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Personalized Medicine

-a viable option for a biotech company

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Executive summary

This thesis investigates and analyzes the potential for a biotech start-up company to use personalized medicine based on MSCs. The thesis focuses on four subjects – (1) the current IP landscape, (2) the path to market, (3) the possibility to generate protection around the personalized part of the medicine and (4) the commercialization of the product.

The patent landscape around MSCs showed a stable patenting trend in the field, with to some extent wide patents. The analysis showed, in line with other investigations, that the industry consists of several small actors. This indicates low barriers to enter from a patent perspective. The analysis of the patent claims showed no homogenous trends for the field as whole. Some trends were however identified when breaking down the field into further subcategories, e.g. procedures.

The path to market analyzed different possibilities to solve the scenario of a blocking paten, e.g. invalidate or invent around. This chapter also addresses different tools to reach the market - licenses, collaborations and exemptions.

The third section analyzed different manners to protect an algorithm. The algorithm represents a good solution to isolate the personal features. The analysis showed that patenting offered the best options for generating protection, which in turn required an investigation of the legal opportunities to protect an algorithm. The legal analysis showed that there where good possibilities in both the US and Europe.

The last section, commercialization, showed the benefits and challenges of the field based on a Porter's five forces. The analysis showed several strengths and weaknesses within the chosen field, e.g. several of the input products are commonly used in the pharmaceutical industry and hence are relatively easy to gain access to. The chapter also addresses benefits and challenges in relation to parameters such as "small biotech start-up vs. big pharmaceutical company" and different pricing strategies.

The conclusion that can be drawn is that personalized medicine offers great opportunities for a start-up biotech company.

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Abbreviations

BM – Bone Marrow

CCE – Counterflow Centrifugal Elutriation

DNA – Deoxyribonucleic Acid

EPC – European Patent Council

EPO – European Patent Organization

ESC – Embryonic Stem Cell

IHD – Ischemic Heart Disease

IP – Intellectual Property

IPSC – Induced Pluripotent Stem Cell

IPR – Intellectual Property Right

GMO – Genetically Modified Organism

LV – Left Ventricular

MI – Myocardial Infarction

mRNA – messenger RiboNucleic Acid

MSC – Mesenchymal Stem Cell

PCT – Patent Cooperation Treaty

PTO – Patent and Trademark Office

SME – Small and Medium Enterprises

TBA – Technical Board of Appeal

TRIP – Trade Related Aspects of Intellectual Property Rights

UC – Umbilical Cord

USPTO – United States Patent and Trademark Office

VC – Venture Capital

WARF – Wisconsin Alumni Research Foundation

1. Introduction

The biotech industry is experiencing an interesting time with rapid technical development, the convergence of several industries and changing of legal frameworks. There are new innovative steps about stem cell development presented on an almost daily basis, where the next is even more spectacular than the previous, e.g. the cloned sheep Dolly that was announced in 1997[1] and the possibility to create life in a cell from 2010[2]. This shows the potential in the field, and how far research already has come.

There is a convergence from several industries, e.g. the agricultural-, chemical- and pharmaceutical sector, into the life science field. This means that the field stands the possibility to become the largest industry in the world if the transaction continues. The movement is motivated by the increasing importance of genetic engineering and the impact it is expected to have on the world, e.g. GMOs and therapies.[3]

The stem cell research has experienced regulatory changes during the last years in both the US and Europe. The largest change has been in the US, where George W. Bush in 2001 decided to re-regulate the policies applying to stem cell research and its funding. He decided that US federal dollars were only to be spent on research using existing approved lines of embryonic stem cells. The law has been modified since 2009 when Barack Obama loosened the regulations. A second hindrance in the US and to some extent for the whole research development has been two WARF patens covering the preparations of primate and embryonic stem cells in a wide manner.[4] The WARF patents have been rejected in a recent decision from USPTO[5], which should open up the field. The WARF patents have not been granted in Europe due to a different view on embryonic stem cells, but they have still had an effect in Europe due to the importance of the US market.

In this thesis we have decided to take a closer look on the biotech field and the developments that are ongoing therein. In order to narrow the scope of our research we have focused on MSC research and the development of personalized medicine.

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[1] Science Museum, Internet
[2] Stengård, M (2010), Internet
[3] Enriquez, J et al. (2000), p. 97 ff
[4] Bergman, K et al. (2007), p. 1 ff
[5] The medical News (2010), Internet

1.1 Aim of paper

This paper aims to show the potential and challenges with personalized medicine in relation to stem cells for start-up biotech companies. The goal is to clarify interesting areas in relation to the chosen field to give an introduction into the industry. The dual educational background of the authors allows the thesis to address a wide scope of subjects that covers legal, technical and commercial elements.

1.2 Hypothesis

The preamble has introduced the current environment of a biotech start-up company. We think that personalized medicine offers interesting possibilities to reach the market for a biotech start-up and have formulated a hypothesis that we hope to verify or dismiss with this thesis.

Personalized MSC medicine offers great opportunities for start-up biotech companies based in Europe to succeed on the market.

1.3 Research questions

We have indentified four questions to allow us to verify or dismiss our hypothesis.

- What is the current patent landscape around MSCs?
- What is the best manner to reach the market?
- What is the best manner for a small biotech company to protect the unique aspect in personalized medicine?
- What would be the main competitive advantages and benefits for a biotech company utilizing personalized medicine?
- In what way does personalized medicine create advantages and possibilities of price setting for biotech companies?

1.4 Delimitations

The biotech industry covers several different application fields, e.g. therapy and GMO. The intended focus on personalized medicine means that we will primarily analyze the questions from a pharmaceutical- and genome industry perspective even if some of the material can be used for the biotech industry as a whole.

The chosen field covers several interesting areas, which in turn allow for a wide variety of questions. We have chosen five research questions that are central for the personalized aspects from a business- and IP perspective. This means that the result might have been different if using another perspective.

We have chosen to limit our analysis to the EU and the US, which cover a majority of key countries of development and commercialization. This means that we only have included patents issued by EPO and USPTO, and regulations and praxis from the US and Europe. There are other important countries, e.g. Japan, China and India that are relevant, but the limited space in relation to the wide scope did not allow for more nations to be included.

The qualitative analysis of patents has only included patents issued in Europe to prove or dismiss the hypothesis. This might to some extent give an inaccurate picture due to the dominance of US patents. However, all solutions of commercial value should have been issued in Europe as well as the US, and hence show if there are any central patents.

There are several IPRs that are interesting for a biotech company, but we have decided to only address protection around the inventions. One interesting dimension that falls outside but is relevant for the commercialization of the personalized aspect is for instance branding,

There are different forms of stem cells, but we have primarily focused on mesenchymal stem cells. The reason for this is dual – (1) MSCs have several positive traits that make them interesting for future development. (2) The majority of the present articles in the field focus on embryonic stem cells. This indicates a lower research level of MSCs, which offers a greater challenge to explore the subject.

1.5 Method

The goal of the thesis is to give a multifaceted picture of personalized medicine and the biotech industry. This has resulted in the inclusion of several areas that have different requirements and hence resulted in a need for different methods. The used methods include literature and article analysis, a case study of a biotech start-up and discussions with persons active in the field, patent searches and analysis, and legal analysis.

We have used literature and articles to provide us with an insight and understanding of the subjects. The relatively fast development in the field means that articles have been a key source of information for the current status in the field. The articles were identified through searches using both proprietary and non-proprietary search tools, as well as directed searches of recognized magazines in the field. The main non-proprietary was Google, while proprietary databases such as Web of Science and SCOPUS were used to gain access to qualitative sources. We also conducted directed searches in Nature, Nature Biotechnology and Harvard Business Review to identify relevant articles that the

searches had missed. The books were identified through searches in Gothenburg University's library search tool GUNDA, and via references in relevant articles.

We followed a biotech company during the spring, which has allowed us to gain insight into the reality of the current industry. This has also allowed us to gain access to persons with insight into different areas of the industry ranging from scientists, business developers to patent lawyers, which has permitted us to test some of our theories on persons active in the field. The interactions have included the possibility to sit in on meetings and to partake in discussions.

The patent searches have been done using non-proprietary databases Free Patent Online and Espasnet. The searches included the US and Europe to allow a good coverage of the major patent regions. Initial searches were performed by using general search phrases to allow the identification of relevant patents. This allowed for the generation of new key words and more specified search strings. We conducted a brief review of titles and abstracts when the individual search string gave less than 100 hits to allow for the identification of relevant patens covering key areas. We have used a classification tool by Robert R. Sachs that places the patents in a matrix by analyzing the claims, in order to identify the patenting trends in the field[6].

We have used legal method when relevant to determine the judicial situation. The legal method included studies of regulations, praxis and doctrines to allow for a good understanding of the chosen areas. When suitable, the proprietary database Karnov was used.

1.6 Disposition

The wide scope of the thesis also makes the investigated areas several. This means that the focus of the chapters varies and does not always match in sequence. The logic can be found in the hypothesis and the research questions. The flow and connections between the different parts can best be described as in Figure 1, where the conclusion shall support hypothesis.

[6] Sachs (N/A), p 1 f

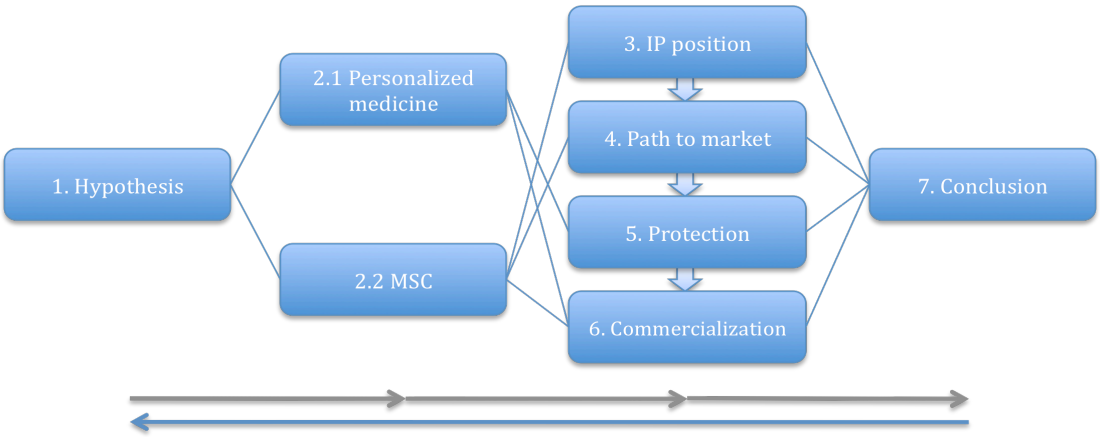

Figure 1 - the flowchart of the thesis and the connection between the different parts. The numbers in the box correspond with the chapter number.

Chapter 2, Background, will serve as an introduction to the two central underlying subjects, personalized medicine and mesenchymal stem cell therapy.

Chapter 3 will show the current patent landscape for MSCs and analyze reference patents in the field.

Chapter 4 shows the different options to take an intellectual property the last step to the market, which is done primarily by highlighting benefits and challenges.

Chapter 5 addresses the best manner of protecting the personalized aspect of the medicine. This will primarily be done from the perspective of an algorithm encapsulated in software.

Chapter 6 analyzes the commercial benefits and challenges of personalized medicine when used in combination with MSCs for a biotech start-up company.

Chapter 7 will combine the previous parts to be able to show that personalized medicine offers a great opportunity for a biotech company.

1.7 Target Audience

The intended audience of this paper are persons that have an understanding of intellectual property and the structure of the biotech industry. The individual is interested in the development of personalized medicine in relation to IP and its commercialization.

2. Background

The intent of this chapter is to give an understanding of the two underlying subjects of the thesis, personalized medicine and MSCs. The broad scope of the subjects means that only key features will be included, which to some extent will result in a simplified presentation.

2.1 Personalized Medicine

Personalized medicine has the potential of becoming the next step in the evolution of therapies. There is no single definition of personalized medicine, and the utilization of the concept varies from the sole use of diagnostic tools to the encompassing of the whole process as shown in Figure 2 below. We have decided to use a definition from the US president's Council of Advisory on Science and Technology from 2008, which covers the whole process.

> *"Personalized medicine refers to the tailoring of medical treatment to the individual characteristic of each patient. It does not literary mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Prevention or therapeutic intervention can be concentrated on those who will benefit, sparing expenses and side effects for those who will not."*[7]

Personalized medicine emphasis a more holistic approach to addressing diseases and a more proactive approach to treatment. This should be compared to the traditional approach of reactive trial and error that is currently practiced. The new paradigm can best be described as seen in Figure 2.

Figure 2 - Paradigm of Personalized Medicine[8]

2.1.1 Benefits of Personalized Medicine

There are several benefits with personalized medicine, but the three main can be defined as – (1) better diagnosis and earlier intervention, (2) more efficient drug development and (3) therapies.

