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Market analysis for cancer diagnostic biomarkers.

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Abstract

In this essay, the market for cancer diagnostic antibodies is explored. The market analysis has been produced using mainly internet research and interviews with key persons in the filed. Also, a technical part that gives background information about antibodies and current cancer diagnostic methods is presented. The information obtained is meant to serve as background information for an antibody discovery company that wishes to develop a strategy for its antibody out-licensing activity. More precisely, this market analysis includes the identification and description of the actors that are active in the field of diagnostic biomarkers, their licensing activity and the structure of the licence agreements that they enter.

Keywords

biotechnology licensing, diagnostic antibodies, immunohisotchemistry, license agreement

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ABSTRACT
One of the tools that modern pathologists use when diagnosing and fighting cancer is significantly gaining importance; The antibody. Diagnostic antibodies are used in immuno histochemichal tumour stainings to reveal the tumours' specific features. Today, more and more important cancer diagnostic antibodies are being discovered and the information they provide will help clinicians to determine what treatment is most suitable for each specific cancer patient.

The request for new and better cancer diagnostic biomarkers is increasing, and more biomarker discovery companies are entering the market for diagnostic biomarkers. A problem for the emerging companies is that it is difficult to access information about the fast evolving market for diagnostic biomarkers that previously has not been satisfactory described. Information about the actors involved in the process of bringing a diagnostic biomarker from discovery to the market and the relationship they have with each other is difficult to access. This information is crucial to possess for companies that wish to enter the market for diagnostic biomarkers.

In this essay, the market for cancer diagnostic antibodies is explored. Also, a technical part that gives background information about how antibodies are obtained and current cancer diagnostic methods is presented. The information obtained is meant to serve as background information for a biomarker discovery company that wishes to develop a strategy for its out-licensing activity. More precisely, this market analysis includes the identification and description of the actors that are active in the field of diagnostic biomarkers, their licensing activity and the structure of the licence agreements that they enter. Also, the financial incentives that drive the development of cancer diagnostic methods are described in a chapter about Pharmaco Diagnostics.

Internet research has led to the identification of the actors involved in biomarker development. The licensing activity of the involved actors has been obtained from a broad collection of press releases and interviews with representatives from the managements of the companies.

The structure of the license agreements between the biomarker discovery company and its possible licensees is discussed and compared to the license agreements conducted between the actors involved in the drug discovery process.

Market analysis for cancer diagnostic biomarkers

Ebba Kraemer

Sammanfattning

Licensierings- och samarbetsavtal är en viktig del av forskningsintensiva bioteknikföretags affärsutvecklingsstrategier. Oavsett om bioteknikföretaget fokuserar på att utveckla potentiella läkemedel, teknikplattformar eller diagnostiska test tecknar det förr eller senare ett licensavtal med ett större farmaceutiskt eller diagnostiskt bolag. På så vis får bioteknikföretaget en inkomst och produkten eller tekniken som utvecklats kan, genom den nya kapitalstarka ägaren, nå marknaden.

Antikroppstillverkaren Atlas Antibodies närmar sig framöver den punkt då de kommer att licensiera ut rätten att använda biomarkörer för cancerdiagnosiska syften. Innan detta sker behöver de göra en grundlig marknadsundersökning för att bestämma licensens rätta prislapp och hitta lämpliga köpare. Som ett steg i Atlas Antibodies marknadsundersökning identifieras i detta arbete de industrier och de specifika företag som är potentiella framtida partners till Atlas Antibodies. In-licensieringsstrategier för dessa möjliga partners liksom deras tidigare slutna licensieringsavtal behandlas i korthet. Avslutningsvis presenteras riktlinjer för en möjlig struktur på licensavtal som passar de speciella förhållanden som gäller för diagnostiska biomarkörer.

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Introduction

Universities as well as biotech, pharmaceutical and diagnostic companies extensively use antibodies for research, diagnostics and therapy. The application of antibodies is very broad, and so is the group of interested parties and media covering the progress of biomarker discovery. The world of researchers are enthusiastic about the antibodies potential in biomarker discovery, and antibodies are therefore one of the hottest topics in scientific journals today. Business people and journalists are cheering the advances of biomarker research as well since the emerging markets of antibodies for diagnostic and therapeutic use so far have been very successful and are growing at a high pace.

But even though the hot antibody research area is in fast progress and even though the companies involved in the discovery of cancer diagnostic biomarkers are facing a double digit market growth, biomarkers for diagnostic purposes have not yet had the enormous impact on modern medicine as could be expected. The U.S. Food & Drug Administration (FDA) in March 2004 released an analysis about the recent slow down instead of expected acceleration in innovative drugs and diagnostics reaching the market[1]. The report points out the emerging techniques to produce biomarkers to target responders, monitor clinical response and serve as biomarkers of drug effectiveness as the solution for the global pipeline draft of today. A problem though is that there are economic barriers which need to be overcome to encourage discovery of biomarkers. There is a lack of capital to support innovative diagnostic development since the pharmaceutical companies are hesitating to invest money in projects that may lead to a decrease of the current market of their therapeutic products.

Because of the fast changes and the young age of the market for diagnostic and therapeutic antibodies, information about the industry and market analyses are greatly desired by the companies and investors that are active on the market. Reports and market analyses are therefore traded at a very high price- the information is hard to access and therefore expensive. A recent example is the report *Biomarker SOPs: Getting optimal value from Your Biomarker Programs* written by Dr. Ken Rubenstain at Insight Pharma Reports which is accessible on the internet for the humble price of $ 3,750.

As mentioned- the possibilities that open with the advancement of biomarker discovery are numerous. This report however, is a result of an initiative taken by the biomarker discovery company Atlas Antibodies, and will therefore focus only on the markets of their interest- the market for cancer diagnostic biomarkers. The first section of the report will concentrate on the technical aspects of biomarker discovery and describe Atlas Antibodies methods of antibody based biomarker discovery as well as other antibody and biomarker techniques that are advancing today. The current methods for cancer diagnostics within this field will be presented as well. The second section will provide more business related information and describe the market and potential for antibodies for cancer diagnostic use. In this section, the problems concerning the lack of financial initiatives for biomarker discovery will be further presented.

[1]The U.S. Food & Drug Administration, *Innovation or Stagnation? Challenge and opportunity on the Critical Path to New Medical products*, (13.03.2004), http://www.fda.gov/oc/initiatives/criticalpath/
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Background of the project

This report is the result of a master thesis project in molecular biotechnology conducted at the antibody producing biotech company Atlas Antibodies. The mission of the project has been to produce a market analysis for cancer diagnostic antibodies that are being developed at Atlas Antibodies in order to facilitate the company's future business development.

Atlas Antibodies and the Human Protein Atlas

Atlas Antibodies is selling antibodies for research use developed by the Human Protein Atlas (HPA) project on the internet. The mission of the HPA project is to map the expression patterns of all non-redundant proteins of the human body. The project involves more than 75 researchers, mainly stationed at the Royal Institute of Technology in Stockholm and the Rudbeck laboratory at Uppsala University. The HPA uses antibody proteomics to systematically explore the human proteome. More precisely, protein-specific antibodies are being systematically generated and applied to functionally explore the proteome[2]. In order to systematically generate mono-specific antibodies to all non-redundant proteins of the human body, the development of antibodies has been scaled up to an almost industrial scale. For more details about the antibody production of HPA and Atlas Antibodies, please see page 8.
Today, Atlas Antibodies has two business areas; direct sales of the HPA Antibodies developed at the HPA program for research use and discovery of novel biomarkers for cancer diagnostics. Validated cancer biomarkers are subjects of patent applications. The biomarkers of which Atlas Antibodies gets the IP rights, will thereafter be out-licensed to in-vitro diagnostic or advanced staining companies to be further validated and marketed as cancer diagnostic reagents. The out-licensing of biomarkers for cancer diagnostic use has not yet been initiated by Atlas Antibodies, but they have several candidates with great cancer diagnostic potential that they wish to out-license in the nearby future. It is however difficult to access information about how previous biomarker out-licensing activities have taken place and what price the out-licensing company obtained for their biomarkers. An analysis over the market for cancer diagnostic biomarkers is therefore needed in order to make the out-licensing of biomarkers as successful as possible.

Project description and methodology

The first part of the master thesis project was dedicated to learn about the structure of general licensing agreements within the biotech industry. More precisely, the learning about license agreements consisted of interviews with key-persons in the field, web-based biotech licensing courses, attending conferences with licensing related subjects and internet research. Thanks to the very helpful board of Atlas Antibodies, many experienced biotech executives with personal experience of licensing deals where convinced to be interviewed and share their knowledge. The insights obtained during the interviews were documented and presented in the report, *The actual problems facing Swedish biotech companies when entering license agreements* by Ebba Kraemer and Daniel Zakrisson, which was presented at the institution of business economics at Uppsala University in May 2007.

After the completion of the general biotech licensing studies, the focus of the project turned towards out licensing possibilities for biomarkers for cancer diagnostic use. Scientific background of how cancer diagnostics is preformed today was, a part from literature studies,

[2] Persson A., Hober S., Uhlén M. (2006), *A human protein atlas based on antibody proteomic*, Molecular Therapeutics, 8(3):185-190 ISSN 1464-8431

primarily obtained during an interview with Dr. Fredrik Pontén, chief pathologist at Uppsala Academic Hospital. Introductory information about the market for cancer diagnostic biomarkers was obtained during a three hour interview with Dr. Rolf Ehrnström who is Vice President of DAKO which is one of the two market leaders for diagnostic instruments and reagents. Considerable effort was dedicated to get free access to the expensive industry analyses and reports about biomarkers and in-vitro diagnostics sold on the internet, but this turned out to be very difficult. Only one industry analysis will therefore serve as background material for this report. Most of the information has been obtained from press releases and annual reports of companies that are active on the in-vitro diagnostic and advanced staining markets.

