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University Research in the Discovery of Oncology Therapeutics

A study of what role oncology research at universities play in the development of oncology therapeutics

Master of Science Thesis in the Master Degree Programme Business Design

TOMAS GILLE
MARCUS GAMME

Department of Technology Management and Economics
Division of Management of Organizational Renewal and Entrepreneurship – MORE
CHALMERS UNIVERSITY OF TECHNOLOGY
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Abstract

Cancer prevalence rates are growing globally, attributed in part by an aging population and to lifestyle changes. The usage of pharmacological treatment of cancer has increased over the last two decades and the global market amounted to $51.7 billion in 2009. The present study will describe and analyze how university research has contributed in the discovery of new oncology therapeutics in terms of claiming and being able to commercialize key patents. The role university research plays for multinational pharmaceutical companies in their drug development programs will also be explored.

A large amount of sales data as well as patent data for a selected number of oncology therapeutics has been studied. The studied drugs are those that fulfill the following four criteria: 1) Oncology drug approved in Sweden, 2) Oncology drug approved in the US, 3) Oncology drug has patent protection and 4) Oncology drug has been awarded US market approval prior to 2008. This resulted in a list of 32 drugs. The total number of drugs studied to get to that list was 178. The conclusions made in the analysis are based on interviews with pharmaceutical companies, biotechnology companies, universities and technology transfer offices. In total, eight people in various positions have been interviewed.

The study indicates that university research plays a significant role in the development of oncology therapeutics. However, the study also indicates that it is rare for universities to keep intellectual property rights and commercialization rights in research collaborations with the pharmaceutical industry. In fact, only 10% of the studied drugs had a substance patent that was assigned to a university or research institute. This is mostly because university research is very far from market ready products and universities lack motive and mechanisms to benefit from such rights. Furthermore, pharmaceutical companies have a much higher potential to exploit such rights and turn it into financial value compared to universities, making it very unlikely that a pharmaceutical company would allow a university to keep such rights.

In the present study, three hypotheses are stated, and at the end validated or invalidated:

- Universities are less successful researching and developing active substances compared to large pharmaceutical companies and biotech companies – **Not validated**
- The extent to which universities and pharmaceutical companies can collaborate is crucial for the development of new oncology drugs – **Validated**
- Competence in collaboration is a competitive advantage in the world of oncology drug discovery – **Validated**

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Foreword

The idea to this thesis began in a curiosity of the actual societal importance of university research. Universities obviously conduct research in many different fields, but as cancer research involves huge investments in developing new and better ways of treatment, while at the same time having tremendous impact on society, it felt natural to focus our study towards this field. Neither of us actually had any idea, in the quantitative sense, of what role universities play in the development of oncology therapeutics, but we were eager to find out.

We thereafter thought of an idea of how to figure this out. The idea was simple in theory, but turned out to require quite a lot of work in practice. Our idea was to find the substance patent of all commercialized cancer drugs and look at the assignee of such patent at the date of filing for the patent. Thereafter, we would group the patents according to if the assignees were big pharmaceutical companies, biotechnology companies, universities or something else. The aim was to find out how many active substances assigned to universities that have been incorporated as the main active substance in an oncology therapeutic. Naturally, university research contributes in several ways in the development of oncology therapeutics and we do not in any way claim that being patent assignee of an active substance, that has been used in an oncology therapeutic, is the only or correct approach. We have, however, decided on using this, a quite pragmatic, way of working and evaluating university contribution.

The way of working with this study has been very interesting throughout the spring. Digging deep in data analysis at times, combined with conducting interviews with stakeholders from different parts of the oncology therapeutics development value chain and finally working with analyzing our findings have given us a good sense of the echo system of oncology therapeutics development. On the same note, we have been touched and impressed by the willingness to share experiences, views and ideas on our findings and related topics, shown by all people we have interacted with throughout this study. All respondents seem to invest a significant amount of energy, dedication and commitment to their work, which has inspired us in getting the most out of this study. As mentioned, cancer is a topic which affects most people in one way or the other, and it has been inspiring to meet enthusiastic people sharing the belief of a brighter future for people suffering from different kinds of cancers.

When we started our thesis, we weren’t sure whether we would be able to answer the questions we had asked ourselves and stated in the hypotheses. But now, nearing the end of this spring, we are quite happy we the results, and hopefully, we have contributed something to the understanding of research collaborations in the oncology therapeutics industry.

1. Introduction

This chapter contains:

- *A brief introduction to the term cancer*
- *The world wide cancer prevalence*
- *The market of cancer drugs*
- *The characteristics of the cancer research industry*
- *Description and introduction of the research question and goal of this thesis*
- *The hypotheses discussed in this thesis*
- *Scope and limitations*

The term cancer is a collective description of the, currently known, approximately two hundred diseases defined and characterized by uncontrolled cell growth in the human body (Swedish Government Official Reports, 2009). Cancer is caused by two factors: internal factors like inherited mutations, immune conditions or random mutations and on the other hand external factors like tobacco, chemicals or radiation. The above mentioned risk factors can act individually, together or in sequence to set off or advance the creation of cancer. If an uncontrolled cell growth and spread is not controlled, it can ultimately result in death (Business Insights, 2010). Early detection, for instance through diagnosis- and screening programs, and treatment decreases the cancer mortality rate (WHO, 2011).

Attributed to an aging population, changing lifestyles in terms of diet and exercise habits as well as an increased pollution level, cancer prevalence rates are growing all over the world (Business Insights, 2010). In 2008, 12.6 million cases of cancer were reported world-wide, 6.6 million in men and 6.0 million in women. Globally, the most common types of cancers among men are lung cancer (16.5%), prostate cancer (13.6%) and colorectal cancer (10.0%). In women, the three most common types of cancer are breast cancer (22.9%), colorectal cancer (9.4%) and cervix uteri cancer (8.8%). (Ferlay, Shin, Forman, Mathers, & Parkin, 2008) Certain types of cancers have different incidence rates in different parts of the world. The sections below describe the cancer mortality and incidence rates for different indications. In Appendix B, the mortality and incidence rates for different regions in the world are described.

1.1 World-wide

The five most common cancer incidence cases accumulated for both men and women globally are lung cancer, breast cancer, colorectal cancer, stomach cancer and prostate cancer. Cancer related mortality is closely linked to incidence. Prostate cancer, however, moves out of the top five cancer types in terms of cancer related mortality, surpassed by liver cancer, cervix uteri cancer and esophagus cancer. (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

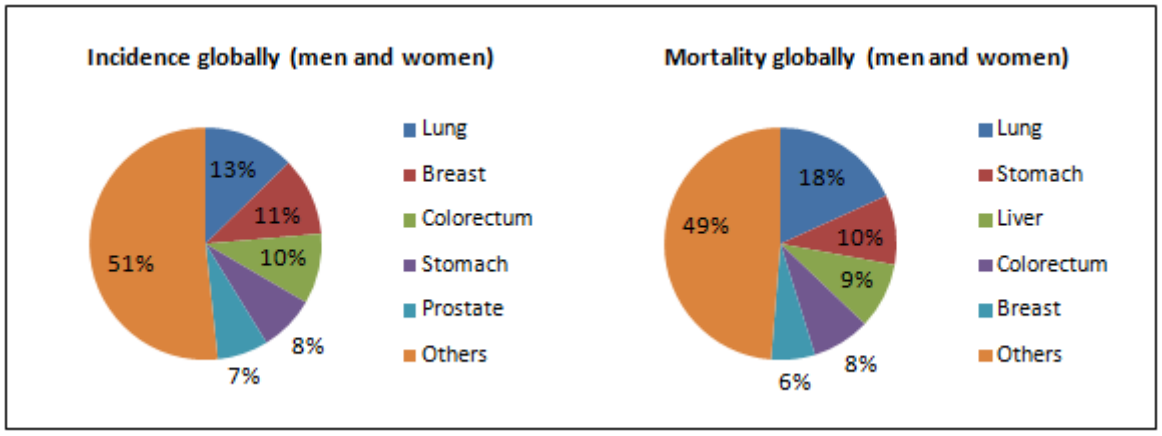

Figure 1 – Global incidence and mortality rate per different cancer type (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

1.2 Market Trends Cancer

There are two distinct cancer markets, one being the market of cancer care and all that is included in that and the other market is the cancer therapeutics market. In this thesis, we will exclusively focus on the later market. Names such as cancer therapeutics, oncology drugs or any variation of such descriptions will be used synonymously.

Two main drug categories are used in treatment of cancer: antineoplastics and cytostatic hormone therapies. The leading drug category of the two is antineoplastics, with global sales of $42.2 billion in 2009 with a year-on-year growth of 7.5%. Cytostatic hormone therapies accounted for sales of $9.2 billion the same year with a year-on-year decline of 1.6%. The major drug in each drug category in terms of global sales 2009 were Avastin (€5.1 billion) in the antineoplastics cateogory, and Arimidex ($1.9 billion) in the cytostatic hormone therapies category. (Business Insights, 2010)

Cytotoxics, another name for antineoplastics, are the most commonly prescribed drugs looking at all the major cancer indications in the seven major markets (France, Germany, Italy, Spain, U.K., U.S. and Japan). The function performed by antineoplastics is that of prohibiting cell division in one of the stages of the cell cycle. They are primarily targeting and killing fast-dividing cells but unintentional targeting of healthy human body cells in the bone marrow, gastrointestinal tract and hair follicles also occur in treatments with antineoplastics. (Business Insights, 2010) Comparably, cytostatic hormone therapy drugs hinder growth- and survival-promoting hormones in cancer cells by slowing down the production of such hormones in the organ where they are originating from.

The quantitative study included in this thesis will use the ATC classification system (Anatomic Therapeutic Chemical classification system) of cancer therapeutics, meaning that the division between cytostatic drugs and antineoplastic drugs won't necessarily be used.

Innovation in cancer pharmaceuticals has developed fairly slowly over the last 60 years but has seen a rapid development and acceleration during the latest decades. Approval for the first chemotherapeutic happened as early as 1942 and the first hormonal cancer drug was introduced in 1977. What significantly improved cancer pharmaceuticals was the market introduction of the first monoclonal antibody in 1997, Rituxan/MabTera. (Seget S. , 2007)

Determining cancer incidence and mortality over time in a historical perspective is hard since the structures of accurately identifying and reporting cancer cases has improved over time, as has

medical technological developments. Perhaps most importantly, however, life expectancy has increased, which results in more people in older age groups where cancer is more common. (Logomasini, 2008) It is possible, however, to draw some conclusions from cancer mortality rates over time in developed nations where reporting of cancer cases have been on-going for a longer period of time.

Looking on aggregated survival for all types of cancers in the U.S. during the 1970´s, 50% of all people diagnosed with cancer survived at least five years, a figure that has risen to 67% in 2010 (American Cancer Society, 2010).

1.3 Industry Characteristics

The global cancer market is growing, primarily due to an aging population. Counting only cancer drug sales, the global market amounted to $51.7 billion in 2009 (Business Insights, 2010). Oncology is today one of the major focus areas for pharmaceutical companies all over the world. The seven major markets in overall pharmaceutical sales, U.S., Japan, France, Germany, Italy, Spain and the UK, also represent the majority of sales ($40.8 billion, 79%) on the global cancer market (see Figure 2). (Business Insights, 2010)

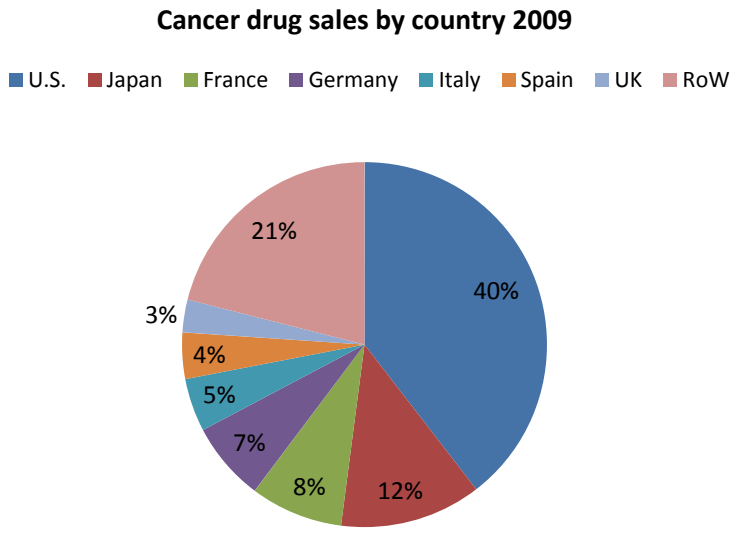

Figure 2 – Cancer drug sales by country in 2009 (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

The ten leading companies account for more than 75% of the entire cancer pharmaceuticals market. The five largest actors and their products are listed in Table 1.

Table 1 – The five largest pharmaceutical companies on oncology therapeutics (Business Insights, 2010)

Company	Sales (2009)	Market Share	Major products
Roche	$15.7 billion	30.4%	Avastin, MabThera, Herceptin, Tarceva, Xeloda
Novartis	$4.9 billion	9.5%	Glivec, Femara
Sanofi-Aventis	$4.5 billion	8.7%	Eloxatine, Taxotere
AstraZeneca	$4.1 billion	7.9%	Arimidex, Faslodex, Iressa, Zoladex
Eli Lilly	$3.5 billion	6.8%	Alimta, Gemzar, Erbitux, Gemcitabine

The industry has always had a tradition of working in close collaboration with universities and public research. This is also true for the Swedish pharmaceutical industry. Astra's blockbuster drug Losec was invented in a joint venture with the University of Gothenburg and Pharmacia was built up around the progress in the biotech field at the University of Uppsala (Ahlqvist, 2011). But that was many years ago. Both those companies have changed dramatically in their structure and organization. Astra has merged with Zeneca and Pharmacia merged with Upjohn and was subsequently acquired by Pfizer. How is the modern pharmaceutical industry collaborating with universities?

Without a doubt, there are large economic and societal incentives for sharing and exploiting public research. When Chesbrough talks about Open Innovation in his book (Chesbrough, 2006), he brings up the following example from the global pharmaceutical company Merck's annual report of 2000:

"Merck accounts for about 1 percent of the biomedical research in the world. To tap into the remaining 99 percent, we must actively reach out to universities, research institutions and companies worldwide to bring the best of technology and potential products to Merck. The cascade of knowledge flowing from biotechnology and the unraveling the human genome – to name only two recent developments – is far too complex for any one company to handle alone."

1.4 Questions to be Answered in This Study

What we want to find out in this thesis is how universities contribute in the development of new oncology therapeutics and what role universities play. Additionally, the authors want to evaluate how successful research collaborations ideally are executed and organized. To identify the role universities play in the development of new oncology therapeutics, one could take several approaches. In this study, however, the authors have decided to approach university contribution based on how many oncology therapeutics that had their active substance developed at a university. The hypotheses of the thesis will be described in more detail in the next section, but a couple of questions that have guided the authors towards the hypotheses are presented here:

- What are ideal conditions for the partakers in oncology research? How does it differ between actors?
- What is the most common place of origin for cancer drugs?
    - Universities, large pharmaceutical companies, biotech companies or is research collaboration a vital part?

- How do revenue sharing models look like in drug discovery collaborations?

These are the questions that we hope to find the answer to in this thesis.

1.5 Hypotheses

In this thesis, we have approached a quite large area. Along the way, every answer has created at least three new questions. It has therefore been a high priority to limit this thesis and to focus on matters that are reasonable to answer. With the decided scope and limitations, we have started with the following hypotheses that will hopefully be adequately validated or invalidated:

- Universities are less successful researching and developing active substances compared to large pharmaceutical companies and biotech companies
- The extent to which universities and pharmaceutical companies can collaborate is crucial for the development of new oncology drugs
- Competence in collaboration is a competitive advantage in the world of drug discovery

1.5.1 Universities Being Less Successful Researching Active Substances

The reason we believe in this hypothesis is based on the actual return on investment and huge risk that is associated with drug research. In the normal case, the success rate for a substance becoming an approved drug is about 1 to 10,000 (Pharmaceutical Research and Manufacturers of America, 2010). The risk in such a venture is therefore huge. In many countries it is difficult for universities and research institutes funded by public money to construct technology sharing contracts to receive royalties for their patents. Even in countries where such difficulties are smaller (e.g. USA), it is unlikely that these kind of technology licenses will be able to pay for the actual money put into the research as any licensee in such an agreement would himself have to take the drug through all or most of the clinical phases and would of course risk adjust any royalty paid. There are of course some cases where licenses have proven to be very rewarding for universities. For instance, Harvard, Columbia University and Cambridge have been very successful in creating patentable research results that they have been able to extract millions of dollars in royalty out of. But part from those, most university are likely focusing on basic science that is not applied enough to be patentable, less creating patents that will lead to royalties.

Therefore, we think that universities focus their research in the oncology field to inventions surround the active substances, to clinical methods etc., as such inventions may have a much shorter time to market, have a much larger application area and are therefore more likely to be adopted, produce more research spin offs and continuation projects.

1.5.2 The Importance of Research Collaborations

Many pharmaceutical companies have matured in symbiosis with thriving research institutions and universities. There have of course been shifts in the different players' relationships to each other. But for most pharmaceutical companies, drug discovery programs, and ultimately their own business success is highly dependent on how well they can both create and leverage research collaborations with universities.

