Preface to Paperback Edition

Internationally, the development and use of new knowledge and innovations is increasingly recognized as one of the crucial explanations for modern economic growth. Basic science, national innovation systems, new growth theory, management of innovation, and so forth are concepts used to understand how and why firms and other organizations develop and use knowledge of economic value. Their decisions and actions hence decide the pace and direction of innovations. Firms try to develop and use new knowledge in their daily activities as they react to, implement, and change market and technical conditions. They are increasingly interested in innovations, alongside traditional concerns of costs, time, and quality. Academics and policy-makers try to analyse and explain the underlying processes of innovations as important phenomena in their own right and in order to propose appropriate guidelines for firms and public policy.

In fact, the intervening period between the original hardback edition of this book and this new paperback edition has been a period where the central themes developed here have been recognized as increasingly important. This book is one contribution to a much larger debate on the knowledge economy, on Schumpeterian economics, and on the management of innovation in firms, in addition to the specific topic of the business of biotechnology.

The tale found in this book is one of how two quite different firms struggle to manage their knowledge-seeking activities, and it gives a good insight into research and development during radical change. It provides case studies for both management and engineering students. At the time of original publication, the genetic engineering techniques analysed here were very new and untried in many dimensions; it was new basic research, new biological processes to control, new government regulation, new business applications, etc. Although the recombinant DNA techniques themselves are quite well established today, the process by which they were improved, implemented, tried, and rejected gives insights into radical innovation processes with other genetic engineering techniques, as well as with other types of knowledge.

Rather than just following established procedure, the engineers, scientists, and managers in the firms described here try to understand and manage changes in technology and knowledge during a period where many dimensions are being called into question. Two dichotomies are useful in order to understand their conflicting perceptions and incentive structures—science vs. technology, and market vs. government.

During the two decades analysed here, public opinion swings from potential fear of the monsters of genetic engineering to acceptance of it for pharmaceuticals. New regulations and tests have to be developed, discussed, and agreed upon in order to set what are considered acceptable standards of safety, efficacy, and so forth. Standards are a process of negotiation. Existing physical processing equipment and methods of assessing pharmaceuticals are found to be deficient and hence new ideas—as well as new sources of ideas—are necessary to solve unexpected challenges. The market expands much quicker than expected, partly as a result of a ban of substitute products, and partly as a result of new and unexpected uses of the product. In other words, from the perspective of management of innovation and of engineering in firms, this book provides exciting case studies of how and why certain firms did, or did not, make a quick move into use and development of new knowledge with high economic value.

Although drawn from the early history of modern biotechnology (e.g. the 1970s) to the early 1990s, the story told here is by no means passé or even finished. The controversies continue for this specific case, and in reflection of larger issues for the biotechnology community in specific and for new knowledge in general. Some particular issues of interest are:

1. The continuing fortunes of these two firms, with implications for the dynamics of knowledge-based firms;
2. Disputes over intellectual property rights, with implications for knowledge spill-overs and the university's role in the knowledge-based society;
3. Management issues for knowledge-intensive sectors like biotechnology.

The firms and organizations involved here, as well as the larger issues they represent, continue to be current issues for all firms in environments characterized by turbulence in technology, knowledge, and markets.

Genentech, the dedicated biotechnology firm analysed here, is generally considered the first dedicated biotech firm, and one of the few American start-ups which developed into a significant independent firm. And yet even they were bought up by a large European chemical-pharmaceutical company (Hoffman-LaRoche; Roche AG), in return for injections of capital. Roche purchased 60 per cent in February 1990, then after another injection of capital in 1995, it was given an option to buy the rest by June 1999. In early June 1999, Roche excercised that option to buy out 100 per cent of Genentech, but immediately said that they would sell 19 per cent in an IPO. The biotech firm could have been bought up and merged into the larger corporation, but will instead continue to have a degree of independence.

In this longer-term relationship between two quite different firms, there have been continuing conflicts of ideas and interests over what to do with a specialized knowledge-producer within the concerns and goals of a large established multinational company. The questions have circled around how to integrate the small into the larger and how to leverage the specialized scientific knowledge in order to make money in other products. Genentech is still a symbol of the American dream of entrepreneurship as well as of overall developments in the biotechnology sector, and yet it also symbolizes the complex, global division of labour within genetic engineering for pharmaceuticals.

In the 1970s, Kabi was a small company in the global pharmaceutical industry—although large in this specific product market for human growth hormone (hGH). It was owned by the Swedish state and was fighting for survival. Kabi signed one of the very first R&D contracts for the biotechnology industry—a contract with Genentech to produce human growth hormone through recombinant DNA techniques. Kabi was later merged into a larger Swedish pharmaceutical company named Pharmacia, and the Swedish state sold its remaining share in a wave of privatization in the mid-1990s. After becoming a publicly-traded company, Pharmacia then merged with the American pharmaceutical company Upjohn to become Pharmacia & Upjohn. The company is no longer particularly Swedish nor has special ties to the Swedish state. P&U is instead more of a major contender in the global pharmaceutical market and reflects continuing trends towards mergers in pharmaceuticals and in industry in general. Human growth hormone is still one of its major products.