Reliability of sources

The background material of the technical part of this report is mainly scientific reports and there is no reason to doubt its trustworthiness. The experienced pathologist Dr. Fredrik Pontén has also contributed to the technical part by explaining the methods used for cancer diagnostics today and the potential of novel biomarkers in the field. Dr. Pontén is probably one of Sweden's most competent persons in the field of immunohistochemistry and the information obtained through interviews with him is therefore to be considered as facts. Dr. Fredrik Pontén is however personally involved in the Human Protein Atlas project as chief of the project's operations carried out in Uppsala. His personal engagement in antibody proteomics may therefore influence the level of importance he considers this approach to have in the field of cancer diagnostics when compared to other cancer diagnostic methods. This possible bias has been kept in mind during the progression of this project and information about alternative cancer diagnostic methods have therefore been obtained primarily from internet research.

The sources that the market analysis section of this report relies on are annual reports of in-vitro diagnostic and advanced staining companies, press releases, industry analysis reports and interviews. A comment about the reliability of the press releases and the information obtained through interviews could be in place to convince the reader of the trustworthiness of this report. The press releases have exclusively been found on the internet and the main part of them concern recent deal activity of companies involved in the cancer diagnostic market. For each event presented, whereto a press release is the source, it has been controlled that the very same information can be obtained on at least one other web page.

Dr. Rolf Ehrnström has made a substantial contribution to the market analysis section of this report. Dr. Rolf Ehrnström's competence within this filed is unquestionable due to his rigid background that includes scientific research, more than 25 years of biotech management and, finally, several years as Vice President at DAKO. A fact that should be taken in consideration though is that DAKO is a possible future partner of Atlas Antibodies. There is reason to believe that DAKO would have a great interest to in-license antibodies from Atlas Antibodies, which took the initiative to this project. A possible bias is therefore that Dr. Rolf Ehrnström answers the interview questions in the role of a licensee speaking with a potential licensor.

Technical section- Antibodies

The technical section of this report does not contain any new material but is meant to serve exclusively as background information for the reader. To understand how the market for diagnostic biomarkers works, which will be presented in the following Business chapter, it is crucial to understand technical details about how antibodies are produced and different methods for diagnosing cancer. In this section a review about Atlas Antibodies' antibody production procedure, an overview of cancer diagnostic methods and a chapter about the financial incentives that drives the development of diagnostic biomarkers is presented. Together, this information will provide the reader with the enough knowledge to understand the rest of the report.

Background: Antibodies

Antibodies are proteins playing a critical role in the immune system of vertebrates. The antibodies have a Y-shaped structure and consist of two light and two heavy chains. In mammals, five different kinds of antibodies, or immunoglobulines, have been discovered that all vary in structure and function in the immune system[3]. Although the basic structure of the antibodies is quite similar, there are two small highly variable regions. These regions originate from multiple gene segments that are randomly combined, and thereafter subject for random mutation. The high variability in these specific regions allows uncountable different versions of antibodies to form and bind to all possible invading objects in the vertebrate body. The target that the highly variable region of an antibody binds to is called an antigen, and the specific sequence of the antigen that the antibody binds to is called an epitope. The target seeking function of antibodies allow them to work as markers for other parts of the immune system that will recognise the antibody marked material and destroy it.

The antibodies possibility of recognizing endlessly variable sequences gives them unique potential as tools for different medical and research applications. For research purposes antibodies have been used in immunohistochemistry to map the location of certain protein's expression, Western Blot experiments to identify size separated proteins and ELISA techniques to detect and quantify proteins just to name a few.

The medical applications of antibodies are of two different kinds; they can either have a therapeutic or a diagnostic function. By binding to specific antigens, the antibodies may be able to inhibit the negative function of dysfunctional or over expressed proteins and thereby cure the disease. Antibodies with this potential are referred to as therapeutic antibodies.
Dr. Claes Wilhelmsson, Senior Advisor at Investor Growth Capital and former Vice President of Research and Development at Astra Zeneca has commented the therapeutic potential of antibodies;

[3] Wikipedia; Antibodies (14.07.2007)
http://en.wikipedia.org/wiki/Antibodies

"Today, there are no more easy projects leading to new pharmaceutical products. Monoclonal antibodies however have a great potential - partly because they are less complex to develop when compared to chemical substances."

Dr. Claes Wilhelmsson, M.D PhD, Senior Advisor, Investor Growth Capital

Dr. Claes Wilhelmsson was Vice President of Research and Development at Astra from 1991 until 1999 when he became Executive Director and a member of AstraZeneca's board. His academic background includes an M.D. and a Ph.D. from the Medical Faculty at the University of Gothenburg in Sweden and more than 270 papers on international medicine and cardiology.

The diagnostic antibodies can identify protein expression patterns that differ between healthy and diseased tissue and blood. The protein expression patterns, revealed by diagnostic antibodies, have in previous studies been related to the outcomes of a big number of patients. The correlation between protein expression patterns and outcome opens a possibility to add new prognostic information to other patients with the same protein expression pattern.

The antibodies used for medical and scientific applications can either be poly- or monoclonal. Polyclonal antibodies are produced from immunization of an animal with an antigen. The polyclonal antibodies may vary in their highly variable sequence and bind to different parts of the antigen. Monoclonal antibodies on the other hand have their origin in one specific cell line and will therefore be identical and bind to one specific epitope of the antigen.

The HPA uses antibody proteomics to systematically explore the human proteome. More precisely, antibody proteomics is the systematic generation and application of protein-specific antibodies to functionally explore the proteome[4]. In the following section, the HPA procedure of antibody production will be described. There after, an overview of monoclonal antibody production will follow.

[4] Persson A., Hober S., Uhlén M. (2006), *A human protein atlas based on antibody proteomic*, Molecular Therapeutics, 8(3):185-190 ISSN 1464-8431

HPA- the antibody factory

In order to map the expression of all non-redundant proteins of the human body using antibody based methods, the production of mono-specific antibodies needs to be highly efficient. A progress, crucial for the success of the Human Protein Atlas project has been the ability to scale up the generation of mono-specific antibodies to an industrial scale. The procedure of HPA today is standardized and very effective. The process of producing mono-specific antibodies that HPA-project uses is described below.

PrEST selection

The first step of the antibody development process is the design and validation of suitable PrEST fragments to use for the immunization. PrEST stands for recombinant Protein Epitope Signature Tags and are, as the name suggests, short amino acid sequences representing a part of the protein of which the expression pattern is desired to study. The use of PrESTs instead of fully sized proteins is advantageous in the immunization process due to the more favourable size and the more precise design of antibodies that will result from the immunization. The PrESTs are normally 100-150 amino acids long and will be designed so that they represent a part of the gene product that is shared by all the protein versions that originates from one specific gene. Another desirable feature of the PrEST is that it should represent a part on the surface of the protein that is exposed to the protein surrounding- otherwise the antibodies produced will not be able to bind to the real protein. For the same reason, for example, transmembrane regions of membrane proteins need to be avoided when designing PrESTs. Further more, the epitope needs to have a low homology to other human proteins in order to avoid cross-reactivity of the antibody. A bioinformatic software, BLAST[5], is used to identify suitable PrEST regions using the human genome sequence from the EnsEMBL database as template[6]. When the desired PrEST of the protein has been chosen, a good pair of primers are identified that successfully will enable the amplification of the PrEST coding DNA from the gene. The amplification of the PrEST coding gene fragment takes place in a RT-PCR reaction where pools containing total RNA act as templates.

Cloning and sequencing

The PrEST coding fragments are thereafter cloned into the pAff8c expression vector. The pAff8c vector contains regions that code for a histidine tag and an albumin binding protein. The PrEST coding sequence will thereby be expressed together with the HIS-tag and the albumin binding protein and form a recombinant protein. The purpose of the HIS-tag and the albumin binding part is to be able to purify the PrEST from the bacterial lysate more successfully in the following steps of the procedure.
The clones are thereafter sequenced to make sure that they contain the DNA code.

Production and purification of PrEST

The recombinant PrEST is expressed in E-coli (Escherichia coli) and thereafter purified. The affinity chromatographic method used for purification of the PrESTs is immobilized metal ion affinity chromatography, IMAC[7]. The immobilized cobolt in the IMAC column has an

[5] Lindskog M., Rockberg J., Uhlén M., Sterky, F.(2005) *Selection of protein epitopes for antibody production,* BioTechniques 38, 723-727
[6] M. Uhlén et al. (2005), *A Human Protein Atlas for Normal and Cancer Tissues Based on Antibody Proteomics.* Molecular & Cellular Proteomics 4:1920-1932, 2005
[7] Steen, J., Uhlén, M., Hober, S., Ottosson, J. (2006), *High-throughput protein purification using an automated set-up for high-yield affinity chromatography*, Protein Expression & Purification 46 173-178, 2006

affinity for Histidine-tags. The His-tags on the recombinant PrESTs in the cell lysate will attach to the column and can, after the flow through has passed through the column, be eluted with an elution buffer that changes the pH of the column.

