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A Review on Purification of Monoclonal Antibodies and Their Use in Cancer Therapy

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A Review on Purification of Monoclonal Antibodies and Their Use in Cancer Therapy
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Abstract

This degree work consists of an individual study (*A Review on Purification of Monoclonal* Antibodies and Their Use in Cancer Therapy) and a study made by 3 students at the Uppsala School of Entrepreneurship (The Establishment of a Small Challenger Company in a Segmented High-Technology Life Science Market).

The individual study is an overview of monoclonal antibodies (mAbs) and their use in cancer therapy and procedures for production and purification has been looked into. The study made by 3 students has been looking into the opportunities and challenges for a small challenger company in a conservative high technology market

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Cancer, cancer therapy, chromatography, conjoint analysis, survey, market analysis

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Exekutiv sammanfattning

Cancer är idag en av de stora dödsorsakerna världen över. Sjukdomen kan komma plötsligt med ett snabbt slut, men likväl vara långsam och långdragen. Tidigare och även idag används ofta strålning och kemoterapi som behandling mot cancer vilket sliter hårt på kroppen och är ofta väldigt obehagligt för patienten.

Ett behagligare och ofta effektivare sätt att behandla cancer är med riktade metoder som enbart angriper tumörvävnaden, vilket strålning och kemiterapi ofta inte gör utan påverkar hela kroppen. Denna riktade behandling utförs ofta med antikroppar, proteiner som är en del av immunförsvaret och förekommer naturligt i kroppen. Dessa antikroppar, även kallade immunoglobuliner, är väldigt specifika och binder sig till en enda antigen som är det protein som antikroppar binder till för att identifiera inkräktare i kroppen. Antikroppar har så stor diversitet att det i stort sett finns en antikropp till varje tänkbart antigen.

Utvecklingen av användandet av antikroppar i cancerbehandling går framåt där utvecklingen mycket handlar om att göra antikropparna ännu mer specifika för att minska risken att de binder till fel molekyl eller kommer till fel plats i kroppen. Även forskning med målet att göra dem ännu mer effektiva genom att kombinera dem med andra molekyler eller mediciner genomförs. Produktionen av dessa antikroppar är också inom ständig utveckling för att kunna möta efterfrågan. Den utveckling som görs handlar mycket om effektivisering och kostnadsreducering.

Vanligen framställs antikroppar genom att rena fram dem ut djur eller modifiera bakterier som producerar dem. Antikropparna renas sedan fram ur den lösning de producerats i med hjälp av en teknik som kallas kromatografi. Denna metod kan liknas vid ett filter där provet appliceras på en bädd av en gel som innehåller massvis med små små porösa kulor. När provet färdas genom denna gel separeras molekylerna i provet beroende på dess egenskaper, till exempel storlek eller laddning, och på så sätt kan olika molekyler separeras från varandra. Antikroppar kan alltså separeras från andra proteiner eller enzymer.

Denna metod är känd sedan länge och utvecklats under många årtionden vilket gjort den väldigt effektiv. Idag finns det flera stora företag som producerar och säljer kromatografitekniken både i bulk, färdigpackade kolonner samt kromatografisystem som kör hela processen för kolonnen. Det finns dock flera exempel på små företag som är sugna på att ta upp kampen med dessa stora jättar till företag som har en stor del av kromatografimarknaden. Hur tänker då dessa små entreprenöriella företag när de ska försöka ge sig på dessa stora företag med starka finanser, är det ens möjligt och hur skall det göra i så fall?

I en del av denna rapport har detta undersökts med hjälp av intervjuer med erfarna personer som har erfarenhet från små och stora företag inom denna bransch, samt en global nätbaserad enkät där forskare som använder denna teknik fått svara på ett antal frågor. Intervju och enkät valdes som passande metoder för att få svar på vad kunder och användare söker information om denna teknik, vad de värderar för egenskaper i dessa produkter samt skillnader mellan mindre och större företag.

Att ett mindre entreprenöriellt företags anställda är dess viktigaste tillgång är en av de slutsatser som dragits i denna rapport. Mindre företag måste vara mer lyhörda på kunders önskemål för att kunna konkurrera med större företag och då krävs det kunnig och driven personal för att kunna möta kundernas önskningar. För att synas och sticka ut bland andra företag är marknadsföring viktigt, men ofta dyrt. Därför föreslås mindre företag hellre delta på konferenser, mässor och liknande sociala evenemang där likasinnade och potentiella kunder kan nås på ett mer personligt och mer direkt sätt än till exempel reklam i någon form av media.

Mindre företag är också i behov av externt kapital innan de kan växa på sin egna försäljning varför en person i företag som kan ge förtroende till investerare är mycket viktigt. En person som inger förtroende talar om för omvärlden att ett företag är seriöst och något att satsa på. Detta områden för entreprenörskap samt kromatografi är två mycket intressanta områden som kan gynna samhället med mångfald och utöka näringslivet vilket gynnar hela samhället med fler arbetsplatser som följd. Mer forskning kring dessa två områden är därför något som bör uppmuntras och drivas vidare.

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1. Introduction

Monoclonal antibodies (mAbs) have been known a couple of decades and important advancements have been made within the latest 10-20 years for the use in cancer treatments (Panowski *et al*., 2014). Now scientists have an idea how they work in the body and how they may be used for different applications, such as attach drugs to them to replace the often uncomfortable and side-affect causing chemotherapy and radiation often used today. According to Mellor *et al.* (2013) there are studies showing promising results where cancer patients can be treated with the help of mAbs and avoid the side-effects from the methods used today.

But why are mAbs so interesting to work with? Firstly, they have an incredible specificity due to its special structure, which make it possible to create millions of different unique antibodies. mAbs can also be modified, i.e. produce them after own-made blueprints, which increases the possibility to find and use the antibody suitable for the purpose of interest. mAbs are never found isolated by itself and thus need to be purified which is relatively easy with high levels of purity in a reasonable time. They are also easy to distribute into and within the body, which are of great importance to be able to use it as a pharmaceutical.

The increased use and demand for mAbs calls for larger and more effective production systems to produce enough mAbs in shorter time and purification processes that can handle larger amounts of mAbs, which is emphasised by Birch and Racher (2006). They also points out that when developing the production processes the final process must be easily scalable and robust and still meet the criteria for safety and quality.

1.1 Antibodies

Antibodies, also called immunoglobulin (Ig), are glycoproteins that are vital to our immune system. When an antibody is exposed to a specific antigen the B-lymphocytes express and secrete corresponding antibodies as a response of protection. The antibodies have strong affinity towards their specific antigen in order to neutralise or visualise it to other cells (Owen, 2013).

Antibodies have a basic structure reminding of the letter Y, see figure 1. The so called heavy chains and light chains, named after their weight, make up the antibody. Heavy chains and light chains are divided into a constant region and variable region where the variable region is what determines the specificity of the antibody and the constant regions determines the class of the antibody. The arms of the antibody are called Fab regions (fragment antigen binding), having a heavy chain and a light chain connected by disulphide bonds.

The stem of the antibody is called Fc region (fragment crystallisable), which is made up of heavy chains. Fc regions are not involved in the specificity of the antibodies, but in effector functions such as binding to cell receptors and class determination of the antibody. The two heavy chains in the Fc region are connected with a disulphide bond that also makes the antibody flexible to increase the chance of good binding to antigens (Vijayalakshmi Ayyar *et al*. 2012).

There are several sorts of antibodies that differ among species. The different classes of mammalian immunoglobulins are divided into classes named IgA, IgD, IgE, IgG and IgM where IgG is most abundant. The classes depend on which subclass the heavy chain is. The classes, also called isotype, are divided after the Greek letters mu, gamma, alpha, delta and epsilon (Owen, 2013).

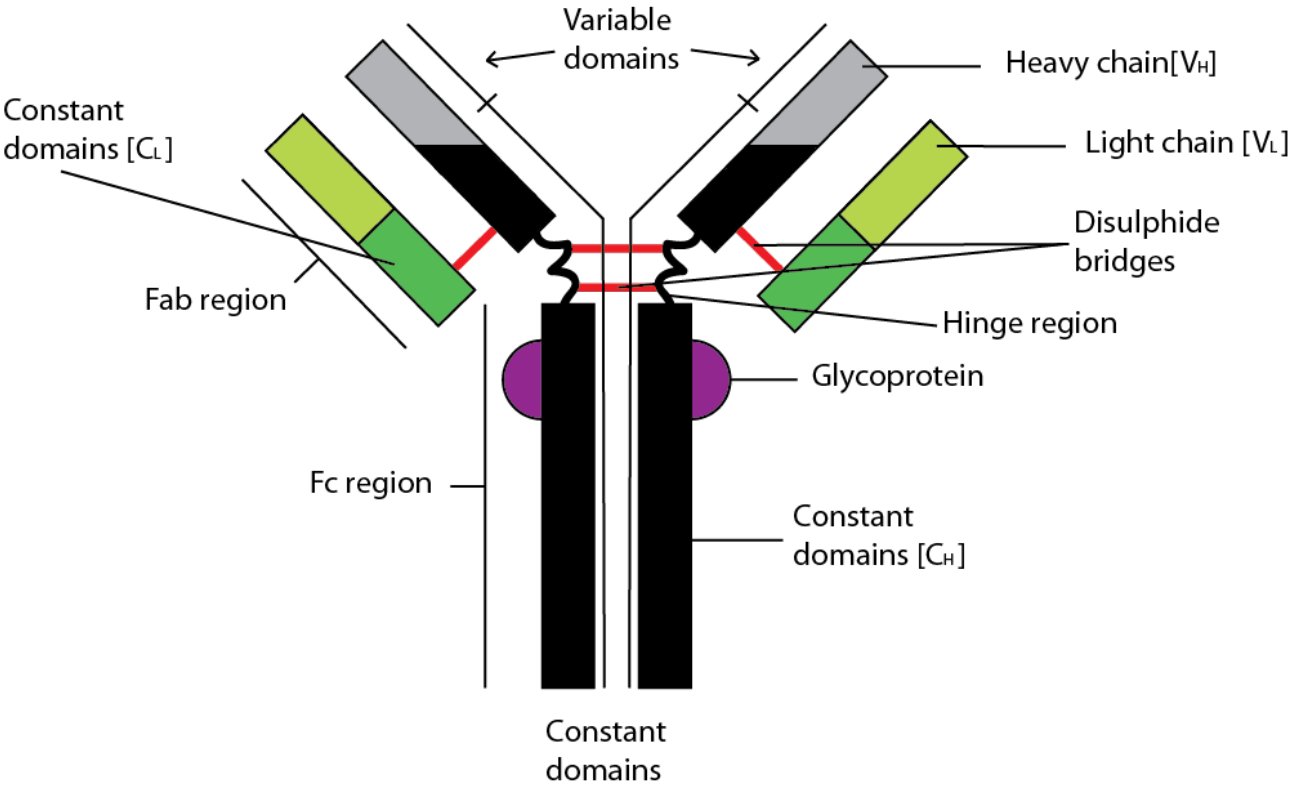

Figure 1. The structure of an antibody with heavy chains in black/grey and light chains in green. The carbohydrate, which differs in abundance between antibodies, is found in purple beneath the disulphide bridges in red. The Fc region, the stem of the antibody, characterise the antibody type and the Fab region, the arms of the antibody, determines the specificity of the antibody (Drawn with inspiration from Vijayalakshmi Ayyar *et al*. 2012).

The constant domain, the Fab-region (CL), is also found to have different variants and differs among species. Lambda and kappa chains make up this part of the antibody and has to be either or, it cannot be both lambda and kappa chains in the same antibody.

Antibodies have an incredible diversity and are made possible by the procedure of antibody generation. When an antibody is constructed in the body of an organism there are different segments in the synthesised amino acid strand, called V, D and J segments for heavy chains and V and J segments for light chains, that determines the antibody class and specificity. The lambda and kappa chains further increase the number of possible antibodies to 10^6, described in the book *Immunology* by Owen (2013) on page 239.

