

# High affinity T cells in immunotherapy of cancer

*An assessment of a business opportunity*

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# Acknowledgements

The work presented here concludes my Master's Degree in Health Administration at the Institute of Health and Society at the faculty of Medicine at the University of Oslo. The work has been performed in the period of June 2008 to November 2010.

The thesis builds upon research performed by Prof Johanna Olweus at the Institute for Cancer Research at Oslo University Hospital. I first learned about her research project spring 2004 when she received the Medinnova's Innovation Award for her project named "Treatment of leukemia with T cells from a tissue-type incompatible donor". She has since then built up a strong group of scientists and lifted her science to a world class level within the field of therapeutic use of T-cells. Working with the commercial aspects of her technology is very inspiring, and I am grateful for being allowed to use her results in this thesis. Thanks also for many good discussions over years, both before and during my work with this Master's Degree.

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# Executive Summary

Cancer therapy exploiting body's immune response has since the introduction of the antibody based drug Rituxan in 1996 been a fast growing market segment. 15 different antibody based drugs had reached the market by 2010, and several of them are commercially very successful. These drugs exploit the so-called B-cell arm of the immune system. Another way of exploiting the immune system is to use cellular based drugs, i.e. the T-cell arm. It has long been known that cytotoxic T-cells can kill cancer cells by specific recognition of peptides on the cancer cells mediated by the T cell receptor. T cells kill by different mechanisms than antibodies and chemotherapy, and thus represent attractive alternative or supplementary therapeutic modalities. Thus, selected T-cells from both donors and the patient himself, as well as genetically modified T-cells, have been tested, also in clinical studies. In allogeneic hematopoietic stem cell transplantation, T cells from the donor can eradicate cancer in the patient, mediating the so-called graft-versus-leukemia effect. This represents the best documented example that T cells can cure cancer, specifically several hematopoietic malignancies. In addition, the group of Steven Rosenberg has demonstrated that malignant melanoma can be treated by T cells expanded from the tumor, so-called tumor-infiltrating lymphocytes, and by genetically modified T-cells. However, although the technology of transferring cancer-targeted T cell receptors has been a subject of research for many years and has been tested in clinical trials, it has not yet reached the market. The slow process towards commercial exploitation of T-cells in therapy may resemble the process for developing antibodies; César Milstein and Georges Köhler developed already in 1975 the hybridoma technique for making monoclonal antibodies (for which they shared the Nobel Prize in medicine in 1984), while the first antibody drug was approved in 1994.

At the Institute for Cancer Research at Oslo University Hospital Prof. Johanna Olweus and her group are working to develop a therapy based on T-cells that can eradicate a specific tissue or class of cells in the patient rather than only the diseased cells themselves. These T-cells will kill not only the cancer tissue as such, but rather any tissue of a specific origin, cancer cells deriving from this tissue included. The rationale behind her approach is that a large number of cell-or tissue-type specific markers are known, in contrast to cancer-specific targets. In addition, she exploits the well-known ability of T cells to vigorously respond to foreign HLA to mount an immune response to such normal proteins that the patient's own immune system does not respond to due to mechanisms of tolerance. Her approach is unique, and may find use in the treatment of cancers where the patient either can live without the specific tissue or class of cells, or where donor transplants can replace the eradicated cells.

Different cellular targets have been, or will be, addressed in Olweus' research, including different subset of blood cells (B lymphoid, myeloid and myeloma), and prostate tissue. Translated into indications her technology may be exploited for therapies for B-cell cancers, such as follicular lymphoma (FL) or chronic lymphocytic leukemia (CLL), multiple myeloma (MM), prostate cancer and induced graft versus leukemia effect after hematopoietic stem cell transplantation, the latter to specifically enforce the anti-cancer effect while avoiding graft versus host disease (mostly applicable in acute myeloid leukemia). The current thesis

evaluates the opportunities, challenges and barriers for establishing T-cell based products in the market for the four hematological indications mentioned above.

Despite the fact that new drugs for all these indications have improved patient outcomes significantly, there is still an identified need for improved treatments for all indications. There are currently no curative treatments for the diseases CLL, FL and MM, and existing treatment regimens are also hampered with serious adverse effects. A major complication in hematopoietic stem cell transplantation causing high morbidity and mortality is graft-versus-host disease (GVHD). This complication is caused by donor T-cells in the transplant graft. Procedures avoiding GVHD while enforcing the graft-versus-leukemia effect, will improve outcome significantly and make the treatment available for a large number who will not tolerate a regular hematopoietic stem cell transplant.

Products resulting Prof. Olweus' research addressing these targets are viewed to create a good business opportunity. There are, however, certain barriers such as market acceptance and regulatory requirements adding risk to a development program. Furthermore, a business model generating good revenues and payback to investors must be chosen. The product development is considered to be complex and to a certain extent groundbreaking as no cellular therapy has yet reached the market. A highly skilled development team and the use of best class external experts is a prerequisite for success. Finally, both regulatory and market barriers should be thoroughly analyzed initially.

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# 1 Introduction

January 1971 the US president Richard Nixon declared in his State of the Union address his war on cancer through his well-known statement:

*“I will also ask for an appropriation of an extra \$100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal”*

This bold declaration was formalized eleven months later through the National Cancer Act promoting discovery of new treatments as well as early detection and prevention of the disease. Thinking back Nixon’s quite ambitious goal of a cure for cancer was in best case optimistic. Cancer constitutes a class of more than 100 *different* diseases characterized by a group of cells growing uncontrolled and often also spreading to other tissue. Cancer is thus not *one* disease, but a set of different diseases sharing certain common features.

Several improvements both in diagnosing and treating cancers have been made over these years, but we are still far away from having a cure for most of them. In fact, the main achievements are made on life prolonging treatments. Cancer remains one of the leading causes of death now 30 years later. Cancer diseases were causing about 13% of all human deaths globally in 2007,<sup>1</sup> and cancer is together with heart disease a leading cause of death in the western world. In the US alone there will be 1,5 million new cases of cancer in 2010 while about 570.000 patients will die from the disease<sup>2</sup>.

Over these three decades society has gained a tremendous knowledge about the disease and mechanisms behind cancers. Cancer drug research has developed from a simple “trial and error” to a biology-driven approach. More or less all drug research in the field of cancer as well as for any other disease has a mechanistic basis for a rational approach. This creates a shift in cancer therapy from the simple approach of killing cells by cytostatic drugs or radiation towards mechanistic and to a certain extent personalized medicine approaches. But the research has not yet fully reached the patients; old cytotoxic chemotherapy regimens still dominate patient treatment.<sup>3</sup> However, there are still high expectations to new therapies for cancer patients.

This increased complexity in the process for identification of new drugs has also consequences on how and where early stage drug development is performed. The pharmaceutical industry itself is of cost reasons neither able nor willing to spend all the resources required to develop the knowledge needed to identify new drug targets and thus new drugs. Therefore a larger part of both the basic mechanistic research and the early stage drug development is performed as part of the academic research, moving costs from industry over to the public budgets.

The pharmaceutical industry is also facing challenges due to loss of income over the next years. Several of the revenue generating drugs will within a few years face generic competition due to patent expiry. Examples are Pfizer's Alzheimer's treatment Aricept, MSD's hypertension medicine Cozaar, and the breast cancer drug Taxotere Sanofi-Aventis. By 2012 many of the large companies will have lost protection on their most lucrative products. The perhaps most significant is the cholesterol-lowering drug Lipitor from Pfizer that reached a sales volume of nearly \$13 billion in 2008<sup>4</sup>.

Three different actions are taken by the industry to reduce the effect of these revenue drains. The first and most pronounced action is mergers. Several larger pharmaceutical companies have recently been through mergers and larger acquisitions to increase portfolio and streamline organizations. The second action taken is to reduce costs. Most of the large companies have over the last decade massively reduced both research and development (R&D) and marketing and sales (M&S) activities. The third is to increase the pipeline through deals with smaller pharmaceutical companies and even academics. Such deals have in fact been quite lucrative for the pharmaceutical companies over the last two years as rising capital for smaller pharmaceutical companies and start-ups have been quite difficult, in particular after the financial crisis in 2009.

Another factor influencing on new technology development is change in the global industrial landscape. Traditional industry and production has moved to countries providing cheaper labor force, leaving the western world with the challenge how to compensate for this loss of income. The answer has been to create value by means of knowledge and creativity. "Innovative" and "knowledge based innovation" are buzz-words used in any context these days, but bottom line is that research and development intensive product development has become the answer from the western world to the changes in the industrial landscape. This also generates expectations to commercial exploitation of results from academic research in both Europe and USA. Here in Norway this resulted e.g. in a change in the legislation ruling the ownership to inventions created by academic researchers implemented in 2003. The expectations from political authorities are that academic research shall generate not only new knowledge and provide education, but also create new product opportunities<sup>5</sup>. An access to innovative ideas and results from academic research should generate industrial opportunities and strengthen Norway's ability to compete on the international arena.

A challenge also potentially influencing on future drug development is the lack of control over health care costs in the western world. Mechanistic based approaches leads to more personalized therapeutic approaches, which again points towards niche indications and thus smaller markets and higher prices for the drugs to be developed. More attention is now given to cost benefit assessments on drugs, with England as a leading force in this development. This may reduce the attractiveness of developing new drugs, in particular niche drugs.

Journal of health economics published earlier this year a paper named "An economic evaluation of the war on cancer"<sup>6</sup>. Their conclusion is in short that the war on cancer so far has been successful based on the following findings:

*“Between 1988 and 2000, life expectancy for cancer patients increased by roughly four years, and the average willingness-to-pay for these survival gains was roughly \$322,000. Improvements in cancer survival during this period created 23 million additional life-years and roughly \$1.9 trillion of additional social value, implying that the average life-year was worth approximately \$82,000 to its recipient. Health care providers and pharmaceutical companies appropriated 5–19% of this total, with the rest accruing to patients. The share of value flowing to patients has been rising over time. In terms of economic rates of return, R&D investments against cancer have been a success, particularly from the patient’s point of view.”*

Whether the picture will be the same for the war against cancer as fought today remains to be seen. At least it seems that more of the burden for early stage drug development is on the academic and thus the public side. One example of publicly financed early stage cancer drug development is discussed further in this thesis.

The immune system has highly specialized cells, the so-called cytotoxic T-cells, responsible for eradicating infected or otherwise harmed cells. Most of the cells that translate into a cancer cell are killed by the body’s own defense mechanisms including these T-cells well before they develop into a serious disease. However, at one stage the mechanisms for suppressing malfunctioning cells and control of cell division loose, and a cancer develops. Therapeutic use of T-cells, so called adoptive T-cell therapy, has long been considered as an option for treating cancers. The research on therapeutic exploitation of T-cells has been a continuous development over years following the improved understanding of cancers and the immune system. The first clinical study of adoptive T-cell therapy was published in 1988 by Steven Rosenberg and his group. Rosenberg injected in his study expanded T-cells extracted from the tumor itself, and obtained good response in 9 out of 15 patients<sup>7</sup>. Rosenberg was also the first to perform clinical studies on genetically modified T-cells, a study published in 2006<sup>8</sup>. Research on genetically modified T-cells for cancer treatment has been ongoing for more than 15 years, and a significant number of academic papers have been published on this subject, also including clinical studies. But the industrial interest for this therapeutic approach is only modest as shown in the discussions below. The lack of interest is likely due to an understanding that the risks associated with the therapy is yet too high.

At the Institute for Cancer Research at Oslo University Hospital prof. Johanna Olweus and her group are working to exploit genetically modified T-cells to eradicate selected tissues or cell types for the use in cancer treatment. This is a publicly financed research project but with the ultimate goal to transfer the results into routine patient treatment. The work in this thesis examines the opportunities, challenges and barriers for establishing products for cancer treatment resulting from this research in the market.

## **2 Methods**

### **2.1 Background**

This thesis builds upon research results generated in prof. Johanna Olweus' group at the Institute for Cancer Research, Oslo University Hospital. She and her group have since 2003 worked to exploit cytotoxic T-cells in cancer therapy, and with the long term goal to get products into clinical use for certain groups of cancer patients.

### **2.2 Objectives for the project**

The project has as the main objective to assess the probability to reach the market for certain products possible to generate based on a novel concept for treating cancer. These products will be developed based on research results generated by Prof. Olweus and her group. Aspects addressed in the assessment include market opportunities, the major barriers, the competitive threat and technical risks.

A separate objective is to identify criteria for choice of first indication to approach in a development program. The possible products further discussed address the cancer indications follicular lymphoma and chronic lymphocytic lymphoma (same product for both indications), multiple myeloma and induced graft versus leukemia effect after allogeneic hematopoietic stem cell transplantation.

### **2.3 Defining the product**

The assessments must be made based upon a thorough understanding of the products to be developed. For this purpose a Target Product Profile (TPP) template developed by the regulatory authorities in USA (FDA) has been used. Interviews with prof. Olweus as well as information from relevant scientific literature have been used to complete the TPP.

### **2.4 Market and medical need**

Under the heading "indication and use" in the TPP we have identified four different indications as potential first targets. To address whether there is a medical need for improved treatment for these indications information from both scientific literature and market intelligence sources have been collected. Aspects such as number of patients suffering from the different diseases, current treatment options and drugs being under development addressing these diseases have been evaluated.

## 2.5 Clinical studies proving safety and clinical benefit

Any new drug including this therapeutic use of modified T-cells requires a regulatory approval to reach the patients outside research based studies. A simple assessment of the differences between the different indications was made comparing a set of characteristics for each of the products. The comparisons were made on

- Expected patient access – evaluated from number of patients and number of ongoing clinical studies
- Expected duration of the studies – made based upon both end point definitions and comparison with timelines for drugs being developed for similar indications

## 2.6 Net present value assessments

Net present values for each indication is calculated based upon certain criteria. Input data for the calculations are:

- A development budget
- A market assessment taking into consideration
  - Price for the product estimated based upon the price for comparable treatments
  - Market development using market data for comparable products
  - Market share expectations based upon competitive threat, user barriers, expected effect and medical need

A base case and best case scenario was established. NPV assessments are often used to evaluate projects and secure investment decisions. However, the NPV assessments made here are rather used to secure a thorough consideration of aspect of the products such as price, market expectations etc. The numbers themselves have minor value except for making comparisons and potentially prioritize between the different indications.

## 2.7 Emerging technologies

Literature studies have been performed to understand the trends in cancer research in general and T-cell based therapy in particular. The results were used both to discuss the competitive landscape and to understand whether prof. Olweus' approach was in line with trends within cancer development.

## 2.8 Other aspects

Both intellectual property protection and a team for developing the technology are important aspects for decisions about commercial exploitation of research results. The aspects are

evaluated in the context of current knowledge and in discussions with employees at Inven2 and prof. Olweus.

## **2.9 Summary and conclusions**

The findings using the methods listed above are compiled to establish an overview over the situation. Recommendations for further work to generate a solid fundament for the decision about commercial exploitation is made based on own experience and discussions with employees at Inven2 and prof. Olweus.

## **2.10 Limitations**

This work was performed based upon the status of the project June 2010. Target development for relevant indications such as prostate cancers was at that stage at an earlier stage, and therefore not discussed in details in this thesis. Further the different indications are assessed equally, ignoring that they are at different stages in the research performed by prof. Olweus. The field is moving rapidly, Prof. Olweus' research included. New information may thus certainly challenge the conclusions drawn in this work.

## **2.11 Sources**

See Appendix 1 for a list of sources used for collection of information.

### 3 The immune system

As basis for an evaluation of the technology to be discussed, knowledge of the hematopoietic and immune system of the human being is advantageous and therefore discussed in brief below. The word hematopoiesis is derived from the two ancient Greek words *haima* meaning blood and *poiesis* meaning *to make*, and simply speaking the hematopoietic system consists of cells deriving from hematopoietic stem cells. These cells are in essence cells found in the bone marrow, lymph system and blood. Figure 1 shows a simplified overview over the hematopoietic system.

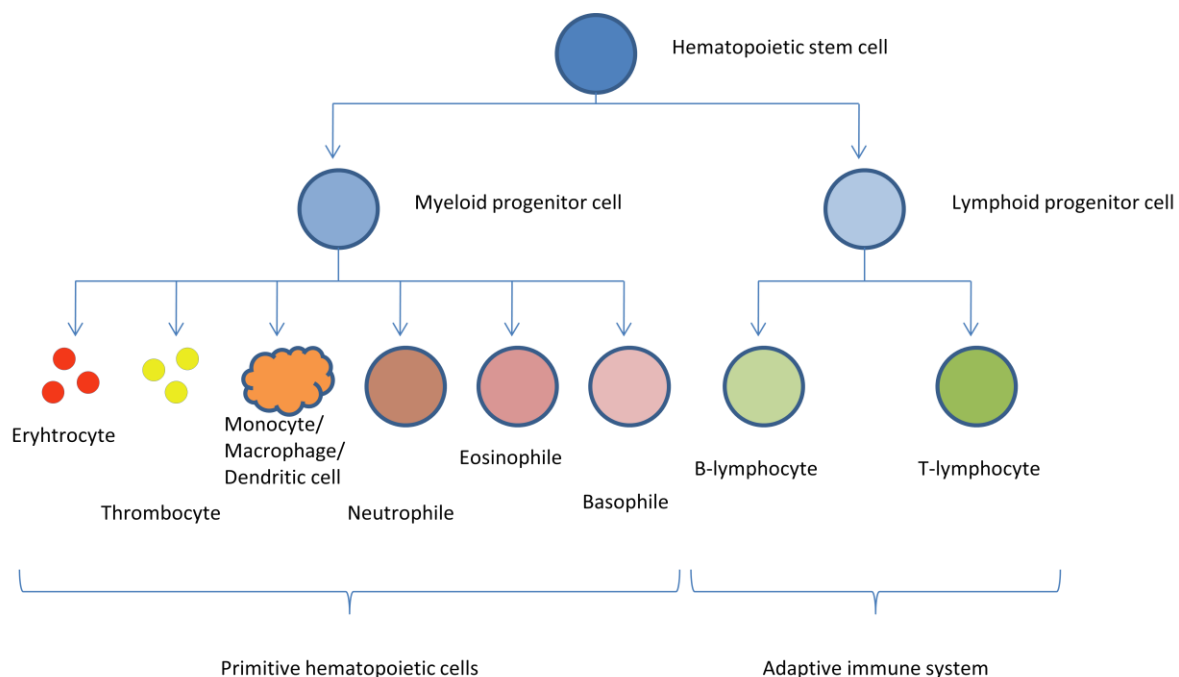


Figure 3.1 Simplified presentation of cells in the hematopoietic system

The hematopoietic system plays a major role in the defense of the body against foreign organisms. The system defending our body against these organisms is called the immune system. In a vertebrate like a human being, the immune system has three different layers with increasing specificity. The first layer is the body surface, being a simple physical barrier. Provided that a foreign organism like a bacterium manages to cross this barrier, the next level of protection is the innate immune system providing an immediate but non-specific response towards an infecting agent. The active cells contributing in the innate immune system is classified as primitive hematopoietic cells as shown in Figure 3.1 above. These cells have a set of different mechanisms for immune responses such as release of protective plasma proteins, inflammation and phagocytosis. These cells are also mature and functioning cells at birth.

The third immune layer is named the adaptive immune system and found in most vertebrates. The key element in the adaptive immune system is the vaccination effect. By the vaccination effect is understood that the body once exposed to a foreign organism, further called a

pathogen, will generate a memory inducing an immediate, specific and strong immune response if exposed to this pathogen again.

Two major classes of hematopoietic cells are hosting this memory, namely the B-cells and the T-cells. The main role of the B-cells is the production of proteins called antibodies. These antibodies react with the pathogen inducing processes destroying it. However, as the technology to be discussed in this context is related to the T-cell response mechanism, only this will be dealt with in more details further in this discussion. There are also three different classes of T-cells in the body, namely cytotoxic T-cells (CD8+), helper T-cells (CD4+) and regulatory T-cells (Treg). These different T-cells have also different missions in the immune system. Although part of what is further described below is related to all T-cells, the main focus will be on the cytotoxic T-cells as the technology to be discussed is related to the therapeutic use of this class of T-cells.