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[7] President's Council of Advisors on Science and Technology (2008), p. 13
[8] Personalized Medicine Coalition (2010:1), Internet

(1) The improvement in diagnosis allows for earlier and with a higher precision the identification of a disease. This in turn allows for appropriate measures to be taken with potentially less discomfort for the patient. To give an example, a patient in a high-risk segment of contracting a disease comes in for a test. Depending on the result, this will allow the physician to address the problem prior to any symptoms have surfaced. The result would be less discomfort and safer treatment for the patient, and lower costs for the medical system by allowing a less invasive response.[9]

(2) The current paradigm of treatment development has prevailed over many of the diseases that have affected mankind. However, several of the diseases that remain have a greater complexity – e.g. diabetes, cancer and Alzheimer's disease – which means that a new approach is needed to tackle the challenges. The more complex diseases are not a result of a single gene or event, but instead a combination of genetics and environmental factors. This means that the individual response to a treatment varies more, which requires several parameters, e.g. genetic variations, to be addressed during the development to allow for an efficient treatment. The current paradigm of developing medicines according to the one-size-fit-all concept has not been able to address the complexity needed as shown in Figure 3. This will be a key area for the personalized medicine paradigm where the individual parameters can be addressed.[10]

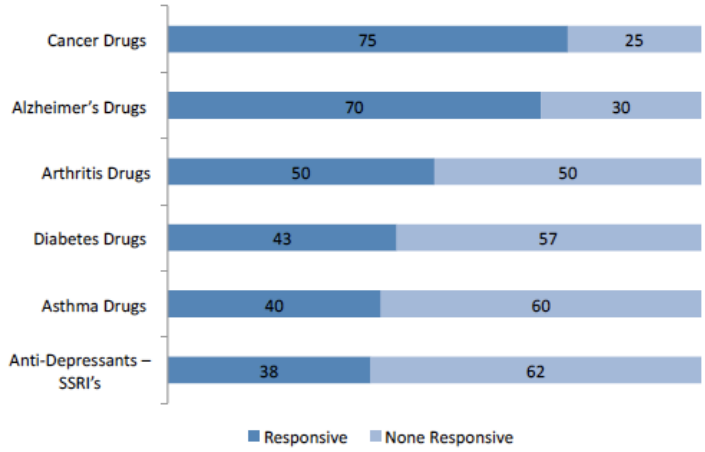

Figure 3 - The receptiveness to traditional medicine[9]

(3) With the more efficient diagnostic the physician would be able to identify which form of the disease a patient has, and subsequently which medicine and optimal dosing that would give the best result for the patient at hand. This would have the benefit of less adverse events for the patient. The new approach should be compared to the current method of trial and error with different treatments until the best solution is

[9] Aspinall, M.G. et al. (2007), p 1ff
[10] Personalized Medicine Coalition (2009), p 4ff

found. This increases the risk for complications due to e.g. negative side effects from the medication, and more discomfort for the patient.[11]

2.1.2 Challenges of Personalized Medicine

There are challenges with the implementation of personalized medicine, and the five main can be defined as – (1) scientific challenges, (2) economical parameters, (3) public opinion, (4) ethical dimension and (5) regulatory issues.

(1) The idea of personalized medicine is not a new concept, but the ability to understand the underlying reasons for diseases have taken a big leap with the development of technologies that allow for a greater understanding of mRNA, DNA and proteins. The current understanding and technical development has allowed for the current generation of personalized medicine to prevail, but there are some issues that need to be addressed to enable a big breakthrough, e.g. further understanding of the relationship between different genes and higher throughput.[12]

(2) The economical challenges are to determine the "time aspect" and motivate the cost of development. The time aspect is to some extent dependent on the structure of the medical system, i.e. if it is paid via the public sector or with private insurances. A private funded medical system is based on the notion of treating a current disease with a high mobility of the customers between different insurance providers. The current system goes against the preventive approach of personalized medicine, which raises the question of who shall carry the costs for the treatment of a disease that has not presented itself, and potentially never will. This will require a reformation of the system to allow for a breakthrough of personalized medicine.[13]

The possibility to derive value for a pharmaceutical company is currently limited in relation to the costs associated with development. This is a result of the current compensation systems that premier the treatment, which makes it hard to reclaim the costs of development and launch of e.g. diagnostic tools.[14]

(3) The public opinion is currently focused on the risk for accidents and abuse of the genome material, and not the possibilities that the treatments can offer. This is prevalent on all markets, but more so in Europe where the accidents have eroded the confident in the industry. The responsibility can to a large extent be put on the industry,

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[11] Personalized Medicine Coalition (2010:2), Internet
[12] Meyer, J. M. et al. (2002), p 434ff
[13] Davis, J et al. (2010), p 2ff
[14] Davis, J et al. (2010), p 2ff

which has not addressed the concerns of the public and downplayed critics. This is however being addressed by the industry by emphasizing the benefits of the treatments and educating key actors, which hopefully will solve the problem.[15]

(4) The social dimension revolves around the selection of diseases to treat and the increased costs of the treatments. There is a risk that the selection of treatments will be tailored to fit the populations in the developed world that can carry a higher cost at the expense of the developing countries. The one-size-fit-all paradigm that currently prevails allows the development of medicines that can help everybody to some extent. This might not be the case with the personalized approach where the medicine will be directed towards a specific group. The cost of the new products have usually a higher cost per treatment, which raises the concern of who will have access, i.e. if it will become a product for the rich.[16]

(5) The personalized medicine falls under the legislations of pharmaceutical- and genetic products. This means that the control and requirements are extensive, which put large demands on the industry.

2.2 Mesenchymal stem cell therapy

Research and publishing of reports around stem cells has grown enormously during the last decade. Stem cell research has become one of the promising areas for personalized medicine and the treatment of various forms of disease and trauma of the human body. The knowledge about stem cells is constantly expanding but there are still many unsolved issues regarding their structure and different influences on the human body.

2.2.1 Stem cells

Cells are the basis of all life. Stem cells are one subcategory thereof and are the first cells formed in the development of a human being.[17] Stem cells are unspecialized cells that have the potential to replicate into identical cells or give rise to differentiated cells. The differentiated cells form the more than 200 other further specified cells of the human body such as muscle-, red blood- or brain cells. As long as the host-body is alive, these cells often serve as a kind of repair system, primarily dividing and replenishing other cells.[18] Mammalian stem cells are divided into two broad types - embryonic stem cells

[15] Enriquez, R. et al. (2000) p 102ff
[16] Smart, A. et al. (2004), p 334ff
[17] Evers P., 2009, p. 16
[18] Stem Cell Information (N/A), Internet

(ESCs) and non-embryonic (somatic/adult) stem cells. ESCs are found in the early stage of embryonic development whereas adult stem cells can be found in tissues of the adult organism.[19] The differentiation capacity of stem cells is divided into their degree of potency. ESCs are pluripotent and can differentiate into all three germ layers of the developing embryo, i.e. the mesoderm, ectoderm and endoderm. Pluripotent adult stem cells are rare. Most adult stem cells are multipotent and can differentiate into a variety of cells, but which has to be a closely related family of cells.[20]

2.2.2 Mesenchymal stem cells

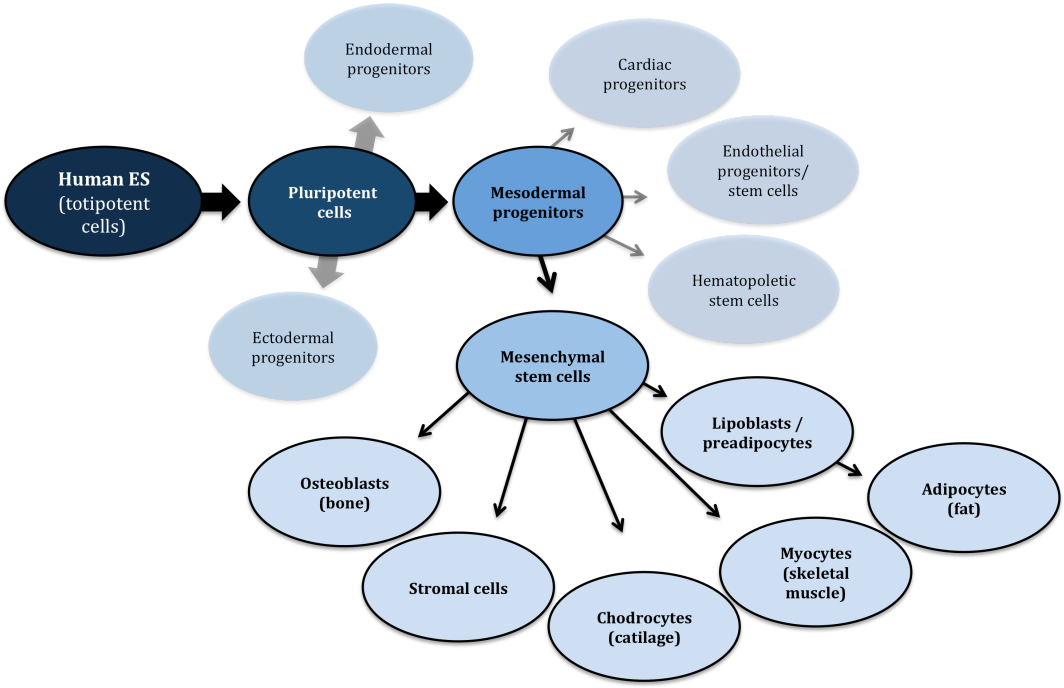

Figure 4 Structure of cell focus[21]

Mesenchymal stem cells (MSCs) are a population of multipotent adult stem cells. MSCs are usually extracted from patients' bone marrow (BM) or other tissues of mesodermal origin such as fat, joint synovium, dental pulp etc.[22], and they can form multiple cells such as cartilage, bone, tendon and ligaments, fat-, muscle-, skin- and nerve-cells. MSCs are suitable for clinical applications as they can be obtained in sufficient large quantities, they maintain their capacity over a long time during culture periods as well as they can be frozen down for preservation without loosing their function. A major object of stem

[19] Evers P., 2009, p. 19
[20] Evers P., 2009, p. 20
[21] Bergman, K. et al. (2007), p. 14
[22] Evers P., 2009, p. 28

cell research is to develop the means to use them as the raw material for tissues that are lacking in the body due to disease.

2.2.2.1 Occurrence

Besides the occurrence of MSCs in BM, blood and the brain,[23] it has recently been suggested that MSCs can be derived from other tissues such as human umbilical cord (UC), that could be used as an alternative to BM-derived MSCs.[24] MSCs have been isolated from the Amnion, Placenta, UC blood, periosteum, skeletal muscles, Synovium and BM. This versatile availability makes them great candidates for different cell based strategies for e.g. the regeneration of bone and cartilage damage.[25] Animal trials indicate great potential for the use of MSCs for reconstitution of human damaged tissue such as cartilage, bone, muscle and tendon.[26]

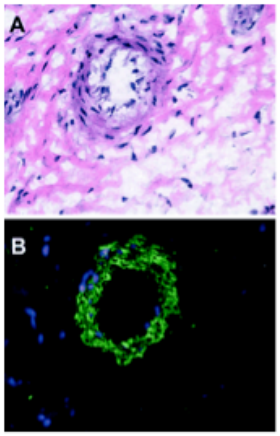

Figure 5 - MSCs arrange themselves after transfer to treat the affacted (green) area

2.2.2.2 MSC Features

MSCs have distinctive proliferation capacity and multiple differentiation potential and are therefore suitable for the regeneration of complex impairments. The immune suppressive and environment modulating characters also enable the control of inflammation- and degradation processes.[27] MSCs have the ability to home to sites of tissue damage or inflammation, which has been demonstrated in settings of bone fracture, cerebral ischemia and the infarcted heart.[28] One of the key features of MSCs is their migration and engraftment potential, which has been shown with the example of MSCs being able to stay in the BM after a transfer or where MSCs even move to the affected area.[29]

2.2.2.3 Substitutes

Cells with similar characteristics as MSCs can be extracted from all post-natal and extra-embryonic tissues such as amniotic membrane and placenta.[30] These findings are thought to have potential for application in the area of regenerative medicine.[31]

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[23] Kadereit, S. (2005), Internet
[24] Majore I. et al., 2009, p. 1
[25] Dehne T. et al. 2009
[26] Kadereit, S. (2005), Internet
[27] Dehne T. et al. (2009)
[28] Pittinger M. F., (2004)
[29] Dehne T. et al. (2009)
[30] Majore I. et al., 2009, p. 2
[31] Majore I. et al., 2009, p. 6

The use of embryonic stem cells is often ethically unaccepted due to the destruction of fertilized embryos. Induced pluripotent stem cells (IPSCs) are artificially produced pluripotent stem cells that derive from inducing an expression of certain genes into non-pluripotent stem cells (often adult stem cells). These cells are believed to have the same features as ESCs but they still pose significant risk for use in humans due to the undeveloped research state. If successful, this technology could have great significance for the development of regenerative medicine.[32]

2.2.3 Treatment

2.2.3.1 Stem cells

Research within this field has had its main focus on exploring the possibilities to use stem cells in regenerative medicine in order to replace by disease or trauma damaged cells and tissues.[33] Treatment and R&D with stem cells has potential in the fields presented in Figure 6. Bone marrow transplants with adult stem cell treatment have successfully been used for many years to treat leukemia and related bone/blood cancers.[34]

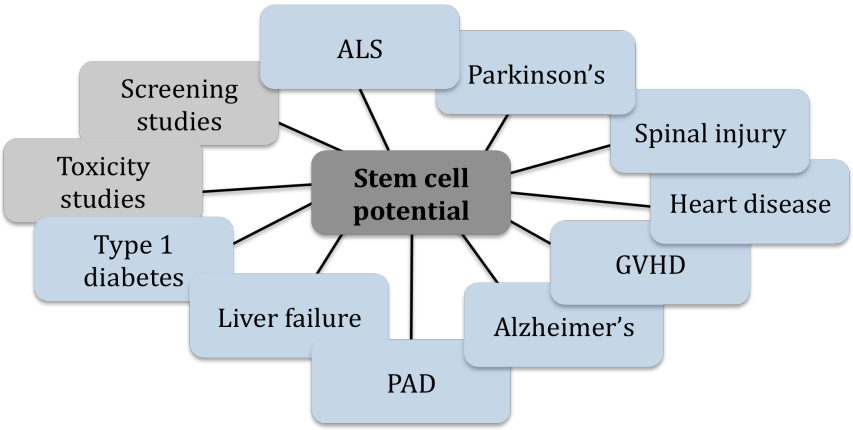

Figure 6 Stem cell treatment opportunities and R&D[35]

2.2.3.2 MSCs

MSCs have the capability to differentiate into various cell types and could be an attractive therapeutic cell type to treat patients with for instance *ischemic heart disease* (*IHD*). Animal studies and initial clinical trials have shown positive effects on the left

[32] Evers P., 2009, p. 30
[33] Evers P., 2009, p. 38
[34] Evers P., 2009, p. 35
[35] Evers P., 2009, p. 40

ventricular (LV) function.[36] 15 days after the myocardial infarction, the transplantation of MSCs showed positive effects on the infarct size and systolic and diastolic LV function.[37]

In contrast to many traditional medical treatments that only are des-inflammatory and stop the disease, MSC treatment is anti-inflammatory but is also able to reproduce tissue and organs and improves recovery, which reduces recurring diseases.