1.2 Monoclonal Antibodies versus Polyclonal Antibodies

Antibodies occur naturally in mammals and birds among other species, but can also be produced with help from bacteria and yeast as examples. If one takes serum from mammalians, the serum will contain lots of different antibodies and the mix is said to contain polyclonal antibodies, due to the mix of different antibodies having attraction to one single antigen, but attraction for different epitopes.

Polyclonal antibodies are produced from different lines of B-cells while monoclonal antibodies on the other hand comes from the same line of B-cells. Monoclonal antibodies are clones from one B-cell line and thus specific to the same epitope of an antigen (Vijayalakshmi Ayyar *et al*. 2012). A pool of monoclonal antibodies will, unlike a pool of polyclonal antibodies, have affinity for one single antigen, which makes them able to target only one type of intended antigen.

To get monoclonal antibodies an immortal cell line is used, called hybridoma cells. A hybridoma is a crossing between an activated antibody-producing B cell and a cancerous plasma cell, called myeloma cell. Fusing myeloma cells with spleen cells from an antigen challenged animal, which often is mouse, makes hybridomas. The hybridomas will now proliferate in a special growth medium and produce the antibody. The cells are then screened and cells producing the antibody, called positive cells, are selected and the antibodies can be harvested (Owen, 2013).

1.3 Chromatography as Technique and the Chromatography Matrix

Chromatography is a method used for the separation of molecules where properties such as size and surface charge facilitates the separation. Chromatography is carried out in a tube shaped column filled with the chromatography matrix called stationary phase, explained below. To carry out the separation, the column is equilibrated with a buffer suitable for the target molecule to give the right conditions. The sample is then applied on top of the column and run through the column to be collected in fractions at the bottom.

The matrix that a chromatography column is filled with contains many small beads in sizes from nanometres to micrometres, which are very porous. This matrix can be either synthetic, inorganic or organic. Acrylamide, polystyrene and polymethacralate derivates are synthetic, and glass and porous silica being inorganic matrices. The common ones used in antibody purification are the organic ones that are agarose, dextrose and cellulose.

All matrices have specific production procedures but all with the goal to achieve as large surface area as possible on each bead. The porosity of the beads will determine the loading capacity of the column. The matrix by itself is called a base matrix to which one attach desired ligands to change the specificity, and it is then called media. It can be trimethylamine to create an ion exchanger or Ni-NTA to create an affinity matrix.

The porosity of the beads is what makes chromatography possible. Smaller molecules will travel slower through the columns since they can enter the pores and thus travel a longer distance than larger molecules that cannot enter the pores and only travel between the beads.

2. Production of Monoclonal Antibodies

Monoclonal antibodies can be produced using different expression systems, mostly using mammalian host cell lines and especially for therapeutical use. The choice of host depend on the end users specifications on quality, quantity and special preferences (Li *et al.*, 2010) where commonly used systems are NS0 murine myeloma cells (Spens & Häggström, 2007), PER.C6® human cells (Pau *et al.*, 2001) and hybridoma cells. As an example, many antibodies needs a proper folding or glycosylation, which bacteria such as *Escherichia coli* or the eukaryote yeast, cannot offer. Mammalian cells however, can often do a proper folding and glycosylation and thus makes them popular for production of mAbs (Potgieter *et al.*, 2009). The drawback with mammalian cells is their need for more careful production processes since they are much more fragile. Mammalian cells thus needs a more gentile process that often takes more time than the processes for bacteria and are more costly.

Ecker *et al*. (2015) clarify that *Pichia pastoris* and *E. coli* are the common non-mammalian systems used, often with an engineered genome to maximise yield, especially for Fab and Fc fragments (Ecker *et al.*, 2015, Li *et al.*, 2010). Using only Fab fragments, instead of whole antibodies, eliminate non-specific binding between Fc portions of antibodies and Fc receptors on cells, thus often used when only blocking a signalling molecule or receptor is desired (Holliger, 2005). Their smaller size also allow for a more efficient penetration of tissue, which often can be a problem due to cancer tumours prominent physical barriers (Christiansen, 2004).

Due to the drive for cost reduction as Potgieter *et al.* (2009) are discussing, engineered bacteria and yeast that can produce immunoglobulin with desired post-translational modifications are researched extensively, which also Li *et al.* (2010) gives several examples of.

3. Purification of Monoclonal Antibodies

To purify mAbs there are several methods available but the purification is hard to deal with and require sophisticated methods. Before the use of cultured cells that produced antibodies one had to use body fluids from human or animals, but with engineered cells that are easy to cultivate the procedure became a easier. However, the purification still has obstacles to overcome since the solution where the antibodies are purified from is very complex. Even though engineered cells for cultivation are used the variety of antibodies that are possible is enormous, which adds the need for a very specific purification method to separate the different types of antibodies.

Depending on where and in what purpose the antibody is intended to be used the method of choice for purification differs. Different purposes require different levels of purify where yield and costs are important factors as well. Often one has to set a "good-enough" level to get a reasonable cost for the purification.

Affinity chromatography is a popular and efficient method for purifying antibodies. The matrix in the chromatography column has specific ligands immobilised to the matrix with high affinity for the specific antibody and that together with the type of matrix determine how efficient the purification will be. There are different ligands available for antibody purification where ProteinA is the most common one due to very high affinity for the antibodies. There are several other non-chromatographic methods such as precipitation. This review will focus on a few chromatographic methods.

3.1 Ligands used in Affinity Based Antibody Purification

When purifying antibodies the ligand must have strong affinity towards the desired antibody to achieve a high purity. To find ligands with high affinity there are many choices available. Antigens are often used when purifying immunoglobulin from a complex mixture of immunoglobulin with different specificities, such as serum from animals. Sometimes the antigens can be expensive, hard to handle or restrictive in use and thus it is better to look for other options (Huse *et al*. (2002), Vijayalakshmi Ayyar *et al*. (2012)). Other bio specific ligands are bacterial proteins, anti-antibodies and lectins where bacterial protein are most commonly used (Vijayalakshmi Ayyar *et al.*, 2012)

Bacterial proteins, often surface receptors, are extracted from bacterial cell walls and can be used when purifying proteins. In the bacterial cell walls, the proteins helps the bacteria send or transmit signals which is what makes them able to work in protein purification. When the proteins are attached to the chromatography matrix, they bind antibodies as they would in their original environment. The two most common bacterial proteins used to capture full length antibodies are from *Staphylococcus aureus* Protein A (SpA) and Streptococci groups C and G, Protein G (SpG), but often called just Protein A and Protein G (Vijayalakshmi Ayyar *et al*., 2012, Roque *et al*. (2007)).

Bacterial Protein A and Protein G do not interact with the variable region of an antibody, like many other molecules, but the Fc-region of IgG. This allows them purify all isotypes of IgG since the isotypes are determined by the variable region. A third isolated bacterial protein from P*eptostreptococcus magnus*, called Protein L, is also used for antibody purification and especially for IgG, IgY, IgM, IgE and IgD due to its specificity for other parts of the immunoglobulin compared to Protein A and G (Vijayalakshmi Ayyar *et al*., 2012).

Carbohydrates, which immunoglobulin contain in various proportions, can be used to purify immunoglobulin. Lectins, which are proteins with affinity for carbohydrate sections in polysaccharides, glycolipids and glycoproteins, can be used for this purpose. Lectin based purifications are used for IgD, IgM and IgA, which the ligands Protein A and G find difficult to

bind. Lectins can be very specific, even down to single sugar molecules and the different conformation of sugar molecules. The sugar content of the antibody as well as its binding and conformation is also an important factor (Vijayalakshmi Ayyar *et al.* 2012). According to Roque *et al.* (2007) another advantage is that the purification can be run at neutral pH that is gentile for proteins.

Anti-antibodies are normal antibodies with high specific affinity for the constant heavy (C_H) and light chains (C_L) of the antibody. When immobilised onto the matrix their strong and specific affinity facilitate purification with high purify for proteins that can be hard to purify with other ligands.

4. Monoclonal Antibodies in Cancer Therapy

Cancer is non-normal and uncontrolled cell division that often spread to other tissues or locations within the body. It has long been treated with surgery, radiotherapy and chemotherapy and surgery being most effective to treat cancer. But since surgery is invasive, radio- and chemotherapy are often chosen but needs several treatments since the therapy cannot kill all tumour cells with one treatment (Urruticoechea *et al*. 2010).

Cancer tissue often expresses specific antigens or growth factors, which makes it possible to target cancer tissue with antibodies. Antibodies are, as mentioned, very specific and this specificity make it possible to create "magic bullets", a term coined by Nobel prize winner Paul Ehrlich in the early 1900s, meaning that drugs can be targeted for specific receptors (Strebhardt and Ullrich, 2008). In this case antibodies only bind to the intended molecule. To target the antigens, a thorough screening of both tumour and normal tissue expression is performed, and also what biological role the antigen has when the tumour is growing (Scott *et al.* 2012).

There are several mechanisms that mAbs can initiate tumour killing: 1) direct tumour cell killing, 2) immune - mediated tumour cell killing and 3) vascular and stromal ablation, which will be explained further in detail. Important mechanisms that antibody therapy uses or engages are antibody-dependent cell-mediated cytotoxicity (ADCC), depicted in figure 2, where the antibodies are recruiting different cytotoxic cells from the immune system and complement-dependent cytotoxicity (CDC) where the complement cascade is activated, which is an important and effective function in the immune system against invading cells.

Direct tumour cell killing
Direct tumour cell killing can be initiated when antibodies bind to cell surface receptors with several outcomes that kill the cells. Induction of apoptosis, programmed cell death can be initiated when mAbs bind to certain surface receptor and mimic the binding of a ligand that occurs naturally. The long used monoclonal antibody *rituximab* is active through this mechanism, and more specifically targeting the CD20 antigen which is expressed by many B-cell malignancies (Mellor *et al.,* 2013). mAbs can also bind to receptors in a competitive way, meaning that it will bind instead of the intended molecule and thus inhibit the signal. *Cetuximab* is a monoclonal antibody that acts as an antagonist by targeting the epidermal growth factor (EGF), which is important for growth in cancer cells, and interfere with its function (Owen, 2013).

Antibodies can also be modified with attachments of molecules, and often molecules toxic to cells. Radioactive isotopes such as ^{90}Y, metal called yttrium, and ^{131}I, iodine, are used today when delivering cytotoxic doses of radiation to cancer cells using monoclonal antibodies and goes under the names *ibritumomab tiuxertan* and *tositumomab* (Owen, 2013).

Immune-mediated tumour cell killing
Scott *et* al. (2012) explains how the activation of mechanisms in the immune-mediated tumour cell killing is involving the immune system. CDC or activation of complement, a series of proteins acting to kill invading unknown cells, is an effective mechanism that kills tumour cells. Induction of phagocytosis, a cell called macrophage engulf the tumour cell, is another recruitment from the immune system.