Simply speaking the T-cell memory function is guided through structures on the surface of the T-cells called the T-cell receptors. A T-cell receptor is formed to recognize so-called major histocompatibility complex (MHC) molecules on cell surfaces of other cells in the body. These MHC molecules have the unique property to bind peptide fragments, these peptides either being made by the organism itself (self peptides) or being foreign peptides originating from infecting agents. There are two different classes of MHC molecules, namely class I and class II. Class I is found on most cells in the body, while class II is found on hematopoietic cells only. Cytotoxic T-cells will add to MHC class I, while helper T-cells add to MHC class II. Upon infection of a cell with e.g. a virus, the cell will degrade proteins from the virus into peptide fragments. These fragments will be presented on the cell surface in a complex with the MHC class I molecule, and this complex of a small peptide fragment from the invading organism and the MHC molecule is recognized by a cytotoxic T-cell by means of its receptors. Each MHC-peptide structure has a unique shape and will be recognized only by a T-cell having a receptor with a shape fitting with the specific MHC complex. This is very much like a key – lock type concept, where there are millions of different T-cell receptors and MHC-peptide complex structures and only a few receptors will fit with a specific MHC – peptide complex. When a T-cell by means of its receptors have identified a body cell that presents an HLA – peptide complex that fits with the T-cell receptor and that the T-cell has been primed to recognized as foreign, the T-cell will simply kill the infected cell by means of release of a set of different active molecules thereby preventing that the infecting agent is able to use the cell as a host for further growth. In humans, the MHC system is referred to as the human leucocyte antigen system (HLA) class I and class II. In the further, this term is used rather than MHC.

The T-cells are developed to a stage called naïve T-cells in the thyme. They are then released into the blood stream and lymphatic tissue. But to act as a cytotoxic T-cell it must be activated. This activation takes place when the T-cell is exposed to an HLA structure loaded with a foreign pathogen that matches the T-cell receptor. When a new pathogen invades a body specific hematopoietic cells called antigen presenting cells such as dendritic cells (see Figure 3.1 above) will encapsulate and digest the pathogen, and as described above small peptide fragments of the infecting agent generated through this digestive process are loaded



onto the HLA molecules on the surface of these antigen presenting cells. If a naïve T-cell has a receptor that fits with an HLA – foreign peptide complex a maturing process is initiated activating these naïve T-cells and transforming them into active cytotoxic T-cells. Part of these activated T-cells will proliferate and attack infected cells in the body, while other will reside in the body as “sleeping” memory cells that is activated upon a new infection by the same pathogen organism. These memory cells will then start fighting the new infection as an immediate action through proliferation and cell killing.

Different HLA complexes are found on cell surfaces. As already discussed, the two major classes are HLA class I and class II. While HLA class I is found on all nucleated cells in the body (e.g. all except red blood cells) class II is found primarily on the antigen presenting cells, i.e. macrophages, dendritic cells and B-cells. The class I peptide HLA complexes are recognized by cytotoxic T-cells, while class II complexes are recognized by helper T-cells, further stimulating the antibody producing B-cells. Thus, the cytotoxic T-cells will destroy any infected cell in the body based on the recognition of a peptide-HLA class I complex that the T-cell has been primed to react towards.

In a non-infected cell the HLA molecules are loaded with peptides generated from the body's own proteins. Such peptides are called self-peptides, and own T-cells will not react towards these complexes. Opposite T-cells received from another human such as a donor during a transplant procedure may well react towards self-peptide – HLA complexes and thereby cause complications. Classification and characterization of both HLA type I and type II complexes are thus highly important when selecting a donor in transplantations to secure that donor and patient have a high degree of overlap between their HLA genes. The current invention to be assessed relates to how to exploit a mismatch of HLA in cancer treatment, e.g. exploiting this recipient's reaction against a donor's tissue therapeutically to treat cancer diseases.

## 4 The current invention

The invention to be addressed in this thesis has been developed by prof. Johanna Olweus at the Institute for Cancer Research, Oslo University Hospital. The basis for the idea was to therapeutically exploit differences in HLA genes between donor and patient in the treatment of cancers.

Allogeneic<sup>i</sup> hematopoietic stem cell transplantation (ASCT, also called allogeneic bone marrow transplantation) is a procedure that in certain diseases, such as relapsed acute myeloid leukemia, is considered the only curative treatment. In allogeneic hematopoietic stem cell transplantation a malfunctioning hematopoietic system in a patient caused by e.g. a hematopoietic cancer is replaced through transplantation of hematopoietic stem cells from a donor after removal of the patients own diseased cells. This removal is performed by means of drugs, radiation or both. If not actively removed from the hematopoietic stem cell transplant, this does also contain donor T-cells. Although these T-cells have no specific role in establishing the new hematopoietic system, the donor T-cells have in fact a curative effect, the “graft versus leukemia” effect. This is proven by the fact that the probability for relapse of the cancer significantly increases if the T-cells are removed from the donor transplant before transplantation. Not all of the patient’s hematopoietic stem cells are removed during the initial treatment. And although not primed for this certain T-cells in the donor transplant may react with HLA self-peptide complexes of residual hematopoietic tissue in the patient, then killing the patient’s own residual hematopoietic tissue this also including remaining hematopoietic cancer cells.

However, donor T-cells may also generate a “graft-versus-host” disease (GVHD) by attacking host HLA-self-peptide complexes of other and healthy tissue. This is a major complication upon allogeneic hematopoietic stem cell transplantation, and causes both high morbidity and mortality.

Both the graft versus host and the graft versus leukemia effect are thus explained by donor T-cells attacking a specific tissue of the host through a host self-peptide – HLA complex over-expressed in the attacked tissue. The graft versus leukemia effect is explained by donor T-cells interacting with and killing the host’s remaining hematopoietic cells, while graft versus host disease is similarly T-cells interacting with tissue like skin, liver mucosa and the gastrointestinal tract. The T-cells causing the graft versus leukemia are however different from the T-cells causing the graft versus host effect as they attack different HLA self-peptide complexes.

Olweus’ basic idea is to exploit these mechanisms in a therapeutic setting, and her research has therefore been directed towards generating tissue or cell type specific T-cells. These T-cells are made to kill a specific tissue or a cell type based on the identification of an HLA – self peptide complex unique for or overexpressed in this tissue. Injecting such T-cells into a

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<sup>i</sup> Allogeneic transplantation means that the patient received a transplant from a donor. In case the patient’s own tissue is removed and transplanted back, the process is called autologous.

patient will ideally result in a complete removal of the attacked tissue or cell type without affection of other tissue or cell types in the body thus copying the graft versus leukemia effect.

As mentioned the donor and host are genetically typed to secure a high degree of match before a transplant is performed. This is done to prevent immunological reactions upon the transplantation. In general one HLA mismatch is accepted as a donor matching completely may be hard to find. In the Caucasian population<sup>i</sup> about 50 % has the so-called HLA-A2<sup>9</sup> gene and thus the belonging protein expressed on the cell surfaces, while the other half does not. An HLA-A2 negative donor may e.g. be accepted for an HLA-A2 positive host provided that all other HLA genes match. This difference is what prof. Olweus has exploited as a mechanism for a selective T-cell attack on self-peptide - HLA-A2 positive cells.

A simplified procedure for the identification of a T-cell receptor specific for a self-peptide HLA-A2 complex as developed by Dr. Olweus is presented in Figure 2. This identification of an active receptor is the first step in the generation of a tissue specific T-cell.

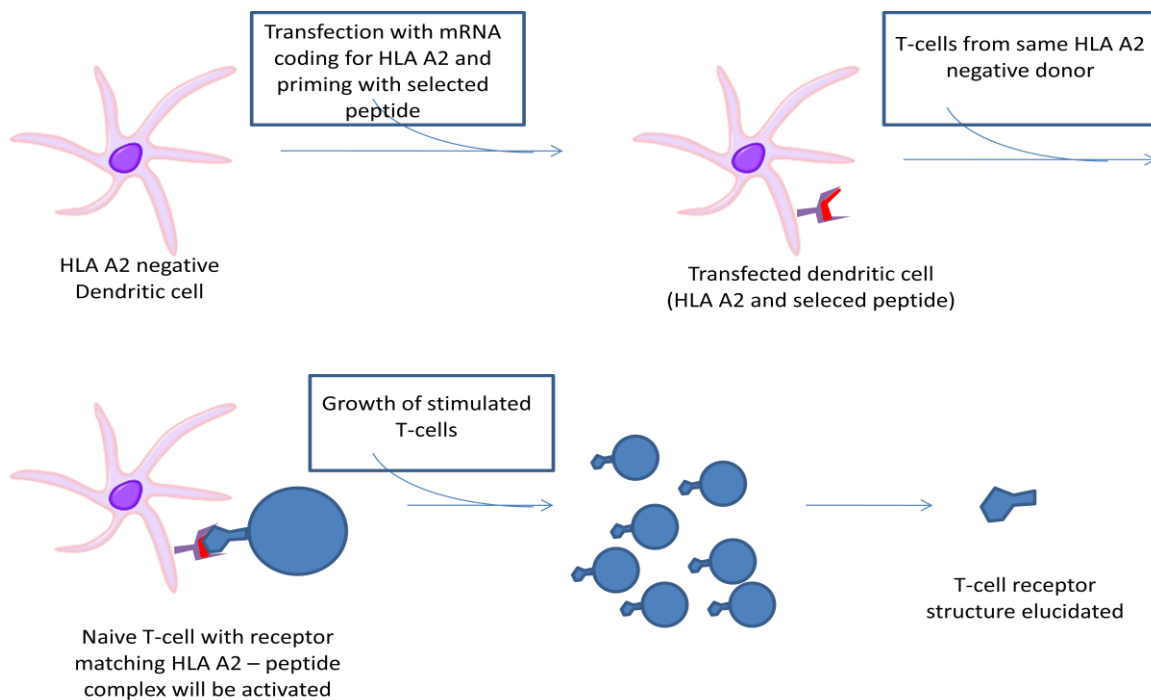


Figure 4.1. Method for determining T-cell receptor structures

The steps in the process are as follows:

1. The first step is the identification of a self peptide being specifically expressed or alternatively over-expressed on HLA-A2 in the targeted tissue or on the target cell type. This may e.g. be fragments of specific proteins found on the surface of the cell or tissue. A lead peptide optimization process is included in this step, being a

<sup>i</sup> The term Caucasian denotes light skin population (the race or phenotypes) of Europe, North Africa, the Horn of Africa, West Asia, Central Asia, and South Asia. The population is e.g. recognized by a high expression of HLA-A2, or to be more precise the HLA-A\*0201 gene.

combination of an iterative testing in cell systems and a theoretical approach for identifying binding properties to the chosen HLA. This step is not visualized in Figure 2.

2. In step 2 a dendritic cell isolated from an HLA-A2 negative person is transfected with mRNA<sup>i</sup> coding for HLA-A2 making these cells expressing HLA-A2 proteins on their surface. Further these cells are also loaded with the chosen peptide known to bind to the HLA-A2 molecule (step 1 in Figure 4.1.) .
3. In step 3 the dendritic cells are cultivated together with T-cells isolated from the same individual. T-cells having a receptor matching the peptide HLA-A2 molecule complex are in this process stimulated to grow and further isolated.
4. In the last step the T cells reactive with the specific HLA-A2 –peptide complex are isolated and potentially used directly for treatment of the cancer patient (hereafter referred to as Alternative 1, not demonstrated in the Figure 4.1). Alternatively, the T cell receptors of the specific T cells are isolated and the structure of the receptors determined. The most efficient T cell receptor is selected in vitro and is subsequently genetically transferred to patient T cells of HLA-A2 positive patients (hereafter referred to as Alternative 2). Through this process a tissue or cell type specific receptor is then identified and can be used in a therapeutic setting for HLA-A2 positive patients.

This is an extremely simplified presentation of the process. The research process is very complex and does for example include procedures for testing different T-cells in different assays to prove efficacy towards cell killing. Where the research is as of today, two T-cell receptors targeting B-cells through expression of peptide fragments of the B-cell specific receptor CD20 has been identified by prof. Olweus and her group. Figure 4.2 below demonstrates how a patient is treated by means of T-cells with an identified receptor for a given peptide HLA complex:

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<sup>i</sup> A defined structure of the nucleic acid RNA coding for the synthesis of the protein HLA-A2 is introduced into the cell. The cell will start a synthesis of the protein using the introduced RNA and further transport the synthesized HLA-A2 to the cell surface.

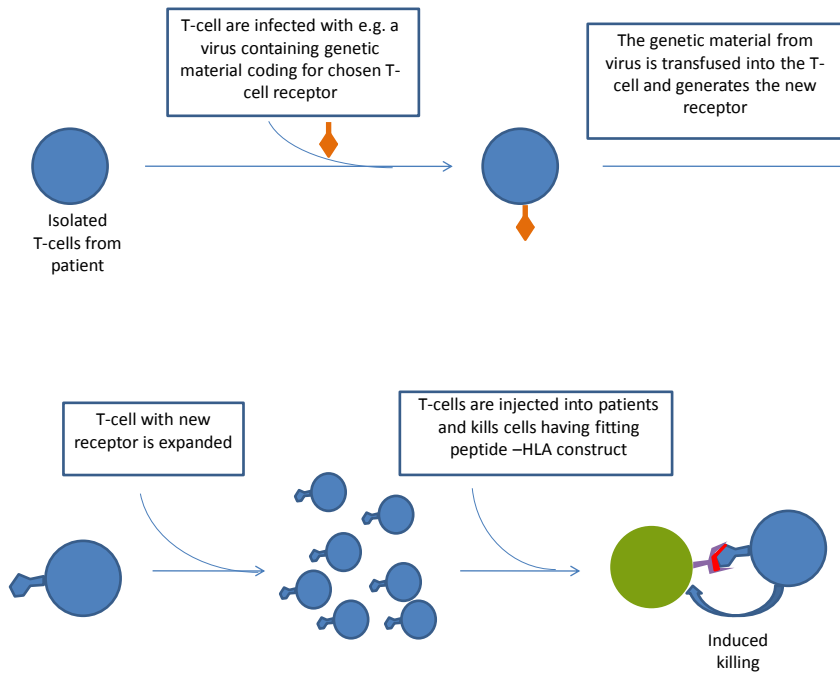


Figure 4.2 Simplified picture of the treatment procedure to be established

The therapy is directed towards a cancer disease located in a specific tissue or cell type. A requirement for treatment defined by this invention is that the patient either can live without the tissue for a shorter or longer period, that the tissue is able to regenerate or that it can be replaced through transplantation.

The treatment procedure consists in rough terms of the following steps:

1. T-cells from the patient are isolated.
2. Genetic material for transcription of a tissue specific T-cell receptor is introduced into the T-cells; likely through viral infection though other methods can also be used (further named genetic modification).
3. The T-cells are expanded and cultured to generate a population of healthy, activated T-cells having the selected receptor on the surface.
4. The T-cell culture is intravenously injected into the patient to attack and kill the diseased tissue or cells.

As discussed below, the procedures performed are in general more complex and also likely combined with other drugs or treatment regimens.

# 5 The product and a general target product profile

Initially, the way to commercially exploit the research results was considered to be sales of peptide based kits making highly specialized hospitals able to generate their own patient specific T-cell cultures through a procedure including the use of donor dendritic cells. The active T-cells were then supposed to be donor T-cells selected through a cultivation procedure as defined by the first two steps of Figure 4.1 above. However, in 2006, Rosenberg et al performed the first human trial with genetically engineered T-cells expressing T-cell receptors identified to attack the melanoma cancer specific antigen MART-1.<sup>10</sup> The patient’s own T-cells were collected and then genetically engineered to express this new receptor. 17 patients received such genetically engineered T-cells, whereof two of these demonstrated a sustained regression of the disease. This study is considered a major break-through in T-cell based cancer treatment.

And for Dr. Olweus this study had an important impact as it pointed towards a simpler procedure for exploitation of her ideas, namely genetic modification of the patient’s own T-cells rather than selection and cultivation of a donor T-cell population. The product is now considered to be either a vector to be incorporated into a patient’s isolated T-cells at the hospital before expansion and reinfusion or frozen suspensions of genetically modified T-cells produced in a specialized, commercial laboratory facility.

## 5.1 Product opportunities

Four different product opportunities are possible based upon prof. Olweus’ research as summarized in Table 5.1 below.

Table 5.1 Product Opportunities

Product	Product description	Comments
1) Magnetic bead based kit for selection of donor T-cells	HLA – peptide tetramers on micrometer range magnetic beads for extraction of T-cells from donor’s blood. The HLA – peptide tetramer structure is specific for selection of T-cells showing affinity for the cell or tissue type being the therapeutic target.	The simplest possible product for the exploitation of the technology is a kit consisting of HLA – peptide tetramers bound to magnetic microparticles. The particles are used to extract donor T-cells with high affinity for the target HLA – peptide complex from donor’s blood. These T-cells are after collection expanded and injected directly into the patient. No genetic modification is needed.
2) Kit for selection of donor T-cells <sup>i</sup>	- Genetic material (mRNA) coding for HLA-A2 for transfection into a mismatched donor’s dendritic cells. -Peptide for expression on HLA-A2 of donor -Necessary tools and reagents for expansion and isolation of T-cells included HLA-peptide tetramers.	This product does not involve genetic modification of cells to be given to the patient. Rather, the product is used to select and expand T-cells from a mismatched donor. These T-cells will express receptors selected based on their “Graft Versus Leukemia”-effect. The procedures of selection and expansion of T-cells will be performed at the hospital.

<sup>i</sup> As discussed this was the initial product idea.

Table 5.1. Cont.

3) Kit for genetic modification of the patients own T-cells including the genetic material coding for a cell or tissue specific receptor	Genetic material (DNA, viral vectors or transposon) and belonging reagents for the transfection or transduction of this material into patients own T-cells.	Patient's own T-cells are isolated, expanded and transfected with vectors coding for the selected receptor. All handle of blood samples and T-cells are performed at hospitals.
4) Genetically modified T-cells expressing a selected receptor	A preparation of T-cells either as a fresh suspension or a frozen suspension to be thawed at the clinic,	Patients own T-cells are collected and sent to a certified lab/factory. This factory is likely part of an operating company commercially exploiting the research results. The T-cells are genetically modified, expanded and frozen before transfer to the hospital treating the patient.

Products 1 and 2 in the table do not involve genetic modification of the T-cells; only selection and optionally proliferation. In opposite, products 3 and 4 do involve genetic modification. Common for the alternatives 1, 2 and 3 products sold to specialized hospitals preparing their own T-cell suspensions, while only product 4 is sold as a preparation provided as a suspension ready for injection.

In the further discussions, main focus is alternatives 3 and 4. However, product 1 may also certainly become feasible as improved international bone marrow registries increase both availability and secure and simple identification of donors.

## 5.2 Target product Profile

United States Food and Drug Administration (FDA) has developed draft guidelines for a presentation of a new drug for the agency by means of a so-called Target Product Profile (TPP). This TPP is made to give a rapid and efficient insight into a product's properties and use as stated in the FDA Guidelines: "Ideally, the TPP provides a statement of the *overall intent* of the drug development program, and gives information about the drug *at a particular time* in development."<sup>11</sup>

The FDA profile cannot be used directly as there are several aspects that are not known as of today. Therefore only those elements where information is available are considered.

The choice of product to develop does not affect the fact that what will be injected into the patient is a suspension of T-cells. Table 5.2 gives a preliminary Target Product Profile of a T-cell suspension of genetically modified T-cells mainly set up according to the draft guidelines recommended by the FDA.

Table 5.2 Target Product profile for genetically modified autologous T-cells.

<p>Indications and Usage</p>	<p>Treatment of cancers. Likely given as consolidation or adjuvant therapy after removal of bulk cancer with state of the art cancer treatment procedures. Preferably adjuvant therapy after 1<sup>st</sup> and 2<sup>nd</sup> line treatment, alternatively consolidation therapy for B-cell cancers, likely the indications follicular lymphoma, chronic lymphocytic leukemia or multiple myeloma. Alternatively for induced graft versus leukemia effect after hematopoietic stem cell transplantation. The treatment will be then given in conjunction with a T cell-depleted hematopoietic stem cell transplant. For further information about indications, see Section 6.</p> <p>The injected T-cells may be constructed to generate a permanent pool of T-cells including memory cells. This will provide a sustainable effect. Alternatively, the T-cells may either decay or contain a suicide mechanism enabling removal of the cells by means of medication.</p>
<p>Dosage and Administration</p>	<p>Intravenous administration of a suspension of genetically modified and expanded T-cells. Patient's T-cells are isolated after e.g. leukapheresis and genetically modified by a viral vector or transposon/sleeping beauty construct coding for the active receptor (Product alternatives 3 and 4). The modified T-cells are further expanded to a therapeutic dose. Between leukapheresis and treatment, patients may undergo an additional chemotherapy treatment depending upon their disease. Repeated injections are expected, but will be based upon the ability for the T-cells to a) proliferate in vivo, b) generate stable memory cells, and c) their ability to kill target cells. Dose must be determined in clinical phase 1/2 studies, but one dose is likely in the range <math>10^7</math> – <math>10^{10}</math> cells/m<sup>2</sup> based upon performed studies.<sup>12,13</sup></p> <p>If donor-derived T cells are used (Alternative 1), very low numbers might be sufficient, and the T cells are not necessarily expanded following isolation and prior to infusion. A similar approach has been successfully used for treatment of CMV infection in transplanted patients.</p>
<p>Dosage Forms and Strengths</p>	<p>Injectable suspension stored in and administered from bags, strengths likely in the range of <math>10</math> – <math>30 \times 10^6</math> cells/ml<sup>14</sup>.</p>
<p>Contraindications</p>	<p>HLA-A2 negative patients. Other contraindications needs to be further elucidated when target indication is chosen.</p>



Table 5.2 Target Product profile (Cont.)