1.5.3 Competence in Collaboration Being a Competitive Advantage

Pharmaceutical companies can never discover everything by themselves. By using universities, each part in a research collaboration can focus on an area they know best. It is also likely that

pharmaceutical companies do a lot of recruiting of key scientists in such collaborations. By being good at collaboration, R&D and drug discovery can become more cost effective.

It is also likely that pharmaceutical companies even compete to work with the most prestigious universities and the most skilled scientists and medical doctors. A pharmaceutical company that is renowned for being easy to work with, fair in sharing research results, IP rights and so on is probably more likely to win such a race.

1.6 Scope and Limitation

In this thesis, we have decided to focus our quantitative study of oncology drugs to those that are approved in Sweden and that still enjoy patent protection on its major markets. We have, however, extensively used data from American authorities. We have decided to not take specifically a Swedish or American perspective in our conclusions, but try to make conclusions that could be applicable on both markets.

This thesis will mostly explore the relationship in university based oncology research versus research originated in large pharmaceutical companies. To a large extent, biotech companies will be grouped together with large pharmaceutical companies.

Furthermore, cancer treatment involves both cancer care as well as cancer drugs. This thesis will only explore the process of discovering and commercializing the drugs and will not explore the dissipation of knowledge in the cancer care area at all.

To understand the process of knowledge transfer of oncology related intellectual property, this thesis will provide a set of detailed case studies, in which knowledge transfer from universities to private sector has been successful. These cases will be selected from the quantitative patent analysis found in 4. Results: Patent Data. The case studies focus both on describing the involved partakers in the process as well as the path from university lab to cancer patient.

2. Theory

This chapter contains:

- *Description of characteristics of oncology research*
- *A discussion on incentives in research, what they mean and how they are created*
- *A historical overview of pharmaceutical research in industry versus university and public institutions*
- *Patenting and intellectual property rights management in pharmaceutical research sector*
- *Pricing and valuation of pharmaceutical research*
- *Role of the Technology Transfer Office*
- *Trends in R&D cost cutting*

Because of the enormous development costs as well as the expensive clinical trials, it is virtually impossible for a small player or university to ever solely develop or commercialize an oncology drug. Looking at the oncology drugs approved in Sweden today that are still non-generic (producing generic drugs are a lot less costly), we can see that there are only big pharmaceutical companies or large biotech companies commercializing the drugs. This does, however, not mean that these large companies necessarily have to be the source of the research. It is generally believed that public research from research institutions and universities are vital and critical to medical research. We will in this thesis try to shed light on this statement and see to what extent it is true.

In the following theory section, we will cover available data and previous research results that we deem are necessary to start validating or invalidating our hypotheses. This theory section will mostly cover the structures of research processes and ways of monetization at universities and pharmaceutical companies.

2.1 The Origin of Oncology Research

The oncology therapeutic development process is undoubtedly an interesting field. Vast amounts of money is invested, tons of excellent people dedicate their lives to find better cancer treatment and it has naturally a severe impact on many parts of society.

The drug discovery process is at the core of cancer treatment. It is likely that future cancer care will be more about the right cancer therapeutics than invasive surgery, or that is at least what many hopes for. There are about 180 cancer drugs that have been approved for use. The oldest one is from the 1950's. More than 25% of the drugs have been approved in the 2000's (LIF (Läkemedelsindustriföreningen), 2011). In other words, a lot is happening on this field. It should also be stressed that the nature of the drugs is changing. The complexity and ability of modern cancer drugs are far higher than the cancer drugs of the 60's and 70's. Many of the therapeutics don't actually get rid of the cancer but are for palliative care, to strengthen or even replace the immune system during radiotherapy, and so on. The state of the art drugs of today have much more advanced feature. Some can actually block DNA-replication in cancer cells and completely shut down the spread of cancer cells.

2.1.1 Rising R&D Costs

The process of finding new drugs is not only very costly, but also extremely complex, serendipitous and time consuming. In many cases, developing a new drug starts with screening several thousands of molecular compounds. Oftentimes, it is not even clear what effect the compounds might have. After finding an interesting compound that may have a healing effect on humans, trials with the drug are initiated. At first, they are experimented on in vitro, and if the tests are deemed successful, they qualify for animal testing. It is only after extensive preparation that testing on humans can even begin. Moving through all phases (Pre-clinical and Phase 0 to Phase VI) takes on average about 8 years (Kaitin, 2006), but a compound can be rejected at every stage. Not only does the testing take a lot of time, they are extremely costly as well, since the later clinical trials involve testing on quite a large sample. The average cost of developing a new drug has increased over the last decades and now amounts to about $1.2 billion (Kaitin, 2006).

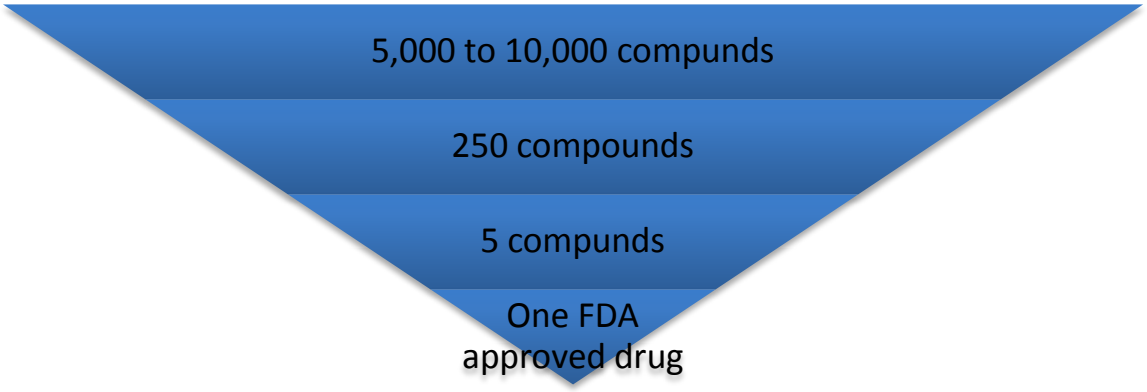

Figure 3 – Drug discovery from initial screening to approval, involves rejecting about 10'000 compounds per success (Pharmaceutical Research and Manufacturers of America, 2010)

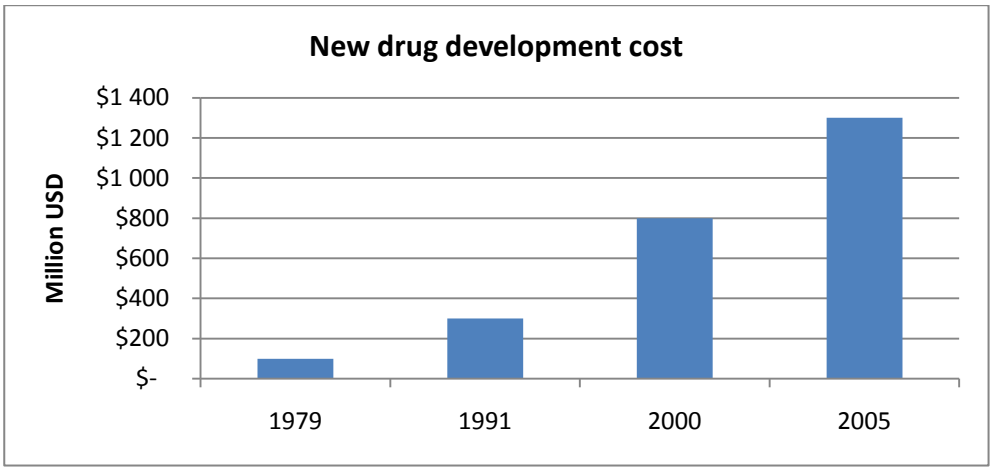

Figure 4 – The development cost of new drugs is increasing (Pharmaceutical Research and Manufacturers of America, 2010)

2.1.2 Generic Drugs and Patent Term Extensions

As most drugs are based on a very specific molecular substance, the patent protection in life science becomes extremely strong. It is also extremely valuable, as the development costs are very high and investments have to be recovered. On average only 2 out of 10 drugs recover their cost of development (Pharmaceutical Research and Manufacturers of America, 2010). In some regions (such as EU and US), it is possible to get a patent term extension (PTE). This is to compensate for long

approval processes. Since it implies prolonged market exclusivity, such an extension is often worth millions of dollars and increases the possibility of recovering development costs.

When a drug goes off patent protection it becomes generic and free for everyone to develop. The approval process for a generic drug is also much shorter and cheaper. On average, the approval process for a generic drug takes 3-5 years and costs only $1.2 million (1/1000 of the total development cost) (Kaitin, 2006). Producers of generic drugs are for instance Teva Pharmaceutical, Mylan and Sondoz (FiercePharma, 2010). However, it is important to note that many generic drugs are produced by subsidiaries of the giant pharmaceutical companies.

2.2 Pharmaceutical Research at Universities and in Industry

During the last couple of decades, the nature of pharmaceutical research has changed its form. Looking at Figure 5, we can see two things. One is that R&D spending in pharmaceutical research has increased tremendously. The other thing is that the R&D spending in the private sector (the pharma sample in the figure reflects the average and the National Institute of Health is the major governmental research body in the US) has grown faster than R&D spending in the public sector. Today, pharmaceutical R&D spending in the private sector vastly outnumbers R&D spending in the public sector. However, according to (Henderson, 2001), a number of detailed case studies highlights the role of the public sector as an absolutely vital part in supporting the development of new drugs.

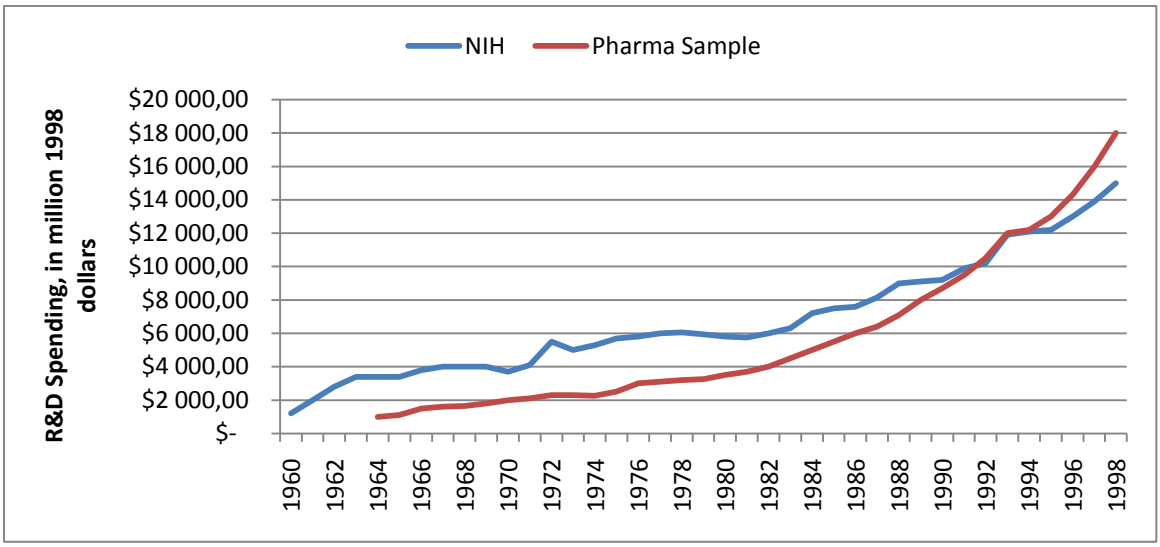

Figure 5 – R&D spending 1960-1998 for National Institute of Health and a sample pharmaceutical company. (Henderson, 2001)

But the pharmaceutical industry has also changed the way universities and industry coexists and work together. In the 1930's, the pharmaceutical industry barely had any research at all. Most new drugs were based on existing organic chemicals or derived from natural sources, such as herbs (Henderson, 2001). The period 1950 to present time is more or less the golden age for the pharmaceutical industry, as the pharmaceutical sector has become accustomed to high growth rates and enormous returns on investment. The sector has also become highly consolidated with many of the large dragons merging together. Many factors have contributed to this sector becoming so innovative. One of the largest drivers is the fact that there were an abundance of targets (i.e. diseases) in the post World War II world, but not many drugs. A research driven pharmaceutical industry happened to be very profitable (Henderson, 2001).

2.3 Patenting at Universities

The focus on patenting research results in general have increased significantly since the 1950's. This is true for most industries and also at universities. A lot of government measures are aimed directly at increasing patenting at public institutions and in the private sectors as it is generally believed that the abundance of long term competitive advantages and growth is accelerated by patents. Many countries have also passed laws, such as the Bayh Dole Act, that greatly simplifies the way universities can derive royalties from its research results.

As a result of this, the rate of patenting at universities has increased significantly. In 1965, only 96 US patents were issued to 28 American universities. In 1992, over 1500 patents were issued to more than 150 universities in the US (Hendersson, 1995). This increasing trend is still valid today. But as focus has lied upon the actual patenting, the number of citations per university patent has actually decreased relative to patents in general, and as a result, university patents are today just as likely to be cited as any patent (Hendersson, 1995). The same report concludes that about 30% of patents rewarded in 1991 come from the top 10 patenting universities. Furthermore, drug and medical related patents are by far the largest area in which patenting at universities occur and accounted for about 40% in 1992 (Hendersson, 1995).

The total industrial R&D spending in the U.S. amounted to about $200 billion in 2004, while U.S. universities and colleges spent about $40 billion on R&D the same year. As a result of new regulations governing government-funded research and the passing of the Bayh Dole Act, universities have, as mentioned, to a larger extent engaged in filing for patents on their own for their innovations. As an example, only 5% of the total university research budget was subsidized by industry in 2004. (Blaxill, 2009)

So, in other words, the rate of which patenting occurs has increased significantly in universities. This is true for drug and medical patents as well, which is an especially patent dense field.

2.3.1 Monetizing From University Patents

Monetization from university patents is a highly relevant but also debated subject. As discussed earlier, some thinks that it is not even intended for universities to partake in such activities with arguments that it does not actually increase publishing. Supporters of university patent monetization claim that it is simply a great way to earn a lot of money.

The extent to which a university has the possibility of monetizing from patents will of course be a strong factor of the willingness to pursue patents in the first place. There are many ways one could make money from intellectual property. One can of course sell the intellectual property or license it. But one can also monetize on the actual revenue streams, i.e., selling the right to future royalties from the underlying intellectual property. This way of monetizing from IP can be quite a good measure of R&D activity, as the buyer of such right has to pay upfront, and not wait the time it takes to enter the market.

According to (Berneman, 2008), there has been a substantial increase in the level of royalty monetization in the life science area since 2000. According to the article, revenue streams from royalty in life sciences amounted to $500 million between 2000 and 2003, but between 2004 and 2007, the royalty stream had grown to more than $5 billion. This is of course not only from universities, but private companies as well. Royalty monetization of university owned intellectual

property has grown alongside the overall market. According to (Berneman, 2008), a number of huge deals in 2007 resulted in revenue streams of more than $2 billion. 2 of these deals were university IP, but they actually made out the vast majority of the value of the deals. As a corresponding figure, the total royalty earnings in the life science business amounted to roughly $18 billion (Berneman, 2008), based on a total life science market of about $500 billion. This is about 10 times the oncology drug market.

2.4 Pricing and Valuing Pharmaceutical Innovation

All developed countries regulate their pharmaceutical industries, both on the demand side (fixing prices to some extent) as well as fueling innovation on the supply side (government sponsored R&D contracts etc.). The only country that has a near free market is the US, where the public opinion for market regulation is fairly low. This has rather large effects on the returns that pharmaceutical companies (and other innovators) can count on getting for their drug development programs.

According to (Seget S. , 2008), the complexity of a drug as well as its inventive step compared to what is already on the market has a huge impact on the price that the commercializing company will be able to get. This would in effect also mean that less novel research generates substantially less revenue.

Oncology drugs (and in effect, oncology research) is among the priciest drugs there are. Oncology drugs are more likely to receive government subsidies and in some cases, subsidies amount to 95% of the wholesale price (Seget S. , 2008). With the current lack of therapeutics for many types of cancer, new oncology drugs have a substantially higher chance of achieving a greater inventive step over existing drugs. Thus, oncology drugs are more likely to produce high margins compared to other fields, in which the actual research may be as complex and expensive. (Seget S. , 2008)

2.5 Research goals may differ depending on actor

A pharmaceutical company conducting research is most likely trying to attain a good financial result in order to pay high dividends to its shareholders. This has a lot of implication since it will affect how they value research results, intellectual property rights etc., in research partnerships with collaborators that may not value financial results as highly (for instance public universities). Obviously, a competent board will have demands that create incentives for strategies that are sustainable long term. This will (or should) lead to creating drugs that people will actually get because they alleviate their pains or even prolongs their lives. It is thus certainly in the interest of a pharmaceutical company to create the best drugs, but the requirement of commercial viability might be higher for a pharmaceutical company than a university.

So, what then, are goals with research from the university point of view? There are a lot of different views on how universities should conduct their business and what their actual purpose is. The traditional view is of course that universities have the role of educating people. These people can thereafter go out in the industry with their knowledge and create great things.

A more modern approach to the purpose of universities is that they are primarily knowledge creators. Educating brilliant people is still an imperative part of course. In this model, universities should publish as much knowledge as much as possible and drive research projects as much as possible. It is up to the industry to commercialize the research findings and actually create products.