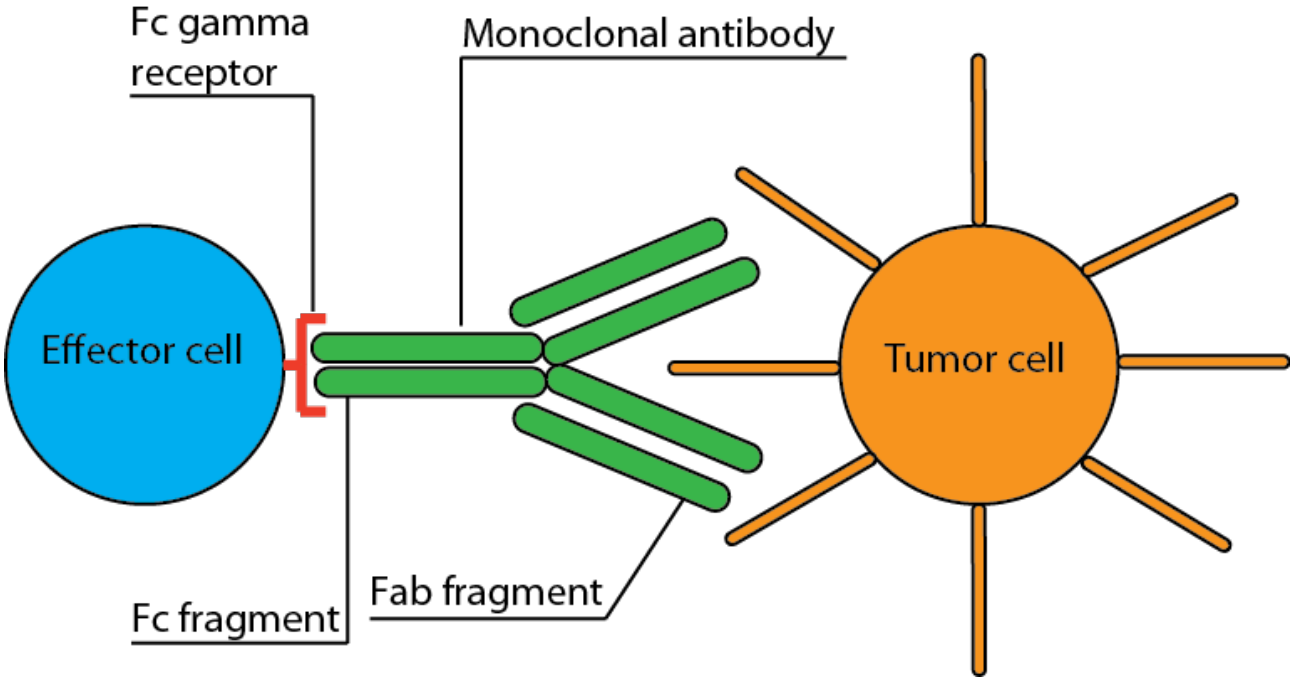

Figure 2.The antibody-dependent cell-mediated cytotoxicity complex. Figure inspired by Mellor *et al.* (2013).

The most used mechanism for carrying out tumour cell killing is antibody-dependent cell-mediated cytotoxicity (ADCC), where the antibodies are recruiting different cytotoxic cells from the immune system, and is used in many clinically approved drugs (Scott *et al.* 2012). The Fc part of the antibody bind to a Fc gamma receptor (FcgR) at any kind of effector cell in the body and creates a complex that can bind to a cancer cell and initiate ADCC. When the Fab fragment of the antibody bind to a tumour cell, and the Fc fragment is bound to the FcgR, the mechanism to kill the tumour cell starts (Mellor *et al.,* 2013).

Vascular and stromal ablation
Cancer tumours have stromal cells and a rich vascular net just like other tissues. Therapies targeted towards these two important parts of a tumour can therefore be utilised to kill the tumour. Therapies inducing vascular and stromal ablation can do so by inhibit stromal cells, deliver toxins to stromal cells or vasculature and have antagonists bind to vasculature receptors. Natural killer cells and the recruitment of major histocompatibility complex (MHC) and membrane attack complex (MAC) are also efficient inducers (Scott *et al.*, 2012).

4.1 What is Next in Cancer Therapy?

As mentioned, ADCC is often used in today's cancer treatments to activate the killing of tumour cells, and is thought to be vital in increasing the efficacy of antibodies for cancer therapy (Weiner *et al.* 2010). Khan *et al.* (2006) is conducting clinical trials with rituximab, an ADCC-based antibody therapy, together with an important signalling molecule in the immune system called *interleukin 2* which could increase T cell activation and thus the efficacy of the tumour cell killing. Scott *et al.* (2012) enlightens the possibilities with combining antibodies and vaccines for cancer treatments and where several studies are to be made.

Mellor *et al.* (2013) examines if individual genotyping can affect the effect and use of antibodies in patients, but found no concluding evidence. But they emphasise the need for more research in this area. Personalised medicine is a growing field and personalised cancer treatment using antibodies might not be to far away in the future.

Not only mAbs are being looked into for targeted cancer therapy. Baudino (2015) are comparing small molecule inhibitors, which decreases enzymes activity and thus can kill the cancer tumour, and immunotherapy, which stimulate the immune system to destroy tumour cells, alongside monoclonal antibodies. Hollie *et al.* (2016) also highlights the advancements using CAR T-cells, T-cell that express engineered chimeric antigen receptors to increase the specificity towards a cancer antigen. Deena Beasley at Reuters has also noticed the advancements and clinical trials of CAR T-cells in 4 June 2016.

5. Conclusion

Cancer is today one of the major causes for death, and better treatments using antibodies could potentially save many lives. The production of antibodies has moved from mostly using animals such as rabbits, to a greater extent use genetically engineered expression host systems such as *E. coli* described by Ecker *et al*. (2015), and thus increased the production rate and lowered costs, both vital in delivering enough antibodies.

As for the purification of antibodies, the amount of protein purified in each step and the time it takes are important factors for a cost effective procedure. When trying to find the best and most cost effective purification method, the quality of the purification is always an uncompromising vital parameter to make sure the mAbs are pure enough for safe use. Research is being conducted to improve the techniques used today by looking for stronger and more specific affinity for antibodies and other ligands. The wish for one single purification step is always there, but can be hard to fulfil.

Antibodies used in cancer treatment acts like targeted “magic bullets”, a term coined by the Nobel Price winner Paul Ehrlich, and can make the treatment more effective and less uncomfortable for the patient. Continuous research on how the therapies mechanisms work is being made to improve and develop the treatments and ensure safety for the patients. Methods using monoclonal antibodies for targeted cancer therapy are used today and their further development looks promising, however other techniques for targeted therapy are being looked into such as small molecule inhibitors and immunotoxins.

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Appendix I - The Establishment of a Small Challenger Company in a Segmented High-Technology Life Science Market

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The Establishment of a Small Challenger Company in a Segmented High-Technology Life Science Market

Challenges and Opportunities - a Model Case Study

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Abstract

The Establishment of a Small Challenger Company in a Segmented High-Technology Life Science Market

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This study aims to identify the challenges and opportunities of a small challenger company in a rigid and conservative high technology life science market. Strategies for finding a foothold, establish a position and creating a viable company is discussed. Qualitative and quantitative data was collected through interviews, online survey and conjoint analysis which were used as market research tools. For an entrepreneurial firm in the life science market it is important to tend to their most valuable resource, the employees, and it is vital that they have an extensive knowledge of the market that they are active in. Strategic planning tools and templates aid in executing and implementing the proposed business model. Recommendations for a model case entrepreneurial company regarding continued market research, increasing sales and strategies for marketing are made.

Handledare: Allan Simpson
Ämnesgranskare: Göran Lindström
Examinator: Ulrika Persson-Fischier
UPTEC FRIST** ***

Projektsammanfattning

Produkter som du ofta är eller har varit i kontakt med har gått igenom en process kallad kromatografi när det producerades eller förädlades. Till exempel har de flesta, om inte alla, läkemedel du tagit renats fram med hjälp av kromatografi. Proteinshaken som ses i de flesta gym är med största säkerhet också framställd med hjälp av kromatografi. Det finns produkter nästan överallt som utnyttjar denna gamla teknik.

När man utför kromatografi har man en cylinder, så kallad kolonn, som är packad med en gel bestående av otroligt många och väldigt små porösa kulor. Dessa kulor kan förenklat liknas vid innebandybollar. Separationen av molekyler sker genom att applicera prover högst upp i kolonnen och sedan pumpas de igenom, längs vägen vandrar de större molekylerna snabbare igenom gelen än de mindre molekylerna. Hålen i kulorna, tänkt hålen i innebandybollen, är tillräckligt stora för att de mindre molekylerna ska komma in, och därmed färdas en längre sträcka genom kolonnen jämfört med de större molekylerna som endast åker mellan kulorna.

Flera av de företag som idag säljer kromatografi är stora med tusentals anställda men det finns idag många små, relativt nystartade företag med en handfull anställda som försöker ta upp kampen om kunderna med dessa bjässar till företag. Hur ska nu det gå till, och varför? Är inte de stora företagen bäst eftersom de är just så stora?

Hur små entreprenöriella företag i en specialiserad marknad kan utmana stora företag och etablera sig på en hårt konkurrenssatt marknad, är en fråga som undersökts i denna rapport. För att få en bild av marknaden, och hur ett litet företag kan ta upp kampen, har en nätbaserad enkät samt ett antal intervjuer med anställda på mindre företag som har erfarenhet från större företag genomförts. Enkäten skickades ut till forskningslaboratorier över hela världen för att kartlägga hur de söker information och vad de tycker är viktigast när de köper kolonner. Liknande frågor ställdes under intervjuerna, men även frågor om hur det är att arbeta på ett mindre företag jämfört med ett större företag.

En av slutsatserna som dragits är att små entreprenöriella företags mest värdefulla tillgång är dess anställda och deras kunskap. För att kunna konkurrera med stora företag bör de ha anställda som är kunniga och erfarna inom sitt område, och ta till vara på och förvalta deras kunskaper. Att små företag kan ta upp kampen om kunder med större företag, handlar också om att de är mer flexibla tack vare lösare företagsstruktur. Detta gör att de ofta kan skräddarsy lösningar till kunder och därmed tillgodose kunders ytterst specifika önskemål. Om tillfället är rätt och kundens idé tillräckligt bra kan det leda till nya produkter, och det lilla entreprenöriella företaget kan ha hittat vägen till ett större och framgångsrikare företag.

Mindre företag är ofta i behov av externt kapital vilket gör dem beroende av investerare. En vital komponent för små företag är därför att ha en person i företaget som kan inge förtroende och sälja företagets idé till personer som kan tänkas vilja investera. En bra säljavdelning som kan sälja produkterna är minst lika viktigt. Marknadsföring är ett effektivt sätt att hitta kunder, det vet vi alla när i går förbi en gatupratare och genast blir sugna på glass, men är ofta väldigt dyrt och blir därför något små företag får klara sig utan. Om de lyckas skaffa pengar till marknadsföring bör de i sådana fall inrikta sig på tidskrifter inom forskning, och deltaga på seminarier och konferenser.

Området för entreprenörskap är väldigt intressant och mångfald inom näringslivet gynnar alla grupper i samhället, eftersom det skapar arbetstillfällen och uppmuntrar kreativitet. Mer forskning på detta område är därför något vi anser nödvändigt och bör uppmuntras.

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Glossary

Agarose	Polysaccharide polymer extracted from seaweed. Agarose is the base from which Bio-Works' chromatography media is made.
Chromatography	A collective term for a set of laboratory techniques for the separation and purification of mixtures.
(Chromatography) Column	The hardware in which a chromatographic separation takes place. Usually made of plastic or glass and are available in different sizes depending on the aim of the separation.
(Chromatography) Media	The matrix, also called medium that is coated inside a chromatographic column. Different media has different properties depending on the sample to be separated, *e.g.* ion exchange, affinity or hydrophobic interactions.
Elution	A term used in analytical chemistry, where one molecule is separated from the other by extracting with a solvent.
SPSS	A computer software for statistical analysis acquired by the International Business Machines Corporation (IBM)

1. Introduction

A constantly changing world has always been a strong motive for companies to update their processes and product lines. For companies active in the high-technology market, busy with the manufacturing of intricate products, technological changes demand that they constantly need to improve their businesses to not be outrivaled.

The market for chromatography media and chromatographic columns is no exception to the need for improvement, although the rate of change is considerably slower than other comparable high-technology markets, *e.g.* the development of electronical devices. The chromatographic market is highly competitive and segmented, and there are many large and well-known actors such as GE Healthcare (GE), Thermo Scientific™ Pierce™ and Bio-Rad Laboratories. For a small company trying to establish their business in such a market, characterised by rigidity and conservatism, there will be many challenges to face. The customer's willingness to deviate from industry standard, overcoming the revenue threshold, or which unique selling point to emphasize to catch interest are examples of such challenges.

