The Relative Value of a Technology: Its Appearance in the Academic, Venture Capital and User Setting

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Abstract

A common strike in contemporary policy endeavours is the ambition to utilise production of science as a source for development of new economic resources. This is due to the recurrent view that science is a basis for new innovations, which, supported by venture capital and entrepreneurial activities, is supposed to lead to new, prospering businesses and economic growth. Or, as the Swedish venture capital company Health Cap expresses it: "Management and Science. 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." (www.healthcap.com) Thus, in the endeavours to create innovations not only the producers of science, but also venture capitalists, play a key role as selectors of which specific scientific research that eventually will become a commercial product. This suggests that it is the role of the venture capitalist to link the solution developed by the knowledge producer to the need of the commercial users (Gompers & Lerner, 2001). This ambition is, consciously or not, based on the understanding that the features that appear as valuable from the science producers' perspective also can contribute to economic values when embedded in a user setting. But what if the user setting is a "rugged landscape" (van de Ven et al, 1999), where the existing resource combinations a new solution has to co-exist with cannot be outlined in advance?

Our paper is based on an empirical study of how the use of a particular scientific knowledge is interpreted in three different but related contexts; among the academic knowledge producers, among the venture capitalists investing in a new company and a new product based on the scientific method, and among the commercial users. The scientific knowledge in focus is the so called pyrosequencing method, a technique intended for sequencing of DNA with different applications. Sequencing DNA, or reading genetic code, is desirable for many reasons, not least for medical purposes where it can be used to establish the cause for certain diseases or conditions. The study reveals that due to their existing resource combinations (Håkansson & Waluszewski, 2002), the understanding of how to create use of the pyrosequencing method was rather different depending on the context. In the academic setting it was regarded as a research technique which provided a more accurate and simple way of performing general DNA sequencing compared to the established method. The venture capital firm investing in the pyrosequencing method had an almost opposite view of how to utilise this new knowledge. Through its investment in 1997, this firm made it possible to form a company, Pyrosequencing, around the development and marketing of an analytical instrument based on the method. However, in this process the focus shifted from creating a research technique, to a specific technology possible to embed in a physical product. From being a rather generic method which could be adapted to each particular researcher's needs it was in its commercial form locked to just a few applications. However, the potential users of the new method were mainly interested in making the technology compatible with their existing technologies and project goals. Through the explanation of resource interaction the reasons for the difficulty of making this scientific breakthrough a commercial success are shown.

Keywords: value creation, technology, academia meets industry, biotech

1. Science and Management – Key Ingredients in the Creation of Successful Companies?

> "Management and Science. 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." (www.healthcap.com)

The statement quoted above is made by one of Sweden's largest and most recognized venture capital firms engaged in the life science area. The great trust in the benefits that can be created by combining "outstanding" science with high quality management is however not only expressed by venture capitalists engaged in the life science based industry; it is also a shared understanding among contemporary policy representatives on both national and transnational level. For example, to facilitate that cutting edge science is not "locked into" the universities, but transferred to the business world, is a prioritized issue to reach the Lisbon target:

> "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, 589)[1]

Similar interpretations, expressing a firm belief that science is an important source of innovation – however not automatically, but with the help of a supporting innovation system consisting of transfer organizations, investors and professional management, is expressed among others in the innovation management, cluster and venture capital literature. (See e.g. Soete, 2002, Powell, 2003, Gompers and Lerner 2001) The basic idea is that scientific knowledge needs to be combined with professional management which can transfer it to "attractive business solutions". (Gompers and Lerner 2001) An investor in scientific knowledge is thus solely not a provider of money, but of equal importance; of knowledge. (Powell, 2003) It is the professional investor that knows how to build a management, a commercial solution and a network of relationships to suppliers and users.

1.1 But if Benefits of a Technology are Relative?

In this paper, we will investigate and discuss how the benefits of a new scientific insight concerning a hot topic in the biotech area; an improved method concerning sequencing of DNA, is interpreted by its academic producers, its investors and its commercial users. As will be shown by the empirical material the perception of the technology's use was quite diverse between these contexts due to the differing preconditions. What is truly fascinating about leaving the model world and studying the empirical process of trials to create benefits from the same basic knowledge in such different settings as the academic, investor and commercial user, is how different also the advantages that can be created are interpreted. In the academic world, the benefits can be the ability to produce scientific articles based on new and path-breaking contributions; i.e. to be able to carry out radically different

[1] http//www.ec.europa.eu/growthandjobs/pdf/COM2006_589_en.pdf

investigations of certain phenomena and/or to advance in the academic career. For the investor, on the other hand, the most important feature of the same knowledge base can be the ability to provide a risky start-up venture with a rapid exit on the stock-market. Finally, in the user setting, the benefits of the new can be the ability to increase the capacity of existing system solutions. (Waluszewski, 2004) When viewing the commercialisation process from such diverse perspectives it is not very surprising that market failures do arise, it is more surprising that sometimes it doesn't.

In the traditional marketing and innovation management literature, "market failures" are explained as a result of the producers' lack of understanding of customer requirements. Thus, the problem of innovations that fail is thought to be possible to solve from the producer perspective; by the developing company's improvement in identifying proper target markets and significant application areas. (See e.g. Cooper, 1975, 1994, Rothwell et al, 1974, Tidd et al, 1997) However, as soon as we assume that the business landscape that the new is going to be embedded into is populated by actors engaged in the exchange of heterogeneous objects – i.e. its full content is partly unknown, then such explanations becomes obsolete. Which benefits that are created when the exchanged object is used cannot be outlined from the producer side –not until the user have reacted on it, and brought in its own "traces and leavings". (Gudeman, 2001) Thus, the benefits of a resource are created in relation to other tangible and intangible resources – which make interaction over time an important ingredient in this process. Rosenberg (1982) defines a technology not as just a physical application of science but as "[…] itself a body of knowledge […]". However, in a new context it is *how* this knowledge is activated that defines its use. Consequently, a main research issue of this paper can be formulated; what are the different benefits of the same technology in an academic, in an investor and in a commercial user setting and what are the consequences of their difference?

2. Theoretical Departure

The theoretical starting point of this paper is the IMP industrial network approach, emphasizing that one of the most important features of the business world is that the exchanged objects are both heterogeneous and interdependent. (See e.g. Håkansson, ed, 1982, Håkansson, Snehota, 1995, Ford et al, 2003) This assumption is rooted in the idea world developed by among others Alderson (1957, 1965), and Edith Penrose (1959). If, as Edith Penrose (1959) suggests, it is the way a resource is activated that creates its "services", then its value is due to how it is combined with other resources within and over organizations. Thus, the IMP industrial network approach abandon the (more or less conscious) legacy of traditional economic theory, in which knowledge is assumed to be developed outside the economy – to be absorbed by the business world ex post. This interpretation fits like a glove with the innovation management, cluster and venture capital literature assumptions that development of new business solution is a problem that can be handled from a producer perspective.