Some people are of the opinion that not only pharmaceutical companies should strive to patent, but also universities. However, some argue that universities aren't designed to work like this. They lack the proper mechanisms to actually extract value from the patents, have not enough resources or experience to communicate their true value and in many cases such solutions imply digging through tons of red tape.

Research, and research success, should be viewed from the perspective of whether or not it is fulfilling the intended purpose. If the purpose of the university is to produce as much knowledge as possible, a fruitful research collaboration should do just that. This would imply that there is no conflict of interest if a pharmaceutical company gets all patenting rights in a research collaboration with a university as long as the university can extract valuable knowledge out of the agreement. But from a societal point of view, the only quality performance parameter that actually matters (other than creating growth, new jobs, etc), is how many drugs that are created from the research and how well the drugs actually fight cancer and how long they can prolong life for the population as a whole and improve the lives of cancer patients.

2.6 Role of the Technology Transfer Office

Along with R&D at universities driven more by collaborations with industry, the role of the technology transfer office has become increasingly important. A technology transfer office (TTO) is a university function (there are however private companies that act as TTO on university contracts as well) that fulfills two functions: Getting knowledge out of the university and getting knowledge in to the university. A TTO does not necessarily have to be engaged in selling university owned intellectual property for royalties. They may also have the function of broadcasting the knowledge that exists at the university to the outside world. This function is getting more important as R&D collaborations both at universities and at pharmaceutical companies is becoming a necessity to stay competitive. By acting as some sort of gate keeper, they can tell pharmaceutical companies (and other universities and research institutions) what knowledge they have, what research projects they are working on and what collaborations they are searching for.

2.6.1 Technology Transfer Office at National Institute of Health

An example of a successful technology transfer office is the TTO at the National Institute of Health (NIH). The TTO at NIH see their purpose as to get the research results and discoveries out on the market, as they perceive a lot of research discoveries having a relatively limited "effect beyond meeting a fairly narrow research result." (National Institute of Health, 2010)

The TTO at NIH was started already 15 years ago and has since issued thousands of licenses (see Figure 7, as well as been award hundred's of patents (see Figure 6). Interestingly, 82% of licenses went to private companies, with about half going to small companies and the other half to large companies in 2010 (Figure 7).

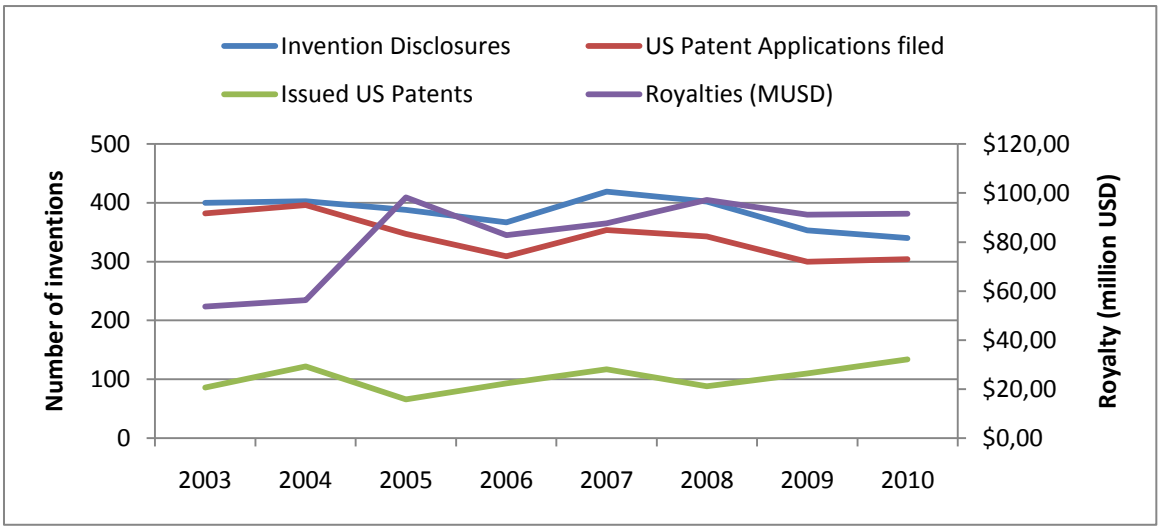

Figure 6 – Invention statistics 2003 to 2010 for National Institute of Health (National Institute of Health, 2010)

The TTO at NIH can be seen as some sort of best practice for how organizations with similar strategic goals, such as most universities and research institutes can work. However, the observant reader may compare Figure 5 and Figure 6 and notices that the royalty generated is hardly noticeable compared to the government spending on the research conducted at the NIH. But the point is that the licenses were clearly not issued to create massive royalty returns and fund the research, but rather as a convenient vehicle of spreading research results and knowledge. That is the same reason why NIH tries to keep licenses non-exclusive (National Institute of Health, 2010).

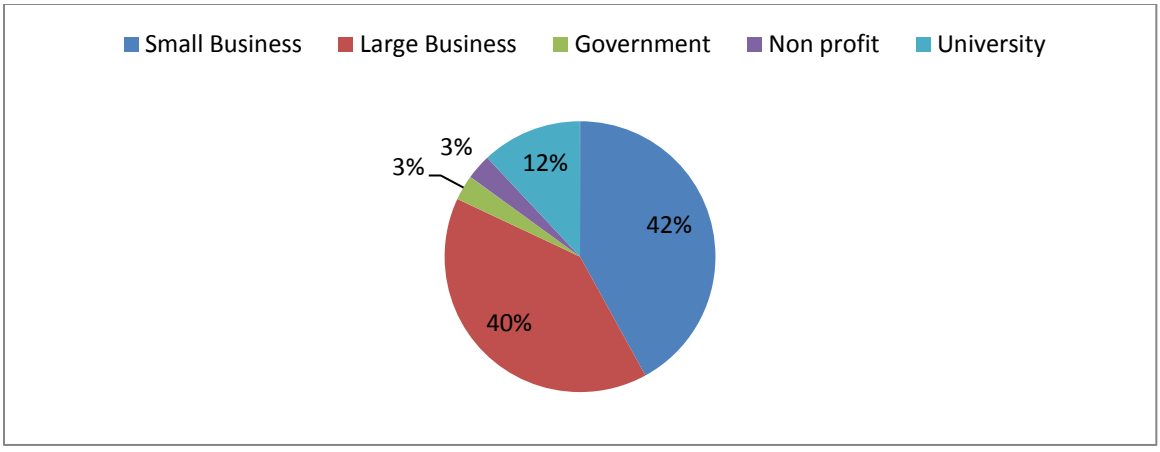

Figure 7 – Distribution of out-licensed inventions at National Institute of Health during 2010. Total number of licenses is 226. (National Institute of Health, 2010)

2.6.2 Collaboration Between Science and Industry

Collaborations between universities (science sector) and industry (enterprise sector) naturally provide a lot of benefits to both parties. However, there are also risks associated, such as uncertainty of outcome, risk of losing control of confidential knowledge, unexpected costs and so on. An overview of incentives and barriers to collaboration between science and enterprise sector is found in Figure 8.

In many ways, it is the purpose of the TTO to overcome or at least minimize such risks.

Science Sector	Relationship	Enterprise Sector
•**Incentives:** •Secure alternative sources of funding •Prospective income for researchers from licensing •Better labor market opportunities for graduates •**Barriers:** •Lack of qualified personnel necessary for handling the interaction •Bureaucratic structures and decision procedures •High cost of interaction, contracting, licensing etc. •Lack of sufficient information on supply and demand •Uncertainty	•**Incentives:** •Cross learning •Personnel mobility •Exchange of knowledge and experience •Knowledge network externalities •Synergies •**Barriers:** •Information asymmetries and low market transparency •Different cultures and incompatible objectives •High transaction cost •Uncertainty of outcome •Large spillovers	•**Incentives:** •Access to new knowledge •Access to R&D resources and infrastructures •Opportunities to open up new business fields •Recruitment of R&D personnel •**Barriers:** •Risk of averse behavior •Lack of knowledge absorption capabilities and innovation management capabilities •Lack of qualified personnel •Fear of losing confidential knowledge

Figure 8 – Barriers and incentives to science-industry collaborations (European Commission, 2002)

2.7 Trends in Cost-cutting in R&D Processes

With an increasing cost of R&D and a fierce competition, cost cutting is an always-relevant strategic target for many pharmaceutical companies. Many blockbuster drugs are also now coming off their patent protection, risking diminishing future returns. Employing thousands of scientists and running large in-house R&D operations have simply become too costly for many firms, as most drugs won't even cover the cost of development. (Nature, 2011) Another reason for need of cost-cutting is the fact that oncology has lost its special status compared to other medical fields, which has somewhat shielded it from budget restraints (Mansell, 2009). The financial crisis has of course also increased the pressure to reduce costs.

As an example of the dramatic costs, in Figure 9, one can see that the cost of R&D has increased steadily, but the number of molecular compounds that are approved for clinical trials have not. In fact, the average cost per approved New Molecular Entity (NME) in 1990 was $370.9 million and in 2008 it was $3,115 million or about eight times higher. That is equal to an annual increase of almost 13%. (Sahoo, 2009)

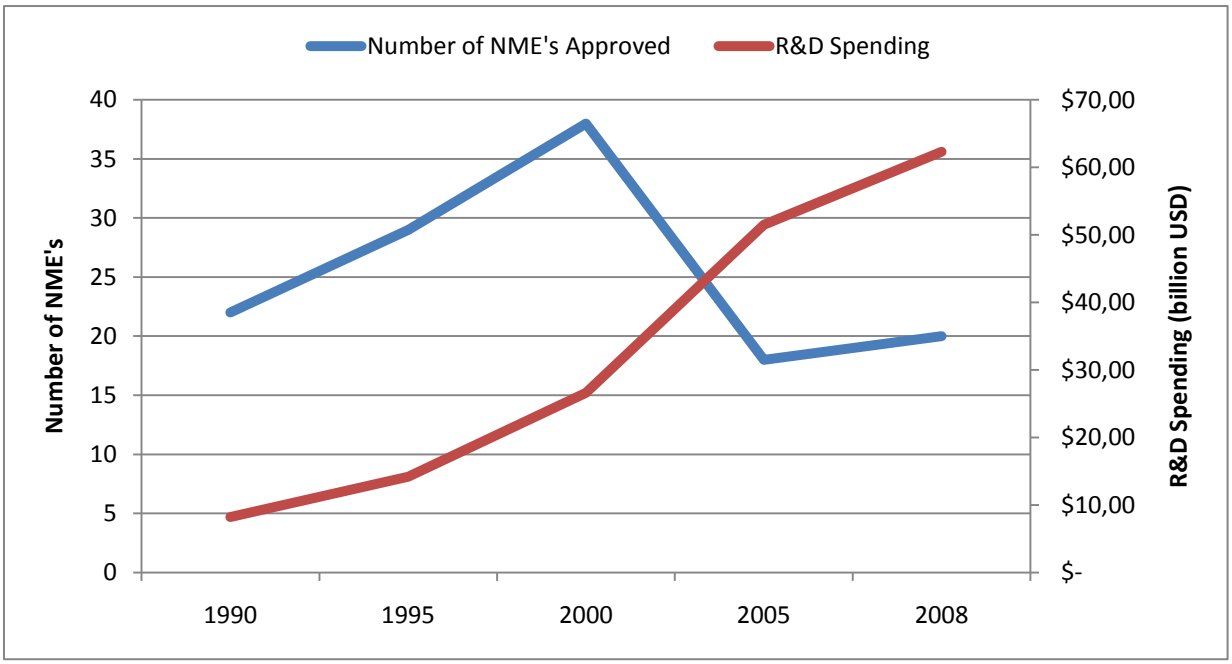

Figure 9 – Number of New Molecular Entities (NME's) approved for clinical trials in US vs. total US R&D spending (Sahoo, 2009)

As a reaction to this, many large pharmaceutical companies have begun to outsource R&D processes to a further extent. Pfizer, for instance, decided to close one of its R&D facilities in the United Kingdom, slicing $1.5 billion from the planned 2012 R&D budget. Many other companies are following them in their tracks, outsourcing early-stage drug development to be able to focus on areas where large pharmaceutical companies are strong: running large clinical trials. (Nature, 2011)

Therefore, the importance of long-lasting collaboration models has become higher. GlaxoSmithKline have during the last couple of years engaged in a number of different open innovation projects for sharing research results and creating incentives for academia (Nature, 2011). In 2009, an estimated $19 billion worth of R&D work was outsourced to research collaborators and contractors (Sahoo, 2009). The same report estimates this outsourcing industry to grow at an annual rate of 8%.

However, one important point is that about two thirds of the cost of developing a drug comes from the actual clinical testing, a requirement that is unlikely to become less strict (Sahoo, 2009). One could of course imagine scenarios where pharmaceutical companies became more cost optimized in their clinical trials, but the savings are probably rather hard to realize.

3. Method

This chapter contains:

- *Description of how the work in the thesis has been organized*
- *Description of data study phase*
- *Description of literature study phase*
- *Description of interview phase*
- *Description of analysis phase*

This thesis can roughly be divided into four phases: A data study phase, a literature study phase, an interview phase and an analysis phase. In this section, we will cover how the different phases were structured, what goal they were supposed to fulfill, what we actually managed to achieve and what definitions we used.

Before engaging in collecting data or contacting interviewees, naturally, the scope, limitation and hypotheses of the thesis had to be created. To achieve practical and usable results in this extremely large data set and area of knowledge, the scope and limitation were set rather narrow so that the hypotheses could be sufficiently confirmed or disconfirmed.

The authors decided to approach this thesis with a rather linear sequence of phases. The first phase was the data study phase, followed by the interview phase and ending with an analysis phase. Literature has been studied parallel to this process. The reason why this structure was chosen was simply because the data phase created the framework for the interviews. The interviews combined with the data resulted in material that could be analyzed.

3.1 Data study phase

The first part of this thesis was to study the origin of pharmaceutical research. As mentioned initially, our aim is to find out what role universities play in the development of oncology therapeutics and our approach to determine this is to identify how many oncology drugs that had their active substance invented at a university. This was to be done by asserting the assignee of the original substance patent of the commercialized oncology drugs. Naturally, the data study phase of this thesis has been quite large.

3.1.1 List of Studied Drugs

In our study, we have looked at all oncology drugs approved in Sweden. As of 2011, there are 178 drugs, excluding some oncology drugs that are put in the X-category (various) of the ATC system (Anatomic Therapeutic Chemical classification system) (LIF (Läkemedelsindustriföreningen), 2011). We have thereafter narrowed down the number of substances based on a set of criteria. The list is comprised of oncology therapeutic drugs that are in FASS (*Pharmaceutical Specialties in Sweden* (LIF (Läkemedelsindustriföreningen), 2011)), i.e. approved for use in Sweden and fulfill the following criteria:

- Oncology drug approved in Sweden
- Oncology drug also approved in the US (by (Food and Drug Administration, 2010))
- Oncology drug has been on the market for at least three years, i.e. approved before 2008
- Oncology drug still enjoys patent protection or have no generic substitutes on major markets

32 drugs fulfill these criteria. A complete list of these 32 drugs can be found in Table 2. Using the ATC system, 26 of these are L01 (Antineoplastic agents), four are L02 (Endocrine therapy) and two are L03 (Immunostimulants). In terms of global sales, these drugs constitute 84% of the market (Business Insights, 2010). In other words, 16% of the market of oncology therapeutics has not been included in the quantitative study. This may also be a result of inconclusive or inaccurate sales figures.

3.1.2 Patent Data

The extensive amount of patent data, such as assignee as filing date that have been assessed for each studied drug (see Table 2 and Table 3 in the appendix) has been collected by using Google Patents as well as the patent database provided by Thomson Innovation.

FDA approval year and applying company as well as original substance patent were found in the annual FDA Orange Book (Food and Drug Administration, 2010). The inventor is defined as the assignee of that patent, and thereafter classified as Big Pharma, Small Pharma, Biotech or Research institute/University. It should be noted that the line between Big Pharma and biotech is not always clear cut. For instance, the largest producer of oncology therapeutics, Roche (defined as Big pharma), is the sole owner of Genentech (defined as Biotech), which is the assignee on many of the company's patents. However, Big Pharma (large pharmaceutical companies) are defined as the incumbent drug producers and researchers with an annual turnover of more than $1 billion. Biotech, on the other hand, we have defined as companies that first and foremost describe themselves as biotech. The actual difference are in some cases very small, but as a thumb rule, biotech companies have less resources to take drugs through clinical trials, run several parallel drug discovery programs, but have more specialized and focused drug discovery programs exclusively for biological compounds. Small pharma (small pharmaceutical companies) are companies that does not entirely fit the picture of a biotech company but are way too small to be a large pharmaceutical company. We have defined them as companies that do not describe themselves as biotech companies and have a turnover of less than $1 billion. Clearly, these definitions are a bit fuzzy, but the intent is only to compare them to universities, which we claim to be of an entirely different nature. Universities and research institutions are defined simply as research organizations that are focused on research and not commercialization. The extent to which they are funded by public money may differ.

It should be noted that we will not in this thesis explore the drugs originated in what we call small pharma. One might criticize this decision as small pharma technology very well could be directly spun out of universities. However, this is a matter of containing the scope as we intend to shed light on our hypotheses, which is how important the actual university research is.