Immunization and antibody purification

The PrEST antigens are thereafter immunized to generate polyclonal antibodies. The sera are thereafter collected and enter the purification step of the process. To make sure that the antibodies are mono-specific, meaning that they will bind only to the chosen epitope region, the purification takes place in two steps[8]. First, the sera pass through a depletion column with His_6-Alb tags where all the tag-specific antibodies are sorted out from the Sera. In the next purification step a NHydroxysuccinimide-activated Sepharose[9] High Performance column coupled with his_6-ABP is used[10]. The recombinant PrESTs containing the his_6-ABP specific region and the PrEST are immobilized on the column. The flow through from the first antibody purification step is added to the column. The junk flow through will pass right through the column whereas the mono-specific antibodies will bind to the PrESTs. The mono-specific antibodies are thereafter eluted.

Validation

To investigate specificity and cross-reactivity, the antibodies are validated by western blot and protein micro array chips.

Western Blot and Protein Assay

The western blot is preformed by running the total protein extract of two cell lines, human plasma, human liver and tonsil on an SDS-Page gel and thereafter transfer the size separated proteins to a PVDF membrane[11]. The membrane is first incubated with the purified antibodies and then with secondary antibodies, which are detectable and binds to the primary antibody. The signal will, if everything has been performed correctly, only be detectable where the proteins of a specific size are present.

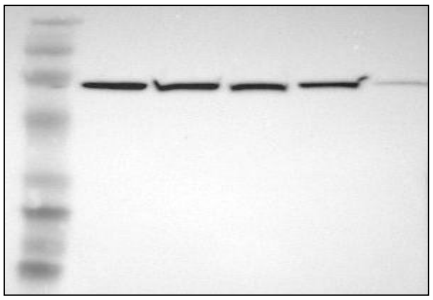

Fig. 1. Western Blot[12]

Cross-reactivity is tested by adding the purified antibodies to a PrEST array. The antibodies are supposed to bind to one specific PrEST sequence if the specificity is precise enough. The signal is detected by using secondary, labelled antibodies.

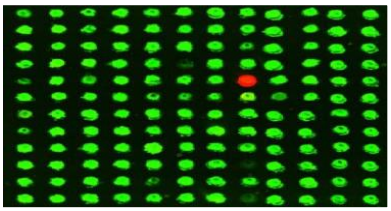

Fig. 2. PrEST microarray[13]

[8] M. Uhlén et al. (2005), *A Human Protein Atlas for Normal and Cancer Tissues Based on Antibody Proteomics*. Molecular & Cellular Proteomics 4:1920-1932, 2005
[9] GE Healthcare™
[10] Nilsson, P., Paavilainen, L., Larsson, K., Ödling, J. et al. (2005) *Towards a human protein atlas; High-Throughput generation of mono-specific antibodies for tissue profiling*. Proteomics 5, 4327-4337
[11] Nilsson, P., Paavilainen, L., Larsson, K., Ödling, J. et al. (2005) *Towards a human protein atlas; High-Throughput generation of mono-specific antibodies for tissue profiling*. Proteomics 5, 4327-4337
[12] Photo is used with permission from Atlas Antibodies.

Tissue Microarray

The tissue in the micro arrays are paraffin embedded and comes from pathology archives. The Tissue Microarrays are constructed out of Tissue Micro Array blocks with 72 tissue cores with 1 mm in diameter[14]. The Tissue Micro Array blocks are sliced into 4 µm thick sheets and placed on top of glass slides. Normal tissues are represented with triplicate from every tissue type.

Immunohistochemistry

The Tissue Microarrays are deparrafinized, boiled and thereafter placed in an autostainer (DAKO). The purified, primary antibodies are added and allowed to incubate. A secondary antibody, goat anti-rabbit peroxidise-conjugate (HRP) is added thereafter and finally, the micro arrays are scanned and evaluated by pathologists.

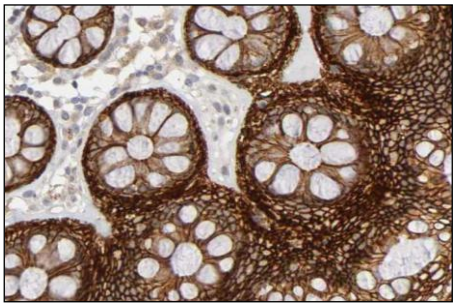

Fig. 3. Immunohistochemistry[15]

Monoclonal antibodies

The antibodies produced by HPA are mono specific and polyclonal. This means that they have their origin in different B-cell lines but bind solely to the product of a specific gene. For all therapeutic use of antibodies, the antibodies are required to be monoclonal. The method of producing monoclonal antibodies was first described by Kohler and Milstein in 1975 – an achievement that gave them the Nobel Prize in physiology 1984[16]. The monoclonal antibodies derived from Kohler and Milstein's hybridoma method, which is described below, originates from the immunization of mice. Antibodies with this origin, murine antibodies, have certain disadvantages and the therapeutic use of them has turned out to be very limited. Murine antibodies may because of their dissimilarity to human proteins, induce an immune response if inserted in the human body. Because of this, a lot of research has been focused on replacing the content that causes the immune response with parts of human antibodies.

Today, three different types of engineered antibodies that induce a less severe immune response than murine antibodies can be produced. These are chimeric, humanized and human antibodies containing 65%, 95% and 100% human protein respectively. In the continuing chapter, the methods of producing monoclonal antibodies will be described. At first, the process of achieving murine antibodies will be described in detail. Thereafter, a brief description about the chimeric, humanized and human antibodies will follow.

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[13] Photo is used with permission from Atlas Antibodies.
[14] Nilsson, P., Paavilainen, L., Larsson, K., Ödling, J. et al. (2005) *Towards a human protein atlas; High-Throughput generation of mono-specific antibodies for tissue profiling*. Proteomics 5, 4327-4337
[15] Picture is used with permission from Atlas Antibodies.
[16] The Nobel Prize in Physiology or Medicine 1984, (20.07.2007), http://nobelprize.org/nobel_prizes/medicine/laureates/1984/press.html

Production of Monoclonal antibodies

Murine antibodies

To produce monoclonal antibodies, the B-cells that produce the antibodies in an immunized animal are removed and fused to cancer cells (Myeloma tumor cells) to form a hybridoma[17], see Fig. 2. The point of fusing the antibody producing B-cell with a cancer cell is to add the cancer cell's ability of indefinitely division. The fusion of the cells can be obtained in various ways, for example by electroporation or virus infection[18]. The antibody producing hybridomas are thereafter tested for sensitivity to bind the antigen. One way of doing this is to use antigen microarrays.

When a hybridoma with a production of antigen specific antibodies has been selected, it must grow and get multiplied. There are two different ways of growing the hybridomas- either by in vitro cell cultures or by injecting the hybridomas into the gut of a mouse. The last mentioned method is the easiest and cheapest method, but it may cause suffering to the animal and is therefore the subject of an ethical debate. When the hybridoma is injected into the mouse it starts to multiply and produce a lot of antibodies. In the abdomen of the mouse, a liquid with high antibody concentration called ascites is produced.

The method of growing the hybridomas in in vitro cell cultures has ethical advantaged, but is more expensive than when test animals are used. Other difficulties with in vitro cell culture are that some hybridomas do not grow well in cell cultures and that the supernatant from in vitro cell cultures has a considerably lower concentration of antibodies than does ascites from mice.

Today, both the mouse ascites and the in-vitro method are used but some countries, Germany amongst others, have forbidden the use of test animals in this context[19].

Chimeric, humanized and human antibodies

Chimeric antibodies are produced by fusing the human antibody sequence coding for the stable regions of an antibody to the murine variable region. This type of antibody reduces the immunogenicity, but does not eliminate it[20].

Humanized antibodies consist of the hyper variable regions from murine antibodies fused on to fully humanized antibodies. Antibodies designed in this way further reduce the immunogenecity, but unfortunately the affinity is reduced when compared to a fully murine counterpart.

The human antibodies that contain 100% human protein have been obtained by the use of transgenic mice or phage display.

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[17] Wikipedia; Monoclonal Antibodies (14.07.2007) http://en.wikipedia.org/wiki/Monoclonal_antibodies

[18] Committee on methods for producing monoclonal antibodies, Insitute for Laboratory Animal Research, National Research Council, National Academy Press Washington DC, *Monoclonal antibody production*, (1999), http://grants.nih.gov/grants/policy/antibodies.pdf

[19] Ranke, M.B., (2003) *Diagnostics of Endocrine Function in Children and Adolescents.* Basel, Karger, 2003, pp 1-29 (DOI: 10.1159/000073541)

[20] Ross, J., Gray, K., Gray, G., Worland, P., Rolfe, M (2003). *Anticancer Antibodies*, 2003, American Journal of Clinical Pathology, 119(4):472-485, 2003.

Cancer diagnostics

Antibodies and immunohistochemistry

The traditional method for diagnosing cancer is through light microscopy examination of stained tissue sections where a thin slice of the suspect tumour tissue is coloured and thereafter analysed by a pathologist. Dr. Fredrik Pontén, chief pathologist of the Uppsala University Hospital, has in a long interview explained the cancer diagnostic methods of today, and the growing importance of antibodies in this field. The following information in this chapter comes, if not otherwise indicated, from the interview with him.

Dr. Fredrik Pontén Chief Pathologist at Uppsala University Hospital

Since 2003 Fredrik Pontén is site director in Uppsala for the Swedish Human Proteome Atlas project.

The morphology of cancer cells are differentiated from the features of normal cells and the usefulness of microscopy is therefore obvious. The pathologist will through microscopy of stained tumour tissue recognize features such as altered mitosis behaviour and variations in the size of nuclei and may thereby be able to determine a diagnosis and give prognostic information. Apart from the morphological features that can be detected by microscopy, altered DNA sequence and gene expression of cancer cells can add valuable diagnostic information. The most common method used today for cancer diagnostics apart from microscopy of stained tissue is immunohistochemistry, where antibodies are used to detect altered expression levels of certain proteins. The information obtained from immunohistochemistry about altered protein expression levels can not be received by microscopy examinations since altered protein expression not necessarily affects the morphology of the cell.