However, if we consider the creation and use of innovations with the IMP assumptions at hand, this process appears as a result of how specific interfaces have been created in interaction over time – where each interface is unique but still contributes to benefits in related interfaces. Thus, production and use of new business solutions appears as a much more thorny issue, which will a) create effects which are impossible to foresee and b) protect the main part of existing investments. (Håkansson, Waluszewski, 2002)

To investigate the innovation process from this perspective, we have used a research tool that allows us to capture the interaction between heterogeneous resources, regardless of what actors are represented. The so called "4R" model approaches each organization or company as representing a unique set of resources – which are developed and used in relation to a larger network. The research model is based on four types of resources. Two are mainly physical: a) products and b) facilities or equipment. Two types of resources are mainly organizational: c) organizational units, and d) organizational relationships. (For a detailed discussion of the theoretical background, see Håkansson and Waluszewski, 2002, chapter 2.) The four types of resources are assumed to be developed over time and in relation to each other. An interesting feature of these resource structures is, as will be

illustrated in the following case, that they appear both in a "physical, or activated form and as an "idea", or as an image. In contrast to the activated structure, the idea structure can be much wider, and include conflicting ideas about how to develop and use the activated structure. (Håkansson, Waluszewski, 2002, p. 72f)

By using the research tool presented above it is possible to catch the relative benefits of a technology; i.e. how the benefits are dependent on which effects it create on the existing resource structure. Thus, it is possible to catch how the existing resource structures, as well as the images of these, in the academic, investor and commercial user setting, have an impact on the ability to benefit from a technology.

2.1 Data Collection

The paper is the result of a data collection encompassing three different contexts. The academic context is represented by the original inventor and two of his colleagues at the Department of Biochemistry at KTH. The investor and start-up perspective is represented by the venture capital funds Health Cap, the related founding partner Odlander, Fredriksson & Company and by the Pyrosequencing company. The user perspective is represented by four different present Pyrosequencing users; Uppsala University (two users), Rudbeck Laboratory and Örebro University Hospital as well as by one former Pyrosequencing user; the New York Blood Centre in New York City. In total, about 15 interviews have been carried out. Besides the traditional collection of primary and secondary data, a seminar has also been held on this issue at the Department of Biochemistry at KTH. The study is also part of a larger study of the emergence of life science based companies in the Uppsala region, where 25 companies and their relations to the academic and business world are mapped over time. (Waluszewski, 2004) It is also related to a study on the role of venture capital in the birth and death of Pyrosequencing as an individual company, reported in Waluszewski & Wedin, 2003.

3. An Academic Success Transformed to a Venture Capital and Start-Up Company Success?

In 1997 a new biotech tool company, Pyrosequencing was founded in Uppsala. The company was based on what in the academic world was considered a scientific success; a new DNA sequencing method called pyrosequencing. The method was developed at the Department of Biochemistry at The Royal Institute of Technology (KTH) in Stockholm.

Through the engagement of one of Sweden's most prominent venture capital fund in the life science area, Health Cap, a flying start on the development journey from scientific success to a business solution was created. The venture capitalist engaged in the design of a start-up company aimed to commercialize the scientific knowledge. The venture capital firm and its start-up company made exactly what the venture capital literature suggests; it translated the rather wide scientific method to a narrow business solution, embedded into a biotech tool for analysis of short DNA strands.

All indications pointed at a success story coming into being. After three years as a company, in the year 2000, Pyrosequencing was among 20 000 companies worldwide listed by Forbes as one of 300 "Best Small Company". The same year Pyrosequencing became rewarded as "Spin-off Company of the Year" by the Royal Swedish Academy of Engineering Sciences, chosen from 80 companies nationwide. In the motivation it was underlined that "Pyrosequencing has developed an existing business opportunity from research environment to a stock-market introduced growth company focused on innovation." [2]

[2] http://www.iva.se/templates/page.aspx?id=769

The only problem was that the users did not see the same benefits of the technology as was appreciated from the producer perspective. Instead of the fixed solution that had been embedded in the Pyrosequencing company's commercialization of the method, the users preferred the more flexible version of it – similar to how it appeared in the academic setting it originated from. After a few years, the situation became too hard to handle and in 2003 the company board decided to merge the company with two other biotech companies. In its new context, the pyrosequencing technology more or less faded away.

3.1 The Pyrosequencing Technique

The pyrosequencing technology is based on the idea of "sequencing by synthesis", meaning that by building the complementary strand of a single DNA strand it is possible to find out the code of that particular piece of DNA. However, to appreciate the sequencing of DNA it is crucial to first understand the content and organization of DNA itself. A DNA-helix is a double stranded molecule where the strands are made up of a certain order of the four nucleotides: A (Adenine), T (Thymine), C (Cytosine) and G (Guanine). A single strand can for example look like this: …AATGCATTGCCATG…. The two strands are complementary, this means that when there is an A on one strand there is always a T on the opposite one. Just as when there is a C on one strand there is always a G on the other. These nucleotides are connected to one another through hydrogen bonds holding the DNA-helix together.

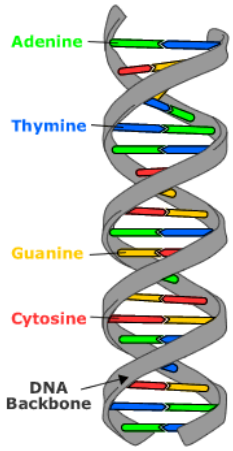

Figure 1. The DNA double helix where the placement of the four bases A, T, C and G is shown. (source: evolution.berkeley.edu/.../ IIIC2ReviewDNA.shtml)

The contributions of the pyrosequencing technology is that through the support of an enzymatic system, bases are added to a single stranded DNA template, which makes it possible to find out which of the four added nucleotides that is incorporated into the growing strand. By keeping track of which of the nucleotides that are incorporated and in what order the genetic code of that particular DNA fragment will be revealed. The reason for the name of the method, pyrosequencing, is that whenever a nucleotide is incorporated in the growing strand a pyrophosphate ion is released which, through an enzymatic reaction, results in a light signal: a "pyro-reaction" takes place.

3.2 The Value of Pyrosequencing in the Academic Setting

The Medical Research Council's Laboratory of Molecular Biology in Cambridge, UK was a totally different research environment than the one the biochemist Pål Nyrén was used to at the Department of Biochemistry at Stockholm University. Under the supervision of Professor John E. Walker, later rewarded the Nobel Prize in chemistry, Nyrén spent a post doctoral year there in 1986. Nyrén recalls being fascinated by the fact that in this laboratory researchers who had had a long and successful

career, won the Nobel Prize even, still were very active and truly committed to continuing their research. Walking in the corridors he never knew when he might see one of them rushing to their latest experiment in the making or an important meeting. (Interview Nyrén)

Nyrén committed his years as a PhD student to research regarding enzyme activity in the photosynthesis. It was with the intention of getting a more profound knowledge within the same area that he was visiting Professor Walker in Cambridge. Working in the prestigious laboratory he was introduced to a DNA sequencing method, used in many different areas within the natural sciences, not least in biochemistry. The method called Sanger, after its inventor Fredrik Sanger, had since its creation in1977 been recognized as the most robust way to read long DNA sequences. Being new to the method Nyrén found it unnecessarily complicated; there were many different steps to learn and in these steps diverse apparatus as well as chemical substances to handle. Nyrén saw it as a problem that such an essential part of DNA related research was so time consuming and started to think that there had to be a better way to perform sequencing. Having worked a lot with method development it came natural to him to start thinking about alternative techniques. With the stand point of his own research field, photosynthesis, he was speculating whether or not the detection of pyrophosphate could be used to sequence DNA. Working actively on such an idea while he was still in Cambridge was however out of the question. It wasn't until he went back to Sweden and the Stockholm University that he could confirm that the basis for his idea actually worked. The first paper he published on the discovery, "Enzymatic Method for Continuous Monitoring of DNA-polymerase Activity" (Analytical Biochemistry 167, Issue 2, 1987), was connected to his research within the photosynthesis area. Hence, he was still working within his area of expertise. The article showed a study of pyrophosphate formation during DNA synthesis, which was the biochemical reaction he based his idea on. Since there was a great general interest in the photosynthetic energy conversion at the time it was beneficial to relate the new idea to this area. However, the strict criteria to show extensive results of a methodological discovery withheld by foundations such as the The Swedish Research Council, hindered Nyrén to acquire any funds to continue his research on the sequencing idea. This forced him to postpone the project. (Interview Nyrén)