The clinical use of MSCs has begun for various diseases such as for instance cancer and MI. MSCs have either been administered intravenously in order for the cells to find their way to the targeted area or directly injected into the concerned area. Some of the areas where MSC treatment could be relevant are MI, cancer, brittle-bone disease and glycogen storage disease. Some of these fields do not have many therapeutic options.

In 1999, the first use of BM cells for cardiomyoplasty in mice was reported. Autologous BM cells were implanted in the LV 3 weeks after cryoinjury.[38]

2.2.4 Advantages of MSCs

Many diseases or physical injuries that are treated in the traditional way only experience improvements in form of pain relief, reduction of destructive inflammation or the stoppage of the catabolizing effect. MSCs treatment on the other hand offers the same features as before but also repairs the affected areas and rebuilds the tissue, cartilage and bone. This is done by secreting anti-inflammatory signal molecules to surrounding cells, and therewith reducing the immune reaction.

Figure 7 Way of treatment

As already mentioned, cells can be extracted from BM, blood, or UC. As we focus on adult MSCs this leaves us with the two first. BM contains a greater amount of MSCs compared to blood, which makes it easier to expand the cells to the amount needed for treatment. On the other hand, BM needs to be extracted surgically with a gauge needle, which is a

[36] Grauss R. W. et al., 2008, p. 1088
[37] Grauss R. W. et al., 2008, p. 1090
[38] Pittinger M. F., 2004

painful process, whereas blood is easy to get. The Isolation of MSCs can be managed through the counterflow centrifugal elutriation (CCE).[39] The patient's sample contains a mixture of tissue and different cells, out of which RMS distinguishes MSCs through manual Ficoll separation. Manual Ficoll is a sterile and ready to use density gradient medium for purifying lymphocytes[40]. The next step is to expand the isolated cells and get them to grow to the required quantity before they can be used for the treatment of the patient.

2.2.5 Allogeneic vs. Autologous MSCs

There are two options for treating patients with MSCs, either with allogeneic or autologous cells. Both of the options have advantages whereas autologous cells seem to be the better alternative in the end, as long as certain processes, such as the expansion rate can be improved.

The treatment within a short time period is crucial for the recovery of the patient and should be within 5 to 10 days after occurrence, at least in the case of bone marrow used for MI treatment as it showed best effect in infarct size reduction in the left ventricular. There is still a need to find out more about optimal treatment time and what the effects would be if the cells were injected 14 days after MI as there are still issues to be solved regarding fast treatment possibilities after infarct occurrence[41].

2.2.5.1 Allogeneic

Allogeneic means that the cells are extracted from one person and injected into another person. This has the advantage that the donor can be selected in advance and the sample can be tested for genetic match and different diseases in order to be available when needed by a patient[42]. There still is a risk of side effects and cell-cell reactions, immune reactions that make the transplant being rejected. Even if allogeneic cells can be extracted in advance, there is still great effort involved as there has to be made sure that the cells will match in order to avoid an immune reaction[43].

2.2.5.2 Autologous

The autologous treatment means that cells are extracted and re-injected into the same person. This removes the risk of rejection and increases the probability of a successful recovery of the patient. The disadvantage of this process is that the cells have to be

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[39] Majore I. et al., 2009, p. 1
[40] Amersham Biosciences (N/A), p. 5
[41] Duncker D. J et al (2007), p. 1
[42] Pittinger M. F (2004)
[43] Evers P. (2009), p. 71

taken from the patient when the damage already has occurred, which gives less time for cell expansion. Neither does it seem clear if the patients produce the right amount of stem cells of required potency at the time needed.[44] Another possibility that would require a lot of effort would be to extract cells in advance and store them for future use.

It is difficult to say which of the two options would be the better solution in the end. If the researchers manage to advance the expansion process of MSCs, the autologous solution is definitely the first choice. In some cases where the disease is treatable by transplant, autologous cord blood stem cells could not cure the disease as the cells have the same defect, and therefore allogeneic stem cells would be better[45].

[44] Pittinger M. F. (2004)
[45] Evers P. (2009), p. 72

3. The patent arena of the MSCs

This chapter has the purpose of clarifying the environment that the start-up is operating in from an IP perspective. This will be done in a two step process, the first is to set the hypothesis in context with the assistance of a theoretical base developed by Ulf Petrusson and the second will show the patents that surround the company.

3.1 The arenas

Actors within the biotechnology field experience great value and importance of IP and IPRs for their establishment on the market. Ulf Petrusson has developed a structural platform including three arenas, the administrative-, judicial- and business arena that can be used for the construction of Intellectual Properties (IP) and Intellectual Property Rights (IPRs).

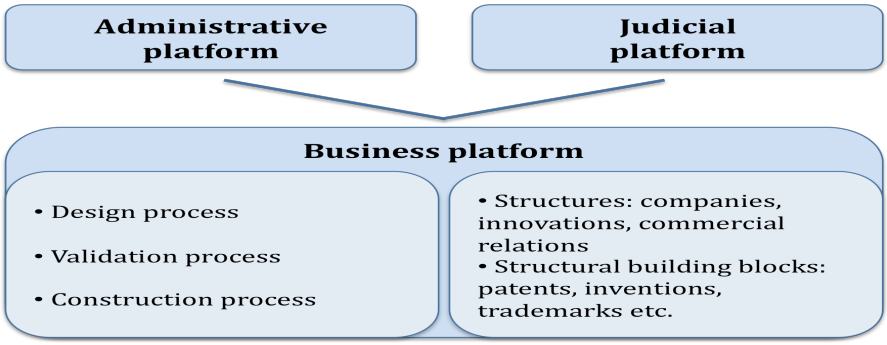

Figure 8: Structural platforms

Start-up companies/entrepreneurs, not depending on which field of work they are active in, have to learn how to divide and monitor IP as communicative actions within these three interacting arenas.

3.1.1 Administrative arena

This arena is a structurally organized arena, covering regulations and policies to instruct actors, as well as structural actors such as patent offices and courts of appeal, and also including the patent examiner and patent attorney roles. The infrastructure of patent information that is used in the administrative procedure is an important factor in this arena.

3.1.2 Judicial arena

The judicial arena is where the law is applied, and is in many ways the structural fundament of states. This arena is of great importance when it comes to the construction of IPRs as legal tools and the use thereof. Therefore judges, prosecutors and defense lawyers play a significant role in this arena. The practical application for companies is

the documentation of legislation and earlier court cases, which form the communicative basis for future procedures and source of information.

3.1.3 Business arena

The business arena is probably the most important of these three arenas when looked at from an entrepreneurial perspective. It is the underlying conglomerated platform of markets, innovation systems, firms and commercial relations, which are sophisticated entrepreneurial challenges for start-up businesses to design, construct and reconstruct.

3.1.4 The three arenas

Entrepreneurs are dependent on existing business as a structural platform, which is superjacent to the supporting administrative and judicial platforms. Both the administrative and judicial arenas are important for the integration of the company into the legal systems. These often have national focus whereas the business arena in the knowledge-oriented sphere often is internationally oriented. Companies often want their business to be internationally recognized, whereas the supporting arenas and people involved therein such as patent lawyers and attorneys often are specialized on the national arena. Legal professionals often lack insight and communication skills to apply in the business arena, which makes it important for entrepreneurs to select experts. The governing of the communication with patent attorneys, patent lawyers, patent examiners and judges for the handling of IP and IPRs in the business arena is crucial for the entrepreneurial process and success.[46]

3.2 The patent landscape

There has been a discussion about if there is a patent thicket[47], also known as anti-commons, covering the stem cell field. This in a field that many argue to be very susceptible to the problem as patent offices previously allowed patents containing broad claims on early inventions.

The four main challenges with a patent thicket are – (1) the possibility to hinder the path to the market due to blocking patents, (2) hindering freedom to operate during the development- and commercialization phases due to several overlapping patents, (3) limiting available capital for financing due to the high risk in relation to the potential profits, and (4) the high costs of gaining access to protected solutions due to compiling

[46] Petrusson U. (2004), p. 104 ff

[47] A patent thicket has been defined as a "dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology.

royalty payments and the related transaction costs. This has the potential risk of slowing down, or even hindering, the development of the field.[48,49]

Bessen et al. argue that there is a problem with "fuzzy" claims, i.e. the claims are vague, in the biotech sphere. The fuzzy claims are a result of the patent offices, and in the next step the courts, allowing patenting of premature inventions. This results in problems for the actors in the field to determine the scope of the patent, and hence if they are at risk of infringing on the protection. The consequence of this might be that investors become reluctant to invest due to the high risks of infringing.[50]

3.2.1 Previous investigations of the patent landscape

There are a number of investigations of the stem cell patent landscapes in the US. The investigations, e.g. Bergman et al.[51], Rohrbaugh[52] and Konski et al[53], have covered stem cells in general and/or directed towards ESC, using both quantitative and qualitative methods. The three reports show an extensive patent landscape, but that there still are possibilities to find new areas to develop and explore.

The studies found to some extent similar results, e.g. they all touched upon the importance of WARF's ESC patents and its influence on the market. Rohrbaugh had a qualitative approach to the landscape analysis, and reached the conclusion that the WARF patents did not hinder the development of stem cells but could hinder the commercial phase.

Both Bergman et al. and Konski et al. used quantitative methods to analyze the patent landscape around stem cells. Both investigations showed the equal division of key patents between the public- and private sector, and the importance of WARF. Bergman et al presented a more complete picture in relation to the other two. Bergman et al presented that the majority of the stem cell patents where issued by USPTO, PCT, or EPO in 2007. This they argued, did not necessary mean that the allocation of researchers, companies and innovations had the same dispersion, but might instead imply that the inventors and owners of the patented innovations considered these markets to be central to protect the technology.[54] Bergman et al showed further that the ownership of the US patents was divided between several actors, and no single company accounted

[48] Bergman, K. et al. (2007), p. 419
[49] Clark, D. J. (2008), p. 969 f
[50] Golin, M. (2008), p. 164
[51] Bermang, K. (2007)
[52] Rorbaugh, M. L. (2006)
[53] Konski, A. F. (2009)
[54] Bergman, K. et al. (2007), p. 420

for more than 3% ownership. The holders of the patents were often small companies with specialization within stem cell research.[55]

3.2.2 The current patent landscape

The quantitative analysis of the patent landscape around MSCs showed a field containing a complex structure. The analysis presented, to some extent, patents containing wide and general claims. This, depending on the intended focus of the personalized medicine, might cause challenges by covering key elements for the start-up. The patent search[56] showed 3357 issued patents in the US and 1581 patents for Europe, which shows the dominating position of the US. The investigation did not reveal any dominant patents in line with the WARF patents for ESC in the MSC field.

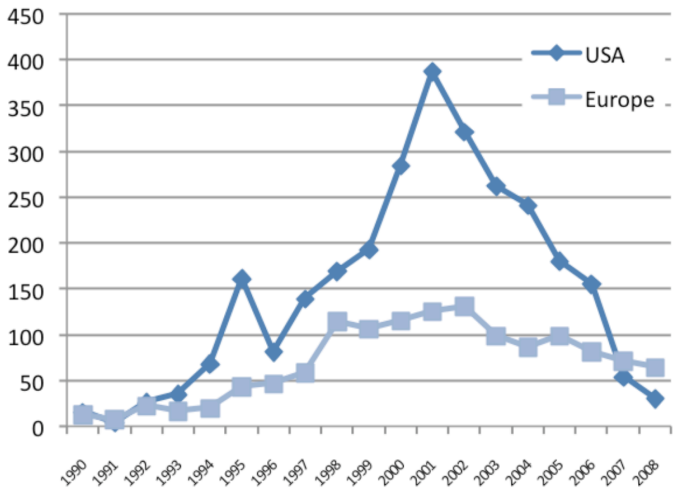

Figure 9 - the graph present the MSC patents in Europe and USA during the period of 1990 to 2009. The search gave 4131, of which 2805 stem from USA and 1325 in European.

The timeline allows for a good overview of the development in the field and shows the commercial novelty in 1990 and 1991. The European patent activity has as shown a stable trend since 1998, which indicates that there is still a good possibility in the field.

The timeline for the US shows a big spike in 2001. This is a result of USPTO changing their publication standard to coincide with the majority of the world, i.e. to publish patent applications within 18 months of filling. This affected all patents filed as of the 29th November 2000 and hence explains the abnormal result in the time line.[57]

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[55] Bergman, K. et al. (2007), p. 421
[56] The search was conducted with a wide string to catch all relevant patents – mesenchym* AND stem* AND cell* (May 2010)
[57] USPTO (2000), Internet

3.2.3 Reference patents

The reference patents[58] have been selected due to being representative for the MSC field by claiming key elements. The patents are all issued in Europe to show the present state in the region, which to some extent differs from the American. This due to a difference in the view on the scope of stem cell related patents.