At present, a lot of research is being done to relate certain expression patterns of proteins to different tumour phenotypes that represent different types of cancer, and different stages of tumour development. If a certain protein expression can be associated to a prognosis, the information obtained from immunohistochemistry will influence the therapeutic actions that follow after the diagnosis. Many antibodies are already in clinical use to detect protein expression of certain cancer types. One example is the antibody that detects HER-2, which is up regulated in some breast cancer patients. Please se case HER-2 page 17 for further details.

HER-2 is an example of a pharmaco diagnostic biomarker which means that it exist a specific therapeutic treatment for HER-2 positive patients. This situation is not very common. Usually, the information obtained from cancer diagnostic biomarkers may tell prognostic information- whether the tumour is aggressive or not and what other features it has, but the biomarkers which indication leads to a specific treatment are unfortunately uncommon.

Other cancer diagnostic methods

Apart from microscopy and immunohistochemistry, in-situ hybridization and mutation analysis by the use of probes are used to diagnose cancer as well. In-situ hybridization is a method where labelled complementary DNA is hybridized to the RNA expression of a cell. This method is not as commonly used for cancer diagnostics, but Fluorescent in-Situ Hybridization (FISH) is for example clinically used for detection of HER2 in breast cancer patients. The FISH approach is, when it comes to this specific case, more accurate than immunohistochemistry, but much more expensive[21]. See case HER2 for further details.

The approach of using labelled probes which bind to and detect cancer causing mutations in DNA sequence has had a limited success so far. The problem with this method is that many different kinds of mutations may cause the same type of cancer. Many different genes that are influencing the same path way will create the same cancer if mutated. This approach is how ever being used to detect for example leukaemia[22].

Pharmaco-Diagnostic

The co-development of diagnostic tests and therapeutic treatments is today becoming more abundant. This co-development, called pharmaco diagnostics, is a crucial step in the progress of fighting diseases such as cancer[23]. Breast cancer, to give an example, is a very heterogeneous disease, where different patients respond differently to the same treatment. Today, many cancer patients are prescribed treatments with problematic side effects that are totally ineffective against their tumours. It is therefore of value to be able to stratify the cancer patients by advanced diagnostic tests before prescribing them treatments. Many collaboration projects between pharmaceutical and diagnostic companies today take place with the incentive to develop therapeutic treatments with accompanying diagnostic tests. However, these collaborations are not as common as could be expected. Due to the pharmaceutical companies' lack of financial incentives to develop diagnostic tests for some treatments, many possible projects that would add tremendous value to patients are left untouched. In some situations, the sales of the pharmaceutical company would be reduced if a diagnostic test helped to sort out a segment of patients that will not respond to the treatment[24]. The lack of financial incentives is however only one of the problems that needs to be over come in order to get more pharmaco diagnostic collaborations. Another obstacle is that the diagnostic companies have problems knowing whether a pharmaceutical company they are collaborating with actually is interested in bringing a diagnostic assay to the market or if they just intend to use the assay and the collaboration to improve the drug development process. The biomarker assays can help the pharmaceutical companies to identify a proper patient selection- thereby improving the clinical trial outcomes and accelerating the clinical trials[25]. Despite the above mentioned problems, a few successful pharmaco diagnostic collaborations have taken place. Presented below is a case where a pharmaceutical and a diagnostic company managed to find a win-win incentive to develop a pharmaco-diagnostic product.

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[21] FISH test better than IHC test at identifying women who may benefit from Herceptin, (01.06.2007) http://www.breastcancer.org/research_herceptin_050002.html

[22] Interview; Fredrik Pontén

[23] Rubenstein, K.,(2007), *Disease-Related Biomarkers: Their potential in Patient Screening, Prognosis and Stratification*, June 2007, Insight Pharma Report, Cambridge Healthtech Institute

[24] Pharmaco-Diagnostic Partnership Programs- a proposal to the FDA, 2004, Jonathan Cohen, Genesystems http://www.fda.gov/OHRMS/DOCKETS/dailys/04/aug04/080204/04n-0181-c000027-vol1.pdf

[25] Burrill & Company 2007 Life Science: A Global Transformation

CASE: Herceptin & Herceptest- A win-win pharmaco diagnostic situation

Mechanisim

25-30% of all women with early-stage breast cancer has an over expression of the HER2 receptor[26]. The over expression of HER2 is associated to reduced survival of the patients when compared to patients with normal HER2 expression[27]. The HER2 receptor is a trans membrane receptor protein that sends out growth promoting signals to the cell. If HER2 is over amplified, this mechanism leads to uncontrolled cell growth. The damage caused by over amplification of HER2 can be reduced by treating HER2 + cancer patients with a therapeutic monoclonal antibody named Trastuzumab, more commonly known as Herceptin. Herceptin binds to the extra cellular part of HER2 and reduces the cell proliferation by slowing down the G1 phase of the cell cycle. Herceptin also has the effect of stopping the tumor induction of blood vessel growth.

Diagnostic possibilities

The Herceptin treatment is expensive- a full treatment costs about $70 000 and there is risk for negative side effects on the heart of the patient. It is therefore of great importance, for the community paying for the treatments as well as the patients suffering the side effects, that only the patients that may gain a positive effect of the treatment get Herceptin. Different methods for identifying the 25-30 % women with over expressed HER2 among breast cancer patients have been developed. The most common methods are immunohistochemistry (IHC), which is the most cost effective method that is being routinely used in pathology labs, and fluorescence in situ hybridization (FISH) which is more precise than IHC and is consulted when the IHC test does not show any clear results. Today, there are 2 FDA-approved diagnostic tests available on the market; The DAKO Herceptest and the Ventana Pathway[28]. Both IHC tests categorise the tissue samples into four different groups with different expression levels of HER2. The tissue samples classified in the two categories with least expression, are determined not to over express HER2 and the patients will therefore not get Herceptin treatment. The category where the tissue samples signalling the highest amounts of HER2 expression is classified as the HER2 positive category, and the patients from whom the tissue samples were taken will receive Herceptin treatment. However, the result is not clear enough if the IHC sort samples into the category for tissues expressing HER2 but not in large amounts enough to be in the highest category. These samples will go through FISH tests before being diagnosed.

History

The Herceptin treatment was developed by Genentech, before the first diagnostic HER2 test existed. Genentech first tried to get an FDA approval fore the treatment without presenting an

[26] Wikipedia; Herceptin (05.07.2007)
http://en.wikipedia.org/wiki/Herceptin
[27] Slamon D, Clark G, Wong S et al. (1987), *Human breast cancer: correlation of relapse and survival with amplification of the Her2/Neu oncogene*. Science 1987;235:177-182.
[28] Wikipedia; Herceptin (05.07.2007)
http://en.wikipedia.org/wiki/Herceptin

accompanying diagnostic test[29]. FDA however found that the treatment did not show enough efficacy when given to the broad spectrum of breast cancer patients. After having received the FDA refusal, Genentech contacted DAKO and asked them to develop a diagnostic test to detect the HER2 positive patients. DAKO succeeded in doing this, and the FDA thereafter approved both Herceptin and the diagnostic test- DAKO Herceptest[30]. In 2006 Herceptin sold for $1.33 billion was ranked number 10 of the world's biotech drugs with highest revenues[31]. The revenues of Herceptin is today shared by Genentech, which owns the right to sell Herceptin in the U.S, and Roche, which is the major shareholder of Genentech and has the right to sell Herceptin in the rest of the world.

Comments

The Herceptin- Herceptest product is an example that shows a successful collaboration project of a pharmaceutical and a diagnostic company. It also however reveals the problems arising from the pharmaceutical companies' wish to maximise their market. If the FDA would have approved the first application by Genentech, the diagnostic test would not have been developed and many HER2 negative breast cancer patients would have suffered from the side effects of the Herceptin treatment.

[29] Interview; Rolf Ehrnström
[30] FDA Press Release, (16.11.2006)
http://www.fda.gov/bbs/topics/NEWS/2006/NEW01511.html
[31] Burrill & Company: Biotech 2007- Life Science: A global Transformation

Business section

Market analysis

A biotech company that discovers biomarkers for cancer diagnostic purposes needs to be well informed about several different markets and actors to successfully out-license their biomarkers. To identify possible future partners and set a reasonable price on a biomarker, the main players of interesting markets and their environment needs to be understood. This report will concentrate on the two most central markets; the huge In-Vitro Diagnostic (IVD) market and the more specific market for advanced tissue staining. The market for advanced staining is a submarket of the In-Vitro Diagnostic sector constituting about 2 % of the total IVD market.

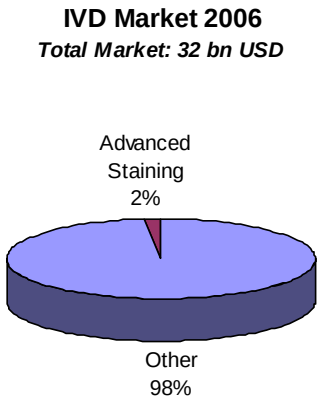


Fig. 4. IVD Market 2006

The IVD market obviously contains many segments that are not directly related to biomarker discovery. Nevertheless it is very important to be well informed about the IVD market when operating in the advanced staining segment. Many acquisitions take place where IVD companies buy companies on the advanced staining market and the activities of companies from the two different markets are highly linked. Below, the two markets will be shortly presented and thereafter a review of the companies that are active on the two different markets and their recent acquisition activity will follow. Information about the origin of the biomarkers used in companies that are active in the advanced staining market will be presented as detailed as possible.