In 1990, Nyrén took employment at the Department of Biochemistry at KTH in Stockholm. His placement was under a Professor in need of assistance in order to build a new laboratory. This meant finding the right equipment, hiring research engineers and PhD students, connecting laboratory activities to teaching and most importantly; conducting proper research experiments in it. Not having worked on the sequencing project for several years, Nyrén once again applied for external funds for further investigations of his idea. However, when not receiving any research money he decided to invest some of the funds from his photosynthesis project to be able to take up his sequencing study. Almost without exception the money were spent on necessary chemicals and enzymes. Nyrén was allowed to spend one day a week trying to make progress with his sequencing idea, remaining days of the week he was engaged in teaching and other research projects. (Interview Nyrén)

There were several steps in Nyrén's sequencing process that required sophisticated solutions but how this was to be achieved was far from self-evident. The basic features of his idea was that by building the complementary DNA strand (with its four letter code consisting of the nucleotides A, T, C and G) to the one in the sample, one nucleotide at a time, and measuring the pyrophosphate level, which would rise every time a new nucleotide was incorporated in the sample strand, the code of that particular DNA strand could be read. So far he had been able to show that pyrophosphate-driven ATP-synthesis could be connected to DNA-polymerase activity, which is the enzyme that drives DNA synthesis. The idea was that the pyrophosphate would give a proportional light signal to the number of the same nucleotide sort being incorporated in one round. But every round that the added nucleotide wasn't incorporated, it was left in the mixture disturbing the pyrophosphate-induced signal in the next round. Hence, some kind of washing step removing redundant nucleotides was needed. There were more disrupting factors to consider; the enzymes essential to the sequencing process were often delivered with many impurities which affected the results of the sequencing experiments. This required a great effort in terms of investigating which these impurities might be and eliminating them. (Interview Nyrén)

As it now had been a sole man project for several years, Nyrén was of course interested in trying to find collaborators. When he, as was expected of an employed researcher at KTH, read through the publications produced at the department he found an article written in 1988 that he regarded as very interesting to his sequencing project. The article was about solid phase DNA sequencing and the author was a friend of Nyrén from his undergraduate studies; Mathias Uhlén, now a Professor. The solid phase technique 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 hence 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. Nyrén saw this as a solution to the problem of redundant nucleotides; by combining the solid phase technique with his ideas on sequencing by synthesis he might make some progress. Nyrén contacted Uhlén who was willing to help Nyrén with the solid phase part of his sequencing project. Even if it initially was the solid phase technique that had made Nyrén interested in Uhlén's research group his agenda was also to legitimize the project; Uhlén was very productive both as a researcher and as an entrepreneur interacting with the business world. Therefore, connecting Uhlén to the sequencing project was from Nyrén's part done both for scientific as well as political reasons. Through a student in Uhlén's group, Bertil Pettersson, Nyrén learnt about the solid phase technique and with his help Nyrén worked on how to combine the magnetic beads with the pyrophosphate detection system. (Interview Nyrén, Pettersson)

For most of his research career Nyrén had been very focused on the photosynthetic research field. Hence, before coming to KTH he was rather unfamiliar with the genetics area which he had now taken a giant leap into through his sequencing project. Because of this he wasn't aware of the influences on the methodological level within the genetics area; what was currently being presented at important conferences, what kinds of methods were considered to be the past and what kinds the future. However, after attending a few conferences within the subject he quickly realized that sequencing by synthesis was considered the past and Sanger the future. No one had really succeeded in reading several nucleotides by using sequencing by synthesis; it was regarded a fine idea in theory but a non-functioning one in practice. The big difference between sequencing by synthesis and Sanger lied in its application; sequencing by synthesis was to be used for reading short sequences with accuracy while Sanger was designed for reading hundreds nucleotides at a time. The potential in qualitatively reading short sequences was hence yet to be discovered, the focus still lied in reaching quantitative goals; to read as many nucleotides at one time as possible. Therefore, since the conviction was that developing and refining Sanger was the right way to go, Nyrén's sequencing by synthesis project was often met with scepticism. To combine the sequencing by synthesis method with a solid phase technique didn't impress either, rather the contrary. Overall Nyrén met much resistance basing his sequencing method on already rejected ideas such as sequencing by synthesis; the common opinion was that if no one had succeeded doing it yet then it just couldn't be done. (Interview Nyrén)

Even if Nyrén had had some assistance from Pettersson from Uhlén's research group the collaboration was very limited; Nyrén did most of the work and met little enthusiasm from the group at this stage. Just being able to work one day a week on his project made every problem a huge obstacle and progress was slow. One particular problem Nyrén still was struggling with was to obtain clear and strong pyrophosphate-generated signals. This took an interesting turn as Pettersson had an idea to reverse the current model; 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). Consequently, if there was no signal then the added (dideoxy-) nucleotide had been incorporated and the sought-after nucleotide would be known. This idea hence eliminated the problem with unclear signals; it was instead the absence of a signal that indicated an incorporated nucleotide. The result was obtained by using a certain form of nucleotides, called dideoxynucleotides, which inhibits further nucleotide extension once it has been incorporated in the growing DNA strand. (Interview Nyrén, Pettersson)

The fact that this method worked was very encouraging for Nyrén and the further development of the sequencing project; now it was "just" a matter of enhancing the sensitivity for the pyrophosphate reaction. They wrote an article (Nyrén. P, Pettersson B., and Uhlén M., (1993) Solid Phase DNA Minisequencing by an Enzymatic Luminometric Inorganic Pyrophosphate Detection Assay, Analytical Biochemistry, 208) showing the basis of the method. However, in its current state the method could only be used for single nucleotide detection making its application rather limited. For Nyrén who was still interested in creating a sequencing method that could sequence several nucleotides at a time the development work continued. (Interview Nyrén, Pettersson)

3.2.1 Support from one of the World's Largest Suppliers of Biotech Tools

Gradually the struggles with the new method became an issue of a larger group of researchers. In 1994 a PhD student who had been working for Uhlén joined Nyrén, his name was Mostafa Ronaghi. To Nyrén he was the first to take interest in technological development; students before him were more fascinated of pure biochemical research. Over the years the group grew bigger: Samer Karamohamed, who at first worked for free, joined in 1995, Tommy Nordström and Nader Nourizad in 1996, Baback Gharizadeh in 1998 and Jonas Eriksson in 2000. In order to solve problems with the method on several fronts, as well as to produce theses to examine the students, Nyrén let them focus on different parts of the project. Up until 1994 the method had been manually operated but as the group began to grow the following goal would be to automate the whole process. A possible solution that the group decided to investigate was the use of a capillary flow system. However, this was a totally new research area to Nyrén, a situation he had experienced several times during this project but this time he felt dejected. Were he and the group to spend countless hours learning this new area maybe just to realize that it wouldn't work? Nevertheless, a capillary flow system study was initialized and different aspects of its use were considered. (Interview Nyrén)