The use of non-proprietary patent databases means that the level of objectivity has been lower compared to if the selection had been done using e.g. citations and/or clustering. However, it does serve as a good insight into the MSC field and allows for an analysis of the claim space that can show the patenting strategy in the field. The reference patens can be found in Appendix A where they have been divided into classes – MSCs, treatment and procedures – to give an easier overview of the development.

The conclusions that can be drawn from the patent analysis is the strong position of Osiris in the field, but it is in no manner dominant. This coincides with other investigations, e.g. Bergman et al, which shows Osiris as a strong actor in other stem cell areas. Several of the reference patents have a relatively fresh publication date. This indicates that the sector is still very much in a development stage. There is a dominance of company owning of the reference patents. Universities are only involved in two of them. This can of course be a result of university spin offs, but the results indicate the maturity of the sector.

3.2.4 Claim space

The analysis of the patent claims, the placement in the matrix and the implication thereof are based on a method by Robert Sachs[59]. The analysis did not show any homogenous trends in the MSC field as a whole. However,

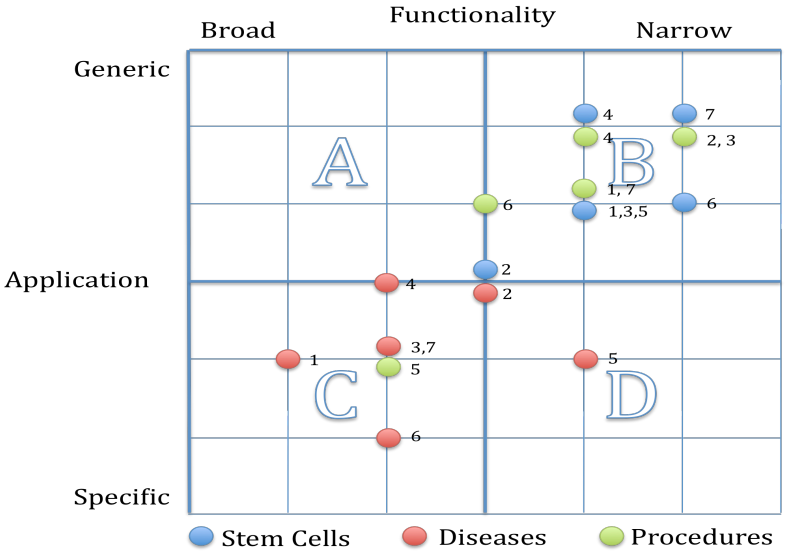

Figure 10 - Claim space showing the three fields – stem cells, diseases and procedures

[58] The patents have been indentified in during the quantitative analysis as described in the method.
[59] Sachs, R (N/A)

some trends were identified when breaking down the filed into subcategories. The claim matrix, Figure 10, shows the positioning of the reference patents using the same division as above in 3.2.2.

All of the stem cell patents can be found in field “B”, which means that they have narrow functionality. This indicates, according to the theory that the inventions are improvements of existing technology and allow the holder to have a relatively strong position. The construction of the claims allows out-licensing to complementary companies by having a wide scope, which is positive if there is a need to access the protected technologies.

The theory regarding a strong position need to be set in relation to the existence of early and fuzzy claims, which means that this conclusion is not fully applicable on the biotech industry.

The other two classes have a less homogenous pattern, which makes it harder to draw any conclusions. The majority of the patents that are focused on addressing diseases can be found in field “C”. This shows that they are constructed to be in line with the companies intended use, and hence leave little opportunity to license-in at an early stage. This is also normally a patent format that is obtained early in a development to give the holder a defendable position. The tool patents are mainly found in field “B”, which has been explained in relation to the stem cell patents.

The result relating to the disease patents was expected due to the nature of the category of treating illness. However, it does indicate a more defensive strategy in the field, which can show an inclination to enforce patents.

4. Possible solutions to reach the market

As for all companies there are different possibilities of reaching the market for a Biotech company focusing on MSC research and the development of medical therapies. The best strategy for reaching the market depends on the company's business plan and intentions of how to commercialize the company's assets and underlying resources, such as the innovativeness of the product, patents, market size, production capacity, competitors, the legal regulations etc. If the companies do not possess the requiring investment possibilities to set up their own R&D, an option is to acquire knowledge contractually. This could be in the form of acquiring technology through for instance licensing agreements, buying companies or establishing alliances such as joint ventures.[60]

For any of the alternatives, if it is to commercialize research outcome, manufacture products, sell patents or to license the IP, a lot of external factors need to be incorporated. These factors can to some extent vary between different regions, e.g. Europe and the US, and range from market demand of different cultures and their certain preferences and regional regulations to already existing competitors.

The development and competition on the market and the future developmental potential lead to the question of which would be the best strategy to reach the market. What are the commercialization options and which path would be the most profitable? These decisions are dependent on if blocking patents exist, on the novelty of the invention and on the possibility to generate IPR's. For start-up companies this process is more crucial than for any other company, as this will be one of the foundations for their future business. This is to some extent also true for larger and established companies, but they might have the possibility to fall back on previous businesses or could stand up against potential lawsuits, which makes them less sensitive.

4.1 Possibilities and hinders

This section will present a selection of steps from the development to commercialization of a product that the actor needs to think about when approaching the market, and in the next stage the possibilities to maximize the opportunities via using the tools of licensing, collaborations and exemptions.

[60] Granstrand, O (2000), s. 119f.

4.1.1 Research outcome

The company can decide to only focus on research and leave the development of products to other actors. This would mean that the research is sold, or licensed, to other development actors engaged in product development and manufacturing. In this case, the aim would probably be to keep the right to use the process for further research. This would be a good alternative for companies not interested, or lack the resources, to develop the whole manufacturing.

4.1.2 Product

A common alternative is to use research to develop a product and sell it on the market. The time from research to product launch can be very long depending on if the product is classified as a medical product and needs to go through tests and verification processes before being allowed to be sold on the market or if a product launch can be carried out without further approval.

4.1.3 Patents

If a Biotech start-up has patented a technology or process they will not need for their product development and that they do not intend to use in the future, they could e.g. sell the patent, given that the patent cannot be used against them. For security reasons the patent can be sold with reservation to being allowed to use the patented solution themselves. This is a good way of creating income with research outcome that cannot be used for proper development and otherwise would be left behind.

4.1.4 Risks

The risks related to the market approach are several, both for a product launch or the commercialization of the generated IP. There might be no demand for the kind of product/IP that the biotech company offers; unnecessary product features, a too high price or that substitute products exist that offer satisfying features can be reasons therefore. Another risk is blocking patents that could hinder the commercialization of the product.

4.1.5 Blocking patents

If the market and competitor analysis shows existing blocking patents there is no need to give up, but to make a well thought through decision on which is the best way to circumvent blocking patents and how to use them for own profits?

4.1.5.1 Invalidate

In case that the patent is too broad formulated or the patent examiners missed out on already existing innovations or information was disclosed before patenting, there is a

possibility of invalidating an already approved patent.

4.1.5.2 Invent around

Inventing around can be relevant if R&D will not be too resource demanding and the benefit thereof outranges costs.

4.1.5.3 Bargaining - acquisition, license, cross license

The acquisition of blocking patents provided by other actors could be a possible option for a small biotech company, whereas larger actors even might acquire whole companies to get access to their IP. This might be an expensive option for a key patent and hence not a viable option for a start-up, but might be the only alternative to gain access. To license specific IP for the use in own production or to cross-license are also viable options that will be addressed below.

4.1.5.4 Ignore /infringe

These options stand in close relation to the development stage of the invention. A company with a finished product might be willing to take higher risks than others. A quite radical alternative is to ignore existing patents and infringe against them, but this will also carry a higher liability if the owner enforces the right. This strategy might be chosen if the IP is not very close related and an infringement might not be discovered.

Another possibility, which might not be relevant for a small biotech company, is to intentionally infringe against patents of small actors. These might be afraid of going to court against big actors and could probably not afford to pay expensive legal fees. This option might be relevant for actors that are not interested in investing more time and money on inventing around the patented technology.

4.1.5.5 Wait

The last and very passive option is to wait out the expiration date of the patent, which in some cases could be very time intensive and give other actors a head start to market.

4.1.5.6 Recommended path

The most relevant option for small biotech start-ups to get around blocking patents seems to be the acquisition, licensing-in, cross-licensing or inventing around the said patents, or to collaborate with other actors. Acquisition would be relevant in the case that the owner of the patent sees no value in the patent and cannot make use of it and the patent therefore could be acquired to a good price. Inventing around could be an option if it is necessary in a limited aspect and needed resources are reasonable.

The creation of IP and especially patents plays a great role for these market approach alternatives. It is important to have a well thought through IP strategy that goes in line with the company's business plan. It is also crucial to make everybody in the company understand the importance of IP and that company internal information or research outcome cannot be disclosed in order to secure the novelty aspect.

Think about the IP strategy and how to protect the inventions before going into market!

4.2 Licensing

It is in theory possible to gain access to all patented technology, but this would be problematic in terms of time and money. The option is to license the key patent. This would be challenging due to the fuzzy- and overlapping claims. The cost of licensing a patent is relatively low, in average 1 percent or less of product revenue, but the problem could be the need to access several patents to allow freedom to operate.[61]

4.2.1 In-licensing

Licensing-in is often used when companies need access to complementary technologies or production methods to develop their own products. They might have access to some but not all necessary technologies or they have invented a certain device that goes with already existing technologies. In-licensing is a good way to save in on R&D costs. The advantage with this alternative is that companies do not have to develop the whole research process and they can bargain the prices and the period of licensing. When licensing, there is no/less need of own research spending and therefore reduces big investment requirement.[62] Problems can arise when the other actor is not willing to out-license. This could make the construction of the intended product impossible or very difficult/cost intensive. The alternative to intentionally infringe against the patent could also be more risky as attention already is aimed at them.

4.2.2 Out-licensing

Licensing-out IP can be done in different ways, e.g. with an exclusive, non-exclusive or sole license. The chosen option depends on the strength of the participating parties, the intended use and of course the business model of the proprietor. The process of licensing-out can occur when the proprietor of the IP does not need the exclusive right to use the patent and/or he sees licensing as a part to create more income for the company. Licensing can create income from both initial payment and royalties. Risks are

[61] Jaffe, A et al. (2007), p 64
[62] Granstrand, O (2000), s. 81

reduced by contractual regulations. If the focus of the company is in another field than the licensee's, respectable income can be generated from a market that never would have been considered otherwise.

4.2.3 Exclusive license

Exclusive licenses give the licensor the right to use the patented technology for alone usage. The advantage therewith is the possibility to be the only actor using the invention, but therefore also the price could be thereafter.

4.2.4 Non-exclusive license

A non-exclusive license means that others could license the same patent and both would be allowed to make use of it. This is a good alternative if the patented technology does not constitute a crucial and innovative part of the new invention or if the third party is active in another field of interest.

4.2.5 Sole license

A sole license gives the original patent holder the right to use the invention, but not exclusively, and he is not allowed to deed licenses to other companies. This is a good alternative in order to still be able to use the patented solution but keep competition on a low level. Income generated from this solution is relatively lower than it would have been for an exclusive license.

4.2.6 Cross-license

Cross-license can be used in different forms, e.g. patent and/or know-how, to exchange access to technologies between two or several actors. The extent of the use of cross-licenses in the biotech industry differs between sources. Gozzo argues that cross-licensing is especially common in the medical and chemical industry[63]. However, according to Jaffe et al. this is not commonly used in the biotech industry, which he thinks is strange considering the set-up of the industry[64]. Cross-licensing is a good option to gain access to technology when other resources are scares and allows for a faster development.

4.2.7 Compulsory license

If the proprietor of a patent has not made reasonable use of the patent within 3 years after patent granting or 4 years after filing of the patent, other actors can get the right to get a compulsory license for a reasonable price. If an actor wants to use the invention commercially he may get a compulsory license if it is of particular importance for the

[63] Gozzo, G (1998), p 109
[64] Jaffe, B et al. (2007), p 67

public. These licenses are only given those actors that are thought to have potential of making acceptable use of the invention and can be assigned by authorized authorities depending on national regulations.[65]

4.3 Collaboration

Collaborations are a necessary mean for a lot o start-up companies and so also for biotech companies. Collaborations do not necessarily have to be in relation to the exchange of IP or research, but can also be in form of complimentary knowledge such as marketing competence if this does not exist in the company itself.[66] Due to the small size of many companies, they may not have the needed resources of possibilities within the company to handle all issues by themselves. In such cases it can be of great value to collaborate with different kinds of actors to exchange knowhow in the different fields.

Another type of collaboration can be found in so called patent pools, where two or more patent owners agree to license their patents to each other or third parties. The advantage for biotech companies is the sharing of knowledge and the increased effect on research. The risks related to these collaborations and sharing of research progress are the loss of potential competitive advantage and being guided into certain market/research fields and loosing creativity. The main cause for the existence of strategic alliances seems to be the possibility to share risks because certain research fails and would cause high costs for a single actor. Another reason is the complimentary effect that pushes development, even if company proper strategies are restrained.[67]

There are several big pharmaceutical companies that have started to collaborate in early state development, such as for instance GSK, AstraZeneca and Roche, whose intention is to co-develop stem cell-derived hepatocytes for use in ADMET[68] studies. Another collaboration has been identified between Pfizer and Cellartis for validation of human ES cell-based models for reproductive toxicology screens.[69]

4.4 Exemption

The two first options require a level of interaction with the counterpart, while the last option, patent exemption, can be used as a sole solution to allow access to patented technologies. This is primarily an option that can be used in Europe, as the introduction below will show, due to the restrictive approach in the US.

