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On the Difficult Relationship Between Scientific Advancement and Innovation

Malena Ingemansson

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Abstract

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Today, a general policy and investment recipe for economic growth and innovation, on both a national and an international level, is to base commercial ventures on novel scientific solutions. From this perspective, scientific research is seen as an untapped source of innovation, and the ambition is to make new scientific knowledge more easily transferable to business settings, where it is supposed to generate direct economic benefits.

Since the instigation of the Human Genome Organisation Project in 1990, which set out to map the entire genetic composition of the average human being, great expectations have been put on biotechnology, and it has been viewed as the new gold mine for both scientific and business advancement. Through research it is expected to deliver new scientific knowledge primarily about previously untreatable illnesses and, as an industry, it is expected to produce new technical solutions realising this knowledge. This expectation has directed large amounts of investment capital to biotechnology in the pursuit of capitalising on new scientific discoveries through their commercialisation.

This investigation is an empirically based process study of one such innovation process. With a network approach, focusing particularly on resource combinations, this study aims to create a better understanding of what is involved in trying to achieve innovation based on new scientific solutions. The specific case of the commercialisation of *pyrosequencing*, a new method for the analysis of genetic material, demonstrates the difficulty of making a scientific breakthrough into a useful business resource. The innovation process is investigated from several perspectives. By looking at the development of something new, at its large-scale production, and widespread use, this study shows how these aspects represent vastly different economic logics. It also demonstrates how great a challenge it can be for these to function together in the attempt of achieving successful innovation.

Keywords: scientific research, commercialisation, innovation, use, biotechnology, economic logic, resource interaction

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As I am putting these words on paper, I cannot believe that I am actually at the finish line. Have I really finished my thesis at last? After five years of work, it is quite a strange feeling and I cannot help but wonder if there is something in my thesis that I could have done better, put differently or developed further; the answer is, of course, *yes*. But at some point the line has to be drawn, it is simply time to finish this part of my research journey and move on to the next one, whatever it may bring.

I have truly enjoyed these five years, but getting to the point of having an actual thesis in print was not easy, and there are quite a few people to whom I wish to show my appreciation for helping and inspiring me along the way. First of all, I must give my deepest thanks to the person who made me interested in pursuing research studies to begin with, the person who, during these years, has always believed in me, encouraged me, and inspired me to stand up for who I am, both as a person and as a researcher – my supervisor Alexandra Waluszewski. Without her, I probably would not have become a PhD student in the first place and the research journey would not have been the same; it would certainly not have been as much fun, or as worthwhile. Thank you, Alexandra, for always showing great enthusiasm, for reading, and for inspiring.

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Uppsala, August 2010

Malena Ingemansson

Contents

Abbreviations and Concepts

CpG-methylation: methylation refers to the replacement of a hydrogen atom (H) with a methyl group (CH_3) in the DNA molecule. CpG refers to the occurrence of methylation at a site where a C nucleotide is followed by a G nucleotide (see nucleotide below). Methylation is normal and occurs at 60-90% of all CpG-sites in mammals. The interest of studying methylation lies in its effect on the transcription of genes to proteins and thus its influence on an organism's phenotype (its physical features).

DNA: Deoxyribonucleic Acid – which constitutes our and every living organism's genetic material.

Nucleotides – the building blocks of DNA which, through their arrangement, constitute the genetic code (also called *bases*).

PCR: Polymerase Chain Reaction – allows exponential amplification, or creation, of short DNA strands. It was first published in 1986 and revolutionised all research within genetics.

SbS: Sequencing-by-Synthesis – the methodological principle on which pyrosequencing is based.

SNP: Single Nucleotide Polymorphism – a type of mutation which occurs in one single nucleotide, and which can cause various diseases and conditions.

1 Introduction

1.1 A New Biotechnical Solution in the Making: Success as Science, Burden for Business?

In the late 1990s, a new method for *DNA sequencing*, or reading genetic code, was presented at The Royal Institute of Technology (KTH) in Stockholm. The new technique enabled an automated procedure for analysing short DNA strands with high precision. Being based on a particular methodology which allowed for an extremely accurate type of analysis, it became the first of its kind and was in due time recognised as a major scientific breakthrough, starting with a publication in *Science*, one of the most prestigious journals within the natural sciences, in 1998. Partly as a result of these successes, the method 'pyrosequencing' was deemed to have big commercial potential. This anticipation was also due to the great progress of the (then ongoing) HUGO project, an international scientific endeavour which set out to determine the full genetic content of the average human being. Together with a general view that the completion of the map of the human genome would lead to various types of studies on human disease and an industrial production of targeted drugs, the anticipation was that this in turn would create a great demand for more accurate analytical equipment for DNA sequencing. [1] The eventual results of the sequencing project were thus expected to benefit both scientific research, in terms of the massive gathering of new research material, as well as business, in an effort to capitalise on the technologies which needed to be developed for the production and analysis of this material.

When commercialising the new sequencing method in order to create a widespread use of it, i.e. to make it into an innovation, the researchers behind it got support from both academic and business collaborators. Early on, the company which was built around pyrosequencing to enable its commercialisation and production, gained an image as a successful business endeavour; it quickly launched a product, was introduced on the stock market and received awards from *Forbes* and the Royal Swedish Academy of Engineering Sciences (IVA) for its "focus on innovation". However, just a couple of years after these initial successes, the financial losses of the

[1] Drugs designed for, or "targeted" at, specific individuals on the basis of their genetic material.

company were so severe that it was forced to merge with another company, making pyrosequencing virtually obsolete within a new group of companies. Thus, as so many times before, the expectations of the development of a new product were too high and the costs of product and process development far exceeded the sales earnings.

The case of pyrosequencing opens up various questions concerning the successful establishment of an innovation: what does it take for an invention to become commercialised? What does it take for a commercialised invention to become an innovation, i.e. to get a widespread use? Last but not least, does it mean something particular for the 'innovation journey' when the commercialised invention stems directly from scientific research? All these questions also constitute the basis of this thesis. However, first let us proceed by taking a closer look at the context in which the particular invention in focus, the pyrosequencing method, was developed and how it grew into becoming a sequencing technique.

1.2 The Dream of Reading DNA

Could it be possible to read, or decode, the entire DNA of a human being? What kind of scientific and commercial breakthroughs would be needed to find new opportunities to diagnose and cure previously untreatable diseases and conditions? Is it possible to develop methods which will produce targeted drugs for each and every disease and individual? It can be said, without overstatement, that such questions regarding our genes (and how they are regulated and expressed through different cellular processes) characterised developments within both the biomedical sciences and business during the twentieth century's closing decades. The opportunity to read genetic code, or to sequence DNA, had been made possible mainly through the construction of the so-called Sanger method, named after its inventor, in the 1970s (Sanger et al., 1977). As the first sequencing method to later also become automated, which meant that most of its different methodological steps did not need to be manually handled, it revolutionised genetic research.[2] Its automation, but also the intrinsic qualities of the method, made it possible to scale-up and thus make it more time and cost-efficient. These qualities made it the only method that could, with great robustness, read a great number of 'nucleotides' (the building blocks of DNA) in a row, which in turn made this technique the focus of further development within genetics and DNA sequencing.

[2] Even though the term *genetics* in this thesis is used as a name for a single research area, it is indeed more of an overall name for the many biosciences involved in developing new knowledge in the fields of genetics and genomics. *Genetics* usually refers to the study of specific genes, while *genomics* refers to the more complex study of genes as a dynamic system.

The possibility of embedding the new knowledge of DNA sequencing into an automated procedure, made the vision of creating a map of the entire human genome seem achievable. Even if there were those who doubted the likely success of such an enterprise, the general anticipation was that this map would create immense improvements in the diagnosis and treatment of previously untreatable diseases and conditions. This vision led to the instigation of a vast international project, the HUGO project, which set out to sequence and map the entire human genome – in other words, the full genetic content of a human being, consisting of approximately three billion nucleotides.[3] (Watson, 1990; Collins et al., 2003)

Even if the Sanger method created new opportunities for sequencing DNA, it also required a highly skilled user and thus put high demands on whoever was to manage it. One of the young researchers who were introduced to the method, while spending a postdoctoral year at Cambridge University during the 1980s, was Pål Nyrén – a newly-qualified doctor in biochemistry at Stockholm University. In a general academic research laboratory in the mid-1980s, Sanger still had to be manually handled, which meant that every step of the sequencing process had to be worked through step by step.

To Nyrén, who was not well-informed about the sequencing procedure or the DNA research area, it all seemed too complicated and he immediately started to think in terms of an easier way to do it. The idea that he started to work on was closely related to his own research area within bioenergetics. Instead of having a time-consuming and complicated procedure like Sanger, where there were many steps to be handled, Nyrén wanted to create a formula where the whole sequencing procedure was taken care of by an enclosed system, and which produced straightforward end-results. After several years of trial-and-error experiments, collaborating with researchers within other knowledge areas, and struggling for financial means, the idea of a new way of performing sequencing finally started to materialise into a new method. That the method, named *pyrosequencing*, was seen as a scientific breakthrough, was first demonstrated through a publication in *Science*, one of the most prestigious journals within the natural sciences, in 1998. Unlike

[3] The Human Genome Organisation project was instigated in 1990 by the US authorities through the National Institutes of Health and the Department of Energy and was officially finished in 2003. It was an international endeavour, including more than a dozen research laboratories worldwide that participated in sequencing the genetic material and developed the technologies used to do so. The project's official goals were to: (1) *identify* all the approximately 20,000-25,000 genes in human DNA, (2) *determine* the sequences of the 3 billion chemical base pairs that make up human DNA, (3) *store* this information in databases, (4) *improve* tools for data analysis, (5) *transfer* related technologies to the private sector, and (6) *address* the ethical, legal, and social issues (ELSI) that may arise from the project. (Human Genome Project Information, http://genomics.energy.gov)

Sanger, the automated pyrosequencing method could read short DNA strands with high accuracy, which meant that it read every single nucleotide present in the material – and with exceptional speed. Furthermore, reading and analysing short DNA strands, mainly in the search for disease-related genetic markers called SNPs was, both within the scientific and business spheres, deemed to be "the next big thing" within the life sciences. [4] As several diseases and conditions already had been traced back to the existence of particular SNPs in the genetic code, there was a widespread belief that the future of diagnostics lay in finding and analysing these markers:

> "Some SNPs may contribute directly to a trait or disease phenotype by altering function. A large, well-characterized collection of SNPs will become increasingly important for the discovery of DNA sequence variations that affect biologic function. Work is already under way […] to develop a catalogue of 60,000 or more SNPs. A recently formed pharmaceutical consortium will support the production of 300,000 more […]" (Collins, 1999, pp. 5-6)

> "Drug companies […] are collecting the genetic know-how to make medicines tailored to specific genes — an effort called *pharmacogenomics*. In the years to come, your pharmacist may hand you one version of a blood pressure drug, based on your unique genetic profile, while the guy in line behind you gets a different version of the same medicine." (Brown, 2000, p. 50)

When it was made automated, the researchers behind the new sequencing method saw great advantages in using it for various types of studies concerning the analysis of DNA; for instance in the search for new genetic markers which might be useful for diagnostic or drug development purposes. However, for pyrosequencing to not be only a scientifically significant invention but also an innovation (in other words to become a widely used commercial solution), it first had to materialise into a product with a set of applications, which in turn needed to become embedded in both a producing and a using setting. With this issue in mind, we are now approaching the theme of this thesis, namely the transition from invention to innovation, and if there are any particular aspects to consider when there is involvement from both scientific and business standpoints. Before we learn more about the context in which the method of pyrosequencing came about and the efforts to embed it into a producing and a using setting, let us have a closer look at what is particular about innovations.

[4] Single Nucleotide Polymorphism.

1.3 The Difficulty of Achieving Innovations – An Empirical Viewpoint

The achievement of *invention* is the attainment of novelty in itself; it is a new idea or a new solution to a specific problem. Achieving *innovation*, on the other hand, implies that an invention, material or immaterial, has become commercialised and has gotten a widespread use. The innovation is thus the invention *in use*, and as such it entails both the organisational and physical structures needed to enable a general utilisation of the new solution. (Fagerberg, 2004; Van de Ven et al., 1999) These structures and how they relate to the achievement of innovation will here be discussed.

Empirically based research produced during the last decades with a process-oriented focus has emphasised the non-linear nature of the innovation process and how few of the attempts to create benefits from engaging in innovation have been successful. (See e.g. Rosenberg, 1982; Hughes, 1987; Van de Ven et al., 1999; Håkansson et al., 2009) From an empirical standpoint, innovation is thus described as a difficult process with a high failure rate. For various reasons, the potential innovation often does not survive and thus becomes a so-called failure. (Tidd et al., 2005) Due to the nature of innovation, transforming an invention to an innovation is, from the standpoint of such empirical observations, regarded a highly uncertain and risky undertaking. (Kline & Rosenberg, 1986; Van de Ven et al., 1999) Coming up with a new idea is one thing, establishing widespread use of it is quite another:

> "An invention or creative idea does not become an innovation until it is implemented or institutionalized. Indeed by most standards, the success of an innovation is largely defined in terms of the degree to which it gains good currency, i.e., becomes an implemented reality and is incorporated into the taken-for-granted assumptions and thought structure of organizational practice." (Van de Ven, 1986, p. 604)

The above quotation implies that the success of an innovation does not lie in the hands of the single inventor or inventing company, but rather in the *context*, or how it is received by its users. Consequently, the focus of how to succeed with an innovation is not solely on the company, but more on the customer, and it is not on the invention itself, but on the interplay between invention and the contexts in which it is used and produced. (Håkansson & Waluszewski, eds., 2007; Harty & Araujo, 2009) Putting focus on so-called "lead users" of a new idea or product is an approach long advocated by von Hippel (1976). Taking the role of testing, diffusing, and often initiating new products, these users are considered a crucial element in succeeding with new product, or service, development. By testing how the new solution

works in a user context, where it is combined with existing material and immaterial investments, further possibilities for it to develop into something which is actually useful, or economically beneficial, are created. Or, as put by Kline and Rosenberg (1986, p. 283):

> "The subsequent improvements in an invention after its first introduction may be vastly more important, economically, than the initial availability of the invention in its original form."

Håkansson and Waluszewski (2007) stress that in order for anything new to turn into an innovation it needs to "survive" in three related, but yet different, empirical settings: in a *using*, *producing* and a *developing*. Thus, before anything can be called an innovation, it has to relate to a *using setting* and the different elements that exist there. (See e.g. also Rosenberg, 1982; Kline & Rosenberg, 1986; Pinch & Bijker, 1987; Van de Ven et al., 1999) In this setting, there are various individual users which belong to different cultures, possess specific knowledge, or are dependent on particular technical solutions. (Pinch & Bijker, 1987) There are companies and other types of organisations which engage in a variety of activities connected to the use of specific organisational and technical solutions. The using setting thus consists of a structure of various types of actors and a number of *activated solutions* already in use. (Håkansson & Waluszewski, eds., 2007; Harty & Araujo, 2009)

Any new solution which is to be commercialised also needs to be relevant to a *producing setting* that is involved in providing products or services to individual users, companies or other organisations. In order for a company to be able to manufacture and offer its products or services, and for these to be of use to various customers, investments are made in relation to user requirements, and to the range of companies, such as suppliers and sub-suppliers, on which the individual producing company depends in the production of a product or service. (Håkansson & Waluszewski, eds., 2007) Here, material and immaterial investments, for instance adjustments to the production process or logistical adaptations, are carried out over organisational borders for the purpose of making operations more efficient and cost-effective. Thus, just as the using setting, the producing setting consists of a set of different actors and interrelated solutions which anything new needs to relate to. (Ibid.)

In considering all products or services which already exist, which are already produced, sold and used, these are the two main settings, a *producing* and a *using*, which permit their continued existence. There are thus suppliers that support the production of existing products and services, and there are users who have activated them by integrating them in their day-

to-day activities. For these suppliers and customers to be able to produce and use these particular types of products or services, investments have been made, and over time a structure of established production systems, routines, logistical solutions and other types of "activated knowledge" has been created. However, for anything *new* to be produced and used it first needs to be developed somewhere and thus move from being a vague idea or concept to become a more concrete solution. This is a different type of process than production and use. (Ibid.)

As stated, when something new has been developed, in order to become a widely used solution it will first need to become embedded in a producing setting where it is manufactured and prepared for distribution, and in a using setting where it is to be utilised as one among many other solutions. (Ibid.; Håkanssson et al., 2009) For instance, in a using setting, a cell phone needs to interact with the operating telecommunication systems consisting of specific transmission technology. A particular part within a car engine requires a fit with not only the rest of the components in the engine, but with the function of the car as a whole and how it is operated by a driver. In addition, in a producing setting both these solutions need to be integrated with the established production system and the supplier (as well as sub-supplier) relationships required to uphold it. This means that for any new solution to become widely used it must fit with, and be able to create benefits for, both a producing and a using setting (ibid.).

In turn this makes the success of any innovation unpredictable; if success depends on how new solutions are combined with established ones, and in such different settings as *production* and *use*, which determine their usefulness or value, how can the benefits of a new solution be stated beforehand? Rather, due to the complex nature of technical, organisational and economic systems, attempting innovation is "a leap into the unknown" (Van de Ven et al., 1999, p. 66) which implies that it is very difficult to state which new ideas will actually become widely used solutions (Rosenberg, 1994).

In the study of innovation and new product development, this is a standpoint argued for in the IMP (Industrial Marketing and Purchasing) research tradition (see Håkansson et al. 2009, Håkansson & Waluszweski, (eds.) 2007 for an overview, or www.impgroup.org). Through a great number of empirical studies on the practices taking place in the "business landscape" (Håkansson et al., 2009), the dominant perspective is that companies operate not as independent units but are, through their interdependencies, embedded in a network-like structure. (See e.g. Håkansson & Snehota, 1995; Håkansson & Waluszewski, 2002; Araujo et al., 2003; Ford et al., 2003) These interdependencies concern organisational and physical adaptations stretching across organisational borders, e.g. logistical, production system or product adjustments. In turn this means that no solution exists in isolation, but depends on various other solutions,

material as well as immaterial, stretching across the organisational borders of a single company. To reduce the inefficiency of needing to combine different solutions over organisational borders, the different solutions, material or immaterial, are chiselled out in reference to each other to create a better fit. Any good solution will therefore be better adjusted to a specific set of solutions than to any other single solution or set of solutions. It is such networks of interdependent and interrelated solutions, represented by a number of different actors, to which any *new* idea or solution will need to relate. (See e.g. Rosenberg, 1982; Håkansson & Snehota, 1995; Håkansson & Waluszewski, eds., 2007)

A simple example of the interrelatedness between different solutions and the actors representing them can be seen in the case of the light bulb. The light bulb is an astonishing invention, but depends on a number of other solutions and organisational requisites for it to be able to function. First of all there needs to be a set of companies providing the different components required to make the light bulb. Just as the physical components of the bulb, such as the glass or the filament, have to fit properly together, so must these companies and their products be compatible with each other in terms of both production and supply. Second, the light bulb's use depends on the existence of lamps with sockets adjusted to the particular size of the bulb grip – these are produced by a set of companies different than those producing the light bulb. Its use also depends on the existence of an extensive system of power lines, and on the supply of electricity. These are products and processes represented by another set of companies and organisations. In addition, its use depends on the presence of a political structure which has enabled the construction of a national electrical power system supplying electricity to households and industries. In parts of the world where these organisational and technical structures do not exist, the light bulb becomes useless. For any widely used solution, there thus needs to be a producing setting in which the solution is related to the other solutions and companies on which its production depends, and there needs to be a using setting which can activate the product by the use of other existing solutions.

Furthermore, as shown by Hughes (1983) and Basalla (1988), even if Thomas Edison had considered not only technical issues with his invention but also economic ones, the invention of the light bulb was also the focus of a developing setting which engaged in solving the technical issues connected to the potential invention's basic function of producing light, such as connecting it to generators, switches and other necessary components. Thus, no solution exists in isolation but depends on a number of other solutions, material as well as immaterial, stretching across time and organisational borders. As will be further discussed in the theoretical chapter of this thesis, these solutions are in turn *used, produced* and *developed* by a number of different actors which, one way or another, are also interdependent.

The idea of interdependence between the establishment of new solutions and context is also generally argued for within the research field of STS (Science and Technology Studies). (See e.g. Jasanoff et al., eds., 1995 for an overview) In a vast number of empirical studies on the practices of scientists and engineers in the endeavour of developing and using new and established scientific knowledge or technology, the general finding is that neither knowledge nor technical solutions exist in a vacuum but are shaped, and reshaped, by the culture, the institutions, and the physical structures related to their development and use. (See e.g. Shapin & Schaffer, 1985; Latour, 1987; Mol & Law, 1994; Jasanoff, ed., 2004; Widmalm, ed., 2008)

This suggests that in order for something new – i.e. a new research result or a technical advancement – to become accepted and widely used, it needs to become integrated and thus be made part of established practices, existing knowledge and related technical solutions. Within the STS research field, this gradual anchorage in both material and immaterial structures is seen as a process of stabilisation or embedment of the new knowledge or solution, which not only involves professional scientists or engineers but also other actors who, through their use of *the new*, influence both its use and further development. This further suggests that the value of neither knowledge nor physical solutions is constant or can be predetermined. As material and immaterial solutions become part of new contexts, their meanings and uses change. (See e.g. Latour, 1987; Pinch & Bijker, 1987; Rosenberg, 1994; Knorr Cetina, 1995; Rabeharisoa & Callon, 2004)

An example of the ambiguous nature of scientific knowledge and how it can be transformed by its use in different contexts is here posed by a study performed by Rabeharisoa and Callon (2004) on the transformation of knowledge about the genetic disease MD (muscular dystrophy). The study investigated an effort made in France of arranging an organisation in which patients, as well as their families, would be able to interact with scientists and actively participate in "the orientation of biological and clinical research" (ibid., p. 142) around MD. As a result, a body of knowledge was produced which would not have been possible if the research had been treated strictly as an area of "scientific expertise". The study shows that at the onset, the patients did not recognise themselves from the description of their condition given by the scientists, nor could the scientists relate to the symptoms described by the patients. Thus, even though the issue of concern was one and the same disease, initially there was no understanding between the two parties. However, through close interaction between the scientists and the patients (or "developers" and "users"), and by letting the patients have an active role in the production of knowledge, the clinical and biological research around MD, as well as the interaction between patients and medical staff, was transformed. This knowledge manifested in new ways of viewing the previously little known disease as well as in new treatment methods. (Ibid.; Jasanoff, ed., 2004)

What the example demonstrates, and what will be further elaborated on in the theoretical chapter of this thesis, is that whether labelled scientific or not, in order for new knowledge to become an "implemented reality" (Van de Ven, 1986, p. 604), it needs to be intimately connected to the settings in which it is developed and utilised.

A further elaboration on the empirical findings within both IMP and STS on the use, production, and development of material and immaterial solutions, is accounted for in the theoretical chapter of this thesis. With this view in mind, inspired by empirical observations of the establishment of new knowledge or technical solutions, we will now turn to the innovation process as viewed in the model world.

1.4 The Vision of Successful Innovation Processes – A Model Viewpoint

To achieve innovation is considered very desirable to the single entrepreneur or company (Cooper, 1982), but it is also viewed as an important goal in terms of creating economic growth on a larger scale. (Nelson, 2008; O'Sullivan, 2004) Therefore, successful innovation processes are advocated by a range of financial and political actors, such as venture capitalists and policy makers. (Gompers & Lerner, 2001; Tidd & Bessant, 2009) The claim that successful innovation is a prerequisite for economic progress is certainly not new, but rather old and acknowledged (see e.g. Marshall, 1920; Teece, 1977; Dosi 1982; Stephan, 1996; Nelson, 2008). In general, novelty, be it technical or social, is regarded as a requirement for economic growth, or as put by Nelson (2008, p. 4):

> "Today economists studying economic growth are in accord that technological innovation is the key driving force." [5]

In spite of the empirically-grounded research that has been conducted during the last three or four decades, underlining the non-linear nature of innovation, its image as a catalyst of economic growth has led much innovation management literature to portray it as the outcome of a rather linear process. This view largely originates from an established economic theory which describes the achievement of innovation as a mainly manageable and sequential process. (O'Sullivan, 2004; Håkansson & Waluszewski, eds., 2007) One tendency is to view it as a "one-party

[5] Here, Nelson is referring to technological innovation as being both physical and social, the latter concerns institutions.

achievement" where either a manufacturer is in charge of producing a potential innovation and pushes it out to possible customers who accept or reject it, or "the market" demands particular technologies, in response to which the manufacturer, learning from the changes in demand and prices, produces a certain output. (Dosi, 1982; Mowery & Rosenberg, 1979; von Hippel, 1976) Another common position is a stepwise perspective known as *the linear model*, which conceives the innovation process as starting with a new idea that later evolves through subsequent phases of development, commercialisation and implementation in a unidirectional order. (Kline & Rosenberg, 1986; Van de Ven, 1986) These types of views direct attention to the issue of achieving desirable outcomes for new investments as a matter of information asymmetry: as long as the economic actors have all the available information about a particular investment they will be able to make an investment decision leading to a predictable outcome. (O'Sullivan, 2004)

The strong desire of achieving the economic benefits to which innovation is supposed to lead has in some ways focused the debate about innovation on how to control or manage it. Thus, these theoretical standpoints have inspired a general view of innovation and technological development as being achieved through a straightforward working order or formula. This means that "the fundamental uncertainty that characterizes the relationship between investments and their outcomes" (O'Sullivan, 2004, p. 257) is largely ignored. (Håkansson & Waluszewski, eds. 2007; Kline & Rosenberg, 1986; Van de Ven et al., 1999; O'Sullivan, 2004)

The view of innovation as resulting in positive economic outcomes, and the subsequent wish to be able to plan the innovation journey, also appears in the rhetoric of policy makers and investors. The following citation is part of the announced innovation strategy of the OECD to create policy tools for a promotion of innovation:

> "Today, innovative performance is a crucial factor in determining competitiveness and national progress. [P]olicy coordination is essential – only a comprehensive and wide-ranging strategy to foster and strengthen innovation can help address social and environmental goals while building a lasting foundation for future economic growth and competitiveness. " (OECD, 2007, p. 26) [6]

This is in line with the view regarding the commercialisation of new solutions amongst those in the world of investment and venture capital. Here the approach is to find and invest in new solutions which are expected to

[6] The Organisation for Economic Co-operation and Development (OECD) is an international participative organisation with 30 member nations working together with the goal of promoting economic growth and activity as well as further international trade, primarily for the member nations. For more information visit www.oecd.org

generate a return-on-investment (ROI) within the near future through the forming of new companies.[7] (Gompers & Lerner, 2001; Baraldi & Strömsten, 2006) The profit is generally achieved by attaining an "exit" out of the investment, i.e. the company, either in the shape of introducing it on the stock market or getting another company to acquire it. (Ibid.) What happens to the company after the exit does not concern or affect the venture capitalist. This implies that in order to justify investments, the venture capitalist expects profit to result from the new solution, which first has to be calculated.

From this perspective, the goal of policy and investment becomes first to achieve *novelty* in itself, second to finance it, and third, if this novelty is found in non-commercial environments, to *transfer* it to commercial actors. (Håkansson & Waluszewski, eds., 2007; Waluszewski, 2010) Explanations as to why innovation processes are not successful are more frequently couched in terms of the problems with the quality of the product rather than the surrounding conditions for its implementation. This means that the problems of introducing a new product are seen as residing in the new idea itself: first to actually come up with a new idea, and second to "succeed" with it. Therefore it is the idea itself which is seen as a "success" or a "failure". (Hall, 2004) As such the potential merit of any new solution is then treated as "fixed" and unaffected by the contexts it is brought into. This also leaves much room for the discussion of financing being a decisive factor for the success of commercialising a new idea, for instance through the acquirement of venture capital. (Gompers & Lerner, 2001; Powell et al., 2002; O'Sullivan, 2004)

The third common focus concerns the transfer of the new idea. This refers to the relocation of the idea from one context to another, for instance from a developing setting to a producing and marketing setting, or from non-commercial settings to business, where the view is that the invention is supposed to be able to create the same benefits in its new environment as was identified in the developing setting. (Utterback & Abernathy, 1975; Håkansson & Waluszewski, 2002) In the effort to identify reasons for the failure of an innovation, focus is thus often put on the qualities of the novelty, its financing, as well as on how it is to be moved from one context to another – but seldom on how it will *fit* into these differing contexts.

In the view of the novelty itself as being the most important ingredient in successful innovation, inventions stemming from scientific research have from a policy and investment perspective been assigned a particular value to serve as the basis for subsequent commercialisation and innovation within business. (See e.g. Eklund, 2007; Håkansson & Waluszewski, eds., 2007; Beckman et al., 2008; Waluszewski, 2010) Novelty developed as science is

[7] ROI is a performance measure made up of three components: *revenue* minus *costs* divided by the needed *investments*.

thus highly regarded as a foundation for creating new products and services useful within business. However, the reason why scientific knowledge does not seem to be smoothly applicable within industry (in terms of scientific research delivering ready-made solutions) is interpreted as a lack of transfer support. (Dasgupta & David, 1994; Håkansson & Waluszewski, eds., 2007) From the observations which have been made in the process-focused innovation literature, let us now consider how scientific research is portrayed, as an important provider of innovation, by what can be called the *transfer perspective* generally adopted by policy and investment actors.

1.5 Scientific Invention Suited to Business Innovation?

During the last few decades, the image that business innovation to a larger extent should be based on scientific knowledge has become increasingly established. (See e.g. Dasgupta & David, 1994; McKelvey, 1997; Eklund, 2007; Beckman et al., 2008; Waluszewski, 2010) Since the late 1990s, both national and transnational policy documents have generally portrayed innovation as a manageable process in which success is brought about by an "organisation of research efforts". (Eklund, 2007; Waluszewski, 2010) The general view is that it can be determined beforehand which type of academic research areas will bring future innovations to business and that research results can be made more easily transferable to a commercial setting. (Ibid.) Or, as stated in OECD policy:

> "[I]n a fast-changing knowledge economy, it is all the more important to ensure that systems are in place to link the work of scientists with the innovators in business who can see a potential commercial use for the product. [T]his vital link between a scientific discovery and practical applications is becoming all the more important as science is increasingly driving innovation." (OECD, 2004, p. 2) [8]

[8] Another example is the Lisbon Strategy set up to guide the European Union towards becoming a "knowledge-based economy": "In the past, universities would develop new knowledge and, when it was mature, it might be picked up by business for commercial application. Far too much knowledge remains locked up in universities and the development of new knowledge takes too little account of the needs of business. This innovation model is out of date. Today, innovation is built around knowledge networks which, by sharing, developing and accumulating knowledge, facilitate a rapid development of products and services out of new ideas. Such cooperation between universities, large and small companies, research and knowledge transfer institutes, investors or even associations of users and consumers is best realised within clusters – geographically delimited areas which allow for a direct interaction between existing stakeholders and which also attract new ones." (EU Communication from the Commission to the European Council, 2006, pp. 4-5)

Since the emergence of such various research policy documents, and a stream of literature pointing towards an ongoing change in the way science and industry interact (See e.g. Gibbons et al., 1994; Nowotny et al., 2005), the idea of new scientific knowledge being a driver of innovation within business has become conventional. Even though it is not an entirely new perspective on the role of science – which has always, to a certain degree, been demanded to stand in the service of society, either as a provider of new knowledge or technology (Brooks, 1994; Widmalm, ed., 2004; Widmalm, 2008) – it seems to have gained new ground in terms of the creation of "productified" economic benefits. Instead of scientific knowledge being seen as separate, and its benefits are only revealed over time, it is now expected that the benefits of this knowledge be stated ex-ante and correspond to specific needs. The basic idea is thus that scientific work should result in ready-made research results which straightforwardly can be packaged into material or immaterial solutions and be "transferred" to business. Furthermore, here, through the availability of financing, it should become commercialised and, at best, spread among various users as a product or service. (Widmalm, 2008; Waluszewski, 2010)

According to this notion, it appears only natural that scientific work should be the most important basis of the newness required for economic growth, and that the knowledge it creates should be taken up by industry far more extensively. (See e.g. Elzinga, 2004; Pavitt, 2004; Eklund, 2007; Håkansson & Waluszewski eds., 2007; Beckman et al., 2008) There is consequently a prevailing image of the production of scientific knowledge as an "untapped source" of innovations and as the following citation implies, one of the areas which great attention is directed to is biotechnology:

> "Technological innovation, particularly in certain high-tech industries such as computers, electronics, aerospace and biotechnology, increasingly is seen as a major driving force behind national economic growth and competitiveness." (Malecki, 1997, p. 245)

In the following section, the relationship between scientific research and business involved in biotechnology is viewed both from a process-focused perspective and from a transfer perspective.

1.6 Biotechnology Within Scientific Research and Business – Heavy Interaction or Easy to Transfer?

Due to new scientific knowledge concerning human genetics and later also technologies involved in its analysis, during the closing decades of the twentieth century, the area of *biotechnology* became a hot topic also in business development circles. (Andersson, 1996; Liebeskind et al., 1996; Zucker et al., 1998) Biotechnology involves, on one side, basic scientific research concerning the biological foundations for life and, on the other side, technology development wishing to exploit this knowledge for practical applications. Or, as it is defined by the OECD (2009):

> "[b]iotechnology is the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or nonliving materials for the production of knowledge, goods and services."

As the biotechnology industry's most important source of knowledge is scientific research, it relies heavily on research within academia for its continued development, both in terms of new technologies and economic advancement. (Liebeskind et al., 1996; McKelvey, 1997; Senker & Sharp, 1997; Zucker et al., 1998) Furthermore, firms involved in biotechnology do not only need to justify their existence on an economic level, but also on a scientific one; to legitimise their presence within biotechnology they need "scientific prestige" to attract new buyers and hire trained scientists. This is commonly achieved by engaging in a close collaboration with academia and obtaining publications in scientific journals. (McKelvey, 1997)

As suggested, within biotechnology, the connection between scientific research and commercial production is strong. It is also the case that the production of scientific knowledge within biotechnology is dependent on the technological development and production taking place within industry; in order to perform and also develop new types of assays, which in turn can create further knowledge, the devices and instruments being produced by industry are crucial. There is thus a strong interdependence between the production of scientific knowledge and technological development within industry. (See e.g. Rosenberg, 1982; Andersson, 1996; Widmalm, 2004) This means that the exchange taking place between scientific research and companies producing new or improved technological solutions is a key process requiring intense interaction between the two settings. (See e.g. Rosenberg, 1976; Mansfield, 1995; Andersson, 1996; McKelvey 1997)

Nevertheless, this connection is often seen as unproblematic and linear which, for example, is indicated by the following citation from one of the actors in this thesis' empirical study and one of Sweden's largest and most

recognised venture capital firm within the life sciences, Health Cap (www.healthcap.se, 2009):

> "We invest in the commercialization of innovations in medical science, and believe that the structural changes taking place in the pharmaceutical industry create significant opportunities for the knowledgeable investor to achieve high financial returns. In our view, the two most important factors required to grow a life science venture into a sustainable and successful company are high quality management and uniquely positioned products based on outstanding science."

The above citation implies that an important component in creating a thriving company is to base it on high quality scientific research which, through its commercialisation, will create financial returns. The relationship between developing new knowledge through scientific research, and implementing it within a business setting to produce new products or services (which, if successful, will be distributed to and used by various customers), is thus depicted as straightforward. This leads us to the main theme of this thesis, namely what it takes for an invention to become an innovation, and if there is anything specific to note about the "innovation journey" when the invention stems directly from scientific research. These general questions are formulated into two explicit research questions in the following section.

1.7 Research Question

We have now considered the idea that the achievement of innovation is desirable for its potentially positive economic effects; however, not only are they considered difficult to accomplish, it is also a challenge to identify where the problem of "succeeding" really lies. From a process-focused perspective, innovation is seen as the accomplishment of making a novelty (based on something new, or on a new combination of well-established knowledge) fit with established material and immaterial investments within both a producing and a using setting. Achieving innovation therefore becomes a matter of relating something new to constellations of established solutions which have been particularly adjusted in reference to each other as to create a greater compatibility. Thus, it is ultimately the *settings* in which any new solution is to be used and produced, and how well it fits with these, which determine its economic benefits as an innovation.

Still, innovation is commonly portrayed as the result of a manageable process and facilitating the innovation journey by providing knowledge or

capital seems to be an explicit policy and investment ambition. There is thus a notion of the possibility of planning the innovation journey in which the most important factor is the invention in itself. In addition, scientific research is viewed as one of the most essential sources of new ideas and solutions for business, and the goal is to make new scientific knowledge more easily transferable to a commercial setting. This leads to the following two research questions:

A first, general research question that can be formulated is:

- What is special about innovation processes for inventions which stem directly from scientific research? Why?

A second, specific research question is:

- In what way is a potential innovation, which stems directly from scientific research, related to the settings where a) it is developed, b) it is taken into large-scale production and c) it is taken into use - and how does this affect its ability to survive the innovation journey?

In order to answer the general and the specific research questions presented above, a theoretical perspective which can be used to explain the interaction between new and established solutions within the settings of *use*, *production* and *development* has been applied.

First, to understand what it takes for something new to go into production, and to get a widespread use, a basic understanding of the business landscape and its processes has been applied according to the IMP research tradition. This research tradition has been employed in a vast number of empirical studies pointing to the interactive and interdependent nature of the business landscape.

Second, to grasp how something new gets developed through scientific research, and what it takes for new knowledge to become established as "scientific", the empirical observations performed within the research field of STS have been the primary inspiration for this study. Just as the IMP research tradition this research field stresses the heterogeneous, and thus interactive, character of material and immaterial resources.

For the specific purpose of observing what happens to the new solution in interaction with established solutions in the different settings of *use*, *production* and *development*, I have used the *4R model* – a research tool which can capture the effects of different material and immaterial solutions relating to each other. This model will be thoroughly explained in the theoretical chapter of this thesis. The next section outlines the thesis' overall purpose and content in full.

1.8 Outline of Study

We now have a basic outline of what characterises the innovation process from a non-linear and process-focused perspective; the subsequent theoretical chapter, chapter 2, will further argue that this process is interactive in nature and involves different and, in one way or another, interrelated actors and established solutions. The three different, but related, empirical settings of *use*, *production* and *development* will be outlined in detail so as to create a deeper understanding of their different structures which affect their respective use of, and influence on, anything new. This chapter will also acquaint the reader with how STS characterises scientific research and the view of how this affects the development of new knowledge and material solutions. An exposition of the theoretical tool, the 4R model, which has been used to catch such specific interactive effects, ends the chapter.

The theoretical chapter is followed by chapter 3, which discusses the research process, the methods used, and the methodological foundation on which the study is based. The subsequent three chapters – chapters 4, 5 and 6 – present the pyrosequencing empirical case study in the three settings of development, production and use. The empirical part of the thesis ends with an epilogue about the continuing "life" of the new solution in focus in a particular setting. Chapter 7 is devoted to an analysis of the empirical case, and presents a discussion of the interactive processes taking place within and between the three respective settings. The following chapter, chapter 8, discusses the conclusions from the research findings and suggests possible policy implications.

2 Theoretical Approach

This chapter will detail the theoretical approach which has been used to analyse the featured innovation process from an interactive perspective.