Nyrén was constantly trying to achieve awareness of his sequencing idea outside of KTH, usually without any luck. However, in 1996 Björn Ekström, the chief of explorative research at Pharmacia Biotech in Uppsala, took personal interest in the method. At that time Pharmacia Biotech was one of the world's largest suppliers of biotech analytical tools and provided equipment both for research and large scale production. It was through Uhlén, who also sat in the Pharmacia company board, that he had found out about the sequencing project at KTH. On Ekström's initiative, Pharmacia began collaborating with Nyrén and his group. The goal was to automate the method by applying the capillary flow technique. (Interview Nyrén, Ekström) Nyrén was glad that his sequencing project finally got some attention, he felt comfortable with the investigative approach that Pharmacia had to his ideas. He was also given equipment to work with the capillaries in parallel. However, even though they had some progress in their joint project with this approach Nyrén felt that the problem of automating the method was strongly connected to the washing step. Consequently, one of Nyrén's group's biggest challenges was to solve the washing procedure that still wasn't working very well. It hindered the method to be as effective as Nyrén knew it could be. In the summer of 1996 he got an idea that he knew was worth investigating further. He had realized that he could get one single enzyme to take care of the whole washing process; the solution was a nucleotide-degrading enzyme called apyrase. After several weeks of testing he could prove that it actually worked. Consequently, by late 1996 the method had developed into a four-enzyme system (see fig. 3) which incorporated the correct nucleotides to the single stranded DNA template (through polymerase), continuously degraded the nucleotides that hadn't been incorporated (through apyrase), and created a proportional light signal (through sulfurylase and luciferase) that could be detected and registered. (Interview Nyrén)

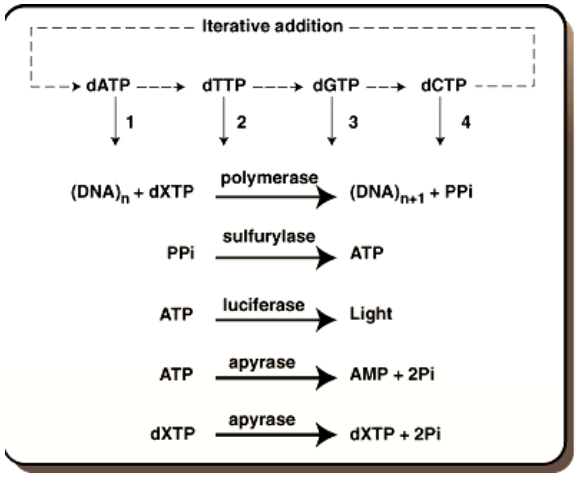

Figure 3. The four-enzyme–system of Pyrosequencing: the four different bases are added iteratively (dATP, dTTP, dGTP, dCTP). When the nucleotides are incorporated pyrophosphate (PPi) is released in proportion to the number of nucleotides included. Pyrophosphate is then quantitatively converted into an energy rich compound (ATP) which is transformed into a detectable light signal. (source: *Science* 17 July 1998, Vol. 281. no. 5375, pp. 363 – 365, *DNA SEQUENCING: A Sequencing Method Based on Real-Time Pyrophosphate*, Mostafa Ronaghi, Mathias Uhlén and Pål Nyrén)

This was a major breakthrough for Nyrén and his group at KTH. Ironically, at this time Pharmacia Biotech decided to withdraw from the collaboration. Pharmacia Biotech was facing a new situation; the company was in the middle of an ongoing merger with Amersham International. One of the first consequences was that the explorative research department was closed down. This meant that Pharmacia Biotech could no longer support the pyrosequencing development work and hence closed down the entire project. At first this seemed as a defeat. However, as Ekström left Pharmacia Biotech because of the reorganisations, a new opportunity gradually outlined. With the support of Ekström, Uhlén, Pettersson and Ronaghi, Nyrén decided that it would be a good idea to go into business and start a company based on his method. (Interview Nyrén, Ekström) This was a venture that, according to Pettersson, would not have taken place without the help of Uhlén. (Interview Pettersson)

3.2.2 A Research Group and a Start-up Company Trying to Create a Product

In parallel with the decision to create an own start-up company the project was presented for a venture capital advisory firm, Health Cap/Odlander, Fredriksson & Company in Stockholm. Besides being one of Sweden's most recognised investors in the life science area, there was already a connection between the emerging Pyrosequencing company and Health Cap/Odlander, Fredriksson & Company. When the advisory firm first heard about the Pyrosequencing method in 1996, it was through one of their scientific advisors – who happened to be Uhlén. After careful consideration, Odlander, Fredriksson & Company mobilized the Health Cap funds to support the new company for the next seven years, financially as well as managerially (Interview Odlander).

For the researcher Nyrén his method was a project that he had been working on for years: it had given him many published articles, approved patents and PhD projects. He was the only one who had believed in the new method from the beginning but he was also convinced that there was a lot of work left to be done before it could be considered an optimal sequencing technology. Hence, after a decade of work he still saw it as an ongoing project. He considered it a puzzle of small but crucial problems to solve in order to make it a good sequencing tool. Starting a company around his project was appealing to him for many reasons, above all it was a financially organized continued development of the method, but he had no plans on leaving the academic world. Therefore, as long as he had a say in the technological development he gladly left the company for Ekström to run. Because of Ekström's

network within Pharmacia Biotech he was able to attract quite a few people to join the starting up activity. (Interview Nyrén) Their first task would be to try to automate the method and the goal was to make the equipment as user friendly as possible. (Interview Ekström, Odlander)

After the founding of the company, which had taken the technology name: Pyrosequencing, the research work continued as usual in Nyrén's group at KTH. Together with Ronaghi, Nyrén was working on the apyrase enzyme in trying to optimize its function in the enzyme system, Nordström was working on the capillary flow system as this idea hadn't been totally abandoned, Karamohamed was involved in cloning and recombining enzymes while Nourizad was working on mutations of the DNA-polymerase enzyme. Realizing that Sanger would be a competing technology to his own, Nyrén was focused on trying to enhance the reading length. He also made this stand point clear to the company board consisting of, among others, Björn Odlander from Odlander, Fredriksson & Company, Ekström and Uhlén. (Interview Nyrén)

For the Pyrosequencing method to be able to attract a large audience Nyrén was convinced that it would have to be generic in the sense that it could be used in many different kinds of projects. It should therefore both be accurate and have a relatively long reading length. However, Nyrén thought that because of its great accuracy in reading short DNA fragments its main application area would be within diverse fields of research (in contrast to industrial applications). (Interview Nyrén) One such application area could be reading EST:s[3] which is done within many research areas for different purposes. Detecting CpG-methylation[4] could also be a rather unique application which no other method did very well. (Interview Odlander) Because of the way the sequencing system was designed accuracy was a quality that came with the system itself, the reading length however, would have to be actively developed. For Nyrén the continuing development of the technology would be about optimizing. Every aspect of the method could be improved; it was just a matter of time and financial resources. (Interview Nyrén)

At first the new constellation consisting of the company and Nyrén's group at KTH worked smoothly; the goal was to automate the technology and being the father of the invention Nyrén played a special part. The first non-commercial automated system was constructed by Nyrén, Nordström and Ronaghi. The first commercial automated system developed by the company was sold in 1999. The system became, in contradiction to the most established sequencing method, directed to short DNA fragments, adapted to what was considered the most important user area; analysis of single point mutations.

The system was designed as follows: The pyrosequencing process takes place inside an instrument, which looks like a square box, where a kit of reagents (the enzymatic system) is necessary for the reactions to happen. The "pyro-reaction" (which occurs when a nucleotide is incorporated in the growing DNA strand) is detected and transformed into a digital indication which is shown on a computer screen. If the signal is twice as strong this indicates that two bases of the same kind have been incorporated into the growing strand, which in turn is transformed to an indication of two bases. The final result is shown in a Pyrogram where the whole DNA sequence is accounted for (see fig. 2).