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[65] Levin L. et al. (2006), p. 79
[66] Terao, J (2005), p. 53
[67] Terao, J (2005), p. 53
[68] ADMET = Adsorption, Distribution, Metabolism, Excretion and Toxicity
[69] Evers P., 2009, p. 60

The US has a very restrictive approach to the use of patent exemptions, with a limited experimental use as the only option. The possibility to use the experimental exemption was first established in Whittemore vs. Cutter[70] in a relatively restrictive manner. This was furthermore limited in Madey vs. Duke[71] to the level of practically non-existing. However, the US Supreme Court expanded the concept of the experimental exemption in Merek vs. Integra[72] to allow the use of patented solutions as a part of pre-clinical experiments.[73] The conclusion that can be made is that it is not possible to use the exemption as an option to reach the market in the US.

The use of exemptions is more extensive in Europe, and it is to a large extent codified in the legal acts. There is a large confirmative in the formulation of the patent exemption on the key markets in Europe (please see the selected market below in Figure 11), with the exception of Austria and Switzerland that do not have the same set-up. The conformities do to some extent allow for general conclusion to be analogized from one market to another.

The exemptions have the benefit of enabling access to protected solutions in a legal manner, but have at the same time large restrictions on what is allowed. The research- and extemporaneous exemptions are the two options that offer possible solutions for a biotech company to utilize patented solutions. The first option allows for research experiments on a patented solution, and might offer an opportunity during the development of the new products. However, the scope means that it cannot be used for commercialization and hence a leverage tool. The second option, the extemporaneous exemption, offers some interesting options as will be presented in the next section.

4.4.1 Extemporaneous Exemption

The extemporaneous exemption[74] offers an interesting option for a biotech company to allow the legal use of patented medical solutions by adjusting their business model to fall under the clause. The extemporaneous clause was constructed prior to the introduction of cell therapy with a different intended use, as presented below. The investigation did not identify any praxis with the suggested use that could have guided the analysis. The limited use of the clause also means that the available doctrine is

[70] Whittemore vs. Cutter, 29 Fed. Cas. 1120 (C.C.D. Mass 1813)
[71] Madey vs. Duke University, 307 F.3d 1351, 1362 (Fed. Cir. 2002)
[72] Mereck KGaA vs. Integra Lifesciences I, Ltd, 545 U.S. 1993 (2005)
[73] Palombi (2006), p 2ff
[74] The exemption has different titles in the jurisdictions, but we have chosen to use the title in the United Kingdom since it allows for a good explanation.

restricted, and the literature that is available has to a large degree a different emphasis than the suggested use.

> The extemporaneous clause – Preparations in a pharmacy of medicines under a doctor's prescription in individual cases or actions with drugs that have been treated in such cases.[75]

The extemporaneous clause has a similar formulation in the investigated jurisdictions (selected countries are shown in Figure 11), which allows the presentation of one to act as the template for the other countries.

The clause was created to protect the pharmacies' personal from the risk of committing patent infringement while doing their work. The extemporaneous clause allows for a pharmaceutical to be prepared according to an individual prescription. This means that it is not allowed to prepare the product in advance and keep it in stock and in the next step sell the medicine.[76,77]

The extemporaneous clause can be found in most of the European countries, as shown in Figure 11. This provides the possibility to make use of the exemption on several markets.

Figure 11 - The countries in Europe that have the extemporaneous exemption.

The exemption allows a biotech company to shape the business model in a manner where the MSCs are prepared as a personalized medicine in accordance with the physician's instruction, and through this circumvent the patent protection that might exist for the last step of

[75] The presented clause is taken from Sweden, which has the benefit of being based on civil law and hence allow for an easy insight. Swedish Patent Act – 1967:837 - §3 Sec 3(5)
[76] Swedish government Bill – 1977/78:1
[77] Jacobsson, M. et al (1980), p 114 f

the process. The process can be seen in two different manners. The first is that all the steps of preparing the product should be viewed as one process, i.e. from isolation to preparation. This would mean that the exemption is not applicable, due to only covering the last step. The second option is to view the process as individual steps, which would mean that the exemption is applicable. This argument is stronger considering the structure of the production where the individual steps are a process in itself, and hence should not be considered as one. The final step could be considered an infringement depending on the patent protection, but this should fall under the exemption, under the condition that it fulfills the prerequisite.

There is a discussion in the doctrine if it should be possible to circumvent the patent protection with the exemption when the intent is commercialization. This they mean goes against the intent of the clause and should hence not be allowed. The intent is to protect action that is sporadic, improvised and medical need, and hence not commercialization.[78]

The unclear legal status of the clause means that it would be a risk to use it as a sole mean to reach the market. This means that it would be better used as a leverage tool for a license or collaboration, and only used if the negotiation does not has a positive result. The concept of adjusting the business model would most likely mean that the action would fall under the prerequisite of the clause, but the question is if it is in line with the intent. The fact that it does not go against the formulation of the clause should give some guidance, but this needs to be addressed by the courts to give a definite answer.

[78] Domeij, B (2000), p 228

5. Possibilities to protect the personalized aspect

The question that will be addressed in this chapter is the possibility to patent the personalized feature of the medicine. This feature is of course a product of the intended technical solution, e.g. a biological marker or an algorithm[79]. The biomarker has some interesting opportunities, but the algorithm offers more possibilities to generate protection by having a more general use. This means that the patenting of an algorithm poses a more interesting question. An algorithm as such is normally encapsulated in software, and the software will hence be the focus of this chapter. The choice of patenting software presents some challenges when it comes to generate protection around the intellectual property but it also offer some interesting opportunities, as will be shown below.

5.1 The best manner to protect software

The best manner to protect software is a product of several parameters – e.g. duration of protection, cost, geographical cover and resource demands. The hypothesis means that the cost and the resource demands are the initial key factors, but of course, this does not make the other factors irrelevant in a comparison. This means e.g. that the scope of the protection needs to be balanced against the cost.

The protection also needs to reflect the company's internal capabilities, e.g. competence about IPRs, and external factors e.g. other IPRs, and the intended use. The presumption in this chapter is that IPR knowledge is low and the resources are limited due to being a start-up. The external factors is normally less clear for a start-up since there might be several protections in the pipe-line and the best use is not clarified due to a continues development.

The three options that will be addressed are (1) patent, (2) trade secret and (3) disclosing of information[80]. IPRs have a limited utility to function as a single entity, and needs to be supported by the business model. The intellectual property rights will be addressed in an isolated way to give an easier understanding.

5.1.1 Patent

The possibility to patent software offers some interesting opportunities and challenges. The respect for patents differs between different industries, which have an impact on

[79] An algorithm is a systematic procedure that produces, in a finite number of steps, the answer to a question or the solution of a problem.
[80] Disclosing does not generate any direct protection, but allows the use of copyright. This is of course under the condition that the object is used outside of the company

the value for the protection. The respect for patent is low in the software- and computing industry due to the normal use of the rights as a defensive weapon. Meanwhile, as the right has a central role in the high-tech industries, e.g. biotech and medical device, which result in a higher respect for the protection. This is a result of the higher cost of product development and hence the value of the patent, which result in a higher propensity to enforce the right.[81]

The central role of patents for the biotech industry means that there should be no reason to suspect that this will be less for patents relating to software. This will to some extent be dependent if which industry that will lead the development of the products, i.e. the biotech or software. The unlikely scenario that the software claims the space will most likely result in a lower value for the patents.

5.1.1.1 Benefits with patenting

The key benefits with a patent, or a pending patent, are: (1) a patent allows for a defined technical solution that can be displayed for a venture capitalist to attract capital[82]. (2) A patent, at least in theory, grant exclusive right for the use. This, as presented above, is dependent on how the industry handles the software patents. (3) There can also be a marketing value due to the credence the public has in the patent system. (4) The possibility to generate royalties in the scenario of a license opportunity. (5) The patent system allows for a high flexibility by allowing an application to be withdrawn and/or modified to fit the development of the company.

(6) One patent might have a limited value but a patent portfolio can be used as a defensive tool to balance other actors as well as gaining access, or create, a patent pool.

5.1.1.2 Challenges with patenting

The key challenges with patenting software can be summarized as follow. (1) Patenting process takes a long time; on average three year but it is not uncommon with closer to five years for more complex patents. (2) It might be hard to define the key features in an early stage in the development and hence what is central to protect. (3) A patent requires information to be disclosed, which opens for the possibility of somebody reengineer the solution.

(4) The cost of patents is relatively high, ranging from US$ 50.000 to 100.000 over the lifetime of the patents in the US. This might sums that are hard for a company to carry.[83]

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[81] Myhrvold, N (2010), p 45
[82] Blonder, G (2005), p 3
[83] Blonder, G (2005), p 1

The application cost for covering all EPO countries can reach US$ 30.000 for a 30-page patent. This amount can be lowered by only focusing on protection for the key markets, which would put less constraint on the start-up.[84]

(5) Few venture-capital-backed companies have the resources necessary to defend a patent in the scenario of infringement. This is due to the high cost, e.g. a case with a compensation for damage of 1 million cost on average $US 300.000 to 750.000 to litigate[85]. (6) The patent application requires a resource demanding process, e.g. prior art investigations and drafting.

5.1.1.3 The use of Patent

There are challenges connected with patenting, even if it is possible to mitigate several of them. The cost can be reduced in the initial phase by a good patent strategy that allows for the postponing of expenses. However, this require the company to prioritize what solutions to protect, and on which markets to apply for, to enable the best use of the available resources. The possibility to use the priority dates from a national patent means that the major costs can be delayed for some time, which allows a better understanding of the needs and acquiring more capital.

The long processing time can be speeded up in some countries, e.g. United Kingdom, but it still takes a longer time compared to the options. The faster option only requires that applicant can motivate why there is a need too hurry the process.

There is a developing market for patent litigation insurance, which to some extent can increase the possibility for a start-up to enforce a patent. However, this option is currently limited in geographical scope, come at a relatively high cost, and with a number a disclosures[86].

5.1.2 Trade Secret

Trade secret can be used as possible manner to protect the software, but it will require that the program is located on a controlled server to fulfill the requirements of the law or inaccessible in some other similar manner.

5.1.2.1 Benefits with trade secret

The key benefits with using trade secret are several. (1) Trade secret has no limit in time or geographical area. (2) There are no costs of acquire the protection. (3) There is no requirement to disclose any of the information, and hence makes it harder for other to

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[84] Bassett, R (2000), p 577
[85] Jaffa A. et al. (2007), p 68
[86] Simensky, M et al. (1999), sec 22:4

reproduce the results. (4) The only requirement on the protected information is that it has a commercial value. (5) There is a possibility to commercialize the information e.g. via license. This is according to Bernitz commonly done in several industries.[87]

5.1.2.2 Challenges with trade secret

The key challenges with using trade secret for software can be summarized as follow. (1) It does not award an exclusive right, which might be problematic if somebody else invent the same function and patent it. This would mean that the original user fall under the prior use right[88], which contains several limitations. (2) Trade secret offer a limited protection due to requiring a criminal- or negligent act has been committed to come into force. (3) It requires technical solutions to protect the software to fall inside the scope of the protection, i.e. the information needs to be controlled. (4) The information is hard to control, even if this to some extent can be mitigated through contractual means. [89]

5.1.2.3 The use of Trade secret

Trade secret offers, in general, a good possibility for a start-up due to the low cost and requirements on other resources. However, it is hard o protect a software when the intent is to distribute the material, which makes it unsuitable. It might however still be interesting if the intended use is to place the software on a controlled server.

5.1.3 Disclosing the information

The third viable option is to disclose the information to destroy the novelty. This can be done in two manners – (1) either via using the invention, which protect the software by means of copyright, or (2) to disclose the information in a manner that destroy novelty but does not spread the information. The second option allows some interesting possibilities, but basically has the same technical challenges as trade secret in relation to software when it comes to commercialization. This means that only option 1 will be taken into consideration.

5.1.3.1 Benefits with disclosing the information

The key benefits with disclosing the information are several. (1) It has the same benefits of trade secrets in relation to geographical area, time and resources. (2) The disclosure destroys the novelty and hence the patentability for others. (3) The options allows for the commercial use of the product under the protection of copyright.

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[87] Bernitz, U et al (2007), p 317ff
[88] Prior use right – the use differs between different countries, but can be summarized as a mean of mitigating the effect of first to file system.
[89] Bernitz, U et al (2007), p 317ff

5.1.2.2 Challenges with disclosing the information

The two key challenges can be summarized as. (1) The main mean of protection is copyright, which are associated with several limitations. (2) There is no manner of controlling the information beyond the source code.

5.1.4 Patents offers the largest benefits

There are benefits with all the option, and the choice needs to reflect the business model. The technical challenges in relation with software means that trade secret will not be a viable option due to the requirement to protect the information. Disclosing the information allows for similar benefits as trade secret, and also allows for the distribution of the software but still offer a limited protection. The patent offers the best prospect by allowing the best protection and opportunities. However, there are legal limitations with patenting software that needs to be investigated prior to making a conclusive recommendation.

5.2 The possibility to patent an algorithm

The possibility to patent software is not an easy question. There are software patents in Europe even if this goes against EPC due to an extensive interpretation by EPO. The possibility has previously been clear in USA, but has recently been limited as a result of new praxis.

5.2.1 The discussion around software patent

It is not possible to discus the legal framework around software patents without first having a short introduction to the current debate on the subject. The pro argument be summarized as that there are no different between hardware- and software patents since they both protect an idea. Meanwhile, the main con arguments are that patents hinder economical development in the software industry and that it is an intangible concept.