Being a challenger company in the high technology life science market can also be connected with opportunities that larger corporations may not have. Chromatography is a versatile and useful analytical and production method, used in different ways in different areas in the market, meaning that there is a broad variety of customers with various needs for chromatographic products. Therefore, there can be many different ways for a small company to make their entry on market, find a foothold, establish a position and ultimately create a viable company. To be able to locate these entry points and identify what approaches need to be taken to create a sustainable company, one needs to have a wide understanding of the market, and what needs the customers in that market have.

What customer's value in a product or service can be assessed in different ways through market research. Customers, their purchasing habits and the value they place upon a current product or service can be identified. This information can then be utilised in the assessment of the challenges and opportunities for a company starting up their business in a competitive market. This study aims to chart said challenges and opportunities associated with the establishment and marketing of a small challenger company in a highly segmented high-technology market.

When a small company wants to gain market shares they grow and undergo changes, the company is maturing. When changes need to be implemented, there is more often than not resistance toward them. To keep a good company culture and reduce the resistance of change, the leadership needs to be great. This study are also going to discuss how to minimise resistance toward changes and keeping employees motivated during changes in a maturing business.

To be able to study such a company, collaboration with a life science company located in Uppsala, Sweden, was started. *Bio-Works Technologies AB (Bio-Works)* were interested in increasing their sales and was found to benefit from the map out of potential customers in the global protein purification market for pre-packed columns. To be able to market and launch their products in a way that reaches more customers on the global market would help them gain higher revenue and keep their company competitive.

The focus of this study was both descriptive and explanatory, as defined in Lekvall and Wahlbin (2001), data was collected from an online survey, interviews with employees in an entrepreneurial company and also a conjoint analysis carried out by experienced users of chromatographic columns. The collected data was compared to known theoretical models about competitive strategies in the business-to-business market.

1.1 Bio-Works: The Story of a Young Entrepreneurial Company with Ambition

Bio-Works is a young, small and globally active biotechnology company based in Uppsala, Sweden. The company started its journey in 2006 and is part of a corporate group consisting of a holding company (Bio-Works Technologies AB) and two subsidiaries, Bio-Works Sweden AB and Bio-Works LTD, see figure 1. These three companies effectively work as a single company and have in the latest year (2015) almost doubled their workforce to 16 employees. Their main field of operation is chromatography, where they sell and produce column media and pre-packed protein purification columns. Today Bio-Works is in the process of expanding their business and will hire more employees in the nearest future. At the moment, their largest existing market is in Asia, with further plans to expand to markets all around the globe.

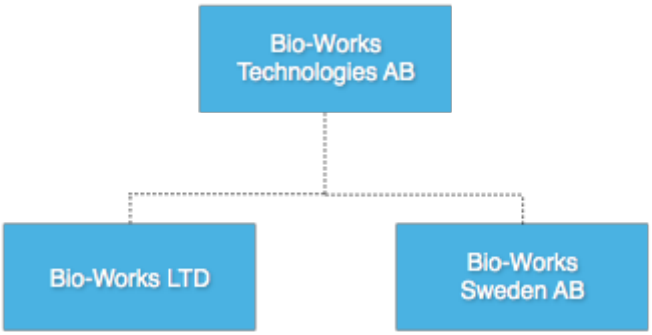

Figure 1. Structure of Bio-Works organisation.

Bio-Works produces their own line of chromatography media and pre-packed columns and their business model is concerned with providing customised protein purification solutions for their customers. The media that Bio-Works produce and sell, in both bulk and pre-packed columns, is made of small beads in micron size, produced from agar extracted from seaweed. The beads are porous with a very large surface area making them excellent for the separation of proteins.

When Bio-Works was founded in 2006 by Jan Berglöf, Andy Bright, John Connelly and Göran Lindgren, it was set up in Bromma, Stockholm. The founders had different backgrounds but all with years of experience to add to the company. After a few years the company had to look for new facilities due to reconstruction reasons, which is when they moved to the location used today in Uppsala which includes production facilities. Bio-Works was not selling much and was mostly using their market contacts for selling products in smaller amounts. Thus, sales were not keeping the company afloat with money was coming from external and private funding.

The move to Uppsala in 2012 was a big change for Bio-Works, almost as a fresh start, with new employees and possibilities to enhance the production with the new production facilities.

In connection with the move, a new production manager was hired as well as COO Allan Simpson. Allan had many years of experience at high positions from large life science corporations such as Pharmacia, Amersham and GE. Allan's task is to run the company effectively and drive the ongoing projects forward using his experience.

Around this time the company changed direction from mostly selling media in bulk to expanding their portfolio with smaller columns. These columns were released under the name BabyBio. In the beginning of 2016 Kristopher Fain became their new CEO bringing lots of experience from sales and business strategy in large corporations. Kristopher was hired for his skills in sales, product management and the ability to raise capital and is now about to organise and restructure the company. Kristopher's strategic experiences from larger companies is seen as an asset in Bio-Works progress to increase sales, and in three years they plan to increase turnover by a factor of 12. He sees a lot of potential in Bio-Works's highly technical products and their production capacity.

Kristophers main task as CEO, given to him by the board, is to set up a sales force to increase sales so the company can become self-sufficient. A model described by Vohora (2004) explains the different phases that start-ups go through, from the early phase based on research and finding an opportunity in the market to creating a sustainable company, described more in detail later in the report. Kristopher's task is, by increasing sales, to push Bio-Works over the *threshold of sustainability* to make the company survive on its own, without additional funding.

Allan was acquired to the company as a consultant to move Bio-Works to its new location and was later hired as COO to run the daily business. One very important task in the beginning was to acquire money so Bio-Works would survive and could keep on growing, thus pushing Bio-Works over the *threshold of credibility* as described by Vohora *et al*. (2004). Money from the government owned company *ALMI Företagspartner AB (ALMI)* and some private equity investors kept the company alive. His previous contact with ALMI, from earlier projects and experience from running businesses before Bio-Works, was very helpful when trying to bring in money.

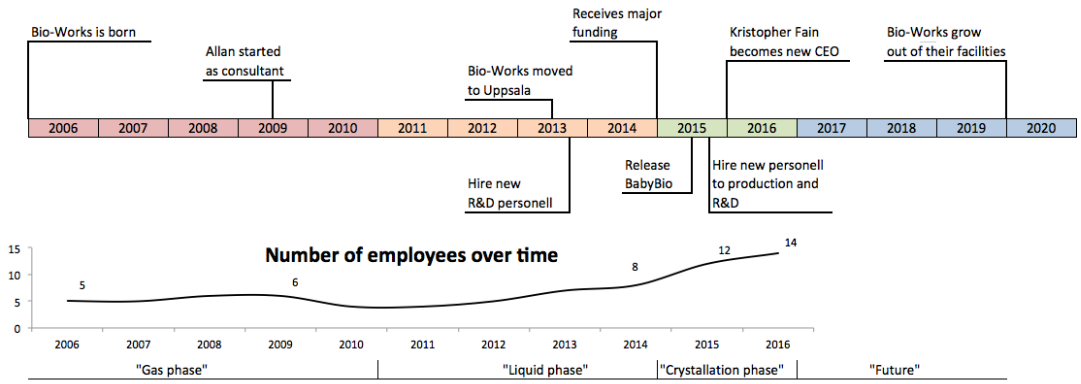

Figure 2. Timeline with major events in Bio-Works history with a graph of the number of employees following the timeline. At the bottom CEO Kristopher's analogy of how Bio-Works have evolved since their start in 2006 is outlined. The coloring in the timeline represents the phases which Bio-Works have gone through and will go through. The marking that Bio-Works will grow out of their present facilities in 2019 comes from the interview with Kristopher.

When Bio-Works started, the founders were working with the means they had at hand and tried to create realistic goals for their business with that, thus practicing *effectuation* as explained by Sarasvathy (2013). As the business grew, Bio-Works drifted away from effectuation towards creating goals and finding means to reach these goals, called *causation*. Lemos and Andreassi (2015) reason that smaller business often start with effectuation and move towards causation as the business grows due to a need of more structure in the company. That smaller companies benefit from working with effectuation, together with understanding competitors, in the beginning of its business is emphasised by Charles and Oystein (1998).

1.2 What is Bio-Works in Need of?

Bio-Works is not happy with their current sales rate and want to gain more knowledge about the market they are active in, and also what users value in a protein purification column. When Bio-Works want to launch a new product or increase their marketing on existing ones, information about the market is very influential on the launch and marketing process. The current product line is made up of different chromatographic media and disposable, pre-packed 1mL and 5mL columns called Baby-Bio's. These columns do not have a desirable sales rate, something that Bio-Works wish to change. They want to analyse what factors are critical for users of chromatography columns when determining which columns to buy, where they are located and how they search for information about new technology. These critical factors would highlight opportunities and challenges that would be of interest when launching and marketing future and existing products.

This study will contribute to the interdisciplinary field of business development and entrepreneurship. What factors that is more important and/or more valuable than others for users regarding chromatography and protein purification columns will be identified. It is important to identify important factors in customer behavior that can be used as arguments in marketing and upcoming launch plans for future products, thus creating a base for a product portfolio. All small entrepreneurial companies need a strategy to market their products by mapping customer needs and demands in the life science area. This will sort out what opportunities one should focus on to penetrate and gain market shares with their media or columns.

1.3 Research Frontier

The topic of entrepreneurship has been extensively researched. Many articles and books explore different topics regarding how an idea becomes a viable company. In a study by Yetisen *et al*. (2015), the importance for technology transfer from academia to industry to fuel economic growth is stressed. They describe the journey of a high-technology entrepreneurial firm from turning an idea into a high-potential commercial product (or service) to finding financial resources from external sources, commercialisation, marketing, and managing a growing company. In another study by Dyer *et al*. (2008) the origin of innovative strategies is traced by examining the attributes of innovative entrepreneurs. The authors developed a theory that explains how entrepreneurial behavior can increase the profitability of a generated idea, and how this becomes an innovative venture.

Further, the link between innovation, small businesses and entrepreneurship is identified by Sahut and Peres-Ortiz (2013). A close relationship between these three topics is found, and they also stress that small businesses have an environment conducive to entrepreneurship and innovation that cannot be found in larger corporations.

A foothold is defined as a position a small company intentionally establishes in a market where they do not yet compete (Upson *et al*., 2013). An investigation concerning how competitor analysis relates to foothold moves was conducted, and they concluded that the actions a small challenger company takes, whether it is an attack or withdrawal, will have a big impact in the market and on the competitors.

Concerning the interdisciplinary field of entrepreneurship and biotechnology, a study by Patzelt *et al*. (2012) explains that these two are intrinsically related. Due to the rapid growth of the biotechnology market, many players are still at an early stage of their lifecycle, and entrepreneurial behavior is of the essence. Managing a biotech firm can be complicated due to the high complexity of the products, and the benefits of working in the so called biotechnology clusters cannot be overstressed. This conclusion is supported by Kleyn and Kitney (2007), who have reported the advantages of working in partnerships in the life science industry.

Another closely related field that have been investigated is the pharmaceutical market where Matikainen *et al*. (2015) identifies key determinants of new product launch success in the pharmaceutical industry. Careful product launch is very important for small challenger companies and this study emphasises that relational aspects are keys for successful launches.

The present study was an opportunity to contribute to the discussion of opportunities and challenges of a small entrepreneurial company active in the biotechnology market. The different aspects of an entrepreneurial environment could be visualised by examine the work progress of a challenger company in the global protein purification market as they work towards establishing a foothold to make the company viable.

1.4 Purpose

Map out the challenges and opportunities of a small entrepreneurial challenger company associated with establishing a foothold, build a position and create a viable company in a rigid and conservative high technology life science market.

Question formulation:

- What approaches could a small company in the life science market take to increase their chances of gaining market shares?
- What do users value most in high-technology products such as chromatographic purification columns?
- What can a small challenger company do to use the restricted monetary resources in the best way possible?
- What value does corporate culture and structure have for small companies as they are maturing?