[3] EST:s or Expressed Sequence Tags are short DNA fragments with known gene expression
[4] CpG-methylation is a chemical modification of DNA which affects the gene expression

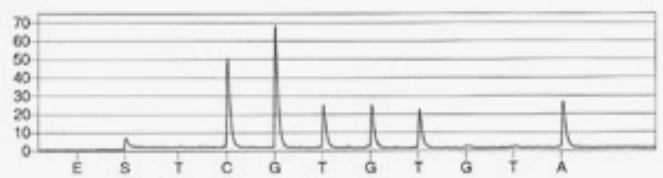

Figure 2. A Pyrogram™ with light intensity on the y-axis and the time for adding different reagents to the reaction on the x –axis. The peaks demonstrate the light reaction to each added base. (E = enzymes, S = substrates, G = guanine, A = adenine, C = cytosine, T = thymine). (source: www.magbio.com, 2006)

Pyrosequencing developed three versions of the instrument; PyroMark™ ID, PSQ HS 96, PSQ HS 96A, including reagent kits as well as complementary equipment. Thus, the customer who owns an instrument continuously has to buy the reagent kits since this is built into the system.

However, as soon as the first commercial system was developed and launched something happened. It was becoming very clear that the technology was spreading outside of Nyrén's group; it was now part of a growing company and many researchers at KTH took sudden interest. The technology had gone from being a sole man's project, to engage a whole research group, to become the foundation of an entire company. As the method had taken a fixed physical shape it was getting connected to many product development projects. Several researchers in Uhlén's group were involved in such projects investigating its use in different areas such as bacteriology and diagnostics. According to Nyrén, this was all fine to him since the development of the method was his main concern but there was however another turn of event that troubled him. The company was no longer open to the new ideas coming from KTH. Every time Nyrén or any other member of his group had suggestions for improvements their ideas were either considered too difficult or too expensive. Nyrén experienced this as some sort of competition from the company's part regarding who came up with the best ideas and who was more efficient than the other. Hence, there had arisen a rivalry between KTH and the company. (Interview Nyrén, Pettersson, Odeberg)

Against Nyrén's and the KTH research group's will the company had mainly focused on one particular application area: SNP-analysis[5]. Nyrén, on the other hand, thought it was too soon to start to market the technology in such a limited way. It was his firm belief that it was far from obvious what the best application would be; SNP-analysis was just one out of many. He wanted to continue to develop the method and hence await which application that would best fit the technology in its optimal state. Therefore, Nyrén's wish was to hold the choice of application an open matter until the most part of the first development phase was over. According to Nyrén, while he as well as his colleagues at KTH saw the potential in the Pyrosequencing method as a flexible sequencing technique with many applications areas, the Pyrosequencing company made an effort in narrowing its use to a few applications. Needless to say, he and his colleagues were in a state of frustration. (Interview Nyrén, Pettersson, Odeberg)

However, the research around the method continued at KTH, both in Nyrén's and in Uhlén's group. According to the KTH research groups there was an initial functioning collaboration between them and the Pyrosequencing company. However, gradually this was lost and from the research groups the explanation was clear. The change was due to the fact that Pyrosequencing got more and more employees from Pharmacia Biotech, used to work under rather special conditions; in a large firm with constant access to financial resources. The KTH researchers had difficulties in handling the new situation; from interacting with a Pyrosequencing that behaved like a small, open and informal project group, the company gradually started to act more like any established "self-confident" firm. The KTH

[5] An SNP (pronounced "snip") is a DNA error represented by one single nucleotide. For instance, the DNA sequence might be altered from A**T**TCGAT….. to A**A**TCGAT…...through a mutation. Most SNP:s don't affect the cell function while others are thought to cause diseases and affect a persons drug response. For a variation to be considered an SNP, it must occur in at least 1% of the population.

researchers were frustrated over the Pyrosequencing company's declining interest in improving the method. Several discoveries and improvements were made on different fronts at KTH. The same year as the first product was launched Jacob Odeberg, a researcher from Uhlén's group, initiated a study of genetic markers connected to heart conditions using the Pyrosequencing equipment. Performing the study Odeberg realized that a substance called SSB (Single-Stranded DNA-Binding protein) improved the quality of a certain type of analysis on the Pyrosequencing machine. The Pyrosequencing company was of course informed about this improvement but made no effort in trying to apply it at the time. Another example is when Nyrén's group presented the use of multi-primer sequencing, invented by a student Gharizadeh, suitable for sequencing of multiple genotypes. Once again the Pyrosequencing company showed no further interest in pursuing a discovery made at KTH. According to Pettersson, who participated in the first company board meetings, he and Nyrén had several talks with the Pyrosequencing staff, among them Ekström, trying to convince them of the usefulness of the ideas coming from KTH. However, the two parties could never come to an agreement on the matter; the researchers were constantly met by the argument that it was too difficult to transform their ideas into globally shippable products. (Interview Nyrén, Pettersson, Odeberg, Ekström)

3.3 The Value of Pyrosequencing in the Venture Capital Setting

In 1996, as the first one of its kind in Sweden, an advisory firm for investments funds restricted to the life science area was established. The firm took the name Odlander, Fredriksson & Company and functioned as a consultant for a number of funds, known as Health Cap. The different funds worked as limited partnerships with diverse investors as owners. (Interview Odlander)

It was while working at ABB Financial Services, that Odlander and Peder Fredriksson saw a void within the life science investment area in Sweden, particularly when it came to investments in research at early stages. They both had profound experience within the area as Odlander with a background within medical research had later made a career as a financial analyst and Fredriksson had 20 years experience within investment banking. The duo's first plan was to start a venture capital activity under the roof of ABB FS in order to do early stage investments in projects which more traditional investors would decline. However, as they were about to carry through their plan, ABB FS was sold to UniBank in Denmark. (Interview Steiner)

However, the major part of the investors which had been mobilized before the separation from ABB FS stayed loyal and invested in the Health Cap funds. Today the funds administers about 750 million Euros (currency value 2007) and investments are made in life science projects in different stages of maturity; it can be anything from a starting up activity to a company that has been selling products for years. 30% of the investments are made in Scandinavia, 20-25% in USA and the rest in Europe. The funds are positioned within life science areas such as pharmaceuticals, biopharmaceuticals, biotech supply and medical technology. (Interview Steiner)

According to Odlander, the Health Cap/Odlander, Fredriksson & Company's business idea is multi-levelled; on the one hand their intention is to commercialize research; to find research that can turn into commercially interesting projects with the purpose of creating strong research based companies. The ultimate goal is to produce industrially useful products. On the other hand the firm's function is also to administer the investor's money and their intent, in turn, is to receive return on investment. However, according to Odlander, as the investments wellbeing depend on the success of the commercialization projects these seemingly different ideas go hand in hand. The firm's main activities are concentrated to evaluating different opportunities for investments and to identify research areas where there is potential for new discoveries. They also have a great responsibility to actively work in the so called portfolio companies, i.e. the companies receiving investments. This means they have a very close dialogue with these companies in their day to day activities. If it is a newly founded company they help recruit the staff, above all in the leading positions, and formulate

strategies for the future activities. Of course, in the end their task is also to realize the investor's investments, which mean that something has to be produced and sold. (Interview Odlander)