<p>Warnings and Precautions</p>	<p>To be decided upon when clinical protocols are designed after decision upon indication. Based on protocols from similar studies it is expected that precautions should be taken if the patient has undergone allogeneic transplantation, have compromised immune system or cardiac failure.</p> <p>A permanent pool of T-cells continuously whipping out a sub-population of B-cells may cause increased risk of cancers and infections. However, experience from Rituximab treatment shows that there are few safety concerns even with long term B cell depletion<sup>15</sup></p>
<p>Description</p>	<p>A suspension of T-cells in a fixed concentration range further to be determined but likely in the range 10 – 30 x 10<sup>6</sup> cells/ml. Suspension medium will be human serum albumin (HSA), phosphate buffered saline (PBS) or other media used for intravenous injections.</p> <p>Autologous T-cells will be collected based upon three selection criteria with specifications to be determined. These criteria will be a) CD8 positive, b) grade of maturation, and c) receptors expressed initially. It might be preferable to select T cells that have a defined specificity, such as anti-CMV or EBV. The collected T-cell sample is likely polyclonal</p> <p>T-cells are modified and expanded either at the hospital or at a specialized factory. In the latter case, the blood will be shipped to the factory as a frozen preparation.</p> <p>After genetic modification and expansion, each T-cell will express two different receptors, the originally expressed and the inserted one.</p> <p>Donor-derived T cells do not need expansion in vitro as they are expected to expand in vivo (Alternative 1)</p> <p>The T-cells will be counted and phenotyped, i.e. the cells will be characterized with respect to a set of surface markers including the inserted T-cell receptor. A set of possible markers are given by DiGusto 2006<sup>16</sup>, but further work to determine markers and release criteria is needed.</p> <p>The suspension will also be characterized with regards to impurities arising from the production process or degradation and sterility/presence of virus and other pathogens</p>
<p>How Supplied/Storage and Handling</p>	<p>Either frozen suspension at shipping (factory prepared suspensions) containing the cryoprotective solvent DMSO, which is removed by washing at the hospital in a standardized procedure before injection.</p> <p>Or alternatively fresh suspension (hospital prepared suspensions).</p>

The product sold may alternatively be a kit for the generation of genetically modified T-cells at the hospital (Product 3 in Table 5.1). A Target Product Profile will then describe the kit used for the preparation of the suspension. Table 5.3 is a simplified product description for the vector used to genetically modify the patient’s T-cells. This product will also be used by a vendor of suspensions of genetically modified T-cells described as product 4 in Table 5.2. A thorough documentation is needed for this vector independent of whether the user is a vendor of T-cell suspensions or a hospital.

Table 5.3. Simplified Target Product Profile for genetic material to be used for the modification of autologous T-cells.

Description	A DNA transfection or transduction agent (a viral vector or more likely a transposon/sleeping beauty construct DNA coding for the $\alpha$ and $\beta$ chain of a T-cell receptor. As the receptor consists of two protein chains, the genetic material must code for both of these. These protein chains are likely modified from naturally occurring structures, both to optimize binding properties of the receptor itself and to secure correct pairing <sup>i</sup> and optimal expression rate of the receptor. This is obtained through murinization of the chains, introduction of additional cysteine bonds between the chains and codon optimization etc <sup>17,18</sup> . The kit will also contain means for extracting and characterizing the cells (e.g. HLA – peptide tetramers).
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The Tables 5.2 and 5.3 above is defining different product opportunities. But as an end result this also defines two fundamentally different business models for a company exploiting the research results. One is to sell a product which may be considered as a drug, while the other is production and sales of blood products.

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<sup>i</sup> A T-cells have before modification already one receptor. As both the original and the inserted receptor contains an  $\alpha$  and a  $\beta$  chain, four different receptors may be generated. Thus the risk that receptors with unwanted and unpredictable properties are generated is quite high. Certain modifications of the inserted receptor are therefore needed to secure that combination of artificial and original receptor chains are avoided.

# 6 Indications and medical need

## 6.1 Background

Use of the patient's immune system in the treatment of cancers has received a substantial attention over the last decade or so. Both use of antibodies, therapeutic vaccines and adoptive T-cell therapy are concepts that have been exploited, but so far only antibody therapy has made success in the market (see also Section 9.1). Therapeutic cancer vaccines designed to stimulate the body's own immune system to attack cancer cells have also been developed, but so far only one such product has entered into the market. The cancer vaccine Provenge from the company Dendreon was approved for the treatment of prostate cancer late April this year. Adoptive T-cell therapy, meaning therapy by means of either own or donor T-cells has also received some attention, but is not yet commercially exploited. The Swedish company Sentoclone is currently in phase II with T-cells collected from the sentinel lymph node<sup>i</sup> and further expanded and reinfused. Adoptive T-cell therapy is hampered with certain challenges such as lack of cancer specific antigens and also risks associated with graft versus host disease.

Therapy by means of genetically modified cytotoxic T-cells may in part circumvent certain of these drawbacks of adoptive T-cell therapy, and has thus also received attention from well recognized cancer research groups (see also Section 9.2). The work performed has mainly been academic, although a few industrial actors have started to look into the technology. Several clinical trials have also been run using both different T-cell technologies and for different cancer indications.

As further discussed in Section 9.2 there are in essence four different major approaches for therapy by means of genetically modified T-cells using either T-cell receptors (TCRs) or chimeric receptors (CARs):

- Tissue or cell type specific T-cell receptors (the "Olweus approach")
- Cancer cell specific T-cell receptors (i.e. receptors targeting cancer specific antigen targets)
- Chimeric antigen-specific receptors (CARs; i.e. artificial receptors where the ordinary T-cell receptor is replaced by a structure resembling a monoclonal antibody. These receptors do not target HLA structures but rather other cell surface proteins. The targets may be tissue specific or tumor specific)
- T-cell receptors identified to target minor histocompatibility antigens

Since the therapies being exploited by prof. Olweus are tissue or cell type specific the use is limited to diseases in HLA-A2 positive patients where one specific organ or a class of cells can be removed without causing danger or serious harm to the patient, or where the

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<sup>i</sup> The sentinell lymph node is the lymph node draining the tissue surrounding a cancer and thus the node first receiving metastatic cells from the tumor.

organ/cells can be replaced by transplantation from an HLA-A2 negative donor. The most important areas thus seem to be:

1. Killing defined hematopoietic cell lineages, including B cells and myeloid cells. This treatment is of relevance for lymphomas, leukemia and myeloma (B cells) and acute myeloid leukemia (myeloid cells). The treatment may or may not be performed in conjunction with a T cell-depleted hematopoietic stem cell transplant, depending on the disease. Thus, patients can do without B cells, but not without myeloid cells.
2. Killing residual tissue after e.g. surgical removal of an organ due to cancer. This is limited to diseases where the whole organ may be removed with or without transplantation. Examples are
  - a) Kidneys, i.e. renal cancers with transplantation from donor
  - b) Prostate
  - c) Ovary cancers
  - d) Liver cancer with transplantation from donor

So far the research program has been directed towards hematopoietic diseases only, and thus only these indications are discussed below.

Two major separate important results have been obtained by Olweus so far. A set of T-cell receptors designed to recognize HLA-A2 expressing peptide fragments of the surface protein CD20 specifically expressed on B-cells have been made, and T-cells transfected to express these receptors have proven capable of killing B-cells expressing CD20 in *in vitro* test assays. Also tumor B-cell lines from chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) patients were efficiently killed. But in addition to the identification of these T cell receptors technology has been established providing tools to develop new receptors directed at novel targets at a much higher speed than what has been obtained for the CD20 peptide specific receptors, thus encouraging research for new targets.

The indications considered include in addition to chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) as mentioned above also multiple myeloma (MM) and acute myeloid leukemia (AML), in conjunction with a T cell-depleted hematopoietic stem cell transplant (induced graft versus leukemia effect avoiding graft versus leukemia).

A product for the indications follicular lymphoma and chronic lymphocytic leukemia may also find use in other B cell lymphomas and possibly acute lymphocytic leukemia thus expanding the market significantly. However, these indications are not addressed in details below as they are not considered as a first indication for development. A variety of other cancer diseases might be treated using the same approach but with different targets and thus products. A number of novel targets are in Prof. Olweus' research pipeline, and an example of a promising indication is the treatment of prostate cancers, not discussed further here.

Exploitation of the T-cell therapy technology for a target indication requires that there is a clear medical need. This is further assessed for each chosen indication below.

## **6.2 Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia – CD20 peptide treatment.**

As discussed the receptors identified so far are selected based on their ability to kill B-cells expressing peptide fragments arising from CD20, a cell surface protein unique for early stage B-cells. CD20 as a therapeutic target for B-cell tumors are well recognized. The blockbuster drug Rituxan with the active drug substance being an antibody named rituximab was first approved in 1997 for B cell non-Hodgkin lymphoma resistant to other chemotherapy regimens<sup>19</sup>, and is today first line treatment of certain subgroups of Non-Hodgkin's lymphomas and also chronic lymphocytic leukemia. The antibody rituximab binds to the CD20 protein thereby inducing cell apoptosis.

### **6.2.1 Non-Hodgkin's Lymphomas - Follicular Lymphoma**

Lymphomas are cancers recognized by their origin in the lymphatic system. They are either derived from B- or T-cell lymphocytes that proliferate uncontrollably to form tumor masses. These tumors are typically located in the lymph nodes, but can also spread to other parts of the body. The lymphomas are a large group of tumors further subdivided in several subclasses. The simplest classification is in Hodgkin's or non-Hodgkin's lymphoma. National Cancer Institute (NCI) estimated through their statistics (SEER) that 74030 new cases of lymphomas would be diagnosed in USA in 2010, whereof 8490 is Hodgkin's and 65540 is Non-Hodgkin's<sup>20</sup>. An estimated number of 601180 people were living with or were in remission from lymphoma in USA in 2009. Of these 148460 were diagnosed with Hodgkin lymphoma and about 452,720 with non-Hodgkin lymphoma<sup>21</sup>.

Non-Hodgkin's Lymphoma (NHL) is the fifth most commonly diagnosed malignancy in USA and accounts for 4% of all cancers diagnosed. However, NHL is further classified in a series of subtypes. One important differentiation is whether the disease is T-cell or B-cell based. Another differentiation is whether the disease is aggressive or indolent. Table 6.1 below

summarizes characteristics of the most important subtypes of NHL as classified by WHO<sup>22</sup>:

Table 6.1. NHL subtypes as classified by WHO.

NHL Subtype	Cell type	Proportion of NHL incidence (%) <sup>23</sup>	Median age at diagnosis (years)	Aggressive (A) or indolent (I)	Forecast incidence, major markets*
Diffuse large B-cell lymphoma (DLBCL)	B	31	64	A	35101
Follicular lymphoma (FL)	B	22	59	I	29638
Mantle Cell Lymphoma (MCL)	B	6	63	A	8680
Small Cell Lymphocytic Lymphoma (SLL)	B	7	65	I	8680
Mucosa-Associated Lymphatic Tissue (MALT) Lymphoma	B	7.5	60	I	9126
Peripheral T-Cell Lymphoma (PTCL)	T	6	61	A	5105
Burkitt lymphoma	B	2	not available	A	not available

\*US, Japan, UK, France Italy, Germany and Spain

Treatment and treatment outcomes depend on whether the disease is aggressive or indolent. Aggressive lymphomas are in general relatively prone to therapies and often with complete remission, but develop rapidly into deadly diseases if not treated. On the opposite indolent lymphomas are more difficult to cure, but patients may live with the disease for years before any treatment is needed.

Rituxan has changed in the treatment outcomes of patients diagnosed with B-cell NHL significantly, and the drug is now approved for the use in the treatment of several NHL subtypes, mainly in combinations with other chemotherapy treatments.

Standard therapy for largest subgroup, diffuse large B-cell lymphoma (DLBCL) accounting for about 1/3 of the NHL cases, is the so-called R-CHOP regimen (Rituxan, cyclophosphamide, doxorubicin, vincristine and prednisone). About 50% of the treated patients will obtain a complete remission. There is however currently no established standard therapy for relapsed patients. Different therapeutic regimens may be considered including stem cell transplantation.

Rituxan is also a preferred drug for the treatment of follicular lymphoma (FL) being the second largest NHL subtype. The drug is then usually given in combination with cyclophosphamide, vincristine and prednisone (the R-CVP regimen). An increase in overall progression free survival (PFS, i.e. time without tumor progression) from 14,9 months for the CVP regimen to 51,5 months with R-CVP has been reported. Studies have also proven that the rituximab treatment is cost effective with incremental cost-effectiveness ratios of €7612 per life-year and €8729 per QALY gained. The overall treatment costs for R-CVP was

estimated to €71.314 vs €62.251 for CVP alone. The total Rituximab costs were estimated to be €11.779.<sup>24</sup>

The market research publisher *Datamonitor* summarizes the status for the treatment of follicular lymphoma (FL) as follows:

*“Current treatment options in advanced FL are rarely curative but Rituxan has been shown to improve prognosis. Patients with advanced disease inevitably relapse and require further treatment. A need remains for novel therapies in the treatment of relapsed/refractory FL to improve survival rates in this hard-to-treat patient population.”*<sup>25</sup>

Two radioisotope labeled antibodies are approved for 2<sup>nd</sup> line treatment of FL, namely Bexxar and Zevalin. But the use of these drugs is limited, likely based on a combination of high costs, difficult handling and administration and concerns over tolerability.

The T-cell therapy is likely not used as a stand-alone therapy but rather as adjuvant or consolidation therapy, primarily after 1<sup>st</sup> line treatment increasing the overall progression free survival rate or in best case act as curative therapy. If this target is reached, the market in US and Europe will be approximately 30.000 patients. Knowing that substantially all patients relapse there is a clear medical need. Upon success with FL, the treatment may also further be documented for other B-cell NHL cancers such as relapsed diffuse large B-cell lymphoma (DLBCL) increasing the use and thus the market substantially.

## 6.2.2 Chronic Lymphocytic Leukemia (CLL)

Leukemia is a class of cancers found in bone marrow and blood and having their origin in the bone marrow. The four major classes of leukemia are chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). Of these four classes chronic lymphocytic leukemia (CLL) is the most common type; 33% of all leukemia incidences in USA are CLL. The predicted number new patients diagnosed with leukemia in USA in 2008 was 37126 and of these 12074 were CLL cases<sup>26</sup>. In the seven major markets<sup>i</sup> the predicted incidence of leukemia was 84654 and with 25419 being CLL. However, two thirds of these patients are categorized as early stage cancers not prone to advanced treatment. Over all stages, 34 % of the CLL patients receive no anti-cancer treatment at all. This is explained by the fact that the disease is found primarily in elderly individuals. The median age for diagnosis was 72 years in USA in the period 2003 – 2007, while median age of death from the disease was 79 years of age<sup>27</sup>, and patients of less than 50 years of age are rare. Being a slowly developing disease many patients do not develop symptoms requiring treatment before they die of other reasons. However, the increasing group of elderly in the population in the western countries will likely lead to an increase in the incidence over the coming years<sup>28</sup>.

Up to now there has been no standard treatment for these patients as demonstrated by Figure 5.1 below:

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<sup>i</sup> USA, Japan, France, Germany, Italy, Spain and UK

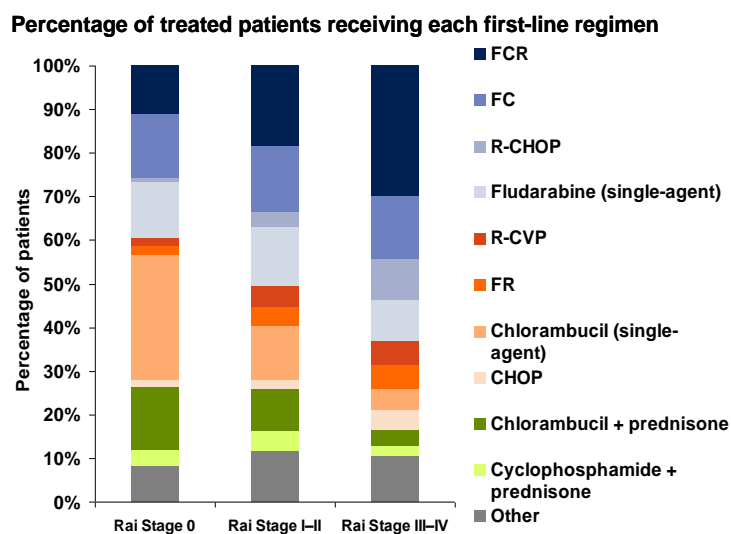


Figure 6.1 treatment regimens for CLL in different stages. ©Datamonitor<sup>29</sup>

This variation in the treatment of patients is explained in part by the fact that there are limited data from randomized studies proving superiority. Such studies would require a large number of patients and they would be long lasting to meet relevant clinical end-points, and have therefore been performed only to a limited extent<sup>30</sup>. Further there is no curative treatment for CLL. Thus any treatment is only prolonging life or helping managing the disease<sup>31</sup>. Follicular lymphoma (FL) and CLL resemble both in the treatment regimen and outcome, and several drugs being documented for FL have also been documented for CLL<sup>32</sup>. About 15 different products are either launched or approved for the treatment of CLL. However, only three drugs are predicted to dominate the market over the next years according to market analyses performed by Thomson Pharma Partnering Forecast, namely Campath, Revlimid and Rituxan. Today Rituxan in combination with standard chemotherapy is believed to become a standard treatment for CLL based on the results from clinical phase III trials concluded early 2009. When an application for the use of Rituxan for CLL was filed at FDA May 2009 Roche stated in a press release that “[...] *Rituxan plus standard chemotherapy for CLL extended the time patients lived without the cancer advancing (progression-free survival or PFS) compared to those receiving chemotherapy alone*”. In the same press release they claim that “[...] *there is no cure for CLL, and the primary goal of treatment is to keep the cancer from getting worse. These data showed that Rituxan was able to extend the period of time before cancer progression by about 10 months for people with newly diagnosed or recurrent disease.*”<sup>33</sup>

18 February 2010 FDA approved the application giving Roche the rights to promote “[...] *Rituxan to treat chronic lymphocytic leukemia (CLL) in patients beginning chemotherapy for the first time, as well as for those who have not responded to treatment with other cancer drugs*”<sup>34</sup>.



Another CD20 targeting antibody recently approved by FDA for the treatment of CLL is ofatumumab (Arzerra™, GlaxoSmithKline, approved October 26, 2009). The approval is given for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. Subsequent randomized trials are, however, required to verify and describe the clinical benefit of ofatumumab in CLL and despite a quite aggressive development the chance to succeed is deemed to be limited.

No assessment of the treatment costs or cost effectiveness of novel CLL therapies has yet been published. Thomson Pharma Partnering Forecast estimates the average annual price per patient to be \$15,000 in Europe and 20,000 in US (2009 numbers).

A recent publication in *Blood* has demonstrated that allogeneic stem cell transplantation provides durable control over the disease in poor-risk CLL patients<sup>35</sup>, providing good indications that a T-cell based therapy may be effective in the treatment of CLL. Only a quite limited number of CLL patients are, however, eligible for allogeneic stem cell transplantation due to the high age at diagnosis.

Despite the progress in the treatment of CLL given by the approval of CD20 targeting antibody drugs CLL is still a disease with high mortality and with a need for improved therapies. The choice of CLL as an indication seems therefore at this stage qualified.

### **6.2.3 New treatment regimens for FL and CLL**

Not only the existing treatment regimens, but also pipeline drugs may affect the potential for a new product.

The success of the anti CD20 drug Rituxan initiated a substantial research and development effort towards competing or even better replacing products within the field of NHL treatments. While Genentech and Roche, being the vendors of Rituxan, have successfully developed this product for several indications through their line extension program, several companies follow developing new drugs for these diseases. Hematological cancers counts for about 15% of all cancers, and the development of new drugs for these indications has receives high attention as there are unmet needs and good margins for successful drugs. This is proven by the fact that of the 74 oncology drugs that received FDA approval between 1990 and 2006, 23 (31%) were approved for the treatment of hematological malignancies. And 14 of these (61%) received marketing authorization under FDA's accelerated approval program<sup>36</sup>.

Early 2009 23 drugs for hematological cancers were identified in phase III or pre-registration. Of these, three had CLL as lead indication and similarly three were registered for FL<sup>37</sup>. Mid 2010 57 drugs are identified in phase III or pre-registration, and three of these target CLL while only one targets FL. It is worth observing that three of the late stage drugs identified in 2009 have been withdrawn, underlining the risks associated with the drug development process.

### 6.1.3.1 New treatments CLL

A thorough assessment of the clinical performance of the three pipeline drugs has not yet been performed, and whether any of these drugs will change significantly the outcome and thereby the treatment for the patients suffering from CLL thus needs to be further looked into. But none of these drugs will likely have a curative effect.

