CD 20 antibody against non-Hodgkin's lymphoma. The subsequent stages were the result of, on the one hand, corporate decisions by Genentech and Roche executives working in South San Francisco and Basel, and, on the other hand, the clinical trials and marketing efforts undertaken in various places. The latter could only happen by combining the application of explicit and analytical knowledge derived from scientific studies with the use of practical and experimental knowledge, figuring out how the trials could best be organized or how commercialization strategies could be designed. Whereas the processes within these spatially concentrated social nodes in Boston, San Diego, South San Francisco or Basel were based on mixing explicit and tacit knowledge, the transfer as well as the analytical combination and recombination of previously produced explicit knowledge could be organized over great distances between these nodes.

Importantly, the crucial knowledge flows all happened through personal relations. Nadler's colleague Phil Stashenko in Boston as well as Leonard Herzenberg from Stanford learned the monoclonal antibody technology in Milsteins lab. Mitchell Reff brought his knowledge of gene expression vectors from SmithKline Beecham. Nabil Hanna came from a predecessor firm of SmithKline Beecham, too. Thus it is not surprising that IDEC was able to convince SmithKline Beecham to begin a close collaboration and fund IDEC's activities. Without the money from SmithKline Beecham, survival would have been difficult in the shaky period between 1992 and 1994. Ronald Levy, as a professor at Stanford and a co-founder of IDEC, was involved in beginning the clinical trials and helped to arrange the deal with Genentech. Former Genentech employee William Rastetter had numerous contacts with Genentech people. This was instrumental to convincing Genentech's executives to finance the clinical trials of *Rituxan* and to entering a broad co-marketing agreement. Finally, the fact that Genentech and Hoffmann-La Roche had already been collaborating for many years facilitated the large scale clinical trials and the marketing strategy in the different geographical areas. Thus personal relations and, respectively, relational proximity, regardless of the geographical conditions of these relations, were crucial to organizing knowledge flow, and consequently helped generate new working relations in project teams – in this case within IDEC as well as between IDEC and Genentech and other collaborating partners.

A striking observation from this innovation biography is that in each key phase, the chosen outcome did not correspond to the original hypothesis or goal (compare with Moodysson's results (2008)). Nadler's thesis of unique structures on tumor cells that would allow making antibodies against tumor specific molecules could not be confirmed. However, he proved the safety of antibodies and laid ground for subsequent work. Levy was also unsuccessful with his thesis focusing on custom-specific anti-idiotypic antibodies. However, he co-founded IDEC, which later found success with another, much more pragmatic strategy. IDEC again, in an early period, focused on anti-idiotypic antibodies, made a relatively successful IPO and also entered into corporate collaborations with the promise of this new technology. However, the company soon used the money it raised for something else: the development of rituximab. When Genentech agreed to collaborate with IDEC and to finance development costs, it had already had some important experiences with monoclonal antibodies

(*Herceptin*). However, its risk was modest. Genentech was financially backed by Hoffmann-La Roche, and in the case of rituximab's failure, it would only lose a relatively modest sum of money. Roche was in the most comfortable and powerful situation; it backed Genentech financially and undertook the responsibility for clinical trials outside the U.S. Based on the strategic agreements with Genentech, Roche now commercializes the drug throughout the world, except the in U.S. and in Japan.

In sum, the drug's innovation path was a roller coaster ride, from Nadler's discovery of the antigen CD20 in 1980, to Levy's experiments with anti-idiotypic antibodies, Reff's chimerization and inventions in vector expression technology, Hannah's decision to focus IDEC's strategy on an anti-CD20 pan B-cell antibody, the highly uneven deal with Genentech and Roche, to final approval and, successful commercialization.

5. Conclusions

The presented study on the innovation biography of rituximab reveals that an analysis of the key processes in the long-lasting trajectory of a product, from basic inventions and early concepts up to sales and marketing, is an insightful approach. It complements studies focused on national, regional or sectoral innovation systems as well as on technological systems. It allows us to understand the geography of the resource and knowledge flows between the involved key actors without defining a priori spatial demarcations. Above all, this approach permits us to focus on the roles of key actors and the relations relevant to promoting innovation processes.

The study elucidates how at each stage of the innovation trajectory a specific logic of decision-making dominates. This means that decisions in an early stage of the entire innovation process are determined by factors other than those made in a later stage. Each hinge point of the innovation trajectory turns on a specific logic of decision-making, and each occurs embedded in a specific societal and institutional context. Köhler's and Milstein's, Nadler's and Levy's inventions were largely shaped by the academic environment of their activities. However, already then, Levy intentionally sought a commercialization outcome for his inventions. The work of IDEC Pharmaceuticals was completely pressured by pure business and financial considerations. All subsequent and decisive key stages and decisions in the development of rituximab by IDEC, Genentech, Roche, Zenyaku Kogyo and all other implicated firms were purely financially and business-driven.

This innovation biography confirms other research findings that biotechnology firms transform basic knowledge created by universities and publicly funded research organizations into marketable products and technologies (Zeller, 2003;2008c). This underscores the role of public universities and the financing of research institutions. The large pharmaceutical companies acquire knowledge, technologies and products, then undertake the marketing and commercialization. The pharma-biotech complex and the innovation processes consist of power hierarchies. The large pharmaceutical firms are in most cases on the top of these pyramids of financial flows and related innovation processes. They strongly influence the innovation processes when deciding the priorities of their financial engagements, Their marketing power and their capital resources are the decisive elements which permit them to acquire, recombine and commercialize new knowledge and new technologies.

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