In-Vitro Diagnostics

The In Vitro Diagnostic market includes clinical chemistry, immunoassays, blood testing, nucleic acid testing, microbiology and cellular analysis. The segments immunoassays and clinical chemistry constitute more than half of the IVD Market. The European market was valued to $5.5 billion, where as the global IVD market is $32 billion[32]. The major players on the IVD market are of two kinds; Large pharmaceutical companies with large diagnostic divisions like Roche, Abbott, Siemens Medical Solutions, Johnson & Johnson and dedicated diagnostic companies

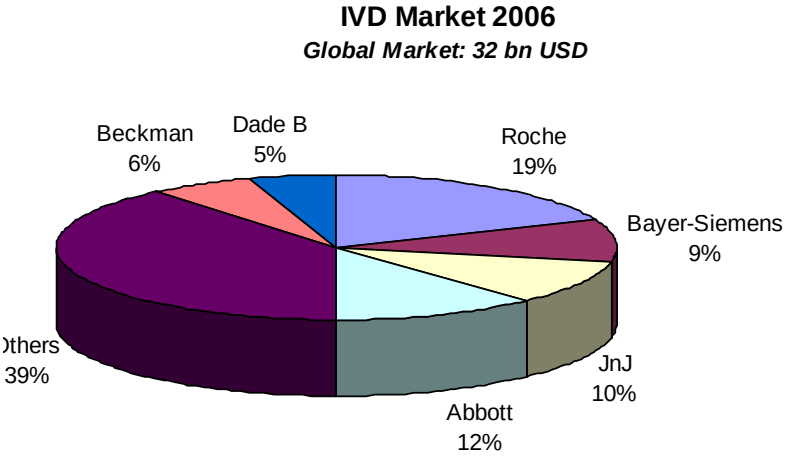


Fig. 5. IVD Market 2006

[32] Enhancing Roche's position as the world's leading fully-integrated personalised healthcare company, VentanaAcquisition: Conference call to analysts and investors. (26.06.2007) http://www.roche.com/pages/downloads/company/irp20070625.pdf

like Beckman Coulter and Dade Behring. The large pharmaceutical companies with large diagnostic divisions have the largest market shares- Roche, Siemens, Abbott and J&J control more than 50% of the IVD market[33], see Fig. 5. The numbers presented in the diagram in Fig. 8 are from the end of 2006 and one major change has taken place since then. Bayer, that by the end of 2006 controled 9% of the IVD market was acquired by Siemenes in January 2007. See page 25 for further details.

Advanced Staining

Three companies are currently dominating the market for advanced staining; DAKO in Denmark, Ventana Medical Systems Inc. in the U.S, and Vision BioSystems in Australia. The advanced staining market includes immunohistochemistry (IHC) and In-Situ Hybridization (ISH). DAKO and Ventana Medical Systems have the largest market shares of 37% and 41% respectively, whereas Vision BioSystems is smaller and has 9% of the total advanced staining market[30] which in 2006 was $576 million and growing with 19% per year, see Fig. 6.

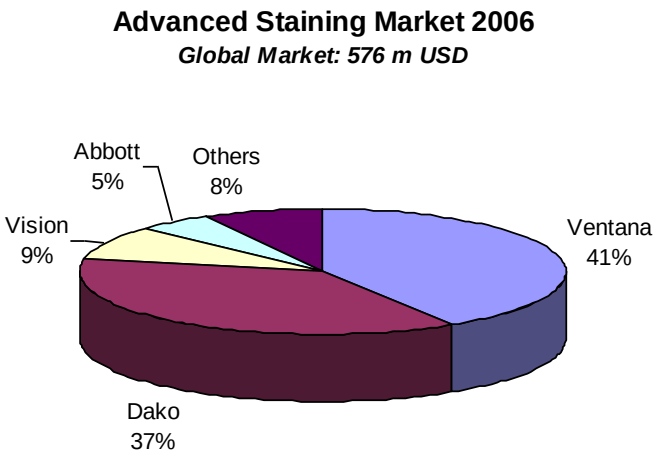


Fig. 6. Advanced Stainig Market 2006.

Since the headquarters of the companies are located on different continents, the market shares are geographically unevenly distributed among the companies- Ventana is the major market leader in the U.S, whereas Dako is leading in Europe. The companies are presented below;

Ventana Medical Systems

Pathologist Thomas M. Gordan founded Ventana Medical in 1985 with the aim to automate the diagnostic procedure in pathology labs. Ventana Medical has since then produced and launched several instrument-reagent systems that automate IHC staining. Today, they offer several different automated instruments for IHC as well as a full set off reagents. The instruments sold by Ventana are "locked" and only work when the reagents sold by Ventana are applied. This situation makes it very difficult and expensive for their costumers to change supplier- once they have bought an instrument from Ventana, they are forced to continue to by products from them. In 1996, the company went public on NASDAQ.

As late as the 29th of June 2007, the diagnostic giant Roche made a hostile bid, $ 3 billion, to acquire Ventana Medical[34].

[33] Burrill & Company 2007 Life Science: A Global Transformation
[34] Roche vill ta över Ventana, (29.06.2007)
http://www.dagensmedicin.se/nyheter/2007/06/29/roche-vill-ta-over-ventana/index.xml

Market
Ventana Medical Systems holds about 41% of the global market and has a very strong position in the U.S. where about 72% of their sales take place[35].

Antibodies used
Ventana Medical does in-licensing as well as own development of primary antibodies. They continuously monitor the primary antibody development at biotech companies and universities and will, if it is possible and appropriate, in-license or purchase them[36].

In August 1992 Ventana signed a distribution agreement with Novocastra Laboratories in the U.K[37] where Ventana obtained the rights to distribute certain monoclonal antibodies, produced by Novocastra, under their own trademark and trade name. The monoclonal antibodies were according to the agreement allowed to be distributed throughout the whole world but only to be used with Ventana's Automated Immunohistochemistry System. In June 2002, Novocastra was acquired by one of Ventana's competitors; Vision BioSystems and the agreement between Ventana and Novocastra were therefore immediately terminated. Ventana is now cooperating with other reagent suppliers.

DAKO

DAKO has about 37% of the market for cancer diagnostic instruments and reagents. The headquarters of DAKO is situated close to Copenhagen in Denmark and the geographical distribution of their sales is, just like the other companies, uneven with a heavy weight on Europe. Only 35% of DAKO's sales take place in the U.S, where 40% of the global market is concentrated. DAKO has subsidiaries and distributors in 50 countries world wide.

Most of the antibodies DAKO provides in their product catalogue are in-licensed from other companies or universities. An advisory group consisting of experts in the field keep track on the progressing antibody related research and discuss what assets to in-license.

Strategy change
Rolf Ehrnström, Vice President of DAKO, has been interviewed about the business strategy of DAKO and their in-licensing activity. The information in this section is if not otherwise indicted obtained from the interview with Rolf Ehrnström.


Rolf Ehrnström,
Vice President of DAKO

Rolf Ehrnström has held the position as Corporate Vice President at DAKO since 2005. Prior to that, he has held various management positions at Gyros and Amersham. His scientific career includes research at Wallac Oy and the Rolyal Institute of Technology, where he also received his MSc in Biochemical engineering.

[35] Interview; Rolf Ehrenström
[36] Ventana Medical Systems Annual report 2006, page 8
[37] Distribution Agreement, Exhibit 10.17, http://www.secinfo.com/dr6nd.9Ru.9.htm

DAKO has recently changed their strategy for in-licensing new antibodies. Previously, DAKO made sure they had access to every new antibody that possibly could be useful for cancer diagnostic purposes and did a lot of in-licensing. In 2005 their product catalogue contained no less than 3700 antibodies. After a deep analysis of their sales, it was found out that 1800 of their products constituted less than 1 % of DAKO's sales. The 1800 products were then removed from their catalogue and DAKO became more restrictive in their antibody in-licensing strategy. Today, about twenty new antibodies are in-licensed every year. Of twenty in-licensed antibodies, DAKO calculates that only two of them actually will sell. DAKO's expenses for aquiering patents, licenses and similar decreased from 95 M DK in 2005 to 71 M DK 2006[38].

An average antibody in the product catalogue of DAKO sells for about 1-1,5 M SEK every year while the most successful antibodies sell for 20 M SEK.

DAKO has two different ways of presenting and packaging the antibodies they sell. The antibodies are either sold in pure form or in kits with other reagents that have been put to gather for a distinctive purpose. The antibodies sold in pure form and in kit's constitute 50% respectively of the total antibody sales of DAKO. It is likely that the sales of antibodies in kits soon will contribute more than the pure antibodies since the sale of kits is increasing more.

There are two more changes in the strategy of DAKO that may have a negative impact on the possibilities for companies and universities that intend to out-license antibodies to DAKO. First, the main objective of DAKO is no longer to search for and find new and better antibodies to use as reagents, but to automate the cancer diagnostic process taking place in pathology labs. 85% of the cost for the diagnostic process in pathology labs is salary for labour. DAKO believes that the process could be much more efficient and demand less labour craft if it was standardized. Due to the high level of human involvement in the process, there is a low success rate for achieving a correct cancer diagnosis; 70-80%. This is considerably less than other diagnostic areas where the success rate is more close to 95%. By automating and standardizing the process of doing tissue based cancer diagnostics, DAKO believes that the success rate will increase to 90%. They have also calculated that the time consumption of the process can be reduced from 5 days to 1 day if the process is optimized and automated.