### 6.1.3.2 New treatments FL

Resistance to Rituxan in the treatment of FL is a problem and further therapeutic options are limited. The development of new therapies is viewed essential “if the concept of advanced FL as an incurable disease is ever to be challenged”<sup>38</sup>.

Table 6.2. Late stage pipeline drugs for FL and CLL

Molecule	Brand	Drug class	Mechanism of action	Company	Lead indication	Phase (2010)
Oblimersen	Genasense	Molecular-targeted therapy	Bcl-2 gene inhibitor	Genta	CLL	III
<i>Alvocidib (flavopiridol)</i>	Not known	Molecular-targeted therapy	CDK and RNA synthesis inhibitor	Sanofi-Aventis	CLL	III
Obinutuzumab	Not known	Immunotherapeutic agent	Humanized CD20 antibody	Glycart/Roche	CLL	III
Not Known	BiovaXID	Immunotherapeutic agent, therapeutic cancer vaccine.	Tumor-specific idiotype protein (Id) and keyhole limpet hemocyanin (KLH) recombinant	Accentia	FL	III

Early stage anti-CD20 drugs in pipeline include ocrelizumab, veltuzumab, GA101, AME-133v, and PRO131921<sup>39</sup>. These antibodies are considered to have improved properties compared with Rituxan, but will still have much of the same limitations. They are e.g. not expected to present a curative therapy for CLL and FL.

### 6.2.3.3 Conclusion

As a conclusion none of the late stage or anti-CD20 drugs in pipeline seem to challenge the need for improved drugs for follicular lymphoma or chronic lymphocytic leukemia. It should however be expected that the pipeline contains drugs improving the current treatments on survival parameters, thus adding pressure to the competition for a position in the treatment regimens used for these diseases.

## 6.3 Allogeneic Hematopoietic Stem Cell Transplantation

### 6.3.1 Background

In allogeneic hematopoietic stem cell transplantation (also named allogeneic bone marrow or allogeneic hematopoietic progenitor cell transplantation) hematopoietic stem cells from a donor are implanted to replace a patient's existing malfunctioning hematopoietic cells (see also Section 4). Stem cells from an HLA identical donor are injected into the patient after his own, diseased bone marrow has been totally or partly wiped out (i.e. myeloablative conditioning or reduced intensity conditioning). The harvested stem cells will then generate a new and healthy bone marrow in the patient. The hematopoietic stem cells can be harvested from in essence three different sources, peripheral blood, bone marrow and umbilical cord blood<sup>40</sup>.

Figure 6.2 gives a brief presentation of the procedure followed in hematopoietic stem cell transplantation as presented by Datamonitor. The procedure is similar for both allogeneic and autologous transplantation, the only difference being the source of the stem cells. While donor stem cells are used in allogeneic transplantation, the patient's own stem cells are used in an autologous procedure. But while allogeneic stem cell transplantation has the potential to be curative autologous transplantation is, however, normally not :

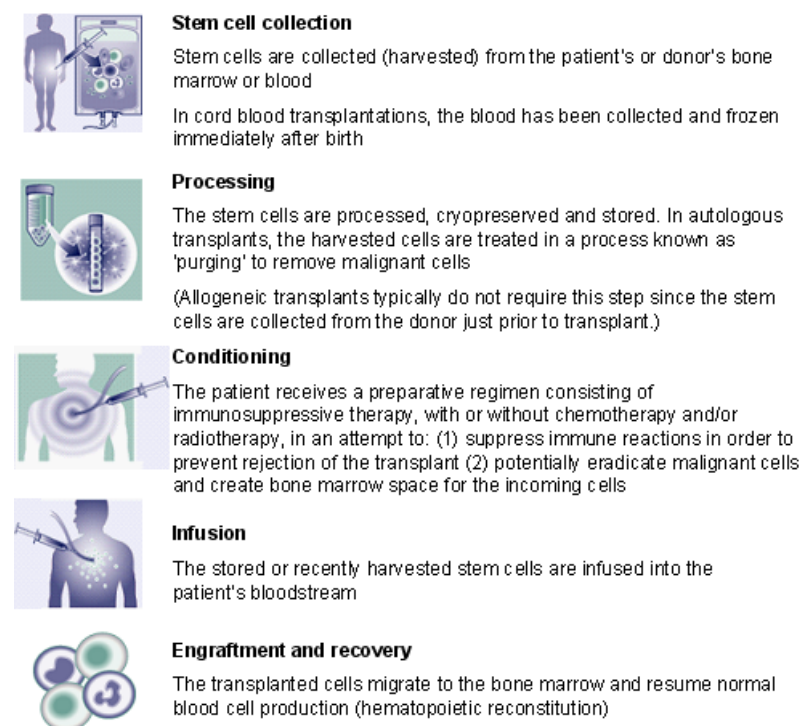


Figure 6.2 Presentation of the procedure followed in hematopoietic stem cell transplantation  
Source: Datamonitor ©(adapted from <http://www.multiplemyeloma.org/>)

Allogeneic bone marrow transplantation is considered to be the most aggressive form of consolidation/curative therapy in the treatment of a series of hematological malignancies based on the ability to eradicate both fast cycling and slow cycling cells<sup>41</sup>. The treatment is increasing in popularity and used in the treatment of many different diseases included hematological malignancies, breast cancer, immune deficiencies and inborn disorders<sup>42</sup>, and the treatment is considered underutilized for e.g. acute myeloid leukemia (AML)<sup>43</sup>. Figure 5.3 below presents an overview over indications for both allogeneic and autologous hematopoietic stem cell transplantation in USA 2008<sup>44</sup>.

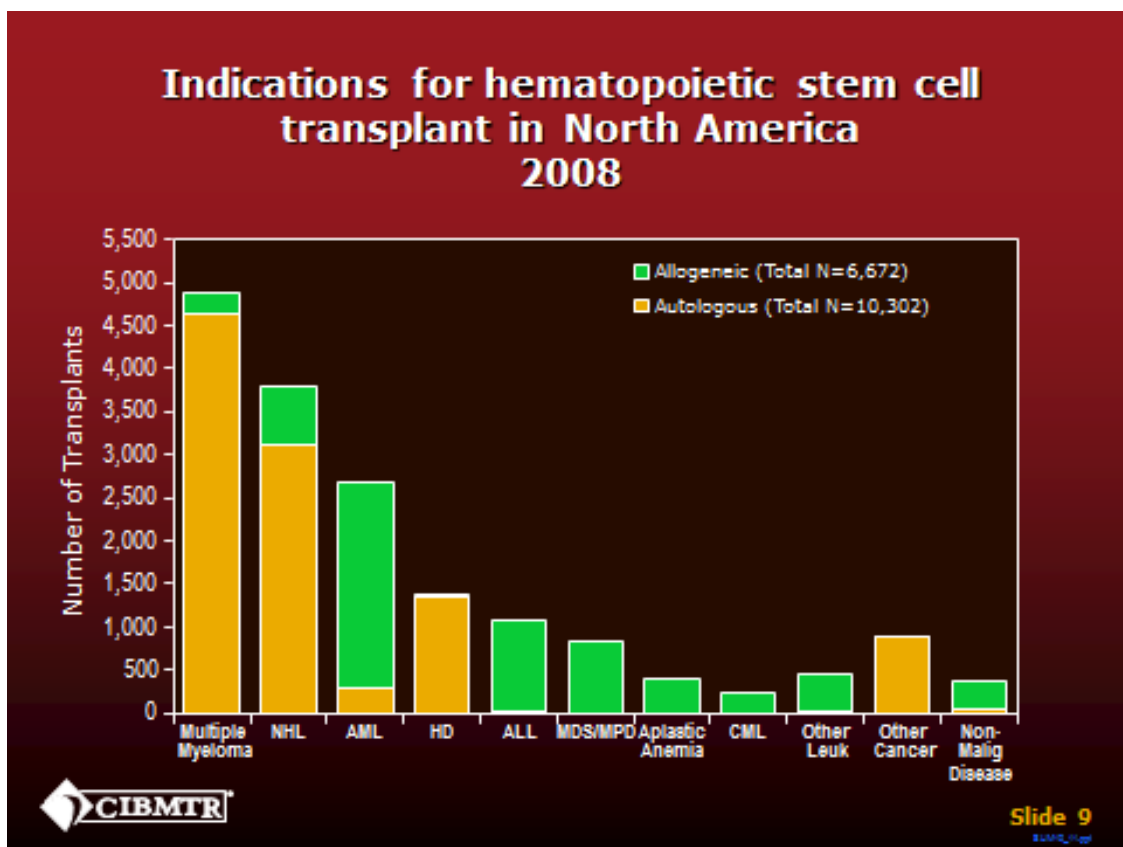


Figure 6.3 Indications for hematopoietic stem cell transplantation in North America 2008 CIBMTR©

A recently published survey over hematopoietic transplantation activity in Europe reveals similar trends. Results are presented in Figure 6.4.<sup>45</sup> The largest patient group in both USA and Europe is acute myeloid leukemia (AML) with about 2500 cases in USA and 3300 in Europe each year.

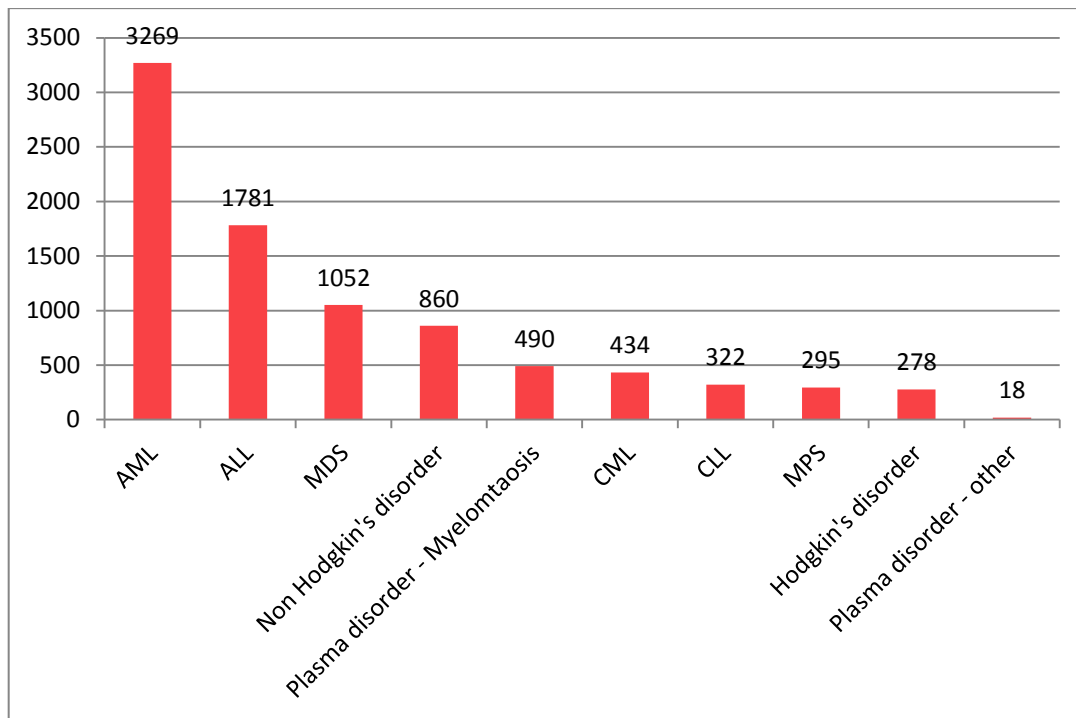


Figure 6.4. Number of allogeneic hematopoietic stem cell transplantations in Europe in 2007.

The number of transplants is increasing, and e.g. from 2003 to 2005 the numbers of procedures performed worldwide increased by 25 %. Improved regimens will likely result in a further increase e.g. through inclusion of patients older than 60. Today patients above this age are not found eligible for this treatment due to increased risk for complications, and are rather given so called reduced conditioning / mini transplantations only, a treatment normally not considered to be curative. As more than half of all leukemia cases occur after the age of 64, the number of patients treated by stem cell therapy may increase significantly upon success with safer and less risky procedures.

Hematopoietic stem cell transplantation is exposing the patient for severe risk for postoperative complications. The target indication for the induced graft versus leukemia treatment is considered to be patient receiving transplantation due to a relapsed acute myelogenous leukemia disease. The three year probability of survival for these is 45 – 60% for early stage disease and 20 – 25 % for advanced stage disease<sup>46</sup>. Survival is significantly better for patients with HLA identical sibling donors, and improved HLA matching does also improve the survival when using a non-sibling donor.<sup>47</sup> Major causes of death include relapse, infections and graft versus host disease. Complications are often a result of the aggressive treatment for removal of the patient's bone marrow prior to the transplantation or infections due to a low functioning immune system over the first period after the transplantation. Generally 12 – 18 months is required to re-establish a well-functioning immune system<sup>48</sup>.

If not actively removed a donor transplant will in addition to the hematopoietic stem cells also contain donor T-cells. As discussed in Section 4 these T-cells may cause both graft versus leukemia effect (GVL) and graft versus host disease (GVHD). The current invention may be exploited to circumvent the GVHD effect through removing the donor T-cells from the

transplant and replace these with the patient's own T-cells activated by genetic manipulation to present a receptor attacking the residual hematopoietic tissue (the graft versus leukemia effect).

Graft versus host disease (GVHD) is a major complication after allogeneic transplantation. GVHD may either be acute (disease manifestation first 100 days after the transplantation) or chronic (>100 days after transplantation) causing both transplant-related morbidity and mortality. Rates of GVHD vary from between 30 - 40% for sibling donors to between 60 - 80% for unrelated donor.<sup>49</sup> In transplantations with unrelated donors relapse accounted for 33% of the mortality, while GVHD accounted for 13%<sup>50</sup>. GVHD also affects the quality of life and health status for the patients after the transplantation. Effective management of GVHD is considered a priority and recommended to be a focus area for research.<sup>51</sup>

### **6.3.2 Treatment of chronic GVHD**

For acute GVHD the most used treatment regimen in USA is a combination of methotrexate and cyclosporine. But the use of methotrexate is hampered by increased incidence of other complications<sup>52</sup>.

Treatment of chronic GVHD consists of immunosuppressive therapy with cyclosporine and corticosteroids such as prednisone. However, treatment with corticosteroids is hampered with complications such as osteoporosis and may also predispose patients to fatal infections. Two studies addressing the treatment with corticosteroids have recently been published in the Cochrane library. Quellmann et al. stated in 2009 that "Despite ongoing progress, acute and chronic GvHD still represent major drawbacks in the context of allogeneic myeloablative hematopoietic stem cell transplantation (HSCT) due to their high morbidity and mortality. Corticosteroids are used as first-line treatment of acute and chronic GvHD. However, their role for preventing GvHD is unclear as the published study results are controversial."<sup>53</sup> In 2010 Salmasian et al concluded that "[t]here is no certain study regarding appropriate use, dose and length of therapy for acute GvHD. Further studies are needed to define the appropriate use of steroids and whether other agents are appropriate as frontline therapy."<sup>54</sup>

Prevention and treatment of both acute and chronic GVHD is viewed unsatisfactory, and better regimens are requested particularly for chronic GVHD<sup>55</sup>.

### **6.3.3 Costs and cost benefit assessments for allogeneic stem cell transplantations**

Allogeneic stem cell transplantation is one of the most complex and expensive medical treatment forms with costs ranging from \$30.000 to \$200.000<sup>56</sup>. Thus the cost-effectiveness of the treatment may be questioned in light of the high postoperative mortality and morbidity. Orsi et al have in a meta study evaluated the cost-effectiveness and event-free survival of patients treated with allogeneic stem cell transplantation<sup>57</sup>. 293 patients treated with allogeneic stem cell transplantation were compared with a control group of 479 patients

receiving either chemotherapy treatment or autologous hematopoietic stem cell transplantation. In short, the authors conclude that the patients undergoing allogeneic stem cell transplantation have a survival gain of about one year, and that the treatment is considered cost efficient as the cost of the year gained is calculated to be about \$45.000,-. Improved allogeneic transplantation procedures maintaining or improving the graft versus leukemia effect while reducing GVDH should affect these numbers positively provided being at the same level with regards to costs. But clearly a significantly increased price may be limiting for introduction of new procedures as the stem cell procedures already today are considered quite expensive. Thus the ability to prove that a new treatment is cost-effective needs to be considered before a decision about clinical development is made.

### 6.3.4 New treatment regimens for GVHD

In June 2007 the consultancy company Wiborg ApS performed an assessment for the Technology Transfer Office Medinnova (now Inven2) of the market opportunities and competing technology for this project in the field of GVHD<sup>58</sup>. The search was further updated March 2008 and again in March 2010. Surprisingly few new drugs have entered into late stage development since 2007. Table 6.3 provides an overview of the late stage product developments considered competing with the T-cell therapy. Of interest is that four of these products define cell based therapies.

Table 6.3 An overview of the late stage product developments considered to compete with the T-cell therapy

Company Name	Product Name	Technology	Stage
Soligenix	orBec (beclomethasone dipropionate)	Anti-inflammatory drug preventing acute gastrointestinal GVHD after allogeneic hematopoietic cell transplantation (HCT) with myeloablative conditioning regimens.	III
JCR Pharmaceuticals Osiris Therapeutics Genzyme	Prochymal (remestemcel)	Preparation of mesenchymal stem cells obtained from the bone marrow of healthy adult donors. Prochymal is currently being evaluated in Phase III trials for steroid refractory GvHD, acute GvHD, and Crohn's disease. Fast Track status by FDA and orphan drug status for EMEA	preregistration
Kiadis Pharma B.V.	ATIR	Mismatched donor lymphocytes depleted of allo-reactive T-cells. Designed to prevent acute GvHD by eliminating the immune cells from the donor graft. ATIR™ enables the use of a mismatched donor improving the availability of a donor.	II
Adeona Pharmaceuticals, Inc.	Anti CD4 802-2	Small molecule drug inhibiting the T-cell CD4 co-receptor.	II

Tble 6.3 Cont.

MolMed SpA	TK	Donor lymphocytes genetically modified to express herpes-simplex thymidine kinase suicide gene. These TK-cells will accelerate immune reconstitution, while controlling the disease status as the T-cells can be wiped out by activating the suicide gene upon severe GVHD.	Phase III
Medipost	Promostem	Stem cell therapy derived from cord blood and mesenchymal stem cells to activate the attachment of hematopoietic stem cells.	Phase II

MolMed presented in April 2009 their results from their Phase I/II studies in the TK product in a publication in *Lancet Oncology*<sup>59</sup>. The results indicated that the TK cell treatment might be effective in accelerating immune reconstitution while controlling GVHD. In a comment in the same paper prof Olle Ringdén et al wrote under the heading “reflections and reactions” that “[t]he study shows that infusions of T cells engineered to contain a suicide gene are safe and enable control of acute and chronic GVHD, even in HLA-mismatched settings.”<sup>60</sup>

In essence this indicates two major issues in relation to the use of prof. Olweus’ genetically modified T-cells to avoid GVDH. One observation is that the use of genetically modified cell therapy is about to enter into the market and seems to find the use in the therapy of graft versus host disease. The second observation is that there are several cell based approaches that may compete in the treatment of GVHD, and the impact of these for a successful development of this technology should be further addressed before a commercial development is initiated. Further the use of genomic techniques to improve the selection of patients for transplantation and to improve donor selection will likely also reduce the risk for transplant-related complications such as graft-versus-host disease (GVHD).<sup>61</sup> On the positive side prof. Olweus’ concept is the only approach identified that eliminates the cause of GVDH while at the same time maintaining the graft versus leukemia effect. However, efficient treatment of GVDH in current treatment regimens or improved selection of donors may reduce the need for her technology.

As a conclusion there is an unmet need for improved transplant procedures maintaining the GVL effect while avoiding the GVHD effect. But the competition from the pipeline technologies needs to be thoroughly considered before development of a product is initiated.

## 6.4 Multiple Myeloma

Multiple myeloma is a cancer of a specific type of B-cells called plasma cells. The main function of these plasma cells is the production of antibodies also known as immunoglobulin destroying invading pathogens. Before these B-cells reach the stage of antibody producing plasma cells they have, however, developed through a multi stage process. At one stage in this



process the naïve B-cell is exposed to an invading pathogen fitting with a unique receptor on the surface of this B-cell. Through a complex process B-cell then starts the production of an antibody having the property that it binds to other pathogens of the same species. The binding of antibodies further initiates a set of processes eventually destroying the invading pathogens. Some of the mature B-cells will continue to circulate in the blood plasma also after the pathogen is completely removed thus causing a permanent antibody defense system<sup>i</sup>. These circulating antibody producing cells are named plasma cells and multiple myeloma is caused by malignant populations of these plasma cells.