3.1.3 Sales Figures

To assess the commercial success of each studied oncology drug, we have looked for two figures: total revenue in 2010 and total revenue three years after FDA approval. Of course, not all drugs are commercialized by its inventor, and the inventor may not actually generate that much revenue from the drug. To be consistent, we have therefore looked at the revenue generated by the commercializer of each drug on the global market. These figures have primarily been found in each company's respective annual report. For the really successful drugs, the sales numbers are often quite easy to find, but the less successful drugs' sales figures are generally not as advertised. In these cases, some estimations and approximations of the actual sales figures have been done. It has also been necessary to go through many company histories, as the pharmaceutical industry has

experienced a lot of consolidation of companies in the last decades. For instance, some Pharmacia drugs are found in the Pfizer annual report and so on.

3.2 Literature Study Phase

The purpose of the literature study phase has been to give a proper background and context to the data that we have studied. We have gone through many reports on innovation management, societal macro studies of pharmaceutical research as well as university patenting as well as studies of intellectual property management and monetization.

As always, it is necessary to limit the thesis to a logical scope that is addressable in a time frame suitable. One could fill a thesis with interesting findings from the available literature, but in many cases, this will hardly add any real value if it is not related to the data we are addressing. Therefore, we have tried to keep the theory part small but still give enough background and context to make the analyses understandable and logic.

A large part of the literature has been found in business databases, such as Business Insights, Wiley and Business Source Premier. These databases have been accessed with permission from the university library at the University of Gothenburg. Another source of literature has come from company websites and financial reports from the same companies.

3.3 Interview Phase

From the very start of this thesis, it has been a clear goal to couple the data findings with relevant interviews. As this is a field were many partakers are very keen on protecting their knowledge best they can, it is not always easy to get a comment from key individuals. We have however, been able to get some interviews, both from the university sector, the start-up sector as well as from large pharmaceutical corporations.

The interview phase was initiated after most of the data collection was finished, as we wanted our interview candidates to be able to comment on our findings. This strategy has been largely successful, and it also helped us to be direct and effective in our interviews, something that we have found was appreciated by our, oftentimes, very busy interview candidates. We have tried to find interview candidates from different parts of the “research value chain” as well as from various companies. Most interview candidates have been found through personal contacts and referrals.

In the process of conducting interviews, we have evaluated several interview methods to select the most suitable approach in order to get relevant information in regards to our research question and hypotheses. After such evaluation, the authors decided to use semi-structured interviews as it enable a necessary amount of structure without limiting the respondents’ ability to freely express their opinions. Prior to each interview, every respondent were given a background to our research questions and a short introduction to the topic. The questions that are found in “Appendix D – Interview Questions” should be viewed more as topics for discussion rather than yes or no-type questions, which the authors made clear to the respondents prior to each interview. Interviews have preferably been conducted in person, as the authors view it as the most suitable interview form in order to enable discussion and limit any uncertainties and misunderstandings. As several of our respondents are based on other continents, some interviews have been conducted over phone for obvious reasons. However, no interviews have been conducted by e-mail as the authors feel that

such correspondence have a significant risk of resulting in misinterpretations and misunderstandings. In the initial interview phase, we had the aim of conducting a larger amount of interviews than we ended up doing, which have two main explanations. The most important reason is that we early got a very high degree of convergence in the answers from respondents in different parts of the oncology therapeutics development value chain. The second reason is that some respondents, primarily executives in the pharmaceutical industry, have extremely full agendas that have made it hard for the authors to conduct interviews with such respondents. This would have been a bigger concern and a more pressing reason for uncertainty if the answers received not would have shown such high convergence as they have done.

As a final remark, the authors would like to recognize the immense value the interviews have added to the current study. They have given valuable insights and food-for-thought and more than anything provided the authors with a high degree of relevant and insightful reflections on the process of collaborations between universities and research institutes and the pharmaceutical industry in the development of oncology therapeutics. The authors have experienced the interviews as very fruitful discussions, both for the sake of the thesis and for the interviewers themselves. In total, the authors have contacted approximately 25 researchers, business executives and university- and research institute representatives.

3.4 Analysis Phase

The most important part of the thesis has of course been the analysis phase. After the data collection, some of the analysis was started. After the literature study phase and interview phase, some of the research could be validated as well as extended into meaningful conclusions. The analysis has resulted into some quantitative statements on the origin of current oncology therapeutics as well as a set of conclusions on how universities and large pharmaceutical companies are collaborating, what is working, what isn't working and why.

4. Results: Patent Data

This chapter contains:

- *Description of analysis of collected data*
- *Results from analysis of collected data*
- *Summary of results*
- *Explanations models from interviews*

The results chapter covers synthesized market and patent data of oncology drugs. A discussion and description of three particular cases can be found in the next section. Actual analyses of the results are kept in the results section of this thesis.

4.1 Share of Number of Commercialized Oncology Therapeutics

There are a number of possible ways in which it would be possible to track origin of research. Most ways, are however, not very clear cut. This is the reason for us choosing a rather narrow, but at least consistent way of defining origin. Our definition of origin is the type of the assignee of the earliest approved patent (lowest patent number) registered with the FDA for a market approved oncology drug. The different types we have looked at is Big Pharma, Biotech, Research Institute/University and Small Pharma. However, as it is previously noted, the comparison should only be applied at Research Institute/University versus everything else because of the problems categorizing all studied research origins into these four groups.

By tracking the origin of oncology drugs according to the method earlier described, we see that only about 10% of active substance patents actually were assigned to a university or research institute (Figure 10). Another 10% come from smaller pharmaceutical companies, and about 80% comes from companies that are either described as big pharmaceutical companies or biotech companies. We will focus on the discrepancy of representation between big pharma/biotech and universities, as small pharmaceutical companies are beyond the scope of this thesis.

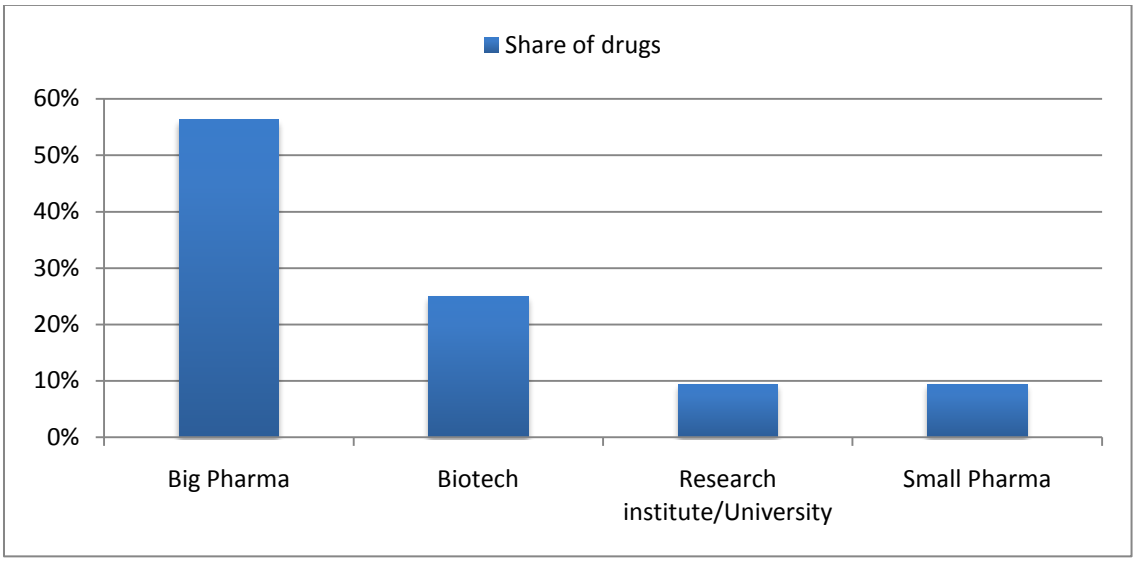

Figure 10 – Share of total number of studied drugs from Big Pharma, Biotech, Research institutes/Universities and Small Pharma

4.2 Share of Revenue Generated from Commercialized Oncology Therapeutics

If one studies the revenues generated from the same list of drugs, the picture is a little bit different. First of all, we have decided to look at two figures, one being total sales generated in 2010 and total sales generated three years after FDA approval. The latter figure is of course to give a less biased comparison, as all substances will have enjoyed the same amount of market presence. However, this is only the market presence on the US market, but the revenue is from all global sales. In other words, drugs that are commercialized on a global scale simultaneously or even in other parts than the US first will be biased in this comparison.

The sales figures three years after approval have been inflation adjusted to 2010 dollars using the average annual US inflation between 2000 and 2010. Now, in Figure 11, one can notice a very large difference in the amount of sales generated depending on the drug's origin. Large pharmaceutical companies and biotech actually make out more than 95% of the sales generated, regardless if we look at share of revenue in 2010 or share of revenue three years after approval. University substances only account for less than 1% of the revenue, but they still make out 10% of the substances. It should be stressed that it is total sales generated by the drug we are measuring, not actually sales generated for the university. In all cases those 10% are commercialized and sold by larger drug companies.

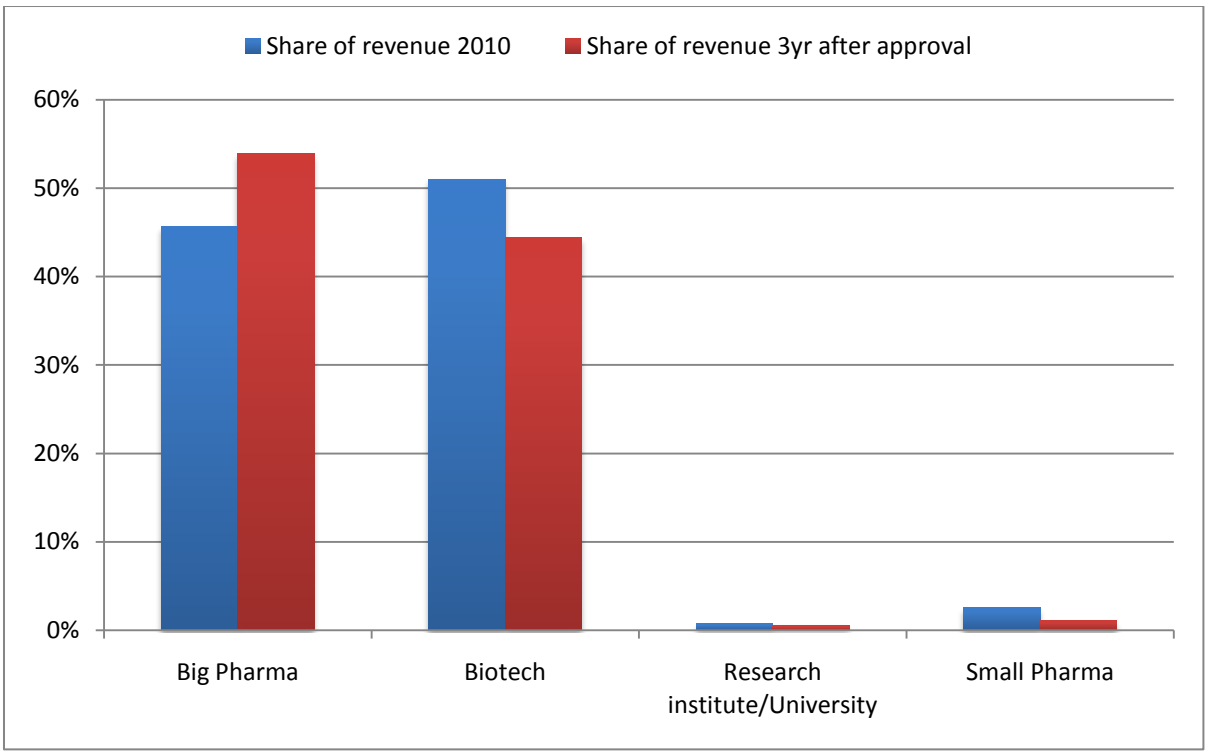

Figure 11 – Share of global revenues generated (research institute/universities account for < 1%)

The average global sales per commercialized drug have been sorted according to category of origin in Figure 12. In this figure, the sales numbers for three years after FDA approval have been omitted, as the number of university based patents are so low, it would produce a very low statistical significance.

In Figure 12, we see that patents that were assigned to either big pharmaceutical companies or biotech tend to generate a lot more global revenues. Biotech-assigned drugs generated 25 times more revenue than university-assigned patents. Large pharmaceutical company-assigned patents generated about 10 times more and patents assigned to small pharmaceutical companies sold for about 3 times more.

One should point out that only biotech-assigned patents are on average higher than the average R&D cost of developing a pharmaceutical drug (Figure 4) (about $1.4 billion). However, the cost of developing a drug spans over several years and lie at least eight years before market entry in most cases. In other words, one should compare 2010 revenues of a oncology drug with costs in the early 2000's or even earlier. In this case, the Big Pharma-group is on average profitable as well. This is of course something that we see is true in the annual reports as well.

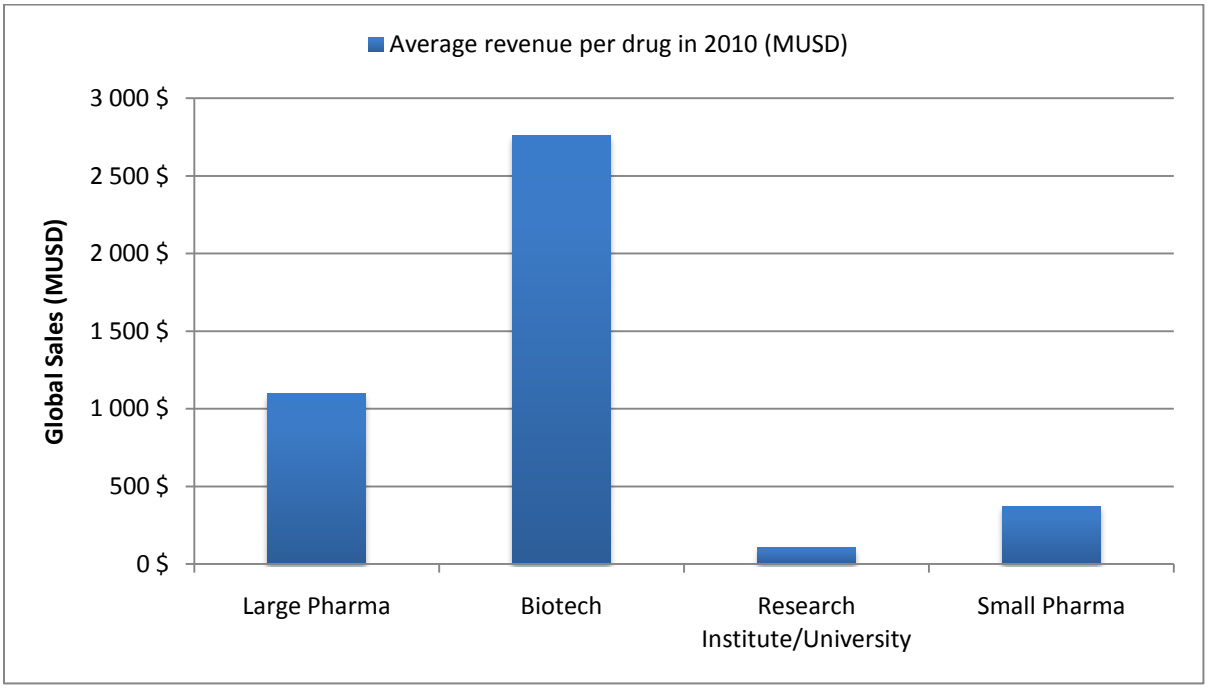

Figure 12 – Average global sales generated per substance for each category of origin in 2010

4.3 Revenue Distribution of all Studied Oncology Therapeutics

The revenue distribution over the 32 studied drugs in both sales generated in 2010 and in sales generated three years after FDA approval (in 2010 dollars) can be found in Figure 13. It is apparent that the uneven rate of return that is generally true for pharmaceutical drugs is true also for oncology drugs. There is an enormously disproportionate amount of revenue generated for the top ten best selling drugs compared to the bottom ten. The standard deviation is above 130%, or about $1,800 million with an average revenue of $1,300 million. For a complete list of sales, with corresponding commercializing company, see Table 3 in the appendix.