The pro side argues that there is no difference between protecting an idea that relates to hardware or software when it comes to patent. The underlying reason with the system is to create an economic incentive and dispersion of knowledge and there should hence be no obstacles against software patents. The pro side also holds that the current problem in the field is not due to the patents but instead the inability of the patent offices to understand to the technical field. This has resulted in the granting of patents that does not fulfill the criteria's of novelty and non-obviousness[90].

[90] Graham, P (2006), Internet

The economical argument of the con side is based on the structure of the software industry, which consists to a large degree of SME, especially in Europe. This means that the costs of patenting will put an additional economical constraint on the individual company with limited additional protection and hence slow the development. The patent trend in the industry will also further increase the patent inflation, which will decrease the freedom to operate and further decrease the value of an individual patent.[91]

5.2.2 The legal status in Europe

The legal situation in Europe is currently not clear regarding software. There is an explicit ban[92] against patenting in EPC, but this has not stopped EPO from allowing patents with software as the key feature. EPO does not allow patents on software or source code directly, but they have instead cloaked it in an "apparatus" that implement a claimed method, i.e. an algorithm. It is not the algorithm as such that can be patented, but instead the effect that the software/algorithm generates.

There is a difference to the scope of patentability at the different regional actors in Europe. The parliament has the most restrictive view and does not want to allow for any software patents. Both the commission and council are positive to software patents, but to different degrees, as shown in Figure 12.[93]

There are arguments for both positions. EPO 's position is based on article 27[94] in the TRIP agreement[95], which states that that all technical fields should be available for patenting. The counterargument, which the European parliament used, is that software is not a technical field but rather should be considered an intellectual property. There are no right and wrong in this matter, which should leaves it up to the policy makers to decide.[96] EPO TBA has addressed the issue on a number of occasions, and a selection will be presented below.

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[91] Pellegrinin, F (N/A), p 10
[92] European Patent Convention Art 52 (2) – The following in particular shall not be regarded as inventions within the meaning of paragraph 1: […] (c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers;
[93] Pellegrini (N/A), p 10 f
[94] Art 27 (1) Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. […]
[95] The TRIPS Agreement is Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994.
[96] Pellegrinin, F (N/A), p 5

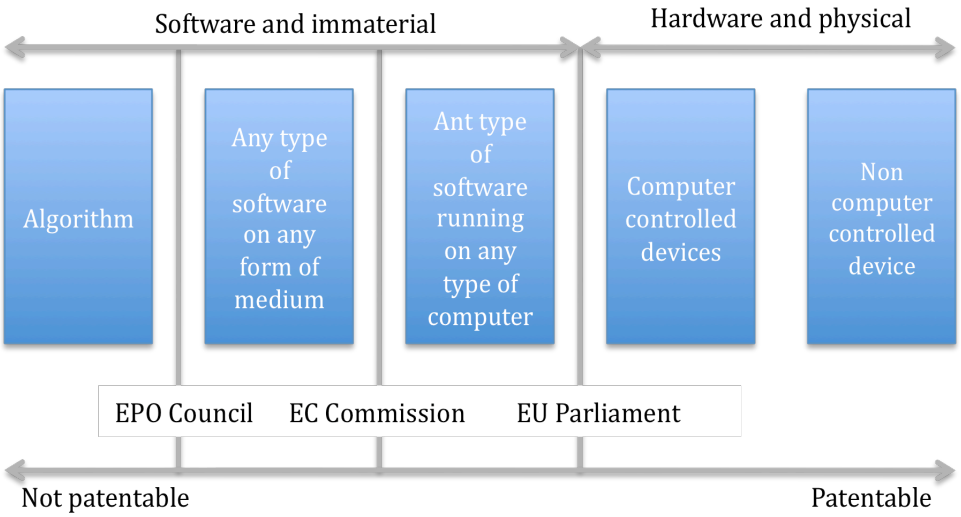

Figure 12 - there a difference in the scope of patentability between the European actors.

5.2.2.1 Cases from EPO

VICOM[97] – created the foundation for patentability of software-based inventions. The case concluded three aspects. (1) The central aspect is not if the underlying invention relates to a mathematical process as such, but if the claims are directed to a technical process. (2) A known computer running a new program cannot be considered the state of the art. (3) A technical process that is carried out under the control of a program should not be regarded as a computer program. The conclusion that can be draw is that the technical process is the central aspect when determining patentability.

Koch and Sterlez X-ray Apparatus[98] – concluded that a mix of technical and non-technical features could be patented. The case also concluded that it was not central to consider the technical and non-technical for patentability, the key was that the invention related to a technical solution.

IBM Computer Program[99] and IBM Program Product[100] – stated that a computer program that it is able to generate a technical effect that goes beyond the normal result during the interaction between hardware and software is patentable.

Auction Method/Hitachi[101] – the board concluded that a method, e.g. software, involving technical means should be considered an invention. The case also stated that a method

[97] T 208/84
[98] T 26/86
[99] T 1173/97
[100] T 935/97
[101] T 258/03

intended to circumvent a technical problem instead of solving it by a technical mean does not contribute to technical character and is hence to patentable.

David Bainbridge summarized the current position from EPO regarding software patents as:

> *"(1) Determine the technical problem which the invention seeks to overcome. (2) Look at the solution to that problem encapsulated in the invention. (3) If it solves the problem by a technical manes it is patentable if those means are new, inventive and capable of industrial application. (4) If it does not solve the problem by technical means that it is not patentable. For example, it may use or modify matter excluded under 52(2), being no more than an automation of non-technical activity. However, the use of such matter designed to be particular suitable for computer-implementation may, arguably, posses a technical character and, if so, the other requirements for patentability should be tested."*[102]

There are good opportunities to patent software in Europe as the praxis and the existence of patents show. The central issue to determine patentability is if the solution produces a technical effect.

5.2.2.2 The general European legal situation

The final decision regarding the software patents in Europe is with the EC court, and national courts of the member countries[103]. There has been no case in the EC court to guide the subject, but there are on the national level. One example is a case[104] from Sweden where the Court upheld a patent that combined software and hardware inline with EPO's decision.

There has also been a case from United Kingdom that might give an indication of where Europe is heading, or at least the current state on a national level. The United Kingdom had previously required software to either produce a new affect outside the computer or solve a problem in the operational issue of the computer to allow patentability[105]. This was changed in the Symbian case[106] where the court rejected the previous

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[102] Bainbridge, D (2007), p. 413
[103] EC court and the national courts are in no manner bound be the decisions originating from EPO. However, it is not uncommon that EPO has an indicative role for the other authorities.
[104] RÅ 1990 ref 84
[105] Cole, Paul (2008), p 1
[106] EWCA Civ 1066 – Symbian Limited and Comptroller general of patents

approach, and argued that the correct way was to look if there where a technical contribution, e.g. an increase in reliability or speed, to determine patentability.

5.2.2.3 Patentability in Europe

The insight that can be drawn from the current situation is that there are good possibility to patent software in Europe, as shown from EPO, UK and Sweden. It is possible to patent the software, however, the safest path would be to patent it in combination with hardware. This combination seems to be accepted to a larger degree, which should allow for more security in the scenario of a higher level of restrictiveness toward software patens in the future.

It can of course be discussed whether it is right that EPO goes against the will of the people's representative in the European parliament. However, EPO is not directly subordinated EU and hence has the freedom to operate within there sphere of responsibility. The question whether it is right or wrong put aside, it is an available tool that should be used when it offers the best solution.

5.2.3 The legal status in the US

The possibility to patent has a stronger legal foundation in the US compared to Europe, but there is a movement toward a more restrictive approach. There is no explicit exemption in conformity with the European; the right is instead derived from the US patent act that has a relative wide scope[107]. The possibility to patent software was established in the patent-eligibility trilogy[108] that established the scope of patentability. This was followed by a handful of cases that expanded the scope of patentability until it reached the widest scope with State Street case, as described below. This has lately been limited in In re Bilski toward a stance closer to the one established by the patent eligibility trilogy.

There is the possibility to file for a provisional patent in USA, which allows for an early priority date but without imitating the application process. The provisional application never becomes public, and is automatically abandoned one year after filling, which means that the real application needs to by filled within this time to allow for the early priority date.

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[107] 35 U.S.C. 101 Inventions patentable. - Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.
[108] The trilogy includes Gottschalk vs. Benson, O'Reilly vs. Morse and Parker vs. Flook

5.2.3.1 Relevant legal cases in USA

State Street vs. Signature Financial Group[109] expanded the opportunity to patent an algorithm. The case established that inventions that involved a practical application that produced a useful concrete and tangible result could be patentable. This wide scope meant that even the result of an algorithm could be patented.

In In re Bilski[110] the US Supreme Court overturned the wide scope established in State Street case and returned to the machine-or-transformation test that had been articulated in the patent-eligibility trilogy. The test can be presented as consisting of two parts to determine patentability – (1) is tied to a particular machine or apparatus, or (2) transform a particular article into a different state or thing.

The impact of re Bilski on the patentability is not clarified at this time, and there is an uncertainty on the impact that it will have on existing and future software patents. A possible benefit of the court returning to a previous patentability test, machine-or-transformation, might be that the opportunity to use old praxis to clarify uncertainties. However, this is not certain based on the interpretations in the Bilski case[111]. There is also additional material to assist in the interpretation of the case. USPTO's board of Patent Appeals and Interference has specified that a general-purpose computer as not being a particular machine, and hence not possible to patent in combination with a software[112]. This has not been tried or referred to in a court at this time, but can provide some guidance when determining the patentability scope.

5.2.3.2 Patentability in USA

The movement toward a more restrictive approach regarding patentability in USA means that a precautious approach is recommendable. This should mean that the best path to patent in USA would be in combination with a specific hardware and use the unit has an add-on to all other functions that can arise during the development.

5.3 The best way to construct an algorithm protection

The best path is to patent the software, i.e. the algorithm, in the short-term. Meanwhile, the long-term benefits are harder to omen about due the legal uncertainty. The software can be patented in combination with hardware to cover against changes and to allow for the possibility to retain protection on several markets. This could be complemented with a patent that includes a "generic" hardware, not a general-purpose computer, and

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[109] 149 F.3d 1368
[110] 545 F.3d 943, 88 U.S.P.Q.2d 1385 (Fed. Cir 2008)
[111] Hulse, R (2009), p 2
[112] USPTO Board of Patents Appeal an Interference – Appeal 2008-1495/6

the software. The second approach would have a higher risk exposure due to the legal situation, but would have larger benefits due to cover a larger scope that allow the possibility to be used as both a defensive tool and better position to generate royalties.

The choice of patent approach is dependent on the intended use. The first option is the better solution if it is only intended to be used in combination with proprietary technology in a defined field, and royalties is secondary. This would allow a stronger position and only control the field of focus. The second option has a wider scope which would be beneficial if the company has activates in several field and/or has a business model of licensing out the technology. This would also enable the possibility of divisional patents.

The recommended initial country to apply in is dependent on the development stage of the technology and the perceived maturity level in the industry. The provisional application in the US offers a good possibility to generate an early protection, but the nature of the inventions normally means that the scope is known at the time of the needed protection. This mean that United Kingdom would be a good option due to – (1) the wide scope of patentability for software, (2) require the application to be written in English which ease the expansion of the protection to other countries in Europe, and (3) they have a relatively efficient system that allows for a speedier process if needed.

5.3.1 The short-term

The short-term benefits are several with the options to patent the software. The key benefits are the increased flexibility and the clearly defined scope of the inventions. The flexibility relates to the possibility to keep all possibilities open, i.e. the option to withdraw the application during the first 18 months and to change the scope of the patent. This allows the modification of the patent to reflect the current need of the company and legal situation. The defined scope of the patents allows to possibility to attract VC capital.

The current changing situation makes it more important to use competent personal when writing the patent application due to the increasing complexity in the field. This also allows for an increased of freedom to operate in a later stage when the company's needs are better defined, due to the more proficient application from a professional.

5.3.2 The long-term

The long-term benefits relate less to the single patent, and more to the capability to create a portfolio. A large value created by a single patent would require the scenario of a key patent, which would but no bet very likely considering the problem to create

generic patents in the field. The benefits of a portfolio, as introduces above, are the possibility to use it as a defensive tool and allowing to access proprietary technologies with cross-licensing.

The last step is to take the theory into action and formulate the patent, but this is only the first phase in the life of the IP of upholding, protecting and monitoring.

6. The commercialization of personalized medicine

In this section, the hypothesis saying: "the price setting opportunities for a small biotech company focusing on personalized medicine, are much greater compared to traditional biotech companies", will be analyzed.

The main focus on this part will be on the possibility for a small biotech actor offering personalized medicine to stand up against the big pharmaceutical companies and to be able to set a product price that exceeds market prices of traditional products and still get the market share they aim for.

6.1 The Intellectual value star

Figure 13 The Intellectual Value Star[113]

In his book "Intellectual Property and Entrepreneurship" Petrusson describes the intellectual value star and its influence on making the firm become a structural platform for the creation of material value, artistic value and moral value from which then financial capital can be extracted.[114] The star symbolizes the activities for value creation and shows that the included processes are parallel, interactive and interdependent. The star is divided into six categories, which will be the underlying basis for the first part of the commercial analysis. The steps symbolized by the six categories are important for

[113] Petrusson U. (2004), p. 249
[114] Petrusson U. (2004), p. 250

the creation of a successful intellectual firm structure in order to continue and move on with the market approach.

6.1.1 Claim intellectual property

The basis of biotech companies and their innovative approach is to develop inventions and to commercialize them in the best manner. Their success is dependent on their ability to control the invention and the underlying IP. Therefore it is crucial for the firm to claim intellectual property and to set up assisting structures and strategies. For biotech companies it is of great importance to have IP protection, as their research and product development often are very cost intensive but reverse engineering can be done quite easily. The company should try to claim the IP in the way that it is valuable even for future use in both internal projects as well as for external use.