When a patient is diagnosed with multiple myeloma the prognosis is in general quite poor and with an expected median survival of 3 – 6 years. However, when multiple myeloma is diagnosed the patient has likely suffered from monoclonal gammopathy of undetermined significance (MGUS) for several years. This premalignant condition is in general never diagnosed due to lack of symptoms. The Mayo Clinic in USA reports that the median duration before its recognition is 11 years, and that “*some 28% of those patients diagnosed at 70 have had MGUS for 20 years or more*”<sup>62</sup>. People with MGUS have a lifelong risk of developing multiple myeloma or other plasma cell disorders.

One characteristic feature of multiple myeloma is infiltration of plasma cells in the bone marrow, and a criterion for the diagnosis is that 10% or more of the plasma cells are found in the bone marrow upon examination. Further, the myeloma plasma cells produce a specific monoclonal antibody named M (monoclonal) protein and also a monoclonal antibody fragment called Bence-Jones protein. Both these proteins will be found in plasma and/or urine. Often there is also evidence of damage to major organs. Certain genetic changes in the plasma cells are also characteristic for the disease. Patients with multiple myeloma require treatment for their disease to reduce bone and organ damage thus improving the quality of their life and increase their life time.

Multiple myeloma accounts for 1% of all cancers in USA and is the second most common hematological malignancy. About 63.000 people were living with the disease in USA in 2008, and of these about 19.920 were patients diagnosed that year<sup>63</sup>. In the seven major pharmaceutical markets<sup>ii</sup> about 40900 new cases of multiple myeloma were diagnosed in 2007. The numbers are also expected to increase due to aging population. As seen from Figure 5.5 the disease is mainly found in the elderly<sup>64</sup>.

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<sup>i</sup> This process defines in short the B-cell part of the adaptive immune system

<sup>ii</sup> US, Japan, France, Germany, Italy, Spain and UK

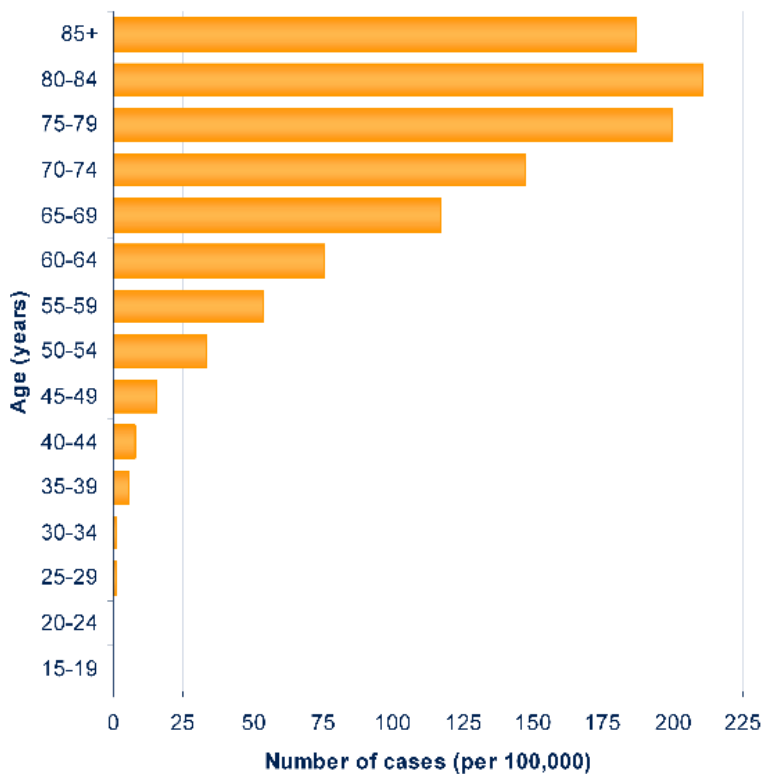


Figure 6.5. Number of cases as a function of age in USA ©Datamonitor

Less than a third of patients diagnosed with multiple myeloma survive beyond five years, but the recent introduction of three new drugs is supposed to improve these numbers. The preferred treatment option is autologous hematopoietic stem cell transplantation, but not all patients are eligible for this treatment. There are differences from country to country with respect to who is given this treatment, but the main exclusion criterion is age<sup>65</sup>.

Approximately 4,600 received autologous transplantation in USA in 2008<sup>66</sup>, which is about 25% of the incidence number. Autologous stem cell transplantation for multiple myeloma is the most performed stem cell transplant procedure, but the procedure is not curative. Median duration of response for the procedure is 2 years.

Allogeneic stem cell transplantation has only modest results in this disease. Still few hundred patients receive this treatment in USA each year. But the initial mortality is high and the treatment is hampered with severe complications. Bensinger et al has published a study showing that of 80 patients only five were alive and disease free 4 – 7 years after transplantation<sup>67</sup>. Despite the lack of convincing data for the treatment of these patients with allogeneic transplantation the results indicate a certain graft versus cancer effect supporting that T-cell therapy may be effective in the treatment of multiple myeloma.

The conventional drug therapy besides transplantation has for almost 40 years been the combination of melpharan and predisone (the “MP” regimen). However, the introduction of the three novel drugs Thalomid, Revlimid and Velcade has challenged this dominance. All of these drugs can prove a significant increased survival. E.g. a study comparing MP with MP plus Thalomid (MPT) shows an increase in response rate of about 50% for the Thalomid arm

(48 % vs 76%). Similarly eight times as many patients obtained complete response (2 % vs 16%).

Prior to the American Society of Oncology meeting in 2009 a group of multiple myeloma key opinion leaders met to discuss the treatment of this disease. The outcome is summarized by Jagannath et al<sup>68</sup>. Besides giving a good overview over current treatment regimens the paper also summarizes ongoing clinical studies with new drugs. It seems that both new combinations of existing drugs and new drugs may improve the survival for these patients. They claim, however, that there is a need for additional and better designed clinical studies to obtain best results from the drugs.

The improvements in the treatment and outcome for these patients have been tremendous over the last decade. But there is no curable treatment, and the drugs used are also hampered with severe adverse effects. So despite the improvements in the treatment there is a need for improved treatment regimens for multiple myeloma. This is also concluded in a recently published report from Datamonitor analyzing the current pipeline for drugs treating this disease.<sup>69</sup>

#### 6.4.1 New treatment regimens for multiple myeloma

The recently published Datamonitor report analyze the pipeline drugs for lymphomas, multiple myeloma and myelodysplastic syndromes, and their identified new drugs for multiple myeloma counts four drugs in late pipeline as given in Table 6.4.

Table 6.4. Late stage pipeline of drugs for multiple myeloma.

Drug substance name	Mechanism of action	Originator company	Phase
Carfilzomib	Proteasome inhibitor	Proteolix/Onyx Pharmaceuticals	III
Panobinostat	HDAC inhibitor	Novartis	III
Perifosine	PI3K/Akt pathway inhibitor	Keryx Pharmaceuticals	III
Vorinostat	HDAC inhibitor	Merck & Co	III

Datamonitor expects that none of these drugs will add significant benefit to the treatment of multiple myeloma, thus leaving a room for improved regimens and thus also a T-cell based therapy.

# 7 Clinical trial design and patient access as factors for determining indications

When deciding to enter into a drug development program, one very important aspect to evaluate is the risks related to the clinical studies necessary to get market approval and authorization. Several factors determine the risk profile such as access to patients, quality both of study design and clinical partners, timelines, endpoints, number of patients needed to get statistically significant results, whether the drug obtains an orphan drug or fast track status<sup>i</sup> etc.

Clinical trials implies that the drug is tested on patients in a structured and regulated way to determine the safety and efficacy, and these studies are also compulsory for getting market authorization and approval. The clinical trials are both costly and also associated with a risk for failure. DiMasi et al have estimated the chance to obtain FDA marketing approval for an oncology drug entering into clinical trials phase I being about 25%<sup>70</sup>. Adams and Brantner estimated further in 2006 the development costs for oncology drugs developed by big pharmaceutical companies to be in the range of \$1.042 million, which is about 20% higher than the average for drugs in general<sup>71</sup>. This number includes costs both for withdrawn and successful drugs. A quite rough estimate for one successful drug points to development costs well above \$250 millions. A clinical program likely to defend such an investment must therefore be identified early in the development of a new drug. Small companies may in general be able to run drug development less expensive than big pharma, but with increased risk for lack of approval, the latter mainly due to lack of quality in their documentation and clinical efficacy<sup>72</sup>.

An ordinary clinical development program is divided into three separate phases, named clinical phase I, II and III. In clinical phase I the toxicity of the drug is documented. For oncology drugs this safety study is normally performed in patients, and quite often some efficacy parameters, often based on surrogate endpoints, are also monitored. To save money and time phase I and phase II are also often combined, in particular in oncology drug development. Phase II studies are performed to document effect and efficacy and to find correct doses for the drug. The phase III studies are those determining the claims applied for in the approval process. These claims determine the patient segment you are authorized to address with the drug and thereby the market size. A clinical phase III study should also prove that the drug is equally good or better than the existing treatment regimens. To obtain premium price, advantages is required.

The design of a protocol for a clinical study must consider the following factors:

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<sup>i</sup> The regulatory authorities in US and Europe has established certain tools to increase the speed of approval for drugs designed for diseases with a limited number of patients. These tools include orphan drug .....

## 7.1 Inclusion and exclusion criteria

This defines which patients to be included in a study, i.e. what kind of disease the patient suffers from, age etc. (inclusion criteria), and if there are patients not eligible for the treatment (exclusion criteria). A market approval will be restricted to the patient group included in the phase III study thus determining the size of the market for the drug. The broader inclusion criterion, the larger is the market. But broad inclusion criteria may also reduce the statistical power of the study. A careful selection of patients is in particular required when documenting modern cancer drugs affecting a specific biological mechanisms being present in some individuals but not others. Broad inclusion criteria may in fact lead to inconclusive results and lost money due to lack of effect in a subpopulation of the patients.

Quite often the first studies with a new drug must be restricted to previously treated patients due to the requirements that a patient at any time should be given the best treatment regimen. This may both reduce the access to patients and impair the monitored efficacy of the drug as second line patients often are less adaptive to therapy.

For this specific T-cell based therapy one inclusion criterion is that the patient is HLA-A2 positive reducing the number of patients to about 50% of the total number of potentially eligible patients suffering from the chosen disease.

## 7.2 Clinical end points

This defines the expected results of a study. The endpoints will besides proving the efficacy of the drug also prove the real value of the drug. To defend the investments made these endpoints should ideally prove that the drug is a premium-price product. Most oncology clinical trials designate multiple endpoints to reduce the risks associated with the outcome of the study, and will also be designed with both primary and secondary end-points. Primary end-points are, however, those defining the quality and uniqueness of the product and also those giving rise to the claims being approved. The most significant endpoints for oncology drug are associated with survival. The most impressive endpoint and therefore what most companies strive for in their documentation is increased overall survival (OS). However a study having overall survival as the primary endpoint is likely to last for a significant time and thereby be quite costly. The choice of this endpoint must therefore be balanced with the investments needed to obtain the results. Other survival-linked endpoints are disease-free, progression-free or event-free survival as found in the FDA guidance, and these are therefore also often used as primary endpoints. Yet another endpoint is improved quality of life. As health authorities are getting more and more cost efficient oriented, this parameter may have certain advantages in an approval process. However, measuring quality of life introduces additional aspects to the study. One is the comparator factor added, the other being the challenge in registering the data and the costs linked to the study design.

## 7.3 Statistical strength in the study

The statistical strength of the study is a direct consequence of the combination of number of patients and the improvements introduced with the new treatment compared with ordinary treatment regimens. As such it is a very important parameter to judge in the design of the study, but will be determined by the other factors to be decided.

## 7.4 Patient access

The access to patients may often be challenging for the performance of a clinical study, in particular in phase III when a high number of patients is required. The number of patients may vary from a few hundred to several thousand dependent on the disease and improvements expected. E.g. the study performed to obtain approval for the anti-CD20 antibody ofatumumab (Arzerra™, GlaxoSmithKline) was quite small and included only 225 patients but enrolled at totally 41 study location in 10 countries<sup>73</sup>. FDA approved ofatumumab based on this study provided subsequent randomized trials were performed to verify and describe the clinical benefit of ofatumumab in CLL<sup>74</sup>. Three new trials are by April 2010 registered in the online database Clinicaltrials.gov. The studies include in total about 1300 patients for this purpose. As shown by the first ofatumumab, trial inclusion of patients may be done at several centers to get a sufficient number of patients in a reasonable time. This is both adding costs and logistic challenges. But as any delay causes both lost income, more money spent and increased competitive threat several centers may be needed.

Clinical trials on a rare disease do increase the cost of the studies due to lower access to patients. Therefore both the American and European authorities have established regulations making clinical trials on small patient groups simpler and less demanding than for larger patient groups<sup>75</sup>. But also other ongoing clinical trials addressing the same patient group may influence on patient access. E.g. large phase III studies performed by big pharmaceutical companies may very well take a significant share of these patients.

Ideally clinical studies should also be performed at well recognized clinics to secure both high quality and not least publicity. Early planning, efficient networking and not least attractive technology giving basis for high rated publications do certainly help.

Products or treatments considered being complicated either for the hospital or for the patient may also reduce the attractiveness and thereby the patient access.

The four different indications considered for the T-cell based therapy have different challenges with regards to clinical documentation. They share, however, that they all are addressing relatively small patients groups. But these patients are also popular both in investigatory and industry driven clinical studies. For all four indications orphan drug and/or accelerated approval status should be obtained.

Further they all share that they are based upon cell therapy with genetically modified cells. This is in itself a major regulatory barrier as no gene modified therapy has been approved at this stage. Rather the US regulatory authorities have established a quite restrictive attitude based upon results from early stage clinical trials. FDA in USA is e.g. currently advising that

patients receiving gene therapy regimens are monitored for 15 years post treatment<sup>76</sup>. Their position creates both a barrier with regards to access to patients in clinical studies and also a barrier getting the required approval.

## 7.5 Assessments of regulatory positions

Table 7.1 compares by means of a few simple parameters some of the above mentioned aspects for the four different indications.

- Patient access - evaluated based on the number of patients eligible for the treatment in Norway held against clinical activity world-wide.
- End-points – suggested based upon what has been used for drugs approved for same indication and known effect of current treatments
- The length of a phase 3 study - estimated e.g. based on comparison with similar studies registered in ClinicalTrials.gov.

Some simple reflections from this assessment are:

Patient access is best for the indication follicular lymphoma. However, study duration may be long based on overall survival data for this disease.

Patients treated for advanced chronic lymphocytic leukemia have significantly lower expectations for overall survival, reducing the time required for clinical trials. However, there are potentially a lower number of patients available for the studies than it is for FL.

Provided that we are able to use reduced acute GVHD as a clinical end point for induced GVL effect in transplantation, this is the indication giving the shortest way to the market. However, only a fraction of the patients gets this adverse reaction. This indicates that the number of patients treated may be quite high to get statistically significant data.

For multiple myeloma Datamonitor argues that a successful drug should demonstrate a median time to progression of at least 15 months<sup>77</sup>. The duration of a phase 3 study is thus likely about three years. The number of running clinical studies is high, reducing the patient access.

Further considerations are needed to conclude. Thus this assessment is only pointing towards important work to be performed, namely a thorough assessment of clinical end-points and patients access early in the planning of a development project. This should be based on market, regulatory and clinical input and performed at an early stage both to prioritize resources and to reduce the risk for investments in the development.

Table 7.1. Considerations on clinical studies for market approval.

	Follicular Lymphoma	Chronic Lymphocytic Leukemia	Allogeneic bone marrow transplantation <sup>iv</sup>	Multiple Myeloma
Number of patients in Norway <sup>78</sup>	170	150	63 <sup>79</sup>	351
Numbers being HLA A2+ <sup>i</sup>	85	75	32	175
Maximum number eligible for the therapy <sup>ii</sup>	85	50	32	175
Ongoing clinical trials registered by Clinicaltrials.gov <sup>iii</sup>				
Phase I	111	170	130	182
Phase II	151	195	227	266
Phase III	27	27	45	60
Phase III sponsored by industry	4	8	5	23
Phase IV	0	2	5	5
Total number of ongoing clinical trials <sup>v</sup>	243	330	372	417
Total number of studies sponsored by industry	35	89	47	159
Drugs in clinical development	7	45	56	78
Drugs in Phase III	1	8	7	15
Possible primary endpoint	endpoints demonstrating improved overall survival	endpoints demonstrating improved overall survival	acute GVHD appearance	endpoints on improved mean time to progression, 2 <sup>nd</sup> line treatments
Duration of study	4 years	3 years	2 years	3 years
Patients access <sup>vi</sup>	***	*	*	*

<sup>i</sup> estimated 50% of all patients, <sup>ii</sup> calculated from percentage of patients treated, <sup>iii</sup> As registered by 20 April 2010 in the online database Clinicaltrials.gov, <sup>iv</sup> All allogeneic transplantations independent of disease. AML is likely 50 – 60% of these. <sup>v</sup> Drugs being in both phase II and III studies confuses total numbers. <sup>vi</sup> Improved by increasing number of asterisks



## 8 Net present value assessments

Net present value (NPV) calculations are often used to anchor decisions about industrial investments. The tool is used to evaluate whether the investments needed over a given time will make generate a cash flow back defending the investments made. Obviously an NPV calculation will be highly dependent upon the input into the model, i.e. the degree of certainty in both investments and the cash return. The earlier stage, the higher is the uncertainty. NPV calculations on a project in an early stage like are for sure indicative only. But NPV calculations force the analyst to consider a series of aspects related to an investment/product development such as market size, competition and uniqueness, development trends, price etc. So the degree of uncertainty the method is found quite useful.

In this specific case the NPV calculations are used to compare the different options for the use of the T-cell technology rather than to defend an investment case. The outcome is a visualization of differences between the different indications with probability for pay-back of investments made, and may be used as part of a tool for making decisions about what to develop as a first product.

Two different NPV models were considered for the purpose of modeling this current project, a standard NPV model and a risk adjusted model. Risk adjusted NPV calculations are often preferred in an early stage as this method takes into account the consequences of failure and also uncertainties in the input numbers. But in our case we have used standard NPV calculations as the purpose is to compare the different indications rather than to defend an investment case. A base case and a best case scenario were made for each indication. Although the NPV numbers presented are highly uncertain the model will visualize the differences between the different of indications.

To generate an NPV value three main elements need to be considered, namely the price to get to the market, the risks associated with the project and the size of the market. Below is the input data for the NPV model discussed. For the sake of simplicity, the development program start is set to 1Q 2011 for all indications and with identical timelines unless other is specifically discussed below.

### 8.1 Development costs

A development program for a new drug is in general divided in different phases as shown in Figure 8.1 below. The first part is the research phase often organized in three separate parts and where the outcome is in the lead selection phase is in essence a decision about the structure of the drug to be developed. In this particular case the outcome is expected to be a concluded structure of a viral vector to be introduced into the T-cells. The next phase is preclinical, where the drug is developed and documented to a level where both developer, trial sites, patient and not least the regulatory authorities have found that the data established strongly indicates that a trial in humans is considered safe. This work is done according to

established guidelines, and includes in general animal studies both to confirm efficacy and safety aspects.

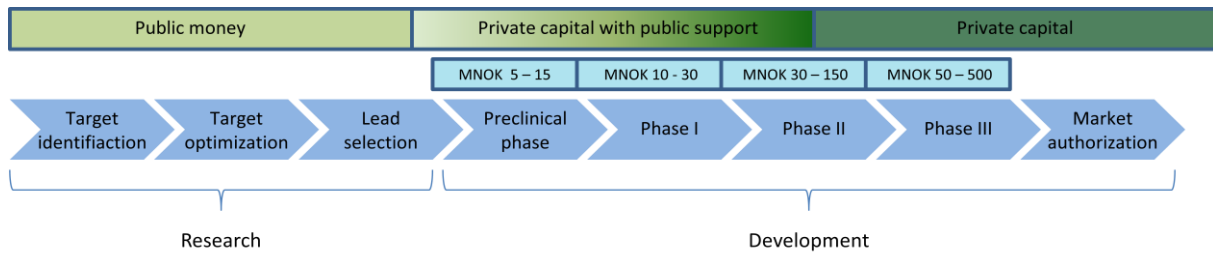


Figure 8.1 Phases in a development program for drug development.

As discussed in Section 7 (Clinical trial design) the clinical trials are in general divided in three different phases as also shown in Figure 8.1.

For the purpose of the NPV calculations a budget for the development of one not specified T-cell candidate is made. The budget is at this stage obviously at best indicative only and the assumptions used provide a best case scenario with both regards to number of patients and success in the clinical development. This is thus a minimum and therefore also a high risk budget. For the complete budget see Table 8.1 in Section 8.1.8 below. A detailed discussion of the input numbers and the assumptions made is presented the follow sections.