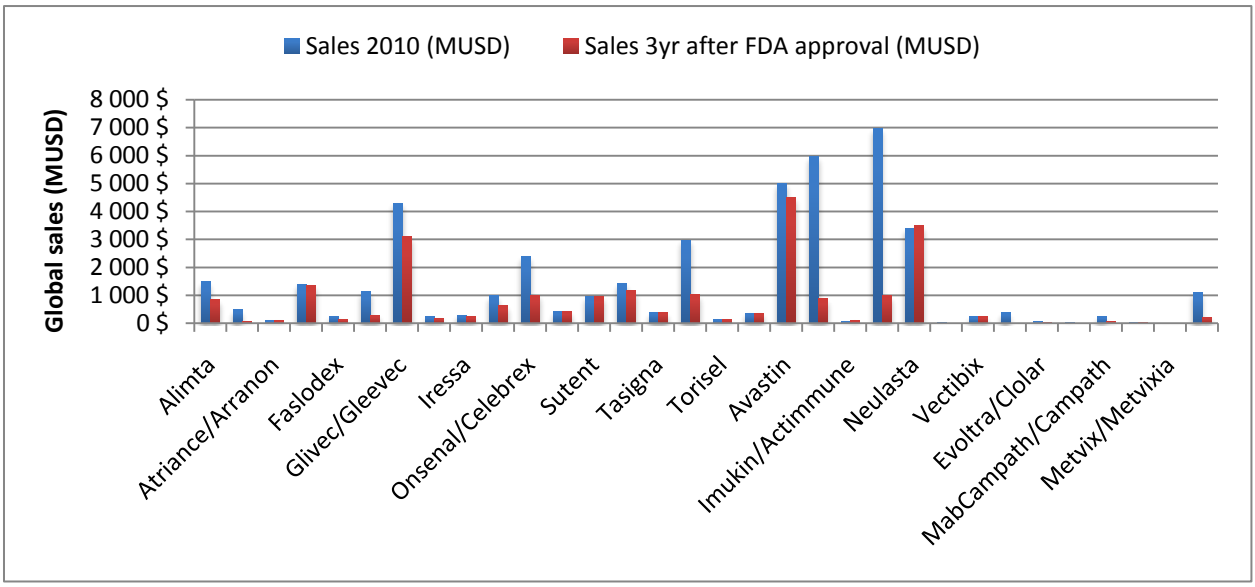

Figure 13 – Global sales per drug

4.4 Small Difference in Time to Market

We have defined time to market as the time between patent filing date on the active substance and market approval by the FDA. The time duration for an entire drug discovery program is in most cases much longer, as the initial screening takes place long before an actual substance is discovered and patented. Nonetheless, the time between patent filing and market entry reflects how efficiently one can collect enough patient data, monitor side effects and communicate with approval agencies. The result of the study is shown in Figure 14. The average time to market from patent filing for all studied oncology drugs is 7.4 years. The drugs originated in biotech companies have the lowest time to market with an average of 6.25 years, or 16% less than the average for all drugs. All other drugs deviate on average less than 6% from average. In other words, there is not a very large difference in time to market depending on patent origin. However, it should be noted that the 1 year earlier time to market for biotech drugs naturally translates to 1 year of patent protection on market, resulting in massive amounts of dollars.

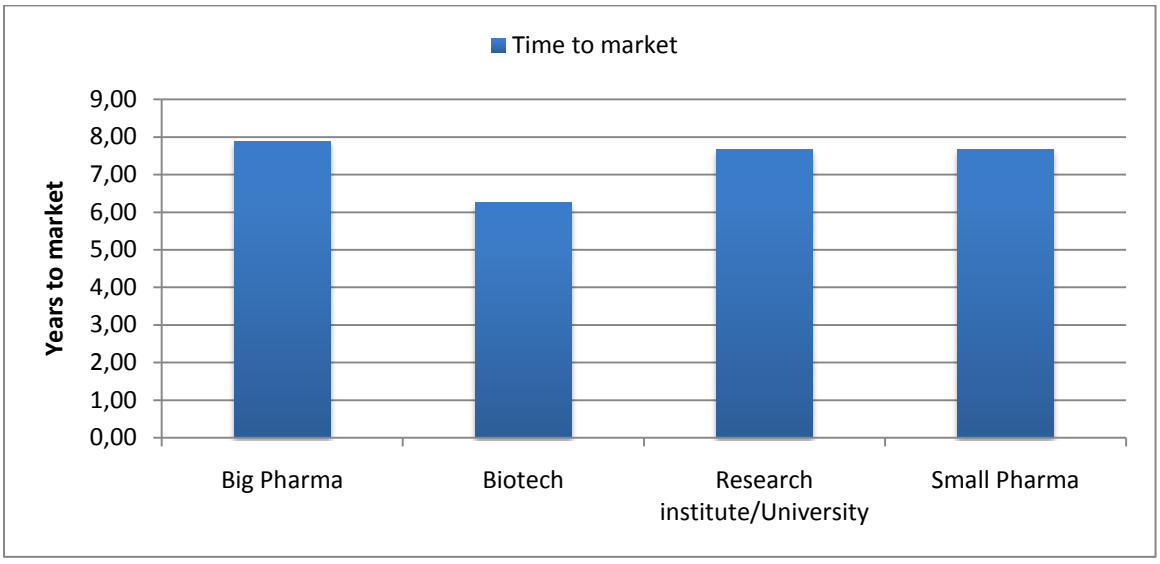

Figure 14 – Average time to market (time from priority on substance patent to FDA approval)

4.5. Summary of results

In the analysis, the following points have been made:

4.5.1 Only About 10% of Commercialized Oncology Drugs had Their Substance Patents Assigned to Universities

We have seen that only about 10% of all oncology therapeutics on the market today (that fulfill the definitions earlier described) comes from patents that were assigned to universities. The vast majority (about 80%) of the patents were in fact assigned to either biotech companies or large pharmaceutical companies.

4.5.2 University-assigned Patents Generated Less Than a Tenth of the Global Revenue Generated by Large Pharmaceutical Companies and Biotech Companies

Not only do large pharmaceutical companies and biotech companies account for the vast majority of the number of commercialized drugs, those drugs also generate a lot more revenue on average. Drugs, which patents were assigned to large pharmaceutical companies generated about 10 times more global revenue per drug on average than drugs, which patents that were assigned to universities or research institute. Biotech companies were even more successful in generating revenue from its research, whose drugs generated 25 times more global revenue on average per drug compared to the university drugs. One interesting finding is that Roche, the most commercially successful pharmaceutical company in the field of oncology (here sometimes denoted as a biotech company, as most of their US patents are assigned to their subsidiary, Genentech) is generates the most revenue per substance. In 2010, Roche generated on average $4900 per oncology drug (in our list), which is about 3,7 times higher than the market average.

4.5.3 The Variance in Sales Generated is Quite High for the Studied Drugs

We see that the commercial success that the studied drugs have achieved varies quite a lot. The standard deviation in terms of global revenue of the set of drugs we have studied is about $1,800 million in 2010, with average global revenue of about $1,300 million. This finding aligns quite well with the serendipitous nature of drug discovery earlier described in this thesis.

4.5.4 There is no Significant Difference in Time to Market for the Different Origins

When measuring time to market in terms of the time between patent approval and FDA market approval, there is no significant difference depending on which category the substance patent was assigned to. There is of course a lot more going in to the actual development process of a drug, so the true time to market stretches beyond the patent approval. Our study does not go in to the groundwork done and does not say anything about the efficiency of the research leading up to a patent. Rather, we can see that it does not seem to take more time to go through clinical trials with a patent assigned to a university compared to a patent assigned to a biotech company or a large pharmaceutical company.

4.6 Explanations Models

As shown in Figure 10, only about a tenth of cancer drugs are based on an active substance patented at a university. The question has been asked interview candidates from both universities and pharmaceutical companies and the offered explanation models have been summed below.

4.6.1 Universities not Profit Maximizing

First of all, the focus is different. Many universities are not profit maximizing, which rational companies are. Since drug discovery is so extremely cost intensive during the development years, there is a direct correlation to patents and future profits. In other words, it will be very important for pharmaceutical companies to patent. This is not true at all for many universities. Universities are first and foremost about producing knowledge. In other words, their main goal is to publish as much as possible – the opposite as patenting! (Lars-Eric Larsson, 2011)

But one should also note that there are universities that have been widely successful in generating applied and patentable research. Examples of such universities are Harvard, Columbia University and Cambridge.

4.6.2 Drug Discovery Programs too Complex

Drug discovery is extremely complex and takes a lot of time. A lot of research projects at universities are well defined and on a small scale for a single or a couple of Ph.D. students to handle. This is way below the complexity of a drug discovery program, which probably would have to involve an entire research department, if it were to be successful. Universities simply aren't equipped to handle this process by themselves – nor do they aim to do so. (Lars-Eric Larsson, 2011)

4.6.3 Patents Negotiated Away in Research Collaborations

A large part of drug discovery is made in collaboration between universities and pharmaceutical companies. They are absolutely reliant on each other, and has become even more so with an ever increasing technical complexity. The pharmaceutical companies need the university hospitals to gain access to large patient lists (Tobias Thornblad, 2011), clinical experience and preclinical research methodology and the universities need the pharmaceutical companies for their resources to do extensive substance screening, regulatory experience and R&D experience. In these partnerships, the pharmaceutical almost always invest more vast amounts of money and it is natural that they become sole assignees on the patents coming out of such partnerships. Therefore, it is not very often that universities are allowed to keep patents on their research. (Lars-Eric Larsson, 2011)

Donna Francher, VP of Global Products at AstraZeneca Oncology (Francher, 2011), claims that AstraZeneca tries to hold on to substance patents if they can. In oncology, all substance patents have been filed by AstraZeneca or Zeneca (Astra did not have oncology drugs before the merger). However, that does not mean that AstraZeneca doesn't collaborate with universities. In fact, Donna Francher claims that the ability with which a company can work together with collaboration partners can be seen as a competitive advantage in the pharmaceutical field.

4.6.4 University Research is too Early

Outside of research partnerships, there is often a large gap between where general university research ends and where commercial pharmaceutical developments start. University research is oftentimes too early to be patentable in the first place. Furthermore, there might be a strategic objective to actually patent as late as possible, to prolong patent protection while the drug is in market. Naturally, this decreases the possibility of a university ending up being the assignee on a high priority patent. (Lars-Eric Larsson, 2011)

4.6.5 University Research is Valued Lower

According to (Seget S. , 2008), the magnitude of inventive step a drug has over the existing drugs on the market has a high correlation to the price that a commercializing company is able to get for such drug. In other words, if universities are less likely to research active substances with a lot of market potential and instead have to focus on surrounding research, they are much less likely to get a good price for it. Even if the university by itself is unable, or has difficulties, to get royalties, that actual value of such research, regardless of who extracts it, is probably substantially lower. This is simply a consequence of the marketplace valuing complexity and inventive step.

5. Results: Case Studies

This chapter contains:

- *Description and results of Clolar/Evoltra case*
- *Description and results of Campath/MabCampath case*
- *Description and results of Levulan/Gliolan case*

5.1 Clolar/Evoltra

The active substance Clofarabine has been incorporated as the main substance in a drug, which has different brand names for different geographical regions. The brand name in Europe and Australia is Evoltra, while the U.S. brand name is Clolar. The drug was initially approved for treatment of leukemia, primarily for pediatric patients of age 1-21, in 2004 (Food and Drug Administration, 2010). Three years after FDA-approval, the drug had reached global sales of $47 million. Clolar is being commercialised by Genzyme. The active substance, Clofarabine, was invented at the Southern Research Institute and was granted U.S. patent protection in 1994.

5.1.1 Southern Research Institute – The "Inventor"

Southern Research Institute (SRI) is conducting both basic and applied research and is a self-sustaining contract research organization and an incorporated affiliate of the University of Alabama at Birmingham (UAB). SRI is mainly active within drug discovery, pre-clinical drug development, advanced engineering and environmental protection. (Southern Research Institute, 2011)

The cancer program at Southern Research Institute comprises three main capabilities and focus areas: Basic research, In Vivo Anticancer Efficacy Testing and In Vitro Anticancer Efficacy Testing. One of these research teams, working with design, synthesis and evaluation of nucleoside analogs, developed Clofarabine. (Southern Research Institute, 2011)

Southern Research Institute actively seeks collaboration alternatives with academic institutions to enhance the development of cancer drug discovery. One example is the Alabama Drug Discovery Alliance (ADDA), which is an alliance between SRI and the University of Alabama at Birmingham formed to facilitate drug discovery and development with oncology pharmaceuticals being one of the prioritized focus areas. To further benefit from research activities conducted in an academic setting at premier universities all over the world, SRI take part in several collaborations with scientists and engineers. Creative partnerships are initiated to address challenging scientific and engineering problems, to seek funding and eventually create intellectual property around high potential inventions. (Southern Research Institute, 2011)

SRI also provides several pre-clinical drug development services on an outsourced basis to various pharmaceutical and biotechnology companies. Services offered by SRI include all phases of early-stage drug discovery to help their clients streamlining their own drug discovery- and development programs. Intellectual property is generated through SRI's internal discovery program, which is available both for licensing and collaborative development. Additionally, SRI also take part in commercial research partnerships, which results in shared intellectual property between involved actors. (Southern Research Institute, 2011)

5.1.2 Genzyme – the "Commercializer"

Genzyme was founded in 1981 and is today part of the Sanofi-Aventis Group. One of the focus areas in therapeutics development is oncology. The focus and outspoken strategy of Genzyme Oncology is to develop and commercialize novel treatments for cancer, both through internal research and active external collaborations (Genzyme Oncology, 2011). Genzyme has a diverse pipeline of oncology therapeutics that is derived from several technologies and origins and currently the company has five therapeutic drugs available on the global market.

Internal approaches for discovery of new oncology therapeutics include target discovery through genomics technologies, antibody and small molecular agents identification and validation through both in vitro and in vivo testing. Although the company has an active internal discovery program to identify new agents for use in oncology therapeutics, Genzyme also works closely with collaborators in academic institutions like universities and research institutes, and is actively seeking in-licensing opportunities. (Genzyme Discovery Research, 2011)

Genzyme has been successful in in-licensing research conducted at universities and research institutes as defined in this study, and two out of the three successful transfers presented in this case study section have been commercialized by Genzyme. Besides Clolar, Genzyme also markets Campath, which will be described in more detail in next section.

For Genzyme, partnerships with universities are a central and critical part in development of new oncology therapeutics. The pharmaceutical industry at large has become increasingly dependent on collaboration with universities, and Genzyme is no exception, according to Genzyme Medical Manager Magnus Bäcklund (Bäcklund, Interview with Genzyme, 2011). He further highlights that on a general level, most large pharmaceutical companies conduct less in-house research than they have done historically. The underlying reasons are both high costs and high risk, and today, carrying costs for a huge in-house R&D department is not commercially attractive enough. Additionally, attracting the most prominent researchers to work within a large pharmaceutical company is not easy, as most researchers are used to work with a large amount of academic "freedom". (Bäcklund, Interview with Genzyme, 2011)

A major shift has emerged in terms of how collaborations between pharmaceutical actors, like Genzyme, and universities and research institutes are administered (Bäcklund, Interview with Genzyme, 2011). Previously, pharmaceutical companies were more willing to finance researcher projects based primarily on a potentially interesting idea, without putting any particular demands, criteria or requirements on the researcher/research group. Now, the trend has shifted towards a more stringent evaluation process. Before Genzyme is willing to finance research projects, the company evaluates, to a larger extent than previously, what a potential outcome of the research project might result in, if the research team have established a large enough knowledge- and experience base and how the project will fit into the overall company strategy. (Bäcklund, Interview with Genzyme, 2011)

When evaluating potential research projects, Genzyme have put an increased focus on the business dimension. The first step when Genzyme evaluates a research project includes a submission from the research group. The submission includes a detailed description of a suggested application. It could either be a completely new active substance or an evaluation of an already existing active substance

for usage in another therapeutic area.In the second step, if the research project is deemed interesting enough based on the submitted data in the first step, a global committee including both oncology specialists and business developers further evaluate if the project should be conducted. Having both research specialists in the oncology field and business oriented people conducting such evaluation is very important. The global evaluation board usually meets once every month to discuss potential and interesting research projects. (Bäcklund, Interview with Genzyme, 2011) On occasions, Genzyme also approach research groups to conduct further research within a specific area. As an example, Genzyme researchers found a potentially new application for Mozobil, which is already marketed for treatment of non-Hodgkin's lymphoma and multiple myeloma, and then identified research groups with specific knowledge within that specific field. (Bäcklund, Interview with Genzyme, 2011)

Magnus Bäcklund is not surprised about the fact that our current study indicates that only 10% of marketed oncology therapeutics have been developed at a research institute or a university. He believes that most universities lack the experience and resources to bring research projects beyond basic research, particularly in Sweden. (Bäcklund, Interview with Genzyme, 2011)

5.2 Campath/MabCampath

The active substance Alemtzumab is the main active substance in a drug which have different brand names for different geographical regions. The brand name in Europe is MabCampath, while the U.S. brand name is Campath. In 2001, the drug was FDA-approved for the treatment of chronic lymphocytic leukemia (CLL), cutaneous T-cell lymphoma (CTCL) and T-Cell lymphoma (TCL), which are different types of blood cancers (Food and Drug Administration, 2010). The active substance was invented by researchers at the University of Cambridge which transferred the rights to British Technology Group (BTG), a research institute in the UK. It received patent protection in 1994 and three years after FDA-approval, the drug had reached global sales of $72 million. Campath is commercialized by Genzyme.