2.1 Innovation as an Interactive Process – The Importance of Use

How innovation happens, and how it actually is turned into economic benefits, is a widely debated issue. As was indicated in the introduction, from an interactive perspective, innovation is not just about coming up with a new solution, but a complex process of combining something new with all the physical and organisational structures needed to enable its widespread use (See e.g. Fagerberg, 2004; Rosenberg & Kline, 1986; Van de Ven, 1986):

> "Whereas invention is the creation of a new idea; *innovation* is more encompassing and includes the process of developing and implementing a new idea. The idea may be a recombination of old ideas, a scheme that challenges the present order, a formula or a unique approach that is perceived as new by the individuals involved." (Van de Ven et al., 1999, p. 9)

Innovation is thus not the same as the invention, but is the invention *in use*. As the above quotation states, the invention is often not completely new in the sense that all its elements are "new to the world", but the newness can be represented by a different composition of old knowledge and ideas or by introducing an old idea within a new context or in a new manner. The "new" idea is thus not without connection to the past; to old knowledge, conceptions or technical systems. (Lundgren, 1991; Van de Ven et al., 1999; Håkansson & Waluszewski, eds., 2007) Nor will it become an "implemented reality" (Ven de Ven, 1986, p. 604) without being relevant to the present and the contexts where it currently exists; to become an implemented solution, or an innovation, it needs to be adjusted to fit the surrounding situations. (Lundgren, 1991; Van de Ven et al., 1999; Håkansson & Waluszewski, eds.,

2007) However, these contexts also have a history of specific knowledge and systems of technical and organisational solutions from which the current situation has emerged. This means that an innovation does not have a single homogenous identity unaffected by history or its present contexts, rather it is a product of history which, in order to become successful, needs also to fit within a current "using system" with a history of its own. (Ibid.) Therefore, for a novelty to be implemented by users and become economically beneficial to produce and use, it needs to function within existing routines, on the basis of existing knowledge and together with already implemented technical solutions in its new contexts. For instance, if we buy a new computer, we still want to be able to plug it into our existing electrical outlets, or if a company implements a new filing system it must be possible for the employees to learn how to operate it. This means that once a new solution is to be implemented it is no longer its individual qualities which are of most importance, but if they can be combined with what already exists. (See e.g. Rosenberg, 1982; Kline & Rosenberg, 1986; Basalla, 1988; Fagerberg, 2004) What does this mean for the development of new products or services?

Empirical observations indicate that a large portion of new product developments fail because the product or service never sells as anticipated. (See e.g. Cooper, 1979; Dougherty, 1992; Pavitt, 1991) When innovation does occur, it often takes place within established producer-user relationships. This suggests that a high degree of relatedness between these two settings, both in terms of past investments and a sharing of knowledge seems to improve the chances of a producer manufacturing a product or service which will actually fit into the using setting. (Harrison & Waluszewski, 2008; Håkansson et al., 2009) Since new solutions in these established relationships are produced from the standpoint of earlier investments and gained knowledge of the requirements of the using setting, the achievement of innovation becomes more attainable. This is also illustrated by the involvement of "lead users" who, by being part of the process of developing and producing new solutions, shape the product or service so as to create a fit between the new solution and the user environment in terms of direct or indirect economic benefits. (von Hippel, 1976) It thus seems important for any producer to relate to the potential users of a new solution in terms of how the product may combine with the existing structure of solutions (material as well as immaterial) within the using setting.

Thus, in regard to the possible economic benefits from innovation, it is how *the new* fits with *the established* that seems to be the key issue, which leaves the technical quality as only one of many requirements for the accomplishment of a useful invention. This means that the individual features of something new cannot be the only focus in an evaluation of the

possible benefits of introducing it in various contexts. Or, as put by Kline and Rosenberg (1986, p. 276):

> "[...] Technical success (or any purely mechanical measure of performance) is only a necessary and not a sufficient condition in establishing economic usefulness."

There is thus something that happens when a new solution is brought into actual use. It is to be made a part of other contexts than the one in which it has been developed, and it is how it can be combined with existing solutions within these environments which will determine its economic usefulness for each such context. The features of the new solution are thus separate from the economic benefits which can be gained from its implementation. (Kline & Rosenberg, 1986; Basalla, 1988) This is illustrated not least by the many examples of the time lag which exists between the advent of new technology, or the assembly of old technology into new solutions, and its economic impact. (See e.g. Lundgren, 1991; Mansfield, 1995; Stephan, 1996) Lundgren (1991) mentions the electronic computer as one such example: even though the original invention was made during the mid-1940s it was not until several decades later that it became the widely used solution we know today. And even now, because of its widespread use, where it has been adjusted to meet specific requirements, the scope of its economic impact is yet to be seen. A similar example is the TV set. (Utterback, 1994) It took several decades before the original invention of the TV became part of a standardised production and a common feature in "every home". Since then there has been a major development in terms of both production and use. The basic technology for displaying moving images has changed drastically and TVs can be used in a number of different situations not originally envisaged. (Ibid.)

Thus, it cannot be ignored that anything new, for instance a new technical solution, will not be used in isolation; as soon as it is to be implemented it will have to connect with the knowledge, the technical solutions and activities already existing in the implementing environment. And it is only when this happens that its "economic dimensions" (Håkansson & Waluszewski, 2004, p. 377) will appear. (See e.g. Utterback & Abernathy, 1975; Rosenberg, 1982; Basalla, 1988: Hall, 2004; Håkansson & Waluszewski, eds., 2007)

Taking the aspect of *use* into account indicates that innovation is not just about novelty, but perhaps even more so about compatibility, or how the new can be made to fit with the established. In order to become economically useful, an invention will have to adapt to its surrounding context and in this process most likely be altered and redefined to fit the requisites of the specific environment. (Pinch & Bijker, 1987; Baraldi et al.,

eds., 2006) The next section will more thoroughly relate innovation, as an interactive phenomenon, to how it is carried out in a business landscape characterised by interdependency.

2.2 The Innovation Process in an Interdependent Business Landscape

From an interactive perspective, companies have always been interdependent in terms of the resources they exchange, and thus combine in particular ways. However, as there has been a transformation in the organisational structure in terms of what is outsourced to other companies, this interdependency has changed over time and has greatly influenced the relationship between producer and user. (Håkansson et al., 2009)

Compared to the common existence of the "integrated firm" (Chandler, 1990) of the mid-twentieth century, the development of business organisation during the last few decades has rather pointed to a "disintegration" of the firm, where more and more companies have chosen to specialise in a small number of activities and consequently outsource many of their former integrated competences to various suppliers and sub-suppliers. Before, users of merchandise such as steel or paper interacted with only one or two companies that would handle production, product and process development as well as input goods development, connected to that merchandise, within the company walls. The general development that followed, however, separated these activities and they are now commonly performed by a number of different interacting companies. (See e.g. Chandler, 1990; Gudeman, 2001; Håkansson & Waluszewski, 2002; Håkansson et al., 2009) Today, the majority of a company's expenditure is usually accounted for by a concentrated number of suppliers which provide technical resources and knowledge in the production of a specific product or service. (Håkansson, 1989; Håkansson et al., 2009) This implies that the single company relies heavily on the products and services provided by its suppliers, and in turn the suppliers' suppliers, for the organisation of its own operations. Therefore, the investments needed to produce a particular solution run across the organisational borders of a single company and connect it to several other companies and actors:

> "The contemporary company uses external specialists/suppliers not only for delivering components and insert material, but also for engagement in development issues, often involving sub-suppliers and technological experts. Complementary suppliers, or what in mainstream economic literature are simply referred to as "competitors", often work together in joint development processes." (Håkansson & Waluszewski, eds., 2007, p. 4)

To increase the compatibility between these different producing and using companies and organisations, such as suppliers, sub-suppliers, financiers etc., investments are made and over time a network of interdependent actors and investments is formed. This implies that in order for *new* products or services to be able to create any benefits for the actors involved, these new solutions need to be made compatible with the existing investments connecting these different companies and organisations. To be able to produce ROI, now or in the future, new investments and solutions must thus be well-matched with earlier ventures and implemented solutions. (Håkansson & Waluszewski, 2002; Håkansson & Waluszewski, eds., 2007) As such, it can be said that the business landscape consists of a number of active and interdependent investments that are currently in use and with which new investments, in order to create any benefits, need to fit.

An example of how the use, production and development of a new solution involves a variety of interdependent actors and solutions, both established and new, is shown by the innovation journey of the typewriter. (Utterback, 1994) The idea for a machine that would be able to put words on paper more efficiently than a person writing by hand came in 1714 when an English patent was obtained for a "writing engine". However, it was not until more than a century and a half later that a similar solution, called a "typographer", would become commercialised in the US. When it was taken on by the Remington Company in 1873, the typographer had gone through an extensive development by its inventors from its original form. Nevertheless, as the machine, now manufactured as a standardised product, was put into use, it became clear that several improvements needed to be made. For instance, the paper was not visible to the typist until the first four lines had been typed – this was not very practical. Also, when two, or more, frequently used keys were sitting next to each other, they would eventually jam and became unusable. This instigated both product and process development within the Remington Company through which a new typewriter with more practical user features was produced. Thus, the use of the first commercial typewriter resulted in new process features within the producing company and in a second edition of the product. With the success of this second model, other companies began producing different models of typewriters and five of these companies became the dominant players in the industry at the beginning of the twentieth century. Through this variety of

solutions, as well as different producers and users, a more or less standardised format of the typewriter was eventually established. (Ibid.)

Thirty years later, electrical products were becoming commonplace and even though a model of an electric typewriter had been available since the beginning of the twentieth century it had, for different reasons, not become a widespread solution. However, the introduction of new actors on the electric typewriter market would take the development in another direction; by purchasing a company involved in manufacturing electric typewriters, IBM became introduced to the typewriter business. Also, as other typewriter models than the ones produced by the Remington Company had become standard in the general office environment this company was by now more or less history in terms of market share. (Ibid.)

By having the War Department as a major buyer for several years, IBM acquired a great deal of experience in designing and manufacturing electric machines. As a consequence, in the 1970s, this company took the first step towards a digitalised word processor. By combining the "old" electric typewriter with new digital computing technology it was believed that the ultimate "office system" had been produced, consisting as it did of a line of products such as a word processor, fax and an electric typewriter. However, as these products were embedded in user environments, their common purpose of enhancing productivity was not achieved. In fear of losing their job assignments and being forced to change their work routines, secretaries and managers resisted the new way of working. The costs attached to putting the system into practice and reorganisation also made companies reluctant to implement it. Thus, it never became the anticipated commercial success. Instead, a mixture of user requirements and the availability of the new technology in combination with established solutions opened the door to the development and production of the personal computer (PC) which IBM, among several other companies, played a large part in. (Ibid.)

The production of this particular solution, however, turned out to be more successful for the component suppliers, such as Intel and Microsoft, which provided the PC assemblers, such as IBM, with microprocessors and software. (Utterback, 1994; Malerba et al., 1999) As put by Utterback (1994, p. 16): "[...] the suppliers had become more valuable than their customers". IBM, which before had gone for an in-house production of computers in the shape of mainframes, i.e. large calculation machines, had neither the technological nor the organisational resources to produce these new components and thus greatly depended on the suppliers for this. Today, through technology development and its frequent use in various situations, PCs are indispensable to our everyday life and are used for many more purposes than performing calculations or putting words on paper. (Malerba et al., 1999; Bresnahan, 2007)

Interdependency, which characterises the business landscape, thus creates *limitations* as to which solutions, new or established, can be combined, as

was shown in the case of users not embedding the new "office machine" produced by IBM. But because of the variety of actors, activities and resources, there are also *possibilities* in terms of new combinations being discovered and realised, such as in the case of the PC. Interacting, i.e. relating resources to a specific set of other companies and their resources, forms new development opportunities but also creates lock-in effects, as in the case of IBM's difficulty in moving from producing mainframes and the "office machine" to the assembly of PCs, but acquiring the resources to do so by interacting with new suppliers. Another, less happy, example is that of the Remington Company which initially was the leading producer of typewriters. However, as users preferred other typewriters and the company did not have the resources to adjust to these requirements other manufacturers eventually took its place. Sets of resources that are tailored to create a fit between them will through this interaction process be less easy, and thus more costly, to combine with any other set of resources. Thus, even though particular combinations provide efficient solutions, they may also rule out or make other combinations more difficult to achieve. (Håkansson & Waluszewski, 2002; Håkansson & Waluszewski, eds., 2007)

What does this interdependency, between companies and their resources mean more specifically for the use, production and development of new solutions? As addressed in the introductory chapter, to understand innovation, or how widespread use of a new product arises, we must appreciate how it has "survived" in three different but related empirical settings: use, production and development. (Håkansson & Waluszewski, eds., 2007) The most interesting aspect of these settings, from this thesis' point of view, is that among them, they will always have different economic logics (ibid.). In the following section, these three settings will be examined more thoroughly.

2.3 Three Related but Different Empirical Settings Which Any Attempted Innovation Needs to Survive

The previous two sections have discussed how the achievement of innovation depends on an invention becoming widely used, but what does it mean to embed a new solution in a using setting? And how does this relate to how it is manufactured in a producing setting? Of course, before either of these settings come into play, the new solution first needs to have been developed somewhere. As any new solution will have to relate to existing solutions, material and immaterial, in both a producing and a using setting, the less related it is to that which is already established, the more difficult, and expensive, it will be to implement it. (Håkansson et al., 2009; Håkansson & Waluszewski, eds., 2007) One way to understand this is

through the measurement of return on investment, or ROI, as constituted by three measurements; *revenue* minus *costs* divided by the needed *investments*, and relating this measurement to how the producing and using settings are affected by the introduction of new solutions. (Ibid.) By using this measurement as an indicator of the economic logic of producing and using new solutions, I will discuss the settings of use, production and development.

Using New Solutions

In measuring the likely ROI of introducing a new solution, it becomes clear that there are three ways for any user to increase it: by increasing the revenue, by decreasing the running costs or by decreasing the needed investments to implement the new solution. (Håkansson & Waluszewski, eds., 2007) The main purpose of investing is to make the combination of certain resources, for instance in the shape of production systems or logistical solutions, more efficient. (Gadde & Håkansson, 1998; Håkansson & Waluszewski, 2002) Thus, one feature of the investment pattern which forms during the interaction between companies is that it revolves around the adoption of certain material and immaterial solutions which are interconnected over organisational borders. (Dosi, 1982; Håkansson & Waluszewski, 2002) The fewer the changes that need to be made to any new solution, or to the established pattern of existing ones, when the new is to be implemented, the less additional investment is required. In turn this might not have any major effects on the total revenue, but neither will it on the costs. (Håkansson & Waluszewski, eds., 2007)

On the other hand, the more changes that need to be made, the harder it will be to estimate the resulting ROI; as more radical or more encompassing adjustments need to be made for a new solution to be implemented, it will also require the involvement of several other connected companies, such as suppliers or customers, which, in one way or another, will become affected by the new. This will create unpredictable direct and indirect effects on the existing structure of investments, related resources (both material and immaterial), and connected actors. However, provided that it becomes a successful implementation, the necessary investments and increased costs might also result in substantially larger revenue than had the changes only been minor, as in the first example. (Ibid.)

There is thus a risk factor involved; even if minor changes are safer and more foreseeable, they may not lead to a large increase in returns. Larger changes, on the other hand, are more expensive and less manageable but may lead to a large increase in returns. Either way, implementing new solutions in a using setting is a matter of making them fit with those that already exist and creating positive "interactive effects" from doing so, regardless of how well it matches from the start. And it is how *the new* and

the established ultimately match which determines the economic benefits of *the new*, as well as how these benefits appear. Let us continue by applying the same measurement to the producing setting.

Producing New Solutions

In the decision to make use of new resources, or new combinations of existing resources, any producer has to develop a way for production to be realised without investment exceeding future prospect of ROI. (Håkansson & Waluszewski, eds., 2007) For this reason, the producer needs to consider the current production system and how a new solution might be manufactured using these existing investments, or by the introduction of as few new ones as possible. Or, as stated by Håkansson et al. (2009, p. 257):

> "The more that the new solution breaks with the pattern surrounding existing solutions, the more difficult it is to embed production of the new solution into that existing structure and the more expensive it will be."

Thus, in regard to ROI and how any new solution fits with the established ones, the producing setting must be subject to the same type of assessment as the using setting. However, the production of a new solution is not only a task involving the single producer, but also other connected companies, such as suppliers, sub-suppliers and not least customers, all of which will be directly or indirectly affected by the introduction of new investments. (Piore & Sabel, 1984; Gadde & Håkansson, 2001; Håkansson & Waluszewski, eds., 2007) As a supplier's revenue is provided by its customers, any company involved in producing a new solution will not only have to relate it to the potential users of the new product or service and how it will fit into this setting. The company will also have to consider how the new solution will fit into the current pattern of investment both internally and those previously made in relation to other specific actors such as suppliers, sub-suppliers and customers. (Utterback & Abernathy, 1975; Gadde & Håkansson, 2001) This pattern of investments crossing organisational borders is the result of interaction over time between these different actors. In order to make this interdependency more efficient, specific solutions, or combinations of resources, are made the focus of repeated investment. As these solutions are the result of chiselling out specific combinations of resources in relation to each other, this eventually makes them difficult to replace or to combine with other "outside" solutions. It thus becomes a network of interdependent solutions connected to a continual pattern of investments. (Gadde & Håkansson, 2001)

In industry, usually such solutions are connected to specific technologies which, through their frequent use and by being the focus of heavy

investments, have become tightly interconnected with the surrounding structure of technological and organisational resources. This implies that related equipment, routines and other solutions over time have become adjusted to fit a particular type of technology, which in turn means that any changes to or a replacement of such a technology requires large changes to the entire structure of solutions. (Håkansson & Waluszewski, 2002) Dosi (1982, p. 148) refers to this phenomenon as being locked into a "technological trajectory"; once particular types of technologies have become established through their widespread use and repeated investment, they will to a large extent define what is considered technological progress and what fits into the current technological context. Leaving the particular technological trajectory for the implementation of another type of solution or technology will therefore become very difficult, not to mention costly.

In turn this means that a replacement will not only affect the particular solution which is to be replaced, but all the long-term investments involving interconnected companies, practices and physical equipment directly or indirectly related to its use. (Håkansson & Waluszewski, 2002) Such established solutions, or "basic technologies", will therefore, through their connection to heavy investments, become the point of reference for the adoption of any new solution. (Dosi, 1982; Rosenberg, 1994; Håkansson & Waluszewski, 2002) Or as Håkansson and Waluszewski (2002, pp.47-48) put it:

> "In almost every industrial structure there are basic technologies, which, due to many and related investments carried out over a long time, are very costly to change towards new directions. [...] Since it is constructed and used by actors, it is continuously exposed to interaction processes, so it will always be exposed to new ideas. However, due to its heaviness, all changes have to be carried out in restricted steps, in certain stable directions building on the existing solutions."

The above citation implies that neither the producing nor the using structure surrounding specific solutions are static. Nevertheless, due to the investments made in a specific set of solutions, all changes that are made are in support of their continuation. (Ibid.) This suggests that in established producer-user relationships, interaction through repeated investments creates a structure of interdependent solutions. It further implies that any solution that has been developed *outside* this established structure (and which, therefore, has not been created with the sole purpose of forming a match between the producing/using structure and the new solution) will become difficult to implement. Next we will consider what holds for the development of new solutions, and the developing setting's relationship to the producing and using settings.

Developing New Solutions

Before anything new can be produced and used it first needs to be developed and thereby move from being just an idea to becoming something more concrete. In any particular case, this development might take place in close interaction with a producing and a using setting – for instance within the same company or in an established business relationship. However, it may also be the case that the developing setting is unrelated to production and use. Regardless of whether development is connected to production and use or not, empirical observation has shown that the development of new solutions is characterised by trial and error processes where different options and directions are tested simultaneously:

> "When developmental activities begin, the initial innovative idea soon proliferates into numerous ideas and activities that proceed in divergent, parallel, and convergent paths of development." (Van de Ven et al., 1999, p. 23)

This implies that the outcome of the development process or how it will be attained is never certain. (Dosi, 1982; Rosenberg, 1994; Håkansson et al., 2009) Also, it is often far less certain how that which will be developed later will be produced and used in a producing and a using setting, where it will need to interact with different sets of interdependent material and immaterial solutions. (Ibid.) Thus, in the search of possible functionalities of anything new, the development of new solutions is an "open" process of trying new directions and combinations. (Ibid; Van de Ven et al., 1999) However, if the new solution is ever to become produced and used, at some point its functionality will need to be defined and thus "locked" to some specific features; for a producing as well as a using setting to be able to derive economic benefit from producing and using the new solution, it cannot remain an open solution. (Håkansson & Waluszewski, eds., 2007)

It is generally acknowledged that the more radical the new solution is (i.e. the less related it is to any known solution), the more uncertain the potential for its development, production, and use will be. (See e.g. Rosenberg, 1994; Van de Ven et al., 1999; Tidd & Bessant, 2009) Thus, the more radical the newly developed solution is, the harder it will be to relate it to any existing producing and using setting. It is further assumed that, just as between the producing and using settings, the more knowledge that the developing setting has of the producing/using settings, the easier it will be to develop something useful to these settings. (Håkansson, 1989; Håkansson & Waluszewski, eds., 2007) Consequently, the "closer" the settings of use, production and development are to one another (in terms of being more familiar with each others' needs and technical and organisational prerequisites), the less challenging it will be to develop something which is

beneficial from both producing and using standpoints. (Håkansson, 1987; Håkansson, 1989) Next we will consider what this means when the developing setting is primarily involved in the production of scientific knowledge.

2.4 Developing New Scientific Solutions

Science as a Social Practice – How New Knowledge Becomes "Scientific"

Is there something unique about scientific knowledge compared to any other kind of knowledge? From an interactive perspective, just as with any other type of knowledge, scientific knowledge is socially embedded and thus contextual. This means that a particular type of knowledge or physical solution is not seen as scientific in its own right, but rather becomes such through a process of becoming embedded in the material and immaterial structures constituting what we call *science*. (See e.g. Latour & Woolgar, 1979; Latour, 1987; Bourdieu, 1988; Callon, 1995; Jasanoff, 2004; Widmalm, 2004; Widmalm, ed., 2008) Or as stated by Knorr Cetina (1995, pp. 143,152):

> "Empirical studies of scientific work in general have demonstrated the negotiability of the elements, the outcomes, and the procedures in knowledge production. [...] Scientific objects are not only 'technically' manufactured in laboratories but also inextricably, *symbolically* and *politically constructed*. For example, they are construed through literary techniques of persuasion that one finds embodied in scientific papers, through the political stratagems of scientists in forming alliances and mobilizing resources, or through the selections and decision translation that 'build' scientific findings from within."

This means that when a new solution has been developed though scientific research, it is not different from other solutions in the sense that it is "truer" or has been developed through the voice of *Nature*, but rather that it has become related to the structure of material and immaterial resources connected to the production of scientific knowledge. (Latour, 1987; Callon, 1995; Knorr Cetina, 1995)

A large part of scientific work is the effort of trying to transform new and uncertain statements into becoming established or "finished" science. (Ibid.) This means that there is a fundamental difference between established scientific knowledge and ongoing research; established scientific "facts" represent certainty and are thus more or less treated as given. Ongoing

research and thus the development of new solutions, on the other hand, deals with new and disputable statements or technical conditions, and thus is more uncertain. (Latour, 1987; Latour, 1998) In order to become stabilised into established scientific knowledge, these uncertain statements and solutions need to be activated by different actors and connected to already established material and immaterial solutions (ibid.; Knorr Cetina, 1995) This is put by Latour (1987, p. 103) in the following way:

> "The picture of technoscience […] is that of weak rhetoric becoming stronger and stronger as time passes, as laboratories get equipped, articles published and new resources brought to bear on harder and harder controversies."[9]

Bringing in the social aspect of scientific research, and thus stating that it is political or cultural, implies that, first, it is a *collective* phenomenon and second, its outcome is never *given*. (See e.g. Latour & Woolgar, 1979; Latour, 1987; Shapin, 1995) In practice, the collectiveness of scientific research means that whether a particular piece of new knowledge can be considered a contribution to science or not is settled through negotiations over time and space – a phenomenon which Latour (1987, p. 104) refers to as a "mobilisation of allies". These allies are not only other scientists, but belong to different "social worlds", which means that actors involved in economic, political or technical issues are co-determining the " […] definition of science and technology developments". (Knorr Cetina, 1995, p.153) From this perspective, the scientific production of knowledge is not a neutral process. Through a collective exploitation of new knowledge or solutions, the features of *the new* will change and create different effects in different contexts. Or as put by Latour (1987, p. 104):

> "Even in the best of cases, they [the allies] do not simply transmit it, but add elements of their own by modifying the argument, strengthening it and incorporating it into new contexts."

The assumption that knowledge and other types of resources are heterogeneous indicates that new statements or artefacts, whether labelled

[9] Latour's use of the word *technoscience* is in one aspect just a simpler way to articulate *science and technology* but also has a greater meaning as the concept blurs the boundaries between what is science and what is technology. As, according to Latour, the content of science never can be distinguished from that of the rest of society, the concept of technoscience demonstrates the involvement of not only scientists or "scientific knowledge" in that which we generally call science, but also other actors or "allies". Science, in his mind, should not be studied or viewed as an *outcome* but as an *activity*. Through this perspective he shows that the making of science involves a whole structure of allies and resources rather than the traditionally imagined small group of scientists, as before. (Latour, 1987, pp. 174-175)

scientific or otherwise, will be subject to interpretation. The meaning, or *use*, of new or established scientific knowledge is therefore never *given*, but is only a consequence of its combination with the social and material structures surrounding it. (Pinch & Bijker, 1987; Woolgar & Cooper, 1999; Jasanoff, ed., 2004) Thus, scientific solutions come about by being related to the context surrounding them; by gradually becoming anchored in the established social and material practices characterising scientific work, they are eventually accepted as science. Therefore, in order to fit in, or to be labelled "science", anything new is shaped in accordance with the surrounding structure of material and immaterial resources such as social relationships, different institutions, established technology and particular sources of knowledge. (Widmalm, ed., 2008)

One way in which this stabilisation of new statements or solutions takes place is through scientific publication. As a result of peer-review, publication stands as a verification of scientific significance, which in turn denotes the new piece of knowledge as a contribution to the stock of scientific knowledge. (Latour, 1987; Latour, 1998; Knorr Cetina, 1995; Stephan, 1996; Nowotny et al., 2005) The scientific publication stands as a material representation of the new statement or solution, and of its position within a particular discipline, which can be spread and thus become part of other disciplines and contexts:

> "The identification of discoveries and their 'authors' could not be stabilized without material devices and rules that codify the formulation of knowledge and its transmission. Thus the scientific article in its present form makes it possible to delimit a piece of information precisely, to organize its dissemination, to identify the authors who produced it, to date their contributions, and to mention what has been borrowed from other authors by means of quotations and citations." (Callon, 1995, p. 39)

To achieve publication can both be considered a goal in itself and as a means to stabilise new knowledge into becoming established scientific knowledge; by being granted a publication the new statement or solution is recognised or rewarded as being "scientific". Through this recognition it can become used by other actors and thus eventually stabilise into an established fact or artefact. (See e.g Latour, 1987; Callon, 1995; Knorr Cetina, 1995) There is also the perspective which considers publication as the means through which further research funding is given, and on which research careers are built – to advance as a scientist it becomes necessary to show productivity by publishing. (Fujimura, 1988; Dasgupta & David, 1994; Stephan, 1996)

Developing new statements or solutions through scientific research and establishing them as "facts" is thus to a large extent about relating them to existing scientific knowledge, in terms of using existing knowledge and established methods, but also to make new and unique contributions which

can be considered “advances”. To be considered a contribution, new statements also need to be highlighted as signifying something unique or different. (Polanyi, 1962; Jasanoff, ed., 2004) To use the words of Polanyi (1962, pp. 54), relating research to established scientific knowledge gives it “plausibility”, while revolting against it brings “originality” to the table. Thus, in some regard, both criteria should be present in order to make a valuable scientific statement or solution. (Ibid.) What does this mean when solutions, which have been developed through scientific research, are to be brought directly into business settings in terms of production and use? The next section deals with this particular phenomenon.

Embedding Scientific Solutions in a Business Setting

How scientific knowledge becomes part of creating new solutions within the economic sphere, and how it is related to the construction of technology, have been the topics of a vast number of empirical studies within research areas such as sociology, history of science and technology, as well as within business and management studies. (See e.g. Dasgupta & David, 1994; Basalla, 1988; Pinch & Bijker, 1987; Rosenberg, 1994; Mansfield, 1995) The indication of these studies is that the link between science and technology, and between science and industry, is non-linear and contextual. (Ibid.) As will be discussed, the production of scientific knowledge is thus not an isolated activity “serving” new knowledge to be applied elsewhere but takes place in interaction with technology and through the use of new solutions. Or, as stated by Rosenberg (1982, p. 153):

> “The growth of knowledge is much more cumulative and interactive than is realized, especially when it is thought of as a one-shot, once-and-for-all affair, with new scientific knowledge supposedly leading to technological applications - period. In fact, continuing experiences with a material in a new environment, subject to new stresses, throw up new problems not dealt with, or even anticipated, before.“

Although scientific research is often viewed as the primary foundation of new knowledge and technology, technology in itself and the use of technology is an equally, or perhaps an even more important source of new knowledge and technical solutions; when used in different contexts and interacting with different sets of material and immaterial resources, scientific knowledge and technical solutions will be subject to further development and accumulation of knowledge. (Dasgupta & David, 1994; Basalla, 1988; Rosenberg, 1994) This means that scientific research contributes to technology, but technology also contributes to scientific research, often in unimagined and tortuous ways. (Ibid.)

The mutual link between science and technology spans over time and space which in any particular case makes the definition of what counts as *science* and what counts as *technology* difficult to distinguish. (Ibid.) When science is involved in technological progress it is often knowledge which no longer is considered science – it is simply too old to be considered something of scientific importance. It is "previous" scientific knowledge which perhaps has been used in other contexts or simply has lain dormant until surrounding resources in the shape of technology or knowledge have made its technological implementation conceivable. (Ibid.) Much of the basic technological equipment we use today can, from a historical perspective, be argued to derive from scientific inventions and discoveries made centuries back in time. For instance, the laser, which builds on theory established by Einstein in 1916, but which was not developed as a technological innovation until the 1960s. (Rosenberg, 1994) Would we call this a scientific invention which was only subject to some product development after the basic scientific theory had been established?

Or radio communication – the origin of this technology can be traced back to the mathematical formulas expressing electromagnetic waves formulated by James Clerk Maxwell in the mid-nineteenth century. (Basalla, 1988) For radio communication to be put into use as a functioning technological system, as within the military by which it was first used forty years later, it required extensive development by various actors in making the original scientific theories into a functioning technology, as well as complementary technology and knowledge derived from its actual use. (Ibid.) Is this a scientific invention or the result of technological development?

A more recent example of this is how one of the main products of Pharmacia Biotech originated from several decades of interaction between academia and commercial production, both within Pharmacia and before that within other companies. The product, a gel used to separate proteins, could not have been realised without preceding scientific research tools, such as the ultracentrifuge (See Widmalm, 2004) and electrophoresis, or without another company becoming interested in using these techniques. (Waluszewski, 2004)

In these examples it can be seen that scientific research contributed to technology through a process of scientific knowledge becoming shaped and re-shaped by the requisites in the implementing environments; by being shaped by new requirements and needing to interact with different resources. However necessary, it was thus not the scientific knowledge that ultimately defined the "resulting" technological artefact and how this would relate to other knowledge and solutions, both material and immaterial. Rather it was the *use* of the scientific knowledge which spurred further development, the requirement of complementary knowledge, and technical equipment. In turn this will toss up new issues to be addressed through scientific research, for

instance how laser, radio communication or protein separation can be used for different purposes and be further developed.

This means that establishing something as scientific knowledge, and how it becomes a functioning and widely used artefact, are very different processes. This is also in line with the argument of Dasgupta & David (1994) who state that the organisation of production of scientific knowledge is suitable for the growth of the stock of scientific knowledge, but far less appropriate for the accumulation of economic growth "by commercially exploiting its potential for technological implementations". (Ibid., p. 518)

What is illustrated is that the step from something being of scientific significance to becoming something of economic importance involves a time factor, but perhaps even more importantly that it depends on the surrounding conditions, such as other knowledge, and technological or organisational circumstances. These are the surrounding conditions with which *the new* needs to interact to enable a possible implementation of that which at least once was labelled "science". (See e.g. Basalla, 1988; Rosenberg, 1994; Mansfield, 1995; Stephan, 1996; Waluszewski, 2004) It is thus a matter of *the new* needing to fit in with the surrounding material and immaterial resources; the more that it breaks with what already exists, the harder it will be to implement it in terms of production and use. (Håkansson & Waluszewski, eds., 2007) As in the example of radio communication or the protein separating gel, these ideas could not have become widely used solutions without a surrounding producing and using setting where they could be made to fit in and which could support their continuing development into economically useful artefacts. As earlier discussed, this further suggests that the more groundbreaking or radical the idea, as with "cutting edge" science, the harder it should be to relate to it to any existing setting of production or use.

It has so far been indicated that for scientific knowledge to have an economic impact it needs to be used in different contexts and thus users play an important part in embedding this knowledge into established or new solutions. A more direct example of how such embedding requires the involvement of users is that of new scientific instrumentation. Here it has been shown that scientific knowledge is the primary source for the development of new commercial products and that these are highly user-driven processes often instigated by scientists themselves. (See e.g. von Hippel, 1976: Rosenberg, 1982; von Hippel, 1988; Riggs & von Hippel, 1994) Being directly involved in determining what can be measured, tested and experimented with, this type of equipment is of high scientific importance and therefore prioritised by scientists. To embed the solutions developed by the scientists into production and to create a use which will be able to carry the costs of large-scale production, the manufacturers are dependent on the scientists to further develop the equipment through using and testing. Thus, in order to develop and produce products based directly on

scientific knowledge that will actually become used, the manufacturers need to work closely with the actual users, in this case the scientists. However, even though initiative and most of the development of the new or improved instrument happens through scientific research, industry is essential for the production and diffusion of the new solutions. (Ibid.)

The described processes of embedding scientific knowledge in technical solutions suggests that users play an important role in shaping commercially viable products originally based on scientific knowledge. It has also been indicated that the relationship between scientific development and industrial production and use is complex as well as highly unpredictable; in each context any new solution needs to interact with different types of material and immaterial resources which in turn will determine if it fits in and whether it has possible benefits in these contexts. Also, the less that the new solution is related to established settings of production and use, the harder it will be to embed into these settings. The following section will deal specifically with the theoretical tool developed within the IMP research tradition, which has been used in this study to investigate and analyse the interaction between a new solution and these surrounding material and immaterial resources.

2.5 An Interactive Perspective on Material and Immaterial Resources

The Development of a Research Tool to Capture Interaction

In mid-1970, the first IMP study focusing on the interactive nature of the business landscape began and its findings have since inspired a long line of studies emphasising the interdependent and heterogeneous character of business actors, the activities they take part in, and the resources that are exchanged. (See e.g. Håkansson, ed., 1982; Laage-Hellman, 1987; Waluszewski, 1989; Lundgren, 1991; Axelsson & Easton, 1992; Håkansson & Snehota, 1995; Gressetvold, 2004) The inspiration for the very first study was the inability of existing economic theory to explain empirical observations regarding companies' inclination to form long-term relationships in their exchange of products and services. Instead of exploiting the price mechanism and playing-off different suppliers against each other for every business transaction, companies seemed to engage in close and long lasting relationships, and thus commit their resources to a specific set of other companies. (Håkansson, 1989; Håkansson et al., 2009) Therefore the development of a theoretical tool, which could capture the interaction taking place between companies, appeared essential. (Ibid.) To understand the rationale behind companies' interdependence and thus

needing to interact, *dyads*, or relationships between specific sets of two companies, were particularly studied. (See e.g. Håkansson, ed., 1982; Turnbull & Valla, 1986)

However, to further understand the structure of business life, the greater network – which every company, as a result of its relationship to any one or several other companies, was embedded in – needed to be understood. It was shown that in order to gain resources from other companies, and also to reduce the long-term costs of needing to interact across organisational borders, companies were making physical and organisational adaptations to each other. Interaction between companies through the acquirement of knowledge or performing technical or organisational adaptations thus facilitated the situation of interdependency by enhancing the compatibility between the companies' resources and activities. (Ford et al., 1998; Gadde & Håkansson, 2001)

However, the business landscape also appeared to consist of connections between technical solutions, between production or other activities, and between other material and immaterial resources not represented by relationships; as they influenced which type of company decisions that could be made and had an effect on which types of new material or immaterial solutions that could be brought in, such connections also seemed essential to explain. These empirical observations resulted in the *ARA model*. (See e.g. Håkansson & Johanson, 1992; Håkansson & Snehota, 1995; Håkansson & Waluszewski, 2002)

The ARA model characterises what is happening within and between companies in terms of three different layers: *activities*, *resources* and *actors*. (Ibid.) The basic assumptions are that companies exchange *resources*, which can be both physical and social. These resources, which are assumed to be *heterogeneous*, (and thus obtain different features depending on the resources they are interacting with) are combined across company borders. The *activities* that are performed through the use of these resources, such as production, product development or logistics, are also linked across company borders. In turn this implies that the *actors*, representing particular resource combinations and linked activities, are interrelated and thus are part of a structure of connected resources and activities crossing over company borders. Through analysis of these layers of business networks, actors representing directly related resources and activities as well as those more distantly related, such as governmental and non-governmental authorities, can be identified. (Håkansson & Waluszewski, 2002)

Thus, the model builds on the assumption that the single company does not itself possess all the resources needed in order for it to move forward; instead some of these must be provided by other companies and organisations which in turn also are assumed to be incomplete in terms of resources. It is this interdependency which creates the need to *interact* and

which, in accordance with the following citation from Håkansson and Snehota (2006, p. 265), defines the single company:

> "It is through its relationships with others that the distinctive capabilities of an organization are acquired and developed. It is therefore the activities taking place between the organization and the other parties, rather than activities within the organization itself, which are the determinants of the bargaining position and of the overall effectiveness of the organization in achieving its goals."

Because of this interdependency, which stretches over time and space, it is not what the single company achieves in terms of new technologies, products, or organisational restructuring which create benefits, but what possibilities any change creates *in combination* with its surrounding conditions, such as related companies, and existing material and immaterial solutions. Interaction between companies is thus a way to deal with interdependency in an attempt to improve resource combinations and activity links. (Ibid.) This makes the realisation of innovation a matter of making a novelty fit with the existing structure of actors, activities and resources. (Ibid.; Håkansson & Waluszewski, eds., 2007) The next section will present the specific tool which has been used in this study to examine what happens between material and immaterial resources when something new is brought in – the *4R model*.

The 4R Model - Catching the "In-Betweens"

To investigate the innovation process from an interactive perspective, and to be able to study material and immaterial solutions regardless of whether they are represented by business or non-business actors, a tool which can capture how the connection between material and immaterial solutions change over time is needed. One such tool is the 4R model, which assumes that each resource, material or immaterial, constitutes a part of a larger network of resources represented by various actors. (Håkansson & Waluszewski, 2002)

From the standpoint of the ARA model, the 4R model was developed within the framework of IMP to allow for the study of the physical and organisational resources assumed as being involved in the interaction processes of different actors relating and adapting to each other. (Ibid.: Baraldi, 2003) It distinctly divides the resources represented by any particular company or organisation into four resource categories; two are mainly physical: (a) *products*, and (b) *facilities*, which represent (a) the products of any particular organisation as the result of producer-user interaction, and (b) the facilities or equipment used to produce these products, often in combination with other facilities in an effort to cut production costs. The other two are mainly organisational: (c) *organisational*

units, and (d) *organisational relationships*, which represents (c) the involved people in the company or organisation in terms of their knowledge, working routines, and their ability to cooperate with other organisations, as well as other social attributes, and (d) the relationships between any other companies or organisations which can be used to create more efficient resource combinations or activity links over time. (For a detailed discussion see Håkansson & Waluszewski, 2002)

It is further assumed that resources exist in a constant interaction, from which they over time develop specific *resource interfaces* in relation to each other. For instance, any product that is related to a particular set of production facilities will develop specific physical features, to which in turn any user has to relate. Also, due to the availability of specific technical components, these production facilities will as a result have particular qualities and so on. However, any physical resource or any combination of physical resources can also create organisational effects – for instance, if a new technical solution in a production process requires a new type of knowledge, or activates a dormant relationship which was of little use in the past. Also, as resources become related to each other, or adapt, their features will become adjusted to a particular resource combination and as a consequence be less adjusted to any other resource combination. Put differently, the features of any resource are seen as being determined by its interface with the resources it is interacting with, and these will define how the resource can be utilised, both directly and indirectly, as well as how it can be combined with other resources. (Håkansson & Waluszewski, 2002; Jahre et al., 2006)

The interface between any two resources represents their "contact surface" and determines which qualities are brought out from each resource; this stems from the assumption of *resource heterogeneity*. The concept implies that the features of a resource are never *given*; rather they are obtained through their combination with other resources. (See e.g. Penrose, 1959; Rosenberg, 1982; Holmen, 2001) In practice this means that it is not the resource in itself that holds any benefits, rather, these are created in interaction with other resources, and lay in the services that can be provided from them. In turn this means that a particular resource can take on different features in different resource constellations and therefore provide different services depending on the particular resource combination. (Ibid.; Håkansson & Waluszewski, eds., 2007)

In this view, it is how resources (such as particular knowledge, technology, production systems or transportation solutions) interact with surrounding structures of other resources which determines their use and therefore neither a single resource nor a combination of resources can be assigned an objective value. (Baraldi, 2003; Bengtson & Håkansson, 2008) In terms of costs, a new resource's compatibility with existing ones will determine the investments needed to activate it in its new setting; the more

that the new resource breaks with the current pattern of investments and resources, the more expensive it will be to activate it. In terms of reimbursements, a resource's possible economic benefit within any setting will be determined by the services that can be provided through its combination with the existing structure of resources. (Håkansson & Waluszewski, 2004) Therefore, in each context, comprised of a particular established structure of resources, any new solution will be assessed in terms of the economic benefits that can be derived through its combination with these existing resources. Resource interaction thus implies the relational use or value of each resource or combination of resources; through interaction, each resource develops particular features in relation to a specific set of other resources which will determine its economic benefits within that and other resource combinations. In addition, this connects each resource to a number of indirectly related interfaces which, in one way or another, will become affected and cause changes in related resources. (Håkansson & Waluszewski, 2002; Brekke, 2009; Hoholm, 2009)

The perspective of resource interaction is an attempt to observe what happens in the "in-betweens" or, put differently, how changes to one resource affects each directly or indirectly related resource, and thereby create economic effects. When a technical component is replaced by another, what effects does this create on related production equipment, suppliers, and logistical solutions? When a company decides to work with a new raw material, how does this affect the related production process, the work routines, or the existing material or immaterial solutions within the customer setting? All these changes represent economic consequences. The 4R model is thus a tool that can be used to trace and analyse the economic effects of technical and organisational changes. It is the very interplay or relationship between the unit of analysis and context which is scrutinised and the central issue is how *change,* i.e. how new resources or new combinations of established resources, comes about and generates direct and indirect economic consequences. (Ibid.)