### 8.1.1 Research Phase

Research for new drugs may be performed both in established companies and in academic institutions. However, as the risk of failure is quite high in the research phase and private capital to a certain extend is risk averse, target research is only occasionally financed by means of investment capital only in start-up settings. Usually this early stage research is either part of academic research or performed in an established company also having a late stage pipeline or cash flow generated through products on the market. We expect only minor investments made in this project during the research phase estimated to NOK 500.000,-.

### 8.1.2 Preclinical phase

The main outcome of a preclinical program is to generate sufficient documentation to get authorization to start clinical trials. The technical part of the preclinical program contains in essence two parts: chemistry, manufacturing, and control documentation (CMC) and pharmacology and toxicology studies (usually mainly animal studies). Budget for a set of different preclinical development program will differ depending on both strategy and complexity of the drug to be developed. A complete program for a drug developed by a lean start-up company may to my experience reach about NOK 35 mill. However, it is possible to reduce the costs down to about NOK 10 – 15 mill. postponing some preclinical studies. A requirement is that this postponement does not compromise safety issues. The duration of a

preclinical phase is normally 1 - 2 years. The content for a preclinical program for T-cell based technology needs further considerations as there are no animal models predicting the behavior of the modified T-cells in man. In our budgets for the prediction of development costs we anticipate two years duration and costs of NOK 15 mill.

### 8.1.3 Clinical phase I/II

It is expected that phase I and phase II (efficacy and dose finding) will be combined and run on terminally ill patients. A combined phase I/II<sup>i</sup> study for this kind of products is in general preferred.

A combined phase I/II study will normally include between 20 and 100 patients. The toxicity of the treatment alone is likely well documented in about 20 patients, but inclusion of efficacy end-points requires probably an increased number. A search performed on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) with search terms “genetically modified T-cells cancer” revealed 14 pure phase I studies having from 12 to 40 patients and with a median of 18. Five phase I/II and phase II studies were identified, ranging from 18 to 57 patients. The only study being designed to generate clinical documentation for regulatory purposes are at this stage a study run by MolMed<sup>ii</sup>. Their study was a combined phase I/II study involving 57 patients.

In our budgets we make the assumption that there are no major difference between the different indications as the price of a clinical trial for a pharmaceutical company only reflects the cost added to the patient treatment introduced by the trial itself and not the cost of the complete treatment.

An industrial average for the cost of a patient calculated to be approximately \$20.000 per patient is used as basis for the calculation<sup>80</sup>. The number of patients included is set to 100 and the duration to two years. A total budget for patient data generation and collection is then roughly NOK 12 mill.

### 8.1.4 Clinical Phase III

The most difficult estimate is the cost of the phase 3 studies. The number of patients may be anywhere between 150 and 4000. However, it is likely that all these indications should obtain an orphan drug status based on the number of patients<sup>iii</sup>. An example of a phase III study likely to be comparable is the study documenting the clinical efficacy of Revlimid in the

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<sup>i</sup> A study combining a dose/toxicity study with an efficacy assessment.

<sup>ii</sup> MolMed develops a technology for the use of donor lymphocytes genetically modified to express herpes-simplex thymidine kinase suicide gene. These TK-cells will accelerate immune reconstitution, while controlling GVHD. Their product is also commented in the Section XX – Indications as a competitor to a product on graft versus host disease treatment.

<sup>iii</sup> Orphan drug status is given for the development of a drug for a disorder affecting fewer than 200,000 people in the United States

treatment of patients with multiple myeloma. This study recruited 351 patients over a period for one year in a randomized trial comparing the state of the art treatment of these patients with either Revlimid or placebo. Primary end point was time to disease progression, which was found to be a mean of 11.3 months in patients given Revlimid compared with 4.7 months for the reference group. Roughly this study can be estimated to have lasted for between two and three years. With this study in mind may assume that a phase III study will have to include in total about 400 patients. Provided the same clinical end points the study needs likely to prove an increased mean time to progression of the disease of significantly more than 11.3 months, indicating a trial of about three years of duration.

An average cost per patient in phase II was in 2006 calculated to be \$26000,-.<sup>81</sup> Based on these assumptions the costs for a clinical phase III is estimated to be about NOK 60 mill. and with a duration of three years.

### **8.1.5 Chemistry, manufacturing and control (CMC) costs**

There are strict requirements to documentation needed to use a product as a drug for humans. The vendor must prove that he can control the quality of manufacturing including impurity profile both as the drug substance and a formulated product, he must prove that the product is stable over a given shelf life etc. And to prove this also a set of analytical techniques for proving purity and identity is needed.

For this particular product we need to document the viral vector to be used for the genetic modification of the T-cell, and we need to characterize the T-cells themselves. In addition, depending on the business strategy we may need to establish a laboratory for production of genetically modified T-cells.

The production and documentation of the viral vector is most likely performed by a contract vendor. We expect that production of T-cells also may be purchased as a service at a research laboratory until phase III is well underway. A budget for establishing facilities for T-cell production is not considered in any details but estimated to be NOK 25 mill to be invested at the end of phase III. This investment is probably necessary only for the first indication chosen, but is anyhow included in all estimates to simplify the choice of initial indication. The price of the viral vector and the gene modification of the T-cells are set to 20% of the patient costs included quality control. In addition the CMC documentation and method development is estimated to cost NOK 2 mill/year.

### **8.1.6 Management costs**

The budget is based upon a management of two persons per indication up to phase III start. At that stage the staff is set to four. Average cost per man-year is set to NOK 1.5 mill.

## 8.1.7 Administrative costs

This includes use of consultants, development and maintenance of intellectual property rights, legal advice, purchase of reports etc. and is set to NOK 500.000 per year.

## 8.1.8 Concluded development budget

The above add up to a total cost of the development program for one T-cell based product of about NOK 200 mill. Table 8.1 below presents the numbers and timelines as estimated. Again, this is a best case scenario budget but obtainable provided a good product, a well planned and run development program, successful end point and inclusion criteria and performed in a lean and highly skilled organization with a good network of consultants at all levels.

Table 8.1. Development budget for one T-cell based drug

Year	2011	2012	2013	2014	2015	2016	2017	2018	2019
Phase									
R&D	500								
Preclinical		15000							
Clinical phase I/II				12000					
Clinical Phase III						60000			
Approval									1000
Production		1500	1500	1200	1200	6000	6000	6000	6000
Building factory							25000		
CMC documentation		2000	2000	2000	2000	2000	2000	2000	
Management	750	3000	3000	3000	4500	6000	8000	8000	8000
Administrative	500	500	500	500	500	500	500	500	500
SUM	1750	14500	14500	12700	14200	34500	61500	36500	15500

## 8.2 On the market

A different set of considerations is used when assessing the market situation. The most important aspects are:

- Price (guided by uniqueness, medical need and patient benefit, reimbursement etc.)
- Market size, acceptance and share
- Number of patients eligible for the treatment
- Production, marketing and sales costs
- Market development
- Time to generic competition

## 8.2.1 Price

The price of a product is set based on several factors such as the patient and society benefits (cost benefit/cost effectiveness aspects), cost of competing or alternative treatment, an assessment of what the market and regulatory authorities are willing to pay (reimbursements) etc. At an early stage like this a best estimate is done comparing with patient costs and approved drugs. Obviously, the price is also quite different depending on whether it is a treatment only adding a limited extra time to the patient's life or whether it is a curative treatment.

The estimated price range for the T-cell therapy used in our NPV assessments have been established based on a comparison with different treatments used today. A few examples of prices of treatments used to guide the choices are given below:

- The cost of an allogeneic bone marrow transplantation is ranging from \$30.000,- to \$200.000 giving a mean survival advantage of one year (see also Section 6.2).
- Rituxan treatment for chronic lymphocytic leukemia costs approximately \$35.000,- giving a mean progression free survival benefit of 10 months<sup>i</sup>
- The annual cost of lenalidomide (*Revlimid*) for a patient with multiple myeloma is \$74,000 giving a mean time to progression benefit of about 7 months<sup>82,83</sup>
- The cost of imatinib (*Gleevec*) for chronic myelogenous leukemia (400 mg/day dose) is NOK 290.000,- per year, corresponding to about \$50.000,- per year<sup>84</sup>.
- The cost for the recently FDA approved therapeutic vaccine for prostate cancer Provenge is \$93.000,-<sup>85</sup>. The main advantage lies not in increased life time compared with standard treatment, but in less adverse events. The increased median survival advantage documented is in fact only 4.1 months.<sup>86</sup>
- The cost of Avastin in the treatment of metastatic colorectal cancer is approximately \$20.000,- giving an increased progression free survival of 12 – 15 months<sup>87</sup>.

To become a commercial success the product do either need to add a significant survival benefit or alternatively a significantly reduced toxicity. Improvements in the range of 15 – 20% on at least one important outcome measure should be obtained to ensure a successful treatment and a good price<sup>88</sup>. Still the price will be in the same range as comparable treatments for the specific indication.

The current NVP calculations are made based on a base case of a low product advantage defining a price of \$20.000,-. A best case outcome is a curable treatment defending a price of \$60.000,- for the GVHD and multiple myeloma. This is likely not obtainable for FL and CCL diseases, also reflected in a lower best case price.

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<sup>i</sup> See also section 5.1.2. Calculated based on price information given by Felleskatalogen and dose recommendations for CLL treatment

## 8.2.2 Market size, acceptance and share

The market size as presented in Table 8.2 is estimated for each of the indications discussed in Section 6 and further adjusted for numbers of patients treated and the restriction due to the requirement of HLA-A2 positive patients.

Market acceptance depends on several different factors. First of all good and convincing data supported by key opinion leaders is important. Good publicity and marketing efforts making both medical community *and* the patients aware of the product is also highly important. There is a trend that media are more often used in the presentation of and thereby the promotion of new drugs based on the increasing empowerment of patients.

Another factor is the change of both routines and responsibilities in the treatment of patients. The two radiopharmaceutical drugs Bexxar and Zevalin have never found acceptance in the US market despite good clinical outcome. This is explained as a combination of high costs, difficult handling and administration and concerns over tolerability. An additional factor discussed for the lack of acceptance is that the ownership to and thereby the payments for the patient is moved away from the oncologist.

The T-cell based treatment will for in particular follicular lymphoma and chronic lymphocytic leukemia change the logistics in the treatment of the patients significantly, potentially being a market barrier. For acute myeloid leukemia/ allogeneic stem cell transplantation and for multiple myeloma treatment procedures used routinely today is much closer to this new therapy.

The fact that the treatment only targets about 50% of the population, i.e. HLA-A2 positive patients, may also in itself generate a barrier as it increases the complexity of the logistics in patient treatment.

Last but not least the market size itself is still to be considered. The treatment may be found to be adaptable to a segment of the target group only. Over the last decade a more detailed understanding of cancers has been obtained based on genetic mapping. This also results in use of companion diagnostic tools, separating responders of a treatment from non-responders. There is a risk that the T-cell based therapy may be found useful for only a segment of the HLA-A2 positive patients based on not yet recognized differences between patients.

In the NPV calculations we have given a score of high, medium or low in the three parameters “Competitive threat”, “Uniqueness” and “Considered Market Adaption” reflecting the issues considered above. These factors are then reflected in the “Expected Peak Market Share” numbers for the different indications and the price given (see Table 8.2 below). Note that the expected market shares used in these estimations are all very high. It is thus the expectation that they provide a significant improvement compared with the state of the art treatments.

## 8.2.3 Production, marketing and sales costs

The induced graft versus leukemia indication has one market advantage in that the number of customers, i.e. centers performing hematopoietic stem cell transplantation is limited, making the effort needed to promote the treatment less than for the other indications. However, no differentiation is made on estimated costs for marketing and sales for the different indications.

A fixed percentage of the revenue of 20% for cost of goods and distribution, 25% for sales and marketing and 10% for administration is used for all indications. An additional cost of NOK in total NOK 55 mill is budgeted for market introduction in 2018 – 2020.

### 8.2.4 Market development

Time to peak sales is an important parameter in the NPV model but difficult to predict. In the NPV model four different scenarios are used as shown in Figure 8.1:

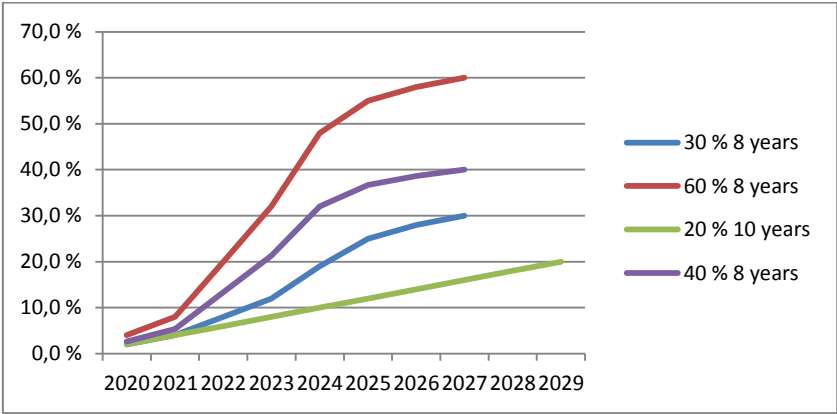


Figure 8.1. Time to peak sales estimates used in the NPV model

The time to peak sales are estimated based on a sales forecast model developed by Datamonitor for selected drugs for hematological malignancies. A graphical presentation is given in Figure 8.2:

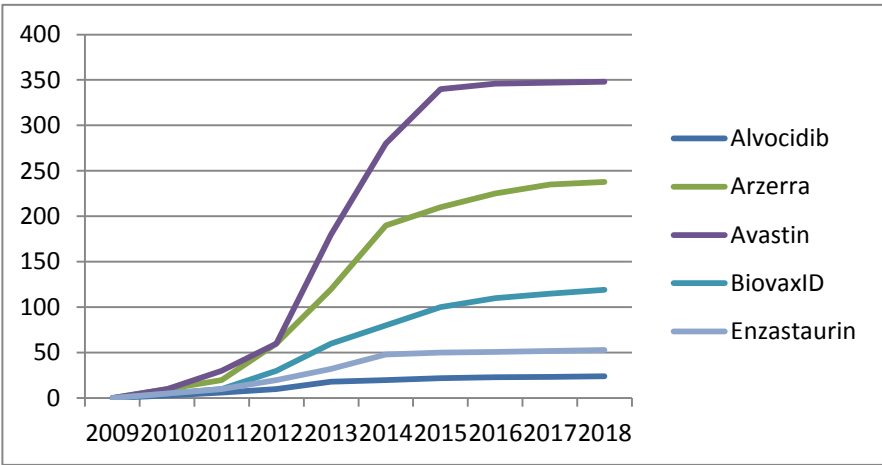


Fig 8.2. Market development for selected drugs for hematological diseases. Source Pipeline Insight: Hematological Malignancies: Companies target niche indications to facilitate market entry, Reference Code: DMHC2507 17 April 2009



## 8.2.5 Time to generic competition

The time to generic competition is ruled by the time to patent expiry for the patents covering the products. Patent protection is given for a period of 21 years from filing of a patent application, but for drugs a patent extension time of 3-5 years may be granted in most countries. As a full patent strategy for the different indications is not yet established, we have for the sake of simplicity calculated the NPV up to 2031, knowing that a product based on the technology may obtain an exclusive position also after this point of time, then increasing the value of the project.

## 8.2.6 Discount rate

In this NPV calculation a 12 % discount rate has been used. This is well below the expectations for a return of investment in a development phase while good for a product on the market. As this NPV calculation is for comparison between the different indications only and that numbers used are quite uncertain, the rate used is at this stage not important.

## 8.3 Conclusions

Table 8.2 below summarizes the NPV calculations for the different options for product development.

Table 8.2. NPV calculations for products developed for the different chosen indications.

		Market size US/EU (all patients)*	Competitive threat	Uniqueness	Considered market adaption	Expected peak market share	Time to peak market share	Price per patient (\$)	NPV (\$ mill.)	Peak sales (\$ mill.)
Induced graft versus leukemia in AML	Base case	5800	H	M	M	30 %	8 years	40.000	-\$15,5	\$15,7
	Best case		M	H	H	60 %	8 years	60.000	\$11,2	\$94,1
Multiple Myeloma	Base case	37000	H	M	M	20 %	10 years	20.000	\$1,1	\$66.7
	Best case		L	H	H	60 %	8 years	40.000	\$160,2,	\$400
Chronic Lymphocytic leukemia	Base case	16000	H	M	L	20 %	10 years	20.000	-\$19,6	\$28.8
	Best case		M	H	M	30 %	8 years	30.000	-\$9,0	\$43.2
Follicular Lymphoma	Base case	28000	M	M	M	20 %	10 years	20.000	-\$7,7	\$50,5
	Best case		L	H	H	40 %	8 years	40.000	\$145,2	\$201,8

For all indications the number of patients is in itself a challenge. This is in particular the case for induced graft versus leukemia in relapsed AML patients, where the competitive threat also seems large. A successful drug is in general found useful for several indications. This may also be the case for the CD20 product candidate, which may find its use also for other

indications that CLL or FL only making this a better case than what is presented as outcome in the table above. Thus CD20 for Follicular Lymphoma may be a good choice as a development candidate. The other preferred candidate would be a T-cell therapy for multiple myeloma.

In the further work to start a commercial exploitation of the research a much deeper look into the barriers for market entrance should be examined requiring expert interviews, preferably American as this is likely the preferred first market.

# 9 Emerging technologies and state of the art for T-cell therapy – threats and opportunities

Increased knowledge of research fields such as the human genome, the immune system, cell communication and signaling and general cancer biology have changed the field of cancer therapy from the simple approach of killing cells by cytostatic drugs or radiation towards mechanistic and to a certain extent personalized approaches. This research has not yet fully reached the patients; despite the increased biology knowledge the old cytotoxic chemotherapy regimens still dominate patient treatment.<sup>89</sup> This still leaves a room for the research of new and improved cancer treatments, and there are several different directions within this research. There is no expectation that one solution will create a therapy for all cancers; the cancer biology is too complex for this target to be met. An increasing age of the population also points towards an increased incidence of cancers in general. These factors leave new and improved cancer therapies a significant market.

As of August 2010 879 drugs are registered in Thomson Pharma database being in clinical development for cancer indications. This drug development represents a broad range of approaches for treating cancers. It is thus beyond the scope of this thesis to give an extensive overview over this field and its emerging technologies. Neither is it an expectation that decisions about developing the T-cell based technology should be made based upon a complete understanding of the trends in the cancer therapy. This topic is therefore only briefly discussed in general, while immunological approaches and in particular T-cell based therapy is discussed in more depth.

The main objective analyzing emerging technologies is to understand whether the technology is within the trends for new cancer therapies, as this in fact may reduce regulatory, financial and marketing hurdles.

## 9.1 Trends in cancer therapy

There are several ways to analyze the trends in cancer therapy, but there are only few scientific papers identified addressing this topic<sup>90,91</sup>. Three main areas are discussed below viewed to define important directions for the cancer research. Of these, immunotherapy is one of these areas and an area also including T-cell therapy.

### 9.1.1 Cancer stem cell drugs

One area having received significant attention recently is the cancer stem cell field. Understanding the microenvironment and transcription mechanisms in cancer is considered important to improve cancer therapy. This field has therefore received a significant attention

over last years, and this research effort has also resulted in a better understanding of the hierarchy of tumor cells and the process of metastasis generation. There is clear evidence that most tumors consist of several different cell types from slow cycling stem and progenitor like cells to mature cancer cells. Thus the term cancer stem cell (CSC) is now established in the scientific community. CSCs are characterized as a subpopulation of tumor cells that possess tumor initiation and self-renewal capacity<sup>92</sup>. The relative population of these CSCs may be quite low, but their stem cell like properties make them resistant to ordinary cancer therapy such as cytostatic drugs thereby causing relapse after treatment. Further it is considered that they have an active role in metastatic processes.

Stem cells have a series of unique pathways controlling their cell division and differentiation both in embryonic development and in tissue regeneration in adults. The most pronounced pathways are Notch, Hedgehog and Wnt, and these pathways are also identified in cancer stem cells and have therefore recently obtained significant interest as therapeutic targets in the treatment of cancers.

It should be noted that T-cell based therapies also have the potential to kill these slow cycling cells as the T-cells are designed to attack a group of cells rather than cancer cells as such. But further investigations are needed to confirm this.

### **9.1.2 Kinase inhibitors**

Another field receiving a significant interest is the kinase inhibitors, in particular tyrosine kinase inhibitors. After Novartis' success with the tyrosine kinase inhibitor Gleevec for the treatment of acute myelogenic leukemia several research groups have worked to develop new kinase inhibitors<sup>93</sup>. Kinases are enzymes regulating the activity of other enzymes by adding phosphate groups to these, so called protein phosphorylation. Cell growth and cell cycle pathways are activated in cancer cells, and often this is caused by mutation in a kinase or phosphatase gen. Blocking these kinases will thus prevent the cells undergo uncontrolled cell division.