6.1.2 Manage human resources and cultures

It is important to take advantage of the resources and cultures that are available within the company. Anyhow, it is necessary to have structures and guidelines in order to make the IP development within the firm successful and to allow for development of the company. It is crucial that everybody in the company knows about how to approach and handle business secrets and innovative information so as not to disclose valuable information that could make control over assets disappear. Another aspect within the company is to manage internal intellectual capital. The employment and caring about employees is of great importance as this creates good working spirit and the innovativeness of biotech firms and the employment of skilled people is of great importance.

6.1.3 Shape the innovation

Continuing on the first two aspects, the firm's innovation has to be shaped in order to fit into the market and satisfy customers' demands. A very important factor is to adjust and construct innovations in a way that they can be protected by the companies' IP and do not obstruct or infringe against other products.

6.1.4 Shape the market

Another important step in the development and commercialization process of companies is the creation of product demand, product recognition, brand awareness, marketing strategies and structures on how to approach the market and how to solve issues such as choice of market and logistics. Theses aspects can be valuable to look into at a very early stage to be able to prepare and react on certain situations. Hurdles such as financial distress, prolongation of expected time to product launch, uncertainties with retailers, etc. can always occur.

6.1.5 Shape the venture

Within the company there is also great potential of intellectual value creation. The designing of incentive structures that nurture the creation of innovative ideas and products is an important variable for the generation of IP and successful products.

6.1.6 Create financial value from intellectual value

With the creation of these structures and the platform-like firm, there will be high potential in creating and extracting financial value from the whole process. The development of a recognized and well-branded firm and the product appreciation on the market will lead the company to success and increase financial income. The increase in intellectual value will also lead to increased financial value.

One aspect that Petrusson also talks about in his book is that we have to learn how to put value to intellectual property in order to use IP for loans and credit, as securitization, etc.[115]. As by now, IP is not used for accounting purposes or to calculate the book value of companies. IP is only included when determining the market value of a company when looking at its commercial potential and its value in comparison to other actors. This is likely to change in the future as companies as for instance RPX Corporation and Allied Security Trust have built up their business around IP and do not have many physical belongings that are of actual value.

6.2 Competitive advantage

> *"Competitive advantage grows out of value a firm is able to create for its buyers that exceeds the firm's cost of creating it. Value is what buyers are willing to pay, and superior value stems from offering lower prices than competitors for equivalent benefits or providing unique benefits that more than offset a higher price. There are two basic types of competitive advantage: cost leadership and differentiation."*[116]

6.2.1 Porter's five forces

The model constructed by Michael Porter is often described as too static in an increasingly fast changing world. The model consists of Porter's main ideas regarding competitive advantage.[117] Anyway, the Porter's Five Forces model serves as a good basis for the analysis of a company's potential on the market and as a checklist of what

[115] Petrusson U. (2004), p. 251
[116] Porter, M (1985), p.3
[117] Stanford University (N/A), p. 2

hurdles there can be. The industry's attractiveness is determined by the sophisticated understanding and rules of competition create the competitive strategy[118].

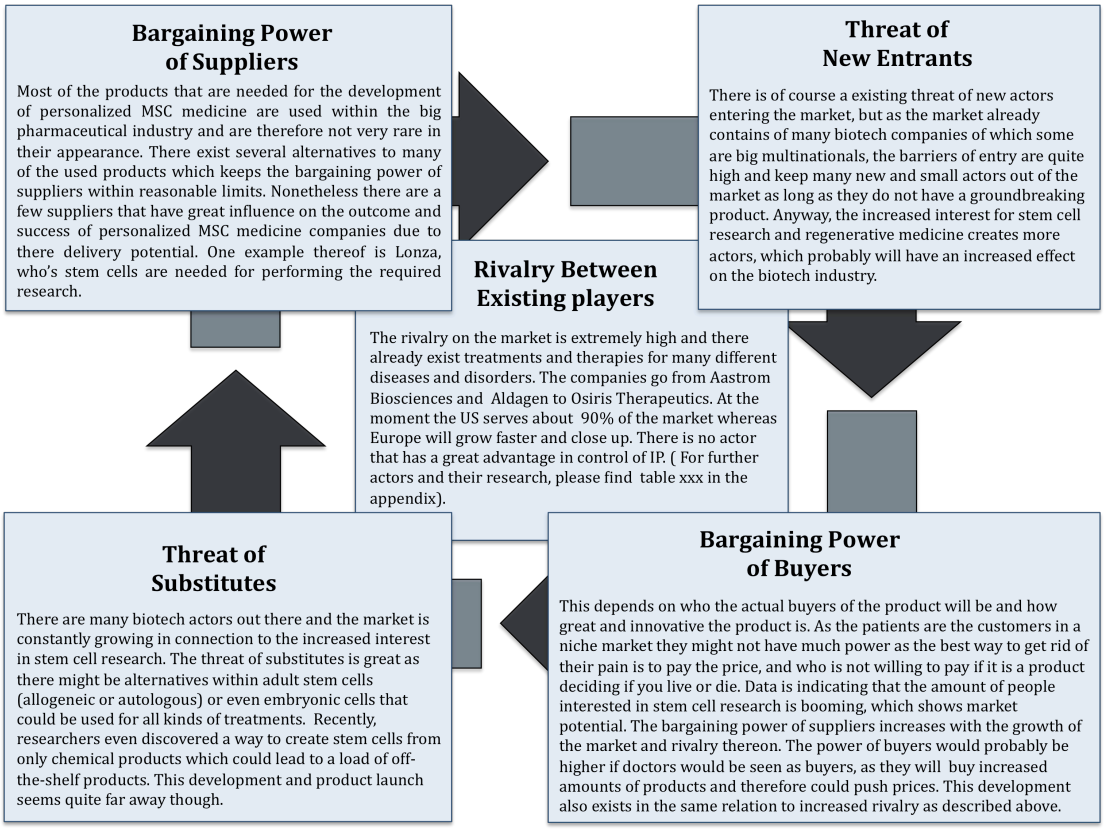

Figure 14 Porter's Five Forces[119][120,121,]

Competitive advantage can be seen as to being created through new and innovative ideas/products that are brought to the market in order to compete in the industry. The competitive advantages shifts at times where competitors are unwilling or unable to respond or just fail to respond to the changing circumstances[122]. In industries were economies of scale play a great role and big actors are involved in market perception, first mover advantage can be of great importance in order to get a head start and to distinguish from the rest.

Some of the most typical causes of shift in competitive advantage are:

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[118] Stanford University (N/A), p. 2
[119] Evers P.,(2009)
[120] Businessballs (N/A), Internet
[121] Quick MBA (N/A), Internet
[122] Stanford University (N/A), p. 3

- New technologies
- New or shifting buyer needs
- The emergence of a new industry segment
- Shifting input costs or availability
- Changes in government regulations[123]

In the life science industry as well as on the biotech market for stem cell research and products, competition is great and it is difficult for a company to generate competitive advantage within this cluster of innovative and competent industry actors. In the following part, an analysis of a small biotech company is made that is doing research and commercializing results within MSCs and personalized medicine.

6.2.2 Advantages and disadvantages of a small biotech company

This section will based on Porters five forces address the pro's and con's for a small biotech company that is active within MSC treatment and personalized medicine.

6.2.2.1 Small biotech start-up vs. Big pharmaceutical company

Advantages:

- Flexibility and ability to make quick changes and to adapt to market needs
- Faster handling times within the company due to less decision steps
- Even a small niche market can be profitable and worth an approach
- Easier to make unnoticed moves such as to generate first mover advantage
- Small companies can often move their research focus faster as they do not need to go through the same amount of entities and switching costs are not as high as for big companies. Big actors can on the other hand often realize projects at a higher pace when actually started due to increased investment potential and resources.
- Less fixed costs

Disadvantages:

- Not likely to have economies of scale
- Dependent on success of first product launch
- Product or company branding is not very developed
- A unknown company has to build trust
- Market and distribution structures are poor developed or non-existing

[123] Stanford University (N/A), p. 3

- Small companies can have difficulties in being spontaneous as they often are dependent on one project. Big pharmaceutical companies can on the other side be risk averse due to high competition on the market and the high costs related to research.
- Difficulties in securing IP from big actors, as it is hard to generate enough money for big lawsuits.

6.2.2.2 Personalized MSC medicine vs. Traditional medicine

Advantages:

- Quality; Improves life expectancy
- Impact; Restoring tissue and re-building the body to regain usual capacity instead of only treating symptoms, reduction of relapse risk
- Patients; Safe treatment, comfort of having especially adapted medicine to the individual's conditions
- Health system; Less relapse, no production loss due to ill or dead people, often shorter treatment time
- Production: There is no need to keep stock of finalized products as every single product is manufactured on demand, whereas traditional medicines are stored in shops to be available of shelf.
- Opportunity costs: Are lower due to regenerative features and decreased relapsing risk.

Disadvantages

- *Ethics: Some people still have ethical issues with stem cell research,*
- *Costs: higher initial treatment costs, but due to its regenerative features the total costs may become less compared to traditional medicine that might be needed over a long period of time.*

6.2.2.3 Autologous MSCs vs. Allogeneic MSCs

Advantages:

- Safe, no side-effects like allergies or rejections
- Psychological advantages for patients to get their own cells back
- Cheaper, due to ensuring of matching of cells to avoid immune reaction[124]

Disadvantages:

[124] Evans P (2009), page 71

- Longer time till treatment due to expansion process
- Risk of patient not developing enough cells at the time needed

> *"It is incredibly arrogant for a company to believe that it can deliver the same sort of product/service that its rivals do and actually do better for very long. It is extremely dangerous to bet on the incompetence of your competitors"*[125]

Porter's saying above should be kept in mind when thinking about the importance to create competitive advantage for the company and its products.

A biotech company that can deploy most of the features described above could generate great competitive advantage on the market. A company that is able to combine the advantages of each category, such as being agile on the market and make use of first mover advantage could have great impact on the market. The first mover advantage could have great effects when entering a market/niche market and attracting a big part of the potential customers/patients. If the company succeeds to tie enough customers to its product before competitors get the chance to enter the market, there will be no incentives to do so as the barriers of entry will be to high and the potential gaining too low. Besides the first mover advantage, a company that commercializes personalized medicine that is adjusting the treatment uniquely to the patient with help of an algorithm and at the same time protects the IP of the innovation has great potential to succeed on the market. Of course there are other factors within the company such as management, marketing and other business related issues that also have to be taken into consideration but having such a great product facilitates success. If the company has succeeded to protect one of its inventions within the personalized medicine market, there is great potential of further success due to correlation of methods and processes used within the medical field.

6.3 Pricing strategy

When approaching the market with a new product there is always the decision to make, which price to set. There are different pricing strategies that can help to set a price that will maximize income but there are only a few that might be of relevancy for a innovative company going into the biotech market. Some of these strategies are:

[125] About.com: Home Business (N/A), Internet

- **Premium pricing** uses a high price when there exist a significant competitive advantage and the product is really unique on the market.
- **Penetration pricing** is used to gain market share and therefore the price is initially very low but increases when the aimed market share is reached.
- **Price skimming** starts out with a high price in order to lower the price when more actors approach the market and the reduced price is need to keep market share.
- **Product line pricing** is used where there are several products and a combination of them would lead to a reduced package price.[126]
- **QALY price setting** is an option that puts the price of the treatment in relation to life expectancy and increased quality of life due to the treatment, which is described in 6.3.1.[127]

Then there is the question of how to get the price. Also here exist different possibilities. These range from setting the price as a multiplication of a percentage of the production costs, adjust the price to competitors prices or to set the price according to customers payment possibilities and demand. Customer's demand and payment possibilities of course has to be taken into consideration for all pricing models but there might be a possibility of approaching different market segments with different capacities.

6.3.1 To take out a higher price for personalized medicine than for traditional medicine

For a young and small biotech company that offers innovative and unique medical products, many of the variables described above are of great importance and need to be considered when deciding about how to go forward when setting a price on the products.

Another aspect that might be interesting to include in the pricing strategy is "quality-adjusted life year" (QALY). QALY is a method that takes the quantity and quality of life generated by healthcare interventions into account and evaluates the benefits that the patient experiences in form of health-related quality of life and survival. This is done by considering the variables mobility, pain/discomfort, self-care, anxiety/depression and usual activities, and assigning each of them a score that indicates the perceived value for one year. 1 QALY, which is the highest, indicates on year of perfect life. O is equivalent of being dead, whereas some health states are considered being worse than being dead.

[126] Marketing Teachers (N/A), Internet
[127] Phillips C. (2009), p. 5

There are even discussions about setting the price of treatments in relation to perceived QALY.[128]

In this case we assume the product to be a personalized medicine based on autologous MSCs and adjusted to each patients personal specifications with the help of an algorithm. A product for the treatment of this disease or injury is highly demanded and the potential market is great. There is claimed IP for the novel parts of the product and its development.

The advantages of a personalized MSC product compared to existing products:

- MSC based products do not only treat symptoms but also restore damaged tissue in order to regain previous functionality
- There is low risk of side effects related to the autologous aspect
- The risk of relapse is very small
- Increased QALY
- The product is freshly produced and adjusted to the patient's needs and not manufacture as a off the shelf product

Even if the market is quite big and there are many companies fighting for market shares, the owning of IPRs for the product and the underlying production methods will be a barrier for other actors to circumvent, especially concerning patents or the inventing of totally different products. Also if current studies have developed cells out of only chemical products which is claimed to have the potential of being used for medical treatment in the future as the researcher Craig Venter and his colleagues have managed to build an exact copy of a cells DNA, which is supposed to have expected phenotypic properties and is capable of continuous self-replication[129].