1.5 Delimitations

Delimitations in this study are mainly dependent on beforehand given directions to the project group from the case principal, Bio-Works. The study is limited to research scale columns for protein purification. Also, government regulations regarding pre-packed protein purification columns will not be investigated in this study.

2. Methodology

This chapter describes which methods that were chosen for the study. The section ends with a discussion around research ethical dilemmas.

2.1 Qualitative and Quantitative Data

Mainly, there are two types of methods that can be used when generating, processing and analysing empirical data, namely qualitative and quantitative (Lekvall and Wahlbin, 2001). The difference is that qualitative data is collected from *e.g.* interviews, and quantitative data is data collected from *e.g.* surveys or statistics.

The characteristics of qualitative data are that it cannot be quantified, since it consists of complex information, and the data is also very study specific. Quantitative data can be quantified and is often mathematically manipulated, since it is structured, and can thus be used in other studies not related to the one where the data was collected (Patel and Davidson, 2003). According to Lekvall and Wahlbin (2001, chapter nine), a quantitative, cross sectional study that is combined with a case study makes it easier to determine what context and factors to investigate, which can give a better understanding of the problem.

In this study both qualitative and quantitative data was collected through an online survey, interviews with key employees at Bio-Works and a conjoint analysis. The survey represented one part of the quantitative data that was collected and was mathematically analysed in SPSS. The project group reached many users of chromatographic protein purification columns worldwide and was, with this information, able to map where users of different chromatographic methods are located. Additional information regarding where customers search for information about new technology and what they value when it comes to customer service could be obtained. The second part of the quantitative data is represented by the conjoint analysis, conducted with users of chromatography columns.

Also, to describe and get an understanding of Bio-Works cultivation and growth as an entrepreneurial company, interviews with employees were chosen as the best method. Qualitative information was gathered during the interviews and later analysed as case studies to generate a deeper understanding (Lekvall and Wahlbin, 2001).

2.2 Deduction, Induction or Abduction?

There are typically two different starting points for a study, theory or empiricism (Wallén, 1996). A deductive study has its starting point in theory while empiricism is the start for an inductive approach (Bryman, 2002). The project group continuously collected data at the same time as reading up on theory, iteratively, that together was analysed to help formulate realistic recommendations (Bryman, 2002). This approach, called abductive approach, is a combination of both inductive and deductive approaches. Harman (1965, p. 88) describes abduction as "*the interference to the best explanation*", an approach that deals with generation of hypotheses and involves evaluation of the same hypotheses that was generated. When situated with different ways to connect theory with empiricism, and vice versa which, the researcher is not limited to work only with one of the approaches. This is something that Patel and Davidson (2003) describe as positive. According to the reasoning above, this study had both a deductive and an abductive approach.

The different approaches can be described as the following:
Deduction: Theory → Empirical Data
Induction: Theory ← Empirical Data
Abduction: Theory ←→ Empirical Data

2.3 Descriptive or Explanatory?

The present study is, as Lekvall and Wahlbin (2001) describes, of both descriptive and explanatory nature. A descriptive focus maps out facts and conditions that describe what the circumstances of a certain case looks like. If the focus of the study is explanatory it has characteristics from describing focus, but is instead trying to explain what the circumstances look like.

The latter part of the present study was explanatory, where the connections and influence between different factors were shown with help from the conjoint analysis. By using a conjoint analysis, conclusions could be drawn as to how different properties of a pre-packed protein purification column will influence the purchasing behavior. It helped the project group to evaluate users' cognitive, affective and behavioral components, as Lekvall and Wahlbin (2001) explained as what a person know and think about a product, the person's valuation in a product and a person's inclination to buy a product.

Secondary data from previously executed studies were also used to support the data collected from the survey. The workflow during the study follow figure 3 based on Lekvall and Wahlbin (2001, p. 183).

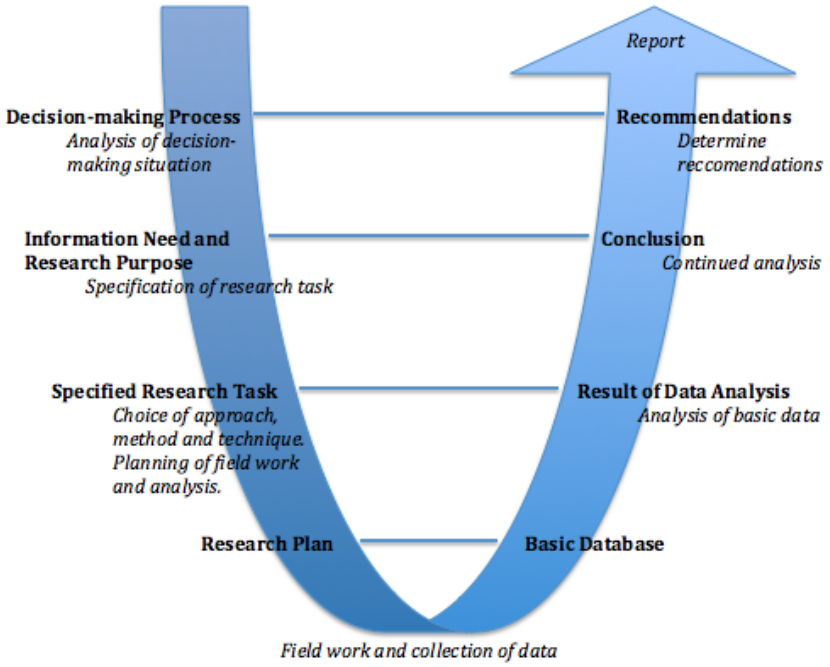

Figure 3. . A schematic picture of the study workflow, inspired by Lekvall and Wahlbin (2001)

2.4 Collection of Background Data

To gain background information about Bio-Works and the chromatography industry, secondary data were collected using a Business Model Canvas and SWOT analysis. The Business Model Canvas, made by Osterwalder and Pigneur (2010), was chosen to get a chance to describe, visualise and evaluate Bio-Works' business model. Through research and interviews with employees, a business model canvas was created and the project group received a greater understanding of the company and business idea. The model also gave an overview of where possibilities and threats can be found and used in strategic planning.

A SWOT analysis is used to get a strategic basis for business development by understanding the company's product or service market position (Hill and Westbrook, 1997). Therefore, a SWOT analysis was chosen as a first tool for analysing Bio-Works and their products. The SWOT analysis and the business model canvas were used as a base for evaluating the business model as a whole by using Porters (1980) five force model.

2.5 Cross-sectional Approach

2.5.1 Cross-sectional Analysis

As reported by Bryman and Bell (2013) and Lekvall and Wahlbin (2001), a cross-sectional study is an observational study conducted by collecting data from a group or sub-set of people for analysis, focusing on one variable in several cases, at a specific point in time. A longitudinal design, that investigates all variables in one case and analyses the case more in depth with a few variables of interest with a more complex relationship. Compared to that, the cross-sectional analysis will need more answers to make an accurate analysis and is also much more sensitive to missing data than longitudinal design. It is also hard to control the environment of the respondent and the risk of poor response frequency is higher than more controlled approaches. A benefit of a cross-section analysis is the ability to collect data about several variables in a short time span. The data collected is extensive and usually analysed by multivariate data analysis.

When conducting research, validity is of great importance and a way of determine if the conclusions of the research are connected in a logical manner or not. The internal validity, measuring the existence of any causality within the variables, is usually low when carrying out cross-sectional analysis. That is because it is hard to see clear connections of reasons to conduct a solid conclusion. However, the external validity, if the results can be generalised and used outside the specific context, is usually high due to the fact that a randomised selection of people is made. In this case the internal validity was low and the external validity will be ambiguous since the selection is not totally randomised, due to the fact that the selection was made on research labs and companies subscribing to the branch magazine Genetic Engineering and Biotechnology News's (GEN).

2.5.2 Survey

The market for chromatography columns is global which makes one find users around the world, many of them located outside of Sweden. To get an understanding of how users use and value their products, place their orders or search for information about new technology, input from users from every continent was desirable. Due to the distance to many of the users, interviews were not ideal and instead an online survey was chosen to reach as many users as possible. The approach to conduct an online survey was also a strong wish from Bio-Works.

The online service SurveyMonkey® was used to structure and collect answers. To send out the survey, a mailing list service provided by the magazine GEN was used. Their mailing list is called *GENmail*, a rental service where one buy the opportunity to send an email to every subscriber at their magazine and choose what fields of research the recipient work in. By using this service the survey was sent to research labs and industrial labs working with protein purification and characterisation.

GEN distributed the survey to selected categories in their database. By using GEN the survey reached 17,775 research labs and companies across the globe, 11,700 in North America, 2250 in Europe and 3825 in rest of the world, working in the following research categories; *Protein Expression and Purification, Protein Characterisation, Monoclonal Antibodies, Chromatography and HPLC*.

The survey was structured so that the respondents were sorted into categories to facilitate data analysis in the beginning of the survey by four anchor questions. The respondents were then guided down the flow chart depending on their answers. The questions were designed together with Bio-Works after their wishes, thus are not all included in this report. The data collected from the survey was analysed using statistical software called SPSS to see trends and possible latent variables. As Lekvall and Wahlbin (2001) points out, because the survey had a quantitative approach, one needed to keep the risk of inference in mind when analysing the data. Another aspect to take in consideration is that the respondents correspond to a sample of the whole target group. Because of that, conclusions drawn from the survey can be affected by interference (Lekvall and Wahlbin, 2001).

Negative aspects when using a survey is the low grade of control. The mail receiver could choose to delete or ignore the mail. When a respondent answered the survey, issues about their thought process, if they have questions or if they not understand a question completely could come up. The project group did not manage the mailing and could therefore not clarify any possible questions. Respondents to an on-line survey are, by their nature, self-selecting adding an uncontrolled variable which is not possible to circumvent.

2.6 Conjoint Analysis

As described by Hair *et al*. (2010), a conjoint analysis is a statistical tool to find what a person really values when comparing similar cases with each other. In product development this is very helpful since the manufacturer can see when the customers really value when choosing product.

In a conjoint analysis the respondent is handed a number of cards, all with different combinations of attributes on a given scenario, or profile, such as price and colour of a product. The respondent is then asked to sort the cards from most desirable to least desirable. The attributes for the cards is chosen carefully and depends on what the tester wants to find out. For a cycle manufacturer the number of gears, colour and tires might be important while a car manufacturer wants to find out how important price, number of seats, brand and rim size are. On each attribute, there are also different levels. The car manufacturer might then pick two, three or four seats and Ford, Volvo or Audi as brands for their conjoint analysis.

For the conjoint analysis in the present project, the chosen attributes were price, brand, ordering and customer service. Price is an often used attribute because it is what many buyers compare the attributes with, and brand to see how important large well-known companies

were compared to small less known companies. Ordering and customer service were chosen from a marketing perspective to see if this conservative biotechnology market would choose products if they had better delivery and customer service conditions.

The participants in the conjoint analysis were chosen by the project group using personal contacts and recommendations from the project principal, Bio-Works. It was limited to eight people working in research labs that are using chromatography columns on a daily basis. To get a broader perspective of what users value, the respondents were chosen with different background and varying years of experience.

The respondents were asked to have a monologue about how their thoughts were going when ranking the cards, and notes were taken by the project group. After ranking the cards, discussions with the respondent were held to understand why they ranked the cards in a specific way, and thus analysed independently as case studies (Lekvall and Wahlbin, 2001). The discussions were combined with the output from SPSS to understand why users valued different factors in a specific product.

IBM SPSS software was used to create an orthogonal design in the creation of profiles used in the conjoint analysis, see appendix I. The data was put into SPSS by following IBM SPSS Conjoint 21 (2016-05-18, IBM). The factors and levels are summarised in table 1. Specifications that were used in SPSS are listed below;

- *Reset random number seed: 2 000 000*
- *Minimum number of cases: 16*
- *Number of holdout cases: 4*

Table 1. Attributes and levels used to create case cards used in the conjoint analysis.