The heart of this study is the process that occurs when a *new* solution is forced to *interact* with *established* resources in terms of activated physical and organisational solutions. Furthermore, in this process, new relationships and new units or groups of people working together are formed, which implies that the interaction between individuals and between organisations is also of interest. In order to catch this process (of new combinations of solutions being formed or clashing and new relationships becoming established or dissolving), it is necessary to learn what happens *between* and *within* these different entities as they become related, and which economic effects it creates. The following chapter will detail the research process which resulted in this thesis, and thus how the previously described research tool has affected both the process and the results of the investigation.

3 The Research Process – Method and Methodology

In this chapter I will detail the research process that led to this thesis, starting from when I was first introduced to the story of pyrosequencing. I will explain the method which has been used to perform the case study as well as the methodology which has guided this approach. On the issue of what constitutes a suitable case study, opinion is generally divided. There is little consensus on issues such as what the appropriate boundaries are, or whether cases should be made up of theoretical constructs or strictly empirical. (Ragin & Becker, 1992) Therefore, the definition of a case study cannot be treated as given. For that reason, by accounting for the methodological choices that were made at the outset and during the investigation, as well as for the research journey of investigating the chosen innovation process, this is a chapter primarily on what was specific about this case study, rather than what can be stated about case studies in general.

3.1 Why Study Pyrosequencing?

The idea for a study on the commercial use of scientific knowledge originated in the interesting story of pyrosequencing, which was introduced to me long before I ever became a PhD student. The account of how a single researcher's struggle for attention for his new sequencing method turned into a commercial venture worth several hundred million Euros, first caught my attention during an undergraduate course within the Department of History of Science and Ideas at Uppsala University in 2002. Here, as part of a group I studied the rise of the (then rather new) company Pyrosequencing, and retrospectively followed its development from scientific idea to commercial product. Even though I did not possess the theoretical or analytical tools as while performing this dissertation study, I was still fascinated by the story and never really stopped thinking about it. Also, being an engineering student and taking courses within the area of biotechnology, I was not only interested in the organisational aspects of this specific commercialisation process, but also in the technical and methodological transformation of a

research group's research results within a biotechnical laboratory into a commercially available analytical instrument. Therefore, when I was given the opportunity to write a C-level thesis within the Department of Business Studies one year later, there was no question what I would write about. This time I went deeper into the development process of how the research results had been obtained, and how the research group had come into contact with the different types of commercialisation opportunities which resulted in a venture-capital financed company. Back then, my view of it all was that of an innovation process with different phases within which diverse actors played certain key roles in making the scientific research result into a commercial product.

When getting accepted as a PhD student at the Department of Business Studies and the Uppsala Science and Technology Studies Centre in 2005, I was involved in a larger study of the emergence of life-science based companies in the Uppsala region. Here, 25 companies and their relationships to the academic and business world had been mapped for the previous five years. (Waluszewski, 2004) One of the companies was Pyrosequencing, which by this time turned out not to have become the success story that everybody thought it would. Having completed the study and then going on to formulate my PhD project, my focus was set on a similar investigation, perhaps not one which would include as many companies, but nevertheless some kind of study investigating the relationship between science and industry. Going back and forth with this kind of idea, it suddenly became strikingly obvious that my dissertation study should focus on a case which was an excellent example of the problems inherent in attempting to commercialise scientific solutions – a case of which I had been aware for quite some time: pyrosequencing. During the few years that I had been aware of its existence as a scientific breakthrough, a company and a product, its innovation process had taken a turn from "commercial success" to "business failure" and the obvious question was: *why*? Thus, unlike the first two times I had committed to the study of this commercialisation story, the company was now in trouble. What had happened with the former success story and who was to blame? Could it be that someone was *responsible* for this "failure", or was there something else at stake here?

Going into the empirical investigation with the theoretical approach of *resource interaction*, it soon became clear that in order to understand the apparent paradox of not being able to accumulate profits from a well-financed research instrument within biotechnology, the study needed to outline the different characteristics of the scientific development, commercial production, and use of this new technical solution. In really getting a sense of what it meant to combine efforts within scientific research and business, in the attempt to achieve a science-based innovation, the study was designed as an in-depth, single-case study, which hopefully would illustrate both the possibilities and the difficulties of such a task, as well as

exploring the relationship between new knowledge or technology and context. In this new light it became apparent what the commercialisation of pyrosequencing was really about; it was not a matter of someone making a mistake or something going wrong, rather it was down to the difficulty of combining a technical novelty with already existing solutions. It was also a case of bringing together very different environments in terms of the resources that were involved and acted as driving forces. Thus, the case of pyrosequencing demonstrates not only the challenges of developing, producing and creating a use for new technical solutions, but also what is at stake when resources within scientific research and business are combined.

3.2 The Research Tools or the Embedded Research Process

An Interactive Interpretation

Carrying out a thesis based on a theoretical view of new knowledge and technical solutions as contextual, and its development as a complex and non-linear process, has implications not only for the results of this study but also for how the research process of performing the study must be explained. As the ontological focus is set on resources being *heterogeneous* instead of *homogenous*, and thus context dependent, and facts are seen as *constructed* rather than the object of *discovery*, the conclusions drawn from the empirical material will not be treated as the outcome of a pre-determined work order, nor will they be taken to apply to *any* context or situation. Rather, this case should be regarded as a specific example of the direct commercialisation of scientific knowledge in a world in which science and technology have been allocated all the more important roles, not only in developing new knowledge and providing new solutions, but also in directly promoting economic growth. Moreover, the further understanding, which I hope this study will provide, rests on the view that the use of new solutions is determined by their compatibility with those that are already established.

Moving away from an understanding of the connection between science, technology and innovation as being in any way linear or simplistic, the process of creating new products, services or companies is often described as "messy". (Håkansson & Waluszewski, 2002) However, according to Håkansson and Waluszewski (2002) it is the view of this process as not fitting into the idea of linearity that makes it *appear* disordered and irrational. If the assumption is that any development process "[…] starts with intentions and ends up in solutions which correspond to these" (ibid, p. 7), then it will be difficult to come to grips with any process involving actors,

both as individuals or as organisations. This is one of the perspectives I take on my case study and can also be applied to the research process of this thesis; it has not followed a linear path seeking of the answer to one particular research question. Rather it has been a learning process within which some questions were particularly important at the outset and which led to new ones being posed and pursued. According to Voss et al. (2002), this is a recurring trait of the case research approach:

> "When conducting case-based research it is not uncommon for the research question to evolve over time and for the constructs to be modified, developed or abandoned during the course of the research." (Ibid., p. 201)

However, embracing that *interaction* is at the heart of all development, resulting in the use of new solutions, and taking this as an explicit research standpoint, there has never been a doubt of what the overall focus of this research study would be or the type of research tools that should be used to perform it. In outlining the development of a scientific solution and its embedding in the business landscape in terms of the combination of different resources, the research tools used in this study were designed to follow such particular resource elements and the interaction between them. Resource interaction has thus been a cornerstone in this study and has worked as a lens through which the empirical material has been viewed. From this perspective, we live in a simultaneously socially and physically fashioned world in which the interaction between tangible and intangible entities such as people, facts and artefacts, creates the game plan for how "things work". It is this perspective that has guided both my research work and my results towards an interactive interpretation.

Using the 4R Model

This thesis is based on an in-depth case study and, as it is necessary at some point in the process of building a case to decide what the particular research focus is and how it should be presented, theoretical tools that can be used to pinpoint this focus and present a certain view are needed. (Voss et al., 2002) Thus, on the general basis mentioned above, the *4R model*, developed within the framework of IMP (See Håkansson & Waluszewski, 2002), has been adopted as a more explicit research tool that has guided the content of the investigation in terms of interview questions and their transcription. It has also shaped the presentation of the empirical material as well as the analysis of the case. This implies that in general, once any such tool has been chosen, the study will bear its mark in terms of what aspects of a phenomenon that

will be studied and how they will be viewed and explained. As suggested by Burke (1992), such "tools" are never neutral, but hold certain stipulations which need to be taken into careful consideration in order for them to be applied properly. This is unavoidable when using any theory and can also be deemed an advantage in case study research, as basing the case study on an explicit and well-grounded theoretical foundation can improve the "explanatory power" of the case. (Dubois & Gadde, 2002, p. 555)

The 4R model is a tool which distinctly divides the resources involved in using, producing and developing new solutions, as well as maintaining them, into four resource categories of which two belong to the social or organisational sphere and the other two to the physical or material one. It is further assumed that resources are interrelated and thus exist only as part of *resource combinations*, in which they develop in relation to each other over time. This creates specific resource structures changing over time and stretching over organisational borders. (Håkansson & Waluszewski, 2002)

Here, in a study of the attempt to achieve innovation based on scientific research, the model has been used as a method to investigate how related material and immaterial resources "co-produce" different contexts and, more specifically, what happens when a resource developed in one context is to be produced and used in other contexts. In the empirical investigation, each context has thus been studied and evaluated from the viewpoint of its organisational and physical resources. An example of this viewpoint is how I modelled the academic development unit in my case as consisting of a specific set of research equipment, a set of methods to assure scientific quality, a certain type of knowledge as well as internal/external relationships shaping the research direction and thus resulting in the development of particular kinds of intellectual and physical resources. From these different existing resources I formulated a specific organisational and physical structure which I assumed to characterise the research environment being involved in developing the pyrosequencing method. The same was done with the other settings in the study.

As resource interaction is assumed to take place across organisational borders, the resource structures of the interacting actors in the empirical case were specified both in terms of their inherent qualities and how they relate to each other. The following section will further detail the research design and how it was applied to the analysis of the case of pyrosequencing.

3.3 Investigating Pyrosequencing

The Pre-Study

The case study of pyrosequencing is based on a pre-study which investigated the relationship between science and industry, looking at more than 25 bio- and meditech companies in the Uppsala region. (Waluszewski, 2004) The project's mission was to follow these small-to-midsize companies for a period of five years, from the year 2000, during which time their economic, organisational and technological development would be investigated. About half of these companies were defined as biotech tooling companies. Entering the project in early 2005, my assignment was to carry out the final round of interviews within these specific companies and perform a concluding assessment of their development for the total duration of the study. Here I performed interviews with people in key positions within the companies. Not only did this study provide me with a good insight of the biotech industry in Uppsala, but it also informed me about the general conditions for starting biotech ventures based on new scientific solutions and on the basis of different types of financing, such as venture capital.

The study showed that in spite of large investments resulting in rather sophisticated technical solutions, few of the companies had managed to grow into sustainable businesses during the study period. This indicated that the problem did not lie in the scarcity of capital or technological solutions, but in the difficulty of transforming such resources into profitable, usable products; thus the problem lay in creating a *use* for the new solutions.

Studying Pyrosequencing from a Resource Interaction Point of View

The general purpose of this thesis was to try to capture, in terms of the present resource elements, what is specific about the process of attempting to achieve innovation based on new scientific research. As focus lies on how the surrounding conditions, from the aspect of resource structure, shape the introduction of new solutions, it is a study of how context matters. Therefore, from a methodological perspective, the process of transforming a new scientific solution into a business innovation needed to be studied on a qualitative level of gaining a greater understanding of the people and thus knowledge involved, the technical equipment and relationships assisting or hindering the introduction of the new.[10]

[10] As the concept *qualitative study*, due to its many dissimilar interpretations, can be problematic (Eisenhardt & Graebner, 2007) I only use it here to refer to the collected data, in the shape of interviews, articles and other secondary material, and not the research approach per se. The nature of my research approach, which might be referred to as an interactive approach and interpretation, will rather be outlined in the account of my research journey of exploring the chosen case.

The proximity to real-life situations which the case study approach offers makes it possible to gain *context dependent* knowledge which can tell us how specific processes developed and for which specific reasons. (Flyvbjerg, 2006) Conducting single, in-depth case studies is thus about *learning* about a particular process, situation or phenomenon, rather than *proving* it; the use of a case study is on the level of gaining concrete experience and knowledge of that which is being studied, not of generalising on the basis of rule-based knowledge. (Ibid.) Neither is it a matter of being able to capture *everything*, as all any researcher ever can hope for is to capture fragments of the "reality" of a process, an organisation or a situation, and there have to be conscious decisions about what aspects are to be investigated and analysed. (Dubois & Gadde, 2002; Håkansson & Waluszewski, 2002) More specifically, this enables studies investigating the underlying reasons for certain actions or events. (Dubois & Araujo, 2004) As Eisenhardt (1989) states, case studies are particularly appropriate for studying the question of *why* an event or action occurs. This is also supported by Yin (1994) who, in addition, considers *how* something happens as a contribution of the case study approach.

Investigating the story of pyrosequencing as an in-depth case study and focusing on the heterogeneity of resources thus made it possible to explore the resource interaction mechanisms through which the specific innovation process developed. Also, case studies are, as indicated, particularly suited for examining the role of context:

> "The interaction between a phenomenon and its context is best understood through in-depth case studies." (Dubois & Gadde, 2002, p. 554)

In my case this involved understanding why the creation of the new sequencing method had been relevant within its originating academic environment of KTH (The Royal Institute of Technology). I had to learn what kind of knowledge, and thus people, was involved in its making, why this kind of research was considered significant, and which other types of scientific methods and knowledge it interacted with and how. How did a particular set of enzymes become useful in decoding DNA? To what end was it a valuable scientific research result and how was it achieved? Put differently, what characterised the developing setting involved in this scientific research and how did the sequencing method contribute to this setting? To answer this question, the structure of the research and development of the pyrosequencing method in terms of the people involved and their knowledge, research methods, physical equipment and collaborations, was studied. Also, to be able to give a general overview of genetic sequencing, and how such research had advanced in the past, a part study was devoted to a history of genetics and some of its methodological milestones.

Another essential component in understanding how this particular sequencing method came about lay in appreciating the larger and prevailing scientific context in which the development took place. The particular temporal setting is often referred to as the *era of genomics* in which the Human Genome Organisation Project (HUGO) – which operated between 1990 and 2003 – was the main driving force. The project's mission was to sequence the full genetic content of the human body and in so doing gain a more profound knowledge of what genetically constitutes us as human beings. The challenges and the short-term results of the HUGO project, as well as the history leading up to it, demonstrate the scientific and technological situation of the time for the use, production and development of the pyrosequencing method. Consequently, learning about the resources involved in enabling such a project was highly relevant in appreciating the development setting from which the new sequencing method originated, as well as of the financial expectations of genetic sequencing which the business world pronounced at the time.

To comprehend why this new scientific method concerning DNA sequencing became involved in not only one but several business ventures, it was important to start evaluating the utilisation of the new scientific method in terms of business structure. It was vital to learn about the people within these environments who adopted it from a business perspective, about the knowledge base on which it was taken up, and how it was characterised as a commercial product. Why was it that the function of a few enzymes suddenly became relevant to a producing setting within business? To what degree was the investment in this new sequencing method considered valuable and how was it executed? In other words, what characterised the producing settings within business where a product based on the scientific method was formed, and how did it contribute to such settings? With this question in mind, I particularly studied the business endeavour which, through venture capital, created a company and a product based on the new sequencing method. In learning why and how this was done, both the financing venture capital firm and the resulting company were investigated to further understand the structure through which the commercial product of pyrosequencing was produced. However, I also studied the resources involved in first attempting to make it part of an already established company, as well as how it much later was given a new function as an embedded component in another product.

In order to understand what happened within these producing settings it was also important to learn about the users, the actual customers, of the commercial product. Without understanding what type of use arose from commercialising the new scientific solution, it would be impossible to grasp the rationale of its economic effects and consequently the characteristics of embedding scientific resources in the business landscape. Therefore, a selection of user environments in which the commercial instrument of

pyrosequencing was brought into use was also investigated. Here, the question of how the pyrosequencing product was incorporated (or not) into the customer contexts necessitated understanding these users in terms of existing knowledge, their current use of established technical solutions and working methods, as well as external relationships, earlier investments and activity goals.

The question of why the new sequencing instrument actually became indispensable to some, while others found it rather useless or simply uninteresting, became central as it touches on the core of what it means to bring something new to a setting characterised by a number of existing solutions, both material and immaterial. The question posed was thus: what characterised the different user environments, and how (if at all) did the commercial solution created by the company contribute to these users? In trying to comprehend the use of the pyrosequencing product within established user structures, a selection of present and former customers was studied. The thesis thus includes customers which have managed to combine the new product with their existing resources, but also an example of one that has not. The purpose of studying this diverse set of users is to demonstrate both the untidiness and the uncertainties of incorporating new technical solutions based on new scientific knowledge and how they affect and are affected by the surrounding resource structure. Next I will address the primary and secondary sources that were used to gain the necessary empirical material in order to perform the study.

3.4 Data Sources

Primary Sources

Interviews as Chief Data Source

Semi-structured interviews were the chief primary source and were very important for studying the chosen innovation process, but also to pinpoint the *perspectives* dominating each of the settings involved in using, producing and developing the pyrosequencing method. The interviews were thus a tool in identifying the different resources involved in developing, commercialising and using the pyrosequencing method, but also to establish the significance of these resources for the different parties involved. The prepared interview questions were designed in accordance with the 4R model, which in practice meant that the different settings of use, production and development involved in the innovation process were pinpointed in terms of existing knowledge, work routines, and relationships, but also products and physical equipment. This in turn meant that what was investigated was the *resource structure* of each setting involved.

On average, each interview lasted an hour and began with the respondents replying to the prepared questions; this, however, often led to a more open discussion between me and the respondent. The interviews were recorded and then transcribed more or less directly after the interview was finished. In several cases, the same respondent was interviewed on more than one occasion. For different reasons, usually due to geographical distance, some of the interviews had to be carried out through email correspondence.

With a Master of Science degree, and having specialised in biological systems, I had the great advantage of having insight into the technical and biological issues which the respondents often discussed during the interviews. This factor greatly facilitated the interview as it made it possible for the respondents to communicate in technical language and thus use the terms they apply in their everyday work. A further assisting factor was my earlier experience, through my educational background in engineering, of using several of the different laboratory techniques which frequently appeared in the interview discussions. This experience gave me additional insight into the activities and procedures mentioned by the respondents.

Different Aspects of Interviews

There are, however, problematic aspects of using interviews as a chief source, not least due to the effect of the respondent talking about events in retrospect; as the person in question can have poor recollection, and may even have generated false memories of the events which took place. (Eisenhardt & Graebner, 2007; Leonard-Barton, 1990) Furthermore, an individual might have motives to explain some events or actions in a certain manner, which must also be borne in mind (ibid.). However, as suggested by Eisenhardt and Graebner (2007), because of my use of at least two sources for every event analysed in the thesis, either by using two respondents, or one respondent and one secondary source, this problem has been reduced. In addition, as the perspective of the individuals acting within each setting shows the settings' inherently subjective nature, the effect of an individual explaining particular events or actions in a certain manner is interesting in its own right, and gives explanatory power to the element of context dependence.

Also, turning the retrospective factor into something positive, there is the possibility that respondents, some time after the events took place, found it easier, or less of a matter of conscience, to honestly tell their actual experience; they were no longer a part of the context they were discussing and may therefore have gained a fuller perspective on events.

An interesting aspect of interviewing the respondents within this study, and the pre-study, several times during the course of more than five years, has been that some of them have changed professional positions or left the

organisations of which they were formerly a part. This often resulted in the aforementioned effect: once they had left an organisation and moved on to the next, they reflected somewhat differently upon their own and others actions than before leaving. Another important aspect which has also influenced the results of the interviews and the investigation in general is that several of the events which are mentioned in this study took place during the actual investigation, specifically those that took place from 2005 onwards. This has thus given some of the respondents the opportunity to reflect on, and give their reactions to, the process as it was taking place.

Selecting Respondents

As it is the involved material and immaterial resources that has been the focus of this investigation, finding the right respondents was a matter of identifying representatives for the resources involved in the use, production and development of the pyrosequencing method. It was thus a process of identifying and interviewing "key people" within each setting representing resources directly or indirectly affecting the innovation process. The initial interviews included individuals who could be considered very central in respectively using, producing and developing the pyrosequencing method: (i) the original academic inventor, (ii) the person who initiated the two commercialisation processes and became the first informal CEO of the new start-up company, and (iii) a very early and close customer/collaborator of the start-up company. These interviews led me to other individuals who were involved, and who represented significant resources, in the process.

It was not known beforehand which the relevant individuals or resources were, which meant that during the investigation an evolving network of individuals, organisations and resources developed, resulting in a different network than initially envisaged in which certain individuals, organisations and resources were more (or less) essential or central than initially expected. Consequently, the interviews were very important in finding further respondents who might have been relevant for the study. In one particular example, an individual who was assumed mainly important from an academic research point of view, turned out to have been far more significant in terms of mobilising capital and promoting the new solution outside the walls of academia. This displayed a formerly "hidden" connection between the developing setting and the producing settings within business. This example illustrates the sometimes evolving representation of actors, and consequently resources and activities, which also formed during this empirical investigation and which in turn led to the further study of other individuals, organisations, resources or directions than initially expected.

A Special Seminar with the Developing Setting

In order to gain a greater understanding of the developing environment of the pyrosequencing method, a special seminar arranged by me and my supervisor was held on the issue of developing and commercialising pyrosequencing at the Department of Biochemistry at KTH, where the main scientific development took place. Here, several of the people involved in developing the method, and also testing the commercial product, took part and discussed their views on both the academic development work around the sequencing method and its commercial use. The seminar gave an additional insight into the continuing research interest in the sequencing method and its role as a "research success" within the department.

Secondary Sources

Next to the primary sources mentioned above, the secondary source of research articles authored both by those in the developing setting at KTH and by academic users, has been very important in demonstrating the *academic* or *scientific* view of the development and use of the pyrosequencing method in terms of its scientific significance. More than 50 scientific publications have been studied for this purpose. On examination of which type of publications they have been granted as a direct or indirect result of the use of the pyrosequencing method, and in what journals, the articles display not only the involvement of the method within these academic environments but also its role in these departments' research work. In addition, the publications have served as a verification of the accounts given by the respondents. Here, my skills within the biological and biotechnical area once again were important in understanding the relevance of particular advancements and concepts. By having knowledge about the technical issues brought up in the text, I could use the content of the scientific publications as indicators of the technical and scientific value of the research results.[11]

Also, the secondary sources of annual reports and press releases from Pyrosequencing, and later Biotage (and other involved companies), have worked both as verifiers of the accounts given by the respondents, as well as a display of the new company's image, which its management and board wanted to make public. Other press releases from various organisations, such as the Royal Swedish Academy of Engineering Sciences (IVA) or companies connected to Pyrosequencing, regarding the scientific as well as commercial progress of the new method and product, have been used as

[11] To further highlight the use of these publications, they are referred to as "Technical Reports" in the list of references.

indicators of the function of the advancements in the scientific and economic spheres respectively.

Lastly, to be able to give a brief account of some of the milestones within the genetics research area, and the development of the HUGO project, both scientific and newspaper articles, as well as literature engaging in describing these events, have been used. In regard to the HUGO project, the articles and books were often authored by individuals personally involved in the project. This is not the same as saying that these writings better display the "truth" about what happened, but rather that it provides an insight of how the project was *viewed* from the inside and within the scientific sphere. This is highly relevant for the purpose of this thesis as it is not only intended to describe the activated structures of the technological and organisational development of this project, but also the expectations and ideas which were in play and had a big part in influencing the concurrent scientific research and business projects concerning genetics and biotechnology in general.

As a concluding remark, it should also be noted that as technical reviewers, both the original inventor of the pyrosequencing method, Pål Nyrén, and a former employee at Pyrosequencing have read and commented on the technical and financial details of the empirical chapters of this thesis.

4 The Scientific Development of Pyrosequencing

In the following three empirical chapters I account for the shaping of pyrosequencing as a scientific resource, its interaction with business resources and its subsequent embedding in user environments as a commercial product. In this first empirical chapter the development of the new sequencing method taking place mainly within the academic setting of The Royal Institute of Technology (KTH) is examined. This chapter also gives a view of what was happening in the broader scientific arena during a period characterised by questions concerning the HUGO project, which set out to map the entire human genome. In addition, this chapter will provide a few insights about the scientific structure of genetics in which the pyrosequencing method was brought forth, by an account of the development of genetic research and some of its methodological milestones.

4.1 The Use of an Established Method Resulting in the Development of a New One

In 1986, an idea of a new way of performing DNA sequencing or reading genetic code occurred to a Swedish biochemical researcher, Pål Nyrén, while attending his postdoctoral year at Cambridge University. At Cambridge he was introduced to the most established way of doing sequencing, the Sanger method, for the very first time. [12] The method was performed manually and included many delicate manoeuvres with different samples, and techniques. During Nyrén's years as a PhD student he had been working with methodological development within bioenergetics and had specialised in photosynthetic enzyme activity. [13] Still, in spite of his experience in laboratory work, Nyrén had great difficulty in learning how to master the

[12] The method is named after one of the inventors Frederic Sanger and it was first published in 1977.

[13] He had been studying the enzymes involved in photosynthesis, which simply explained is the process where solar energy, water and carbon dioxide is transformed into dextrose (a sugar) and oxygen. This process constitutes the foundation for life on earth.

Sanger method's numerous steps and procedures. By using a generally well-known and established technique and not being able to master it, Nyrén began a thinking process of starting to develop a different method. However, since his background was within the research area of biochemistry, and not molecular biology which is traditionally connected to DNA-related research, his idea of how to design a new method originated not in genetics per se but in energy conversion processes using enzymes. The methodological principle was based on the idea of detecting DNA synthesis by measuring the constant release of a by-product during the process.[14] By being introduced to genetic sequencing and wanting to simplify the procedure, Nyrén was entering a new research field. It was the connection of the research field of genetics to his knowledge within the area of photosynthetic enzyme activity which made the new idea arise. Even before he had made any proper experiments, Nyrén had a strong belief that the idea would work and that it would be an easier procedure than the Sanger method. (Interview Nyrén; Nyrén, 2007)

When Nyrén returned to his university in Sweden, Stockholm University, he was eager to try his new idea and when doing so the preliminary results indicated that there was reason to believe that it might actually work. The way the assay was set up, a connection between a certain enzyme activity and the mechanisms involved in synthesising, or building, DNA could be created and detected (Nyrén, 1987). Even though the results were published, they were still very preliminary findings; hence, whether or not this was a useful result within genetics, or more specifically DNA sequencing, was at this point difficult to recognise. The article, which Nyrén published in 1987, described a *sequencing-by-synthesis* method based on the detection of the by-product pyrophosphate. (Interview Nyrén; Nyrén, 2007)

Sequencing-by-synthesis, or SbS, was at the time a rather unexplored methodology, in which DNA was sequenced through its reconstruction. It had been the focus of several research efforts, but as there never had been any real progress of making it into an efficient sequencing technique, it was more or less abandoned as a methodology for sequencing. It was based on the idea that by synthesising or rebuilding the complementary strand to single-stranded DNA, sequentially added nucleotides (which constitute the basic structure of the DNA molecule) would reveal the DNA sequence.[15] Two years earlier a patent had been granted for this type of sequencing technique, but as it had been missing essential parts it did not have a significant impact on methodological genetic research. (Melamede, 1985;

[14] The production of DNA.

[15] DNA is a double stranded molecule, a double helix, which is held together by bonds between nucleotides. There are four different nucleotides A (Adenine), T (Thymine), C (Cytosine) and G (Guanine) which make specific pairs: A pairs with T, and C pairs with G. By adding nucleotides to a single strand and detecting which of the four nucleotides that become incorporated, the sequence becomes known. (also see *Figure 2*)

Ahmadian et al., 2006) There was nevertheless one particular feature in the design of this type of method which made it advantageous compared to Sanger and other sequencing techniques. Since it was through a continual detection of incorporated or rejected nucleotides that the sequence became known, any use of electrophoresis or fluorescent or radioactive labelling (which otherwise have to be used as a final step in sequencing and are applied in all other sequencing procedures) was unnecessary. [16] [17] There was thus no need for a separate step of using gels in this method, which was unavoidable in methods like Sanger. (Hyman, 1988) One of the essential parts that was missing in the patent was, however, the procedure of determining whether or not the added nucleotide had been incorporated into the growing DNA strand. This was where Nyrén's idea of the enzyme-controlled energy conversion made its contribution; by measuring the by-product pyrophosphate every nucleotide addition could be detected.[18] (Interview Nyrén; Nyrén, 2007)

Nyrén's article, which was published in 1987, was primarily based on an earlier article written by himself and his colleague Arne Lundin in 1985. However, in the earlier article, Nyrén and Lundin had presented a luminometric[19] method to track pyrophosphate synthesis, while in the later one Nyrén described a combination of this method and the detection of DNA synthesis; in other words, the rejection and incorporation of added nucleotides.[20] (See Figure 1) (Interview Nyrén; Nyrén & Lundin, 1985; Nyrén, 1987)

[16] Electrophoresis is a method used as a final stage to sequence DNA or proteins. By letting the molecules run through a gel holding a certain current, the fragments produce a separation pattern based on their charge and size. This pattern is used to identify the molecules.

[17] Whenever a molecule is to be identified, for instance through electrophoresis (see 16), fluorescent or radioactive labelling of the molecule is used as a probe for detection through a fluorescence or radioactivity reading instrument.

[18] The patent did, however, not become known to Nyrén until ten years after he began his sequencing research.

[19] A reaction based on the event of light emission

[20] The main component of this combined method, the by-product pyrophosphate, is a salt which in this case is released by the enzyme responsible for incorporating nucleotides during DNA synthesis: DNA polymerase. This released pyrophosphate then works as a substrate for ATP sulfurylase (an enzyme) and together they produce ATP, a highly energy rich compound. By adding luciferase (another enzyme) this compound is converted into light which can be detected by a camera. It is thus the continuous detection of released or non-released pyrophosphate through this bioluminescent reaction that exposes the DNA sequence. Also, the light emissions are both time dependent and proportional. This means that it is a real-time reaction where the results are shown at the same time as the light reactions take place and also demonstrates how many nucleotides that are added. (Interview Nyrén; Nyrén & Lundin, 1985; Nyrén, 1987)

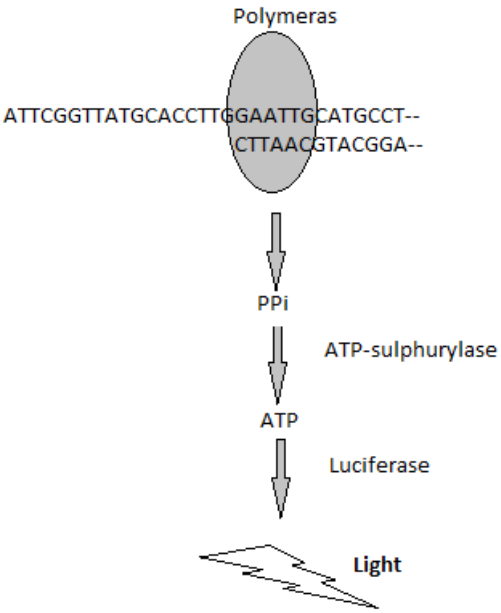

Figure 1. The principle of Nyrén's first ideas about DNA sequencing through the detection of pyrophosphate (PPi). The uppermost row of letters represents the single-stranded DNA string on which the complementary strand is built by adding nucleotides (A, T, C and G). If the nucleotide makes a pair with its corresponding nucleotide (A always pairs with T and C always pairs with G and vice versa) on the single strand the by-product pyrophosphate is released which produces a flash of light through ATP. This light emission is detected and registered. Polymerase is the enzyme which incorporates the nucleotides in the growing DNA strand.

In this reaction, firefly luciferase converted ATP, an energy-rich compound, into pyrophosphate shown as a flash of light which revealed the incorporation of the added nucleotides. [21] This energy conversion, which was described by Nyrén and Lundin in 1985, was by no means a new discovery; rather, the research on this particular reaction went back at least 40 years, and since then there had been several articles describing ATP analysis with firefly luciferase (see e.g. McElroy, 1947; Balharry & Nicholas, 1971; Hammerstedt, 1972; Lundin et al., 1976; Drake et al., 1979). Nyrén was thus building his research on already familiar and established research but which was totally unconnected to genetics and DNA synthesis, which in turn meant that the novelty of Nyrén's article from 1987 lay in the use of this energy conversion in detecting the activity of DNA polymerase. It was, in other words, established research that Nyrén applied in a new area

[21] ATP: Adenosine-tri-phosphate

and in a novel way. He was also using an old and abandoned technique, SbS, as a methodological principle for his idea. However, as it was not able to perform the actual sequencing process, Nyrén did not yet claim it to be a SbS method per se. [22] Such a claim was nevertheless made by Edward Hyman in 1988 (Hyman, 1988), but this SbS method was far from optimised and needed major improvements in order to be a sequencing method of significance. The three papers by Nyrén and Lundin in 1985, by Nyrén in 1987 and by Hyman in 1988 demonstrate the first tentative steps towards a SbS method based on the detection of pyrophosphate. (Nyrén & Lundin, 1985; Nyrén, 1987; Hyman, 1988)

Although there had been research progress already at this stage, the new idea for sequencing which Nyrén presented in his article in 1987 did not cause any excitement in his department at Stockholm University, nor within various funding committees which Nyrén turned to, to raise research funds for a continuous development of the idea. The published findings were considered too vague to be the basis of a methodological research project and the committees rejected Nyrén's grant applications. There was thus no belief in the idea of a SbS-based method becoming an alternative way of performing DNA sequencing. In Nyrén's opinion, the only person really believing in the new idea for sequencing at this point was himself. According to him, solving a methodological problem in genetic sequencing by using knowledge from his own research area, bioenergetics, was a fruitful combination which the genetics research community at the time failed to see. (Interview Nyrén; Interview Pettersson; Nyrén, 2007)

4.2 Genetics in Retrospect

In trying to enter the methodological research area of genetic sequencing, Nyrén met with an outspoken opposition to his new sequencing idea. His research results were considered too preliminary and unclear to indicate a potential scientific success in creating a new and efficient sequencing method. Unfortunately, it was precisely within this area that his new research idea was supposed to make a contribution. Despite using established research from his research area, the outcome of Nyrén's new findings would not be relevant within this context; it was rather what this knowledge would bring to the area of *sequencing* that was the significant research result. Therefore, to ever become a scientific success, the new idea needed to be recognised within the scientific structure of genetic sequencing. In order to

[22] It was rather more of a method to register the activity of DNA polymerase which is strongly connected to DNA synthesis as the polymerase adds the nucleotides which constitutes DNA.

understand what kind of research area Nyrén was getting into by wanting to simplify genetic sequencing, we now leave the development of the new method and turn to a brief overview of the field of genetic research.

> "Genetics underlies all of the biology of cells, including development biology, or embryology, but also enzymology and the study of cancers and the study of many other diseases; all of immunology, and of endocrinology; neurobiology generally as well as many disorders of the nervous system and of the mind; and, ultimately, the process of evolution"
> (Judson, 1992, p. 37)

One of the most central issues within the scientific structure of biology has always been to understand and explain the mechanisms through which *heredity* functions and how it is expressed throughout the lives of living organisms. Already in 1856, Gregor Mendel had laid out the basic rules for how heredity is expressed in the physical features (the phenotype) of the organism. By crossing generations of pea plants, he showed how different combinations of specific characters, such as colour or stem length, allowed certain traits to be passed on while others were not, at least not in the first generation. From these results he founded the concepts of *recessive* and *dominant* traits, which nowadays is common knowledge.[23] However, the work of Mendel lay dormant for many years and was not recognised until the early 1900s. Through the continuing efforts of several biologists, the idea of something resembling and functioning as *genes* began to form.[24] The knowledge that the phenotype of an organism was controlled by its genotype was thus beginning to emerge. Around 1918 the theory of *one-gene one-enzyme* appeared which, among other things, stated that "[…] the gene is expressed through the action of an enzyme" (Kevles & Hood, 1992, p.53); this was a fundamental finding as it showed the direct expression of a gene. However, since methods to study this in further detail did not exist, ideas around what *molecularly* constituted genetic material did not appear until the 1940s. (Kevles & Hood, 1992)

A major breakthrough in the quest for this "holy grail" of biology was the presentation of the DNA double helix structure made by James Watson and Francis Crick in 1953. [25] The significance of this model lay in the fact that previously the knowledge regarding genes and their hereditary function had only comprised the physical outcomes, or phenotype, of their characteristics and not the characteristic's origin and constitution - its genotype. For instance, regarding plants one could detect and influence physical traits such as colour, size and proportions. With the model of DNA, however, this

[23] For more information see Kevles & Hood, 1992
[24] The word *gene* first appeared in 1909 (Kevles & Hood, 1992)
[25] DNA stands for deoxyribonucleic acid.

understanding was deepened to comprise also these traits' genetic foundation. The model showed that not only was the DNA molecule a double helix, but it was also an assembly of nucleotides, or bases, which formed pairs in a specific order; thus DNA constituted a code. There were four different nucleotides spelling out this code: A (Adenine), T (Thymine), C (Cytosine) and G (Guanine) from which A formed pairs with T and C formed pairs with G (see Figure 2). It was now understood that the order in which these nucleotides appeared determined the genetic code and thus played a crucial role in all the physical and behavioural features of the living organism. However, to read the code formed by this DNA structure, thus to perform the task of DNA sequencing, was not possible at the time. (Ibid.)

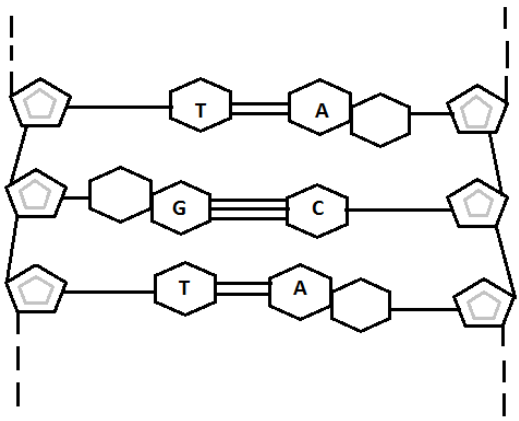

Figure 2. A simplified schematic picture of the DNA molecule showing the placement of the four nucleotides, or bases, of A, T, C and G and how they form specific pairs: A with T and C with G.