The combination of product features that are protected by IPRs and being the only actor on the market offering this kind of product the price setting options are great. As the demand for this kind of product is high and the volume of people having interest in this kind of treatment exceeds a start-up's capacity due to limited manufacturing and distribution facilities in the starting period, the initial market approach could be focusing on a niche market with people having high income. They would be willing to pay a bit higher price than common in order to experience the great increase in treatment outcome and gained quality of life. Therefore the premium pricing strategy could be applied for the price setting of this product.

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[128] Phillips C. (2009), p. 5
[129] Gibson D. G. et al. (2010), p. 1

For a future setting, where competitors might have the possibility to offer similar treatments, there is still a possibility to move over to the price skimming strategy and adjust the price to competitors in order to keep market share.

An additional pricing possibility would be to adjust the price according to the amount of expansions that is needed to get enough cells for the price to be adjusted to each patient in the way the treatment is.

7. Conclusion

The aim of the thesis has been to present and clarify the benefits and challenges of using personalized medicine for a start-up company in the biotech sector. The scope was delimited to the genetic sector in general, and MSC in particular, due to the growing importance personalized medicine in this area.

The hypothesis that has been the guiding light in the thesis:

> Personalized medicine offers great opportunities for start-up biotech companies based in Europe to succeed on the market.

The hypothesis allows for a wide selection of subjects to investigate, but the scope was limited to the relation between IP and its current landscape, protection and commercialization. This resulted in four questions that have been answered during the thesis.

- What is the current patent landscape around MSCs?
- What is the best manner of reaching the market?
- What is the best manner to protect the unique aspect in personalized medicine for a small biotech company?
- What would be the main competitive advantage and benefits for a biotech company utilizing personalized medicine?
- In what way does personalized medicine create advantages and possibilities of price setting for biotech companies?

The conclusion will recap the key outtakes from the different chapters chosen for the structure of the thesis, in order to be able to show the aggregated benefits that can be gained from personalized MSC treatment. The theory and analysis together with the conclusion drawn thereof allows for interesting insight in the biotech field but also opens up for further research and possible investigation areas.

7.1 Background

The presented background shows the potential of personalized medicine and MSCs and acts as a foundation to build the thesis on.

The holistic approach of personalized medicine offers several benefits for the patient and the biotech industry. The personalized aspect offers earlier diagnosis possibilities, more proficient therapies and efficient development of new treatments. The two first

parameters offer a better product to the patients, while the last allows the industry to have a higher success rate and address more advanced diseases. There are of course also challenges that need to be addressed. The four key factors are; scientific challenges, economical parameters, public opinion and the ethical dimension. The scientific and economical challenges are becoming less prominent as the acceptance and development progress.

Stem cell treatment has shown to have great potential for regenerative therapy and the treatment of for instance Parkinson's or heart disease. Research within different fields and application areas has already been ongoing for some time and knowledge around stem cells and their potential is growing fast. So is also R&D around potential treatments with MSCs and adult stem cells with embryonic stem cell features. As by now, it seems as if autologous MSC treatment could have great potential on the market for regenerative therapies as it shows that adult stem cells have regenerative features, but in contrast to some other alternative cells, without being rejected or risk of side effects. A successful treatment with autologous MSCs presumes that it will be possible to expand MSCs in a sufficient pace to treat patients within the necessary time period.

7.2 Outcome of study

7.2.1 IP landscape

The three arenas that open the chapter allow understanding of the context that the start-up operates in, and show that the key arena for the start-up, in this stage, is the commercial arena. The commercial arena often has an international focus in the knowledge sphere, which means that there are special requirements on the company and the multinational scope of investigations that need to be conducted in the following sections.

The patent landscape around stem cells is susceptible to patent tickets due to the existence of patents that are broad, fuzzy and approved at an early stage. The quantitative and qualitative investigation into the patent landscape around MSCs showed that there is a stable patent trend in the field and that there still is freedom to operate. This investigation together with other investigations showed that the industry consists of several small actors, which indicate parameters of low barriers to enter.

The analysis of the claims in the analysis did not show any homogenous trends for the field as a whole, but it was possible to identify trends when breaking it down into smaller sections.

7.2.2 Possible solutions to reach the market

The possibilities for a small biotech company to set its foot onto the market are combined with a number of factors and base on the intentions of the company that can be put in connection to the company's business plan. When focusing on personalized autologous MSC treatment, own research will probably be the basis of the product but can also be combined with in-licensed technologies or collaborations. Preferably the company has created IP around the product in order to reduce the risks combined with a product launch.

If not all aspects have been possible to protect and other companies keep the rights to needed IP, the opportunity may exist to make use of an exemption in the patent law, stating that preparations of medicines in a pharmacy that are conducted under a doctor's prescription are allowed and therewith give a possibility to circumvent the blocking patents. If there is a possibility of introducing the product as a medical product and hence avoiding to be stuck in years of test processes for receiving allowance to enter the market it should be investigated. An alternative market approach that can be used in combination with a product launch is the out-licensing of the IP to bigger pharmaceutical actors that have more and faster possibilities to reach the big market.

7.2.3 Possibilities to protect the personalized medicine

This chapter addresses the possibility to protect the personalized aspect of the medicine in the form of an algorithm encapsulated in software. All the available options, i.e. patents, trade secrets and disclosing the information, offer interesting alternatives, but patents showed to have most benefits. This motivated an investigation into the legal requirements for patents in Europe and the US.

The two investigated areas offered the possibility to patent software and hence the algorithm. The legal situation in both regions is in transition. The patenting trend in Europe tends towards being quite liberal, but the legal situation is unclear due to differences in opinions of the decision-making authorities regarding the extent of the patentability. The situation in the US is the other way round as the trend is moving from a very liberal position towards a more restrictive position.

The best patent strategy would be to patent the software in combination with a non-generic hardware to allow a safe position in the case that the situation becomes more restrict. In addition it is worth complementing this non-generic hardware with a more generic hardware patent since this would have larger benefits, but might not be upheld

if the situation becomes more restrict. This of course needs to be adapted to the intended use to the company.

7.2.4 The commercialization of personalized medicine

The commercialization of personalized medicine is dependent on the company's strategy, its structure, and the competitive advantages of the product. During the whole innovation process the company needs to have the claiming of IP together with its innovative ideas in focus. A unique product offering personalized treatment with the patient's own MSCs that gives them the possibility to regain lost medical functionality and at the same time being a safer alternative to existing products, will in combination with the IPRs connected to the innovation create great opportunities for a biotech company. If all necessary features of the aimed product are in place and relevant substitutes to their product are not available, the company has the possibility to reach a market and use a premium pricing strategy. People will be willing to pay for the increased value they experience from this kind of treatment. The focus of the initial phase of the product launch may need to be reduced to a niche markets as a small biotech company does not have the resources or capacities to serve the whole market.

7.3 The combined outcome

The background showed good potential in the sector, which strengthens the hypothesis and motivated the continuation of the investigation and the connected analysis.

7.3.1 The administrative arena

The administrative arena showed the current patent landscape, which indicated for good opportunities in the chosen field. It also showed that there are possibilities to patent the personalized aspect in the form of software. This means that there is a good opportunity to generate protection, which is of great importance in the biotech industry.

There are large regulative demands on a biotech company in general, and genome in particular. This has been investigated in other contexts, and showed no larger obstacles that would create any hinders.

7.3.2 The legal arena

The legal arena has not presented anything that would be an obstacle for proving our hypothesis.

7.3.3 The business arena

The business arena has showed several positive traits. Several of them are general for the whole sector, but the analysis also showed some traits that are more specific for the chosen sector and hence strengthen the hypothesis. The good possibilities to generate a control position via the patent allow for a good starting position, which in turn is strengthened by the possibilities to reach the market. The niche markets in combination with first mover's advantage and a lack of dominating actors allow for a good position to enter the market and gives a good position to claim the needed space. The ability to offer a competitive product directed towards a problem that is not sufficiently addressed will allow a overcoming of the problem facing the genome and personalized medicine. This will in turn also allow for covering the development costs by permitting the extraction of a higher price.

7.4 Final reflections

The hypothesis has been proven to uphold from an IP perspective as shown in the main body and highlighted in the thesis. All the chosen areas of focus have shown opportunities and obstacles, but none that cannot be overcome.

We recommend a biotech company in the MSC field to aim for the personalized field due to the possibilities that can be gained in the commercialization aspect, which are higher in comparison to a traditional path. The IPR's are to a large extent the same, but personalized medicine offers an additional level with the personalization aspect.

There are some areas that would be interesting to investigate in order to make a comprehensive recommendation. The first would be to look into the scientific perspective to indentify in which medical application that the concept, i.e. personalized medicine based on MSCs, would have the largest potential from a commercial and scientific aspect. The second perspective would be to analyze the price strategy, i.e. the level of premium price and if the concept offers additional benefits as for instance personalized pricing. The third perspective that would be interesting to investigate is the commercial landscape to give a more holistic perspective of the potential. A fourth interesting field to do further investigation in would be to analyze how the different countries relate to personalized medicine and the payment thereof, e.g. insurances and social welfare.

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European Patent Convention – 13th Edition

Patent Act – 1967:837

TRIP – Annex C

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IBM Computer Program – T 1173/97

IBM Program Product – T 935/97

In re Bilski – 545 F.3d 943, 88 U.S.P.Q.2d 1385 (Fed. Cir 2008)

Koch and Sterlez X-ray Apparatus – T 26/86

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Symbian Limited and Comptroller general of patents - EWCA Civ 1066

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VICOM – T 208/84

Whittemore vs. Cutter, 29 Fed. Cas. 1120 (C.C.D. Mass 1813)

Appendix A

Patents relating to MSC

1	EP 0592521	Monoclonal Antibodies Specific for Marrow-Derived Mesenchymal Cells	Osiris Therapeutics Inc	Apr 23, 1992
2	EP 1 028 737	Human Mesenchymalstem cells from peripheral blood	Osiris Therapeutics	Jun 1, 1998
3	EP 1082410	Human CD45+ and/or Fibroblast + Mesenchymal Stem Cells	Osiris Therapeutics Inc	Dec 2, 1999
4	WO2006037649	Identification and Insolation of Multipotent cells from non-osteochondral mesenchymal tissue	Cellerix	Apr 13, 2006
5	EP 1361267	Mesenchymal stem cells and their use	Caplan & Haynesmith	Nov 12, 2003
6	EP 1812558	Identification and Isolation of Multi potent Cells From Non-Osteochondral Mesencymal Tissue	Cellerix S. L	Aug 1, 2007
7	EP 1970446	Nuclear Reprogramming Factor	Kyoto University	Apr 7, 2010

Patents relating to treatment

1	EP 2105138	Regeneration and augmentation of bone using mesenchymal stem cells	Osiris Therapeutics, Inc.	Apr 17, 1997
2	EP 1059929	Isolated stromal cells fos use in the treatment of diseases of the central nervous system	MCP Hahnemann University Philadelphia	Feb 24, 1999
3	EP 1572071	Joint Repair using Mesenchymal Stem Cells	Macropore Biosurgery INC	Nov 1, 2001
4	WO2005093044	Mesenchymal stem cells and uses therefor	Osiris Therapeutics, Inc.	Oct 6, 2005
5	EP 1978977	Mesenchymal Stem Cell Isolation and Transplantation Method and System to be used in a Clinical Setting	Christopher Centeno	Aug 2, 2007

6	EP 2110431	Cartilage regeneration using human mesenchymal stem cells	Osiris Therapeutics Inc & Case Western University	Oct 21, 2009
7	EP 2123747	Mesenchymal stem cells for use in treating a pulmonary disease or in reducing scar tissue	Osiris Therapeutics, Inc.	Nov 25, 2009

Patents relating to procedures

1	EP 0874991	Method of selecting a population or subpopulation of a sample utilizing particle and gravity sedimentation	Coulter International Corp	May 11, 1996
2	EP 0869838	Magnetic Separation Apparatus	Miltenyi Biotech Inc	Jun 4, 1996
3	EP 1144026	Blood separation system particularly for concentrating hematopietic stem cells	Biosafe	Dec 24, 1996
4	EP 1893253	Integrated system for collecting, processing and transplanting cell subsets, including adult stem cells, for regenerative medicine	Biosafe	Mar 26, 2003
5	EP 1745125	Cell Culture Environments for the serum-free Expansion of Mesenchymal Stem Cells	Becton, Dickinson and Company	Jan 24, 2007
6	WO2009142770	Compositions and methods for generating musculosketal tissue	The Regents of the Uni of Cali	May 22, 2009
7	WO2009072003	Sample processsing systems and methods	Miltenyi Biotec GMBH	Jun 11, 2009

Appendix B

Actors in the stem cell field

Organization/Company	Cell type	Point of treatment/disease
Aastrom Biotechnologies	Autologous cells	Cardiac and vascular tissue generation
Advanced Cell Technology Inc.	Combination of embryonic and adult cells	Regenerative medicine
Angioblast Sysmtems	Adult SC	Heart failure
Bioheart Inc	Autologous cells	Chronic and acute heart damage
HepaLife Technologies Inc.		Liver
Massachusetts General Hospital	SC	Diabetes
Novocell Inc	Cells	Diabetes
Osiris Therapeutics	Allogeneic cells	Heart disease/MI
Osiris	Adult SC	Diabetes
Pfizer		Alzheimer's, arthritis, osteoporosis
Pluristem Therapeutics	Allogeneic	Degenerative, ischemic and autoimmune

Table 1 Actors in the stem cell field