### **9.1.3 Immunotherapeutic approaches to cancer therapy**

Immunotherapeutic approaches may in essence be defined as the use of the body's own immune system to fight the cancer. Three main classes of approaches may be identified: the use of monoclonal antibodies, vaccines (B- or T-cell vaccines) and administration of activated cytotoxic T-cells.

#### **Antibody therapy**

The success of the antibody based drug Rituxan initiated a substantial research effort towards other antibody based drugs, and as of August 2010 there were 15 different antibody drugs approved for different cancer indications including two radioactive drugs (Bexxar and Zevalin, see also section 6.2.1) and another 22 in late pipeline (phase III or under

registration). Antibodies bind to antigens on cell surfaces thereby e.g. inducing apoptosis (cell death). Antibody based cancer therapy has strongly influenced the cancer treatment over the last decade not least through Rituxan (see also Section 6.4).

### **Therapeutic cancer vaccines**

Cancer vaccines may be either preventive or therapeutic. Preventive vaccines are vaccines generating an immune response against foreign organisms known to cause cancers such as e.g. human papillomavirus (HPV) in cervical cancer. Therapeutic cancer vaccines are vaccines stimulating the immune system to destroy already established tumors, and this is yet another field having received significant attention over years. The idea is to stimulate the body's own immune system to kill cancer cells through generating either cytotoxic T-cells recognizing cancer cells or idiotypic antibodies initiating an immune response against the cancer cells. A major challenge is the lack of cancer specific antigens, i.e. antigens only expressed on the cancer cells. Most antigens expressed on cancer cells are so-called self antigens also found on normal cells. An immune response against these may therefore also cause an autoimmune response<sup>i</sup>. At this stage only one cancer vaccine has been launched, namely Provenge for the treatment of prostate cancer (see also Section 8.2.1), while the product BiovaxID is in phase III for the treatment of Follicular Lymphoma (see section 6.2.3.2). By August 2010 18 different therapeutic cancer vaccine products were in clinical phase III. The disease obtaining most attention is melanoma, a cancer known to be immunogenic but with no efficient therapy. Despite the quite active effort to bring forward therapeutic cancer vaccines it is questioned whether the cancer vaccine concept will bring important value to cancer treatment.<sup>94</sup>

### **Adoptive T-cell as a therapeutic approach in cancer<sup>ii</sup>**

As earlier discussed the immune system consists of two different mechanisms for destroying invading organisms, namely the antibodies generated by the B-cells, and the cytotoxic T-cells. Antibodies have been long exploited therapeutically; the first antibody based drug was approved by FDA in 1994<sup>iii</sup>. By 2010 a total of 28 different antibody based products had been launched on the market. It has long been the goal to exploit the cellular response mechanism, namely the cytotoxic T-cell, in a therapeutic setting in a similar manner. This "adoptive T-cell therapy" involves *ex vivo* selection, manipulation and expansion of either autologous or allogeneic T-cells for administration into the patient as therapeutic agents. The technology is developed as a method to circumvent the poor results of vaccines in cancer patients.<sup>95</sup> A requirement for therapeutically efficient treatment in cancers is that the cancer to be treated expresses tumor antigens, i.e. antigens that are found expressed on HLA class I molecules on cancer cells only (tumor specific antigens) or alternatively antigens overexpressed on tumor

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<sup>i</sup> See e.g. <http://www.csa.com/discoveryguides/cancer/review.php>, a review paper named "Cancer Vaccines" written by PG Kochar in 2006.

<sup>ii</sup> Adoptive T-cell therapy has also been used in e.g. the treatment of HIV, but this aspect of T-cell therapy is not further discussed here.

<sup>iii</sup> Abciximab, approved for the treatment of cardiovascular diseases

cells but also found on other cells in the body (tumor associated antigens). One tumor having received a significant attention with regards to adoptive T-cell therapy is malign melanoma. This is due to a lack of efficient treatment regimens combined with a high degree of expression of the tumor associated antigen MART-1. Dudley et al published in 2002 a clinical study on 13 patients receiving highly selected autologous T-cells after having been treated with immunodepleting chemotherapy. Six of the 13 patients had objective clinical responses to treatment and four others demonstrated mixed responses with significant shrinkage of one or more metastatic deposits<sup>96</sup>. This study is considered to “represent a milestone in cellular cancer therapy and a turning point for ACT<sup>i</sup> in cancer treatment”<sup>97</sup>. However, adoptive T-cell therapy is still not established as a therapeutic alternative for treatment of cancers. One explanation for this is the technical challenges in producing the tumor-specific T-cells, which is characterized by the key opinion leader Carl June to present a formidable barrier to conduct randomized clinical trials.<sup>98</sup> As of June 2010 80 different clinical studies involving adoptive T-cell patient treatment were registered at Clinicaltrials.gov. Of these only four active trials are sponsored by industry, pointing towards the challenges in commercial exploitation of the technology. The industrial initiatives are discussed further below. Note that HIV treatment is not considered in the discussions below, despite the fact that therapeutic use of modified helper T-cells is one approach being considered for this disease.

#### *Cell Medica Ltd*

The most advanced is a phase III study run by the UK based company Cell Medica Ltd., which is examining the potential clinical benefit of prophylactic cytomegalovirus (CMV)-specific adoptive cellular therapy following T cell depleted allogeneic hematopoietic stem cell transplantation (HSCT) for reducing recurrent CMV reactivation.<sup>99</sup> The therapy is given to avoid potential viral infections from CMV due to reactivation of the virus after transplantation and consists of giving virus-specific memory T cells from an HLA-matched donor to a patient following allogeneic bone marrow transplantation<sup>100</sup>. The study is recruiting about 110 patients. The commercial outcome is not clearly expressed, but Cell Medica is according to their home page a “cellular therapeutics company developing and providing clinical-grade cell-based products for individual treatment of immunocompromised patients suffering from life-threatening infections”.<sup>101</sup>

#### *Novartis Diagnostics*

Novartis Diagnostics (former Chiron Corporation) is currently running a clinical trial phase II study on metastatic melanoma patients based on lymphodepletion plus adoptive cell transfer with or without dendritic cell immunization. The product considered is not well defined in the study description.<sup>102</sup>

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<sup>i</sup> ACT – Adoptive Cellular Therapy, i.e. transfusion of T lymphocytes into patients

### *Sentoclone AB*

The Swedish company Sentoclone AB is also running clinical trial phase II study on malign melanoma and has also recently published data from a pilot study on colon cancer patients. The Sentoclone technology is based upon collection and expansion of helper T-cells (CD4+ cells) found in the sentinel lymph node, i.e. the lymph node draining the tissue where the cancer is located. The isolated T-cells are clonally expanded in vitro and thereafter administered back to the patients. This therapy is based on helper T-cells rather than cytotoxic T-cells but the challenges related to making the technology commercially attractive is similar. Their phase I study on colorectal cancer was in fact quite successful given that in four out of nine stage IV patients, complete tumor regression occurred. Median survival time in the stage IV patients (n = 9) was 2.6 years, as compared with 0.8 years in conventionally treated controls.

### *Kiadis*

Kiadis started recently a combined phase II/III study on their product ATIR™ which consists of mismatched donor lymphocytes depleted of allo-reactive T-cells and is designed to prevent acute graft versus host disease by eliminating the immune cells from the donor graft. The product thus enables the use of a mismatched donor improving the availability of donors.<sup>103,104</sup>

### *NKBio Co. Ltd*

NKBio Co. Ltd is a Korean company running a Phase III study aiming to compare the event free survival for 3 years of R-CHOP plus Biocell Natural Killer Cell to R-CHOP therapy with diffuse large B-cell lymphoma patients.<sup>105</sup> Only limited information about the company and its product is available in western languages.

### *Lentigen Corporation*

Lentigen Corporation is a US based company developing products based on their technology platform on delivering genes using lentiviral vectors. Their pipeline also includes T-cell based products for CLL and GVDH treatment<sup>106</sup>. They are currently running a clinical phase I pilot study using genetically modified T-cells on patients with chemotherapy resistant or refractory CD19 leukemia and lymphoma (CART-19).<sup>107</sup> Lentigen should be viewed as an important industrial actor, and through their product development they may in fact facilitate the route through the FDA bureaucracy for genetically modified T-cells.

### *Micromet AG*

Micromet AG is a German company developing novel antibody-based drugs for the treatment of cancer, inflammation and autoimmune diseases.<sup>108</sup> Their technology is not based on adoptive T-cell therapy, but rather on antibody like structures having a bispecificity enabling them to connect any cytotoxic T-cell to a cancer cell thereby killing the cancer cell. Two different cancer products are under development, namely Blinatumomab targeting CD19<sup>109</sup> and MT110 targeting the epithelial cell antigen EpCAM often overexpressed in tumors.

Binatumomab is currently developed for lymphoma and leukemia indications including follicular lymphoma. The concept is quite unique and exciting.

#### *Adaptimmune Ltd*

Adaptimmune Ltd is a British company focused on the use of T cell therapy to treat cancer and infectious disease. They aim to utilize the body's own machinery – the T cell – to target and destroy cancerous or infected cells by using engineered, increased affinity T cell receptor proteins (TCRs) as a means of strengthening natural patient T cell responses. Adaptimmune holds an exclusive license to the use of “this unique T cell receptor engineering technology” in adoptive T cell therapy from its sister company, Immunocore Ltd, and they are currently running a phase I study using gene modified T-cells on HIV patients in collaboration with University of Pennsylvania<sup>110</sup>. Adaptimmune's first cancer clinical candidate is based on a MAGE A3 TCR and is scheduled to begin clinical testing late 2010. On their webpage they claim to work with TCRs for the HLA-A2 antigens for NY-ESO, Melan A, gp100, HTERT and MAGE A3.

#### *MolMed SpA*

MolMed is currently in Phase 3 with genetically modified donor lymphocytes expressing herpes-simplex thymidine kinase suicide gene. The donor lymphocytes will accelerate the immune reconstitution and improve outcome through graft versus leukemia effect. However, upon severe graft versus host effect the T-cells can be wiped out by activating the suicide gene with a targeted drug mechanism.

#### *National Cancer Institute*

Of interest is also that the probably strongest research group in the field of genetically modified T-cells, namely Prof. Rosenberg's group at National Cancer Institute (NCI) in USA has made certain patents covering their adoptive T-cell technology available for licensing. The license opportunity is presented on the web-site of the company Inovaro Pharmalicensing, a leading partnering facilitator<sup>1</sup>.

## **9.2 Genetically modified T-cell receptor based approaches, research groups**

As also discussed in section 6.1 there are in essence four different major approaches for therapy by means of genetically modified T-cells using either T-cell receptors (TCRs) or chimeric receptors:

- Cancer cell specific T-cell receptors (i.e. receptors targeting cancer specific antigen targets)
- Chimeric antigen-specific receptors (CARs) (i.e. artificial receptors where the ordinary T-cell receptor is replaced by a structure resembling a monoclonal antibody. These receptors do not target HLA structures but rather other cell surface proteins. The targets may be tissue specific or tumor specific)

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<sup>1</sup> <http://pharmalicensing.com/public/outlicensing/view/4544/adoptive-t-cell-transfer-after-lymphodepletion-promotes-tumor-regression> (August 2010)



- T-cell receptors identified to target minor histocompatibility antigens
- Tissue or cell type specific T-cell receptors (the “Olweus approach”)

Table 9.1 below presents an overview over ongoing research in the field. The table presents the major target indications for the research performed with genetically modified T-cells with further reference to target, receptor type and research group.

Despite being an activity that has been ongoing for more than two decades there has been few groundbreaking results over the years; rather there has been a steady development towards improved results. One such example of continuous development is signaling improvements for the chimeric receptors, where the currently used receptor technology is often characterized as “third generation receptor technology”.<sup>111</sup>

Further, the most extensive research effort has been directed towards developing the chimeric receptor technology. However, a major challenge exploiting the CAR technology has been the lack of signaling properties, i.e. generating T-cells that are able to kill the target cells. So-called third generation receptors at least partly circumventing this problem have only recently been tested. Several review papers summarize the results, and reference is made to some of these for further reading.<sup>112,113,114</sup>

The use of genetically modified T-cells defines as can be seen from Table 9.1 several options both with regards to potential approaches and indications. The first study using genetically modified T cells in patients with cancer was published as early as 1990. The goal in this study was to track tumor infiltration by marking the T cells. Their pharmacological function was thus not altered<sup>115</sup>. The pioneer was Steven Rosenberg, who still is actively working in this field at National Cancer Institute in Bethesda. Rosenberg and his group over the years have had a dominant position in this field. They have worked both with chimeric and HLA directed T-cell receptors and also several different indications, although their major focus has been on malign melanoma. The National Cancer Institute runs currently six different clinical studies with genetically modified T-cells, whereof prof. Rosenberg is responsible for five.

Table 9.1. overview over academic research within genetically modified T-cells

Cancer type	Target antigen	Receptor type	Research institution	Highest development phase	Reference
Leukemia and Lymphoma	CD19	Chimeric	Baylor College of Medicine	Phase 1	116
			Lentigen, University of Pennsylvania	Phase 1	117, 118
			M.D.Anderson	Phase 1	119, 120
			Memorial Sloan-Kettering Cancer Center, National Cancer Institute	Phase 1	121, 122
			City of Hope Medical Center	Phase 1	123
			Childhope	Preclinical	124
	CD19L	HLA class II, minor histocompatibility complex	University Medical Center Utrecht, 3584CX 100 Utrecht, Netherlands	Discovery	126
	CD20	Chimeric	Fred Hutchinson Cancer Research Center, City of Hope, National Cancer Institute	Phase 1	127, 128
	CAR-K (kappa light chain of human immunoglobulin)	Chimeric	Baylor College of Medicine	Phase 1	129, 130
	CD33	Chimeric	Childhope	Preclinical	131
undisclosed		Christie Hospital Manchester	Preclinical	132	
Friend Murine Leukemia Virus derived gag HLA-A2	TCR	Fred Hutchinson Cancer Research Center Beth Israel, Boston University of Washington, Seattle	Discovery	133	
EBV latent membrane protein AdE1-LMP	likely not genetically modified	Queensland Institute of Medical Research	Phase 1	134	
WT1 peptide pWT126 Wilms Tumor Antigen I		UCL University College London	Preclinical	135, 136	
GVHD	Suicide gen	-	Washington University School of Medicine	Phase 1	137
	HA-1 / HA-2 (minor histocompatibility complex)	TCR	Leiden University Medical Center	Preclinical	138
Hodgkin's Lymphoma	CD30	Chimeric	Baylor College of Medicine	Preclinical	139
Melanoma	MART-1	TCR	National Cancer Institute (NCI)	Phase 2	140, 141
	p53	TCR		Phase 2	142
	MART-1/Melan-A - HLA	TCR	Laboratory of Clinical and Tumor Immunology, Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam University of Padova Imperial College, London San Rafael Institute, Milano	Phase 1	143
	NY-ESO-1	Chimeric	Fred Hutchinson Cancer Research Center	Closed?	144
	diasialoganglioside GD2+EBV		Baylor College of Medicine	Preclinical	145

Glioblastoma, Neuroblastoma, Medulloblastoma	LI-CAM	Chimeric	Baylor College of Medicine	Phase 1	146
	IL13Ralpha2	Chimeric	City of Hope Medical Center	Phase 1	147, 148
	HER2	Chimeric	Baylor College of Medicine	Phase 1/2	149
	diasialoganglioside GD2+EBV	Chimeric	Baylor College of Medicine	Phase 1	150
Breast cancer	HER2	Chimeric	City of Hope Medical Center	Preclinical	151
	CEA	Chimeric	Roger Williams Medical Center	Phase 1	152
CEA positive cancers, including adenocarcinoma, colorectal cancer, prostate cancer, gastric cancer and metastatic CEA-expressing cancer	CEA	Chimeric	Christie Hospital Manchester	Phase 1	153
		Chimeric	Beth Israel Deaconess Medical Center (Harvard)	Phase 1	154
		TCR	National Cancer Institute (NCI)	Phase 2	155
		Chimeric	Roger Williams Medical Center	Phase 1	156, 157, 158
Osteosarcoma	HER2	Chimeric	Baylor College of Medicine	Phase 1	159
Lung cancer	HER2	Chimeric	Baylor College of Medicine	Phase 1	160
Epithelial cancers including breast, ovarian, lung, prostate	Lewis-Y carbohydrate antigen	Chimeric	University of Melbourne, Australia	Preclinical	161
Renal Cell Carcinoma	Carboxy-anhydrase-IX (CAIX)	Chimeric	Erasmus University Medical Center–Daniel den Hoed Cancer Center, Rotterdam, the Netherlands	Phase 1	162
	HLA-A2 with tumor specific antigen	TCR	Helmholtz Zentrum München	Discovery	163
	DR4 or TRAIL	not disclosed	National Cancer Institute (NCI)	Phase 1/2	164
Testis class cancer	NY-ESO-1	TCR	National Cancer Institute (NCI)	Phase 2	165, 166
metastatic cancers	HER2	not disclosed	National Cancer Institute (NCI)	Phase 1/2	167
Ovarian Cancer	p53	Chimeric	National Cancer Institute (NCI)	Phase 1	168

In discussions with prof. Olweus the differences between T-cell receptors, chimeric receptors and minor antigen approach has been discussed and is further summarized in Table 9.2. Despite the high degree of attention given to the chimeric technology the approach of generating T-cell receptors attacking HLA-peptide complexes have several advantages. The major *disadvantage* is the lack of cancer specific targets. This is, however, circumvented by prof. Olweus through defining the target as being a cell or tissue specific antigen.

To summarize the situation in short as analyzed from the discussions with prof. Olweus and analysis of the scientific literature, the major conclusions seems to be:

- Both genetically modified T-cell receptors and chimeric receptors receive significant attention in research communities developing the technology towards clinical use

- However, the industrial interest in bringing the technology to the market is modest, pointing towards that this is still a premature technology with significant hurdles for bringing the technology into the market.
- Chimeric receptors have an advantage with regards to broad selection of targets
- T-cell receptors have a clear advantage in the ability to obtain efficient killing of diseased cells.
- The approach used by Olweus to identify new T-cell receptors as described in Section 4 is quite unique, and there are two groups only working on this aspect of generation of new T-cell receptors. This is prof. Olweus' group and prof. Schendel's group at the Institute of Molecular Immunology, GSF National Research Center for Environment and Health in Munich, Germany.
- As such the major competitor scientifically seems to be prof. Schendel. The major difference in research approach is that while Schendel's work is directed towards cancer specific antigens, Olweus has her focus on tissue or cell type specific antigens.
- Schendel does also seem to have ambitions to commercialize her results as she has been quite active in filing patent applications on her new research results<sup>169</sup>. However, no signs of industrial collaboration or start-up company activity have been identified so far.

Table 9.2. Comparison between different approaches for T-cell therapy

<b>Asset</b>	<b>TCR targeted at major Hag<sup>1</sup></b>	<b>CAR</b>	<b>TCR targeted at MINOR Hag</b>
<b>Targets</b>	Intracellular targets (i.e. peptides produced inside the cell and presented on HLA) in addition to extracellular targets. The number of IC targets is manifold higher than the number of EC targets.	Extracellular targets only, either as tissue or cancer specific receptors	Difficult to identify targets that are expressed on commonly expressed HLA molecules
<b>Binding properties</b>	Anticipated lower binding strength but then higher degree of serial killing properties for the T-cells (ability to kill more tumor cells)	Higher binding strength likely to lead to lower degree of serial killing	Anticipated lower binding strength but then higher degree of serial killing properties for the T-cells (ability to kill more tumor cells)
<b>Signaling</b>	Strong signaling properties	Likely lower signaling properties than for TCRs	
<b>HLA dependency</b>	Dependent of correct HLA type => One product will never catch more than 50% of the market	Independent of HLA typing => One product may target the whole patient population	Dependent of correct HLA type => One product will never catch more than 50% of the market
<b>Clinical data</b>	Proven effect in melanoma patients (MART-1)	Clinical studies ongoing on several cancer diseases. Safety issues have in a particular case shown to be a concern.	
<b>For B-cell cancers</b>	CD20 is viewed to be a preferred target for indolent cancers such as FL and CLL	CD20 studies have not been successful so far. Main focus CD19, which is primarily acute B-cell cancer target.	
<b>Risk for unwanted immunological response</b>	Dependent upon choice of peptide	Risk for HAMA-response	Not suitable for B-cell therapy
<b>Receptor expression</b>	Modification needed to avoid mis-pairing	Modification needed to obtain signaling. Current research is on third generation receptors modified to obtain this	Modification needed to avoid mis-pairing

<sup>1</sup>Hag – histocompatibility antigen

## 9.3 Conclusions

Adoptive T-cell therapy is one of a broad range of different approaches for cancer therapy. But as demonstrated by Table 9.2 above, the technology has the potential to be used for the treatment of a broad range of different cancer diseases. The commitment demonstrated by several strong research groups gives an indication of a technology with a good potential for success. However, low industrial interest shows that therapy by means of genetically modified T-cells is at an early stage with respect of commercial exploitation,

However, two companies have started a process to get this technology out on the market, namely Lentigen and Adaptimmune. Their activities should be monitored thoroughly. Prof. Olweus' approach for exploitation of the technology is different from the approach chosen by other research groups and the industry, generating an option for a unique position in the market.