The last change in DAKO's strategy that may have a negative impact on the sales of antibodies is the focus the company has on developing better visualisation systems. The visualisation systems enable the pathologists to see where in the tissue the antibodies assemble. If the visualisation system is very effective, fewer antibodies are needed for detection. It is therefore a substitution relationship between the amount of sold antibodies and improved visualization systems.

[38] Financial Report DAKO 2006.

Vision BioSystems

Market

Vision BioSystems holds about 9% of the maket share and is thereby considerably smaller than Dako and Ventana Medical Systems. Vision BioSystems, unlike DAKO, is not developing any antibody reagents themselves, but only the instruments used for histopathology[39].

Antibodies used

Vision BioSystems has solved its need of reagents by acquiring Novocastra Laboratories for £ 36 million in June 2002. The acquisition was strategically important for Vision BioSystems since they are developing medical instruments that utilize Novocastra reagents. Furthermore, the acquisition came with the advantage that the license agreement Novocastra had with Vision BioSystems' competitor Ventana Medical Systems was terminated. Ever since the acquisition took place, Novocastra antibodies and reagents have been sold on Vision BioSystems webpage. The list of Novocastra produced primary and secondary antibodies sold on the webpage of Vision BioSystems is rather extensive and includes about 1400 biomarkers. In June 2006, Vision BioSystems received FDA 510(k) clearance for an Esterogene Receptor Antibody which aid in the prognosis and prediction of therapy outcome for breast cancer. The antibody is the first Novocastra product that receives an FDA 510(k) clearance[40].

Strategic Alliances

In 2006, Vision BioSystems expanded its cancer diagnostic product range to a system that fully automates In-Situ Hybridization[41]. The new system will allow for detection of cancer by identifying specific DNA sequence by using probes. Another acquisition that Vision BioSystems made in 2006 was the take over of Immunovision Technologies Inc. Vision BioSystems thereby securing their access to a visualization reagent used in immunohistochemistry staining.

Vision BioSystems recently joined with Leica Microsystems. Leica Microsystems produce and sell all the instruments pathologists need, apart from the actual histology instruments that are produced by Vision BioSystems, to make diagnostic tests on tumours. These instruments include histology printing systems, tissue processing instruments, instruments that embed the tissue in paraffin, instruments for sectioning and staining preparation.

[39] Vision Biosystems- Company presentation (13.07.2007)
http://www.ausbiotech.org/directory/
[40] Vision BioSystems receives FDA 510(k) clearance for Estrogen Receptor Antibody , (20.06.2006)
http://www.vision-bio.com/pdfs/media_releases/
[41] Vision Biosystems launches into Molecular Diagnostics (13.07.2007)
http://www.vision-bio.com/pdfs/media_releases/

In Vitro Diagnostics

Roche

Roche is divided into a pharmaceutical and a diagnostic division[42]. The company is actively trying to coordinate the two divisions and have several pharmaco diagnostic programs in progress. The diagnostic division is world leading, controlling 19% of the global market, and operates within the following areas; Diabetes care, Centralized diagnostics, Molecular Diagnostics, Near patient testing and Applied science. The Centralized diagnostics business , which includes immunodiagnostics, and the Diabetes care are the main diagnostic areas of Roche contributing with 35% of Roche's diagnostic sale respectively. The key areas of interest within Centralized diagnostics are cardiovascular disease, cancer and rheumatoid arthritis.

The product portfolio of the Centralized diagnostic segment includes automated systems for immunohistochemistry testing as well as reagents and immunoassays. Roche has invested heavily in new biomarker programs[43], but the biomarker programs involving antibodies are primarily focused on CRC and Alzheimer.

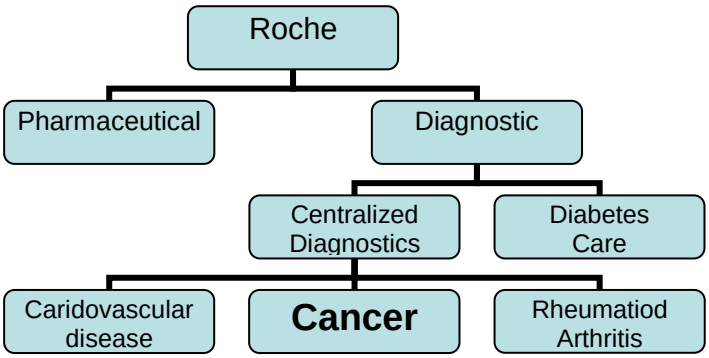


Fig. 7. Roche's organisation structure

Roche's approach to early detection of breast, colorectal and prostate cancer and tumor profiling of breast, colorectal, prostate and leukaemia cancer was previously to use genomics. Roche holds a PCR patent that they intended to use in predictive genetic tests to find out who is predisposed to, among other diseases, cancer[44]. In febuary 11 2003, Roche entered a five year strategic alliance with Ameripath[45] to establish a series of Molecular Centers to perform esoteric genomic diagnostic testing using Roche's patented PCR and other advanced genomic technologies. Two years later, In March 2005, Roche entered another collaboration agreement with Iceland Genomics. Together, Roche and Iceland Genomics aimed to analyse patient samples to validate novel molecular markers for diagnostic tests to predict recurrence of cancer for selected tumour entities[46]. In the nearby future, Roche is hoping to launch a microarray for detection of mutations in the p53 gene that allow cancer cells to proliferate.

[42] Roche Webpage, www.roche.com, (10.07.2007)
[43] Roche; Corporate overview for investors, (10.07.2007) http://www.roche.com/inv-corp-prof-e.pdf
[44] Roche's application of PCR,(08.07.2007) http://molecular.roche.com/roche_pcr/applications_of_pcr.html

[45] Press Release; Ameripath announces agreement with Roche Diagnostics Molecular Center of Excellence, (20.08.2007)
[46] Press Release; Iceland Genomics announces research collaboration agreement with Roche Diagnostics (17.03.2005)

It is clear however, that Roche now is interested in using immunoassays for cancer diagnostics as well since they are trying to acquire Ventana Medical Systems which is one of the market leaders in the advanced staining market.

Roche is the major shareholder of Genentech and Chugai. The investment in Genentech has turned out very well for Roche. Amongst other co operations, Roche has acquired the rights to sell Herceptin[47] in the whole world, except from the U.S. where Genentech still holds the right to the therapeutic antibody drug. Herceptin is the second best selling drug of Roche for the moment. Taking that and the fact that Roche has an ambition of combining drugs and diagnostic tests in consideration, it is not surprising that Roche has laid a hostile bid to acquire Ventana Medical[48]. Ventana Medical Systems got an FDA approval for a diagnostic antibody test to detect HER2 in January 2007[49] and now, half a year later, Roche wishes to acquire the company. The outcome of the hostile bid will not be known until September 20th 2007, when the Roche's offer of buying all outstanding shares of Ventana Medical for $75 will expire[50].

Siemens

Market

In January 2007 Siemens drastically entered the immunodiagnostic area by acquiring Bayer Diagnostics- thereby positioning them selves as number two in the world after Roche Diagnostics in that field. The acquisition of Bayer diagnostics for $5.3 billion, is just one in a series that Siemens has conducted during the last years. Apart from Bayer diagnostics, Siemens as bought both the in vitro diagnostic company Diagnostic Products Corporation in April 2006.

Acquisitions and formation of new business units

The acquisitions have led Seimens to found a new business entity, Siemens Medical Solutions Diagnostics, with more than 8000 employees . The new business unit has it head quarters in Tarrytown, N.Y. and Los Angeles, CA. The purpose of the new business unit is to further improve the full service concept of Siemens Medical Solutions, which combines medical imaging, healthcare information technology, managment consulting and laboratory diagnostics to improve laboratory efficiency[51]. By acquiring Bayer, which is a world leader in clinical chemistry and has a far developed near-patient testing section, Siemens hopes to be successful in the field of in vivo biomarkers for diagnostic purposes[52]. Given that Siemens by itself is an imaging giant, the newly recruited capabilities make them suitable to take on the challenge that in vivo biomarkers involve.

In Febuary 2007, a month after the formation of Siemens Medical Solutions Diagnostics, Siemens opened a new research facility called Siemens Medical Solutions Molecular Imaging Biomarker Research facility. The new facility's purpose is to Discover and develop new

[47] See Case: Herceptin & Hercep test, page 17
[48] Press Release; Roche vill ta över Ventana, (29.06.2007)
[49] Press Release; Ventana FDA approval, Rabbit Monoclonal Antibody (18.01.2007)
[50] Press Release, Roche extends tender offer for Ventana (26.07.2007)
[51] Press release: Acquisition of Bayer´s Diagnostic Division Finalized, Tarrytown/New York (03.01.2007)
[52] Burrill & Company 2007 Life Science: A Global Transformation

imaging biomarkers to be used for in vivo molecular diagnostics[53]. The facility that today mainly focuses on biomarkers for Alzheimer's disease and cancer, will in the future further move in to the area of neurological and cardiovascular disease. The in vivo biomarkers for imaging does not require any tissue, blood or urine samples, but are inserted into the body directly and thereafter scanned by either PET (Positron EmissionTomography) or SPECT (Single Photon Emission).

GE Healthcare & Abbott Laboratories

Until July 2007 it was believed that another new gigantic player would enter the field of In Vitro Diagnostics[54]. GE Healthcare and Abbott Laboratories for a long time worked together to accomplish GE Healthcare's acquisition of two of Abbott's main laboratories; Primary In-Vitro Diagnostics and Point-of-Care Diagnostic Business. The price for both divisions was set to $8.13 billion and would have meant a big step for GE Healthcare in realizing their strategy to combine early diagnosis with information technology to develop pre-symptomatic disease detection. Abbott is world leading in immunoassays and their Primary In Vitro Diagnostics has been focused on blood and urine tests. GE Healthcare's contribution to the constellation would have been their capabilities of In Vivo imaging by x-rays, magnetic resonance and ultrasound[55].