Attributes	**Levels**
Price	1000, 1200, 1400, 1600 (SEK)
Brand	Bio-Works Pierce (Thermo Fisher Scientific) GE Healthcare Bio-Rad
Ordering	Express Delivery (1 day) Order Confirmation Order Delivery Confirmation
Customer Service	More Than One Way to Contact Company Technical Support On Site 24/7 e-mail Support Office Hours Phone Support

2.7 Ethical Dilemmas Concerning the Participants

This study involves interviews, a survey and a conjoint analysis which means that ethical principles need to be considered. Even though the interviews were not recorded, ethical principles that involve freedom, integrity, confidentiality and anonymity for the participants in research studies had to be satisfied.

The following requirements were found in guidelines from Vetenskapsrådet (2002) and Bryman and Bell (2013) for research ethics. Before the interviews and conjoint analysis, the purpose with the study were introduced to the participants to cover the *information requirements* that Bryman and Bell (2013) describes as the information the researchers needs to pass along to the participants. Participants in the survey were informed by the e-mail that was sent with the survey link, where they had the chance to decline to participate by not clicking the link.

Respondents participating in the conjoint analysis where the project group could not meet them were informed about the specifics of the participation in invitation e-mails. They could decline if they did not want to participate, satisfying the *consent requirement*, meaning that the respondent participate voluntarily and can leave the study whenever they would like to. The *anonymity requirements* were achieved by keeping the respondents anonymous in the report and to others outside the project group.

There is a demand that data collected in a study should not be used outside the current study (the *use requirement*) as described by Bryman and Bell (2013). This study has been written by students at Uppsala university in association with Bio-Works, and the data that has been collected has been given to Bio-Works and it is unclear whether it meets the use requirements or not. Respondents were informed about this prior to clicking the survey link. The present project had Bio-Works as an industrial sponsor which was communicated to the respondents before conjoint analysis and the survey. As Bryman and Bell (2013) discuss, this is of great importance to communicate to avoid getting confidential or other sensitive information and thus minimise the risk of giving false pretenses.

The participants of the interview were also ensured anonymity, except for Allan Simpson and Kristopher Fain. Consent was given to the project group to keep them identifiable since they are the most prominent key persons at Bio-Works and are essential to telling their story correctly. Thus, to be able to carry out a correct analysis of the company's current situation, anonymity could not be granted for these two individuals. The assurance of anonymity posed a problem because of the possibility that the respondents might not be a hundred percent anonymous due to the small size of the company. For people employed at Bio-Works, it could in some cases be easy to link a certain response to a specific person since they all work so closely together.

All respondents were assured anonymity before the interview, conjoint analysis and survey to make them feel confident to participate. As for the survey, the respondents were not e-mailed personally but through GEN, which ensured their anonymity. The only breach in anonymity regarding the survey was the respondent's choice to submit their e-mail to get a summary of the survey results. The e-mail addresses received were only used to send the summary.

The summary did not contain all conclusions from the survey but a selection what Bio-Works chose to share and distribute. Some may say that it might give false pretenses, but since it was clarified that Bio-Works was an industrial sponsor the participants should understand that the

summary was a filtered version of the results by Bio-Works. In the analysis, all the interviews are anonymised to protect the person's privacy and sensitive information. The respondents were also offered to get the material transcribed for approval via email.

3. Establishing a Foothold in the Life-science Market - a Theoretical View

The following section presents the theoretical framework for the study and its purpose. The chapter will highlight theories and models regarding business strategies, company culture and maturation, and will help the project group answer the asked research questions.

3.1 Conditions for and Reasoning about Entrepreneurship

Defining entrepreneurship is a hard task, but one definition made by Harper (2008) explains entrepreneurship as a "*profit-seeking problem-solving process that takes place under conditions of structural uncertainty*". The perception of entrepreneurs taking risks and dare to try new things is common, but taking risk is something entrepreneurs learn to calculate and must be able to handle. According to Sarasvathy (2001, p. 5 and p. 9) entrepreneurs do not perceive risk the same way as non-entrepreneurs, instead they see it more as an "*affordable loss*" and are "*reducing the cost of failure by enabling the failure to occur earlier and at lower levels of investment*".

To venture out in a market where oligopoly conditions apply, which is the reality of the protein purification market where Bio-Works are active, taking risks are inevitable. To understand the journey of a company such as Bio-Works, one needs to understand the mindset, workflow and risk calculation that defines an entrepreneur.

Further, Read *et al*. (2011) discuss risk in their book *Effectual Entrepreneurship*, and reject the myth of entrepreneurs being risk takers, and stress that they instead minimise and calculate risk. This is done to be able to manage a risk and take it down to a level where it can be handled and the entrepreneurs feel comfortable with it. A comparison between bankers is that bankers pick a target return for their investment and reduce risk in different ways. Entrepreneurs on the other hand pick a risk they are comfortable with and increase return by pushing creativity with the means they have (chapter 3). They further discuss the financials, and many whom have not started their ventures yet claim to not have enough funds. Instead Read *et al*. (2011) sees it from another perspective and how to be creative about it. This claim, to not have enough funding, could be solved by having another job as main source of income and doing the entrepreneurial start-up on the side which Thorgren *et al*. (2014) look into.

Entrepreneurship or entrepreneurial businesses often start small, for logical reasons, and by a single or a few persons. Harper (2008) emphasise the benefits of entrepreneurial teams, consisting of at least two people, and how that might increase the chances for a start-up to survive, grow and expand faster. He concludes that the structural uncertainty and common interest among the individuals increase the chances of forming an entrepreneurial team.

Effectuation is a way of thinking entrepreneurs often uses in their work, explained by Sarasvathy (2001), and is discussed more in detail below. In short it is a way of working with the means one have at hand and being creative with them to set up goals. Effectuation thus can create opportunities. Luck and timing is crucial for a start-up which Read *et al*. (2011) give examples of in chapter 5: *Entrepreneurs are extraordinary forecasters* in their book *Effectual entrepreneurship*.

3.2 How an Industrial Origin can benefit an Entrepreneurial Start-Up

Effectuation is a word taken from the Latin verb *effectuare* which means "*to cause things to happen*". As a concept, effectuation is commonly used when wanting to achieve better results (Sarasvathy, 2013), in other words, when one needs to adapt to a situation for attaining gratifying results. Charles and Oystein (1998) say that it is crucial to work with effectuation and carry out changes for a company to survive, and also understand their competitors because of the constant market change. Read and Sarasvathy (2005) agree on this and mean that effectuation is about understanding the environment and knowing what stakeholders want, one can work on what you know. Sarasvathy (2008) concludes that with effectuation one wants to create new ends with non-predictive strategies but by using given resources. Also, the effectual logic is based on "*To the extent we can control the future, we do not need to predict it*" (Sarasvathy, 2008, p.17).

Causation is the inverse of effectuation (Sarasvathy, 2008), there is an effect that wants to be created and the causal model has this as a starting point. According to Sarasvathy (2008) one can achieve these pre-selected end effects by finding or creating new means. She also state that causal logic is based on "*To the extent we can predict the future, we can control it*" (Sarasvathy, 2008, p.17).

One can work with effectuation and causation in different ways. Vohora *et al*. (2004) presents a model that describes different phases and junctures that a company spun-out from academia usually passes on to the market as a sustainable business. As many start-ups in the life science market are spun-out from academic research, this model depicts a clear view over the whole process from idea to a viable company. Although Bio-Works is not a spin-off from academia, there are similarities and the model can be comparable with phases that Bio-Works has gone through.

As can be seen in figure 4 there are critical phases and junctures. The first phase is research, which is done at the university where the spin-off is based. In the research phase, facilities and technical assets are found and it is important to look for intangible value creation that hopefully can bring commercial success later.

Comparing the first phase of the Vohora *et al*. (2004) model with Bio-Works, the founders worked with protein purification media at other companies, which now are competitors with Bio-Works. There were restructures and a company was bought. One of the founders of Bio-Works had a patent that the employer was not interested in. The company had the impression that their products were already good enough and was not interested in starting with more research. This lead to the creation of Bio-Works, since the founders now had the necessities for a start-up; the knowledge about chromatography, techniques and research and also a patent.

The second phase in the model describes opportunity framing. The discovery is reformulated into an opportunity that can be the base for a business. Of course investigations of the discovery value are required. The technology and the interest from society are evaluated, and a market research needs to be done to see if the discovery is good enough on which to start a business. Evaluations about how the technology or product fits the market, *e.g*. through a customer survey. The unique selling point is created in this phase. At Bio-Works, the founders already had a vision about what was missing in the industry. They had a lot of knowledge,

industrial wisdom and predicted that the protein purification industry had a need for the chromatography media for which they had a patent on. The technical excellence it owned were in some cases better than competing products.

In the phase called pre-organization, one needs to find ways to organize and implement a strategic plan for the business, important decisions are made. Knowledge and resources needs to be inventoried. This phase usually determine the direction of future work. Bio-Work had funding but needed to create resources and make strategic plans. The founders were committed to the business and were willing to work for shares in Bio-Works instead of a salary. Even though they had funding, there was very little money and they funded Bio-Works a long time with money from their own pockets, as Schilling (2013) describe as family, friends and credit cards.

Under re-orientation the company has the credibility and the resources that are needed to start the business. The goal here is to generate returns by identified market deals. The company is challenged and the business has changed, developed, updated and the benefits are evaluated. Further development of the technique is made and it is important to identify more resources.

Because this model represents an iterative process, Bio-Works has been in this phase before. In a growing company which finds itself facing critical decisions making people need to change along with the company. The previous goal was approximately a year ago when Bio-Works was working with causation toward development of a new pre-packed column that they planned to launch the summer of 2016. Due to the failure of sub-supplier the plans were changed and they had to work with existing products and use effectuation to make the best of it. The main priority changed from research and development to improve sales. Along with the change of focus, the board hired a new CEO in January 2016. The new CEO, Kristopher, is a man with significant experience from big global companies, however without any knowledge from the life science industry.

Sustainable return is the last phase in the model created by Vohora *et al*. (2004). In this phase, the company is stable and now works to achieve long term sustainability. In this phase companies often move out of the University premises to expand and manage themselves more independently. Connections with the university usually consists but without financial support. Sustainable returns are necessary for every company and Bio-Works now aim to become a company with sustainable returns, this thesis is an attempt to help them find and understand the market and the customers/users.

According to Lindström and Olofsson (2001) technology-based companies with new technologies have significantly more problems to receive venture capital than less technological start-ups. This is probably because the products are complicated and the concept might be unproven. The high-technology firms in the study of Lindström and Olofsson (2001) originated more often from university and research related environments than other firms. The most important investor group were business angels and such firms favoured by them ended up to be the most growth-oriented (Lindström and Olofsson, 2001).

In the figure below one can see junctures at each transition state between each phase. According to Vohora *et al*. (2004) each threshold must be overcome to enter the next phase. The second juncture is a typical threshold every company has and if an entrepreneurial commitment lacks it the business will fail.