5.2.1 University of Cambridge/British Technology Group Ltd. – The "Inventor"

Geoff Hale and Herman Waldmann were the head researchers behind the development of Campath at the University of Cambridge. Their work were initially primarily funded by the UK Medical Research Council at a time when universities had no organizations in place enabling commercial exploitations of inventions, which ultimately led to the licensing of the results to NRDC, which today is British Technology Group (Hale & Waldmann, 1998). BTG, however, did not see the need of patenting the intitial application suggested by the research team. Instead, BTG acquired all rights to the Campath cell lines. The researchers behind the development of the Campath cell lines admit being inexperienced and frankly quite naïve regarding legal agreements, and did not realize the difference between assignment and license. According to the reseach team, they were only lucky to obtain a clause allowing them to continue their academic and clinical research with the permission of BTG. (Hale & Waldmann, 1998)

British Technology Group (BTG) was formed in the U.K. in 1981, through the merger of the National Research and Development Council (NRDC) and the National Enterprise Board. The National Research & Development Council was created in 1948 by the U.K government with the objective to develop and commercialize publically funded research. (British Technology Group, 2011) Between 1950 and 1990, BTG developed and patented several technologies and compounds that have been

utilized in the pharmaceutical industry and medical technology industry. In 1992, BTG was privatized and three years later BTG was listed on the London Stock Exchange. Thus, the authors of this report are well aware that it can be discussed whether or not BTG actually should be defined as a research institute. However, since the development resulting in the patenting of the active substance Alemtzumab traces back to research conducted at University of Cambridge in the 1970's and 1980's the authors have defined the development as university research in this report. Besides developing Alemtzumab, BTG has developed compounds included in pharmaceuticals for treatment in several areas, including cephalosporin antibiotics, MRI and rattle snake anti-venom. (British Technology Group, 2011)

While the research team headed by Geoff Hale and Herman Waldmann at Cambridge University continued several research projects during the 1980's and 1990's, including evaluation of potential applications for Campath as well as conducting several small scale clinical trials for various applications, BTG approached several large pharmaceutical companies to out-license Campath for large scale commercialization. In 1985, research rights on what were to become Campath was out-licensed to Wellcome Biotech, a subsidiary of UK Wellcome Foundation. Wellcome Biotech invested approximately £50 million during seven years in their efforts to successfully launch a product on the market. Unfortunately, the two indications selected by Wellcome were not the most favorable ones in terms of how effectively Campath treated them, rather the ones with the largest commercial potential. (Hale & Waldmann, 1998) Thus, after reviewing disappointing results from clinical trials for the selected indications, Wellcome decided to cancel any further investments in Campath development in 1994, despite the fact that it showed potential for treatment of other, less commercially attractive, cancer indications.

After a long period of negotiations between BTG, who as mentioned was granted a patent for Campath in 1994, Wellcome and a new interested actor, US biotechnology company LeukoSite Inc., a license were agreed upon between the involved stakeholders granting LeukoSite the right to commercialize Campath in 1997. LeukoSite believed that Campath was a good opportunity and initiated investments in several clinical trials and extended research for new indications (Hale & Waldmann, 1998). Since then, Campath have also been out-licensed to other actors, including Ilex Oncology and Bayer HealthCare, but in 2009, worldwide commercialization and development rights were acquired by Genzyme. Genzyme will continue the clinical development of Campath and has through the acquisition expanded its hematological oncology portfolio. (Genzyme press release, 2009)

The research team, headed by Geoff Hale and Herman Waldmann, emphasize that developing a new pharmaceutical is extremely complex and involves countless rounds of development efforts and refinement to overcome obstacles of various kinds. They further acknowledge the importance of close collaboration between laboratory research groups and practising clinicians and clinical teams, to establish adjustments for different applications and indications. Utilizing the opportunity to conduct clinical trials under the Clinical Trial Exemption (CTX) and Doctor and Dentist Exemption (DDX) systems have according to the researchers been an integral part of the development of Campath. (Hale & Waldmann, 1998) Conducting trials under CTX and DDX decreases regulatory requirements compared to standardized clinical trials, enabling faster evaluation for scientists and researchers when developing pharmaceuticals and finding new applications. It involves far less people than standardized clinical trials and one person is all that takes to conduct such a trial.

Usually, people suffering from late and advanced stages of cancer development are willing to parttake in clinical trials of such kind. The research group behind the development of Campath highly admires the individuals that have been willing to take part in their trials, and states that without such patient contribution, development of Campath would most likely never have happened. (Hale & Waldmann, 1998)

Further, the research team behind the development of Campath believes that it only is actors in the pharmaceutical industry that has the capacity, experience and ultimately the financial muscels to bring an oncology therapeutic to market (Hale & Waldmann, 1998). Therefore, working closely with pharmaceutical actors will enable successful technology- and knowledge transfers from universities and research institutes, resulting in new oncology therapeutics launched on the market. The research team also highlight the importance of fair licensing terms that will provide a reasonable flow of cash back to the academic institution once a product is put on the market and starting to generate sales. Working and interacting with small pharmaceutical companies or biotechnology companies is easier compared to interactions with the big pharmaceutical giants according to the Campath research team. In their experience, the main point of contact with large, multinational pharmaceutical companies is primarily done through lawyers that seem obsessed with details of low importance to a researcher. (Hale & Waldmann, 1998)

The company commercializing Campath on the US market, Genzyme, has been described in the previous section about Clolar/Evoltra.

5.3 Gliolan/Levulan

The active substance Aminolevulinic have been incorporated as the main substance in a drug which have different brand names for different geographical regions. The brand name in Europe is Gliolan, while the US brand name is Levulan. The drug was FDA-approved in 1999 for the treatment of actinic keratosis, an early stage of skin cancer. (Food and Drug Administration, 2010). Three years after FDA-approval, the drug did not have any reported sales. The active substance, Aminolevulinic, was invented at Queen's University and received patent protection in 1993. Levulan is being commercialized by DUSA Pharmaceuticals in the US.

5.3.1 Cancer Research Institute at Queens's University – The "Inventor"

The Cancer Research Institute at Queen's University is located in Kingston, Ontario, Canada. Research at the Insistute includes several initiatives including cancer etiology, tumor biology and health services. Transdisciplinary investigation of areas of cancer control is promoted at the Institute where fundamental, clinical and populational research all is emphasized. (Queen's University Cancer Research Institute, 2011) The scientists at the Institute are involved in several studies of cancer biology, including drug resistance and metabolism, tumor progression and regulation of cell growth. The Cancer Research Institute of Queen's University is actively seeking collaboration possibilities with government bodies, non-profit organizations and has secured funding of $3.5 million from such partnerships since the institute was established. (Queen's University Cancer Research Institute, 2011)

5.3.2 DUSA Pharmaceuticals – The "Commercializer"

Dusa Pharmaceuticals is a pharmaceutical company based in Wilmington, MA, focused primarily on the development and marketing of the Levulan photodynamic therapy (PDT) technology platform, consisting of Levulan Kerastic (compound) and the BLU-U Blue Light Therapy Treatment Illuminator

(proprietary blue light technology and product). Besides Levulan, DUSA also markets other products focused on patients with common skin conditions. The company was listed on the Nasdaq stock exchange in 1992 and today has a total of 86 employees.
Treatment under the Levulan photodynamic therapy is a two part process. In the first process, targeted aktinic keratosis cells are made extremely sensitive to light through the application of the Levulan Kerastic Topical Solution. In the second process, the cells are exposed to blue light from the BLU-U Blue Light Therapy Treatment Illuminator, which destroys the actinic keratosis cells (DUSA Pharmaceuticals, 2011). Levulan is used for the treatment of minimally to moderate thich actinic keratoses on the face or scalp (DUSA Pharmaceuticals, 2011). Actinic keratoses are considered the earliest stage in the development of skin cancer and can be described as dry, scaly, rough-textured marks or patches on the skin as a result of extensive exposure to ultra-violet light (Skincare Physicians, 2011). DUSA is supporting external research collaborations, including development of treatment of early stages of oral cancer in collaboration with the NIH. (DUSA Pharmaceuticals, 2011)

5.4 Case Study Results

After examining the actors involved in the successful transfer of research institute- and university research results observed in this study, several interesting findings have emerged. Research institutes and universities identified in the case studies presented all have an outspoken willingness to collaborate with pharmaceutical actors to commercialize their research results, some say it is not even feasible to do at all at a university. The university or research institute actors identified have arguably quite broad programs for cancer research. All three developing actors promote both fundamental research in the oncology field, but they also provide opportunities for more focused studies and applied projects. One of the developing actors describes the activity of finding suitable licensee's as being important for the development process, as such collaborations can facilitate funding for continued research and development of a certain active substance. Collaboration between laboratory research and more hands-on, clinical practitioners is another integral part of oncology therapeutics development. While in-vivo testing and animal in-vitro testing are easily administered in laboratories, results need to be verified in humans. Conducting large-scale clinical trials is, as mentioned, extremely time- and resource consuming and for researchers to utilize clinical trial exemptions (CTX) to receive early indications and fast feedback has been mentioned as very important by one of the university and research institute actors.

The two pharmaceutical companies that have in-licensed university research and commercialized it, Genzyme and DUSA Pharmaceuticals, also take active part in and put great value on collaboration with universities and research institutes. Another interesting point is that even though Genzyme and DUSA Pharmaceuticals are not of equal or even comparable size in terms of employees or turnover, they are not multinational pharmaceutical giants. One of the developing actors expressed a desire to rather work with such, less intrusive, huge and bureaucratic, pharmaceutical companies.

Looking at the developed oncology therapeutics in more detail, there are two types of cancers that are being treated with the oncology therapeutics developed at a research institute or a university as defined in this study. Two of the marketed pharmaceuticals are used in the treatment of different blood cancers and the third is used in the treatment of early stages of skin cancer.

6. Analysis

This chapter contains:

- *Technology transfer in oncology*
- *Smaller companies more likely to in-license active substances*
- *Importance of personal relationships in R&D collaborations*
- *Collaboration models from the university point of view*
- *Collaboration models from the pharmaceutical company point of view*
- *Importance of technology transfer offices*

The need for collaboration between industry and universities cannot be stressed enough. There are several reasons for this, one being the need to cut costs in R&D processes. Following are conclusions made in this thesis related to such collaborations.

6.1 Technology Transfer in Oncology Compared to Other Industries

Oncology drug discovery, and even most pharmaceutical drug discovery in general is an extremely knowledge intense field. It has, during the last decades, also become an increasingly patent dense field. This has two strong implications. One is that the partakers in the drug discovery value chain have to be careful about their knowledge and how they share their knowledge. The other implication is that it is relatively easy to transfer key knowledge as it can be so satisfyingly described in a patent. However, to fully access this key knowledge, it is also important to have key people that can interpret it. A discussion of the human assets of this industry is discussed further below.

Because of the knowledge intensity, technology transfer is a highly relevant subject in this field. There are other industries that have an equally high level of knowledge intensity, but in most other industries, one would need so much more than just a key patent and a key researcher that could interpret it. For instance, if you would give the blueprint of a car to a couple of mechanical engineers, it is very unlikely that they would be able to produce a car without an enormous effort. But if one would provide a couple of bioengineers with a patent covering an active substance, they could very well produce (albeit in small scale) the substance with relatively small means.

In the authors' minds, this makes the technology transfer so much more interesting in this field. The proficiency with which a TTO may work can decide the future of a new revolutionary drug. The willingness a pharmaceutical company engage in research collaborations can dramatically decrease their costs even if they decide to investigate more indications than they could possibly do themselves.

Comparing the results from our patent data (as seen in Figure 10), where approximately 10% of the identified oncology therapeutics had their active substance developed at a university, with university research contribution in other industries is, however, quite challenging. A benchmark study with other industries would need significant amounts of data collection, definitions and limitations in order to find a suitable comparison with our study. What should be noted, as discussed in Section 2.7, is that R&D costs have increased in recent years, and the willingness from the pharmaceutical industry to collaborate with, and outsource to, universities have increased. Such trends indicate, which is further confirmed through our interviews, that technology transfer and research

collaborations between the pharmaceutical industry and universities is becoming an integral part of oncology drug development.

6.2 Smaller Pharmaceutical Companies More Likely to In-license Active Substance

As seen in this study, some university researchers and research groups have expressed uncertainty regarding partnerships and collaborations with large pharmaceutical companies. The main reason is that universities view interactions with large pharmaceutical companies as being too ambiguous, that large pharmaceutical companies are overly concerned with legal agreements that are not the primary focus or the area of expertise for university researchers. However, they are equally aware that collaborations need to be implemented in order to successfully bring their research results to market.

Large pharmaceutical industry actors have, as described in the present study, expressed similar views on the importance of working with university researchers in the development of oncology therapeutics. They have routines for screening interesting research ideas developed at universities and research institutes. Such evaluations should naturally be done on criteria established by the pharmaceutical companies. After a decision is made on whether or not proceeding with further development and collaboration of research developed at a university, however, it is crucial to structure collaborations in a way that is non-intrusive to the researcher or research group.

The pharmaceutical industry has, as discussed initially in this study, seen several consolidations, mergers and acquisition as the industry dynamics have changed during the last decades. For instance, giant multinational pharmaceutical companies like GlaxoSmithKlein, Pfizer and Sanofi-Aventis, have acquired smaller pharmaceutical actors and biotechnology companies to strengthen parts of their portfolios, both in terms of discovery pipeline and marketed drugs. A good example is the recent acquisition of Genzyme by the Sanofi-Aventis Group, aimed at strengthening and growing the Sanofi-Aventis' development platform and increasing their activity in biotechnology.

As the long-term detailed corporate strategies of large pharmaceutical companies for obvious reasons are not available to the public, the authors cannot confirm the long-term strategic goal with such acquisitions. However, based on the findings in the current study, the authors strongly believe that it is no surprise that acquisitions of smaller pharmaceutical companies, with a more extensive experience from working closely with university researchers, is an integral part of large multinational pharmaceutical companies long-term growth strategies. In doing so, large pharmaceutical companies can benefit from the experience small pharmaceutical companies have established with certain universities and research groups in specific oncology therapeutics field. It will most likely enable a faster technology transfer process compared to conducting screening and identification of interesting research projects and finding experienced researchers on their own, especially as the field of oncology therapeutics is huge.

6.3 The Importance of Personal Relationships in R&D Collaborations

In the case of Campath, the personal relationship between the inventors and practicing physicians were extremely important (Hale & Waldmann, 1998). The physicians provided a stream of the right patients in need of treatment at critical stages in the development process. This is just one example of when a personal relationship has been crucial. In our interviews with both pharmaceutical

companies and universities, the personal relationships and trust in collaborations have been claimed as make or break factors (Lars-Eric Larsson, 2011) (Francher, 2011).

Experience in working with different people, which research collaborations most often implies, is important to be able to create the trust needed for the R&D collaboration to become productive and sustainable. Good personal relationships also create the ability of letting people work with what they do best. For instance, in the Campath case, the researchers could work with research, while the commercializer (BTG) focused on identifying licensing and marketing opportunities. BTG, in this case, could thus be described as taking the role of a technology transfer office. It has become obvious that both pharmaceutical companies and universities have a lot to gain by becoming even better at working with each other, creating trust for each other and facilitating good collaboration environments.

6.4 Collaboration Models from the University Point of View

A once notorious Swedish pharmaceutical company, Pharmacia (now part of Pfizer), had extensive research partnerships with Uppsala University. It was even called "the third university of Uppsala." These relationships had many sides to it. It was extremely common that Ph.D. students started their non-academic career in Pharmacia. This depend the relationship. There were very few regulatory barriers on how the two could collaborate. According to (Lars-Eric Larsson, 2011), regulatory barriers take a lot of time. It has become another competence that both universities (in order to collaborate) as well as the pharmaceutical companies (in order to commercialize) need to know.

Oftentimes, one hears about how much certain universities earn from their research. But according to (Lars-Eric Larsson, 2011), this is exaggerated. In fact, there are only a few number of universities (MIT, Stanford, Columba, Cambridge, etc.) that actually earn a lot on their patents, and the money bringing patents are actually quite few in numbers. But for many universities, it is not return on investment that drives their research at all. They are simply not designed to work like that. (Lars-Eric Larsson, 2011) mean that universities are built to create and spread knowledge. Therefore, universities should strive to stick to this role in research collaborations just as well as pharmaceutical should strive to commercialize products on the knowledge as good as possible.

The view of universities as knowledge-creators is certainly not wrong. Through the course of the present study, however, it has become evident that such a view of universities' role in pharmaceutical development should be widened as the pharmaceutical industry have expressed an increased willingness to collaborate with universities, in part because of rising R&D costs, as discussed in Section 2.1. University research in life science should by all means, and is certainly not even likely to ever solely focus on the development of new pharmaceuticals. However, combining the role of being knowledge-creators with the role as developers of new technology and through IPR-license agreements, will position universities in the center of development of new therapeutics in the long term.

6.5 Collaboration Models from the Pharmaceutical Company Point of View

The pharmaceutical sector is huge, very profitable and less affected by economic downturns compared to many other industries. One might ask why such an industry would need to collaborate at all?

According to (Francher, 2011), the leaders in the pharmaceutical industry actually compete with each other to work with the best universities and scientists. This is first and foremost because these people and institutions are opinion leaders and the people actually buying and ordering the drugs (i.e. medical doctors and hospitals) look up to these people. But it is also common that universities contact the pharmaceutical companies to initiate collaborations by themselves. For a company like AstraZeneca, that get maybe 2-3 suggestions on large-scale collaborations per month, it is important to set up criteria for such collaborations. Is the science sound? Does it fit in with what AstraZeneca is doing and what products may come out of it? It is not uncommon that collaborations are initiated with institutions that aren't actually in oncology at all. (Francher, 2011) This is further confirmed by Genzyme as described in a previous section (Bäcklund, Interview with Genzyme, 2011).

Furthermore, university hospitals have access to patients, a critical component in clinical trials. Secondly, pharmaceutical does not have the ability to research everything. According to (Francher, 2011), universities are a great resource to find alternative indications for a drug. It has become apparent for many large pharmaceutical industries that university collaborations are one of the best ways to cut costs in R&D while still maintaining high quality (Forsberg, 2011).