Thus, the firms analysed here reflect larger issues related to entrepreneurship and mergers, to specialized division of knowledge production, and to the relative importance of the national context vs. globalization. Without giving definitive answers, this book provides a structûre and content which allows a discussion of the modern dynamics of high-tech sectors. In doing so, it goes beyond the firm *per se* to see the relative importance of other factors such as university science and regulation, and also goes beyond the American context to the global one.

A second very important issue involves disputes over intellectual property rights. Making claims of ownership through patenting, licensing, and the like is one means of capturing economic benefits from new knowledge. In this book, the issue is the development of new scientific knowledge in relation to ownership and commercial exploitation of that knowledge. Conflicts over intellectual property rights involve an established pharmaceutical company, Eli Lilly; a prestigious medical research university, the University of California San Francisco (UCSF); and the first dedicated biotechnology firm, Genentech. The two firms and one university have had complex relationships related to ownership of knowledge, and have been embroiled in legal disputes for many years at a cost of millions of dollars.

Between the three, there were early licensing agreements, flows of personnel, and flows of money. Disagreements are focused around the limits of patenting and licensing agreements related to genetic engineering, but are relevant to all knowledge-intensive sectors which are changing rapidly. As detailed in the book, Eli Lilly bought techniques and knowledge relevant for their primary product, insulin, as well as for hGH. They had agreements with both UCSF and Genentech. UCSF has had a prestigious scientific name in the relevant basic science, and the university was also early in patenting research results. Genentech was started by a venture capitalist and by a leading UCSF scientist who continued working at the university. Genentech hired a number of researchers from UCSF.

The University of California spent nine years and $20 million trying to prove that Genentech had used their rDNA material and infringed on their patent. UCSF filed a patent in 1977 (patent continuation in 1982; US Patent No. 4,363,877) with three co-authors. It provides human growth hormone sequeces (rDNA transfer vectors). As detailed in the book, one of the three UCSF scientists then moved to Genentech after having conflicts with the two senior scientists at UCSF, taking some cell material with him. The material contained sequence information vital for Genentech's success with a scientific experiment and in fulfilling an R&D agreement, but using it would constitute patent infringement. Genentech has always claimed to have sequenced the human growth hormone independently—and differently. Claims of patent infringement and breach of licensing agreements have linked all three.

The strongest claim for the UCSF patent infringement case in 1999 has been the testimony of the researcher who moved from UCSF to Genentech. He had carried out similar experiments at UCSF and had taken the material with him. He is currently head of a major research unit in Germany. He now testifies that he and the other Genentech scientists faked their data and used the university material instead. Genentech and some press articles insinuate that it is somewhat strange that this case comes to the fore two decades later. Why is he willing to testify now for UCSF? When under oath, he has testified previously that they never used the material. Was he finally tired of the lies and the 'secret pact' to cover it up? Did he fall for the temptation of being eligible for 17 per cent of any royalties (e.g. several million dollars) to be paid to UCSF in case of patent infringement, since he was co-author of the original UCSF patent? If they did use the university material, then this is grounds for patent infringement today—and hence implies that the firm would be liable to pay royalties of 3 to 12 per cent on Genentech's $1.2 billion sales over almost twenty years, plus punitive damages. The lawsuit between UCSF and Genentech continued to June 1999 with the jury not being able to decide whether the evidence proved stealing or not. As it was a hung jury, this has meant that UCSF has not won a victory—unless they want to go to the courts again to appeal the decision.

Thus, there are major issues here about ownership of knowledge which are relevant to the entire biotechnology sector as well as to other highly knowledge-intensive sectors. One of the first obvious issues is the difficulty of defining and maintaining ownership rights at a time when the very boundaries and definitions of what is patentable are being questioned—and where scientific knowledge is developing very quickly. The question for managers, engineers, and scientists is how to determine which knowledge has economic value and whom has ownership claims over it. By granting ownership over novelty through intellectual property rights, the government hopes to increase incentives to innovate. Being able to trade rights in the market may also enable, and encourage, transfer of new knowledge and techniques compared to a counter case of keeping them secret. It might, however, prevent diffusion, thereby reducing the collective benefits. Going beyond the economists' trade-off lies the question of our understanding of knowledge, of what can be sold in a market, as well as the limits and boundaries of intellectual property rights. Along with software, biotechnology has been the centre of many disputes over which techniques and knowledge are, and should be, patentable. This is an on-going discussion, and one which has challenged the existing agreements over intellectual property rights. How does new knowledge of economic value develop? Who has a claim in contributing to the development of such knowledge and what do conflicts tell us about the overall process?