According to Eugen Steiner, who is a partner of Health Cap and serves as CEO of certain companies in which Health Cap has invested, an academic research result is interesting if it satisfies an unmet medical need, which means that there should be a clear demand on the market for such a discovery. (Interview Steiner) According to Health Cap's investment approach the two most important aspects to consider when turning a new discovery into a prospering business activity are, as quoted above, "high quality management and uniquely positioned products based on outstanding science" (www.healthcap.se, 2007). The Odlander, Fredriksson & Company's advisory staff consists mainly of two professional groups: investment bankers and physicians with a PhD degree. Every project is inspected by two members of the respective groups and if they agree that it is a good proposition, meaning that they see both a potential unmet medical need and a profit to be made from it, the firm may decide to advise for an investment. (Interview Steiner, Odlander)

3.3.1 Investment in Pyrosequencing

After investigating the Pyrosequencing case the advisory firm became conscious of a need for a new DNA sequencing method since, in their opinion, nothing had really happened within this area since the 1970:s when Sanger was invented. According to them there was a need for a more accurate and exact sequencing method, which many researchers had tried to achieve but still not been able to. The firm perceived the technology that Nyrén and Uhlén had been working on as the answer to this need. (Interview Steiner)

According to Odlander, who sat in the Pyrosequencing board from day one, the company board saw clear application areas where the Pyrosequencing product would serve an important purpose. They realized that there was very few other technologies that could perform CpG-methylation-analysis or EST-analysis which made clinically applied diagnostics the primary area for the new method. However, somewhere along the way this focus was lost and another one took its place; SNP-analysis. According to Odlander the newly gained understanding about the human genome through the HUGO-project[6] led to the idea that this was the source of all knowledge. It was the general belief that polymorphisms could be used in all sorts of different contexts and since SNP-analysis was used to identify and analyze these mutations it was considered a profitable application area. However, this was a niche where already cheaper and equally good methods to Pyrosequencing were available. (Interview Odlander)

Since Steiner was made CEO of Pyrosequencing Odlander, Fredriksson & Company was very much operationally involved in the development of the Pyrosequencing company. They formed tactics of how to proceed with the company development which also made them strategically involved. Hence, it was difficult to determine where Odlander, Fredriksson & Company ended and Pyrosequencing began, the company was a borderless blend of the two. (Interview Odlander) Ekström also played a significant role in the development of Pyrosequencing as he initially became a key person for the company, internally as externally. He was practically involved in all of the company's divisions and also acted as its face outwards. He was more or less convinced that SNP-analysis would make Pyrosequencing a world leading company within genetic analysis. (Interview Ekström, Nyrén)

The first goal for the company was to produce an efficient and user friendly automated system for the Pyrosequencing method which was considered achieved as the first product was sold in 1999. At an early stage they started to work on enhancing the reading length in close collaboration with Nyrén. However, at the time the improvements that were being made didn't go into production. This was,

[6] The HUGO-project (Human Genome Organization) was initiated in 1990 by the U.S. Department of Energy and the National Institutes of Health with the purpose of mapping the human genome. The project finished in 2003.

however, not an active choice from the company board. According to Odlander the board took decisions on a yearly basis that the research conducted at KTH should come into commercial use. Why these strategic plans were not carried out is unclear to him. (Interview Odlander)

In 2000 Pyrosequencing was introduced on the stock-market and valued to nearly €430 millions (currency value 2007). This put the company in a whole new situation; being forced to prove commendable of such a high valuation they needed to increase their sales to reach a certain turnover. However, for the next three years this didn't happen. Instead Pyrosequencing was run with a loss of over €30 millions (currency value 2007) per year, this just couldn't stand. (Interview Odlander) So, in 2003 the company board decided that the best strategic move would be to merge with another Uppsala-based company within the field of biotech called Personal Chemistry. This was a different company in the Odlander, Fredriksson & Company portfolio; it was based on a microwave technique to reduce the reaction time in chemical synthesis of organic substances. In spite of its customer base it still wasn't profitable and unlike Pyrosequencing, not a stock-market company. The board's main arguments for the merge were that Pyrosequencing was in need of a broader offer of products and that there were synergy effects to be expected in the R&D division. Their ambition was to become a broad biotech supply company that could offer a number of products that a general science laboratory would need. (Interview Odlander, Steiner) After the merger another acquisition followed; it was an American company, Biotage LCC, producing chromatographic equipment[7] that would be a complementary technology to Personal Chemistry's. The new corporation consisting of the three companies took the name Biotage and was divided into two main divisions: Biosystems which was Pyrosequencing and Discovery Chemistry which was Personal Chemistry as well as Biotage LCC. Since then there have been several acquisitions, so far only compatible with the Discovery Chemistry division which made this part of the company profitable before Biosystems. (Interview Odlander, Ekström)

For the first time since its creation Pyrosequencing became, through the division Biosystems, profitable in 2006. (Biotage Year End report 2006, 9 February 2007) According to Odlander this is due to the fact that the company now has refocused and taken up the original ideas regarding development and application areas for the technology. In his opinion they have now acknowledged Nyrén's ideas regarding further development and also realized that diagnostics is the proper implementation area. Even if he thinks that every product is a child of its time, in Odlander's opinion they made an unprofessional positioning by focusing on SNP-analysis as the specific application area for Pyrosequencing. (Interview Odlander) According to Ekström the stock valuation was both a blessing and a curse; it's always nice to receive money but the fact that the valuation was unreasonably high put too much pressure on the company. Further it is his opinion that had the company invested in the diagnostics area from the start Pyrosequencing would have saved a lot of money and probably been able to reach its goals much sooner. (Interview Ekström) Steiner thinks it's sad that the valuation in the 2000 stock introduction no longer stands but according to him the money received at the time was useful in the sense that it broadened their supply chain portfolio through the acquisitions of Personal Chemistry and Biotage LCC. According to Steiner's philosophy "[…]the most important thing is to get critical mass on the market; the sales personnel need something to do and then it's not enough to sell just one technology, unless the market loves it". (Interview Steiner)

The merger with Biotage became the final conclusion for the interaction between Pyrosequencing and Nyrén and his research group at KTH. The researchers consider the Pyrosequencing system developed by the company as a small niche for DNA sequencing brought into practice in Sweden. However, as a methodology in the academic setting it is still very much alive, through continued use and development at KTH and other research institutions. (Interview Nyrén)

[7] A technology used for protein purification

3.4 The Value of Pyrosequencing in the User Setting; Experiences from New York Blood Center

One of the first users of Pyrosequencing's equipment and method was the New York Blood Center, NYBC, which is a private non-for-profit organization. Its primary mission is to collect and distribute blood to hospitals for patient care. They serve about 200 hospitals in the New York area and about 20 million people in the region. In USA 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 blood centres like NYBC. Even though the centre is a non-for-profit organisation it operates as a business, but the purpose is not to make a large profit, just enough to stay alive. In addition the centre has a relatively large research institute as well as a large stem cell activity. The stem cells are mainly extracted from placental umbilical cord blood from which they have managed to build up an immense inventory. (Interview Valinsky)

According to Jay Valinsky, Vice President of Information and Technology at NYBC, the centre made contact with Pyrosequencing in 2001. It started with an idea regarding an expansion of the health service offered at NYBC; since they collected blood from around 2000 people every day they wondered if, besides of building a blood bank, this blood couldn't be used for diagnostic purposes as well. At present they were offering health services such as checking blood pressure, studying haemoglobins as wells as performing other types of physical exams, why not also do genetic screening? Their first concern was how they would do this within the context of routine blood drive; for people to accept this additional service it couldn't be too disruptive. Asking around 1000 people if they would accept genetic testing, NYBC was very surprised at the positive response to an otherwise controversial question. Their second concern was how they would do large scale screening effectively in an automated fashion. This question led them to Pyrosequencing which, in NYBC's perspective, offered a good technology for the kind of study they would like to perform; analysis of single point mutations (SNP:s). The centre was particularly interested in a genetic disease called hereditary hematomacrosis. This was attractive for two reasons: they had an interest in iron metabolism but more importantly the therapy for this disease was blood donation (an iron overload is cured by giving blood). This meant that once NYBC had made the diagnosis they could also offer the cure; blood donation. (Interview Valinsky)

NYBC wanted to create a process from automated DNA extraction at the "front end", by collecting the blood, to genetic screening and analysis on the "back end". The purchased equipment from Pyrosequencing would take care of screening and analysis at the back end which meant that it had to be connected to what happened at the DNA extraction stage; the front end would have to be compatible with the back end. Hence they were put in a situation were they had to think in terms of a whole process where the Pyrosequencing equipment was just one of the components. Much effort was put into finding a good automated DNA extraction method which would collect the blood as well as to separate the important substances, e.g. DNA, from non-desirable blood substances.