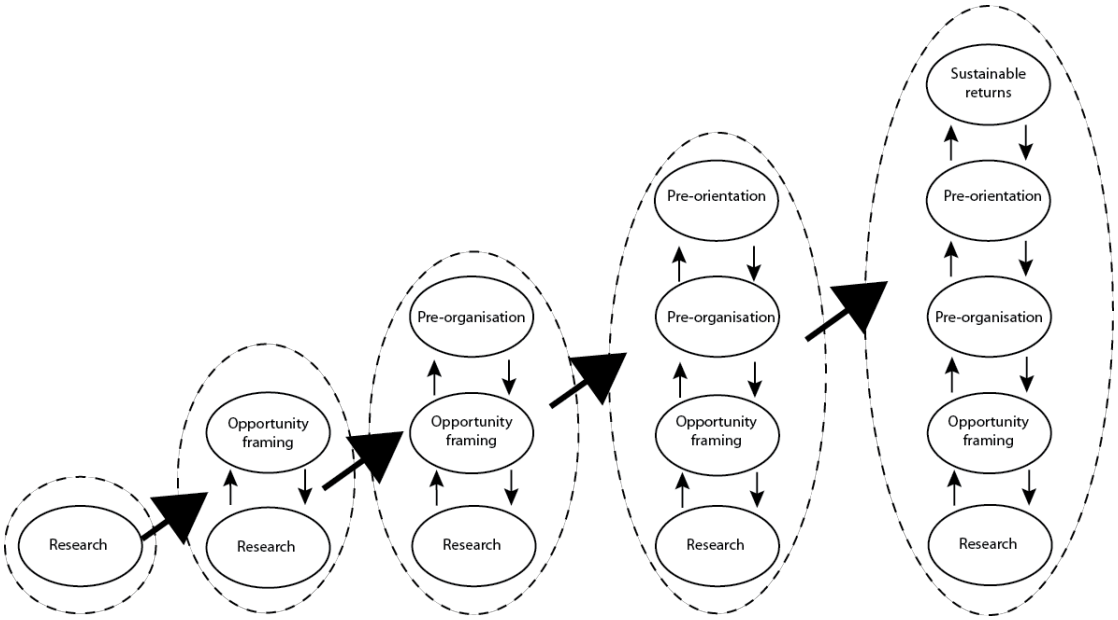

Figure 4. Model of phases and junctures that a spin-off from academia goes through, figure inspired by Vohora et al. (2004).

3.3 Why Entrepreneurial Companies Also Need Traditional Business Strategies

Small and young companies often benefit from being flexible and work with effectual thinking. The theories discussed above are suitable for small and ambitious companies, but to be able to keep their business competitive and analyse the threats and problems that may appear, traditional business strategies still need to be applied. Below are two traditional models by Porter (1980) described to increase the understanding on what and why entrepreneurial ventures also have the need for traditional business models.

3.3.1 Strategy to Remain Competitive

To develop a competitive strategy is to formulate a plan for how a business is going to compete in their market. The formula created by Porter (1980) is a classical approach to a competitive strategy plan, and still widely used today. Figure 5 depicts the context in which competitive strategy is formulated in its broadest context. The four key factors *company strength and weaknesses, industry opportunities and threats (economic and technical), personal values of the key implementers* and *broader societal expectations* need to be considered to determine the limit of what a company can successfully accomplish when maneuvering the market.

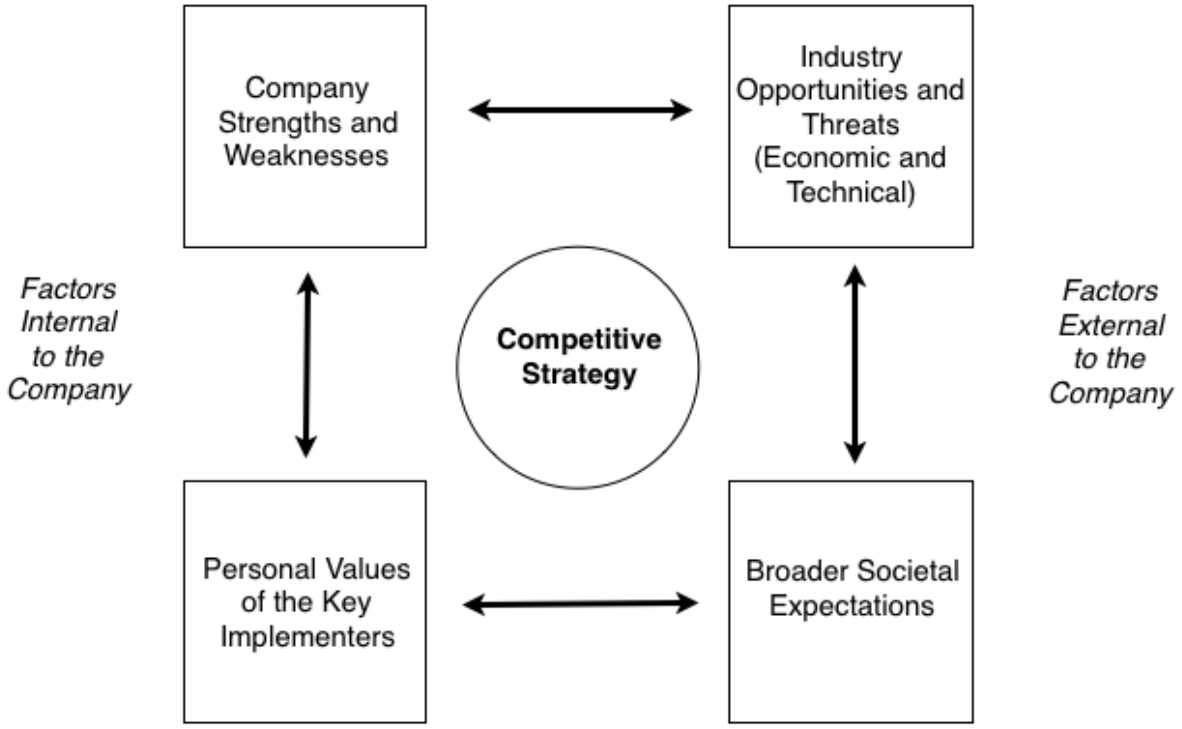

Figure 5 Context in which competitive strategy is formulated. Figure inspired by Porter (1980).

The *company strengths and weaknesses* are what the company possesses in terms of skills and assets relative to the competitors. This includes financial resources, technological postures, brand identification, and so on. The *personal values of key implementers* are defined as the motivation and needs of key executives and personnel that have to implement the chosen strategy. Together with the strengths and weaknesses of the company they make up the internal limits to the competitive strategy the company can (successfully) adopt.

External limits are set by company's industry and broader environment. The competitive environment, defined as *industry opportunities and threats*, is accompanied by both risks and potential rewards and must be assessed with caution. Such things as government policy, social concerns, and evolving mores will make an impact on the company, and is referred to as *societal expectations*.

A business wishing to set realistic and implementable goals and policies need to consider these four factors when formulating their strategy to stay competitive in the market (Porter 1980).

3.3.2 Forces a Company Needs to Consider When Running Their Business

"The goal of formulating a competitive strategy for a business unit in an industry is to find a position in the industry where the company can best defend itself against these competitive forces or can influence them in its favour" (Porter, 1980, p. 4).

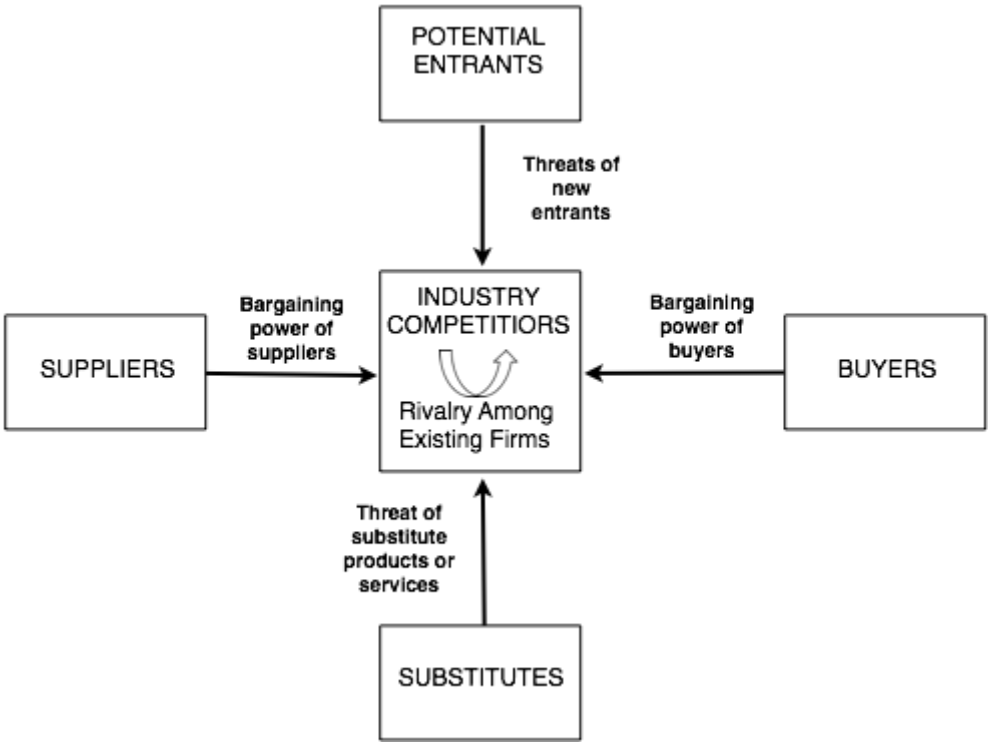

Figure 6. Forces driving industry competition. Figure inspired by Porter (1980).

The collective strength of the five competitive forces - *entry, threat of substitutes, bargaining power of buyers, bargaining power of suppliers, and rivalry among current competitors* - determines the profit potential in an industry, where the profit potential is measured in terms of long run return on invested capital. They also reflect the fact that competition in an industry is made up of more than just the established players, see figure 6. Consideration has to be taken to customers, suppliers, substitutes, and potential entrants as they all play a role as ”competitors” in the industry. They may be more or less prominent, but are all influential on a single company.

When entering an industry, there will be different barriers to overcome. Together with the reaction from existing competitors, this is what spans up the *threat of entry*. Porter (1980) talks about seven major barriers of entry, *economies of scale, product differentiation, capital requirements, switching costs, access to distribution channels, cost disadvantages independent of scale*, and *government policy*.

Rivalry among competitors can be anticipated when one or more competitors either feel pressure from the surroundings or see the opportunity to improve their position. Jockeying for position is done by *e.g.* price competition, advertising battles, or increased customer service or warranties.

What makes a market interesting is the ability to make potential big returns, and more competitors wish to make its entry on such a market with substitute products. *Substitutes* place a ceiling on the prices and limit the potential returns of an industry. If substitutes offers an alternative having a more competitive price, the lid of the industry profits will be firmer and firmer (Porter 1980).

Bargaining power of buyers is exerted when buyers compete with the industry. This power is exerted by forcing down prices, bargaining for higher quality or more services, and playing

competitors against each other (Porter 1980). Depending on a number of characteristics of its market situation and relative importance of its purchases from the industry compared with its overall business, the power of each buyer group varies.

Also, suppliers can exert power mirroring those that make buyers powerful, such as threatening to raise prices or reduce quality of purchased goods and services. Just as the buyer power, *bargaining power of suppliers* is also exerted at the expense of industry profitability.

Porter's five forces model is a well renowned theoretical model that is universally applicable on a variety of markets. The versatility and the possibility to use the five forces model in more than one market is one of its strengths and why it is still valid today. However, this particular strength is also one of its drawbacks. It is general but can lack in its description of intricate markets, such as the life science market. It is also not falsifiable, which can make it tricky to use.

In the case of Bio-Works, trying to establish their foothold in a highly segmented and conservative market, it is crucial that they assess their current place in the market and also where they want to be in the future. Utilising Porter's model is a substantial aid in this work for Bio-Works to figure out how to maneuver the market. To be able to use this model in assessing a small challenger company in an intricate market, the project group had to utilise other theoretical tools such as *The Business Model Canvas, the SWOT analysis, Diffusion of Innovation,* and others. Some of these are further described below.

3.4 Factors that Affects the Spread of Bio-Works Products

According to Lekvall and Wahlbin (2001) there are internal and external factors that can affect a business idea, and these can be divided into micro level (business environment), meso level (industry environment), and macro level (social environment).

3.4.1 Micro Level - the Business Environment

Factors such as company policy and resources can affect the spread and implementation of Bio-Works columns and media. The resource aspect is important since they need financial resources to develop new products, *e.g*. a new column. Other vital resources are human and technical resources. Bio-Works' employees have important knowledge and technical expertise in this business, which is a large contributing factor to the success of the company, and it is one of the assets that sets Bio-Works apart from other companies manufacturing chromatography media. But just as important as the resources, Bio-Works goals and policies are needed to keep all employees informed and involved, which contribute to a good company culture and organisation.