Another issue relates to the value of scientific integrity and reputation, both to research scientists and to firms dependent on selling specialized knowledge. This is relevant to all knowledge-producing firms dependent on having a good reputation for scientific work in order to sell to other firms. In this case Genentech has always claimed that it did its own research in a way that did not infringe on the university's patent claims which cover knowledge which could not have produced practical results. They did so at the last moment under strong pressures to fulfil the external research contract. The biotech firm claims to have done so mainly due to the efforts of a second scientist from a different university, who worked closely with university researchers from yet another university.

Although synthesizing the gene may not seem to be such a major issue to the uninitiated—or even to today's scientific researchers or their students—at the time, doing so successfully was a major scientific accomplishment. It gave this new and untried biotech firm scientific prestige and reputation; a necessary and perhaps sufficient condition in order to sell their specialized scientific knowledge in directions relevant for other firms. Failing to synthesize it would not only have meant that the biotech firm would fail to fulfil their R&D contract for this particular project, it would also have meant not getting a reputation for selling high quality science. This in turn would have reduced their chances of receiving additional R&D alliances from other firms. The value of their knowledge would have been considered lower. Note that it was not scientific knowledge in itself that was valuable; it was the combination of basic scientific knowledge and techniques with other knowledge and techniques in order to do something of value to firms. Thus, if Genentech did not in fact independently do the experiments and research they claimed to have done, then this would be a form of intellectual dishonesty—what the university and press would call stealing. This would also mean that the firm misrepresented their abilities to future buyers.

However, Genentech is so concerned about their reputation and/or so sure of their case that they made photocopies of their lab notebooks, with details of all the experiments, open for inspection for all viewers on their website. They want scientists to have direct access to the facts and be able to judge by themselves. They claim their evidence proves that their experiments were different and that since the experiments were succeeding, there were no motivations to 'cheat/steal' at the last moment. They also published a short version of their arguments in *Nature*, the leading scientific journal where the original article was published. Scientific reputation is clearly important to this biotech firm and is reflected in the fact that they have published over 4000 articles between 1978 and 1999.

The rather complex conflicts over intellectual property rights as detailed in the book also lead us to re-examine the role of the university. Today, many argue that the university has a crucial role to play in stimulating regional economic growth and development. One way of doing so is through spin-off companies. Although opening a start-up firm is currently applauded as scientific entrepreneurship, at the start of the biotechnology revolution, basic scientists who started a company (and who also remained at the university) created many controversies, as discussed in later chapters. This was a breach of the traditional view of the scientist working for other types of intellectual rewards. Obviously, however, there were strong incentives to start firms, as basically all the senior scientists at UCSF with economically-valuable knowledge about gene synthesis were quickly allied with firms.

The current discussion seems to increasingly view stimulating growth as synonymous with creating spin-off companies. In that case, stimulating growth is not a process of the diffuse spill-over of the benefits of knowledge from the university to the surrounding area and society. It is a very specific one, where intellectual property rights play a prominent role. Someone has to have scientific knowledge which has economic value. In this situation, ownership over knowledge, techniques, etc. are crucial for reaping private economic benefits—for individuals, universities, firms, and so forth. In the meantime, governments worldwide have either flattened out, or else cut, in real terms the funding for basic science, leaving many universities to view patenting, start-ups, and the like as one form of making up lost revenue. However, in addition to focusing on direct revenue and direct linkages, the university can contribute to regional economic development through many direct and less direct ways, not least through stimulating basic research. Empirical research has indicated that although firms will generally not list direct contacts with universities as the source of specific innovations, the firms do recognize the importance of the general development of knowledge.

In this particular case, the university is claiming ownership over knowledge and techniques developed there. Although this practice is accepted and increasingly encouraged today, this book details an early case where an American university took a large step away from the post-World War II view that the university creates knowledge which is a public good and usable by all. By taking a patent, the university stood to benefit directly. If the university only fulfils that role of developing knowledge as a public good, then there would be no conflicts and lawsuits. If the firm takes knowledge and techniques developed by a university and translates that into a product or process innovation of economic value, then that is what is supposed to happen. Here, however, there is a conflict because the university is clearly trying to assert its claims of ownership. The university can then no longer claim a special distinction as an organization which develops knowledge as a public good, because it is actually acting in the same way as a firm.