A prerequisite for sequencing DNA was knowledge of the expression of separate genes. This was made possible by the use of *recombinant DNA*. In the 1960s-1970s it became known how to recombine DNA from different sources (mainly bacteria) which opened the door to study separate genes. The use of recombinant DNA thus resulted in an overall comprehension of the function and expression of DNA: not only was the function of the gene determined by the code through which it was spelled but also by how it was translated (into proteins) to determine the features of the organism. It was this new knowledge that laid the groundwork for also being able to sequence DNA. (Judson, 1992; Watson, 1990; Collins & McKusick, 2001)

In 1977, Allan Maxam and Walter Gilbert and Fredrick Sanger independently presented two different methods to perform DNA sequencing. (See Maxam & Gilbert, 1977 and Sanger et al., 1977) Both these methods

were capable of *de novo* sequencing which meant that they could be used to sequence unknown sequences.[26] Over the years, these have been the two most often used sequencing techniques around the world - Sanger's being the single most used still to this day. In 1980, Gilbert and Sanger shared the Nobel Prize in chemistry for their two sequencing methods. Due to the necessity of handling dangerous chemicals using the Maxam and Gilbert method, as well as the continuous improvements of Sanger, the Maxam and Gilbert method has lost its former status, leaving the floor to Sanger.[27] (Judson, 1992; Nyrén, et al., 1993; Collins, 2001; Ryan et al., 2007) Soon after being published, the Sanger method was used to sequence the very first whole genome, which was the 5 386-nucleotides-long sequence of the bacteriophage ΦX174 (a virus). However, to put things in perspective, by using this first version of the manually-handled Sanger method, it would literally have taken a million years to sequence the human genome. [28] (Bentley, 2003)

As with the many other sequencing techniques that were being developed at the time, Sanger was a gel-based system which meant that the last step of the method which gave the ultimate sequencing result was performed by the use of *gel electrophoresis*. The length variation of the DNA fragments, which had been produced earlier in the process, would be run in a gel under an electric current. The order in which the fragments ended up would reveal

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[26] To be able to sequence known sequences is desirable when wanting to identify if an organism has a certain gene or mutation which previously has been classified. However, when wanting to sequence a new gene or the entire genome of an organism, methods that can sequence unclassified sequences are needed.

[27] In 1975, two years before these two big inventions, Ed Southern (Southern, 1975) had obtained a sequencing method for identifying *known* DNA sequences, which means that it could not be used for de novo sequencing. The reason for this was that the method was built on the prerequisite of an existing template of the sought-after sequence. The technique, called Southern blotting, was however further developed and laid the foundation for the sequencing-by-hybridisation technique (SBH) first presented in 1988 (Lysov et al., 1988; Drmanac et al., 1989). This is now a vastly used method and is continuously being developed. (Ahmadian et al., 2006)

[28] The Sanger method is also called the dideoxy-termination method (or the chain-termination method) as it relies on special nucleotides - dideoxy-nucleotides (dd-) - for its function. Before tackling the issue of studying and sequencing DNA the inventor had done the same with proteins (or amino acids, which are the building blocks of proteins) which was a somewhat easier task. His idea for sequencing DNA (or nucleic acids, which are the building blocks of DNA) was based on the complementarity between the two strands in the double helix mentioned earlier - A always pairing with T and C always pairing with G. It was through this principle that by separating the two strands and only using single-stranded DNA, added nucleotides (A, T, C and G) would make pairs with their complementary base on the single strand. Due to the use of dd-nucleotides, which stop further elongation of the DNA strand once incorporated, and a specific ratio principle, the Sanger procedure produces different lengths of the DNA sequence in which every nucleotide in the sequence is represented. The last step in the sequencing procedure, which also reveals the sequence, is *polyacrylamide gel electrophoresis*. By letting the DNA strands run through the gel under an electrical current, the fragments display a separation pattern depending on their size and charge. The separation pattern thus shows each nucleotide in the sequence. (Judson, 1992)

the sequence of nucleotides. This was a technique which laid the foundation for many different sequencing methods and was thus in many regards considered an inevitable step in performing sequencing. The larger part of the methods that were being developed thus belonged to a "sequence/fragment-length paradigm" (Trainor, 1990, p. 425) which shaped their construction and qualities. (Interview Nyrén; Interview Pettersson; Trainor, 1990)

4.3 The New Method to Be –Standing a Chance?

The research area that Nyrén entered with his new sequencing idea had thus far presented several different ways of performing sequencing but was dominated by Sanger which was ever-evolving through its frequent use. There was also a general acceptance of the idea of gel-based sequencing as the only successful method. Development of Nyrén's new method began in the Department of Biochemistry at KTH in Stockholm in 1990. Nyrén had, by this time, left Stockholm University, where he had been given no time or funding to work with his sequencing research. Here he worked under a Professor with the task of building up a new laboratory in terms of equipment, PhD projects and staff. Next to this rather time-consuming undertaking, as well as teaching, he was given one day a week to work on his idea. Mostly due to the lack of research funding nothing happened with the development of the new method between 1987 and 1990. In 1990, its status was still very much a preliminary demonstration of a connection between research performed within bioenergetics concerning light-driven pyrophosphate synthesis and the genetics area concerning detecting DNA synthesis. (Interview Nyrén; Nyrén, 2007)

At the same time as Nyrén took employment at KTH, there was a momentous event taking place in the international arena which concerned DNA sequencing, namely the initiation of the HUGO project. Instigated in the early 1990s, this project set out to sequence the entire human genome and thus directed great attention to the task of DNA sequencing. Due to the vast nature of this project, the focus was mainly directed to quantitative sequencing. The attention was thus completely drawn to the ability to sequence as many nucleotides in as few sequencing runs as possible. As stated at the start of this chapter, the research driven by Nyrén was based on the idea of an easier and faster way to perform DNA sequencing. Even if the dominant sequencing method, Sanger, was appreciated for its robustness, it was also considered very time consuming, labour intensive and complicated. Every analysis required highly skilled operators who manually had to work through the different steps of the method. Though there had been significant attempts at automating it, it had not yet reached a satisfactory condition in

terms of efficiency and accuracy. Therefore, most laboratories were still using the manual method (Trainor, 1990). However, even if it required large amounts of insensitive DNA material, as well as trained operators, what counted in its favour was its ability to read several hundreds of nucleotides at a time. In the early 1990s, no SbS method had ever achieved such a great read-length. Within the genetics research community this resulted in the belief that the Sanger method, and gel-based sequencing techniques in general, were the future. Consequently, it became difficult for SbS methods in general to gain any real support within genetics. (Interview Allen; Interview Nyrén; Trainor, 1990; Nyrén, 2007)

4.4 The HUGO Project –Influencing the View on How to Sequence

The Project Initiation

With the methods of how to sequence DNA at hand, the idea of sequencing the human genome - the entire genetic content of the human body - had begun to surface in the mid 1980s, and the first meetings of how to realise such a task were held. In the very beginning it started as a concern of a rather small group of researchers led by Robert Sinsheimer, chancellor at the University of California at Santa Cruz. However, the idea was quickly picked up by the US authorities. At a meeting in 1986, the director of the Department of Energy (DOE) decided to devote a few national laboratories to the common task of sequencing the human genome. This was, however, just the beginning of a long process to initiate such an endeavour. Many more meetings would still be held bringing forward just as many arguments as counterarguments as to whether or not such a huge undertaking would benefit science and society. (Watson, 1990; Collins et al., 2003) One concern was that it would consume enormous amounts of research funds leaving other smaller projects without financial support, which in the long run would have a negative effect on biological research in general. There were also the social and ethical consequences of having total information about one's genetically determined past, present and future.[29] From a health care point of view, others argued that the benefits of sequencing the human genome were so tremendous that not engaging in such a project would be unthinkable. (Watson, 1990)

[29] There were the ethical considerations concerning people's ability to handle such information about themselves, but also the risk of discrimination due to genetic circumstances when it came to e.g. insurance and employment issues. (Kevles & Hood, 1992)

Finally in 1988 the US Congress decided that a project sequencing and mapping the human genome would be carried out, and appointed the DOE and the National Institutes of Health (NIH) the official leaders of this huge task. Together, these institutions would create a plan for how to proceed with the project and there were of course many aspects to consider: what were the technology requirements? Which and how many scientists would be interested in participating? How long would it take? What were the societal and ethical consequences? Some of these questions could not be answered until well into the project, if at all, while others had to be addressed immediately. (Collins, 1999)

The Challenges of HUGO –Science, Technology and Society

In 1990, the HUGO project was officially initiated as a joint endeavour of the DOE and the NIH. None other than James Watson, who, together with his research colleague, Francis Crick, had brought forth the model of the DNA double helix, was appointed Associate Director of the Human Genome Research at NIH. (Watson, 1990) Thorough plans for the factors that needed attention were created and the idea was to finish the project within a period of 15 years. The following goals were formulated:

- "*Identify* all the approximately 20,000-25,000 genes in human DNA
- *Determine* the sequences of the 3 billion chemical base pairs that make up human DNA
- *Store* this information in databases
- *Improve* tools for data analysis
- *Transfer* related technologies to the private sector
- *Address* the ethical, legal, and social issues (ELSI) that may arise from the project." (Human Genome Project Information, http://genomics.energy.gov)

As there were many technological challenges to overcome in order to achieve these goals, the first five years were devoted to technical development and to study genomes of smaller laboratory organisms such as viruses and bacteria. (Cantor, 1990; Collins, 1999; Collins & McKusick, 2001) In 1990, the largest genome that had ever been sequenced consisted of approximately 250 000 nucleotides which paled in comparison to the *three billion* nucleotides of the human genome now to be sequenced. There simply were no large-scale sequencing techniques that could carry out such a task at the time. (Watson, 1990; Collins, 1999; Collins & McKusick, 2001) Not only did the technologies used in this project need to be efficient enough to keep to a reasonable time frame but also efficient enough to keep to the

budget. Hence, one part of the initial mission was to reduce the cost per each sequenced nucleotide. A very important aspect was also the precision of the results which these technologies would produce - the DNA code needed to be read with an accuracy of at least 99.99%. (Collins, 1999)

The most important and single most used technology within the HUGO project was the Sanger method which was heavily developed both before and during the project. (Collins & McKusick, 2001; Collins et al., 2003; Ryan et al., 2007) Before the initiation of the project, Sanger had been developed into an automated sequencing technique, which meant that all its different steps did not need to be performed manually. (Martin et al., 1985) Its robustness and ability to sequence several hundred nucleotides at a time made it very useful in sequencing large DNA materials. Still, in its early automated state it would have taken up to a thousand years to sequence the entire human genome (Bentley, 2003). However, it was continuously developed to meet the standards of large scale sequencing:

> "It is remarkable indeed that the Sanger dideoxy method for DNA sequencing remains the basic technology on which the genetic revolution is being built." (Collins & McKusick, 2001, p. 540)

During these five years of technological development, funding was given to a dozen different research centres which all contributed novel solutions of how to improve the Sanger method (see Figure 4). (Collins et al. 2003) It was these and several other large investments in improving sequencing technologies in the early 1990s, which made the goal of completing the sequencing of the human genome during the next decade achievable. (Bentley, 2003)

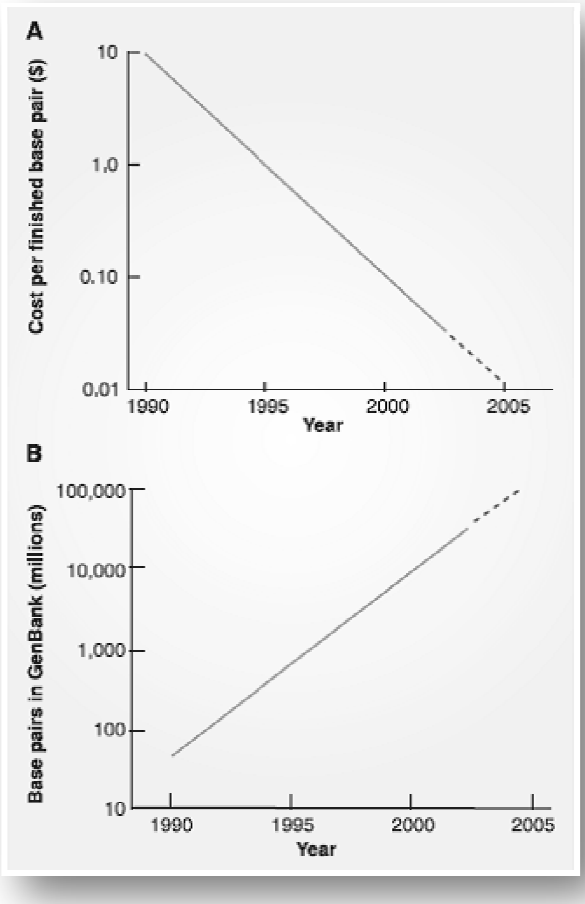

Figure 3. A) Demonstrates the decrease in sequencing costs ($) per nucleotide/base pair during the HUGO project. B) Demonstrates the increase in the number of sequenced nucleotides/base pairs during the HUGO project. (Source: Collins et al., 2003. Reprinted with permission from AAAS)

4.5 The Development of the New Method at KTH

The Difficulty of Being Alone – Development Stands Still

Alongside the ambitious research endeavour of sequencing the human genome, what was happening at Nyrén's department at KTH in Sweden? As earlier stated, even if it was a procedure for DNA sequencing, the method presented by Nyrén did not have its roots in genetics per se. Having spent his

academic career within the area of biochemistry and focusing on photosynthetic enzyme activity, the method originated from this particular source of knowledge. The new method, the function of which was to deal with DNA, did thus not spring from a research area focusing on analysing genetic material; rather it rested on research conducted within biochemistry regarding cellular functions and enzymatic energy conversion. However, the factor tying together a method for sequencing with this type of research was the focus on methodology - the search for methods to examine the biological cornerstones of life. (Interview Nyrén; Nyrén, 2007)

At this time, the basic principle of the method was clear: by building the complementary DNA strand (with its four letter code consisting of the nucleotides A, T, C and G) one nucleotide at a time, and measuring the pyrophosphate level induced by nucleotide incorporations, the code of the particular DNA strand could be read. The reaction's time dependence and proportional quality allowed the results to be given in real-time, which is to say at the same time as the nucleotides were added, and in proportion to how many nucleotides of the same kind that had been incorporated. Two incorporated nucleotides gave twice as much light emission as one. There were, however, still many questions regarding how such a principle would be transformed into not only a functioning, but also an efficient sequencing technique. How could excessive nucleotides which had been left over from former additions be removed in order not to disturb the subsequent incorporations? How could the light-emission intensity be enhanced? How could the enzymes which were a part of the process be trimmed to work more efficiently? Besides all these questions, Nyrén's limited knowledge within genetics was at this time reflected in the state of the method. For the one-man project to progress, additional knowledge, particularly concerning DNA, was needed. (Interview Nyrén; Interview Pettersson; Nyrén, 2007)

Further Development Through Additional Knowledge

Since 1987, the Department of Biotechnology at KTH had had in-house expertise within research concerning *solid-phase sequencing*. The technique was first presented in a joint article by the department in *Nucleic Acids Research* in 1988 (Ståhl et al., 1988) and then the following year in an article in *Nature* by Mathias Uhlén (Uhlén, 1989), both very prestigious journals within the natural sciences. It was based on the use of magnetic beads to separate different substances in a sample. The beads could, for instance, have DNA attached to them (or any other molecule with an inclination to chemically bind to a certain substrate) and thus bind to certain nucleotides. As these beads were pulled to a magnet, the substrate bound to the DNA on the bead would be separated from the rest of the sample substances. In the

late 1980s and early 1990s, Uhlén and his research group had been working on a particular sequencing method using this solid-phase technique. The sequencing method itself was derived from the Sanger method and the solid-phase technique was used as a preparation step before the actual sequencing process. (Interview Nyrén; Interview Uhlén)

Uhlén was involved in the HUGO project and wanted to improve the sequencing methods that could be used for this venture. His idea was to develop the solid-phase technique for this particular purpose. However, there were some problems with the technique. Due to the use of fluorescently labelled nucleotides for detecting incorporations, the system did not work as efficiently as anticipated.[30] The fluorescence constituted an artificial building block in the DNA, which interrupted the sequencing process. Therefore, the solution appeared to lie in replacing these labelled nucleotides with natural nucleotides, like the ones that were used in Nyrén's new method. Consequently, there were two research projects at KTH involved in DNA sequencing which needed complementary knowledge in order to proceed; Nyrén needed additional knowledge within the field of DNA sequencing in general to solve specific problems, and Uhlén and his group needed to solve the problem of detecting nucleotide incorporations using unlabelled nucleotides. While this simultaneous quest for knowledge was taking place, Nyrén found out about the solid-phase research through the article written by Uhlén in 1989 - this ultimately brought the two projects together. (Interview Nyrén; Interview Pettersson; Interview Uhlén; Uhlén et al., 1992)

Initially the collaboration between the two projects was not very extensive. It took the shape of Nyrén working together with a PhD student from Uhlén's research group, Bertil Pettersson, in trying to improve the pyrophosphate-based method. Pettersson brought knowledge concerning how to work with DNA and magnetic beads into the joint project and assisted by producing DNA material through PCR (Polymerase Chain Reaction).[31] At this point the research progress was halted by problems with getting the method to produce enough deflection for the luminometer to register it as added nucleotides.[32] The luminometer available in the laboratory could not detect the light emissions which was a combination of the DNA material used for the tests and the qualities of the luminometer. Thus, the experiments intended to test and improve the light intensity of the method became pointless - the laboratory instrument simply could not show

[30] Whenever a molecule is to be identified, for instance through electrophoresis (see 16), fluorescent or radioactive labelling of the molecule is used as a probe for detection through a fluorescence or radioactivity reading instrument.

[31] PCR is a method which allows exponential amplification or creation of multiple short DNA sequences. As this creates a larger DNA material to work with it enables scrutiny and analysis of DNA. It was first published in 1986 and revolutionised all research within genetics. For a detailed description of this method's coming about see Rabinow (1996).

[32] A luminometer is an instrument for measuring illumination.

if there had been any enhancements. (Interview Nyrén; Interview Pettersson; Nyrén, 2007)

Because of this combination's poor outcome, of the particular DNA material and the qualities of the luminometer, the project needed to change direction and the question posed was then: if it is not possible to measure the light intensity when nucleotides are incorporated, is there another way of testing if this kind of SbS method works? This problem made an idea of a "reversed" system surface. The concept was to alter the system so that every pyrophosphate-generated signal indicated a non-incorporated nucleotide (this was the opposite of the original idea where a signal indicated an incorporated nucleotide). Thus the absence of a signal would now indicate that the added nucleotide had been incorporated and the sought-after nucleotide would be known, thereby eliminating the problem of unclear signals. The system was set up to create massive elongations of DNA strands not containing the sought-after nucleotide, which created strong light signals detectable even to the luminometer, while the strand containing the complementary nucleotide did not show a signal at all.[33] However, since this method could mainly be used for single nucleotide detection (only one nucleotide per run) its use was rather limited. Nevertheless, the fact that this reversed idea worked was an encouraging result since it showed that there was great potential in making the original idea work as well. (Interview Nyrén; Interview Pettersson; Nyrén et al., 1993)

In 1993, Nyrén, Pettersson and Uhlén published an article based on the combination of this reversed sequencing idea with the solid-phase technique: the single-stranded DNA was bound to magnetic beads from which the elongation process and signalling took place. This combined method was also patented. At this point the development of the still immature method had thus resulted in the merging of two initially different projects at KTH. The joint project rested on two fused sources of knowledge, the combination of which, in this first phase, had resulted in both a publication and a patent. (Interview Nyrén; Interview Uhlén; Nyrén et al., 1993)

[33] This was achieved by using four aliquots (in chemistry aliquot refers to the use of a known volume of liquid that represents a part of some larger volume) containing single-stranded DNA and dd-nucleotides, the special kind of nucleotides terminating further elongation of the DNA strand. One aliquot contained ddA, another ddT, a third ddG and a fourth ddC. If for instance C was added to all four aliquots it would only be incorporated in the one containing ddG. When then washing away all the remaining dd-nucleotides and adding regular nucleotides to all the aliquots there would be a lot of incorporations in all the aliquots except for the one where the incorporated C would be hindering further elongation. This would create massive light signals in all the aliquots not containing the sough-after nucleotide while the aliquot where a nucleotide incorporation had taken place had no signal at all. (Interview Nyrén; Interview Pettersson; Nyrén et al., 1993)

4.6 Development Support from One of the World's Largest Suppliers of Biotech Tools and a Scientific Breakthrough

A Growing Research Group and the Need for an Automated Method

From 1994 the research group led by Nyrén grew bigger as several PhD students joined the project. The factor which enabled this project expansion was the acquirement of external funding. Up until this point the project had had great difficulty in getting attention from various funding committees. The committees had all required "hard evidence" that the method actually had potential to become a functioning sequencing technique; sufficient evidence had not been possible to present until that time. The attainment of funding enabled a new grip on the research project; new people, new equipment, for instance a different luminometer, and improved DNA material for the tests. This enabled the research project to proceed in its initial direction, namely that of developing a method detecting nucleotide incorporations through elevated levels of pyrophosphate. One of the remaining issues was the concern about light intensity, but perhaps even more so the procedure of removing excess nucleotides. In its current state, the method compelled the user to manually wash away remaining nucleotides after each added nucleotide. Clearly, for the idea to work as an efficient sequencing method and become automated, this was not an acceptable inconvenience. At this point there was thus no question as to *what* needed to be done, the question was rather *how*. (Interview Nyrén; Interview Pettersson; Interview Uhlén)

The first PhD student to join after Pettersson in 1994 was Mostafa Ronaghi. The second, Samer KaraMohamed, joined in 1995, while Tommy Nordström and Nader Nourizad became the third and fourth in 1996. In 1998, Baback Garizadeh joined the team and in 2000, Jonas Eriksson. The great advantage of more people becoming connected to the project evidently lay in a greater working capacity but also in the more efficient division of labour; thus, someone could focus on the thinking process while others performed the actual experiments. However, the drawback was that this same change made it necessary to construct suitable PhD projects, which in some ways distracted the group and Nyrén from the initial goal of the project - to create an efficient sequencing method. It meant that the development project could not just be about problem solving on a general level but also had to be broken down into smaller and more comprehensible assignments. Even if this in some regard helped to push the general project in the right direction, it also had the effect of slowing it down since this shifted part of the focus onto the students rather than on the development of the method. Nevertheless, with a larger group different ideas could be tested in a more

efficient way, which in turn enabled the group to move towards the development of an automated method. As its condition at the time could be likened to a brew of various enzymes which, if not handled correctly, gave no guarantee of accurate results, the method needed to be standardised in order to be usable for researchers outside the focal research group; therefore, a prerequisite for the new method was that it be automated. (Interview Nyrén; Nyrén, 2007)

The key to making the manual step-by-step process into an automated method lay in solving the problem of excess nucleotides which were left in the mixture once nucleotides had been added. Consequently, there needed to be some kind of washing step incorporated into the process which would remove the abundant amount of nucleotides between each iterative step of adding nucleotides. At this point, the solid-phase technique presented by Uhlén's research group made a manual washing procedure possible, but it was far from an optimal solution as, first, the solid-phase beads to some extent also were being washed away in the process and second, there was no obvious way to automate this particular procedure. (Interview Nyrén; Ronaghi et al., 1996)

The first real step towards a possible automated solution was taken in the form of using a capillary flow system in combination with surface immobilisation. The idea was to immobilise DNA on a plastic tube, and after each added nucleotide perform a washing step using a flow system of capillaries. Both capillaries and surface immobilisation were new areas of knowledge to Nyrén as well as to the rest of the research group and therefore it seemed like a complicated approach to the problem. Nevertheless, the group decided to try this direction as it appeared to be the only option at the time. Different approaches to developing this idea were tried and after a few months the group had found a stable format for DNA immobilisation. With this encouraging progress, the solution to the washing step seemed to lie in the capillary flow system approach. (Interview KaraMohamed; Interview Nyrén; Interview Pettersson)

Development Collaboration with Pharmacia Biotech – the Pyrosequencing Method's First Encounter with Business

In 1996, ten years after Nyrén first had the idea of a new sequencing method, one of the world's largest suppliers of biotech tools, Pharmacia Biotech, showed interest in starting collaboration with the research group at KTH around the sequencing method. At this time, by sequencing 15 nucleotides, the research group had managed to set a new world record in the number of nucleotides that could be sequenced in a row by the use of a SbS method (Ronaghi et al., 1996); this was of course an encouraging accomplishment of

the research group. As a scientific advisor to the board of directors at Pharmacia, Uhlén had informed Björn Ekström, the Chief of Explorative Research, about the development work being done at KTH. After further deliberation, the two parties of the joint research project led by Nyrén and Uhlén and the department led by Ekström decided to collaborate. The method that was, at the time, being developed by Nyrén's research group, assisted by Uhlén's research group, was thus taken on by an already established company for further development and possibly for production of a new product. It was, in other words, an encounter between scientific development of a new method and standardised production within business. For the research group at KTH a joint project was a very positive development as it had been difficult to attract any attention to the new method outside KTH. Working together with such a large cooperation as Pharmacia Biotech meant that the initially small and financially poor research project was now part of a bigger endeavour. Also, the exploratory approach which Pharmacia Biotech had to the further development of the method was very compatible with the team's academic way of working. The goal was to try to automate the method by applying the capillary flow technique, and Nyrén's group were given equipment to work with the capillaries in parallel with the Explorative Department at Pharmacia. (Interview Ekström; Interview Nyrén)

Even if Nyrén's group was still actively working on the capillary flow idea, the joint project with Pharmacia Biotech in many regards transferred this particular part of the development to the Department of Explorative Research. Some further progress was made by the KTH group, but since it was not really its primary research area, it was also working with many different ideas for a possible automation of the process. As most of the system so far was based on the function of enzymes, and this was Nyrén's main research area, a new idea based on a washing step performed by yet another enzyme, *apyrase*, was tested. After several weeks of experiments, the new idea proved to be very effective. Consequently, by late 1996 the method had developed into a four-enzyme system (see Figure 5) which incorporated the correct nucleotides to the single-stranded DNA template (through *polymerase*), continuously degraded the nucleotides that had not been incorporated (through *apyrase*), and created a proportional light signal (through *sulfurylase* and *luciferase*) that could be detected and registered. The latest addition of another enzyme taking care of the washing procedure replaced the solid-phase technique. (Interview KaraMohamed; Interview Nyrén; Gharizadeh, 2003)

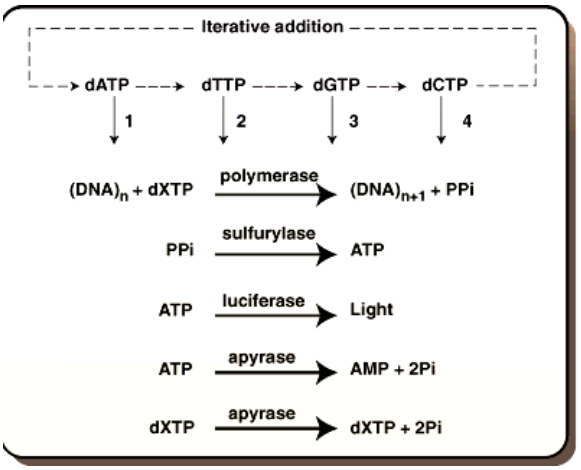

Figure 4. The four-enzyme system of the new method using polymerase, sulfurylase, luciferase and the last addition, apyrase. The four different bases are added iteratively (dATP, dTTP, dGTP, dCTP). When the nucleotides are incorporated, pyrophosphate (PPi) is released in proportion to the number of nucleotides included. Pyrophosphate is then quantitatively converted into an energy rich compound (ATP) which is transformed into a detectable light signal. (Source: Ronaghi et al., 1998. Reprinted with permission from AAAS)

To be able to add this piece to the sequencing puzzle was a major breakthrough for the research group at KTH. This was also scientifically recognised through the publication of an article in ***Science***, one of the most highly ranked journals within the natural sciences. It was in this article that the name of the method, *pyrosequencing*, appeared publicly for the first time. (Ronaghi et al., 1998) Even if this represented a scientific advancement, the method was far from optimised and there were still many issues to be dealt with, still, the essentials of the method had been determined. There was no doubt that this was a functioning sequencing method which could be further developed and automated. Also, just as with the former discoveries involved in developing the method, the four-enzyme system of pyrosequencing was patented. (Interview Nyrén; Interview Uhlén)

During the same time as this research progress was taking place at KTH, Pharmacia Biotech decided to withdraw from the joint project which was a big disappointment to the KTH group - this will be covered in greater detail in subsequent chapters. However, Ekström, the Chief of Explorative Research at Pharmacia who first had taken interest in the method, was not ready to lose the opportunity of commercialising it, which resulted in him resigning from Pharmacia Biotech. The new focus was to create a company around pyrosequencing which was a joint endeavour of Ekström, Nyrén,

Uhlén, Pettersson and Ronaghi. (Interview Ekström; Interview Nyrén; Interview Pettersson; Interview Uhlén)

4.7 The Technological Development within HUGO – Setting a Standard for Sequencing

The HUGO Consortium

Meanwhile, in the same year, 1996, the international HUGO *Consortium*, consisting of 25 laboratories from around the world was officially formed. Even though the HUGO project was mainly funded and controlled by the US government, it was indeed an international endeavour as it involved research laboratories in Britain, France, Germany, China, Japan and Canada. From the very beginning this international character was seen as a prerequisite for the carrying out and completion of the project. (Collins & McKusick, 2001)

As it was an open conglomerate, the number of involved laboratories kept increasing until the completion of the project. This meant that the task of sequencing the human genome and developing the essential sequencing technologies engaged thousands of researchers worldwide. The many undertakings involved in sequencing the human genome demonstrated the multifaceted nature of the HUGO project – not only was it an enormous scientific challenge that required a large portion of the world's scientists from many different research fields to come together and work towards a common technological and scientific goal, it also necessitated discussions about new legislation and ethical consequences. The HUGO project was thus not just about sequencing and laying out the map of the human genome but also about finding scientists and developing technologies capable of performing such a task as well as handling the social consequences of its outcomes. (The Sanger Center & The Washington University Genome Sequencing Center**,** 1998)

The Race of Finishing the Sequencing Task

In 1998, the publicly-funded HUGO project got unexpected competition in completing the sequencing of the human genome as Craig Venter announced that his newly-founded company, Celera, would finish the task before the Consortium. The company had been formed together with Perkin Elmer, a global manufacturer and supplier within the life sciences and optoelectronics, and was about to launch a new automated large-scale sequencing system. Their ambition was to use this new system to

independently sequence the entire human genome in less than three years and thus finish in 2001, four years before the HUGO project. Venter's idea was to focus on sequencing the genes in the human DNA material and not the remaining "junk DNA", which supposedly constituted about 80-90% of our DNA and was considered non-functional at the time. [34] The new system was based on *shotgun sequencing* through the Sanger method. [35] (Venter et al., 2001; Roberts, 2001) The approach of the HUGO project was somewhat different and it took the view that since there was no knowledge of *where* in the vast DNA material the genes were to be found, one would have to " sequence the whole thing" (Watson, 1992, p. 169).

The leaders of the Consortium, as well as the researchers involved in the public project, were naturally stressed by Venter's announcement and decided to re-evaluate their own timeframe. As the sequencing technology development had made good progress, a new deadline of finishing two years before schedule, in 2003, was considered achievable. The following three years consisted of a fierce fight in reaching stage goals - nothing could be done fast enough. However, in 2001, Venter made the first publication of an individual's genome in *Science* (Venter et al., 2001) but was quickly followed by a publication by the Consortium in *Nature* the same year (International Human Genome Consortium, 2001). As these were publications displaying only a first "draft" of the sequence, the sequencing work continued. (Roberts, 2001) The Consortium finished their project according to the new plan, in 2003.

The Gains of Knowing the Human Genome

Winning the race of mapping the human genome was, however, of little importance compared to the overall scientific gain of the task being completed. One of the major reasons for initiating the HUGO project, and the most anticipated use of a map of the human genome, was its great potential value in solving health-related issues. (See e.g. Watson, 1990; Collins & McKusick, 2001; Van Ommen, 2002) From the very beginning it was strongly argued that for this goal to be realised the results of the sequencing process needed to be continuously and immediately published in the public domain; this was also something Celera considered to be of major importance and consequently carried through. (Watson, 1990; Roberts, 2001)

[34] Even if so called 'junk DNA' is not translated into proteins, the argument that it is non-functional is nowadays largely contested as this DNA is thought to have a great influence on genes and their expression.

[35] The name "shotgun" refers to the DNA material being fragmented and then reassembled by the detection of overlapping sequences.

With a template of the genetic constitution of the average human being, the idea was that it would be possible to compare a healthy genetic chart to an unhealthy one, and in so doing find disease-causing genetic deviations. As we are all genetically 99.5% identical, the project was to a great extent not about defining what makes us similar but rather about identifying the 0.5% that separates us. Before, during, and after the project, there was much talk of the many advantages that a greater knowledge of human genetics could bring. In the eyes of "gene hunters" the potential contributions of genetics to health care seemed endless as "[…] virtually every human illness has a hereditary component" (Collins & McKusick, 2001). [36] Not only was there the expected use of identifying all disease-causing genes (or mutations), but also to monitor drug response and create individually-targeted drugs. As the following quotation suggests, the expectations were great:

> "The vision of genetically based, individualized preventive medicine is exciting, and it could make a profound contribution to human health." (Collins, 1999, p. 35)

Irrespective of the expectations that existed, the knowledge and technology development within the life sciences gained during the HUGO project were certainly massive. Due to heavy investments and efforts, the Sanger method, as well as other sequencing techniques, was greatly improved and new ones invented. These technological advancements were made in a great number of research laboratories around the world, and this meant that the specific development direction of the HUGO project affected and became standard within a large portion of the scientific community involved in genetics. Thus the HUGO project, as well as the parallel effort by Celera, had a big impact on which technologies were developed and became standard sequencing methods.

[36] Gene hunters is a nick name for scientists within genetics that seek the connections between genotype and phenotype and do so by identifying genes and how they are (or are not) expressed as proteins.

4.8 The Research Focus at KTH After the Founding of Pyrosequencing

"Science as Usual" - Improvements and New Ideas

In the creation of a start-up company around pyrosequencing, the start-up group managed to mobilise venture capital through an advisory firm called Odlander, Fredriksson & Co. based in Stockholm. Leaving the administrative minutiae of creating the company, located in Uppsala, to Ekström and Odlander, Fredriksson & Co., the research at KTH around pyrosequencing continued much as before. To the research groups of both Nyrén and Uhlén, the development was still in many regards a basic research project with many unexplored possibilities. There was much more to learn about the optimal conditions for both the different parts of the enzyme sequencing system, and the system as a whole. Therefore, just as before, Nyrén's group was focusing on diverse parts of the project to explore the potential and further development of pyrosequencing. Together with Ronaghi, Nyrén was working on the apyrase enzyme in trying to optimise its function in the enzyme system, Nordström was working on the capillary flow system (as this idea had not been totally abandoned). KaraMohamed was involved in cloning and recombining enzymes for further optimisation. Nourizad was working on mutations of the DNA polymerase enzyme, and Gharizadeh was focusing on overall improvement of the chemistry. (Interview Gharizadeh; Interview KaraMohamed; Interview Nourizad; Interview Nyrén; KaraMohamed & Nyrén, 1999)

To Nyrén, a central issue was the short reading-length of pyrosequencing.[37] Realising that the long-established Sanger method would be tough to replace, Nyrén was determined to try to enhance the reading length of the new method to make it more generic. It was not so much about competing with Sanger but rather about the belief that a longer read-length could be achieved as long as time and effort was put into such an endeavour. Because of its vast size and its purpose of sequencing a massive amount of genetic material, the HUGO project had put all its focus on *quantitative* not *qualitative* (with great accuracy) sequencing; thus the goal of reading short sequences with great precision had yet to be realised. At the time, the big difference between a SbS method and Sanger lay in the application: SbS methods had so far only been used for reading short DNA sequences (20 to 40 nucleotides) while Sanger was designed to read several hundred nucleotides at a time. This was considered a major downside of SbS methods and reason enough not to explore this type of approach. (Interview Nyrén; Interview Pettersson; Nyrén, 2007)

[37] The reading length refers to the number of nucleotides that the technique can manage to "read" in one sequencing run.

However, when comparing Sanger and pyrosequencing (or quantitative and qualitative sequencing) in one specific regard, we see that pyrosequencing starts to read the specific DNA sequence from the first available nucleotide, while Sanger is unable to begin the sequencing procedure until 40 or 50 nucleotides into the sequence - this can be a major downside if the DNA material being examined is fragmented and thus only a few nucleotides long. This demonstrates that there is not one method which suits all sequencing tasks and that the choice of sequencing method depends on the condition of the DNA material and, ultimately, if the purpose is to perform qualitative or quantitative sequencing. However, the ultimate goal which Nyrén's research group wanted to achieve was to be able to do both qualitative and quantitative sequencing at the same time using the same method. Therefore, one part of the continuing development of pyrosequencing was to enhance its read length so that it would not only be the most accurate method but also one with quantitative qualities; this was mainly done by trying to make the enzymes work more efficiently and using nucleotide analogues.[38] (Interview Gharizadeh; Interview Nourizad; Interview Nyrén)

Pyrosequencing as a Commercial Product Within the Developing Setting

In 1999, the first commercial product embodying the now automated pyrosequencing method was launched by the company. How this happened is accounted for in detail in the subsequent chapter. With a physical instrument produced, the interest concerning the use and further development of pyrosequencing spread at KTH. More people at both Nyrén's and Uhlén's departments got involved in several projects around different types of applications. One such project was led by Jacob Odeberg, a researcher at Uhlén's department. The study involved the search for polymorphisms, or genetic markers, connected to heart conditions (see e.g. Odeberg et al., 2002; Magnusson et al., 2004; Holmberg et al., 2005; Samnegård et al., 2005). In this study Odeberg worked with the commercial reagent kit (the mixture of enzymes) manufactured by Pyrosequencing and saw many possibilities for improvement. One such improvement had already become an established working procedure when using the pyrosequencing method at KTH and concerned a substance called single-stranded-binding protein (SSB). The function of this protein was that it uncoiled the DNA strand before the sequencing process began which made it easier for the

[38] Nucleotide analogues are synthetic molecules that lack the bond site for other nucleotides to attach to it, for instance dd-nucleotides which prohibit further elongation of the DNA strand.

enzyme *DNA polymerase* to incorporate nucleotides along the strand. Consequently, the addition of SSB hastened the sequencing process and made it more efficient. (Interview Odeberg; Interview Pettersson)

Nyrén's group was making many advances in its continuing work on the pyrosequencing method. After the launch of the first product the read length was increased to as much as 150-160 nucleotides in one run (compared to around 20 previously). Various kinds of assays suitable for different applications were also developed and overall improvement of the chemistry was achieved. [39] One particular project had focused on an application to make it possible to identify several species or genotypes in one sample. Nyrén and Gharizadeh developed the procedure by using multiple primers thereby enabling multiple sequencing in one and the same run. [40] As the identification of various genotypes in one sample (e.g. the presence of multiple infections) had long been a problem when using both pyrosequencing and Sanger, this improvement was a real breakthrough. (Interview Gharizadeh; Interview KaraMohamed; Interview Nyrén; Gharizadeh et al., 2003; Nyrén, 2007)

But it was not just at KTH that the knowledge and use of pyrosequencing had spread, there were several other universities which were interested in testing and further developing the new sequencing instrument, such as the Karolinska Institute and Uppsala University. Through joint projects, often initiated by collaborating universities, several more improvements and application discoveries were made and published (see e.g. Lindström et al., 2004; Holmberg et al., 2005; Andréasson et al., 2006; Käller et al., 2006). The collaborating partners often discovered specific applications useful for their particular research area which otherwise would have been hard to envision. (Interview Allen; Interview Odeberg)

Conflicting Views on the Commercial Solution

The Scientific Intent

In the very beginning of the parallel effort of the KTH researchers and Ekström (along with a few other recruited people) to develop the pyrosequencing method into a product, there was an exchange of ideas of how to proceed with the creation of an automated sequencing instrument; however, in time this radically changed. Both before and after the launching of the first commercial product in 1999, there was great difficulty in introducing most of the research results from KTH (and from their academic

[39] ATP sulfurylase assay, PPI (pyrophosphate ion) assay, Apyrase assay etc. (Interview KaraMohamed)

[40] A primer is a short nucleotide sequence which initiates the sequencing process.

collaborators) to the start-up company as well as to the production of the commercial product. A conflict regarding both the further development of the pyrosequencing method and its application areas therefore soon arose. The researchers at KTH were determined to make pyrosequencing a generic sequencing method applicable to many different types of analytical tasks, but this view was largely met with indifference from the company representatives. In their view, the company was limiting the potential of the pyrosequencing method by directing all development focus of the product towards one particular application; this one application was called single-nucleotide-polymorphism-sequencing (SNP), which is a method for identifying genetic markers consisting of single nucleotide mutations (e.g. an A has been replaced by a C).[41] With its great accuracy of reading each single nucleotide in a sequence, this was indeed a suitable application for pyrosequencing, but to make it the sole focus was viewed as far too narrow by the KTH researchers. (Interview Nyrén; Interview Pettersson; Interview Uhlén)

With the background of their many published research results, the KTH researchers saw almost limitless possibilities of further developing the method into covering many different types of applications, traditional long-read sequencing being one of them (to replace Sanger). The expectations of what could be achieved were thus very high and it was seen as having a major advantage compared to Sanger:

> "The limitation of Sanger is its use of gel since it simply gets worn out after seven- to eight hundred nucleotides. With Pyro[sequencing] there is no such limit, I could not see the limit then and I don't see it today. Pyro[sequencing] just does not have this kind of limitation." (Author's translation) (Interview Pettersson)

Nyrén's group's ultimate objective was to develop a generic, accurate and easy-to-use research method for sequencing. In their minds, it was researchers much like themselves who would be the primary users. They were familiar with the phenomenon of many researchers having to ask or even pay someone else to perform sequencing on their behalf and that this was a time-consuming process. The ambition was to erase this obstacle by developing a sequencing instrument which anybody could put in their laboratory and easily use. (Interview Nyrén; Interview Pettersson)

[41] SNP-mutations can affect the phenotype of the organism and thus cause various deficiencies or diseases.