No specific reasons were given for why the companies decided to terminate the deal, but it has been said that both companies agreed that it was in the best interest for both of them not to reach an agreement.

[53] Press release: Advancing Personalized Medicine: Siemens to emphasize emerging field of Oncology, Neurology Biomarkers with exclusive New State-of-the-Art Research Facility.Los Angeles & Hoffman Estates (07.02.2007)
[54] Press Release: GE, Abbott agree to drop deal, (12.07.2007)
[55] Burrill & Company 2007 Life Science: A Global Transformation

License agreements

License agreements are frequently appearing between various actors on the life science market. Their structures and the objects they regulate are of many different kinds. For example- Many of the techniques and methods used within these industries are protected by patents that require the users to pay a license fee to the person, university or company holding the patent. Other, more complicated license agreements are constructed when drug development projects are being transferred from a research intensive company to a pharmaceutical company at some point during the drug development process. The transfers of drug development projects that are regulated by license agreements are naturally occurring today, since the procedures a drug development project needs to pass on its way from discovery to the market is far to long and expensive for one kind of company to efficiently control.

Biomarkers for cancer diagnostic use often go through license regulated transfers between companies as well. The structure of the license agreements that concern biomarkers for diagnostic use is similar to the structure of those that concern drug development projects. The similarities and differences between the license agreements concerning these two kinds of projects will be discussed below. The point of comparing the license agreements is that the structure of license agreements concerning drug development projects is more or less standardized today, and therefore can give an indication of how it makes sense to construct a license agreement concerning the use of biomarkers for diagnostic use.

A biotech company that wishes to out-license an antibody for cancer diagnostic use has an advantage if it can compare the incoming offers with license agreements from previous deals. Unfortunately it is very difficult to access bench marks since the license agreements are kept confidential by the involved parties. It is in the interest of the licensee who wishes to purchase the license that the licensor is unaware about what the licensee has paid for licenses in previous deals. The author of this report has however been able to gain access to a distribution agreement that regulates the supplier-distributor relationship between Novocastra, which is an antibody producer, and Ventana, which is market leader in the field of advanced staining. The distribution agreement was signed in 1992 and is no longer valid, but there is no reason to believe that the features of written agreements between suppliers and distributors in this filed has changed. The agreement does not reveal the precise terms for the payment, but the general structure is presented.

To summarize, this chapter will start with an overview of how drug development related license agreement generally are structured. Thereafter, the special features of license agreements concerning antibodies for cancer diagnostic use will be discussed and compared with general license agreements. Finally, a license agreement between an antibody supplier and an advanced staining company will be discussed.

The structure of license agreements for drug development related projects.

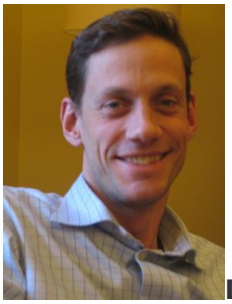
Dr. Jacob Lindberg and Dr. Joachim Werr who are senior partners at the venture capital firm Investor Growth Capital have in an interview shared their broad experiences of biotechnology licensing. Jacob and Joachim have taken part in several license agreement negotiations that their portfolio companies have been involved in. The information that follows in this section has if not otherwise indicated been obtained from the interview with Dr. Werr and Dr. Lindberg.

License agreements that regulate the transfer of drug development projects from one company to another are unique. The different features of the projects they concern and their different development stages cause all license agreements to vary in structure. There are however some variables that always are regulated in the drug development related license agreements. These variables concern the following issues[56];

Exclusivity- is the license exclusive or not?
Territory- where may the license be used?
Market- for what purpose may the license be used?
Future- does the licensee have the right to sell, export or out license the license to someone else?

The payment for the license is divided into three different parts[57]. The different parts vary in size between different license agreements, but most drug development related license agreements contain all the three types of payment. By the time of the signing of the license agreement, the licensor, who is selling the license, obtains an up-front payment from the licensee, who is the license buyer. There after, the development of the drug related project will continue in the hands of the licensee. If the project successfully passes certain mile stones of development, mile stone payments are being paid from the licensee to the licensor. Finally, the licensor obtains a

Dr. Jakob Lindberg MD, Vice President, Investor Growth Capital
Background: Before joining IGC in 2006 Dr. Lindberg has worked at McKinsey & Co and he is the co-founder and former CEO of Cellectricon AB. Dr. Lindberg has an M.D. degree from the Karolinska Institute and a B.A. in finance from Stockholm University



Dr. Joachim Werr MD, Senior Associate, Investor Growth Capital
Dr. Joachim Werr joined IGC Europe's Healthcare Team in January 2007. Prior to that, he was a practicing physician in the emergency room at Karolinska University Hospital. Dr. Werr has also worked in the health care team of McKinsey. His medicine studies were conducted at the Karolinska Institute.

Dr. Lindberg's and Dr. Werr's experiences within biotechnology licensing:

Dr. Lindberg and Dr. Werr are very much involved in the license agreements Investor Growth Captial's portfolio companies enter. The portfolio of Investor Growth Capital includes 14 biotech and medtech associated companies.

[56] Pitfalls of valutation in biotech, Ralph Villiger & Boris Bogdan, 01.04.2006, Journal of commercial Biotechnology, vol 12. No 3. 175-181
[57] Interview with Joachim Werr and Jakob Lindberg.

royalty of the sales of the product if the project successfully goes through all the phases and gets accepted as a new pharmaceutical product.

The purpose of splitting the payment in the three above explained parts is mainly to divide the risk of the project between the licensor and the licensee. By the time the licensee takes over the project, expensive and time consuming development and testing of the product still remains before it can reach the market. Most projects that enter the clinical pipeline fail in one of the clinical phases, and the licensees are therefore unwilling to pay a large one time payment to the licensor before time has revealed the true potential of the project.

The up-front payment is highly valued by the licensor who often is a small research intensive company in need of instant money to keep the business running. This type of payment is given out as soon as the license agreement is signed and the licensor therefore avoids the risk of loosing all income if the project fails at a later time point. The licensors therefore often put significant energy into the negotiations about the up front payment.

The mile stone payments may be given out at several different time-points when the project manages to pass certain development stages. A common deal structure is to give out the mile stone payments when the project successfully finishes one clinical phase and move on to the next one. The mile stone payments gain importance if the project is out-licensed at an early development stage and has a long way to go until it reaches the market.

The royalty percentage that the licensor obtain from the sales of a product if it reaches the market varies in size depending on how much of the risk and development costs the licensor has carried.

License agreements for cancer diagnostic antibodies

DAKO is one of the two market leaders in the cancer diagnostic market. According to Rolf Ehrnstöm, Vice President of DAKO, most of the antibodies in DAKO's product portfolio have been in-licensed from other companies or universities. DAKO does in-license antibody sources at various development stages. They may in-license hybridomas, clones or ready-to-use antibodies. The antibodies are in-licensed one by one and the payment often consists of up-front, mile stone and royalty payment. The in-licensed antibodies are always validated before they are introduced on the market. The validation procedure varies depending on the purpose of the biomarker. A brief description of the validation process for biomarkers is presented for the interested reader in appendix one; Biomarker Validation.

The development that follows after an in-licensing event depends on in what form the antibody was in licensed. An in-licensing of a hybridome requires more development than ready-to-use antibodies, and the mile stone payments will be influenced thereof. There are occasions when the payment consists of up-front payment solely. In general, the mile stone and the royalty parts of the payment are not as prevalent when biomarkers for diagnostic use are out-licensed when compared to the out-licensing of drug development related projects.

The structure of the license agreement also depends on what purpose the antibody is designated to have; if it will be sold in pure form or if it will be sold as a part of a kit. A kit not only contains the antibody but also control cell lines, visualization systems, buffers and instructions. Therefore, says Rolf Ehrnström, a biotech company who has out-licensed an antibody can not expect to receive a royalty payment if the antibody will be sold as a part of a kit.

Distribution agreement between Ventana and Novocastra Laboratories.

In August 1992 the market leader of the advanced staining market, Ventana, signed a distribution agreement with the antibody producer Novocastra Laboratories. The distribution agreement gave Ventana the right to distribute certain monoclonal antibodies produced by Novocastra Laboratories. Below, a selection of central terms for the agreement is presented.

The antibodies distributed by Ventana were in the distribution agreement limited to be used with Ventana's Automated Immunohistochemistry System only[58]. Furthermore, the market was limited so that antibodies were only allowed to be used for research, investigational and in-vitro diagnostic. The distribution agreement allowed Ventana to sell the monoclonal antibodies through out the world, which meant that the territory subject was left unregulated in the agreement. The agreement did not however give Ventana exclusive right to distribute the antibodies. The IP rights of all the antibodies remained with Novocastra, which ment that Ventana did not have the right to out-license the use of Novocastra's antibodies to a third party.

The distributor, Ventana, was obliged to repack the antibodies before distribution and sell them under their own trademark and trade name. The financial terms of the agreement were not structured in a way that would have been normal for a license agreement, but simply said that Ventana should purchase the monoclonal antibodies from Novocastra in concentrated form on weight basis. The price, which was kept confidential in the agreement, was given in dollars per milligram of active antibody protein.

The life time of the distribution agreement was 5 years. During that period, the price of the monoclonal antibodies was not allowed to be raised more than 10% per year.