# 10 Intellectual Properties

An in depth assessment of the intellectual property position for this technology is beyond the scope of this thesis and will thus not be discussed in details. However, the intellectual property position is a key parameter for success in the market as it determines the ability to position the product in the market. For pharmaceuticals patent protection is the major way to obtain market exclusivity for a product. In general patent protection is obtained through filing of applications for patents to national patent authorities, and the patent rights are obtained through negotiations with these authorities. The requirements for obtaining patent rights are that the invention claimed should be novel, inventive and industrially exploitable. When obtaining a patent the owner of the rights can prevent other from making, marketing and selling a product covered by obtained claims. It does not, however automatically give the rights to sell a product covered by the obtained claim, as rights to other aspects of the product may be held by a third party. Thus, assessing intellectual property rights is both to understand own patent protection and to understand whether a third party can claim rights to part of the technology and thereby challenge the freedom to practice selling the product.

## 10.1 Patent protection

At this stage a patent covering key elements of the CD20 technology has been filed, and claims covering a product are expected<sup>170</sup>. New patent applications should be filed for the other indications

## 10.2 Freedom to operate

The term “freedom to operate” denotes the ability to sell a product without being dependent upon a license from a 3<sup>rd</sup> party. A freedom to operate assessment has not yet been performed. There is, however, a risk that certain elements of a possible product design are covered by third party patents eventually result in royalty obligations. Third party rights may thus influence on choices in product design.

## 10.3 Conclusions

It is expected that a product resulting from Dr. Olweus research will obtain patent protection. However, third party patents possible being infringed by a product may reduce the freedom to operate thereby resulting in royalty obligations. Third party patents potentially covering aspects of the products should be identified and analyzed before important choices in product development are made. It seems unlikely that any third party should completely block the possibility to get a product to the market.

# 11 The team developing the technology

One conclusion possible to draw from the former Sections is that developing a new drug is a complex and competence intensive process. The technology assessed here defines also to a certain extent a new class of products not yet having entered the market. Thus the technical and commercial risks associated with the products are considerable. Developing a new drug requires in general a strong team representing a broad range of skills. And this is not least valid for this technology.

## 11.1 The team today

The team as of today represents highly skilled researchers with prof. Olweus as the key driver. They are located at Institute for Cancer Research at Radiumhospitalet, Oslo University Hospital, a center that is housing 300+ scientists within the field. The research performed at this center holds a high international standard. Prof. Olweus and her group have also established a strong network of academic partners outside Norway. They have through the results obtained proven the ability to perform academic research at a high international level.

Business development is at this stage performed by the technology transfer office (TTO) for Oslo University and Oslo University Hospital, namely Invent2 (former Birkeland and Medinnova, now merged. See also [inven2.com](http://inven2.com)). Inven2 holds the rights to commercial exploitation, and handles also all contractual, intellectual property and business development issues. Invent2 is staffed to act professional and make sound business development decisions on projects like this.

## 11.2 The team of tomorrow

When appropriate, further development of the technology has to be performed in an industrial setting. Inven2 makes the final decision about when this should take place and the way to develop the product. They have in essence two options, either to license the technology to an existing pharmaceutical company or make a start-up company further developing the technology. If the latter is chosen, there are two different models for running the company:

- The technology can be developed in a lean organization purchasing all services from contract research organization and other specialists. The core team should have high skills on business development and pharmaceutical project management.
- The technology can be developed in a company staffed with key competence people running an in-house research and development. Further core skills should be business development and likely also regulatory and clinical development. An extensive use of contract research organizations will still be needed.



Development in a start-up requires investment capital. Thus part of the business development performed by Inven2 is to identify risk capital willing to invest in product development in a start-up company setting. The choice between the two company models will be made by the board of the start-up company. Recruiting skilled people both on the board and in the company and identifying strong service providers and collaborating research organizations will be a main element for success.

Despite the chosen model for commercial exploitation a strong collaboration with prof. Olweus is a prerequisite. She represents a unique competence regarding several important aspects of both product characteristics and the clinical effect of these products. It is also likely fruitful to have a strong collaboration with other key persons the Institute for Cancer Research.

A skilled team for the first phase of the product development phase and agreements giving access to both research results and core competence in the research environment should be organized early.

# 12 Summary of the findings

In the former sections a set of different aspects have been analyzed to understand the opportunities, barriers and the probability to succeed getting products from the research of prof. Olweus to the market for use in patient treatment. The assessments have been made assuming that products for all indications are at the same stage in in the research process and thus ready for initiating product development.

In the following a summary of the findings are made with a particular attention on the opportunities and barriers for product development.

In Figure 12.1 below the information is classified in five different areas further discussed.

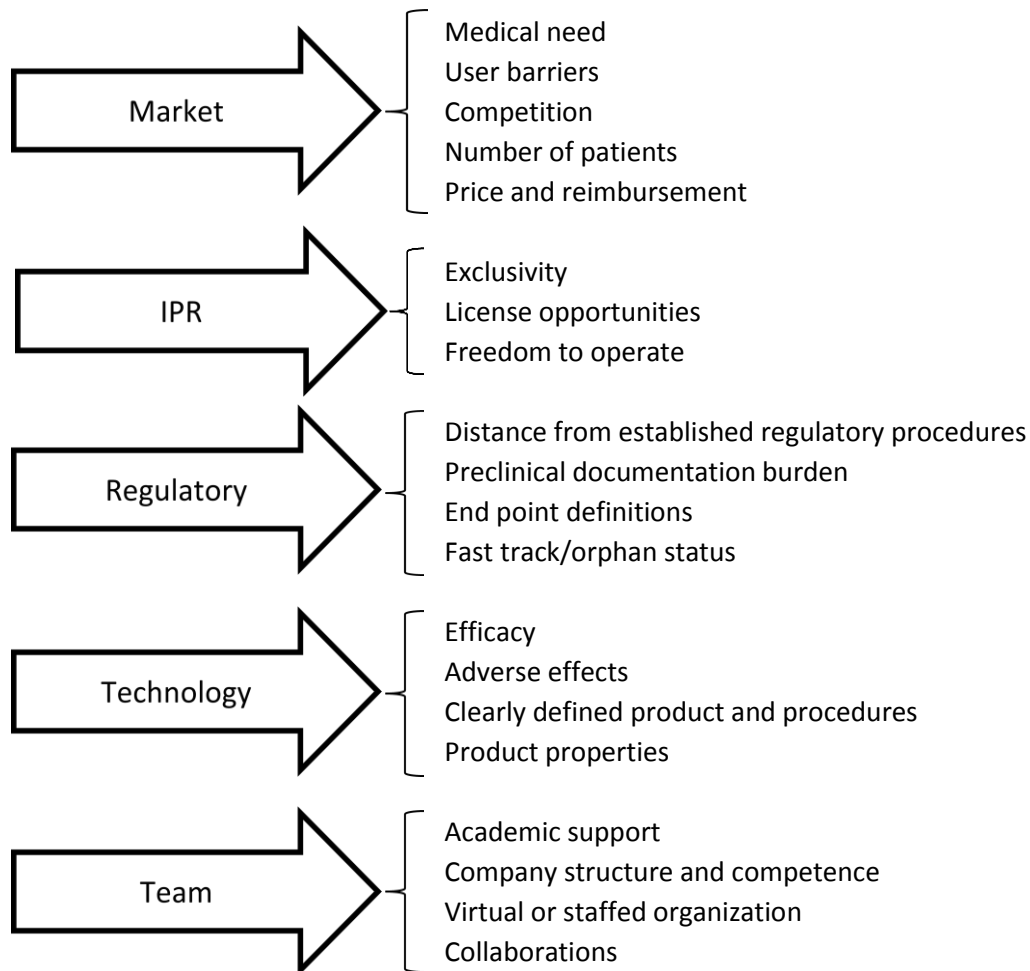


Figure 12.1 Assessed areas

## 12.1 Market

Four different indications have been addressed, namely treatment of the cancers follicular lymphoma, chronic lymphocytic leukemia and multiple myeloma and induced graft versus leukemia effect after hematopoietic stem cell transplantation. For all these indications a clear medical need is identified.

The number of patients eligible for the treatment has been identified for all indications. Further a reasonable price for the products are estimated based on comparison with existing drugs and treatment regimens. NPV calculations have then been performed using a low end development cost budget and time to peak sales in the market as expected for drugs for these indications. Market shares for the different indications were estimated based on medical need, expected user barriers and competitive threat.

Based on this analysis, the indication that stands out as a preferred starting point for product development is multiple myeloma. Induced graft versus leukemia effect after hematopoietic stem cell transplantation scores low based on a limited number of patients combined with a higher competitive threat. Chronic lymphocytic leukemia also scores low, and this is primarily due to the risk of low market acceptance due to a considerable change of treatment regimens (i.e. a high user barrier) combined with high age on the patients likely making a lower number of the eligible for the treatment.

The NPV numbers calculated are obviously far from carved in stone, and the only use they find at this stage is a direct comparison between the different indications. But for this purpose they are considered to add value to the assessment.

## 12.2 IPR

Patent protection for all products is expected, leaving an exclusive right to produce, market and sell these.

No assessment of infringements of third party patents has been made, and further there has been no work performed to identify possible patent hurdles caused by third party patents.

## 12.3 Regulatory

This may turn out to be the main barrier for getting a product out on the market in a reasonable speed. The main hurdle is the use of gene modified cells. Further carefully designed clinical studies are critical for a success. The two most important aspects for clinical design are

- a) the inclusion criteria of patients, which eventually determines the size of the market
- b) the end points of the study, which both determines the uniqueness of the product thereby the price and also the time required to perform the study.

## 12.4 Technology

An outcome of the research will be a proposed structure of a T-cell receptor for the use in each target indication. This represents a well-defined structure for the receptor – HLA interaction. However, there are characteristics by an eventual product likely governed by other parameters than research results only. Aspects to be considered include besides the receptor itself elements such as:

- Permanent or transient T-cell population, and how to control this
- Technology for linking the two chains
- Choice of genetic vector
- Details in all process steps
- Selection of patient's T-cells
- Methods for characterization of all products and intermediates
- Stability requirement and stability control

A preliminary target product profile (TPP) has been established as part of this work, but an in-depth analysis of these elements has not been performed. Permanent or transient T-cell population will likely impact the adverse effect profile of the product.

## 12.5 The team

A strong research team is performing the research generating the fundament for this business opportunity. They are working together with a good team at Inven2 performing the early stage business development.

The product development is considered extremely complicated and multi-disciplinary. Thus recruitment of skilled and experienced team members and the identification of strong collaborating organizations and clinical research groups is a requirement for success.

# 13 Financing product development

As discussed in Section 8 the capital needed to develop these drugs are substantial. Further the risk associated with the product development is also quite high. Thus it might be difficult to identify risk capital in early phase willing to invest in the technology development.

The investment decisions are in general made on few parameters. In short this may be summarized to:

- Is there a market and a need?
- What are the major risks, and can we tackle them?
- Is there a skilled team or a way to build one?
- How is the IPR situation?
- What is the business model, and how do we earn money
- Can we identify value adding milestones, and is there a revenue generating exit?

A business plan made to raise capital must address all these issues.

There are both positive and negative aspects about raising capital for drug development in a Norwegian setting. The unique combination of world class academic cancer research and a strong link between academia and industry is viewed to strengthen the chance to succeed doing cancer drug development in the Oslo area. The Oslo Cancer Cluster initiative being internationally recognized is a major asset in this context. On the other side there is a lack of Norwegian investors doing early stage drug development. As this is an above average challenging product development, skilled investors should be the target in the fund-raising process.

# 14 Conclusions and recommendations

The aspects discussed above indicate that the risk for failure associated with developing a product for the market based on genetically modified T-cells is high at this stage. The most pronounced risk factors seems to be

- the regulatory requirements
- the market acceptance and user barriers
- technical success, i.e.
  - Clinical effect - identified patient groups should obtain measureable disease improvements within reasonable study duration
  - Adverse effects

Certain risk reducing activities can be initiated early in the development process, such as

- Regulatory
  - Seek advice from competent consultants as part of the early stage planning
  - Establish dialogue with regulatory authorities immediately after product development is initiated
- Market acceptance
  - Interviews with key opinion leaders and industrial consultants.
  - Establish dialogue with larger pharmaceutical companies at an early stage

The increased requirements for cost effectiveness for patient treatment should also be addressed at an early stage in the process of developing this product. This is deemed to be expensive products, pointing towards challenges getting reimbursement and thus market acceptance.

Clinical effect is often proven in well considered animal models in preclinical phase. Here few effect models are available. Thus proven effect will be an issue until late in the product development. To reduce this risk Prof. Olweus has initiated a clinical study using donor T-cell clones selected on basis of their ability to attack CD20 peptide expressing B-cells in the patient.

The most pronounced adverse effects are likely due to a permanent removal of B-cells in the treatment of FL, CLL and MM. This lack of B-cells may lead to both infectious diseases and cancer development in treated patients post treatment. The effect can be avoided securing that the T-cells are present only temporarily, i.e. that they are either removed by means of suicide gens or that they else can be proven not to establish themselves as memory T-cells in the body. This adverse effect aspect is not viewed as a high risk for a product directed towards induced graft versus leukemia effect after hematopoietic stem cell transplantation.

T-cell based technology represents a unique business opportunity potentially also reaching further than the current research performed by Prof. Olweus. Both for cancer and for autoimmune diseases cell based therapy performed by genetic modification of the patients

own T-cells may well be an established technology 15 – 20 years from now. Thus there may be room for an industry specializing in making and shipping genetically modified cells for the treatment of patients within a set of different diseases. There are a few companies working today to enter into this niche, and Prof. Olweus' research may open for this as an industrial opportunity in a Norwegian setting.

The following recommendations are made for the further development of this technology in a commercial setting:

- Await investments made in product development until at least one receptor structure is decided
- In the meantime secure the patent situation for the project
- When initiating product development, start the process with a small investment in risk reducing activities on regulatory and market aspects of the product, including
  - Get regulatory advice
  - Get market input both from industrial consultancy companies and key opinion leaders. This input should be used
    - to identify market opportunities and barriers
    - to evaluate business model / product (i.e. vector or cells)
    - determine willingness to pay, reimbursement options and patient populations
  - Analyze the freedom to operate with regards to important elements of the product
  - Get industrial feedback on the concept
- Identify a skilled team for the development
- Chose a first product and indication as one with the lowest risk profile. This may initially be more important than market size.

For complex product like these, the major market is likely found in USA. However, the restrictions introduced in England based on cost effectiveness of new treatments should be taken into account, as they points in a direction likely to be followed by health authorities in most countries including USA. The need for cost control may generate additional barriers for the development of complex personalized medicine concepts.

# Appendix 1 Dictionary

1st line treatment	Initial treatment used to reduce a cancer. First-line therapy is followed by other treatments, such as chemotherapy, radiation therapy, and hormone therapy to get rid of cancer that remains. Also called induction therapy, primary therapy, and primary treatment.
2nd line treatment	Treatment of relapsed or refractory cancers
adenovirus	A member of a family of viruses that can cause infections in the respiratory tract, eye, and gastrointestinal tract. Forms of adenoviruses that do not cause disease are used in gene therapy. They carry genes that may fix defects in cells or kill cancer cells.
adjuvant therapy	Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy
allogenic	Taken from different individuals of the same species. Also called allogenic
allo-reactive	Pertaining to the immune response in reaction to a transplanted allogeneic graft
antibody	A protein made by plasma cells (a type of white blood cell) in response to an antigen (a substance that causes the body to make a specific immune response). Each antibody can bind to only one specific antigen. The purpose of this binding is to help destroy the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen.
autologous	Taken from an individual's own tissues, cells, or DNA.
B-cell	Lymphocyte cells in the adaptive immune system responsible for making antibodies
codon	Tri-nucleotide units in the genetic material coding for a specific amino acid in protein building
complete remission	The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete response.
consolidation therapy	Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy
cryoprotectant	A substance protecting biological tissue from damage upon freezing
cysteine	A naturally occurring amino acid
cytotoxic	Cell-killing
dendritic cell	A special type of immune cell that is found in tissues, such as the skin, and boosts immune responses by showing antigens on its surface to other cells of the immune system. A dendritic cell is a type of phagocyte and a type of antigen-presenting cell (APC).



disease-free survival	The length of time after treatment for a specific disease during which a patient survives with no sign of the disease. Disease-free survival may be used in a clinical study or trial to help measure how well a new treatment works. Also called DFS and disease-free survival time.
HAMA-effect	Allergic reaction to the mouse antibodies
hematopoietic tissue	Tissue in which new blood cells are formed.
HLA	One of a group of proteins found on the surface of white blood cells and other cells that play an important part in the body's immune response to foreign substances. These antigens vary from person to person, and HLA tests are done before organ transplantation to find out if tissues match between a donor and a recipient. Also called human leukocyte antigen and human lymphocyte antigen.
idiotype	Shared characteristic between a group of immunoglobulin or T cell receptor (TCR) molecules based upon the antigen binding specificity and therefore structure of their variable region
inflammation	Part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants
lentivirus	Lentivirus is a subclass of the Retrovirus family. A lentovirus can deliver genetic information into the DNA of the host cell and have the unique ability among retroviruses of being able to replicate in non-dividing cells. Lentiviral vectors are therefore used to introduce genes into a broad range of tissues and can be used in vivo.
leucocyte	A type of immune cell. Most leukocytes are made in the bone marrow and are found in the blood and lymph tissue. Leukocytes help the body fight infections and other diseases. Granulocytes, monocytes, and lymphocytes are leukocytes. Also called WBC and white blood cell.
leukapheresis	Removal of the blood to collect specific blood cells. The remaining blood is returned to the body.
lymphodepletion	Non-selective method of eliminating several known regulatory, or immunosuppressive, subsets of immune cells, such as regulatory T cells.
macrophage	A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells.
maintenance therapy	Treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy. It may include treatment with drugs, vaccines, or antibodies that kill cancer cells, and it may be given for a long time.
major histocompatibility complex	see MHC
mesenchymal	Cells that develop into connective tissue, blood vessels, and lymphatic tissue.
MHC	One of a group of proteins found on the surface of white blood cells and other cells that play an important part in an organisms immune response to foreign substances. In humans named HLA
murinization	Replacement of parts of human proteins with corresponding murine domains
myeloablative	High-dose chemotherapy that kills cells in the bone marrow, including cancer cells. It lowers the number of normal blood-forming cells in the bone marrow, and can cause severe side effects.

myelogenous	Produced by or originating in the bone marrow.
overall survival rate	The percentage of people in a study or treatment group who are alive for a certain period of time after they were diagnosed with or treated for a disease, such as cancer. The overall survival rate is often stated as a five-year survival rate, which is the percentage of people in a study or treatment group who are alive five years after diagnosis or treatment. Also called survival rate.
pathogen	A biological agent that causes disease to its host.
peptide	A molecule that contains two or more amino acids (the molecules that join together to form proteins). Peptides that contain many amino acids are called polypeptides or proteins.
phagocytosis	The process by which a phagocyte (a type of white blood cell) surrounds and destroys foreign substances (such as bacteria) and removes dead cells.
phenotype	Any observable characteristic or trait of an organism: such as its morphology or biochemical or physiological properties,
progression-free survival	The length of time during and after treatment in which a patient is living with a disease that does not get worse. Progression-free survival may be used in a clinical study or trial to help find out how well a new treatment works. Also called PFS.
protein	A molecule made up of amino acids that are needed for the body to function properly. Proteins are the basis of body structures such as skin and hair and of substances such as enzymes, cytokines, and antibodies.
quality of life	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out various activities
receptor	A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell.
refractory cancer	Cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment. Also called resistant cancer.
relapse	The return of signs and symptoms of cancer after a period of improvement.
response rate	The percentage of patients whose cancer shrinks or disappears after treatment.
T-cell	Lymphocyte cells in the adaptive immune system important in cell-mediated immune responses. There are several different subclasses of T-cells.
therapeutic cancer vaccine	see vaccine therapy
transfection	Introduction of DNA into a cell
Transposon	semi-parasitic DNA sequences which can be used e.g. for introduction of DNA into cells
vaccine	A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms.
vaccine therapy	A type of treatment that uses a vaccine

## Appendix 2 Sources for information, databases

Thomson Pharma	Business Intelligence database for pharmaceutical industry. Pipeline and market data.
Thomson Pharma Partnering Forecast	As for Thomson Pharma, in depth information on market shares and market prognosis
Datamonitor	Business Intelligence reports for pharmaceutical industry.
SEER Review Cancer Statistics	The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute
Globocan	Database for cancer incidence and mortality for all countries
BioMed Experts	Literature-based scientific social network service

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