Clash Between the Researchers' and the Business People's View on Pyrosequencing

As it was growing, the start-up company had to a large extent come to consist of people from old Pharmacia Biotech. Hence, the majority of Pyrosequencing employees had made a transition from one of the world's largest producers of laboratory and large-scale biotech equipment to a very small start-up company. With this increasing portion of former Pharmacia Biotech employees at Pyrosequencing, the KTH researchers experienced a diminishing company interest in their research results. When demonstrating their new research achievements concerning read-length and enzyme optimisation at meetings they were often told that it was too difficult to transform their ideas into "globally shippable products." The message they received was that achievements in the laboratory did not always equate to commercially-viable products - this response frustrated the researchers immensely. Correspondingly, the KTH researchers did not want to accept the technical test results provided by the company's researchers. In the KTH researchers' view, the methodological achievements within the company did not correspond to the potential of the sequencing method which they were developing. Their outspoken opinions, however, only resulted in the same recurring arguments. (Interview Ekström; Interview Gharizadeh; Interview KaraMohamed; Interview Krabbe; Interview Nourizad; Interview Nyrén; Interview Pettersson)

From the perspective of the researchers at KTH, the development of pyrosequencing in collaboration with the company almost solely became an issue of "doing business" and making money - it was not about what could be achieved from a technological or scientific standpoint but what needed to be done in order to manage a company. For this to be a commercial success, they were told that the major focus of the further development of the method would be to optimise it for SNP-applications. This greatly disturbed the researchers since they wanted to optimise every condition of the technique and thereby explore its overall potential. Even though this also was being done at KTH, the results rarely went into the production of the commercial products. The continuing research at KTH and the production taking place within the company thus became disconnected processes proceeding in their separate ways. (Interview Gharizadeh; Interview KaraMohamed; Interview Nourizad; Interview Nyrén; Interview Pettersson)

Besides the more than thousand scientific articles that have been published regarding the development and use of pyrosequencing, by the KTH department, its academic collaborators and other users, the method was in 2006 ranked as the second most important scientific discovery of the year by the journal *Science*. Furthermore, in 2008 Nyrén was awarded the prestigious Wilhelm Westrup Prize by the Royal Physiographic Society in Lund, Sweden, for his scientific achievement of pyrosequencing as: "[…]

the first alternative method of the classic Sanger method (awarded the Nobel prize in 1980) for de novo DNA analysis" (The Royal Physiographic Society, press release, 2008). (Interview Nyrén; The News Staff, *Science*, 2006; *Dagens Nyheter*, 2009-01-12) The pyrosequencing method can thus be stated to be an achievement of scientific significance.

4.9 In Summary

The scientific development of pyrosequencing took place concurrently with a massive effort to learn more about our hereditary components by sequencing and mapping the entire human genome. The HUGO project signifies the questions which scientists currently were addressing and pursuing which means that it was balancing on the very edge of new scientific knowledge. If yet of a smaller magnitude, so was the research project around pyrosequencing.

Nyrén started to develop a new method with the ambition that it would eliminate some of problems with the established Sanger method. The research around the pyrosequencing method eventually allowed his research group at KTH to formulate and finish PhD projects, to publish in highly-ranked journals and to get access to research funding. Thus the development work on pyrosequencing constituted the foundation of the involved researchers' scientific work and academic careers. From the KTH researchers' perspective, the use of the pyrosequencing method lay in the academic and scientific advancements it enabled - it was the central purpose of their work. For this reason the researchers at KTH constantly published about the development of the new sequencing method in order to show their work and progress. They did not want to leave any opportunity for continuing development and publication unexplored and this created a rift between them and the company, which wanted a narrower, commercial focus.

Another striking feature shown by the account of the scientific development of pyrosequencing is that the knowledge produced within the KTH research group was not found very useful in the context of producing a commercial product. As soon as the basis for a first product sprung from the pyrosequencing method, collaboration between the KTH research group and the company became very limited. From the perspective of the researchers at KTH, the initially meaningful relationship regarding the continuing scientific and commercial advance of the method ended as the company shifted to prioritising commercial activities instead of exploratory research. This vexed the researchers and many technical meetings with company representatives ended in great frustration. The collaboration with other academic research

departments, however, was flourishing. Through the KTH unit's relationships with other academic departments and universities the academic use of the commercialised pyrosequencing method was spread. The researchers at these departments and universities wanted to be involved in testing and developing the new sequencing instrument which led to joint projects between them and the researchers at KTH. Therefore, many publications were made through joint testing and development projects which earned pyrosequencing a position as a useful sequencing method at prestigious universities such as KTH, the Karolinska Institute and Uppsala University. Within academic environments, then, pyrosequencing, a research result in itself, supported further research both around its own function and what its analytical results could mean for other types of research. It thus acted as a catalyst for scientific research.

One of the major reasons for the end of the collaboration between the two factions of scientific development and commercial production was the company's decision to restrict the instrument to just one application: SNP-analysis. The researchers considered the pyrosequencing products developed by the company as only a small part of the method's true potential. However, as a methodology in the academic setting it is still very relevant, and continues to be used and developed at KTH and other academic research institutions. Thus the pyrosequencing method was a research work which provided the research group with academic and scientific recognition which in turn enabled a continuing development of the method. Furthermore, it was not only a scientific breakthrough within the group but for science at large, as it in time was recognised as a very important scientific discovery by highly-ranked journals and scientific committees. This scientific recognition was, however, for many years not widely recognised as the Sanger method was, and in many regards still is, considered to be the basic technology on which the future of genomics is to be built. This notion became all the more clear during the HUGO project for which this technique was heavily developed and used.

5 Embedding Pyrosequencing into a Producing Setting

In this chapter I will examine the process by which pyrosequencing was shaped into a business resource. As detailed in the previous chapter the first encounter which pyrosequencing had with business was the exploratory project within the large biotech tool company Pharmacia Biotech. Secondly, it became the foundation of a new company and a line of products through the involvement of a venture capital firm and, as will be covered in greater detail, later it became part of a larger business constellation through several company mergers. The chapter will thus demonstrate the transformation of pyrosequencing into a commercial solution from the perspective of business, first as part of an already established firm and then as the foundation of a new one.

5.1 Pyrosequencing Within an Established Company - Pharmacia Biotech

The founding of the Department of Explorative Research at Pharmacia Biotech in the early 1990s was a personal initiative from Ekström who also was made Chief of Department. Before that he had spent 15 years as a product specialist at the marketing department and had also been involved in various development projects at the R&D department. In his view, there needed to be company resources focusing particularly on novel ideas with unknown potential and outcomes. The goal of starting the new department was thus to focus on long term projects, which made the immature but promising sequencing idea developed by the research group of Nyrén a suitable undertaking. When the method was taken up by the department in 1996, there were still several fundamental problems with the technique that needed to be solved, for instance the procedure of removing excessive nucleotides. The Pharmacia group, which was involved in the project, consisted mainly of Ekström himself and a few instrument developers. (Interview Ekström; Interview Nyrén)

From the perspective of the Pharmacia department, the goal of the sequencing project was to achieve "proof of concept." This meant the production of concrete evidence that it was possible to automate the method and for it to function as a commercial sequencing technique. If this could be accomplished the next step was to develop a prototype. Under the condition that these preparation steps went well, Pharmacia was set on developing the commercial product. However, before a proof of concept could be considered, the group needed to establish a development direction. The basis for this direction was to solve some of the problems with the method using a capillary flow system. However, at this point it was unclear whether it was the pyrophosphate-based sequencing technique developed mainly by Nyrén which held the answer to an automated method or if it needed to include the solid-phase-technique developed by Uhlén; therefore, both options were explored. (Interview Ekström; Interview Uhlén)

During the project of exploring the commercial potential in the new sequencing method, Pharmacia was holding negotiations with British Amersham International, one of the largest pharmaceutical and biotech tooling companies in the world. The negotiations concerned a possible merger of the two companies. Because of this possibly forthcoming change, Pharmacia enforced reorganisations which affected some of the company's departments and ongoing projects. As a direct effect of these organisational changes, the Department of Explorative Research was shut down and all its projects were terminated. At this point the Pharmacia project concerning an automation of the pyrosequencing method had come to the stage of constructing a prototype based on a capillary flow system. This was, however, never put into effective use before the project ended. There was also another reason for the rather quick abandonment of the project, namely several of the directors in the company board found the sequencing method as being desirable to only a very specific type of customer and thus difficult to promote within a wider market. In turn, this would make it difficult to create the needed income which could cover the production and marketing costs. Nevertheless, as Ekström saw great potential in basing a commercial product on the pyrosequencing method he chose to leave the company in the pursuit of starting a new company around it. (Interview Ekström; Interview Nyrén; Interview Uhlén; Ingemansson & Waluszewski, 2009)

5.2 Building a Producing Structure Based on the Pyrosequencing Method

The Start-Up Company

Starting a new company based on the commercialisation of the pyrosequencing method was, as earlier mentioned, a joint decision of Ekström, Nyrén, Uhlén, Pettersson and Ronaghi. It was based on a firm belief that the method could form the basis of a viable commercial product but also on the very real prospect of attracting venture capital funding. In parallel with the decision to create a company, the sequencing research project had been presented to the venture capital firm Odlander, Fredriksson & Co. supporting the Health Cap funds. Being one of Sweden's first and most recognised investors in the field of life science, it should not be surprising that there was already a connection between the emerging company and the Health Cap funds. When Odlander, Fredriksson & Co. first heard about the pyrosequencing method in 1996, it was through one of their scientific advisors in the board – Uhlén. During his time in the board, Uhlén had given many investment suggestions, some of which the firm had decided to proceed with and some of which they had not. In this case, after careful consideration, Odlander, Fredriksson & Co. mobilised the Health Cap funds to support the business venture around pyrosequencing for the next seven years, financially as well as managerially. With this decision, the company Pyrosequencing, taking the same name as the method, was founded in early 1997. (Interview Odlander; Interview Steiner; Interview Uhlén)

Initially the start-up company consisted of Ekström and just a few other people needed to create the basis of a company and a plan for how to proceed with the automation of the sequencing method. In their view, the first task was to determine what kind of product would be developed. The second was to build up the infrastructure around this idea, such as employees, consultants, premises and technical equipment. The small number of people that were involved handled questions ranging from technical development to marketing and sales. The start-up company was hence much more like a small project than a usual company. At this stage the collaboration with KTH was very strong and there were frequent meetings concerning technical details and possible application areas. (Interview Ekström; Interview Nyrén)

Soon enough, Odlander, Fredriksson & Co. appointed one of its own partners, Eugen Steiner, CEO of Pyrosequencing. In doing so Odlander, Fredriksson & Co. to a great extent became operationally involved in setting the guidelines for how Pyrosequencing would develop, both as a company and as a product. They devised the operational and marketing strategies, which also made them strategically involved. Because of this high level of involvement it became difficult to determine where Odlander, Fredriksson &

Co. ended and the company Pyrosequencing began; the commercial venture around the new method was more or less a borderless blend of the two. Ekström continued to play a significant role in the initial development of the company as he was a key person in many of its functions. He was involved both in the product development and the marketing as well as being in management and handling external business relations. Because of his extensive network within the Uppsala biotech industry, he was able to recruit highly-competent staff, largely from old Pharmacia Biotech. He also associated Pyrosequencing with well-established suppliers, such as the local division of Partnertech. [42] With an expanding working force and the formation of separate divisions for technical development, marketing and sales, Pyrosequencing was no longer just a small and informal project - it had grown into real company. (Interview Ekström; Interview Nyrén; Interview Uhlén)

The New Production System and the Construction of a Product

The production system built-up around the manufacturing of the commercial product was divided mainly between two companies; Partnertech and Pyrosequencing. Partnertech, a well-established producer and supplier of various technical equipments set up production of the instrument needed for an automated procedure of the method while Pyrosequencing set up a production facility for the assembly of reagent kits containing the enzyme formula developed at KTH. (Interview Alm; Interview Ekström)

Partnertech got involved on a very early stage of constructing a product based on pyrosequencing and was a crucial partner in developing and manufacturing the rather sophisticated mechanical construction required for this type of instrument. The company had extensive knowledge and experience of electromechanical products and display screen technology, and had also been involved in designing medical products in the past. The initial mechanical construction which was handed to Partnertech consisted of partially automated parts provisionally put together in the laboratory at KTH. This meant that the company more or less had to start from scratch in regard to constructing an efficient and standardised instrument. Two crucial functions which the instrument needed to possess was an efficient way of detecting the light created by the "pyro-reactions" and a dispenser system distributing the right amount of chemicals for these reactions. Both these

[42] Partnertech manufactures and develops technical equipment on a contractual basis for large firms within areas such as telecommunications, IT, engineering and medical technology. Previously the company went under the name Facit and specialised in two areas; electromechanical products and display screen technology. For more information go to www.partnertech.se

functions required state-of-the-art technology concerning sensor chips and valves respectively. In the case of the sensor chip, the technology used was a CCD chip manufactured by another company and originally intended for the use of studying distant stars. [43] In order for Pyrosequencing to use the chip the licence rights needed to be acquired from this company. The valve system, on the other hand, was constructed and delivered to Partnertech by a set of suppliers. (Interview Alm; Brennan et al., 2009)

During the phase of designing the product there were several issues concerning how to make a number of different existing solutions work together and fit with the conditions of the method. However, there were also technical modifications that needed to be made in the continuing production of the product. One example is the introduction of the ROHS directive which by law prohibited the use of certain environmentally hazardous substances in the production of electrical and electronic equipment. [44] One such substance was lead, which Partnertech used to solder different technical components to printed circuit cards, for instance in the pyrosequencing instrument. Initially this did not concern the production of the pyrosequencing instrument as medical products were not included in the ban of such substances. However, it did include the larger part of Partnertech's suppliers which as a consequence stopped producing components suitable for lead soldering. Thus, even though the ban did not include products such as the pyrosequencing instrument, its production was still affected as the ban did concern essential suppliers of Partnertech. This meant that Partnertech needed to adjust their printed circuit cards and how the technical components were attached to them. Pyrosequencing was consequently not only dependent on its supplier Partnertech for the production of the instruments but in turn also this supplier's suppliers, which manufactured and delivered various essential components to the production of the pyrosequencing instrument. (Interview Alm; European Commission Environment, 2010)

For Pyrosequencing to manufacture the reagents kits the company also required a set of suppliers specialising in producing and delivering enzymes. The enzymes were produced and supplied in a standardised fashion by the suppliers. This standardisation resulted in a significant feature of the enzymes. In order for them to be part of an industrial production, where they needed to be transportable and last for a long time without being spoiled, they had to be freeze-dried. Thus in the production of the reagent kits at Pyrosequencing, it was the quality of the enzymes in a freeze-dried condition which had to be the starting point for the properties of the resulting product. This was very different from the fresh chemicals which could be

[43] Charged Couple Device. A CCD camera converts light into electrical signals.
[44] ROHS stands for restriction of the use of certain hazardous substances in electrical and electronic equipment.

experimented with in the laboratory at KTH. (Interview Ekström; Interview Krabbe; Interview Söderbäck)

The instrument supplied by Partnertech was designed much like a box which required an input and subsequently delivered an output (see Figure 5). The input was the test samples of DNA, which the user would provide, along with the reagent kit of enzymes supplied by Pyrosequencing. Once these inputs had been inserted the sequencing procedure would take place inside the box with the help of complex mechanical constructions and chemical reactions creating an output of the DNA sequence shown on a computer screen. Due to the advanced sensor chip, the instrument transformed the biochemical reactions into digital indications shown as a "pyrogram" (see Figure 6). The pyrogram revealed which nucleotides had become incorporated into the growing DNA strand and in which order, thus revealing the sequence. The first product was called PSQ96 because of the 96 wells in which the biochemical reactions took place.[45] This product was later followed by two subsequent versions, the HSA and the Q24. (Interview Alm; Interview Ekström; Interview Nyrén; www.biotage.com) The next section covers what needed to be done in order for the first product to be manufactured, and the expectations that were put on its production and use.

Figure 5. The PSQ96 instrument. (Source: www.biotage.com)

[45] In molecular biology, assay plates with 96 wells are standard procedure.

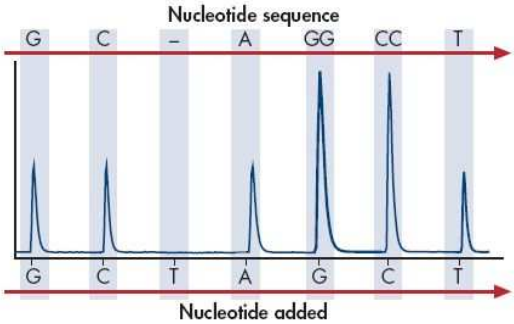

Figure 6. A pyrogram as shown on a computer screen with light intensity on the y-axis and the time for adding different reagents to the reaction on the x–axis. The peaks demonstrate the light reaction to each added nucleotide. The height of the peaks is proportional to how many nucleotides of the same kind that has been incorporated in a row. (G = guanine, A = adenine, C = cytosine, T = thymine). (Source: www.qiagen.com)

Establishing a Company and a Product Based on Venture Capital –Focus on What is Achievable Now

The company board consisted of representatives from Odlander, Fredriksson & Co. as well as several prominent people from both the business and research world. Two of the members were, for instance, the former CEOs of Ericsson and SEB (Skandinaviska Enskilda Banken) and one was a Nobel Prize winner in chemistry from the Karolinska Institute. The board thus comprised knowledge both within business and academic research and was therefore expected to be able to propose an appropriate development direction for the new company and its products. The intention behind formulating the board was that it would be a composition of people representing "[…] strategy, vision and control" (Interview Walldén). [46] In evaluating the future for the new sequencing method, the board saw defined application areas where the Pyrosequencing product would serve an important purpose. It concluded that there were very few other sequencing methods that could perform CpG-methylation-analysisor EST-analysis, applications which would make pyrosequencing a breakthrough technology on the biotech tooling market. [47] [48] These applications would direct the new

[46] Erik Walldén was the second CEO of Pyrosequencing.

[47] In this context methylation refers to the replacement of a hydrogen atom (H) with a methyl group (CH_3) in the DNA molecule. CpG refers to the occurrence of methylation at a site where a C nucleotide is followed by a G nucleotide. Methylation is normal and occurs at 60-90% of all CpG sites in mammals. The interest in studying methylation lay in its effect on the transcription of genes to proteins and thus it effects on an organism's phenotype.

method towards clinically-applied diagnostics. However, this focus was put on hold for the benefit of another application: SNP-analysis.[49] Considering the features of the method in its initial state, SNP-analysis was seen as a more reasonable first goal. (Interview Ekström; Interview Odlander; Interview Walldén)

The potential of the method was at this stage rather unexplored, which put focus on what it could achieve in its current condition. The technological perspective on which the board based its decision saw the product solely as a sequencing method which specialised in sequencing short DNA fragments with great accuracy. This characteristic was highly applicable to SNP-applications. Also, the decision was based on the fact that in order for Pyrosequencing to become an acknowledged company within a certain time frame, it needed to establish a producing structure and sell products. (Ibid.)

SNP-analysis was also an application which matched the scientific and technological advances of the HUGO project.[50] Since published research already had provided the insight of how some illnesses could be traced back to the origin of SNPs, there was a general belief that with the human genome sequenced, many health-related businesses and research areas would want to find and analyse more of these single nucleotide deviations. It was considered an application area which was moving extremely fast and which had a need for more accurate methods. The anticipation and clear vision was that the strong focus on SNP-analysis would make Pyrosequencing a world leading company within genetic analysis. Consequently, SNP-analysis became the vision on which the development of the product and the production system relied and the only source of information upon which the investors based their investment decisions. (Ibid.)

After having established the company within SNP-analysis, the plan was to move towards EST-analysis and the final goal, which was considered potentially the most profitable application, namely clinical diagnostics. However, because of both the method's and the company's undeveloped states at that time, these goals would have to wait; first the company needed a customer base which could bring fast returns. For the new CEO, Erik Walldén, who had taken over after Steiner's initial effort, the work order was thus perfectly clear. First they had to go for SNP-analysis and after further research and development they would enter the area of clinical diagnostics. According to Walldén and the company board there was no other way to go about it. (Ibid.)

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[48] EST stands for "expressed sequence tag." EST is an expressed gene which means that it has been translated into amino acids which are the building blocks of proteins. ESTs are thus useful tools in studying genes and their function.

[49] SNP-analysis aims at finding and analysing *single* nucleotide mutations which can lead to different diseases and conditions.

[50] For a longer account of the HUGO project see chapter 4.

A Company and a Product Based on the Pyrosequencing Method – A Positive Financial Outlook

The reason why the venture capital firm decided to invest in the commercialisation of the pyrosequencing method was that the future prospects for such a product were very positive. Such a view was also later expressed in one of Pyrosequencing's annual reports:

> "Financial analytics suggest that the market for applied genomics will be a market of several billion dollars." (Author's translation) (Pyrosequencing Annual Report, 2000, p. 5)

In general, the market for biotech tooling was considered a potentially highly lucrative business area and as a company, Pyrosequencing seemed to have the perfect timing and product. The company aimed for a diverse customer base consisting of large corporations within areas such as pharmaceuticals, genetics and agriculture, but also of academic research departments and hospitals. Furthermore, there was anticipation that many customers would buy at least two or more instruments for which they would need a continuous supply of reagent kits. The anticipated sales earnings were therefore high and were thought to lie somewhere in the range of 1000 to 2000 instruments per year. The instruments were forecast to account for only about half of the revenue, the other half would be provided by the patented consumables (the reagent kit) which the customer would have to buy in order to operate the instruments. The reagent sales would thus play a very important part in making Pyrosequencing a profitable company:

> "We are confident that the revenues from reagent sales will constitute a large source of income […]." (Author's translation) (Pyrosequencing Annual Report, 2000, p. 3)

The cost of purchasing a pyrosequencing instrument would lie in the range of about one hundred thousand Euros which would make it a rather costly analytical instrument. (Interview Ekström; Interview Nyrén; Pyrosequencing Annual Report, 2000)

The Venture Capital Firm - Odlander, Fredriksson & Co.

Founding a Venture Capital Firm

The commitment of Odlander, Fredriksson & Co. to support Pyrosequencing for seven years got the venture capital firm highly involved in the shaping of

Pyrosequencing both as a company and as a product. Also committed were the investors who expected a return on their investment. Odlander, Fredriksson & Co. was thus the mediator between the company Pyrosequencing and its investors. In order to understand the role of the venture capital firm Odlander, Fredriksson & Co. in the producing structure around Pyrosequencing it is important to understand the grounds for founding this venture capital firm and the basis of its business strategy.

In 1996, Odlander, Fredriksson & Co. became the first Swedish advisory firm for investment funds restricted to the life science area. Now, as then, it functions as a consultant for a number of funds under the name Health Cap. The different funds work as limited partnerships and have diverse large investors as owners. [51] It was while working at ABB Financial Services (ABB FS), that Björn Odlander and Peder Fredriksson started to think about the possibility of making early investments in life science ventures. They saw a void within the life science investment area in Sweden, particularly when it came to early stage investments in academic research. Together they brought a wealth of experience both within the investment and the life science areas; Odlander, with a research background within medicine, had later made a career as a financial analyst, and Fredriksson had more than 20 years experience within international investment banking when he came to ABB FS. The plan was to start a venture capital section within ABB FS and do early stage investments in diverse life science research projects, which because of their uncertain progress would be uninteresting to more traditional investors. In order to assemble the funds needed for such a venture they contacted large Swedish institutions and companies which showed great interest in the idea. However, during the process of mobilising

[51] Venture capital funds can be managed in several different ways. Over the years the two most common structures have been *closed-end funds* and *limited partnerships*. A closed-end fund is raised through various investors' acquisition of shares which can be traded just like individual stocks. This means that the original investor can trade their stocks to any other investor. However, since the shares can end up in the hands of inappropriate investors, this particular quality of this type of fund has been considered a problem. (Gompers & Lerner, 2001) The structure of a limited partnership is in this sense stricter, since it is only selected investors that are allowed to own shares. Also, the investors are not permitted to trade them. Another characteristic feature of limited partnerships is that they are arranged to self-liquidate after a certain amount of years which means that the investors get return on investment within a set time period. (Ibid.) According to Gompers & Lerner (2001) this quality can have both positive and negative effects on the performance of the venture capitalist firm and its portfolio companies. On the one hand it becomes an incentive for all parties to work for a constant improvement of the investment while on the other it can put too much pressure on new start-ups to prove successful too quickly. (Ibid.)

investors for the new venture, ABB FS was acquired by UniBank in Denmark. This meant that Odlander and Fredriksson would have to find another way to operate their business. As they found that the majority of the investors, which had been mobilised before the acquisition of ABB FS, still wanted to proceed with their investments, Odlander and Fredriksson decided to start an advisory firm controlling limited partnership funds. Consequently Odlander, Fredriksson & Co. was founded and from the start the firm was connected to established actors on the financial market such as the Swedish National Pension Funds, large insurance companies and banks. (Interview Odlander; Interview Steiner)

Ten years later the Health Cap funds administered about seven billion Euros and investments had been made in life science projects in different stages of maturity, from start-up companies to established firms. Thirty percent of the investments had been made in Scandinavia, 20-25% in USA, and the rest in remaining Europe. These investments were positioned within life science areas such as pharmaceuticals, biopharmaceuticals, biotech supply and medical technology. Health Cap is presently the largest provider of venture capital within the life sciences in the Nordic countries and one of the largest in Europe. (Ibid.)

Venture Capital Business Strategy

Odlander, Fredriksson & Co. describes its business strategy as multi-levelled; on the one hand their intention is to commercialise research, to find research that can turn into commercially interesting projects, with the purpose of creating strong research based companies. On the other hand, the firm's job is to administer the investors' money and their intention, in turn, is to receive return on investment. However, as the investments' wellbeing depends on the success of the commercialisation of projects, they see no contradiction in these seemingly different ideas. The goal is thus to achieve industrially useful products which will generate the needed returns. In planning for new investments, the firm's main activities are concentrated on evaluating different investment opportunities and to identifying research areas where there is a potential for new and profitable discoveries. They also work within their portfolio companies and often have very active roles in the companies' boards of directors as well as their day-to-day activities. In start-up investments the advisory firm recruits the staff, at least those in the leading positions, and formulates strategies for the future of the business. Ultimately, all this work has to result in a realisation of the investors' return on their investment, which means that something has to be produced and sold. (Interview Odlander; Interview Steiner)

According to Steiner, who is a partner of Health Cap and serves as CEO of several of the portfolio companies, an academic research result is

interesting to the firm if it is thought to satisfy an "unmet medical need." According to their investment approach the two most important aspects to consider when turning a new discovery into a prospering business activity are "[…] high quality management and uniquely positioned products based on outstanding science" (www.healthcap.se, 2009). To be able to offer the required knowledge and competence to both their investors and their portfolio companies Odlander, Fredriksson & Co. has focused on retaining both biomedical and financial expertise which are represented by two professional groups: investment bankers and physicians with a PhD degree. Every venture is first studied by members from these two groups and if they agree that the new idea could satisfy a potential unmet medical need, and that there is a profit to be made from it, the firm may decide to suggest an investment to the investors. (Ibid.)

Odlander, Fredriksson & Co. is a typical venture capital firm. In general these firms have many companies in which investments have been made and together they constitute the firm's portfolio of investments. Except for recruiting investors and raising funds, a venture capitalist's everyday activities consist of managing this portfolio by taking a more or less active part in the strategic planning and everyday activities of the portfolio companies. For Odlander, Fredriksson & Co. the degree of involvement in the portfolio company's activities depends on how well-established the company is. If the investment is a brand new start-up, the firm often takes a very active role in recruiting staff and forming company strategies. Conversely, the firm takes a more passive role when investments are made in already established companies. In any case, it is a prerequisite for an investment to take place that the firm takes one or more seats in the board of directors of the portfolio company. (Interview Odlander; Interview Steiner; Gompers & Lerner, 2001)

Investment in Pyrosequencing

A Product on the Way –A Focus on Fast Returns

Pyrosequencing was the ninth investment made by the Health Cap funds. When investigating the potential in commercialising the new sequencing method, the advisory firm evaluated it from both a financial and a medical standpoint. In their opinion, there had been very little progress within the sequencing area since the 1970s when Sanger was invented and therefore they saw a potential "unmet need" for new analytical sequencing methods. The largest deliverer of sequencing instruments based on the Sanger method

was then the company ABI, Applied Biosystems Inc.[52] With its two business segments of "Analytical instruments" and "Life sciences" it had a net revenue of more than one billion USD in 1996, from which approximately half could be accounted for by the sales of DNA sequencing equipment. It was, in other words, a very large and thriving corporation and it was also dealing with a growing demand for sequencing instruments. (Interview Steiner; Interview Odlander; ABI Annual Report, 1996)

Even though Sanger was the single most used method by the larger part of the life science research area and industry, the venture capital firm's evaluation suggested that the Sanger users were rather unhappy with their current instruments and demanded more accurate sequencing methods. From the firm's investigation of the commercial potential of the pyrosequencing method, the conclusion was that in general much research had been done in the pursuit of more accurate sequencing techniques, but no one had succeeded in producing one. The firm perceived the sequencing method presented by the researchers at KTH to be the first successful attempt at a more accurate way of performing sequencing. The primary feature of the pyrosequencing method which interested Odlander, Fredriksson & Co. was its accuracy, as this represented something different from many other techniques already on the market. It was partly the firm's appreciation of this particular attribute of the method which promoted their vision of a future sequencing product profiled for fast and highly accurate genetic sequencing within an application area which required such methods: SNP-analysis. (Interview Odlander; Interview Steiner)

With a set focus on SNP-analysis, there was little time to waste. The plan was to enter the *post genomic era* (the time after having sequenced the human genome) as a biotech tool supplier offering a product for fast and accurate identification and analysis of single nucleotide mutations. At the time Walldén entered the company the general opinion of the board (an opinion shared by Walldén) was that Pyrosequencing was already behind; with seven or eight other similar technologies already on the market, the company had to rush. It was also a question of the financial situation. In terms of financing, the company was entirely dependent on venture capital which forced it to act quickly. It needed to establish an efficient production system, start selling products and become financially independent within seven years. (Interview Ekström; Interview Walldén)

[52]ABI was owned by the Perkin Elmer Corporation, a global manufacturer and supplier within the life sciences and optoelectronics. Today, ABI has formed 'Life Technologies' through a merger with Invitrogen in 2008.

> "Venture capital is hungry, it's in its nature and it should be: it goes in and finances generously but then it wants quick returns. This was our frame of mind: generous financing but act as quickly as possible." (Interview Walldén)

According to the company management led by Walldén, the three most important goals to achieve during the start-up years were first to secure the finances of the company, second, to create market acceptance for the products and, third, to make it into a public limited company. The technological development of the pyrosequencing instrument would be dealt with in parallel to these tasks. With regard to technical issues, the first goal was to produce an efficient and user friendly automated system for the pyrosequencing method. The ambition was to make it understandable and operational "even to a child." This goal was considered to have been achieved as the first product, the PSQ96, was launched in 1999. The process of constructing and producing the instrument was a joint achievement of Partnertech and Pyrosequencing and the launching of a first product only two years after founding the company was considered a great success. Few other companies in the same situation as Pyrosequencing had ever made such an achievement. (Interview Alm; Interview Ekström; Interview Walldén)

A Commercial Success or Not?

In 2000, Pyrosequencing was made a public limited company and valued at nearly four hundred million Euros on the stock market. This put the company in an even more distressed situation than before. Not only was it forced to become profitable within the time perspective given by the investors, but it also had to prove itself worthy of the high valuation set in the stock market introduction. Hence, the company needed to increase its sales to reach a certain turnover. In retrospect, the early stock market introduction was described by the company management as both "a blessing and a curse"; through the new issue of shares (which produced 87 million Euros) they were able to make new investments but at the same time it put additional pressure on sales and expansion. The initial plan had been to go through with the introduction already a year earlier in order to raise capital. This idea came from an entirely different business concept where Pyrosequencing would mainly consist of one division for technological development, leaving the marketing and distribution divisions for a well-established partner to handle. The negotiations with such a potential partner were, however, closed down. One year later Pyrosequencing had started to make sales and the company was therefore capable of going through with the introduction on its own. (Interview Ekström; Interview Walldén)

In terms of recognition and initial sales, the formation of a public limited company was the beginning of a successful time for Pyrosequencing as a company. Products were being sold and the company got a lot of attention from the press. By this time the company had offices in the USA, Japan and Europe. Furthermore, because of the company's successes in launching a product after just three years and shortly thereafter being introduced onto the stock market. It was also awarded prizes such as "spin-off company of the year" by the Royal Swedish Academy of Engineering Sciences (IVA) and was mentioned on Forbe's list as "best newcomer." One of IVA's quotations when electing Pyrosequencing as the most successful and innovative new company in Sweden was:

> "Pyrosequencing has developed an exciting business opportunity from research environment to stock market introduced company with a focus on innovation." (IVA, press release, 2000-12-14)

Ekström made many promotional tours on which he and other representatives from the company demonstrated the new instrument to potential customers. His experience was that most people thought it was a brilliant sequencing tool which they could consider investing in. This great interest from potential customers nurtured the idea that there was a vast market for this kind of product and that Pyrosequencing as a company would be able to live up to the stock market valuation. Pyrosequencing was thus a company which seemingly had managed to transform a scientific breakthrough into a successful business venture:

> "With only 85 million SEK invested in development costs we have transformed an idea to a globally commercial product." (Author's translation) (Pyrosequencing Annual Report 2000, p.3)

At this time of "success" there were many ideas of how to diversify pyrosequencing as a product. One attempted direction was to scale-up the sequencing process and construct a high throughput sequencing system which would be used for the purpose of sequencing many samples in parallel. Instead of 96, there would be 384 wells where the biochemical reactions took place in parallel. This required that the method was made more cost-efficient and thus, from a user perspective, cheap enough to run on such a large scale. As every sequencing run required costly reagents which made the cost per each sequenced nucleotide fairly high, pyrosequencing was a rather expensive sequencing method in practise. Even though a great deal of company resources in terms of time, people and money were put into realising such a product, the format for the scaled-up

system could not achieve the required cost-efficiency. A few customers showed interest but as the board realised that the product would become too expensive to ever be interesting to a broader customer base the product development project was closed down. (Interview Ekström; Interview Pettersson; Interview Söderbäck; Pyrosequencing Annual Report, 2000)

Within a couple of years after the stock market introduction it was becoming clear that the company did not have the ability to live up to the original stock market valuation. Just 18 months after the introduction, the company's value had decreased to a tenth of the original valuation and Pyrosequencing was run with a loss of over 30 million Euros per year. According to the company management this could not go on. In a press release it was announced that Pyrosequencing now would focus on "near-term profitability" and therefore reduce expenses and personnel in administration, product development and central marketing (Pyrosequencing, press release, 2002-10-10). As the effort to direct all technological development towards SNP-applications had not received the expected response from the users, the company therefore tried to widen its application offer and identify new areas where the sequencing technique could prove useful. This was done by devoting R&D resources to explore areas such as microbial diagnostics and plant refining. However, the company board also took further action and soon several company mergers were implemented. (Interview Hjortsmark; Interview Odlander; Interview Steiner; Interview Söderbäck; Interview Walldén)

5.3 Mergers, Acquisitions and Divestment- Radical Changes in the Producing Structure around Pyrosequencing

Between 1997 and 2008 the company sold a total of around 500 pyrosequencing instruments of which only 275 were in active use in 2009. This means that on average, ten years after launching the first product, the company sold a little over 50 instruments per year, of which about only half remained in use. These numbers were drastically lower than the initially calculated sales statistics by the start-up team. The situation of customers buying an instrument but not continuously using the product was very unprofitable for the company since it was the constant purchases of consumables (the reagent kit) which were supposed to bring in a large part of the earnings. An attempt was made to resolve the situation of products not being sold by several company mergers. In 2003, the board decided that a good strategic move would be to merge with another Uppsala-based biotech

company in the Odlander, Fredriksson & Co. and Health Cap portfolio called Personal Chemistry. This company's products were based on a microwave technique to reduce the reaction time in chemical syntheses of organic substances. In spite of its rather large customer base, it was still not profitable and unlike Pyrosequencing, not a public limited company. The board's main arguments for the merger were that Pyrosequencing was in need of a broader range of products and that there were synergistic effects to be expected in the R&D division. Odlander, Fredriksson & Co., was represented on both of the companies' boards, and had an ambition to merge the two companies into one broad biotech supply company that could offer a number of products that any general science laboratory would need. Also, as Pyrosequencing and Personal Chemistry had a mutual supplier of components, Partnertech, there were anticipated synergistic effects on the supply side as well. (Interview Joergensen; Interview Odlander; Interview Schanche; Interview Steiner: Interview Söderbäck; Interview Walldén)

After this initial merger another acquisition followed; it was an American company, Biotage LCC, producing chromatographic equipment that would be a complementary technology to the one offered by Personal Chemistry.[53] The new corporation consisted of the three merged companies, took the name Biotage, and was divided into two main divisions: Biosystems (previously Pyrosequencing), and Discovery Chemistry (previously Personal Chemistry and Biotage LCC). As there had long been in the Pyrosequencing board the vision of having at least three lines of products and becoming part of an established production structure, they were pleased with the mergers. With a new CEO in place, Jeff Bork, focus was set on cutbacks in order to slowly become a profitable business. The re-organisations were harsh: of the 360 people employed after the merger, just 267 remained, which left only the sales and marketing division almost fully intact. The R&D department was severely cut down. The approximately one hundred million Euros, which Pyrosequencing had earned at the stock market introduction, was all spent on the acquisitions which meant that nothing was spent on developing the technique or the products. After 2003, more acquisitions followed.[54] However, being in the same type of area as the already acquired companies, these were only compatible with the Discovery Chemistry division. It was also clear that the users of the two divisions were very different in terms of application areas; Discovery Chemistry represented a supply of pharmaceutical molecules while Biosystems represented applications within genomics. These products neither represented the same type of user nor the same type of user behaviour. (Interview Odlander, Interview Ekström:

[53] A technology used for protein purification, for instance connected to drug development.
[54] One such acquisition was that of Argonaute which produced consumables for chromatographic equipment. (Interview Schanche)

Interview Schanche; Interview Steiner; Interview Söderbäck; Biotage Annual Report, 2008)

A Financial Upswing –The Result of Economic Tightening and the Involvement of a New Actor Interested in the Pyrosequencing Method

For the first time since its creation the production formed around pyrosequencing became profitable in 2006 through the division Biosystems. (Biotage Annual Report, 2006) However, the answer lay not in an emerging demand but rather in the new cost-cutting focus. Under the supervision of Bork, Biotage had become an economically tight organisation, focusing only on becoming profitable. This meant that rather than being involved in technological development and creating new products (which within the Biosystems division had practically been a non-existent activity for the previous couple of years), financial and human resources within R&D were cut down to a minimum. The major reason for Biosystems' profitability was thus the consolidation of Biotage and the economic tightening of the research and product development activities. (Interview Ekström; Interview Joergensen; Interview Odlander)

Another reason for the financial upswing was a company called 454 Life Sciences based in Branford, CT, USA. In the early 2000s, 454 was a very small start-up company which had spun off from CuraGen - a midsized biopharmaceutical company formed around the time of the beginning of the HUGO project, focusing on identifying disease-causing genes. 454's plan was to put together a high throughput sequencing system with the goal of enabling cheap whole genome sequencing. Through the acquisition of the licence for the pyrosequencing technique, the idea was to make it a part component in this larger sequencing system. As Pyrosequencing had earlier supplied CuraGen with a PSQ96 as early as 1999 it had made the American company familiar with the pyrosequencing technique and thus interested in using the same principle as a component in their own sequencing product. The licensing contract signed in 2003 prohibited Pyrosequencing's involvement in whole genome sequencing - this would be an exclusive area for 454 during a 5-year period. After this period, 454 would have the option of maintaining its exclusive rights for the remaining lifetime of the licensed patents for the cost of 0.5-1 million USD per year. However, as the incomes from the 454 acquisition of the licence would improve the financial situation of Pyrosequencing and also spread the use of the sequencing technique, the exclusion from the whole genome area was considered a tolerable downside

by the Pyrosequencing board. [55] (Interview McLeod; Interview Uhlén; 454 Life Sciences, press release, 2003-08-19)

The Termination of Pyrosequencing Within Biotage

Despite Biotage becoming a profitable business in 2006, in early 2008 the company was still more than a fifth dependent on venture capital from Health Cap as well as from Investor; therefore, the strategic focus of cutting down costs remained strong.[56] The plan for 2008 was to start developing the products that were within the company rather than going after new ones through acquisitions. These goals were left for the new CEO, Joergensen, to fulfil. However, in spite of declaring high hopes in the business division based on pyrosequencing, in late 2008 the company board decided to divest itself of Biosystems. The division was acquired by the German company Qiagen which is a global provider of sample and assay technologies. This divestment concluded pyrosequencing's existence within the Biotage business constellation (see Figure 7).[57] Consequently, even though it was Pyrosequencing's funds that initially enabled the construction of Biotage, the Pyrosequencing-based division's existence within Biotage was eventually considered an economic burden and was thus dropped. During all these structural changes Partnertech has, however, remained the supplier of the pyrosequencing instrument still to this day (2010). (Interview Ekström; Interview Odlander; Interview Schanche; Interview Steiner; Interview Söderbäck; Biotage Annual Report, 2008)

[55] It would result in at least 4.5 million USD over 5 years.
[56] Investor is a well-established venture capital firm owned mainly by the Swedish Wallenberg family.
[57] For more information about Qiagen go to www.qiagen.com

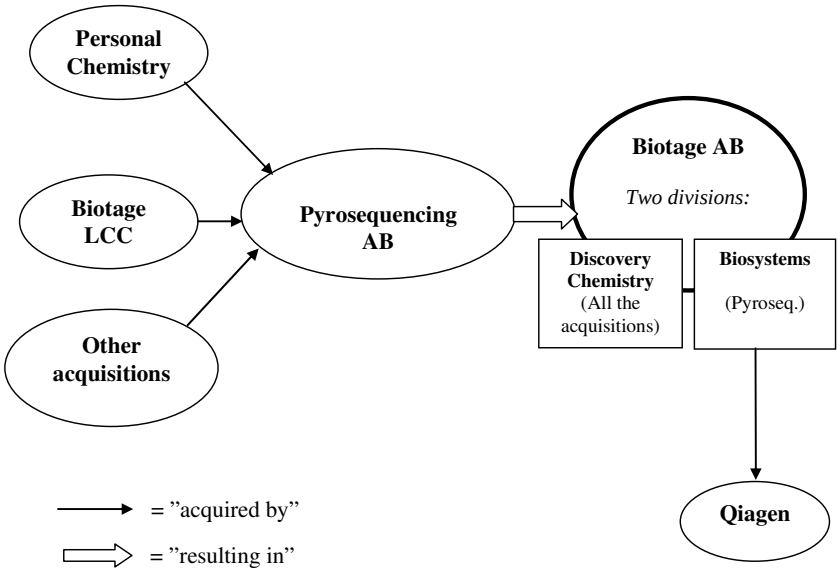

Figure 7. The picture demonstrates the acquisitions of Personal Chemistry, Biotage LCC and a few other companies by Pyrosequencing. These mergers resulted in Biotage AB with two business divisions: Discovery Chemistry (consisting of all the acquisitions) and Biosystems (consisting of Pyrosequencing). Biosystems, and thus the former Pyrosequencing, was later acquired by Qiagen which was Pyrosequencing's conclusion within the business constellation Biotage.