[58] Distribution agreement between Novocastra Laboratories Ltd and Ventana Medical Systems Inc, 19.08.1992, exhibit 10.17

Conclusions

The conducted market analysis about biomarkers for cancer diagnostic use has above been presented in two main chapters; one that describes the technical background and one that describes the market. The technical background includes the antibody production procedure as well as the current methods for cancer diagnostics. This session serves as background information for the reader and does not provide any new research. Therefore, there will be no conclusions drawn from that chapter. The conclusions presented below are derived exclusively from the business section.

The actors on the market

The market for cancer diagnostic biomarkers, just like the market for drug development, involves several different actors. If generalized, three different actors with different roles can be identified.

The biomarker discovery company

One actor is a company or a research institution, which discovers biomarkers with cancer diagnostic potential. This actor will, in a licensing negotiation, be the licensor, who is out-licensing the rights to use a biomarker for cancer diagnostic use to a licensee.

The advanced staining company

The second actor on the market for cancer diagnostic biomarkers is the advanced staining company that sells the automated systems for immuno histochemical staining and the reagents that their systems require. The diagnostic biomarkers for advanced tissue staining are the active ingredients in these reagents. The customers of the advanced staining company are usually pathology laboratories and research institutions.

Even though the advanced staining companies in-license most of the antibodies used for their reagents, they often have an in-house development of antibodies as well. This can be compared to pharmaceutical companies that has own drug discovery institutions, even though they in-license most of their drug development projects from drug discovery companies.

The similarity between advanced staining companies and pharmaceutical companies; that they both play the role as licensees in licensing negotiations with antibody and drug discovery companies, will be mentioned again further on in this chapter to make a comparison between the advanced staining and the pharmaceutical market.

The pharmaceutical company

The third actor on the market for cancer diagnostic biomarkers is the pharmaceutical companies. The pharmaceutical companies are usually not in direct contact with biomarker discovery companies, but are important since they, under certain conditions, have financial incentives to fund the development of diagnostic tests to accompany their therapeutic

products. The co-development of diagnostic and therapeutic products is called Pharmaco Diagnostics and is presented more closely with a case on page 16.

Even though the pharmaceutical companies have a big impact on the market for cancer diagnostic biomarkers and their incentives are important to understand, they are not directly involved in the process of bringing cancer diagnostic biomarkers to the market. Their relationship with antibody development companies and advanced staining companies has therefore not been further analyzed.

The licensor- licensee relationship

The first and the second of the actors described above represent the licensor and licensee in licensing negotiations about antibodies for cancer diagnostic use. The biomarker discovery company discovers and gets the IPR for promising biomarkers. There after, they can out-license the antibody that the advanced staining company wants to use in their reagents for their automated immuno histochemistry systems.

As in all licensor-licensee relationships, it is important for the licensor to be well informed about the situation of the licensee and to, if possible, have access to previous licensing deals that can serve as bench marks. Therefore, the major advanced staining companies, which are possible licensees for biomarkers, have been presented in detail in this report. Relevant facts about these companies, their market shares as well as their in-licensing activities, is presented in page 19-22.

A comparison with pharma licensing.

The relationship between antibody discovery companies and advanced staining companies has great similarities with the relationship of drug discovery companies and pharmaceutical companies. Just like the antibody discovery company, who wants to out-license their antibodies to advanced staining companies, the drug discovery company aims to out-license their drug development project to a pharmaceutical company at some point.

Out-licensing of biomarkers for diagnostic use is a rather unexplored area, and it is therefore difficult for an antibody discovery company to decide what would be a reasonable licensing deal or not. Since license agreements concerning drug development projects have occurred more frequently in the passed and there are numerous bench marks available, it makes sense to do a comparison between the licensing situation for drug development projects and diagnostic biomarkers.

In both situations, the licensor believes that out-licensing their project is a more successful strategy than trying to bring the product to the market them selves. The licensee, which generally is of much greater size than the licensor, has a more advantageous situation when marketing a product. Also, a larger player, regardless if it is a pharmaceutical or an advanced staining company, has unlike the small licensor enough resources to pay for the last development, validation and tests that are required before the product can be released. The development cost and time of a product that still remains by the time of the licensing negotiation causes the complex structure of payment from the licensee to the licensor.

In licensing deals for diagnostic biomarkers as well as drug discovery projects, the payment usually consists of three parts; up-front payment, milestone payment and royalty of sales.

The up-front payment is paid directly by the time of the licensing deal's closure. The milestone payments will first be paid when and if the project manages to pass certain development stages in the regime of the licensee. Finally, if the product is released on the market, the licensor will receive a royalty of sales.

A fundamental difference when comparing the out-licensing of diagnostic biomarkers to the out-licensing of drug development project is that the remaining costs and time for development of the project is much less in the diagnostic biomarker case. This fact causes the up-front part of the payment to constitute a bigger proportion of the total payment. Sometimes, the milestone and royalty payments are even left out and the advanced staining company simply buys the biomarker from the antibody discovery company.

Another difference between the two licensing situations that are being compared is that the number of possible licensees is much smaller in the case of diagnostic biomarkers. This is a disadvantage for the antibody discovery company since the possibility of creating a competition between the possible licensees that could drive up the price is reduced.

Apart from the above presented fundamental differences between licensing of biomarker and drug development projects, the licensing deals can be expected to have a similar structure. The variables concerning exclusivity, market, territory and future, that are further described on page 29, should be dealt with in both cases.

Discussion

Access to knowledge about the market for diagnostic biomarkers is crucial to possess for antibody discovery companies that wish to out-license antibodies. How ever, knowledge about this specific market segment is not easy to obtain. It is a challenging job to map out the market, identify the different actors and obtain information about previously conducted licensing deals in the area of diagnostic biomarkers. As mentioned previously, reports which claim to provide the management of antibody discovery companies with important information about the market are being sold on the internet for thousands of dollars. Some biotech executives[59] are of the opinion that the quality of the information that these reports contain does not always equal the price they cost.

This report is aiming to give the management of an antibody discovery company market knowledge and provide information that will be helpful in the future when the company will enter licensing negotiations about their antibodies. The collection of the background information that this report is based on has not been easy. The main difficulties encountered during the creation of this report are presented below.

When conducting a project that has been assigned of a company, the persons that get interviewed during the research process might give an answer that is biased. The interviewed persons keep in mind that the information they give out will fall into the hands of the company that the interview conductor is sent out from. The risk for bias is significant if the interview object and the company that has taken initiative to the study may turn out to have a licensee- licensor relationship in the future. This is the case for one of the interviews on this report; the interview with Rolf Ehrnström, Vice President of DAKO.

[59] Marianne Hansson, CEO, Atlas Antibodies

It is difficult to avoid this problem. The interview object deserves to know the address of the interview conductor when answering the questions. If the initiative to a market analysis like this would have originated from a university institution instead of a company, it is possible that the risk for biased answers would have been reduced.

Another difficulty when conducting a market analysis like this is that a lot of the information that would have been valuable as background information is confidential. I am now referring to license agreement concerning diagnostic antibodies that previously have been conducted and could be useful as benchmarks. Both the licensor and the licensee wish to keep their agreement secret and do not want to share the information if the license agreement still is valid. If the market is young, which is the case for the diagnostic biomarker market, the expired license agreements are rare. Therefore, only one relevant license agreement has served as background information for this report. In further studies, it would be very valuable to access more license agreements. In a few years, it is likely to believe that it will get easier to access these agreements since more and more of them will expire when time passes.

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Appendix

Biomarker Validation

Crucial information for all kind of out-licensing activity is how long and expensive the validation process for the product will be before the product reaches the market. Below follows a brief description of the validation process for biomarkers.

Before biomarkers for diagnostic use can be sold on the U.S. market, the biomarker has to be approved by the Food and Drug Administration, the FDA. The American FDA system classifies the biomarkers in different categories; Class I, Class II or Class III according to the level of control needed to assure the diagnostic biomarker's safety and effectiveness. In 1997, FDA published rules about how biomarkers should be classified. The rule is valid for all ARS, Analyte Specific Reagents which are defined as "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reactions with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens." The ARS rule briefly implies that most biomarkers should be categorised in class I, thereby simplifying the process of FDA approval. The classification does however depend on the risks associated to the outcomes of using the biomarker. Below are the guidelines of the classification system summarized;

Class I

The biomarkers with the least need for control will be categorised into Class I. The biomarkers in Class I, as well as the Class II and Class III biomarkers, will be subjects for the FDA's general controls. The general controls, among other things, involve the testing of the biomarker's stability and assuring that the biomarker always gives the same result. The Class I biomarkers serve the pathologist only as a source of extra information, but will not have a crucial impact on the diagnosis of a patient

Class II

Apart from the general controls the biomarkers in Class I need to go through, the Class II biomarkers will be subjects to special controls. The impact of the diagnostic information received from Class II biomarkers is higher than from the Class I biomarkers, but it is still just to be looked upon as an extra piece of information for the pathologist, who makes the final judgement.

Class III

Class III biomarkers are the ones that are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury[60]. The impact of the results from Class III biomarker tests is heavy, and the diagnosis and therapy of a patient will be decided according to the diagnostic test result. The Hercep-test developed by DAKO to investigate over expression of HER2 in females with breast cancer is an example of a class III biomarker test. Based upon the Hercep-test's results, it will be decided whether a patient should receive Herceptin treatment or not. Documented clinical tests are required for FDA approval of Class III biomarkers. The process of receiving a Class III approval from the FDA is time consuming and comparable with the clinical phase trials of pharmaceutical products.

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