In fact, the reason that some American universities have successful 'technology transfer offices' is that they hold a few patents of high economic value. It can be a lucrative business. UCSF and Stanford hold a joint patent by Professors Cohen and Boyer on recombinant DNA cloning technology, and this patent is easily Stanford's most valuable one. From financial year 1975 to financial year 1997, this patent grossed royalties of $221 million. By way of comparison, the next best patent for the period has grossed $22 million, or one tenth that amount. By implication, they hold many patents that are of medium to no value. That the value of patents can vary greatly is a fundamental point that many universities worldwide seen to have missed when they try to imitate what they think is the American model. Having a technology transfer office is not enough. Technology transfer offices generate money for the university when they manage a portfolio of patents to sell those of higher economic value. Doing so implies a trade-off, because it may be increasingly difficult to justify government expenditures for the university as a producer of general knowledge. The demands start shifting towards producing knowledge which is immediately useful, rather than knowledge which may or may not have a longer-term benefit for society and the economy.

Thus, the case discussed cannot be thought of as an accusation of a minor theft. The universities and researchers involved can make millions through a handful of specific patents, or else spend money on monitoring and taking out patents but without returns. Currently, biotechnology and software patents are important for creating revenue for American universities, and worldwide, the idea of patenting scientific research is particularly popular in a time of decreasing government funding for universities. The question remains, however, as to what demands governments will increasingly try to put on research at universities and research institutes.

This case, and its continuing saga, brings to the fore a number of other questions directly relevant to those wishing to start-up—and/or deal with—firms in knowledge-intensive sectors. One of the obvious issues facing engineers, scientists, and management is how to determine the economic value of your own, and others', knowledge. This comes into play, for example, when deciding whether or not to engage in joint ventures, collaborative alliances, and the like. The problem is how to evaluate the uncertainty about the actual content of the others' knowledge, about its economic value, about the enforceability of any ownership claims, and so forth. Patents, conflicts, lawsuits, and changes of testimony can happen many years and many millions of dollars later. After all, Kabi/Pharmacia & Upjohn are similarly being sued for patent infringement, through their association with Genentech. This lawsuit will undoubtedly cost more than the original R&D contract. Even for a short-term contract, there is a longer-term risk of getting hit by lawsuits which cost lots to fight—and even more if you lose. Engaging in an alliance and/or licensing agreement must be a question of making sure that the person you are buying from actually has reasonable ownership claims over the knowledge and/or techniques he or she is purporting to sell you exclusively. Engaging in agreements means facing the additional uncertainty that the legal system is under pressure to change, and different parts of the world may have very different intellectual property rights. Such differences are rapidly becoming one of the key issues in international trade.

Balancing potential risks and opportunities under uncertainty is, however, a reality for firms. The option of not doing anything is generally not a real option for firms engaged in fast-moving environments and products. Not doing anything means being left behind and out of business. These are challenges that have to be addressed by all firms which are selling or buying intangibles. The picture becomes more complicated when the knowledge being developed is done partly through public funding and partly through private.

A final point on the implications of this case for management of innovation addresses the question of true uncertainty. Knowledge which has economic value in a narrow application may not be as broadly useful as initially thought. Finding out requires trying out as well as explicit strategies to decide where to go next. In fact, the use of genetic engineering detailed here is one of the minor uses in pharmaceuticals today. Initially, it was thought to be a major trajectory for developing new pharmaceuticals. Partly, however, due to the high costs of production, using genetic engineering to make human proteins is currently seen to be a minor use in pharmaceuticals. The major use of genetic engineering is to improve the efficiency of the drug discovery process, in combination with a better understanding of the workings of the body. Combining that knowledge implies that pharmaceuticals can be more directly designed to do certain things. In the last few decades, the pharmaceutical industry has increasingly put money into research and development, only to see a decreasing efficiency of results in terms of new block-buster drugs. Genetic engineering has been put to good use to try to again improve the efficiency of the drug discovery process. Production through recombinant DNA still faces significant problems in terms of costs, and delivery and process control. Thus, genetic engineering for pharmaceuticals has seen a branching-off of knowledge towards new innovation opportunities and towards dead-ends over time.

In closing, I would like to thank the International Joseph A. Schumpeter Society and Wirtschaftswoche for awarding this book the 1996 International Joseph A. Schumpeter Society Prize for the best scientific work in the field of 'Learning, Entrepreneurship and the Dynamics of the Firm'. The prize committee was made up of an international group of acclaimed academics, and their motivation follows.

'This study represents a highly original and careful application of evolutionary ideas to biotechnology, tracing the history of the technology and the roles played by various individual actors, especially the interaction of an American and a Swedish firm, both early leaders in the field. It is an impressive piece of empirical work, which provides a good balance between theory, empirical analysis and policy relevance. It also spans the potential gap between micro and macro and brings into the analysis a thorough understanding of the technology underlying the dynamics of evolving industry and firm structure.'

I am proud to acknowledge this prize as a reflection of the growing importance of research about innovations for firms and economic change. The future offers interesting possibilities to combine case studies and quantitative work in order to develop our theoretical and analytical understanding of the relationships between firm innovations, development of knowledge, and economic growth.

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