In return, pharmaceutical companies can of course offer the industrial drive to take a drug through clinical trials, offer universities to partake in research projects they could never afford themselves, partake in extensive industry-wide as well as university-wide collaborations and learn from industrial expertise.

6.6 The Importance of Technology Transfer Offices

Our interviews have indicated that it is both common that pharmaceutical companies initiate contact with universities as well as the other way around as a first step of engaging in research collaborations (Francher, 2011) (Bäcklund, Interview with Genzyme, 2011). National Institute of Health states that one of the biggest challenges their technology transfer office faces is to actually make external people aware of their research in the first place (National Institute of Health, 2010). Without a technology transfer office, research results are more likely to only be utilized in one-time projects or never get utilized at all. A pharmaceutical company is of course much less likely to ask for a research collaboration if they don't know that a certain type of research is going on at all.

By serving both as gatekeepers and broadcasters of research results, a TTO can help both universities and pharmaceutical companies to utilize the same research results over and over. This will lead to cheaper R&D and more indications and drugs per substance.

A TTO will in the same process be able to negotiate better terms for the university as well as offer fair terms for the pharmaceutical company. Even in countries where it is hard for universities to monetize of patents, there might still be other terms worth negotiating, such as dual employment for researchers, assignment of intellectual property rights and so on.

A TTO can also act as an efficient intermediary during the research collaborations as well. This is especially true when universities and pharmaceutical companies collaborate that may not be used to this way of working. The inventors of Campath (Hale & Waldmann, 1998) indicate that large pharmaceutical companies can at some times be difficult to work with and overly concerned with detailed legal negotiations. Having an active TTO can both enable new fruitful research

collaborations by making actors in the drug discovery value chain aware of the research results available and also smoothen the collaboration once it has been initiated.

6.7 Common Ground

Perhaps not surprisingly, universities and pharmaceutical companies seem to agree on a number of issues regarding collaborations. First of all, both of them are striving for long term relations. There are several reasons for this. One is the ever-increasing legal complexity of collaborations. Most collaborations start with drafting several non-disclosure agreements, contracts on right to intellectual property etc. By initiating long-term relations, a lot of the legal work does only need to be done once. (Lars-Eric Larsson, 2011) (Francher, 2011)

A successful collaboration should generate experience and understanding for both parts. Universities may perhaps strive to get a better understanding of industrial processes and a better general understanding of a broader scientific field while pharmaceutical companies will aim to get a better understanding for a certain active substance and also understand if there might be more indications that the drug could work on.

7. Conclusions

This chapter contains:

- *Validation and invalidation of hypotheses*

7.1 Validation of Hypotheses

Following is a discussion on how the hypotheses relate to the findings made and analyses done in this thesis.

7.1.1 Universities are Less Successful Researching and Developing Active Substances Compared to Large Pharmaceutical Companies and Biotech Companies – Not Validated

Universities only accounted for about 10% of oncology drugs according to this thesis' definitions. That is, only 10% of the drugs studied had their substance patent assigned to a university or research institute. This figure was much less than we initially thought it would be and one might think that this is because universities are less successful in their research. This conclusion is however false as it is not really fair to compare university research with research at large pharmaceutical companies. In our interviews as well as in studied literature, we have seen that a vast majority of the research is done in R&D collaborations to some extent. It seems to be common that universities supplies industry as well as public domain with fundamental research as well as applied research that pharmaceutical companies can turn into products. The other part of the university research is the role they fill within drug discovery programs. We have seen that oftentimes, universities help pharmaceutical companies with patient lists, recommendations from practicing medical doctors as well as experience from other universities and competing pharmaceutical companies. It also seems to be common that universities explore alternative indications that pharmaceutical companies don't want to spend resources on.

Another thing to be aware of is that we have only focused on the actual substance patents in this thesis. While we have found that it is uncommon that these are assigned to universities, it might be more common that universities get to keep method or use patents that may come out of R&D collaborations. The reasoning behind this is that the actual product (substance) patent will give better control both of the product and the market; the pharmaceutical company is likely more eager to keep it. It is also much better positioned to extract value out of it.

All in all, this thesis has not shown that universities in any way are less successful in their research, rather, they are a vital part in the drug discovery process.

7.1.2 The Extent to Which Universities and Pharmaceutical Companies can Collaborate is Crucial for the Development of new Oncology Drugs – Validated

We have seen that universities aren't assignees to many crucial patents. However, in our study we have also found a number of key people in the industry stating the necessity of working together with universities. It also seems so that the necessity of collaborating is becoming even more important.

Drug discovery is becoming more expensive all the time and the expected return of any drug is associated with extremely high risk. Most drug candidates won't even make it to market, and even if they do, we have seen that the variance in generated revenues is enormously high. Many large

pharmaceutical companies have an outspoken objective of out-sourcing R&D and engaging in open innovation programs. Most of these programs involve universities to a large extent, which obviously leads to universities becoming an even more important part in the drug discovery value chain.

It should be stressed that the universities in no way can replace pharmaceutical companies. They should instead fill different roles as they have different capabilities and different objectives.

7.1.3 Competence in Collaboration is a Competitive Advantage in the World of Drug Discovery – Validated

Not only is collaborating becoming a necessity to produce high quality oncology drugs, it is even becoming a competitive advantage. In our interviews we have heard a number of reasons why large pharmaceutical companies should strive to become the most wanted collaboration partners:

- There is a competition to work with the best universities and the best researchers (not all of them). To do this, one has to have the power to drive through a drug discovery program as well as offer good terms of collaboration.
- In the interviews conducted at Uppsala University, many of the interviewees talked about the open-door policy between Pharmacia and Uppsala University, meaning that many people switched jobs fluently in between as something that spurred creativity, openness and overall attractiveness of the region. Such a policy is probably only viable in long-term relations, but this is also something that many large pharmaceutical companies are pursuing to a higher degree than short-term collaborations. Such a policy can imply certain risks, especially associated to intellectual property rights assignment, loss of novelty and so on. Knowing this and simply being aware can mitigate many risks associated.
- Universities are a resource of key individuals, which can be employed by the large pharmaceutical companies. Many of these transfers occur in successful collaborations.

8. Concluding Remarks

This chapter contains:

- *A discussion of suitable extensions of this thesis*

8.1 Areas of Improvement and Ideas for Future Studies

Even though the results of this study have been largely satisfactory, one could always do more. Especially, it would be possible to expand the quite narrow scope of this thesis, by interviewing more partakers in the research value chain as well as other partakers, such as government, medical doctors etc. Specifically, we have thought of a couple of different things one could do to further expand the research beyond this thesis.

8.1.1 Focusing on Drug Development in Certain Countries or Regions

Our geographical perspective in this thesis has been rather strange, but as we have explained, we have chosen to look at the drug development field globally with a Swedish and American bias, simply because it has made the research work easier. By doing so, we have been able to combine the best publicly available information that we have been able to come across. This global perspective has also made interview questions more general and less specific. It has become apparent that it is easier to get an answer on such questions in a field that is filled with non-disclosure agreements.

But, as an expansion of this thesis, it would be interesting to look more closely at regional differences, for instance, the difference in ability for universities to collaborate with pharmaceutical companies in the US, Europe and Asia. It would be interesting to see how collaboration models differ, since the culture of the universities of those three regions is quite different in nature.

8.1.2 Study Therapeutics Over a Longer Period of Time

In this thesis, we have only studied therapeutics that still enjoy patent protection on their major markets. There are several reasons for this. One is that the oncology market has been growing from virtually nothing in the 1950's. We were afraid that the selection of drugs would be too biased in some way if we went too far back in time. Furthermore, since we decided to compare sales figures of 2010, it would be unfair to compare substances that do not have any patent protection with substances that still do.

However, if someone would take the time to look up sales figure for say, three years, five years and ten years after market approval, it would become comparable. Such study would also be able to say something about trends in universities being able to produce (or keep) patents on active substances.

8.1.3 Comparing With Other Medical Fields as Well as Other Industries

Another possible compliment to this study would be to investigate how research collaborations between industry and universities are conducted in other medical fields as well as in other industries. In some way, a lot of the conclusions made apply to the pharmaceutical drug discovery field in general and the distinct characteristics of the oncology field aren't always crystal clear, but since we have had the focus of oncology, we have chosen market data, patent data, interview candidates and so on that are connected to oncology in some way or another.

By looking at other fields, one might be able to make more general conclusions on how successful research collaborations should be conducted. Such an investigation would likely be able to make more general

8.1.4 Comparing Therapeutics Based on Royalty Generated for its Inventor

One of the fundaments behind the analysis of this thesis was the decision assess the commercial success of a therapeutic drug by looking at the global sales generated and linking this to the original assignee of the substance patent. The big problem with this approach is that the original assignee does not necessarily have to be the actor that has received all that revenue. In many cases, and especially when it comes to universities, this is the case. The authors of this thesis have argued that it does not really matter if you approach the oncology drug discovery industry from a macro perspective, as long as someone has generated the revenue. This thesis has also only skimmed over universities ability to generate royalties from its inventions.

A more specific approach, which would also require vast amount of more work, would be to actually look at the royalty generated by each rights holder. A mapping of this would give a better picture of how good universities and other small pharmaceutical actors, without own ability to commercialize a drug, really are at monetizing their IP. Such an investigation has its problem too, as a drug can generate a lot of revenue without creating royalty for anyone, i.e. such an analysis does not necessarily reflect how good someone is at commercializing a medical compound. Another problem is that royalty agreements most often are classified and hard to get by.

8.1.5 Finding Surrounding Patents as Well as Other Research Results

This thesis has only looked at the patent first awarded by the USPTO in the FDA submission. That is, the patent with the lowest patent number in the FDA submission papers. It is fair to say that these are the actual substance patents, i.e. covering the molecular substance of a drug. But, there might be more than one substance patent in a drug and there might be several other key patents that might not cover an active substance but nonetheless are critical for the final therapeutic drug. Furthermore, there might exists key patents that aren't even in the FDA submission papers at all.

An appropriate extension of this thesis would be to look at these additional patents. After assessing the origin of each one, one should try to weight the importance of the different patents, as there might be different assignees behind them. This would provide a quantified weight for the studied origins. Ideally, one would also like to have a discussion of the importance of each patent with the inventor, commercializer and other possible stakeholder behind each studied drug.

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Appendix A – List of Studied Drugs

Table 2 – List of studied drugs (Abbott, 2010) (Amgen Inc, 2005) (Amgen Inc., 2009) (AstraZeneca AB, 2005) (Baxter Healthcare, 2009) (Bayer Healthcare, 2010) (Biovitrum, 2009) (Boehringer Ingelheim, 2009) (Bristol Myers Squibb, 2009) (Celgene Corp., 2010) (Dusa, 2010) (Eisai, 2002) (Genzyme, 2009) (GlaxoSmithKline, 2010) (Intermune, 2003) (Intermune, 2010) (Johnson & Johnson, 2010) (Ligand Pharmaceuticals, 2002) (Novartis, 2010) (Orion, 2010) (Pfizer, 2009) (Roche, 2010) (Sanofi Aventis, 2010) (Watson Labs, 2008) (LIF (Läkemedelsindustriföreningen), 2011) (Food and Drug Administration, 2010)

#	ATC code	Drug name	Active substance	Company (EU)	Company (US)	US market entry
1	L01BA04	Alimta	Pemetrexed	Lilly	Lilly	2004
2	L01BB06	Evoltra/Clolar	Clofarabine	Genzyme	Genzyme	2004
3	L01BB07	Atriance/Arranon	Nelarabine	GlaxoSmithKline	SmithKline Beecham	2005
4	L01BC07	Vidaza	Azacitidine	Celgene	Celgene	2004
5	L01CD02	Taxotere	Docetaxel	Sanofi-Aventis	Sanofi-Aventis	1996
6	L01XC02	Mabthera/Rituxan	Rituximab	Roche	Genentech	1997
7	L01XC03	Herceptin	Trastuzumab	Roche	Genentech	1998
8	L01XC04	MabCampath/Campath	Alemtuzumab	Genzyme	Ilex Pharmaceuticals	2001
9	L01XC06	Erbitux	Cetuximab	Merck	ImClone	2004
10	L01XC07	Avastin	Bevacizumab	Roche	Genentech	2004
11	L01XC08	Vectibix	Panitumumab	Amgen	Amgen	2006
12	L01XD03	Metvix/Metvixia	Methyl aminolevulinate	Galderma	Galderma Labs	2004
13	L01XD04	Gliolan/Levulan	Aminolevulinic acid	Medac	Dusa	1999
14	L01XE01	Glivec/Gleevec	Imatinib	Novartis	Novartis	2001
15	L01XE02	Iressa	Gefitinib	AstraZeneca	AstraZeneca	2003
16	L01XE03	Tarceva	Erlotinib	Roche	Osi Pharms	2004
17	L01XE04	Sutent	Sunitinib	Pfizer	CPPI CV	2006
18	L01XE05	Nexavar	Sorafenib	Bayer	Bayer	2005
19	L01XE06	Sprycel	Dasatinib	Bristol-Myers Squibb	Bristol-Myers Squibb	2006

20	L01XE07	Tyverb/Tykerb	Lapatinib	GlaxoSmithKline	SmithKline	2007
21	L01XE08	Tasigna	Nilotinib	Novartis	Novartis	2007
22	L01XE09	Torisel	Temsirolimus	Wyeth	Wyeth	2007
23	L01XX17	Hycamtin	Topotecan	GlaxoSmithKline	GlaxoSmithKline	1996
24	L01XX25	Targretin	Bexarotene	Cephalon	Eisai	1999
25	L01XX32	Velcade	Bortezomib	Janssen-Cilag	Millenium Pharms	2003
26	L01XX33	Onsenal, US: Celebrex	Celecoxib	Pfizer	GD Searle	1998
27	L02BA02	Fareston	Toremifene	Orion	GTX	1997
28	L02BA03	Faslodex	Fulvestrant	AstraZeneca	AstraZeneca	2002
29	L02BG04	Femar, US: Femara	Letrozole	Novartis	Novartis	1997
30	L02BG06	Aromasin	Exemestane	Pfizer	Pharmacia & Upjohn	1999
31	L03AA13	Neulasta	Pegfilgrastim	Amgen	Amgen	2002
32	L03AB03	Imukin, US: Actimmune	Interferon gamma	Boehringer Ingelheim	Intermune Pharms	1999

Table 3 – List of drugs with patent origin, patent number, sales 2010 and sales three years after market entry (Abbott, 2010) (Amgen Inc, 2005) (Amgen Inc., 2009) (AstraZeneca AB, 2005) (Baxter Healthcare, 2009) (Bayer Healthcare, 2010) (Biovitrum, 2009) (Boehringer Ingelheim, 2009) (Bristol Myers Squibb, 2009) (Celgene Corp., 2010) (Dusa, 2010) (Eisai, 2002) (Genzyme, 2009) (GlaxoSmithKline, 2010) (Intermune, 2003) (Intermune, 2010) (Johnson & Johnson, 2010) (Ligand Pharmaceuticals, 2002) (Novartis, 2010) (Orion, 2010) (Pfizer, 2009) (Roche, 2010) (Sanofi Aventis, 2010) (Watson Labs, 2008) (LIF (Läkemedelsindustriföreningen), 2011) (Food and Drug Administration, 2010)

Drug name	Sales 2010 (MUSD)	Sales 3 years after approval (MUSD)	US patent no.
Big Pharma	Subtotal: 19,740 $	Subtotal: 12,421 $	
Alimta	1,495 $	854 $	US5217974
Aromasin	483 $	58 $	US4808616
Atriance/Arranon	90 $	90 $	US5424295
Erbitux	1,398 $	1,337 $	US6217866
Faslodex	262 $	140 $	US6774122
Femar/Femara	1,145 $	298 $	US4978672
Glivec/Gleevec	4,300 $	3,093 $	US5521184
Hycamtin	230 $	188 $	US5004758
Iressa	297 $	237 $	US5457105
Nexavar	987 $	647 $	US7235576
Onsenal/Celebrex	2,383 $	1,000 $	US5466823
Sprycel	421 $	421 $	US6596746
Sutent	964 $	964 $	US6573293
Tarceva	1,430 $	1,168 $	US5747498
Tasigna	399 $	399 $	US7169791
Taxotere	2,971 $	1,042 $	US4814470
Torisel	122 $	122 $	US5362718
Tyverb/Tykerb	363 $	363 $	US6391874
Biotech	Subtotal: 22,066 $	Subtotal: 10,237 $	
Avastin	5,015 $	4,517 $	US6054297
Herceptin	5,972 $	887 $	US6165464
Imukin/Actimmune	48 $	106 $	US4855238
Mabthera/Rituxan	6,992 $	990 $	US5736137
Neulasta	3,400 $	3,504 $	US5824784
Targretin	19 $	0 $	US5780676
Vectibix	233 $	233 $	US6235883
Vidaza	387 $	0 $	US6962940
Research institute/University	Subtotal: 328 $	Subtotal: 119 $	
Evoltra/Clolar	64 $	47 $	US5661136
Gliolan/Levulan	34 $	0 $	US5422093
MabCampath/Campath	230 $	72 $	US5846534
Small Pharma	Subtotal: 1,121 $	Subtotal: 248 $	
Fareston	16 $	25 $	US4696949
Metvix/Metvixia	5 $	4 $	US6034267
Velcade	1,100 $	219 $	US5780454
Grand Total	**43,255 $**	**23,025 $**	