However, there was some trouble getting the Pyrosequencing equipment to work properly, which resulted in the laboratory staff working on more conventional assays in order to produce test results. In Valinsky's opinion the problem was connected to the blood sample quality which required a special design of a particular part of the Pyrosequencing reagent kit (primer design). Even if they eventually received the special kit, Valinsky experienced difficulty in getting this information through to Pyrosequencing. The delay resulted in a low usage of the Pyrosequencing equipment as the staff was getting more used to working with the conventional assays. After some time the centre used the equipment more as a screening tool than as an analytical instrument since once they had identified the samples that would be of interest to them, with the Pyrosequencing equipment, they used the conventional assay to continue the analysis. This had not been the initial plan.

It was not that the Pyrosequencing equipment didn't work but rather that the centre was under time pressure; since they needed to produce test result and didn't have enough skill to efficiently operate the Pyrosequencing instrument they focused on what they already knew by using the conventional assays. According to Valinsky the centre repeatedly gave recommendations to Pyrosequencing

regarding new applications and improvements that could be made. At one occasion Valinsky had a long discussion with Pyrosequencing regarding the significant diagnostic use for the device. Speaking from his own experience of the diagnostics field regarding FDA (Federal Drug Administration) regulation and other restrictions he tried to convince them to develop assays proven for diagnostic use. Because of the regulatory environment which NYBC exists in as a clinical laboratory they must use assays specially proven for diagnostic use which puts constraints as to which supplier they can use. In Valinsky´s opinion, not having clinically proven assays seriously limited the use of the Pyrosequencing equipment within the diagnostic sector. The equipment stayed a research instrument which narrowed its use at NYBC. (Interview Valinsky)

However, the centre had yet another idea for how to use the equipment from Pyrosequencing; this new application was blood typing. Instead of determining a person's blood type through its phenotype; i.e. its physical features, they wanted to do it genetically; i.e. study the genes that determine these features. Since it greatly improved the chances of giving the right person the right type of blood it would be a very advantageous application for the centre. It was particularly useful when determining the blood type of a person that had been multiply transfused; it became increasingly complicated to identify the blood type through the phenotype since if the patients were given the wrong blood type once, they started to develop antibodies which made them sensitized to the next transfusion and so on. To be able to identify the more complicated cases, where knowing the surrounding sequence of the SNP was of importance, they needed a method with great accuracy. Hence, in order to identify the SNP for the specific blood type the analysis required great sensitivity. Therefore, Valinsky argued that this would be a perfect application for the Pyrosequencing method. However, once again the same scenario repeated itself; Pyrosequencing showed some interest at first but never materialized the idea. (Interview Valinsky)

After having used the Pyrosequencing equipment effectively for about two to three years in the screening project, it has been kept in a box in the NYBC basement. In the blood typing case they by-passed the whole Pyrosequencing idea and went for micro-chip technology instead. According to Valinsky it is not entirely Pyrosequencings "fault" that the centre couldn't find more use for the equipment; had they put more time and effort in bringing it into the projects it might have turned out differently but the constant resistance to their new ideas at Pyrosequencing probably held them back. (Interview Valinsky)

3.4.1 Experiences from Current Users

If New York Blood Center represents the typical user; an instrument was bought, tested for a while, but never became embedded in practice, there were some other users that actually managed to embed the product. One of them is the Department of Medical Biochemistry and Microbiology at Uppsala University. Whenever there is SNP-analysis involved in a project at this department then so is the Pyrosequencing equipment. They use the technology in a project where they perform SNP-analysis on horse DNA. The purpose is to find genetic markers that cause cancer on horses. The department performed a test where they compared several sequencing techniques and found pyrosequencing to be the fastest and most accurate. They are convinced that pyrosequencing is the best method available for this kind of research. They have had some collaboration with the Swedish University of Agriculture regarding the technology which has taken the shape of discussions concerning applications. The close contact that the department had with the Pyrosequencing company in the beginning is gone. This is partly because the department seldom has anything to complain or ask about and partly because of the company merger. (Interview Pielberg)

Another Pyrosequencing user is the Department of Genetics and Pathology at Rudbeck Laboratory in Uppsala. At this department pyrosequencing is one of several instruments used in parallel to answer DNA related questions in criminal investigations. Part of the purpose of getting the Pyrosequencing machine was to compare it to other more established methods; therefore it was never a problem to combine it with the other machines. To use a technology in parallel with other equipment is very

common within the forensic area. It's partly because its takes a long time before a new instrument becomes approved at a forensic department as safe and partly because it is more secure to work with several instrument to make sure that the final result is correct. Another advantage discovered at the department was the quantification made possible by pyrosequencing; it could be used to measure the relationship between two different DNA types in one sample and give the answer to which type that contributed the most. According to the department, this is a new and very useful application that separates pyrosequencing from other sequencing methods. Sanger is still the method most frequently used but the staff thinks that there are some parts of that method that are very time consuming. An analysis that takes two days for Sanger takes only an afternoon for Pyrosequencing. A few years ago the department had a collaboration with KTH and Pyrosequencing financed by Vinnova[8]. This resulted in several dissertations and published articles for KTH and the Rudbeck Laboratory as well as suggestions for further applications for the technology. However, a specially developed reagent kit intended for forensic medicine never went into production which means that the only party that did not take the opportunity to profit directly from this collaboration was Pyrosequencing. The connection between the company and the department was very strong up until the company merger, now it just goes as far as the continuing purchase of reagent kits. (Interview Allen)

When the Department of Clinical Chemistry at the University Hospital in Örebro received their Pyrosequencing machine they started to use it in their everyday routine directly, which quickly made it an important part of their daily work to analyze blood samples. When it had become an established method at the department they also started to use it for research purposes, mainly to perform SNP-analysis. They trust pyrosequencing as a method and see its accuracy as a great advantage since patients depend on the department for their health and wellbeing. The department is full of different kinds of equipment which they use for both research and routine purposes. Hence, they are very technology dependent and the PSQ HS 96A is just one of many machines. However, it has a very central position in their routine work since they depend upon the equipment for analyzing blood samples which they receive from patients every day. The result of the pyrosequencing analysis leads to a referral and then treatment or a note in the protocol about the patient. The contact with the company has never been very extensive but they are connected through continuous purchases of reagent kits and occasional technical support. (Interview Olsson)

4 Discussion

Viewing a technology from the three perspectives presented in this paper one thing is obvious; the value of a technology is relative. This implies that, in order to be useful, any technology – or combination of physical and human resources –has to be adapted to its context.