Before the divestment of pyrosequencing, the latest application for the pyrosequencing instrument which the company developed was one of the first which was ever considered: CpG-methylation analysis. Hence, in some ways the company refocused and took up the original ideas regarding development and application areas for pyrosequencing. In the view of the new CEO, Torben Joergensen, in the end, the company finally acknowledged the KTH group's ideas regarding further development of the method and also realised that diagnostics was the proper implementation area. However, they never got involved in any close collaboration with KTH as they were focusing on "[…] getting the company to make money, not to primarily engage in research." (Interview Joergensen) One of the main reasons for the conflict between the KTH researchers and the company, the improvement of read-length, was never really prioritised but the company management felt that it had taken several other ideas from the KTH researchers to heart.[58] (Interview Joergensen; Interview Odlander)

[58] In 2008 the company reached a read length of 60 bases.

5.4 Scientific and Business Resources in Conflict

Except for establishing the grounds for an automated version of the pyrosequencing method, an early collaboration with the KTH researchers also included work on enhancing the read length. However, even though the board, meeting on a yearly basis, decided that the research conducted at KTH should come into commercial production and use, this and other improvements did not go into production at the time. As the company was focused on producing an instrument that specialised in reading short DNA fragments for SNP-analysis, the read length was not considered a decisive factor - this aspect was therefore left for future developments. The researchers at KTH and representatives from the company met on a monthly basis, mostly discussing the development of the reagents (the enzymes). As the sequencing method relied on the function and optimisation of the enzyme system, most of the development issues fell back on this particular part of the product. The company representatives, including board members and senior scientists at the company, had a difficult time taking the KTH researchers' ideas and results to heart. In retrospect this can be explained by poor communication between them and the KTH researchers. The experience of the company representatives was that the KTH researchers could not see the difficulty of transferring the results achieved in an academic laboratory environment to an industrial production of a commercial reagent kit. In order for the industrial product to be producible and distributable around the world, the biochemical components needed to be freeze-dried which created very different conditions compared to using and experimenting with fresh chemicals, as was the case in the academic laboratory. (Interview Ekström; Interview Krabbe; Interview Odlander; Interview Söderbäck; Interview Walldén)

Also, there were financial aspects to consider. Because of existing patents, the company was not allowed to use some of the techniques or substances proposed by the KTH researchers in their production without paying a substantial amount of money to various patent holders. One such example was the SSB protein meant for uncoiling the DNA strand to facilitate and quicken the sequencing process. Since this protein was protected by patents, the company would have had to acquire the rights to use it.[59] When taking such factors into account many of the development ideas coming from KTH were not considered realistic by the company representatives and management. (Interview Ekström; Interview Krabbe; Interview Odlander; Interview Söderbäck; Interview Walldén)

[59] Nevertheless, when becoming more established the company bought the rights for this particular substance.

5.5 In Summary

The pyrosequencing method's first encounter with a production setting only involved a few people within a smaller developing unit at Pharmacia which was to construct the commercial prototype. However, as soon as issues regarding its actual production and use were assessed by the company management, it was considered a risky investment and the project was shut down. Still, after the company Pyrosequencing had been founded it took the management only three years to make it a public limited company with a launched product. This achievement was acknowledged as a great success in turning groundbreaking scientific knowledge into a commercially attractive venture.

According to IVA and Forbe's list (among many other sources of lavish praise) the Pyrosequencing management had accomplished that which every "science-based" company wishes to achieve - transforming a new scientific idea into a commercially successful product within a relatively short timeframe. In the formation of such a company as this, it was necessary to focus on certain technical elements of the new method in order to launch it as a commercial product as fast as possible. The invested venture capital was generous but required fast financial returns. The backing of the investment lasted only seven years and it was essential to find a way to satisfy investors before that time elapsed; therefore, at an early stage, restrictions were imposed by the company as to how much the first product would be technologically developed, and for what type of applications it would be designed. These restrictions and the positive financial prognosis for a product of this kind steered the company and its product towards a strict focus on SNP-applications.

The business venture around pyrosequencing succeeded in making it a publicly limited company and launching a first product within a short period of time. However, creating long-term financial returns from the original pyrosequencing product turned out to be more difficult. The amount of sold products and consumables did not live up to the original expectations; only 500 instruments were sold in about ten years, of which only a little over half were still in active use some years later, compared to the initial sales estimate of about 1000-2000 instruments per year. The preconception that the company's customer base would consist mainly of large companies or research facilities, each demanding several instruments and therefore having a constant need for large amounts of consumables was not realised. This made the company management and board look for alternative solutions to create a quick return for the company's investors. Ultimately, this resulted in several company mergers and a subsequent divestment in the Pyrosequencing business division, Biosystems.

In the process of building a company and a product, the formed company and the method's academic originators ended up in conflict regarding the

appropriate development direction for the commercial product based on the pyrosequencing method. From the company representatives' perspective this was due to the researchers' naive attitude towards producing an industrial, commercially viable and globally-shippable product. In an academic laboratory the conditions could be altered and optimised during the research course. In an industrial setting, on the other hand, the very same conditions needed to be fixed so as to enable an efficient production and supply process. The construction of a company and a product thus did not allow for an exploratory approach, it was rather about the immediate commercial utilisation of the product and to be able to reach the short-term goals demanded by the investors.

6 Embedding Pyrosequencing into a Using Setting

It can now be seen how pyrosequencing evolved from its origin as an idea from a researcher's discontent with the Sanger method, to how it was developed within academia into a functioning method through the involvement of two different knowledge sources as well as research dating almost half a century back in time. It can also be seen how commercial ambition propelled it into a business setting where it became the basis of a new manufacturing structure, and as a commercial product was supplied to various customers. However, what was the reaction when pyrosequencing was embedded into a commercial using setting where the customers were both business and non-business laboratories?

This chapter will focus on five customers of Pyrosequencing to gain an insight into the user experience. Four of them are present users while one represents a former user. The first three are rather small customers within academia who have purchased one or two pyrosequencing instruments and use them for various research projects. The fourth is a test laboratory as well as a research facility within a hospital while the fifth is a larger clinical research facility which, despite several attempts, has not been able to find a use for the instrument in its activities. Since most pyrosequencing users are either academic or health related research departments, these customers represent the most frequent users of the pyrosequencing product.

6.1 Successful Embedding of Pyrosequencing Among Users –Four Customer Examples

The Department of Genetics and Pathology at Rudbeck Laboratory

In 2000, two PSQ96 instruments were purchased by the Department of Genetics and Pathology at the Rudbeck Laboratory in Uppsala. The department had agreed on being a beta-site (a user test site) for an improved version of the first pyrosequencing instrument. This implied that they would

work in close collaboration with the company in providing test result information and further development suggestions. The purchased instruments had a longer read length than the first commercial product and this improvement was mainly due to enhancements made in the reagent kit and software done by the group at KTH led by Nyrén. The user's expectation was that the instruments would provide fast and accurate genetic analysis within the context of forensic analysis. The group that would be using the instrument, led by Dr. Marie Allen, worked mainly with improving methods for forensic DNA analysis and undertook assignments provided by SKL (The Swedish Criminological Laboratory) and the Swedish Police. In these projects the group functioned as a criminological laboratory seeking answers in DNA collected at crime scenes. The laboratory thus played a decisive part in criminal investigations, which made the reliability of the methods and the results that these presented vital. (Interview Allen; Interview Ekström)

How would pyrosequencing as an analytical instrument contribute specifically to an environment involved in forensic analysis? The user's assignments often concerned assays which go beyond routine analysis and the DNA samples might be very small, old and deteriorated. Since reliability is a necessity, the group works with at least two methods in parallel to assure a test result's precision. A test result is valid only if the parallel methods produce the same answer. Working with parallel methods is also a way of verifying the accuracy of newly introduced analytical techniques. To become a trusted and useful method, a new instrument continuously needs to produce similar results to more established methods during a test period. Once it has gone through this lengthy process of gaining dependability it can be considered reliable enough to verify even newer methods. (Ibid.)

When introduced in the forensic group, the pyrosequencing instruments were placed in this particular work routine of using parallel sequencing instruments for the production of accurate and reliable test results for criminal investigations. Initially, the main application for which the forensic group wanted to use pyrosequencing was for the analysis of *mitochondrial* DNA, a type of DNA which is often used when there are limited amounts of evidence material. The group worked closely with the company to set up the proper assays for the particular application of mitochondrial DNA analysis. Meeting twice a month with company representatives and discussing possible improvements and different kinds of applications, the group was very enthusiastic about the pyrosequencing instrument and what it could offer to the forensic area. The possible improvements that were discussed (and in some cases carried out) concerned user-friendliness, the reagent kit composition and software. (Interview Allen; Interview Ekström; Nilsson et al., 2006)

The method which pyrosequencing was placed in parallel with was Sanger. Sanger was, and still is, the method which the forensic group uses

the most in their DNA analysis work.[60] Since it is the most well-established sequencing method, and is known for its robustness, it is highly valued in the forensic area in which reliability is absolutely key in a sequencing method. In Allen's forensic group, Sanger is therefore the technique to which newer methods, like pyrosequencing, are compared. However, since Sanger was very time consuming in some of its steps, the group saw great advantages with the newly introduced pyrosequencing instrument. The most obvious advantage was its ability to perform quick analyses. A typical analysis which required two days work with Sanger could be performed in just a few hours using pyrosequencing. The new method thus provided the group with a speedy way to produce results - a quality lacking in Sanger. (Interview Allen; Interview Ekström; Andréasson et al., 2002)

After setting up the proper assays for mitochondrial DNA analysis, the group instantly started to use pyrosequencing in their daily work routine as well as within their research. The continuous use of pyrosequencing in parallel to Sanger gradually resulted in the discovery of additional benefits of the new method. The most significant new feature, which no other sequencing method had yet been able to offer, concerned quantification. This meant that the method made possible the measurement of a sample containing two different DNA types (DNA from two different people) determining which of the two types had the highest presence. For several reasons this was an important new function in forensic analysis that provided helpful information in criminal investigations. The quantification function was thus a unique application made possible by the pyrosequencing method. In exploring other applications, the group also discovered the instrument's use in identifying and analysing genetic markers in nuclear DNA (for instance SNPs). As there are very scarce amounts of this type of DNA, one single copy in each cell, such analyses require highly sensitive methods. A third application, explored and found very useful by the group, was identifying and analysing SSRs.[61] SSRs are sequences of repeated nucleotides which show length variation between different individuals and are therefore a helpful tool in identifying a specific individual. (Interview Allen; Andréasson et al., 2006; Styrman et al., 2006)

As a beta-site to the pyrosequencing instrument, the forensic group entered a collaboration project funded by Vinnova, a research funding authority, which involved the founding research group at KTH led by Nyrén as well as Pyrosequencing as a company.[62] The purpose of the project was to

[60] This is stated in the year 2010.
[61] Simple Sequence Repeat (SSR) is a sequence of 2-5 repeated nucleotides which can occur 9-30 times in a row and thus demonstrate length variation among different individuals; by taking a DNA sample collected at a crime scene or other and comparing it with the DNA material of a specific individual it will demonstrate a match or a non-match.
[62] Vinnova is a Swedish governmental institute with the purpose of supporting innovation systems, for more information go to www.vinnova.se

find new applications for the pyrosequencing method and the three competences of the founding research group, together with the producing company and an active user was considered a good project constellation for such a goal. In this process the three parties started to work on a specially designed reagent kit that would be customised for forensic DNA analysis. The idea was that in collaboration with both Allen's and Nyrén's groups the company would develop, manufacture and sell a tailored reagent kit to be used in the pyrosequencing instruments for a more straightforward way of performing forensic DNA analyses. During the funded project many different sorts of solutions were discussed and experimented with. However, after some time the company terminated the work concerning the customised kit. The company's explanation for this was that the forensic area was considered too small for such a large investment and the reagent kit therefore never went into actual production. Even if this was considered a disappointment by the two research groups led by Allen and Nyrén, they nevertheless benefited from the funded collaboration project as several dissertations and publications came out as a result. The result of the collaboration between the three parties could thus be considered a great advancement within academic research for the two research groups, even though it did not have any direct benefit for the company. (Interview Allen; Interview Ekström; Interview Nyrén; see e.g. Allen & Andréasson, 2005)

After the termination of the Vinnova-funded project there has not been much contact between the company and the forensic group. According to Allen this is partly due to the re-organisations at Pyrosequencing in the early 2000s as well as the company merger, and partly because operating the instrument had by then become a routine procedure for the group. Since everything worked smoothly there was little reason for frequent interaction. The pyrosequencing instrument has been in constant use in Allen's group ever since it was purchased and the application areas for which it has been found useful have, as shown, increased. However, even though pyrosequencing has displayed many advantages compared to Sanger, because of its superiority in reading large quantities of DNA material the latter is still the most used sequencing method in the forensic group. For instance, during the beginning of 2008, the group was mainly involved in a project of screening mutations in very large genes. As this is an area that concerns long-read sequencing, Sanger was a more suitable technique. This left pyrosequencing outside the group's current work. During times of infrequent use of pyrosequencing, the group is not in need of the reagent kit supplied by the company. (Interview Allen; Andréasson et al., 2006; Styrman et al., 2006)

The Department of Medical Biochemistry and Microbiology

In 2001, The Department of Medical Biochemistry and Microbiology at Uppsala University purchased a pyrosequencing instrument with the intention of using it for a specific sequencing project. Pyrosequencing had offered the instrument to the department at a reduced price with the intention of spreading its use in different user environments. In general, the department performs research around molecular and cellular processes which regulate living organisms such as mammals, viruses and bacteria. Many of the projects concern the relationship between genotype and phenotype which makes genetic analysis a large part of their activities. The idea at the department was that the pyrosequencing instrument would be used for a specific project concerning diversity in pig DNA. However, since it was a rather large investment for such a small research facility, before the actual purchase the department wanted to make sure that they would be using the best available sequencing technique for their purposes. Therefore, the department performed a test where several different sequencing techniques were compared, pyrosequencing being one of them. According to the department's requirements and needs the pyrosequencing method proved to be the fastest and most accurate sequencing technique for SNP-applications. (Interview Pielberg; Pielberg et al., 2002; Fang & Andersson, 2006)

Having made sure that pyrosequencing met the standards of the department, the PSQ96 instrument was set up for use in the pig DNA project. This installation took place in collaboration with the company. The project aimed at genotyping coat colour variation in domestic pigs and in so doing establishing the connection between a particular gene location and its resulting phenotype. An additional aim was to compare pyrosequencing to another new sequencing technique: minisequencing. This was a new method which also specialised in identifying SNPs but, unlike pyrosequencing, it was based on the detection of a single nucleotide incorporation using labelled components (fluorescence or other). Both of the methods were considered suitable for this kind of application and significantly better than the formerly used technique of real-time PCR.[63] The department published several articles about their findings on DNA diversity in pigs when using the pyrosequencing instrument, demonstrating the effectiveness of implementing this kind of method. (Ibid.)

Once pyrosequencing had proved its value in the pig project, the instrument was also used in one of the department's most important projects, which concerned the connection between a certain coat colour in horses and the occurrence of melanoma (skin cancer). There is a particular horse breed

[63] Real-Time PCR is a molecular biological method which measures the amount of genetic material in a sample. It works like PCR (see 31) but also involves a fluorescently-labelled probe, the presence of which is measured.

that develops a grey coat at just a few years old which often also develops melanoma later in life. The project's goal was to test if there was a connection between the colouration of this horse type and the development of melanoma. The aim was thus to find the grey-causing mutation and investigate its link to a possible occurrence of skin cancer. With the use of several different methods, pyrosequencing being one of them, this goal was reached in 2008. The achievement received great attention and resulted in a publication in *Nature*, one of the most prestigious journals within the natural sciences. However, even though pyrosequencing was a contributing method in this particular project it was not mentioned in the published article due to limited available space in the journal. In only being given a certain amount of space for describing the methods and results of their project the authors were forced to exclude some parts of their research; one of the exclusions was pyrosequencing. This obviously meant that in spite of its value in this successful research project, the pyrosequencing instrument was not scientifically recognised. (Interview Pielberg; Pielberg et al., 2008)

A couple of years after their first purchase of a pyrosequencing instrument, the Department of Medical Biochemistry and Microbiology decided to upgrade their PSQ96 to a later model - a HSA. The purpose of the upgrade was to lower the reagent costs by using the function of *multiplexing* which was made possible by this later model. To multiplex is to run several samples in parallel. As the continuous purchases of reagent kits were a relatively large cost for the department, an initially expensive investment which in the end would lower the run costs was considered an advantageous deal. However, the incorporation of the newer model did not work as planned. The researchers at the department formed an opinion that the multiplexing function would ruin their samples and thus destroy hours of preparation work. Therefore, very few at the department used the function for which the newer model had been purchased. Instead the newly-acquired instrument was used in the same way as the old one, leaving little advantage in the upgrade to the newer model. (Ibid.)

The staff had, however, found other ways of making the otherwise expensive sequencing runs cheaper. The methodology was to use a universal end-part of the *primers*, the DNA fragments which initiate the whole sequencing process. This made the primers non-specific and they could thus be used for different genomic variants. As they bypassed the procedure of designing new primers for every different sequencing-run, these universal primers directly reduced the time and money spent on sequencing. Even though pyrosequencing is mainly intended for reading short DNA strands, the department often uses the instrument for "pure" sequencing tasks (reading longer strands) as well and think that it works excellently for this purpose. They do not see it as a problem that the instrument only has the ability to sequence 40 base pairs at a time; after one such run they simply re-use the DNA sample from that run, put in a new reagent kit and then read

another 40 base pairs. This procedure goes on until the entire required DNA string has been read. (Interview Pielberg; Guo & Milewicz, 2007)

Another research team which is also involved in animal genetics in Uppsala is the Department of Animal Breeding and Genetics at The Swedish University of Agricultural Sciences (SLU). Because of their overlapping research areas, this and the Department of Medical Biochemistry and Microbiology are in close collaboration which has also resulted in an exchange regarding the pyrosequencing instrument. When the Department of Medical Biochemistry and Microbiology acquired an instrument, their collaborator became interested in the method. However, since they had access to the pyrosequencing instrument owned by their research partner, the SLU department did not purchase an instrument of their own. Instead they let their collaborator perform sequencing analyses on their behalf or they used the instrument at Uppsala University. The two departments have also had meetings regarding how to operate the machine and to discuss possible new applications. The collaboration involving the common use of pyrosequencing has had great academic success in that it resulted in co-published articles in highly-ranked journals. (Interview Pielberg; see e.g. Jacobsson et al., 2004; Pielberg et al., 2005; Wattrang et al., 2005)

During the purchases of the two instruments, the Department of Medical Biochemistry and Microbiology was in close contact with the company and for some time thereafter. However, as there has been little trouble with getting the instrument to work this contact is now more or less non-existent. (Interview Pielberg; Pielberg et al., 2002)

The Department of Evolutionary Biology

In 2001, the Department of Evolutionary Biology at Uppsala University purchased a pyrosequencing instrument for analysing *ancient DNA*. By using fossil DNA as the basis of their analyses, this research group hopes to find answers to two different research questions. The first concerns the domestication and breeding of cattle, specifically finding out more about when and how this process took place, and which traits were selected. The second addresses the colonisation of Scandinavia, investigating the origin of the first colonisers. The DNA that they work with is often retrieved from very old bones which are rather hard to come by. In addition, the genetic material that can be gained from these bones is very sensitive and can easily be destroyed; this makes the research very specific in terms of how the research material is handled and of which analytical methods can be used. (Interview Svensson; Malmström et al., 2007; Svensson et al., 2007)

SbS methods have in many regards reformed the research area of ancient DNA analysis. Better techniques of how to retrieve, amplify and sequence

such delicate DNA material have contributed greatly to the advancement of this research area. The specific features of the pyrosequencing instrument which appealed to the department the most were its sensitivity and accuracy. Since ancient DNA is often deteriorated and damaged, as well as only found in fragmented condition, the methods used to analyse it need to be both sensitive and accurate. This means that, compared to the analysis of modern DNA, ancient DNA puts greater demands on the analytical instrument's precision. In addition, much of the DNA which the group retrieve is nuclear and, as mentioned before, since this type of DNA is much rarer than other DNA, the sensitivity of the method used is of even greater importance. For the ancient DNA group, the sensitivity of the instrument was its ability to start sequencing from the first available base in the unknown and sought-after DNA strand. Other methods, like Sanger, started reading the sequence from the 50th nucleotide at best. Such methods were clearly not useful in such situations, as the DNA fragments that the group wanted to analyse were very small, sometimes only 20 base pairs long. The accuracy of the system, on the other hand, was manifest in the reading of each single nucleotide, one-by-one, present in the sough-after sequence. It was this combination of sensitivity and accuracy that made pyrosequencing a uniquely advantageous sequencing technique to the ancient DNA group. (Interview Svensson; Gilbert et al., 2007: Malmström et al., 2007; Svensson et al., 2007)

The instrument was introduced in the group's research projects by the setting up of assays suitable for the detection of SNPs in ancient DNA material. In this context, the SNP markers were used to trace genetic changes over time in trying to answer questions regarding domestication and colonisation. As earlier mentioned, the physically delicate nature of the research material dictates the methods used in the laboratory environment at the evolutionary biology department. The samples of the ancient DNA material, which are mainly retrieved from prehistoric bones, must be handled very delicately. Therefore, the samples can only be worked on in a particular safe room where all precautions have been taken for the ancient DNA not to be spoiled. Also, the researchers working with this DNA must wear protective clothing in order to prevent the samples becoming contaminated with other DNA from hairs or skin; such contamination would make the test results misleading as they would display a mixture of different kinds of DNA. Consequently, the context in which pyrosequencing was placed put high demands on the method as a deliverer of accurate results and intact DNA samples. Even if there are some improvements that could be made to the software, the group mainly sees the instrument's advantages as its user-friendliness, speed, accuracy, sensitivity and robustness. (Interview Svensson; Svensson et al., 2007; Svensson et al., 2008)

Another application for which the group started to use the pyrosequencing instrument was CpG-methylation analysis. As methylation is a molecular change which can influence the regulation of gene expression, it can affect

the phenotype of the organism. This particular application was appealing to the ancient DNA group as it was an important aspect to consider when tracing the genetic origin of a certain physical attribute. It is specifically the two applications of SNP and methylation-analysis that have proved so valuable to the ancient DNA group. Since its introduction, the instrument has spread from mainly being involved in the domestication and colonisation projects to also having been incorporated in such projects as tracing mutations in fungi. However, taking the whole department into consideration the instrument has remained somewhat underused as a specialist item. Even though there are several other research groups within the department working with SNP-analysis they use other technologies, often more expensive and time-consuming than pyrosequencing. (Interview Svensson; Svensson et al., 2008)

In setting up the instrument for its different applications in the study of ancient DNA, the department got much support from the company. During the initial phase of the use of the instrument there was thus a close collaboration between the two parties. However, due to the reorganisations at Pyrosequencing, this gradually changed. The company became rather inaccessible which broke the initially close connection. This was, however, not considered a big problem at the department as they were satisfied with how the instrument worked. They would nevertheless have preferred a closer collaboration than was subsequently the case. (Interview Svensson; Svensson et al., 2008)

The Clinical Chemistry Laboratory at the Örebro University Hospital

The Clinical Chemistry Laboratory at the Örebro University Hospital was founded in 1937 and is one of the oldest hospital laboratories in Sweden. Every day, the staff of around 70 people receives approximately 1500 to 2000 test tubes with samples which are to be analysed; they come mostly from the hospital but also from primary care centres around the district. As the laboratory performs many different types of analyses it is in need of a wide range of analytical tools and methods. It currently employs about 250 different types of methods and operates about a 100 instruments - this makes the laboratory a device-dense environment. Besides being a provider of hospital services, such as running diagnostic tests, the laboratory also operates as a research facility and publishes several articles each year. Being within a university hospital, research is an important part of its activities. (Interview Nilsson; Interview Olsson; www.orebroll.se)

The pyrosequencing instrument now located at the Clinical Chemistry Laboratory was initially purchased by the Center for Clinical Research. This

center purchased the instrument after attending a demonstration performed by the company for the Department of Microbiology. The Department of Microbiology was not interested but the Clinical Research centre saw a use for the instrument in a study which they had recently begun and which required SNP-analysis of child DNA. However, due to lack of funding, the project could not be carried through. The whole project was terminated which left the pyrosequencing instrument without a direct use at the Clinical Research Centre. Therefore, as a neighbouring department also involved in DNA analysis, the Clinical Chemistry Laboratory decided to try to incorporate the instrument into their activities. The aim was to replace their current instrument for DNA analysis which was based on the method of PCR-REA, which used *restriction enzymes* to cut the DNA sequence at certain positions, revealing the locations of different sought-after nucleotides and, in this way, giving answers to sequencing-related questions.[64] It was an uncertain and rather time-consuming process which did not always produce dependable results, which was unacceptable in a hospital laboratory providing services directly involved in maintaining people's health. (Interview Nilsson; Interview Olsson)

Initially the pyrosequencing instrument was set up to run the same three types of routine assays which the previous device had handled. It turned out to be particularly useful in blood analysis, testing for conditions like lactose intolerance or hemochromatosis, but also for identifying risk factors which later might lead to dementia or similar conditions.[65] Besides SNP-analysis, the laboratory also found use for the instrument in performing CpG-methylation analysis. This adaptability quickly made the pyrosequencing instrument a part of the daily work routine concerning blood analysis at the laboratory. Also, compared to the previous method, pyrosequencing delivered quality results which improved the laboratory's ability to offer safe and accurate genetic analysis services. In addition, it was easy to train the laboratory staff to operate the instrument. This made it possible to maintain a full complement of pyrosequencing-educated people at the hospital which allowed the laboratory to offer genetic analysis around the clock, throughout the year. The "work routine cycle" set up around pyrosequencing worked in the following fashion: each cycle started with a blood sample that needed to be analysed with reference to a particular condition. The first action was to extract the DNA from the blood. The extracted DNA was then amplified by the use of PCR (see 31) and subsequently run in the pyrosequencing instrument. Depending on the test result, the outcome was either a simple note in the person's protocol or a referral for further testing and treatment. (Ibid.)

[64] Polymerase Chain Reaction Restriction Enzyme Analysis.
[65] Hemochromatosis is a genetic disorder resulting in an iron overload.

Through the use of pyrosequencing, the Clinical Chemistry Laboratory became the first Swedish laboratory to offer genotyping of lactose intolerance. Because of the influx of test samples, both nationally and internationally, it also became possible to perform research studies based on vast amounts of data. By developing a particular assay on the pyrosequencing instrument, an international study concerning the discovery and diagnostics of alternative lactose mutations could be performed and published. The provision of a standardised working procedure in developing new genetic assays with the pyrosequencing instrument resulted in the possibility of performing this and several other research studies. In turn, this has contributed to a more efficient production of articles at the laboratory. (See e.g. Nilsson & Johansson, 2004; Börjel et al., 2006; Almon et al., 2007; Nilsson et al., 2008). Hence, through the pyrosequencing instrument's input to the daily work routine at the laboratory, the instrument also became an integrated part of its research projects and, through the many publications it enabled, it has contributed to the laboratory's international recognition as a research facility. (Interview Nilsson; Interview Olsson; Nilsson & Olsson, 2008)

The research projects at the hospital cross intra-organisational borders - which means that the laboratory is involved in research ventures with several other departments at the hospital. One particular project that involved the pyrosequencing instrument was run in collaboration with the Department of Microbiology (the department at the hospital to which the company originally presented the instrument). The collaboration was based on a doctorial project concerning standard procedures of how to use the instrument for different applications. These methods were later incorporated as routine in the use of pyrosequencing at the laboratory. The setting up of new standard assays was also something with which the laboratory had help from the company. Both as a research instrument and as a routine procedure at the laboratory, the instrument is mainly used for SNP-analysis. As one of more than a 100 analytical instruments in the Clinical Chemistry Laboratory, pyrosequencing is an integrated and highly used method for different kinds of genetic testing. Its speed, accuracy and above all, its dependability, are crucial features in the laboratory's diagnostic and research activities. (Interview Nilsson: Interview Olsson)

In Summary

What the accounts of these user environments successfully having embedded pyrosequencing into their activities demonstrate is that the development of the pyrosequencing method continues through the use of the instrument. To be able to incorporate it into their activities, users modify it, develop new

types of assays and use it in specific ways that were not originally envisioned. The Department of Medical Biochemistry and Microbiology for instance adjusted their use of the instrument to make the sequencing runs cheaper and carry out "pure", or long-read, sequencing. Another example of this user adaptation is the forensic group at the Rudbeck Laboratory which, by using pyrosequencing, discovered a new way of identifying individuals which in certain circumstances before had been impossible.

It has thus been shown that the use of pyrosequencing has provided customers with further means to do research and publish their findings. This was also found to be the case in the original development setting at KTH and their academic collaborators; in using and developing the pyrosequencing technique, the method works as a promoter of scientific research as it allows for further research, both by producing research results regarding how it can be used and by the analytical results it in turn produces. A striking feature about these users are, however, that they are all rather small, financially-restricted research facilities which have only bought one or two instruments and a relatively small amount of consumables. The Clinical Chemistry Laboratory at the Örebro University Hospital stands as a partial exception to this trend, as it is a large laboratory facility, but still its frequent use of pyrosequencing has not led it to buy several instruments or large amounts of consumables. This is a common quality among Pyrosequencing customers. Thus, even though the users find their purchased instruments highly valuable for their research and daily routine work, their use does not generate a large or steady demand for either instruments or consumables.

6.2 Unsuccessful Embedding of Pyrosequencing in the Using Setting – The Example of New York Blood Center

Introducing New York Blood Center

The New York Blood Center (NYBC) is a private, non-profit-making organisation with the primary mission to collect and distribute blood to hospitals for patient care. In total, it serves about 200 hospitals in the greater New York area, including New Jersey, and about 20 million people in the region. In the USA, unlike in many European countries, blood collection is a private enterprise. The Red Cross handles about half of the country's blood collection and the rest is handled by regional, independent blood centres like NYBC. Even though the centre is a non-profit-making organisation, it operates as a business. The official objective is, however, to keep the business running rather than to make large returns. In addition, the centre has

a large research organisation, The Lindsley F. Kimball Research Institute (LFKRI), which separates NYBC from any other blood centre in the world. LFKRI is supported by about 140 researchers who, in order to gain new knowledge around blood-related diseases, cover varied research areas such as chemistry, biology, molecular studies, genetics, virology, immunology and epidemiology. The institute performs basic as well as applied research. To be able to safeguard the results from this vast research activity, NYBC also has a patent and licensing department which evaluates, protects and markets new discoveries made by the institute. In addition, NYBC has the world's oldest and one of the largest public umbilical cord blood bank from which they have managed to build up a large stem cell inventory. The inventory was developed mainly during the 1990s. Gaining acceptance as part of public health care, cord blood is increasingly being used as an alternative to bone marrow in blood transplants. It is, however, still an experimental treatment. In addition to collecting the donors' blood, the centre offers them related services such as checking blood pressure, studying haemoglobins and other types of physical examinations. (Interview Valinsky; www.nybloodcenter.org; NYBC Annual Report, 2007)

Wanting to Offer More to the Donors – the Need for Sequencing

Today, genetic screening is also a natural part of the centre's range of therapeutic services. This was, however, not the case a few years ago. Collecting blood from around 2000 donors every day, Dr. Jay Valinsky, Vice President of Information and Technology at NYBC, and his team wondered if there was not anything more, besides building a blood bank that the centre could offer its donors. Being a medical research institute, they were mainly interested in diagnostics which led them to the question whether or not they could perform genetic screening among these healthy individuals. Screening is a process of studying an individual's genetic material in search of known genetic defects that are connected to diseases. The screening would thus be used for tracing potential genetic conditions that might impact the donors' lives. The centre was particularly interested in a genetic disease called hereditary hemochromatosis. This is the most common disease resulting from iron overload as well as one of the most common genetic disorders in the USA. A major reason for the centre's interest in this particular condition, except for its prevalence, was the peculiar nature of its cure. It so happens that the treatment for hemochromatosis is continuous blood donation. To be able to diagnose the condition, as well as offer the patient treatment, made diagnosing this genetic disease fit well into NYBC's activities. (Interview Valinsky; www.nybloodcenter.org)

According to Valinsky, the intention of this development towards diagnostics was primarily to provide yet another service for the donors, not for the benefit of the centre itself. Therefore, a first and major concern was how the genetic screening procedure would be done within the context of routine blood drive; for people to accept this additional service, it could not be too disruptive. The team saw many difficulties with introducing an element of such contentious nature as genetic testing within the frame of blood donation and were not sure how people would react to it. In order to find out how their donors felt about the matter, the centre set up a test where they asked about 1000 donors about genetic screening. The result was very surprising; NYBC realised that these individuals were willing to accept both genetic screening and being told the results. However, it was not just a matter of not upsetting the donors. NYBC understood that genetically screening donor blood would be a multi-step process with a front-end and a back-end. At the front-end they would handle blood collection and DNA extraction, and at the back-end the extracted DNA would be screened and analysed. Hence, the centre's next concern was how it would do large-scale extraction and screening efficiently in an automated fashion, as well as how the front and back ends would be made compatible in terms of which type of DNA that was extracted and which methods that would be used. (Interview Valinsky; NYBC Annual Report, 2007)

Trying to Embed Pyrosequencing Part One: Genetic Screening

Setting up the screening project meant finding and incorporating new methods both on the front and back ends of the process. The centre already had conventional methods of performing both DNA extraction and screening but the intention was to find automated solutions that would do this much more efficiently. While the search for automated solutions progressed, the laboratory staff started to use conventional methods since there was some time pressure in getting test results. While still trying to locate a solution for the front-end of the process, NYBC started to investigate an analytical instrument suitable for the back-end that had been recommended to them by one of their many collaborators, Colombia University in New York City - a pyrosequencing instrument. NYBC was interested in studying SNPs in tracing hereditary hemochromatosis, and was consequently looking for a method that would offer that kind of automated service. Since identifying and analysing SNPs was what the pyrosequencing instrument was specialised in, it seemed like a very attractive solution to the centre. After some consideration, in 2001, NYBC therefore bought a pyrosequencing device to make it a part of the back-end of the screening project. At this stage, the idea was that the method would work as an analytic instrument

and hence analyse the identified SNPs. However, once they received the instrument and started testing it, they immediately ran in to trouble. Some of the problems were related to blood sample quality and some of them to *primer design* (the short nucleotide string which initiates DNA synthesis). This forced NYBC to design special primers in order for the screening to work. Due to difficulties in getting organised with the people at Pyrosequencing, this was not an easy task but eventually NYBC got the new primers to work according to plan. (Interview Valinsky; NYBC Annual Report, 2007)

Even though the centre had bought a pyrosequencing instrument, it was not the only method being used for the analytical part of the project; they were actually doing three things in parallel: i) sending some samples to other laboratories which performed tests by conventional methods, ii) testing some samples by using conventional methods themselves, and iii) trying to develop the pyrosequencing instrument as part of a program that would link automated DNA extraction on the front-end to pyrosequencing on the back-end. This resulted in pyrosequencing being used just as a screening tool, identifying samples that could be of interest to the project. These samples were then put in more conventional assays for the analysis. This meant that the intended use of pyrosequencing, as an analytical instrument taking care of the entire back-end of the project, was not realised. Also, for a long period of time the project members at NYBC were so focused on making the automated extraction on the front-end work smoothly that this part of the project got more attention than the analytical part. In addition, when it came to the back-end, they spent more time working with the conventional assays than with pyrosequencing. The reason was not that the pyrosequencing equipment did not work, but rather that the centre was under time pressure. Since they needed to produce test results and did not have enough skill to efficiently operate the pyrosequencing instrument, they focused on what they already knew by using the conventional assays. (Interview Reid; Interview Valinsky)

There was yet another reason for the pyrosequencing instrument not becoming a natural part of the work practice at NYBC. The basis for the screening project was to diagnose people who had hereditary hemochromatosis and to do that they needed to determine whether an individual was *homozygote* or *heterozygote*; this meant that they needed to determine whether the donor had double or single traits for the disease or, put more simply, whether the individual had a variant of the same gene which could compensate for the defective one. This is a very simple procedure since the test results are very "black and white" - it is either there or it is not. Therefore, it was not difficult to achieve useful results with a rather simplistic method. In this regard, the pyrosequencing instrument was perceived as far more advanced than required; as equal results could be produced by a rather poor and imprecise method, the testing did not require

the features of sensitivity or accuracy provided by the pyrosequencing method. To sum up, the instrument was perceived as difficult to operate as well as too sophisticated for the type of analyses performed by the research team. (Ibid.)