Appendix B – Cancer Incidence and Mortality Rates

Africa

Among African women, the two most common cancer types represent almost 50% of all incidence cases. Those two cancer types are breast cancer (24.5%) and cervix uteri cancer (21.3%). Among African men, there is a wider spread over different cancer types, and incidence rates does not show significant differences from incidence percentages per cancer type in men for other regions. The three most common types of cancer in African men are prostate cancer (13.0%), liver cancer (11.4%) and Non-hodgkin lymphoma cancer (7.2%). The top five cancers aggregated for both men and women are the same looking at both incidence and mortality rates and are breast cancer, cervix utare cancer, liver cancer, prostate cancer and Non-hodgkin lymphoma cancer. (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

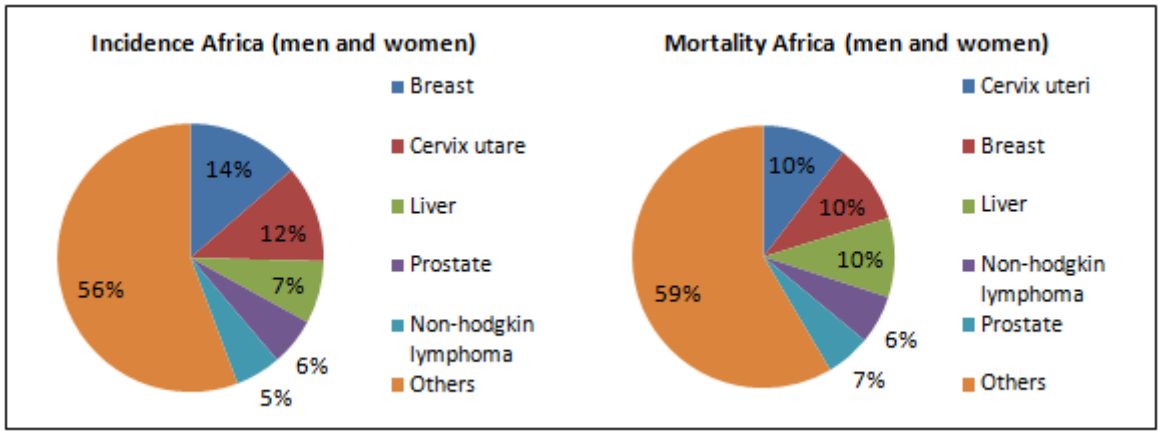

Figure 15 – African incidence and mortality rate per different cancer type (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

Asia

The three most prominent types of cancer in Asian men are lung cancer, stomach cancer and liver cancer, representing approximately 46% of all incidence cases. Those three types of cancer, however, have a higher accumulated percentage in terms of cancer related mortality in Asian men, accounting for approximately 55%. Incidence in Asian women are dominated by breast cancer (18.6%) followed by cervix uteri cancer (11.0%) and lung cancer (9.4%). Mortality percentages among Asian women follow incidence rates, with breast cancer being the most common cancer related mortality type, but representing a far lower percentage (11.3%) compared to the incidence percentage. Looking aggregated at men and women, the top five most common types of cancer make up a larger portion of total incidence and total mortality compared to other regions and global statistics. (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

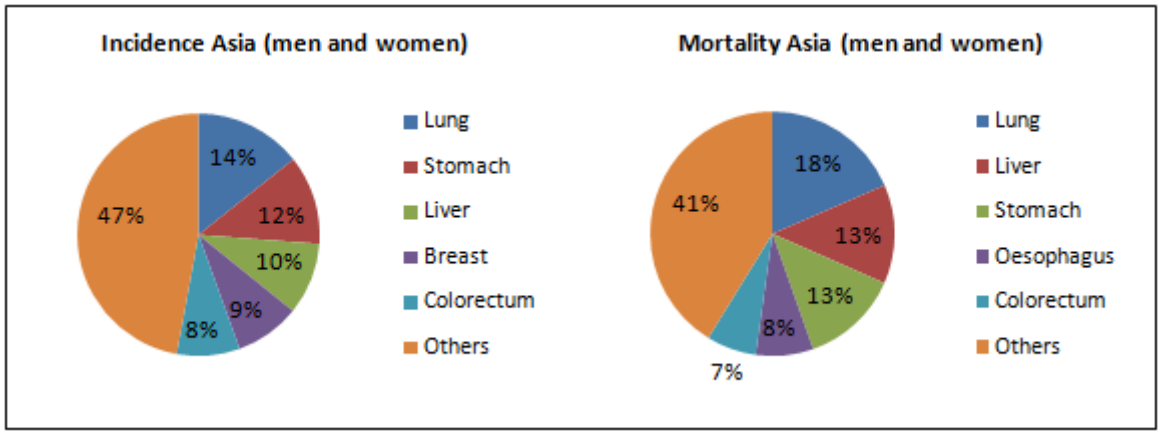

Figure 16 – Asian incidence and mortality rate per different cancer type (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

Europe

The three most common types of cancer in European men are prostate cancer, lung cancer and colorectal cancer, making up a total of 52% of all cancer cases. Lung cancer, making up 16% of cancer incidence in European men, stands out in terms of mortality, representing 26% of all cancer related deaths in European men. Prostate cancer, being the most common type of cancer in European men with a 21.8% incidence rate, however, does only represent 9.4% of cancer related deaths in European men. In European women, breast cancer is by far the most common type of cancer, with a 28.2% incidence, followed by colorectal cancer and lung cancer. Breast cancer is the leading type of cancer not only in terms of incidence for European women but in terms of mortality as well, however, representing a far smaller percentage. Looking aggregated at men and women in Europe, the four most common types of cancer represent 50% of all cancer cases. Incidence levels among those four types of cancer are distributed fairly even. All of them have an incidence rate double that of the fifth most common type of cancer. (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

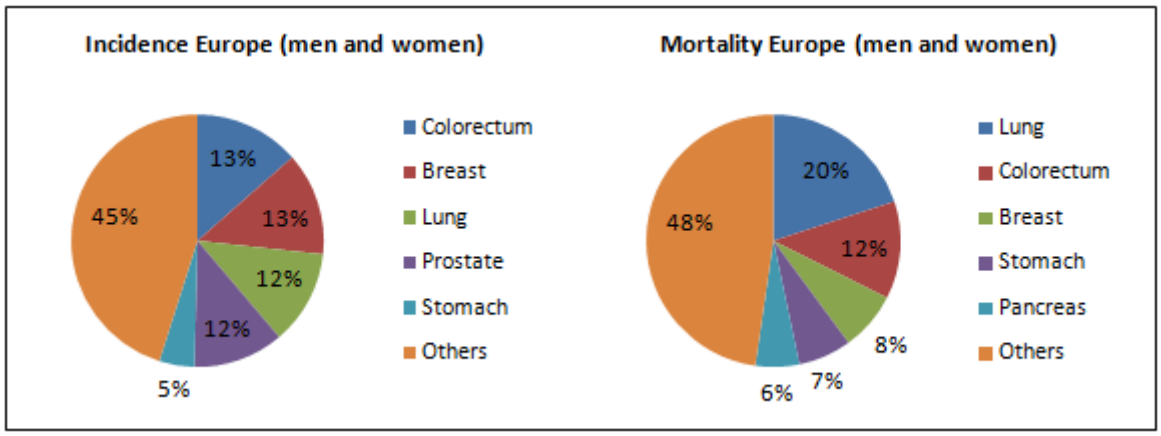

Figure 17 – European incidence and mortality rate per different cancer type (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

North America

Not surprisingly, since the standard of living, access to health care and pharmaceuticals and way of life are similar in Europe and North America, the three most common types of cancer in North American men are the same as for European men: prostate cancer (25.7%), lung cancer (15.1%) and colorectal cancer (11.0%). Those three cancer types even make up the exact same percentage in terms of percentage of all cancer cases as for European men, namely 52% for North American men as

well. The leading cancer type in terms of mortality in North American men is also the same as for European men, however, representing an even larger share of all cancer related deaths in North American men of 30.4%. Similarly, the three most common types of cancer in North American women are the same as for European women, but with slightly altered percentages: breast cancer (26.6%), lung cancer (14.3%) and colorectal cancer (11.1%), representing 50% of all cancer cases. Those three types of cancer also represent approximately 50% of all cancer related deaths in North American women, however, lung cancer being the leading type of cancer representing 25.9% of cancer related deaths in North American women. Aggregated for men and women in North America, lung cancer stands out as the leading type of cancer in terms of mortality, representing 28.9% of cancer related deaths, which is three times more than the second largest cancer type in terms of cancer related deaths. The top four types of cancer are the same for both incidence and mortality and represents very close to 50% in both incidence and mortality. The four types of cancer are lung cancer, breast cancer, colorectal cancer and prostate cancer. (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

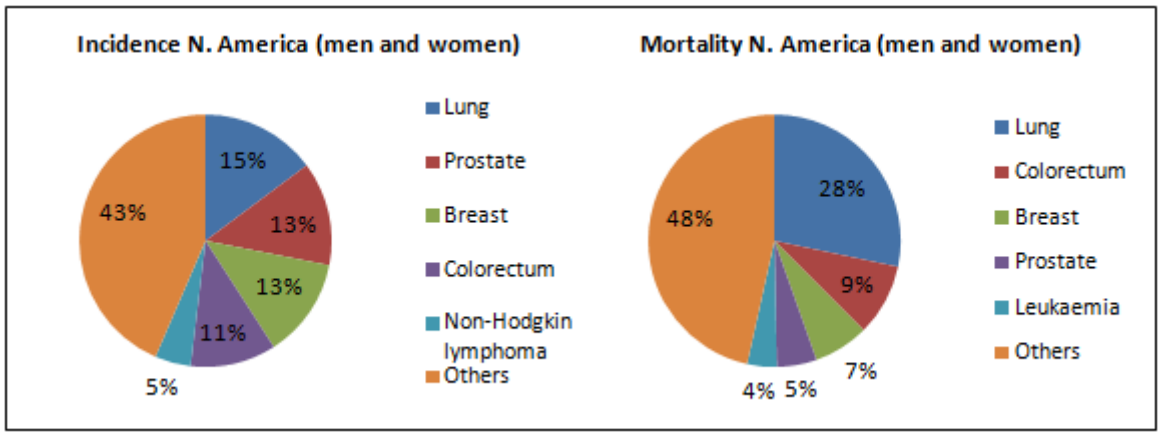

Figure 18 – North American incidence and mortality rate per different cancer type (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

South America

The three most common types of cancer in South American men are prostate cancer (26.4%), lung cancer (10.6%) and stomach cancer (9.2%). The three most common types of cancer in terms of cancer related deaths are the same three, however, with a more even distribution compared to incidence and lung cancer accounting for the largest number of cancer related deaths. For South American women, breast cancer is the most common cancer type (26.6%) followed by cervix uteri cancer (14.4%) and colorectal cancer (7.6%), making up a total of 49% of cancer incidence cases. The three most common types of cancer in terms of cancer related deaths in South American women are breast cancer (14.6%), cervix uteri cancer (11.8%) and lung cancer, not being in the top three in terms of incidence, representing 8.4% of mortality. Aggregated for men and women in South America, the top five types of cancer in terms of incidence represent 49%, but only 39% in terms of cancer related deaths. The distribution for cancer related deaths in South American men and women are more scattered among different types of cancer compared to Asian, European and North American men and women, but less scattered than in African men and women.

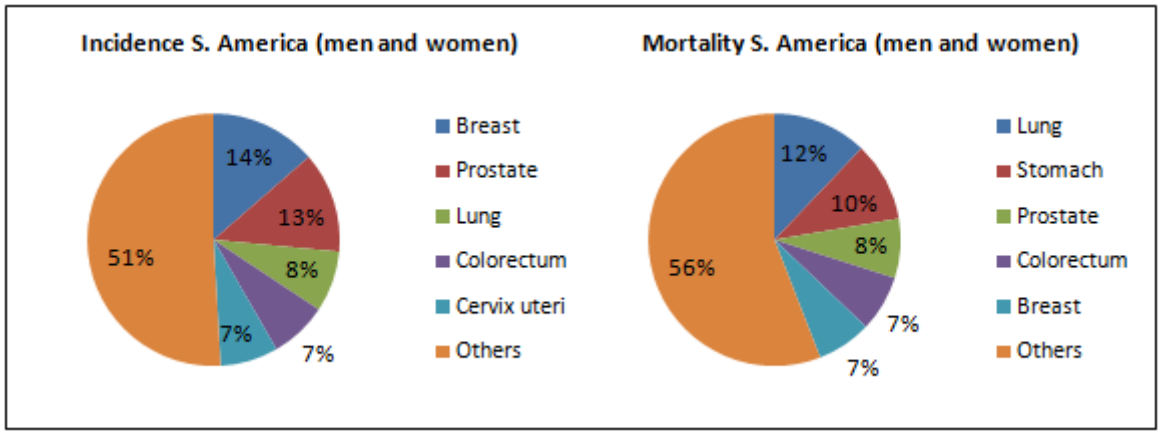

Figure 19 – South American incidence and mortality rate per different cancer type (Ferlay, Shin, Forman, Mathers, & Parkin, 2008)

Appendix C – List of Interviewees

Table 4 – List of interviewees

Date	Interviewee	Position	Company/University
17/03/2011	Björn Carlsson	Business Developer	Isofol
17/03/2011	Tobias Thornblad	CEO	Dermafol
13/04/2011	Lars-Eric Larsson	Deputy Manager	UU Innovation
13/04/2011	Andy Browning	Project leader in life science	UU Innovation
13/04/2011	Karin Meyer	Business developer	UU Innovation
19/04/2011	Donna Francher	VP Global Products	AstraZeneca (Oncology)
16/05/2011	Magnus Bäcklund	Medical Manager	Genzyme
16/05/2011	Erik Forsberg	Managing Director	Uppsala Bio

Appendix D – Interview Questions

Following is the interview questions. It should be noted that the questions here are a bit generalized, as each interview has had its set of specialized questions. Most questions were approached as discussion topics rather yes or no questions.

Interview Questions for Universities, TTOs and Research Institutes

Table 5 – Questions used in interviews with universities, TTOs and research institutes

Questions/discussion topics for universities, TTOs and research institutes
1. Our study has shown that it isn't very common that universities are assigned the substance patent for oncology drugs. Why might this be? Does it depend on universities having a different focus? That there aren't enough resources?
2. How can universities become better at producing its own active substances?
3. Why would you want that?
4. Is it better that innovation is done in a university setting compared to private companies?
5. Why/Why not?
6. Universities often don't have enough resources to take a drug through clinical trials. Should they? How far do universities usually get?
7. How has patenting strategy changed over time?
8. How has collaboration with industry changed over time?
9. Is there a big difference working with large companies compared to small companies?
10. How good are universities at attaining and extracting knowledge in industry collaborations? How can you get better?
11. Is there a big problem that key researchers change jobs in these kind of collaborations?
12. Is there a big difference in the way collaborations work over different technology areas such as automotive, telecom, biotech, oncology, infection diseases etc.?
13. Is there a big difference between different regions such as Sweden, EU, USA and the rest of the world?
14. How much of a problem is the teacher's exemption in Sweden? What other regulatory barriers to you see?
15. How would you like to cooperate with industry? What is the ideal situtation in terms of regulation, business models, IP etc.?
16. How can you de facto work together today?
17. How can you get better?
18. On what terms can Swedish pharmaceutical industry compete?
19. Do you think that research would become better (in terms of quality) if it was easier to get paid for it?
20. Other questions?

Interview Questions for Pharmaceutical Companies and Biotech Companies

Table 6 – Questions used in interviews with pharmaceutical companies and biotech companies

Questions/discussion topics for pharmaceutical companies and biotech companies
1. We have screened several hundred oncology therapeutics and found that approximately 10% have been developed at a university or at a research institute. What is your comment on that?
2. How does your company generally work with evaluating potentially interesting drug candidates developed outside the company?
3. Does your company have any long-standing collaboration with universities/research institutes in the field of oncology therapeutics?
4. Do interesting and high-potential drug candidates have to meet certain milestones, before they become of interest for your company as a potential acquisition candidate?
5. What is your general opinion on working with university researchers? Has it developed to the better over the last decade, or has collaboration been harder to facilitate?
6. Does your company consider university collaboration as a critical part in screening for new drug candidates and in drug development?
7. (In case of in-licensed active substance) Were the active substances in-licensed or fully acquired from the university/research institute? What did the payment model look like?
8. (In case of in-licensed active substance) When did your company license/acquire the active substances? How long after license/acquisition was the pharmaceutical put on the market?
9. (In case of in-licensed active substance) How were the active substances selected and identified? What are the most important criteria when in-licensing a drug candidate?
10. Do you perceive your company as working better in collaborations compared to your competitors?
11. Do you think that ability to collaborate is an important competitive advantage?
12. How many of your company's commercialized oncology therapeutics are in-licensed to some degree?
13. How many of your company's commercialized oncology therapeutics are developed in-house?
14. Do collaborations/partnerships differ for oncology therapeutics compared to therapeutics in other medical fields?
15. How do you value university research?
16. Are most drug discovery programs run as collaborations with universities, or what is the most common model?
17. Is there ever a problem or conflict regarding revenue sharing and patent assignment in such collaborations? Has this attitude changed?
18. In your opinion, how important is university research for the development of oncology drugs at your company? In general? All universities or just a few key institutions?
19. Other?