It appears as technologically there was no other method than pyrosequencing demonstrating the same accuracy and precision within genetic analysis at the time. Still, it was not easy to embed the technology in user settings. A method with a huge technological advantage turned out not to be valuable in itself. It was rather its use, and its adaptation to each specific context that determined its diverse values.

In the academic context the new method's function represented a technological and scientific success; the researchers had managed to create a technology that did what no other technology had done before. But what was even more important was what the method represented in relation to the academic environment at KTH. In their view an experiment that had taken years to complete had gone well, it had succeeded and now there was no end to how it could be further developed. More questions needed to be asked and new experiments had to be done around this discovery. Therefore, as in most other academic environments a very strong existing resource at the KTH department was

[8] A Swedish governmental institute with the purpose of supporting innovations systems, for more information go to www.vinnova.se

the research tradition never to be satisfied but always try to develop further, to improve and to optimise. Nothing goes by unchallenged and nothing is considered complete, there is always work left to be done and always other ways to see the world. Also, another resource within the academic environment that is strongly connected to the motivation always to think and develop further is one of its main products: publishing in all its forms. In order to show that you are a productive and respectable researcher it is of outmost importance to be published. Whether it is in the shape of books or articles a researcher needs to show hers/his findings to the rest of the research society. Since the number of publications also determines your professional rank and number of granted scholarships the will to produce publications is great drive force within the academic community. This contributed to the fact that the pyrosequencing technology was never considered finished at KTH; there was always the determination to explore all its possibilities and to produce more research results for publication.

In the venture capital and business setting the technology interacted with resources structures highly focused on financial interests. The greater part of the venture capital firm's business idea is to produce ROI for its investors; if they don't their business will simply collapse. Therefore, in order for their company to survive all their knowledge is fixed on how to produce this kind of capital. It is however the valuation of the entire investment portfolio that determines the venture capital firm's result, not the single investment. As a result, what happens to one of the companies in the investment portfolio is secondary to the effect on the total collection of investments. In turn this means that acquisitions of or by companies within the portfolio are encouraged as long as it enhances the value of the portfolio. In their view the pyrosequencing technology was only worth something as long as it could produce ROI and increase the value of the total investment portfolio. Consequently, for the venture capital firm to be able to guarantee a certain ROI within a short period of time they were interested in stabilising every possible variable. Their strategy to obtain predictability was to freeze as many conditions as possible, one of them being the product's application areas.

Placed in the user context the technology had taken the shape of a locked physical product. As the empirical material shows there were quite diverse reactions to this particular solution depending on the user. Where the technology interacted with the user's existing resources in a satisfactory way there was no problem of using this fixed solution; the interaction between the pyrosequencing technology, the user's existing technologies and project goals was functional. However, in the NYBC environment the fixed solution was not very pleasing. The center had been looking for an analytical instrument with the same utility as pyrosequencing was offering, just like the other users. However, once the instrument was delivered a number of use-related problems arose. The problems had nothing to do with the technology's function not working properly; it was working just the way it was supposed to. It was rather what this function represented in relation to their existing technologies and activity goals that created the problems. As the laboratory staff started to operate the instrument, with the purpose of reaching their project goals, it became clear that the pyrosequencing technology did not add any value to their production of research result. Since the technology could not facilitate the research process it was found useless. However, weather the technology actually was compatible with the NYBC environment or not is not really clear since it seems that perhaps not all its possibilities were thoroughly scrutinized. Still the technology was abandoned which demonstrates the influence of the inactivated form of a resource structure; the idea structure. Even if the full technology potential was not explored, NYBC had an "idea" of the technology as not compatible with their resource structure and therefore discarded it.

Above all the empirical material shows two interesting phenomena concerning the use of a technology in different contexts. As mentioned before, one is the perception of a technology's value or benefits in any particular context. It is not how a technology functions that is of most importance but rather what this function represents in relation to the context's prerequisites. Hence, it is the interaction with the environment's existing resource structures, tangible or intangible, activated or non-activated, that determines a technology's value in a certain context, not the technical function in itself. The second is the lack of "interactiveness" in the knowledge transferring process (Håkansson & Waluszewski, 2002). In this case there is an obvious unawareness between the contexts of their

different prerequisites of handling the technology. The technology producer takes over a technology that has been developed in a highly academic influenced environment. When determining the features of the new research instrument this producer primarily considers monetary requirements, which of course affects all decisions being made, financial as well as technical. Not very surprisingly these features are far from optimal for all potential users. In resource interaction terms this means that the technology is shaped by the existing resources in one context, transferred and, at best, used in a context with a very dissimilar resource structure. Of course this is not an unusual situation, often this is the way technologies are produced and used (or not used), which makes it even more fascinating. Technologies are being transferred from one environment to the next with little mutual understanding of what affects the use of them in the different environments. In turn it is this ignorance which makes it almost impossible to foresee the effects of trying to embed a technology in a certain user context. How could someone from one context ever predict which benefits that will appear around a resource in another context without much knowledge of that particular environment? A more interactive approach of transferring knowledge between contexts in order to find compatible solutions might increase the parties' knowledge of the technology's use and how to improve it (Håkansson & Waluszewski, 2002).

The interactive approach challenges the view that there is a unidirectional relationship between science and technology (or a commercial success/failure). This is also done by Rosenberg (1982) who states that "It is likely that 'linear' models of innovation greatly exaggerate the extent to which the flow of ideas and resources from basic to applied research is unidirectional in nature" (Rosenberg, 1982). Further he states that advances in knowledge are only possible when a technology is used in real-life situations; the consequences and nature of its use can never be foreseen in fabricated or imagined environments. This is shown through history as there has always been a strong connection between science and technology where the experiences from a certain technology is later dealt with by science. (Rosenberg, 1982) Hence, there is an interactive relationship between the creation of science and technological solutions. This suggests that for new knowledge to evolve around a technology there need to be an awareness of its surrounding contexts, otherwise still unknown aspects of it could be lost.

List of Reference

Ford D., Gadde L. E., Håkansson H., Snehota I. (2003) *Managing Business Relationships*, John Wiley & Sons Ltd, West Sussex, England

Gompers P. A. and Lerner J. (2001) *The Money of Invention: How Venture Capital Creates New Wealth*, Harvard Business School Press, Boston

Gudeman S. (2001) The *Anthropology of Economy: Community, Market, and Culture*, Blackwell Publishers

Håkansson H., editor (1982) *International Marketing and Purchasing of Industrial Goods, An interactive Approach*, John Wiley & Sons Ltd, West Sussex, England

Håkansson H., Harisson D.,Waluszewski A. (2004) *Rethinking Marketing –Developing a New Understanding of Markets*, John Wiley & Sons Ltd, West Sussex, England

Håkansson H. & Snehota I., editors (1995) *Developing Relationships in Business Networks*, Routledge, London

Håkansson H. & Waluszewski A. (2002) *Managing Technological Development -IKEA, the Environment and Technology*, Routledge, London

Penrose, E. (1959) *The Theory of the Growth of the Firm*, Oxford University Press, New York.

Rosenberg, Nathan (1982) *Inside the Black Box: Technology and Economics*, Cambridge University Press, Cambridge

Tidd J., Bessant J., Pavitt K. (1997) *Managing Innovation –Integrating Technological, Market and Organizational Change*, John Wiley & Sons Ltd, West Sussex, England

Van de Ven A. H., Garud R., Polley D. E (1999) *The Innovation Journey*, Oxford University Press

Soete, L., 2002. "The European Research Area: Perspectives and Opportunities." Paper presented for the international workshop on Research Policy: Incentives and Institutions, Rome.