Trying to Embed Pyrosequencing Part Two: Blood Typing

Even if the instrument was not being incorporated as planned into the screening project, NYBC had many other kinds of uses in mind for the pyrosequencing instrument; one of them was for the task of determining the donors' blood types. Normally this is done through analysis of the person's phenotype, which means that it is the physical features of the blood that are examined. However, the centre wanted to do this by looking at the person's genotype, which meant that they wanted to examine the blood on a genetic level. In other words, they wanted to study the genes that determined the blood's phenotype. Being able to determine an individual's blood type genetically was very interesting to NYBC since this would eliminate the risk of the centre giving people the wrong blood type. People who frequently get blood transfusions may very well have been given the wrong blood type on occasion in the past. This makes them develop antibodies which sensitises them for the next transfusion and further complicates the transfusion procedure. It also becomes difficult to determine such a person's blood type by looking at the blood's phenotype. Studying the same person's genotype bypasses these problems and directly accesses the original blood type information. For NYBC, which was in the business of collecting and distributing blood, as well as offering blood-related health services, this was considered an important competence to have in-house. (Interview Valinsky; Reid, 2002; Lomas-Francis, 2006)

To be able to proceed with this plan, they needed help from the company in setting up the proper assays and protocols. NYBC was confident that this kind of project would be very interesting to the company since it would require analysis of complex sequences, where knowing the sequence adjacent to the sought-after SNP would be crucial. The pyrosequencing method's specificity qualities seemed ideal for this task and could also offer NYBC the throughput that it needed in order to sequence as many donors during as little time as possible. Yet, when discussing it with the company, the centre experienced a very unenthusiastic response. In their view, Pyrosequencing just did not seem interested in pursuing the project. Disappointed in not getting the help that they needed, NYBC decided to carry on without using the pyrosequencing instrument. Instead, the research team chose to go along with a method based on microarray technology which, unlike pyrosequencing, was approved by the Federal Drug

Administration (FDA) - a governmental department which sets safety regulations for drugs and medical devices in the US.[66] (Ibid.)

A Regulatory Environment – a Hindrance to the Embedding of Pyrosequencing

The factor that makes NYBC a complex organisation is that it simultaneously represents two different types of operation - in some aspects it is a scientific research facility and in others it is a clinical laboratory within the diagnostic sphere. These two contexts represent rather different environments with dissimilar working procedures. Within a scientific research setting, people work according to scientific methods and can thus be considered to be confined to these conditions. However, these conditions also apply to a clinical laboratory in addition to a set of entirely different rules: when an organisation enters the area of diagnostics, it has to adjust to a complex regulatory environment that demands total transparency at every stage. In order for a clinical trial or a new drug to be approved, there are certain demands that need to be fulfilled which make clinical projects expensive and time-consuming. In the USA, these regulatory demands are set and controlled by the FDA. (Interview Valinsky; NYBC Annual Report, 2007)

When the research team at NYBC bought the pyrosequencing instrument, they wanted to see if they could incorporate genetic screening within the context of routine blood drive. However, as this and other projects developed and branched into several areas of use, the importance of making them valid as diagnostic applications became apparent. As the pyrosequencing instrument, in its current condition, was not approved for clinical trials, it was becoming an obstacle instead of an asset in the daily work at the NYBC

[66] Microarray is a general methodology based on miniaturised chemical reaction areas placed on a single plate which, through fluorescent labelling, demonstrates the presence of sought-after genetic markers. In the case of BioArray Solutions (www.bioarrays.com) which was the company producing the product used by NYBC, it uses beads as a solid support instead of plates. The technology can be used for SNP analysis, gene expression analysis, protein analysis, as well as cellular analysis. One example of how to use microarray technology is when wanting to determine which genes are activated and which are switched off during the course of a certain disease. In this case, each reaction area on the plate or bead contains a sequence representing a certain gene. When adding both "healthy" and "unhealthy" sequences (sequences from both healthy and unhealthy individuals with regard to the disease) to the plate with different labels (red and green), base-pairing in the different reaction areas representing different genes will take place. However, base paring will only take place if the gene represented in the reaction area also was present in the healthy or unhealthy individual. By using a laser scanner for the detection of the red and green labels, the plate will reveal which genes are activated or switched off in the healthy respectively the unhealthy individual by the demonstration of red and green colour in the different reaction areas. (www.bioarrays.com)

laboratory. The way it usually worked at NYBC was that instruments that were strictly confined only to research were only used as research instruments, and instruments purchased for diagnostic purposes were already FDA-approved. The pyrosequencing instrument however, needed to make a transition from being a research instrument to an approved diagnostic tool in order for it to remain useful at NYBC. For the more simplistic research questions, the pyrosequencing instrument was not distinguished, just acceptable, and there were other methods which could provide quicker and easier "yes or no" answers. It was rather in the diagnostics area, where features such as specificity and sensitivity were crucial, that the pyrosequencing technology excelled, but here it was off limits. For the pyrosequencing instrument to meet diagnostic standards, its assays needed to be diagnostically approved, it was thus up to the company to adjust their instrument, there was nothing NYBC could do about it. (Interview Reid; Interview Valinsky)

However, as the centre became aware of this problem and contacted the company, they once again met with little enthusiasm on the company's part. Even if it was under discussion, the company did not put the idea of FDA-approval of their instrument into practice during this time. As the company was not interested in approving their instrument for diagnostic purposes at the time, which would have been a rather lengthy and expensive process, it remained a research tool which severely limited its use at the NYBC laboratory. The purchased instrument was in use for two to three years but as it was never truly incorporated in the daily work routine it was completely replaced by other more well-known techniques at the centre. Another contributing factor in its decline was a general price escalation on reagents which was taking place at the time. As this reduced the benefits of exercising high-throughput sequencing this further limited their use of pyrosequencing, which demanded rather expensive reagents in order to be operated. (Interview Valinsky; Lomas-Francis, 2006)

In Summary

In the account of the NYBC setting, another picture of the use of pyrosequencing is outlined. Here, the instrument was not incorporated in any of the genetic analysis projects. Despite the fact that the tool was bought specifically for its ability to identify and analyse SNPs, it was not able to prove its worth at the centre. NYBC thus purchased an instrument with the intention of using it for the very same purpose for which it was designed but this still did not guarantee its usefulness. The new solution could not be combined with the existing knowledge at the laboratory, nor was it approved for use in diagnostics, which made the conventional methods seem more

attractive. This was most frustrating to the centre as it was not on the research side of a project that the method was most valuable. It was rather at the diagnostic level where qualities such as sensitivity and accuracy were crucial and in which the pyrosequencing instrument made a difference. However, as the regulatory environment of the diagnostics area prevented the pyrosequencing instrument from being used, it was bound to an area where it did not have anything unique to offer to the centre.

Epilogue - Pyrosequencing Re-Embedded Within Business

The following epilogue will show that, as a consequence of its commercialisation, the method of pyrosequencing appeared and became embedded in yet another business context. This chapter will describe 'what happened next' but perhaps even more importantly it will augment the view of resources, tangible and intangible, as ever-evolving through their introduction in new contexts over time. So far we have followed pyrosequencing through its development within scientific research to its commercialisation, and thus production within business, and to how it was embedded in user environments which in turn enabled further development through scientific research. What this very last empirical section will reveal is the appearance of the pyrosequencing method as a part component integrated into another product. Here, the company 454 Life Sciences, and its effort to incorporate pyrosequencing as a part of its new system solution for whole genome sequencing, will be examined.[67]

Introducing 454 Life Sciences

454 Life Sciences, today a subsidiary of one of the world's leading pharmaceutical companies, Roche, started out as a small project within the company CuraGen in Branford, Connecticut in 1999. The 454 project began with the founder and CEO of CuraGen, Joseph Rothberg, who had an idea to create an automated system for massive DNA sequencing in parallel. The vision was to make sequencing both fast and cheap enough for it to be possible to sequence individual human genomes on a routine basis in hospitals or other medical facilities. The goal was thus to create an instrument designed for high throughput sequencing which easily could be operated by medical staff. From this vision, CuraGen formed a project and started to work on a technical solution based on parallel sequencing. After working with the idea for a year, it seemed to have enough substance to

[67] Whole genome sequencing refers to the task of sequencing any organism's full genetic content.

actually work. However, as CuraGen's main activities were within drug development, and not biotech tooling, they needed people with a different set of skills to be able to continue the work. Also, since the project was in need of outside capital, it seemed easier to attract investors to a company involved in biotech tooling than to one within drug development. Therefore, the project was made into a subsidiary of CuraGen and 454 Life Sciences was founded. (Interview McLeod; www.nature.com/news)

Pyrosequencing – a Functioning Component?

The design of the first edition of the high-throughput system was a five-year-process which started with a very general idea of sequencing in parallel (the sequencing of several DNA strings simultaneously). However, which actual technologies would make this possible was, in the beginning, still a puzzle. The idea was based on using a SbS method as a sequencing principle but as there were a number of available SbS methods which had to be considered, the group needed to review which one would best fit their idea for a sequencing system. Christopher McLeod, the CEO of 454 since 2005, took an active part in this review process. From the perspective of 454, the main advantage of considering a method like pyrosequencing was its use in bioluminescent detection of incorporated nucleotides. This feature made pyrosequencing faster than SbS methods using fluorescent detection. Also, in the 454 assessment, bioluminescent detection did not require sophisticated optical scanning systems which constantly required re-focusing and experienced frequent run failures. However, a major downside of pyrosequencing was that in its current state it had a read length of merely 20-25 base pairs (nucleotides). This was not an acceptable quality in the system that 454 intended to build. Yet, with the knowledge that the 454 board had gained about pyrosequencing (not only during the review process but also from using a pyrosequencing instrument which CuraGen had purchased a few years earlier) it decided that the read length, along with other features, was something they would develop once they had a licence for the technology. (Interview McLeod; Davies, BioITWorld.com, 2006)

Building a Sequencing System –Embedding Pyrosequencing

In 2003, 454 and Pyrosequencing signed the contract regarding 454's purchase of the licence for pyrosequencing. With this licence, 454 was granted exclusive rights to use pyrophosphate-based SbS in whole genome sequencing. Pyrosequencing, as a company, thus maintained the right to use their instruments for any other purpose than whole genome sequencing. However, for the technique to ever be useful for 454, the read length needed extensive enhancement. In order for their sequencing system to sequence entire genomes within a reasonable time and cost, the pyrosequencing method would have to be able to produce at least 100 base pairs in one run. Therefore, to optimise the method in terms of read length was the first and very important goal. (Interview McLeod; Davies, BioITWorld.com, 2006)

In the system that 454 intended to build, the part that pyrosequencing addressed, the incorporation of nucleotides in a growing DNA string, was just one of many components needed. The preparation steps of amplifying the DNA material to a detectable amount and arranging it to enable a massive parallel read were other such important mechanisms. A major difference between the original pyrosequencing instrument and the 454 instrument was that the original instrument read 96 strings in each run while the 454 instrument would have to read several hundred thousand strings in one run. The 454 sequencing system would thus be an assembly of several different techniques that needed to fit together in order for the system to be as efficient as possible. (Interview Irzyk; Interview McLeod)

Another technology that interested 454 and seemed to fit their purposes was emulsion-based clonal amplification. This method amplifies the DNA strands on very small beads in an emulsion. By attaching unique single-stranded DNA strings to beads, mixing it with oil and a "PCR cocktail" containing all the essential ingredients for amplification to occur, the amplification process takes place on the bead surfaces inside the oil drops. These drops are called micro-reactors. In the next step, the beads, now containing millions of copies of the unique DNA strings, are separated from the emulsion and can be used for the subsequent steps in sequencing. This bead-based method was considered a technically suitable preparation step to precede the pyrosequencing process. However, as it was a matter of sequencing not one, but hundreds of thousands of such beads, the step of parallel sequencing also needed to be solved. For this, 454 applied a special kind of plate, the PicoTiter Plate™ (PTP), which was a glass substrate with 1.6 million small wells, where each well would hold one bead. This was an already existing technique which 454 further developed for their system solution. The pyrosequencing reaction would take place in each well where the nucleotide incorporations would be detected through the pyro-reactions and reported in a flowgram, revealing the sequence of each string (see Figure

8). Hence, pyrosequencing, the emulsion-based clonal amplification method and the PTP were techniques that 454 modified or enhanced to fit into the 454 instrument. (Interview Irzyk; Interview McLeod; Margulies et al., 2005)

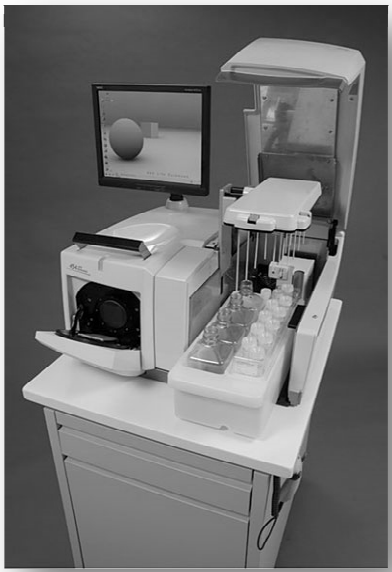

Figure 8. The 454 Genome Sequencer instrument based on the 454 sequencing technology, including the pyrosequencing principle. (Source: Blow, 2007. Rights of 454 Sequencing © 2010 Roche Diagnostics)

In 2005, the 454 company published a research article in *Nature* displaying the kind of fast and cheap analysis which could be performed with their instrument. By sequencing a bacterial genome with unprecedented speed and accuracy, the new sequencing technique was put forward as being equal to Sanger with greater development potential. Three years later, the company participated in another *Nature* article having sequenced the entire genome of James Watson (the researcher to first present the DNA double helix) using the 454 instrument. It was reported that compared to traditional capillary electrophoresis methods, such as Sanger, this method finished the task for one hundredth of the cost. Also, the article reported finding novel genes which would not have been possible if using traditional methods. However, the system also had its problems. For instance, the sequencing system had some difficulty in sequencing long repeats of a single base type and was therefore by some considered more suitable for sequencing short DNA

strands. There were thus improvements to be made. (Margulies et al., 2005; Blow, 2007; Wheeler et al., 2008; www.nature.com/news)

Continuing Development of the 454 Product and Company

Besides continuing the capacity development of the instrument, the company has also focused on finding different applications. One such application, which is made possible by the 454 instrument, is to identify and analyse specific genes or panels of genes. For instance, when studying a virus like HIV, the instrument can identify all of the different variants of HIV that are present in a sample. Since different HIV strains are susceptible to different drugs, by knowing which of the HIV strains that a person has, it is possible to individualise the medication for each HIV-infected person. With any other instrument this kind of analysis would be too expensive. Another consequence of cheap sequencing is the ability to find unknown mutations. While other methods can be used to sequence fragments of DNA in search of known or unknown mutations, the 454 instrument can sequence a whole genome which can be compared to the template of the human genome thereby displaying any deviations. Through this comparison differences can thus be identified for further analysis. Whole genome sequencing is useful in determining disease-causing mutations which makes the 454 sequencing system an alternative to "targeted" sequencing. (Interview McLeod; Goldberg et al., 2006; 454 Life Sciences, press release, 2007-06-15)

According to the official stance of the company, it planned to widen its product range and focus on the diagnostic field ever since its founding. However, in 2008, these were still plans for the future. Until then, their main focus is to develop the sequencing instrument to make it even faster and cheaper. This is partly done by miniaturising the conditions of the sequencing process. By using smaller beads and thereby getting higher bead density, it is possible to sequence even more strings in each run. Also, since the launch of its first instrument it has managed to enhance the read length of pyrosequencing from 100 to 200 base pairs in one run. By the end of 2008, the goal of being able to sequence 400 base pairs was reached - the same number of bases that the Sanger method handles. (Interview Irzyk; Interview McLeod)

During the first seven, 454 was mainly owned by CuraGen which held two-thirds of the company. From two rounds of financing, the company raised 60 million USD and the work force increased from ten to 130. In 2005, 454 entered a five-year partnership with Roche allowing it to be the distributor of 454's instruments and reagents worldwide. With Roche as their

distributor, 454 could remain a single business division with its main focus on developing the technology and still be globally represented through Roche's offices in Europe, USA and Asia. Three years before this partnership was scheduled to end, Roche made an offer of acquiring 454 with the goal of keeping it as an independent company with the focus still on whole genome sequencing. 454 accepted the offer and, in 2008, the company became wholly-owned by Roche. It has, as agreed, remained an "independent" company with its own facilities in Branford. In 2008, the company had a customer base of 125 users which were almost exclusively research departments around the world. (Interview McLeod; Varmazis, www.BioITWorld.com, 2007)

In Summary

By acquiring the licence for the pyrosequencing principle with the purpose of performing whole genome sequencing, 454 Life Sciences shows that it is perhaps not as a stand-alone product that the pyrosequencing method will prove most useful, but as a component in a larger system solution. However, in order for the new method to fit into this system, it had to be further developed and connected to other technical resources in the 454 device. When incorporated into the 454 instrument, pyrosequencing was both quantified and enhanced: the sequencing process took place in more than a million small wells simultaneously and the method's read length was increased many times over. This meant that 454 Life Sciences had recognised pyrosequencing as a method with great potential and therefore "re-opened" and optimised it in order for it to actually contribute to their own instrument. The use of the pyrosequencing method by 454 has earned it further scientific recognition and once again the anticipations are high; there are expectations that the 454 technique might be the next sequencing method to replace the classic Sanger technique. The anticipation is that this will be done with an improved version of the sequencing system built by 454. Pyrosequencing's role in this potential achievement will, if so, be as a "hidden" or embedded resource.

7 Analysis

The empirical chapters examined the three different but related settings, in which pyrosequencing needed to become embedded in order to possibly become a successful innovation. This chapter will present a deeper analysis of the empirical account, by emphasising which technical and organisational interdependencies would have needed to function, both within and between these settings, for pyrosequencing to have possibly had a chance at commercial success. The analysis of these interdependencies identifies and discusses the recognised resource interfaces of the pyrosequencing method, within and between the using, producing and developing settings. This analysis will give a deeper understanding of how these interfaces create directions in the innovation process, and how this affects the likelihood of achieving a commercially-solid innovation.

7.1 The Interfaces Within Scientific Research as a Developing Setting

The academic development of the pyrosequencing method was connected to a specific set of organisational and physical resource interfaces. These interfaces affected the initiation of the development process and shaped the way that the development work was organised, as well as the physical features of the sequencing method. This will demonstrate that: (i) as the physical features of the new method emerged in interaction with related resources, it was impossible to determine these features beforehand, and (ii) the development work was highly influenced by a "development logic" which was characterised by a constant testing of new development directions, and by an "academic logic" focusing on the scientific quality of the research work through publications and PhD projects.

The mixed interface between the new method and the established solution: the idea for a different way of performing sequencing arose in a time when the Sanger sequencing technique was dominant. The physical qualities of this technique put great demands on the knowledge and skill of

its users, which meant that when an untrained researcher needed to operate it, there were serious organisational problems. Thus the interface between the Sanger method as a physical technique and the level of user expertise instigated the development of a new technique for performing the same task. Sanger also indirectly affected which qualities were sought in the development of the new method; in setting the standard for what was considered robust sequencing and a pleasing "read length", Sanger worked as a point of reference for setting the technical goals of the new method. In addition, the existence of Sanger as a conventional sequencing method, and the fact that sequencing-by-synthesis (SbS) was an old and abandoned technique, affected the way in which the new method was received by other researchers and the scientific community in terms of funding and publicity. There was a great scepticism that the research group would succeed in doing what no one else had managed before: constructing a functioning SbS method which might create new ways of examining DNA. Also, more than twenty years later, when the method had been officially declared a great scientific achievement, it was still being compared to Sanger. Thus, in relation to the inventor, the new method itself, and the wider genetic science community, Sanger gave rise to a number of interfaces which not only instigated and influenced the development of the new method, but which also affected how the new method was evaluated as a scientific finding by the rest of the scientific community within genetics.

The physical interface between the method and the laboratory facilities: the laboratory equipment played a crucial part in the development of the new method, as it was the means through which progress with the experiments could be determined. In turn, this was connected to the composition of the method, the basic physical features of which were DNA, enzymes, and other reagents being experimented with in a very exploratory fashion. Creating the biochemical conditions for making the method work properly was the main issue and it was often unknown which of the reagents were hindering or enabling certain outcomes, or why particular combinations worked better than others. The technical properties of the method were thus determined by the physical interfaces in the enzyme mixture and which biochemical reactions they produced. This means that even though it was pretty clear which functions the separate components had individually, it was the effect of combining them which was unknown and thus needed research. This was very time-consuming work and often did not result in the expected outcome. As this process was so reliant on laboratory work, the properties of these facilities exerted a great influence on the development work. For instance, as the development of the method became all the more sophisticated, the combination of the luminometer and DNA material made it impossible to measure progress. As a consequence, the research development temporarily

took another direction, resulting in a different combination of the technical and biochemical components – this gave rise to a "reversed" method.

Thus, due to the interface between the DNA material used in the method and the luminometer, the features of the method were altered. Similarly, due to the use of different DNA material, and a new luminometer, it became possible for progress to be made using the original method. This shows that it was the combination of the method's features, and established research equipment, which determined research progress. It did not matter which physical features the method had if they could not be measured or visualised by the use of other equipment; it was by using the luminometer that the physical features of the method were ultimately determined and could be further understood. In this sense, the interface between the method and the luminometer was interrelated to the physical features of the method: the luminometer determined the measurability of the reagents, and thus which of them were to be included and experimented with. Hence, the availability and nature of laboratory facilities were highly influential on how the method could be experimented with, and therefore also on the ultimate physical character of the method.

The physical interfaces between the new method and complementary solutions: to solve various methodological problems in the sequencing or automation procedure, the initial method was at different times combined with other technical solutions. First it was combined with a different sequencing preparation procedure, the solid-phase technique, which came from another research group. This combined method solved some of the issues of developing a functioning sequencing technique, such as providing a manual washing step. It did, however, also create new problems. As it turned out, this particular resource combination did not present a straightforward way of creating an *automated* sequencing procedure; as long as the two methods were used with individual enzymes, different substances and mechanical parts (temporarily assembled together and optimised for each single reaction), the combined method could be made to work manually. However, when these same physical parts had to work in a more standardised and strict fashion, as in an automated technique, the components connected to the solid-phase technique created too many problems. The same applied with the approach of using a capillary flow system – the physical interface between such a system and the rest of the method did not seem to create a good match. Ultimately, it was the use of a similar component to those already used, another enzyme, which allowed the automation of the sequencing method. Thus, different resource combinations were tried in a trial-and-error fashion, and through this process one particular combination turned out to be more suitable for automation than the others.

The organisational interface between the two research groups: with regard to the organisational units, and thus the knowledge used in the development of the new method, there were two research groups which represented two knowledge areas: biochemistry, with particular focus on enzyme activity; and biotechnology, a fairly applied research area, in this case with a particular focus on DNA sequencing. These two research groups represented two different approaches of sequencing which, in many regards, reflected the groups' respective knowledge areas and backgrounds; the pyrosequencing method was based on the "natural" functions of enzymes, while the solid-phase technique was based on actively steering different components and reagents in a more technical manner. Ultimately, the two methods did not result in a successful combination, but the process of the two research groups learning from each other, and trying different directions, still had a great influence on the development of the pyrosequencing method. Thus, the combination of these two different sources of knowledge enabled new types of experiments which probably would not have been possible otherwise.

In addition, this interface indirectly related the original research group involved in developing the new method to other important resources. Already renowned within academic research, the research group involved in solid-phase research brought not only new knowledge to the development work, but also an association of scientific quality and relationships to business actors and financers. Just by being associated with the work of this group, the development of the pyrosequencing method was strengthened as a project of scientific significance, something which was demonstrated by the jointly-published articles and the further financing of the project. The research also became connected to an established manufacturer within biotech, and to a venture capital firm. The interface between the two groups thus affected the development of the method, both in terms of which knowledge was used and how the method became more scientifically recognised, but also how it made external physical and organisational resources available in the shape of business relationships and capital.

The mixed interfaces between the method and PhD projects: a significant feature of the developing setting was that much of the manual labour connected to the experiments of the method was performed by PhD students, who gradually joined the research around the new method. As more people got engaged in the project, this decreased the workload at the laboratory for the people initially involved, but it also meant that time needed to be devoted to assisting with their PhD projects. The development process was thus adjusted to the academic task of educating new researchers. The topic of these PhD projects needed to be specified separately, although still related to the same overall goal of optimising the sequencing method. In

this regard, there was not *one* project, but several smaller individual projects related to the same issue. These interfaces, between the method and the related PhD projects, created a work order in which very specific aspects of the method were scrutinised to produce publishable research results. This in turn incorporated the development of the method in various PhD theses, and several other publications, which fortified the method as a significant scientific finding.

The "physical" interface between the method and the publications: when the method could produce physical evidence that it worked as a sequencing technique, its successes could also be reported in scientific articles. Publication verified the ongoing research, and it could be made known within academia and elsewhere. To publish the various research results connected to the development of the new method was thus necessary for the method to be widely recognised as a scientific accomplishment. This, and the general requirement to publish in order to earn a position within academia as a scientist, therefore created an interface between the method and its publications in terms of which experiments were considered important and how they should be carried out. All directions and ideas needed to be tested and documented prior to publication. Such scientific publication can thus be seen as a product which was used to make the (initially unknown and ignored) research results into scientifically recognised research, and which also affected which type of results that were sought after. In addition, publication connected the new method to other resources, such as financing and new research projects. This meant that not only was the publication a resource in itself in verifying the scientific quality of the new method, but it also created other important resource interfaces.

Summing Up: The Making of a Scientific Resource Through Physical and Organisational Interfaces in the Developing Setting

Through interaction between a number of resources in the developing setting (i.e., specific technologies, physical equipment, research results, scientific publications, funding, PhD projects, and so on), a new method gradually emerged and became "stabilised" and accepted as a scientific resource. These resource interfaces created a development process, characterised by an academic logic of testing new ideas related to a certain research area, and by attempts to stabilise these ideas as "finished" scientific knowledge.

7.2 The Interfaces Within Business as a Producing Setting

The production of the pyrosequencing method taking place within business was also related to a specific set of organisational and physical resource interfaces which affected how the method was "locked" and "productified" as a commercial solution. This process, however, took a somewhat different direction than it did in the developing setting. In the producing setting the new method needed to be shaped as a standardised product in order to become embedded into a producing structure capable of standardised large-scale production; for this to happen, a product needed to be developed, and a producing structure – dealing with both the physical product and a set of applications – had to be built. This connected the new method to both new and established production facilities, other commercial products, venture capital, and management knowledge. As will be discussed below, these physical and organisational interfaces necessitated: (i) a "locked" commercial product, and (ii) a short-term perspective on profitability. First, let us take a look at the resource interfaces involved in the attempt to commercialise the new method within an established production structure, in which it was deemed to fit neither into the existing production system nor into the using setting.

The Interfaces Within the Established Producing Setting – Pharmacia Biotech

The short period of time during which the pyrosequencing method was a commercialisation project within Pharmacia, it existed only as a development project and a prototype. It was thus never brought into a production system to be shaped as a standardised product. In this regard the explorative unit, which was involved in developing the prototype, can be regarded as a developing setting of the producing company to which this unit belonged and which was tasked with transforming the prototype into a standardised product. The reason this never happened concerns the different existing interfaces both within and outside the organisational borders of the producing company which, directly or indirectly, would have become affected by the production of the new method.

The mixed interface between the prototype and the developing unit: the developing unit, within which the new method was being developed as a prototype, had been set up particularly to explore new solutions for future commercialisation. It was a very small department, rather detached from the

rest of the company operations, and it dealt exclusively with the technical features of potential commercial solutions, such as the new sequencing method. Within the developing unit, there were only a few selected people working on the prototype of the new method. The development approach was explorative, which meant that even though the goal was to achieve a prototype that could be transformed into a commercial product, there were still many different options for an automation that needed to be tested. At this point, the method was still a combination of two different techniques: pyrosequencing, and the solid-phase technique. It was not yet clear which of the technical and biochemical features of the merged method were to be focused on and which needed to be eliminated to maximise the efficiency of the automated version. The trial product, which came out as a result, was therefore a very preliminary and incomplete automated version of the sequencing method. Thus, the interface between the unit's open development approach, and the open-ended state of the method, resulted in a very experimental format of an automated sequencing technique.

The mixed interface between the prototype and the producing company: the producing company would, unlike the developing unit, have to deal with a range of possible situations in relation to commercialisation of the prototype. The product based on the prototype would have to fit into the existing production system (consisting of both internal facilities and those placed at key suppliers, within which a wide range of other products were being manufactured) as well as become embedded in the company's existing using setting. However, should the product be brought into and become embedded within this producing setting, it would be one of many products sharing the costs of maintaining the established production system. Nevertheless, the company management overseeing all the different operations assessed that a production of this type of product would require investment in production equipment, marketing and sales. This meant that, even though there was an already existing structure of production and marketing in which the new product might be able to become embedded (and thus share the costs with other existing products), it was still not considered able to support itself in terms of manufacturing and sales costs. One part of the explanation lay in that the use of the potential product within a using setting was considered very limited – and therefore not very profitable. The management also had to consider the implications of the forthcoming company merger, which made additional investment in research and development of new products, and with no immediate connection to the company's existing products, difficult to justify. The company thus not only assessed the costs of the prototype's development in relation to their internal production facilities and products, but also to their connected suppliers, customers and collaborators. Therefore, what the developing unit considered to be an exciting new technique was, due to the existing physical and

organisational resource structure both inside and outside the organisational borders of the company, considered a product with a small range of applications and therefore a costly as well as uncertain investment from the producing perspective.

The Interfaces Within the New Producing Setting – The Start-up Company

Setting up a new producing structure supporting the commercialisation of the pyrosequencing method, involved the establishment of new physical and organisational resources in the shape of a production process, knowledge, business relationships and a product. These new resources in turn needed to fit with an existing structure of investors, suppliers and other companies representing a variety of different resources. As will be discussed, the combination of these new and established resources influenced the features of the product and how it was produced.

The organisational interfaces related to the financing unit: the construction of a start-up company based on venture capital strongly affected the way that the producing unit was set up and the physical features of the product. The venture capital firm's most central relationships were those with its investors and to its portfolio companies. The investors were represented by established actors on the financial market such as the National Swedish Pension Funds, large insurance companies and banks which required investment plans and set procedures for every investment that was made. The relationships with these investors provided the capital needed to create possible profits for both the venture capital firm and the investors. The portfolio companies were various investments in the range of new start-ups to established companies and in all of which the firm had more or less central board and management positions. These relationships enabled capital generation through the realisation of an "exit" either through a trade sale or a public offering, and every investment had a limited time to present such an exit.[68] The construction of the producing structure around the new product was thus indirectly related to a set of investors with capital generation as their primary goal and a variety of other companies which the venture capital firm managed as an investment portfolio, from which a certain level of return on investment had to be produced. Therefore, the organisational interfaces between the venture capital firm, its other portfolio companies, and its investors, greatly affected the interface between the

[68] A public offering is when a company offers public shares or stock. A trade sale is when the portfolio company is acquired by another company.

venture capital firm and the company Pyrosequencing. This will be further discussed below.

The organisational interface between the company and the financing unit: the organisational interface between the venture capital firm and Pyrosequencing affected which people were placed in the company management and board, which in turn had a great influence on the company's strategic and managerial agenda. The demand to create return on investment within seven years required a speedy process of establishing the needed physical and organisational resources such as: appropriate supplier relationships, production equipment, a work force, and the technical grounds for an automated sequencing instrument. This interface also connected the company with a set of other portfolio companies, one of which it eventually merged with. This merger directly connected Pyrosequencing as a company to a new set of suppliers and customers. However, as the merged companies had very dissimilar user structures in terms of which the general user was and how the products were used, the combination did not create the expected economic benefits. This will be further elaborated on in the discussion of the interfaces between the producing and using settings.

The mixed interface between the product and the financing unit: the prognosis, which the original investment decision was based upon, forecasted a great use of a sequencing technique specialised for one particular type of application. This was based partly on the general scientific and technological development taking place (not least within the HUGO project) and partly on a general notion that there was a need for more accurate sequencing techniques. The pressure of creating quick earnings was also a very decisive factor in which type of application was deemed suitable for investment. The company board and management wanted to spend as little time and money as possible on transforming the method into a commercial product. The interface between the venture capital firm and the sequencing product, therefore, resulted in a physically-locked commercial solution which was specialised in one particular application area, which the method already could perform satisfactorily. This both formed the basis on which the product was designed and determined the production focus; the product would only excel in one area, which left all other factors irrelevant to the process from that point on. Thus, the interface between the venture capital firm and the product shaped a commercial solution that was physically restricted to perform only a certain type of genetic analysis. This, then, required an appropriate production system.

The mixed interface between the product and the production system: the production system set up to manufacture the instrument, and the consumables, needed to relate to an existing structure of suppliers and their products. It also needed to relate to the conditions for distribution of the finished product. The reagents had to be based on a supply of freeze-dried enzymes – something necessary for industrial handling of these substances. Thus, even if an enzyme displayed a set of features in its "natural" state, the function of the commercial reagent kit was only related to the features of this enzyme in its freeze-dried condition being delivered by the suppliers. This was also a necessary condition for the reagent kit to be able to be distributed in an economically sustainable fashion; the kit needed to be stored for long periods of time as well as be shipped to various places around the world – this required a robust and stable product. Also, the production of the physical instrument was handled solely by one of the suppliers which in turn depended on various sub-suppliers for the construction of several key components in the instrument, such as the valve system and electronic components for circuit cards. Thus, due to the physical and organisational resources to which the new production system needed to relate (such as available suppliers and components and the distribution of the product), the commercial solution was given certain features. Also, for the instrument to retain its qualities during the continuing production, there needed to be a constant interaction between the supplier of the instrument and the sub-suppliers.

Summing Up: The Making of a Business Resource Through Physical and Organisational Resource Interfaces in the Producing Setting

As the new method was introduced at Pharmacia Biotech, its development potential created a fit with the company's explorative unit, which further developed it into a prototype. However, as it was to be introduced into standardised production, and thus needed to be compatible with the existing resource interfaces which were connected to the established producing and using structure, its commercialisation was terminated. Thus, even though there was an established producing structure, in terms of production and marketing facilities, the potential product was deemed to require investment which may not be subsequently recouped. Consequently, when a new company was founded upon the very same product, a new and economically viable producing structure needed to be built, which the benefits of utilising the product within a using setting had to be able to support. Within the new producing setting, the product was connected to various resources represented by investors, other portfolio companies and suppliers. These

interfaces shaped the product into a strictly defined commercial solution, with the ability to perform a restricted number of tasks. In turn, this enabled quick product development and launch. As a business resource, the pyrosequencing method thus became embedded in a structure with an established supply of technical components and venture capital which, in turn, determined its ultimate physical features. Next we will learn what this meant in relation to the developing setting.

7.3 The Interfaces Between Scientific Research as a Developing Setting and Business as a Producing Setting

For something new to turn into an innovation, it cannot only be the focus of a developing setting, it also needs to be incorporated into a large-scale production. When, as in this case, the developing setting is involved in scientific research and the producing setting is within business, *the new* needs to develop interfaces with resources of a dissimilar character. In this case, representatives from the developing setting first interacted with one of the world's largest suppliers of biotech tools in an attempt to incorporate the new solution into an established production system. However, when this failed, a second attempt was made, as representatives from both the developing and the new producing setting jointly constructed a new start-up company. This created a number of physical and organisational resource interfaces between the developing and the producing setting which affected the way that they interacted and which direction the development and commercial production of the new method took. As will be shown, these interfaces resulted in the new sequencing procedure being one type of method with specific qualities within the developing setting, and another type of method with a different set of qualities within the producing setting. The commercialisation process thus did not result in *one* new solution, but in both a locked commercial product and in a method continuously being developed through scientific research. The resource interfaces which were developed in the respective setting would in turn create different types of benefits which could be gained from commercialisation of the new solution. In order to provide a deeper understanding as to why the scientific advances within the developing setting were irrelevant to the product and process development within the producing setting, these interfaces will be discussed in more detail below.

The interfaces between the developing setting and the established producing setting: in constructing a prototype for a potential product, the developing unit within Pharmacia Biotech collaborated with the developing setting within KTH. At the developing unit within the established producing structure, an exploratory development approach was taken, but it was nevertheless related to a specific kind of technical solution in solving the automation issue – the use of a capillary flow system. The academic developing setting, on the other hand, used an even more open approach and considered different kinds of automation solutions. When the prototype was finished within Pharmacia and it was considered for a standardised production, it was evaluated in relation to the existing production system and the existing using setting. As there was no clear fit between this new potential product and the existing ones (in terms of production facilities and user requirements), it was deemed uneconomic in terms of necessary investments and uncertain returns. At the same time, the development direction was changed within the academic developing setting and a more obvious way, at least in the laboratory, of carrying out automation was found. This connected the method to important publications and more research grants, which made it an essential resource within the academic developing setting. However, as this did not change anything in relation to the production system or the using setting connected to Pharmacia, it was still not considered a suitable investment. As a potential commercial product it could not present any economic benefits in relation to the established producing and using settings, which is why it was dropped altogether.

The mixed interfaces between the developing setting and the new producing setting: when the method gave rise to the construction of a new start-up company, it was embedded in a producing setting consisting not only of the new company but also of already established physical and organisational production resources such as suppliers, technical components and venture capital. As the new method needed to become part of a large-scale production in order to become commercialised, it had to connect with this established producing structure, which in turn had an effect on the method's features as a commercial solution and a business resource. This process was detached from the continuous development process around the method, which took place within the developing setting. Here it was connected to a totally different set of resources in the shape of laboratory equipment, PhD projects and publications. The physical features of the method, in which the connection to this particular set of resources resulted, were very different from those achieved in the producing setting. Also, the methods and components which were used within each setting differed greatly in terms of to which other resources these were indirectly connected. The producing setting had to consider patents and licences, and physical

circumstances connected to industrial production, which was more or less irrelevant to the developing setting. For a continued existence in an academic developing setting, on the other hand, the formulation of new research and PhD projects to acquire research funds were prerequisites, but to which a producing setting did not need to relate.

The difference between the scientific research results and those achieved within the start-up company facilities created great problems in organising any type of interaction between the two settings. The interaction that did take place in the shape of meetings, or co-published articles, rarely resulted in any physical alterations or development of either the product or the production system. This not only resulted in two different directions regarding development and production, but also in the existence of two methods with different features. One of these was a method displaying features such as enhanced read length and a variety of applications within the developing setting, both in regard to the original method and to the commercial solution which was continuously being experimented with. These features were however not considered transformable into a standardised product within the producing setting. The second was a commercial solution restricted to specific qualities and applications within the producing setting; this was considered a too narrowly defined method in the developing setting, but enabled a quick product launch and therefore created return on investment within the producing setting. It was nevertheless through the existence of this commercial solution which the developing setting could make new research progress and connect its research to other important resources such as publications and new research projects. Thus, even though the interaction between the developing and the producing settings became problematic, in regard to the commercial solution which resulted, it was initially in many regards creating benefits for both settings.

Summing Up: Scientific and Business Resources in Interaction

The way in which the method was combined with physical and organisational resources in the producing setting (in the shape of investors, investment plans and new and established facilities), resulted in a product in the form of a restricted commercial solution from which economic benefits could be reaped in terms of capital stock and venture capital. In the developing setting, the method, as well as the commercial solution, interacted with a totally different set of resources which in turn created and made other benefits important. Here, through new research findings, it was the opportunity to publish in highly-ranked journals, acquire research grants, establish research groups, and graduate new researchers that were considered

the main benefits. This in turn induced the original research finding to remain an open method for further development, as well as the commercial solution to be "re-opened" and experimented with within the developing setting.

7.4 The Interfaces Within the Using Setting

Within the using setting, the utilisation of the commercial solution was related to a set of physical and organisational resources which affected how the method was "re-opened" and further developed as a sequencing method by some users, and more or less abandoned by others. The main part of the using setting was academic research departments and hospitals. Here, the solution had to relate to different types of research projects associated with specific types of knowledge, methods, sample material, and equipment. Its use was also connected to governmental regulations concerning clinical testing, ethics regarding patients and their genetic information, as well as to criminal law. These physical and organisational resource interfaces put different demands on the method than those seen within the developing and producing settings. As will be shown, depending on the specific, and ever changing, resource structure within each user context, the resource interfaces resulted in either an adapted use of the sequencing instrument or in no use at all.

The Mixed Interfaces Within the User Contexts in Which the Commercial Solution Became Embedded

Within the user contexts, where the commercial solution was seen as useful, both the new solution and existing resources in the user environments needed to be adjusted in one way or another for the new solution to be useful. The new solution and existing resources thus needed to be related to each other in order for the new to be able to create any benefits. As will be exemplified, this was done either by making physical adjustments in the features of the solution, to how it was used or by complementing it with other resources. For instance, within the user group performing research at the Department of Evolutionary Biology, specific assays were developed for the analysis of ancient DNA. Within another user environment, the forensic group at Rudbeck Laboratory, the new instrument needed to be complemented with the use of Sanger both due to legal requirements and

because of the need to have two sets of results for verification purposes. A third example is posed by the user context of the Department of Medical Biochemistry and Microbiology where a specific feature of the reagents was altered to reduce the time and money spent on sequencing. Finally, within the user context of the Clinical Chemistry Laboratory at Örebro University Hospital, specific assays were developed for the analysis of lactose intolerance making it the first Swedish laboratory to ever offer genotyping of this condition. Thus, to create value within these user contexts, the commercial solution, as well as existing resources, was adjusted, further developed or combined with other resources in order to create a better fit between the new solution and the established resources.

The mixed interfaces between the commercial solution and the delimited research projects: the users of the new sequencing instrument presented an ever-changing usage in terms of regularity and application. In one of the user contexts, the Clinical Chemistry Laboratory at Örebro University Hospital, the instrument was initially purchased by a different department which, because of lack of funding, never put the instrument into use. Nevertheless, when picked up by the Clinical Chemistry Laboratory, it gradually became integrated in its new environment and the everyday operations. Before that, however, it was an abandoned piece of equipment. An even more obvious demonstration of the many irregular uses of the instrument is the academic departments' connection to specific time-limited research projects. In formulating different research efforts and goals over time, the features of the commercial solution turned out to be useful in varying degrees. This is for instance demonstrated in the use of the instrument by the forensic group; while proving very useful when used for the identification of individuals from DNA material collected at crime scenes, it could not be employed in a subsequent effort of screening mutations in very large genes. Similarly, although it was a highly used technique within the ancient DNA group, it did not get embedded to any further extent in the other research projects' similar work on SNPs within the same department. Or vice versa, as in the case of the Department of Medical Biochemistry and Microbiology, which could utilise the features of the instrument in the equine malignant melanoma project, due to the knowledge which had been gained in a previous project concerning pig DNA.

This means that within each user context large parts of the resource structure, to which any new resource needed to relate, was constantly changing; over time research focus changed, which connected the user to different types of sources of knowledge, established methods and other research groups. Thus, while specific types of knowledge or equipment became crucial in one project, it could be irrelevant within the next. It was also sometimes the case that because of the resource combinations which

were used in one research effort, the knowledge gained and the equipment also became useful within a subsequent project. This means that it was far from self-evident when and within which projects that the commercial solution could be combined with the existing resources and therefore become useful.

The organisational interface between direct and indirect users – sharing pyrosequencing as a common resource: in two of the user cases it was demonstrated how the instrument became a resource also to "indirect" users, and how this created effects both for the direct and the indirect user. In the example of the Department of Medical Biochemistry and Microbiology, the pyrosequencing instrument also became a resource to a collaborating research group within another university. Due to earlier collaboration, as well as by sharing the same research goals and knowledge base as the aforementioned department, the Department of Animal Breeding and Genetics was given access to the instrument, which thus became a shared resource between the two departments. Therefore, even though it was purchased by the Department of Medical Biochemistry and Microbiology, it also became an important contributor to the research performed by the Department of Animal Breeding and Genetics. Their separate, as well as joint, use of the instrument resulted in benefits such as both individual and co-authored publications.

In the second example, the instrument was jointly used by the Clinical Chemistry Laboratory and the Department of Microbiology, both within Örebro University Hospital. For a particular doctoral research project within the Department of Microbiology, the instrument was lent for the purpose of studying and developing standard procedures of how to use the instrument for different applications. The collaboration resulted in a PhD thesis presented within the Department of Microbiology, and in the developed assays being established as standard procedure within the Clinical Chemistry Laboratory. This means that by sharing the instrument with another department, the laboratory was able to gain new benefits in their own use of the instrument. Thus, as an effect of the resource interfaces, which the use and further development of the instrument created within an "indirect" user context, both the direct and indirect user benefited from using the instrument. Consequently, the commercial solution did not only create benefits from its use within "direct" user environments but also by being related to resource interfaces of connected and indirect users, which in turn created effects both for the direct and indirect users.

The mixed interface between the commercial solution and the using researchers: in each user context, the use of the instrument was profiled towards specific types of applications and was also adapted for these within

the user environment. This means that each user in a sense made attempts at "re-opening" the technique for further development and new applications. However, by connecting the research projects to new types of results and allowing for different types of assays, which in turn enabled publications, the instrument did not only itself get a part in producing new research results but also it was further developed as a research instrument, and promoted the users' roles as producers of scientific knowledge. The use of the instrument was included in a vast number of publications, and enabled research studies which would most likely not have been possible otherwise, and such benefits are evident in all the included user environments which have embedded the instrument. It is perhaps most obvious in the case of the Clinical Chemistry Laboratory at Örebro University Hospital, which became the first Swedish laboratory to offer genotyping of lactose intolerance through the use of pyrosequencing. In turn this use enabled a number of research studies and publications. The use of pyrosequencing in promoting further research and scientific progress clearly facilitated its embedding within the user setting; in creating important physical and organisational interfaces between the user environments and resources such as new research results, publications and different research projects, the instrument became an essential resource within the users' existing resource structures.

We now have a deeper understanding of what it took to embed the new instrument in diverse user environments and through this process become a useful resource in each such context. The indication is that embedding the new solution was a process strongly influenced by the resources already in use in each setting, and that the combination of *the new* and *the established* had to result in an added value for the user. Next, we will learn more about a situation in which this value could not be created despite several attempts at embedding the instrument into the existing resource structure.

The Mixed Interfaces Within a User Context Where the Instrument Was Not Embedded

Within the NYBC setting, the new instrument could not be successfully combined with the existing physical and organisational resources which eventually meant that it became redundant. Initially, the properties of the instrument seemed ideal for the application which NYBC had in mind, but when it was implemented and in that moment related to the existing knowledge at the laboratory, the established methods, the test samples, and governmental regulations, these resource interfaces made utilisation of the instrument virtually impossible.

The mixed interface between the commercial solution and the existing physical and organisational resources: the first attempt at trying to embed the new instrument was by introducing it in a project concerned with genetic screening of human DNA in the search for SNPs. Since this was the main focus of the design of the pyrosequencing instrument, it was believed to perform this task very well. However, for the particular type of SNPs which were the focus of the screening project, the laboratory already had methods which they considered to be more straightforward for performing the search and the analysis. In relation to these well-known methods, the new instrument was considered too complicated to operate. On the second attempt, the instrument was introduced in a project concerned with determining blood type. Due to the qualities of great accuracy and sensitivity, which were not required in the first project but which would be crucial in this one, this application was by the NYBC considered a good fit with the new instrument. However, once again the use of the instrument appeared suitable in theory but in practice it could not be made to fit with the existing resource structure. The laboratory did not have the knowledge to develop the proper assays, and in addition did not get any assistance from Pyrosequencing. This meant that the existing knowledge and methods within this user environment influenced the individual users' perception of how user-friendly and applicable the instrument was. As a consequence, instead of working as a supplement or a replacement to the already established methods within the laboratory, the new instrument was considered redundant and was therefore not combined with the existing solutions.

The organisational interface between the user and a governmental unit: a great hindrance to the new instrument becoming a useful resource within NYBC, was the fact that it had not been approved by the FDA – a governmental unit which sets safety regulations for drugs and medical devices in the US. As all the equipment used within NYBC's clinical research and testing needed to conform to these regulations, the non-approved instrument was prohibited from entering any clinical trials within this user environment. The organisational interface between the NYBC and the FDA thus connected the use of the instrument to a set of regulations which did not allow it to be combined with the existing resources involved in clinical research – an area which NYBC determined to be the most suitable application area for the pyrosequencing method. This feature of the instrument was not something which NYBC could control, but instead needed to be addressed by the producing setting, which however did not attempt to resolve the problem at the time. Ultimately, this put an end to any further attempts at embedding the instrument at NYBC.

In the NYBC context, the instrument was immediately dependent on a number of physical and organisational resources with which the lack of

interaction resulted in an unusable solution. These resources, both internal and external, created problems which could not be solved within this particular user context. Thus, even though the laboratory intended to use the instrument for the original application for which it had been designed and produced as a commercial solution, the existing physical resource structure, i.e. established equipment and sample material, and organisational resources, i.e. the existing knowledge base and governmental regulation, hindered the embedding of the new instrument.

Summing Up: The Making of a Useful or Useless Resource Through Physical and Organisational Resource Interfaces in the Using Setting

From the analysis of both the user contexts which managed to embed the new instrument and the one that did not, it is clear that in order to be valuable in each particular user context the new solution needed to get interfaces with the existing resource structures. In the user environments where it became an embedded resource, it was through adaptations of both the new solution and the related resources that such interfaces were created, and which enabled the instrument to offer new services in relation to the investments already made. In the case of NYBC, where it could not be combined with the existing resources, it instead became obsolete. As the instrument could not or, as in the case of clinical research, was not allowed to create interfaces with the existing resources in terms of knowledge, established equipment and test samples, neither the instrument nor the existing resources could be adjusted to create a better fit. Having learned how the commercial solution became embedded (or not) within various user contexts, I will now discuss how the use of the instrument in general within this using setting in turn affected the producing setting.

7.5 The Interfaces Between Business as a Producing Setting and Scientific Research as a Using Setting

The economic effects of the producing-using interface did not become evident until the products were embedded within the using setting. That is to say, that it was not until the new instrument had created resource interfaces with the existing resources within the using setting that the effects of its embedding, for this setting as well as for the producing setting, were shown. These effects could thus not have been determined beforehand, but rather

took time to appear. As a commercial solution the instrument was produced in accordance with a frequently used type of business solution – a device which was locked to the use of a particular set of consumables that were expected to bring in a great part of the incomes. However, the typical customer interested in the pyrosequencing instrument was not the "average" commercial buyer or company that the producing setting had had in mind, but individuals and departments involved in scientific research or health related services. As we have seen, this induced a particular type of user behaviour; due to the nature of scientific research these users' needs were changing over time and were very specific. This made their requirements different from other types of customers in a number of ways; their research projects were oriented towards constantly performing new types of task and finding answers to new types of questions – it was not about doing the same thing over and over again in a standardised fashion. This makes this type of user a generally difficult customer for any company; since the type of methods, equipment and consumables which they require, and in what quantity, is constantly changing there is not a standardised type of need.

The mixed interfaces between the using setting and the producing organisational unit: as the product became integrated in the using setting it was clear that the way in which the commercial solution was combined with physical and organisational resources (in the shape of established equipment, joint and time-limited research efforts as well as a sparse utilisation of laboratory consumables) created a type of economic effects that the producing setting had not anticipated. The producing setting anticipated a large need for instruments as well as a continuous and steady demand for consumables. This did not match well with a using setting presenting a sporadic and unpredictable use of both instruments and consumables. Three effects became obvious in the interface between the using and the producing settings: first, there were not as many purchasing users as anticipated. Second, those who did purchase an instrument, and consequently consumables, did so in small quantities and in an irregular manner. Third, about half of the instruments were put out of use after a few years, which meant that a large proportion of the sold instruments did not generate any kind of sales earnings connected to consumables. One such example is the case of NYBC, which purchased an instrument but stopped using it after a couple of years. It is also exemplified by the way that the instrument could be made useful in some user projects but not in others within the same department – this meant that for periods of time, some customers were "silent users" not requiring any consumables.

The economic effects created by the embedding of the instrument within the using setting ultimately led to radical organisational changes in the producing setting. The producing setting could not stimulate the needed

returns from the use of the pyrosequencing instrument, which prompted various attempts within the producing setting to try and solve this fundamental problem. At first, new types of possible application areas were explored in an attempt to make the method more flexible and widen its commercial scope. However, as the effects of adapting the instrument and embedding it within the using setting took time to appear, and were uncertain, more radical measures were taken. Instead, through the acquisition of several other biotech companies, a strategy of expanding the producing structure to include a set of other established suppliers, and their products, was implemented. This meant that rather than basing the producing setting on a single product, which was solely responsible for generating the needed returns, it was decided to include a set of other products which would share the costs of production and marketing. Thus, the start-up company and the venture capital firm realised that they could not create an efficient producing structure based solely on the new solution and simultaneously adjust the production to reflect how it was being used in the using setting. Therefore, they had to abandon the idea of opening up the method to other applications and of making it more flexible. Such flexibility would suit the economic logic of the using setting, but could not create production efficiency within the producing setting.

Through the acquisition of several other companies, the start-up company became a new venture consisting of two business divisions within different areas of biotechnology – one division focusing on the production of pharmaceutical molecules as well as related analytical equipment, and one division involved in genetic analysis. The first division was a combination of several organisational units and products which fitted together in terms of both production and use, but the using setting of this division and the using setting of the one representing pyrosequencing were fundamentally different, and very few users were involved in purchasing products from both divisions. On the production side, however, there were no problems in combining the two as there was a mutual key supplier and the production methods were rather similar. Nevertheless, as there was no fit in terms of a related using setting, combining production and marketing of the pyrosequencing instrument with the products of the other division did not create the expected economic benefits. This meant that in spite of the adaptations which were made within the producing setting, the pyrosequencing instrument could not create the needed economic benefits.

Thus, since the different types of benefits that were created from the same solution's production and use could not support the producing setting, the economic logics of the producing and using settings were not compatible. Ultimately this led to a divestment of the division involved in genetic analysis, which terminated pyrosequencing's existence within the producing setting.

The interface between the using setting and the production system: in spite of the economic effects which the use of the instrument created for the producing setting, the using setting which embedded and used it for various research studies found it very useful, and in some cases even indispensable. There was thus a using setting consisting mainly of academic and health service related departments which used the instrument intensively, and by so doing advanced within their respective research areas, and a producing setting which could not benefit from the economic effects that this use created. A specific example of how the resource structures of the producing and the using settings affected the possible benefits of the development and production of the instrument is the Vinnova-sponsored project.

The project involved the forensic group at the Rudbeck Laboratory, Pyrosequencing and the developing setting at KTH. The project aimed at developing a tailored commercial reagent kit for forensic DNA analysis, and the development work resulted in several finished PhD projects and publications in both the developing and the using setting. The research results, however, were never transformed into a standardised product in the producing setting. Due to the prohibitively large investment required in the existing production system of both internal and external production facilities, the start-up company could not actually produce the kit. It was considered marketable to only a small number of potential users, which basically made it uneconomic. Thus, both the developer and the user greatly benefited from the project as it connected their development and use of the instrument to important resources such as publications, PhD projects, and funding. In the producing setting, on the other hand, the potential new product was instead related to an existing production system, consisting of suppliers and internal production facilities with which it must be made to fit – this required investment. It would also have to create resource interfaces in an existing using setting, which were considered too limited to cover the investment. This demonstrates how even a close collaboration between the producer and user, as well as the developer, did not result in profits for the producing setting.

This type of interaction between producer-user appears in every single included user study as the start-up company initially always assisted the users in developing specific types of assays for their individual application areas. Nevertheless, as this allowed the individual user to perform research and produce new types of results, but did not necessarily generate any benefits for the producing setting, this interaction constantly created more value for the user than for the company.

The interface to another organisational unit hindering user-producer interaction: as has been shown, one of the problems connected to the lack of sales earnings was the lack of large-scale users. The majority of users were small research departments that had small-scale use of the instruments and the consumables. The case of NYBC, however, demonstrated that a user who was interested in scaling up its use of the instrument could be hindered by the producing setting not being adapted to specific governmental regulations regarding diagnostics. Approving the instrument for clinical trials in an American setting meant that the instrument needed to be adjusted in accordance with the regulations set by the FDA – this was an expensive and time-consuming investment that the producing setting determined to be too costly. By not being in compliance with these regulations, the instrument was hindered from being connected to the resource structure related to the clinical laboratory within the NYBC as well as any other user involved in diagnostics and thereby controlled by the FDA. Thus, since the instrument could not be engaged in such a large-scale usage, in this situation neither the user nor the producer could benefit from the usage of the instrument. This meant that, due to an interface between the user and a governmental unit, the producer-user interaction was hindered, leaving the instrument unable to create a fit within the user context.

Summing Up: The Making of a Resource Which was Useful in Scientific Research but a Burden for Business

The economic effects of embedding the pyrosequencing instrument within the using setting turned out not to create benefits either for the start-up company or the larger business venture based on the constellation of several other products. As we have seen, the resource interfaces created between the producing and the using settings (in the joint development projects and adaptation of the instrument and consumables to particular types of uses) created benefits for the users by connecting their use of the instrument to other important resources; the same cannot be said for the producing setting and the production of the commercial solution. We have also seen how the resource interface between the user and another organisational unit hindered this producer-user interaction, and thereby any generation of benefits for either setting.

Thus, by being related to the using setting, the producing setting became indirectly related to a set of resource interfaces, which created direct economic effects on production, and which resulted in the termination of this particular product within this producing setting. The product created within the producing setting could initially provide economic benefits *within* this setting in terms of capital stock and venture capital, but due to a set

production focus and the existing resources within the using setting, it could not create economic benefits from its use within the using setting.

7.6 The Interfaces Within Scientific Research Between the Developing and Using Settings

The commercial solution created within the producing setting directly connected the developing and using settings through joint research projects and publications. As the method had become embedded in a commercial solution, and was "re-introduced" in the developing setting, it became the object of further experimentation and testing. Just as when the method was in its original state, it became connected to resources in the shape of diverse research projects, different test samples, and publications. It was also incorporated in the using setting, which also consisted mainly of academic research departments which thus related it to a similar type of resource interfaces. Just as within the developing setting, a central goal was to perform research both on the instrument and on other research material with the help of the instrument. As will be discussed below, this affinity between the developing and the using settings related them in the development and use of the new commercial solution.

The mixed interface between the developing setting and a set of users: the integration of the commercial solution in their research work connected the developing and (parts of) the using setting in terms joint performing studies on the usage of the instrument. The resource interfaces which were created between the developing setting and a set of users (in terms of existing knowledge, physical equipment and established as well as new research results) gave rise not only to adaptations of the instrument so as to create a better fit for the user, but also benefits such as publications and funding for both the developing setting and the users. Both these settings could benefit, even in the same way, by developing and using the instrument and from interacting with each other. The correspondence in resource structure between these two settings (which were constantly starting new projects developing the instrument and connecting it to valuable resources such as publications, further research projects and research funding) made the embedding of the instrument within the developing and the using setting very similar. Therefore, in connection to the commercial solution, development and use became almost identical activities.

One example illustrating the indistinct difference between developing and using the instrument was the SSB protein project, which aimed to speed up

the sequencing procedure by uncoiling the DNA strand before every analysis. In this case the user, based within the same department as the developer, himself became a developer who, in collaboration with the developing group, brought forth a technical enhancement of the commercial solution. The aforementioned Vinnova-funded project, including the forensic group at the Rudbeck Laboratory, Pyrosequencing, and the developing setting, was an example of the similar benefits which can be gained by engaging in development and use of the instrument through scientific research. In this case both the developer and the user could combine the commercial solution with their existing resource structures in a way that created benefits such as publications and funding. The start-up company could, on the other hand, not derive any direct benefit by incorporating the modifications to the solution into production. Thus, due to the similarity between the resource structures of the developing and the using settings, they could interact in a way that promoted even greater benefits then when acting individually.

The resource structures of the developing and the using setting hindering an efficient production: the situation of the developing and the using setting being so similar in terms of existing resources was something which the producing setting did not anticipate and to which it could not adjust. In forming the base of a new producing setting, the production of the commercial solution had to be separate from the logic of the developing setting, which constantly tried new directions and thus kept the method in a flexible and ever-evolving state. In order to become efficient, the start-up company needed to be based on a standardised large-scale production which in turn required a fixed product. The company was thus founded on the notional existence of a using setting with a steady use of the product, and which did not demand major or constant application development. However, the actual using setting demonstrated the same type of economic logic as the developing setting – the logic from which the producing setting needed to move away; in their usage of the commercial solution the users wanted continual flexibility, change and adjustment, but these were conditions on which the company could not base a standardised large-scale production.

Summing Up: The Making of a Scientific Resource Through Physical and Organisational Resource Interfaces in the Developing and Using Settings

As we have learned, the economic effects of embedding the commercial solution within the using setting were devastating to the start-up company,

which ultimately could not continue producing the product. However, as we also have seen, both the developing and (parts of) the using setting could gain major benefits from developing and using the new solution. In addition, this was done in close collaboration between the developing setting and a set of users, out of which the interfaces between developer and user created new opportunities for applying the solution and benefits in the shape of publications, new projects and funding. The new solution thus became an embedded resource both within development and use, which in turn connected both settings to other important resources. This suggests that due to the related resource interfaces, the new solution could create benefits within production of new scientific knowledge, but was hindering efficient production within business. This made it an economic burden within business and an asset within scientific research.

7.7 Epilogue Discussion: Pyrosequencing Embedded in the 454 Device – A New Economic Resource

What does the incorporation of pyrosequencing in a new product tell us about the embedding of scientific resources in business? In further developing the original method of pyrosequencing from its earlier use and incorporating it in its product, 454 represents a using, producing, and developing setting within business. When acquiring the licence, the company was not really concerned with the existing commercial product originating in pyrosequencing, but rather went back to the original idea of sequencing-by-synthesis and saw unique advantages of the pyrosequencing method. Thus, they started to develop it not from the standpoint of the existing commercial product, but from the basic principle originated at KTH. However, this did not take place through interaction between 454 and the research group at KTH, but was instead a contract settled by the company Pyrosequencing. Indeed, there has never been any interaction between 454 and the KTH group.

454 first encountered the pyrosequencing method by the use of a commercial instrument purchased by CuraGen, around the same time as 454 was started. It is a reasonable assumption that 454 would not have become interested in pyrosequencing as a potential component in their product without first having used it as a commercial solution. It was thus the *use* of pyrosequencing as a commercial product within CuraGen and 454 that preceded the *development* and *production* of pyrosequencing as a component within the 454 product. Hence, through its use, both as a scientific and a business resource, the original scientific solution got a new "life" and consequently new economic significance over time when being introduced in

a new resource structure. Pyrosequencing appearing within a new product, with the high expectation of it becoming an alternative sequencing method to Sanger, is thus not the result of a straight path from development, production and use within either scientific research or business. It is a "back and forth" process of use and development within scientific research leading to production within business, resulting in use within scientific research and development within business, and so on. What is particularly interesting is that pyrosequencing would probably not have been developed into a currently useful product, both within scientific research and business, without it first becoming a standalone product and an economic failure within the start-up company setting. What this eventually will result in, in terms of new resource interfaces and economic use, is yet to be seen.

8 Conclusions

In this concluding chapter I will discuss the research results of the study. The main issue of this thesis is how new scientific solutions are embedded in settings of commercial production and use, and how this can be viewed as making something new fit in related, but different, resource constellations. The chapter begins with a recapitulation of the research questions. A discussion of the findings of the case study is then had from the standpoint of the three empirical settings of development, use and production, and in that order. I end the chapter with a personal view about possible policy implications about the economic use of new scientific solutions.

8.1 Investigating Scientific Solutions as a Direct Source of Innovation

The purpose of this study has been to better understand what it means to bring in something new, which stems directly from scientific research, into settings of commercial production and use. Are there special factors to be taken into account when that which is to be commercialised (i.e. embedded into large-scale production and widespread use) stems directly from scientific research? Or, as formulated in the first research question:

What is special about innovation processes for inventions which stem directly from scientific research? Why?

The question implies that there is something different with this situation compared to when the novelty stems from commercial development, or from interaction through established business relationships. So is also implied by various actors – for instance the venture capital firm presented in this thesis – including policy makers at national as well as transnational levels. This claim, however, sees only the assumed advantages of directly basing business innovation on advanced and "excellent" scientific knowledge, rather than the difficulties. As has been indicated and will be further argued, this study takes a somewhat contrasting position.

A key element of this study has also been to understand how the three empirical settings of use, production and development are interrelated in reference to anything new being commercialised, the respective benefits that can be created as a result and how this affects the potential innovation. This was formulated in a second research question in the following way:

In what way is a potential innovation, which stems directly from scientific research, related to the settings where a) it is developed, b) it is taken into large-scale production and c) it is taken into use - and how does this affect its ability to survive the innovation journey?

As was implied in the introductory and theoretical chapters of this thesis, in order for innovation to be achieved, anything new needs to become related to and create benefits in these three related, but different, empirical settings. An ambition of this study was to understand how this happens and what implications it has for the innovation process. This has necessitated an investigation of what is specific about these three settings, as well as how their respective interaction with the new solution affects the innovation process and the benefits that can be derived. The following three sections deal with the findings from this investigation in regard to the new solution being developed and used within scientific research and what this meant for a producing setting involved in large-scale production.

8.2 A Developing Setting Making Scientific Imprints

From the empirical account of the innovation process of pyrosequencing, there is no doubt that the new solution stemmed from scientific research. The question is rather what implications this fact had for the innovation process: what was the significance of the fact that the method was a new and groundbreaking result of scientific research? Being a scientific breakthrough, and becoming scientifically recognised both nationally and internationally, the sequencing method developed at KTH carried scientific imprints in its connection to ongoing international research and contemporary scientific goals, as well as to the applied research methods and the available scientific instruments. It was connected to what was happening in the larger scientific arena concerning the expansion of knowledge of our hereditary components and how to study as well as analyse them; it was part of a general scientific development of understanding our genes and their different mechanisms. As was shown in the previous chapter, it was of course also related to the particular resources existing within the laboratory environment at KTH in the shape of specific knowledge, relationships, and physical equipment.

The fact that it was developed within a scientific setting, and became acknowledged as an important scientific discovery, meant that it was highly

related, or adjusted, to other scientific resources such as established scientific knowledge and research results, as well as existing research methods. Also, the published results of testing the method in different situations, with different reagents or mechanical solutions, were always based on laboratory conditions, using "fresh" chemicals, manual experiments and constant modification. This meant that both as a research result and as a sequencing method, pyrosequencing was a resource made to fit into a scientific research environment. It was a resource shaped by scientific research for scientific research.

8.3 A Using Setting Requiring Specificity and Flexibility

In the using setting it was scientific researchers that found the sequencing instrument most useful. Thus, because of the clear imprints which the new method carried from its developing setting, it was considered most valuable within the same type of environment where it had been developed. However, even if these user environments were very similar to the one where it had been developed, the new sequencing method had to interact in its using setting with new types of products, knowledge and ongoing research projects. To create any user benefits, the instrument needed to fit with these products and with established systems of material and immaterial solutions. Its use, and the benefits which it could create within these user contexts, were therefore far from self-evident and could not be predicted before it was activated by the users.

Many of the users could gain great benefits from using the instrument and they found new and inventive ways of putting it into use. However, these new ways of using the instrument were very specific, and pointed in different directions how the instrument could be developed and modified. Therefore, as the instrument was embedded in the using setting, a specific user-pattern characterised by great variation, but also small-scale usage, became apparent. The instrument was incorporated in time-limited projects with different applications in focus, which put demands on both the instrument and the start-up company to be flexible. As will be discussed, this did not match the requisites of the producing setting. Also, because of the nature of the research projects and their timescales, there was no need for either a large number of instruments or a constant supply of consumables. This was another major issue of concern in regard to the standardised production setup of the start-up company.

An application area which was more suitable for a standardised product and thus more appropriate for a large-scale production instead meant other problems. NYBC, a user that wanted to utilise the instrument in a more

consistent and standardised manner for diagnostic purposes, represented a user environment where flexibility of application was not as crucial. However, among other things, at NYBC the instrument instead fell foul of regulations standardising the methods allowed for diagnostic and clinical purposes. Thus, since the product was locked to a certain set of features it was, from a user perspective, more useful for research purposes than within more standardised work such as diagnostics. How did this type of using setting relate to the producing setting, and what were the effects of the interdependency of these two settings?

8.4 A Producing Setting Based on Standardisation and Economies of Scale

The producing setting, consisting of the start-up company and related resources, was based on a standardised production of the new instrument and the reagent kit. In order to support this producing structure, a certain level of cost efficiency was needed. This required interaction with other companies, such as suppliers and distributors, but also a large-scale production of both instruments and reagent kits – a certain volume of production had to be reached in order for economies of scale to be realised. In turn this required that the instrument was restricted to a specific set of features, and that the number of applications supported by the consumables were limited. This meant that specific standards for the quality of the instrument, the appurtenant kit, and the system as a whole, had to be fixed in regard to which components the suppliers could deliver, but also for production conditions and reductions in unit costs. To achieve this type of fixed technical product from the materialised solution was, however, not the main predicament. On the contrary, it was the quick transformation of scientific research into a sellable product which earned the start-up company its initial image as a commercial success story. Rather, the main issue was that the economies of scale and interrelatedness with suppliers, which was needed by the producing setting, was incompatible with the specificity and flexibility required by the using setting – this was the fundamental problem with the commercialisation of pyrosequencing.

The difficulty of basing a standardised production on the pyrosequencing instrument thus lay in combining the using setting's demand for a variation of specific applications and flexibility with the producing setting's requirement of cost-efficiency. This complexity was in many regards acknowledged by the established producing structure of Pharmacia, which realised the potential economic consequences of such a specialised type of product. The company's extensive experience of producing new products and applications (as well as of user-producer interaction, and thus of the

interrelatedness between production and use) showed it that investing in the production and marketing of pyrosequencing was simply too costly. This connection between production and use, and the difficulty of maintaining large-scale production, was vastly underestimated by the actors involved in setting up the new producing structure and formulating the economic goals of the commercialisation of pyrosequencing. The ambitions of arranging capital, constructing a sophisticated technical product, and becoming a public limited company, turned out to be less of a challenge than maintaining production based on the product's actual use within a using setting. Thus, the economic potential of pyrosequencing as a standalone product did not become apparent until it had become embedded in the using setting, and had created resource interfaces with this setting's material and immaterial resources. This is a fundamental part of the process of commercialising any new solution and achieving innovation; *the new* has to become embedded in large-scale production *and* get widespread use. This implies that before anything new can be called an innovation, it needs to have become embedded in not only developing and producing settings, but also in a using one.

8.5 From Scientific to Economic Significance – A Matter of Creating Benefits Through Different Economic Logics

The case of pyrosequencing illustrates the complexity of trying to achieve innovation based on new scientific solutions. What was considered an important and highly usable method from a scientific standpoint, from both the developer and user perspective, became an economic burden for the producing setting to maintain its production. Because of the method's unique qualities, which solved key methodological issues within specific research areas, it was highly relevant within scientific research and was, in due time, considered of great scientific significance. In order for the method to contribute to the *developing setting*, it needed to contribute to the existing stock of scientific knowledge about DNA sequencing. This meant that it needed to work on an experimental level and be included in scientific publications. It was not a matter of making it work on a large-scale basis or spreading a standardised procedure for sequencing; rather, its value was measured in terms of what type of knowledge contribution it was making. In the *producing setting*, on the other hand, scale was essential; in order to cost-effectively maintain production of the new product, economies of scale needed to be achieved both in regard to in-house production and in collaboration with suppliers. However, to become embedded in the *using*

setting, the instrument needed to interact with the existing resources within a setting also involved in scientific research. This was, once again, not a matter of scale but rather of making the instrument contribute to specific research questions and projects – to make knowledge contributions.

As a business resource within a setting focused on achieving fast and large economic returns, the method's value was thus limited; the combination of being embedded in a producing setting of a sole product, having venture capital as the main source of finance, and having a using setting involved mainly in scientific research, created an economically unsustainable situation for the start-up company. These different economic logics, through which the method needed to create benefits, turned out to be incompatible. However, through the method's continued use within diverse research projects, and as a part component in a different sequencing system and, as well as its continuing life as a standalone product by being acquired by another company, pyrosequencing was creating economic effects but not in the anticipated way, time or place. Also, for these effects to appear, the method needed to interact with different material and immaterial resources in both a producing and a using setting.

I will conclude this discussion by considering the implications of pyrosequencing not being a unique case. If there are other such stories out in the world, then what does this entail for innovation and research policy strategies, if it is believed that scientific and economic significance are two sides of the same coin?

The general policy recipe for the achievement of innovation and economic growth, presented for instance by the OECD and the EU, is to create "links" (OECD, 2004, p. 2) between scientific research and "innovators within business" (ibid.). This will supposedly facilitate the transfer of scientific discoveries to settings of commerce where the new scientific knowledge can gain practical application. (See e.g. Eklund, 2007; Waluszewski, 2010) However, if achieving innovation based on scientific knowledge is a matter of creating benefits from the standpoint of vastly different economic logics, then how will such links bear fruit? The different logics remain and will in turn affect the economic benefit of the new solution as it is implemented in the different settings.

It is also indicated that through appropriate strategies and management, for instance through the involvement of venture capital, economic benefit can be created through controlled innovation processes based on a direct commercialisation of new scientific knowledge. (Waluszewski, 2010) It is thus believed that it is the qualities of the novelty itself which decide the outcome of the innovation process, rather than how it becomes embedded in different structures of material and immaterial solutions. (See e.g. Hall, 2004; Håkansson & Waluszewski, 2002) In this view, it is possible to predict the outcome of new investments and plan the innovation journey. (O'Sullivan, 2004) However, if an economic use of scientific knowledge

appears through interaction between different material and immaterial resources over time, often in unexpected ways, times and places, is commercialisation of new scientific research a good way to create fast economic benefits?

This study has shown that scientific and economic significance are not two sides of the same coin – they are not even values within the same currency. Rather they are determined through different economic logics and through different processes at different times. Scientific establishment of a new piece of knowledge is about making a specific knowledge contribution, and it is the extent to which this contribution is considered a leap forward which determines the level of benefits it can generate within this setting. This suggests that in order for anything new to represent an important *scientific* resource, it must be connected to the value-creating resources and processes which exist within the production of scientific knowledge, e.g. publications, research grants, and new research projects. To establish anything new as an important resource within *business*, i.e. commercial production and use, it must represent economies of scale. This means that in order to support a large-scale production, the new solution needs to become connected to resources which enable reductions in unit costs. These resources constitute a standardised supply chain involving production and supply processes, various suppliers and distributors, as well as other products and technologies to which *the new* needs to relate. Evidently, these are vastly different value-creating resources and processes than those constituting the production of scientific knowledge.

Also, in accordance with earlier empirical studies on scientific instrumentation (See e.g. von Hippel, 1976: Rosenberg, 1982; Riggs & von Hippel, 1994), this study has shown that the imprints of scientific development on *the new* makes it valuable mainly within the same type of setting in which it has been developed. This makes users essential to both the development and production of the new solution. It also means that, as discussed above, the producing setting, in need of economies of scale, needs to adjust to a using setting representing neither a large-scale nor a standardised type of use.

In contrast to the policy and investment orthodoxy of achieving innovation from groundbreaking scientific knowledge, this study shows that this is not only an unpredictable process but also a matter of creating benefits through vastly different economic logics. This implies the importance of acknowledging the relationship between the producing and using settings; since they are highly related, but still dependent on different types of benefits, understanding their interconnection is both crucial and problematic. What is required for the producing setting to actually be able to cost-effectively sustain production of the specific solution? What is required to achieve economies of scale? Which established solutions and investments need to be taken into consideration? And what demands do these conditions,

in the producing setting, put on the solution's use, in terms of standardisation and volume, in the using setting? In considering commercialisation of new scientific solutions, these are factors which must be taken into consideration. If not, the difference between scientific and economic significance is not taken seriously.

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Appendix I: Interviews

Name	Position	Type of Interview	Date of Interview
Alm, Bertil	Manager Design and Development, Partnertech. Project leader of developing the pyrosequencing instrument	Telephone	2010-05-12
Allen, Marie	Associate Professor, Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University	In person	2005-02-28
		By email	2005-05-26
		By email	2008-04-24
Ekström, Björn	Co-founder of Pyrosequencing	In person	2003-11-04
		In person	2005-10-14
		By email	2005-05-27
		By email	2008-04-17
		By email	2009-01-12
		By email	2010-02-15
Gharizadeh, Baback	Former PhD student in Nyrén´s group KTH	By email	2008-06-03
Hjortsmark, Maria	Vice President of Technology Development at Biotage	By email	2005-10-24
Irzyk, Gerard	Laboratory technician at 454 Life Sciences	In person	2006-04-25
Joergensen, Torben	CEO of Biotage since 2007	In person	2007-05-07

KaraMohamed, Samer	Former PhD student in Nyrén´s group KTH	By email	2008-06-05
Krabbe, Margareta	Former Senior Scientist at Pyrosequencing 2001-2004	In person	2005-12-05
McLeod, Christopher	CEO of 454 Life Sciences	In person	2006-04-26
		In person	2008-01-16
		By email	2008-02-26
Nilsson, Torbjörn	Senior physician and Professor at Örebro University Hospital	By email	2008-07-14
Nourizad, Nader	Former PhD student in Nyrén´s group KTH	By email	2008-06-04
Nyrén, Pål	Professor, Dep. of Biochemistry, KTH. Inventor of pyrosequencing.	By email	2003-11-10
		In person	2005-09-22
		In person	2007-01-31
		By email	2009-02-11
Odeberg, Jacob	PhD, Department of Biotechnolgy, KTH	In person	2006-03-29
Odlander, Björn	Co-founder of Odlander, Fredriksson & Co.	In person	2007-02-15
		By email	2009-01-13
Olsson, Lovisa	Chemist at The Clinical Chemistry Lab., Örebro Univ. Hospital	In person	2005-11-11
Pettersson, Bertil	Former PhD student in Mathias Uhlén's research group, KTH. Co-founder of Pyrosequencing	In person	2007-02-23
Pielberg, Gerli	Ass. Professor, Dep. of Medical Biochemistry and Microbiology, Uppsala Univ.	In person	2005-11-25

		By email	2008-09-23
Reid, Marion	Former PhD at the Laboratory of Molecular Analysis, NYBC. Now Head of the Immunochemistry Laboratory, NYBC	By email	2008-05-21
Schanche, Jon Sverre	Vice President of R&D at the division of Discovery Chemistry, Biotage	In person	2005-05-11
Steiner, Eugen	Partner of Health Cap and Odlander, Fredriksson & Co. CEO of Pyrosequencing 1997-1998	In person	2005-10-11
		By email	2009-01-14
Svensson, Emma	PhD student, Department of Evolutionary Biology, Uppsala University	In person	2005-11-07
		By email	2008-04-29
Söderbäck, Erik	Former Senior Scientist at Pyrosequencing 2001-2004	In person	2005-12-05
		By email	2008-08-28
Uhlén, Mathias	Professor, Department of Biotechnology, KTH. Co-founder of Pyrosequencing	In person	2007-04-02
Valinsky, Jay	Vice President of Information and Technology, NYBC	In person	2006-04-27
Walldén, Erik	Former CEO of Pyrosequencing 1998-2003	In person	2007-03-29

Special Interview

2006-03-11: A joint arranged seminar at the Department of Biochemistry at KTH by the department and this project concerning the development of the pyrosequencing method.

DOCTORAL THESES

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