Working closely with customers to build trust and long lasting business relationships is vital in this type of market. Bio-Works awareness of their strengths and weaknesses is important when building trust. With good products and hard work, customer service and flexibility, they hope to offset their weaknesses.

According to Rogers (1983) there are five attributes of innovations; relative advantage, compatibility, complexity, trialability and observability. Relative advantage describes how an innovation is better than the ideas, which often is expressed in status giving (social) or economic profitability. The degree of how an innovation is perceived as consistent to sociocultural values, experiences with already introduced ideas and with the adopter's needs

of the innovation is described as the second attribute compatibility. Complexity is to which degree the innovation is perceived as difficult to use and understand. Trialability, the more an innovation is seen as trialable the less uncertain it is meaning that an innovation has different degrees where they can be experimented with. Observability, the degree of how an innovation is visible to others, how easy it is to communicate and describe it to others. These attributes are connected with the rate of adoption.

Comparing the attributes with Bio-Works products, they are not very innovative. Chromatography is an old method used worldwide, the products that Bio-Works offer are media for the columns. These medias differs from other existing medias but are used in the same way meaning that the observability, complexity, compatibility and trialability are not diversified in comparison to existing products. The relative advantage is the attribute that differ, Bio-Works have tested their media and can state that it is as good as the competitive products and in some cases better.

3.4.2 Meso Level - the Industry Environment

Competitors, suppliers and customers influence what happens at the meso level for Bio-Works business. In the chromatography industry for protein purification columns there are several competitors, where competitors with the strongest trademark have the largest market share. In the case of operating at the life science market, the largest market share is owned by GE which is one of the largest competitors on this oligopoly market.

Today, Bio-Works can see a void left by competitors; there is a problem with customer care, flexibility, and service that they aim to fill what they think the customers demand. Although it is important to all companies to analyse the market they are in, it is vital to small and medium enterprises to stay competitive. Analysing the end user and getting to know their needs, wishes and preferences will make a first starting point for Bio-Works to start gaining market shares. This study will help Bio-Works with their demand analysis and gives an example of how a market analysis can be conducted for a small challenger company.

3.4.3 Macro Level - the Social Environment

The macro level does not affect Bio-Works much, there are restrictions and requirements that the products produced need to meet, and there are also economic factors that can influence their business. Political, legal and social factors affect Bio-Work's operations to a very small extent.

A summary of the contextual analysis (external factors) is to define the threats and opportunities in the industry and social environment. These threats and opportunities can then be compared with the strengths and weaknesses that are found in the business environment (internal factors), which give rise to a SWOT analysis.

3.5 How to Handle Changes in a Maturing Business

When a company is maturing, modifications in the organisation are very common, Jacobsen (2013) mean that companies need to "change or die". Lemos and Andreassi (2015) propose that a company with a simple structure can save time when reorganising and chasing opportunities if they use an effectuation decision making model. When a company stands before a decision that is critical to the growth of the company, Lemos and Andreassi (2015) recommend using causational decision models.

3.5.1 Resistance to Change

Coch and French (1948) investigated how a company can overcome the resistance to change. According to Oreg (2006) the knowledge of ambivalent reactions towards change can help a manager deal with the situation and come up with an early solution. The recovery rate after a change is, according to Coch and French (1948), linked to the amount of workers' participation, and also that the result of a change is connected in a higher extent to the change management than to individual factors. They concluded that it is possible for management to minimise the group resistance to changes in work. To achieve this they recommended group meetings where the management communicate the need for change, and also that they encourage group participation in planning for the changes.

Oreg (2006) mean that a manager needs to be aware of the employees feelings about a change, negative feelings can lead to change in attitude and the willingness to stay in the organisation. The commitment to the company can change depending on the employee's beliefs of opportunities and challenges. Attitude toward changes is important, which depends on personality, and to have trust in management and social influence. The attitude in the team affects the feelings of the individual (Oreg, 2006). Important factors are also to have good leadership and group dynamics, which helped to reduce the resistance (Coch and French, 1948).

3.5.2 Prepare for Change

About 70% of all change initiatives fails (Nohria and Beer, 2000). Changes in an organisation are common and necessary for a company to survive. Armenakis *et al*. (1993) describes how important it is to create readiness among employees before a change is implemented in an organisation. To start with, they point out that resistance for change is common. To create readiness for change is important, the employees need to believe in the change, have good attitude and intentions with the change, something that is also stated by Jacobsen (2013). He means that the leader needs to make the change feel effective, good and important. The second factor Armenakis *et al*. (1993) describes is to offer a model that describes the influence strategies, the importance to change, the credibility and interpersonal, social dynamics. The third step is to combine urgency of, and employee readiness for the change which create a readiness program. The model is a tool for creating readiness in the process.

Kotter (2008) point out eight steps that is necessary for a change to be successful; (1) *create a sense of urgency*, (2) *pull together the guiding team*, (3) d*evelop the change vision and strategy*, (4) *communicate for understanding and buy-in*, (5) *empower others to act* (6) *produce short-term wins*, (7) *don not let up*, and (8) *create a new culture*. If you stick to these steps, according to Kotter (2008), the risk to fail the implementation of a change is minimised. He mean that a change process contain these eight phases that each need time. In an earlier article Kottler (1995) states that it is important to communicate information about the first phase to make employees motivated to help. Jacobsen (2013) stress the importance to declare that the change will contribute to improvement and solve problems, thus the purpose of the change is communicated and clear to the employees.

A rule of thumb is formed in connection to step three where Kotter (1995, p. 63) says; "*If you can't communicate the vision to someone in five minutes or less and get a reaction that signifies both understanding and interest, you are not yet done with this phase of the transformation process*". The communication part is also really important to make employees committed. The last step, to create a new culture, is important to anchor the change and root the behaviour. Kotter (1995) states that one need to convince near 75% of the managers that

the change is needed, especially if the business already is successful. Summarised, Kotter (2008), mean that one need to set the stage, decide what to do, make it happen and make it stick.

Rubenowitz (2004) describes the psychosocial environment as an important factor to consider when preparing for change. To keep a good psychosocial environment, Rubenowitz (2004) has identified five factors that seem to be extra important; (1) *controlling your own work*, (2) *having a positive work management climate*, (3) *feel stimulance from the work*, (4) *having a good working climate*, and (5) *having optimal workload*. These aspects might be extra important when it comes to small companies in a changing environment. In a small company, the employees have to be prepared to work with things that are not defined in their work description. This is likely to cause tension if the employee comes from a larger corporation and are used to only carry out tasks specified in the work description.

3.5.3 Leadership

A change of leadership is made to help changes become successful with new actors pursuing the tasks (Jacobsen, 2004). It is important to have a good leadership when carrying out changes. Nadler and Tushmar (1999) describe different changes and challenges an organisation faces, they mention different organisational changes that need different types of leadership. All the organisational changes require change in management, because of that Nadler and Tushmar (1999) mean that the executive team is really important. They mean that it is impossible and absurd to think that a single person, usually the CEO, would have the combination of leadership skills, talent and technical knowledge to fulfill the strategic and necessary challenges. This doesn't mean that the role as a CEO is not important but rather the opposite, the CEO will be a more effective and skilled leader of the team. They mean that the CEO and the team will work together and understand changes in the environment before critical strategic decisions are made.

Nadler and Tushman (1990) describe different types of leadership and stress that executive leadership is a critical factor when a large-system organisational change is initiated and implemented. To receive commitment and inspire co-workers the leader needs to be charismatic, but to make everyone keep acting correctly according to new goals, the leadership needs to be instrumental (Nadler and Tushman, 1990). If the leadership is either charismatic or instrumental it is weak but a combination makes a strong leadership (Nadler and Tushman, 1990). They also point out that flexibility and including learning is important for management. If a leader can incorporate charisma, structure and attention to detail and broadening leadership the change will be successful. Jacobsen (2013) believe that it is preferable if the leader is a symbolic role model in the start-phase of a change, thus being a charismatic leader. He means that it is important to create a vision and then plan and communicate it to the employees.

As mentioned earlier, Nohria and Beer (2000), state that 70% of change initiatives fail. They stress that it is primary because the loss of focus and that the managers get too many advices to why and how an organisation need to change. Nohria and Beer (2000) have studied the corporate change in over 40 years and conclude that there are two types of strategies for change; *Theory E* (hard approach) and *Theory O* (soft approach). Theory E responds to changes based on economic value with focus on structures and system, and Theory O that responds to changes based on organisational capability with focus on human resources and organisational culture.

According to Nohria and Beer (2000) problems can occur when attempting to implement both strategies without solving the tension between them, but they also stress that a strategy that contain both strategies is important for the survival of the company. Theory E is more old-fashioned due to the top-down management where goals are set without involvement from employees, plans are clear and focus is on changing the structure. Theory O has a bottom-up management where initiatives from employees are appreciated and encouraged, teamwork and communication is important (Nohria and Beer, 2000). To make a good combination of the two strategies, Nohria and Beer (2000) propose that goals should be set from the top and then encourage initiatives from the bottom, and in parallel focus on both soft and hard values.

3.6 Diffusion of Innovation

To be able to thoroughly assess the forces impacting a challenger company after identifying the elements of the business model and what threats and opportunities may be present, one needs to consider the technology that is being produced. How it is diffused into the market and what customer segments that should be addressed it is important to be able to build a competitive strategy.

According to Rogers (1983) communication channels are important factors in the diffusion of innovations, so that the social system can take part of the information. Diffusion in the market is often slow and time-consuming (Rogers, 1983). It is described as the process where an innovation is communicated through various channels over time between members of a social system. The process can be difficult if one doesn't have the knowledge about the customers, their social system, culture, and what products they currently use. Knowing who is facing the marketing is important to be able to communicate the advantages of a new technology.

Rogers (1983) stress that opinion leaders are a very important communication channel as their great knowledge are seen as reliable sources, which leads to confidence around the innovation. For a larger corporation, already with an established name in the market, the need to rely on opinion leaders is less than that of a smaller company. Since the brand value of a well-established corporation usually works as an advertisement in itself, the need for marketing and reliance on others to speak well of the company is minor compared to a challenger. Opinion leaders are often used in the persuasion process where they can help the possible adopters to understand the technique. The opinion leader can influence by homophilic or heterophilic communication.

Communication is often more effective when two homophilic persons communicate (persons with similar background and knowledge), in contrast to two heterophilic individuals. If the communication is between two heterophilic people, problems can occur and thus the communication will be ineffective. Despite this, heterophilic communication is desired in the diffusion process because the homophilic relations often share the same network. To understand the adoption of technology products one needs to know that culture and nationality have an impact (Slowikowski and Jarratt, 1996). The understanding, the social system and the cause-effect relationship might be more important than the understanding of the technology itself.

In this case study, Bio-Works think they are well aware about how to spread their products due to extensive knowledge about common distribution channels throughout the management group, there is another issue to overcome, the resistance to innovations and to change. Berna-Martinez and Macia-Perez (2012) means that users in the private sphere welcome innovations

and as a contrary there is a resistance toward innovations in the professional sphere. Good communication around the products can help Bio-Works in the diffusion of their products.

There are, according to Schilling (2013), five different adoption groups, see figure 7. *Innovators*, the first adopter group, are active searchers of new technology and are prone to purchase the product before it is released in the market. The second adoption group is *Early Adopters* which is also a group of active searchers of new technology. They are well integrated in the social system and are very respected among others. Early adopters are usually the ones who spread an innovation to other potential users because of their recommendations. *Early majority* is the third group of adopters, that are a little bit careful in their search for technology, and wants clear references before they try a new product. *The late majority*, the fourth group, is sceptical and will most likely not start using a product until they feel pressure from their environment. This group is often described as price sensitive. Last there are *Laggards* who are very sceptical to new technology and want to be absolutely sure of the robustness of a product before they adopt it, making sure it will not fail shortly after purchasing it. Sometimes, they won't try the new product before there is no other option.

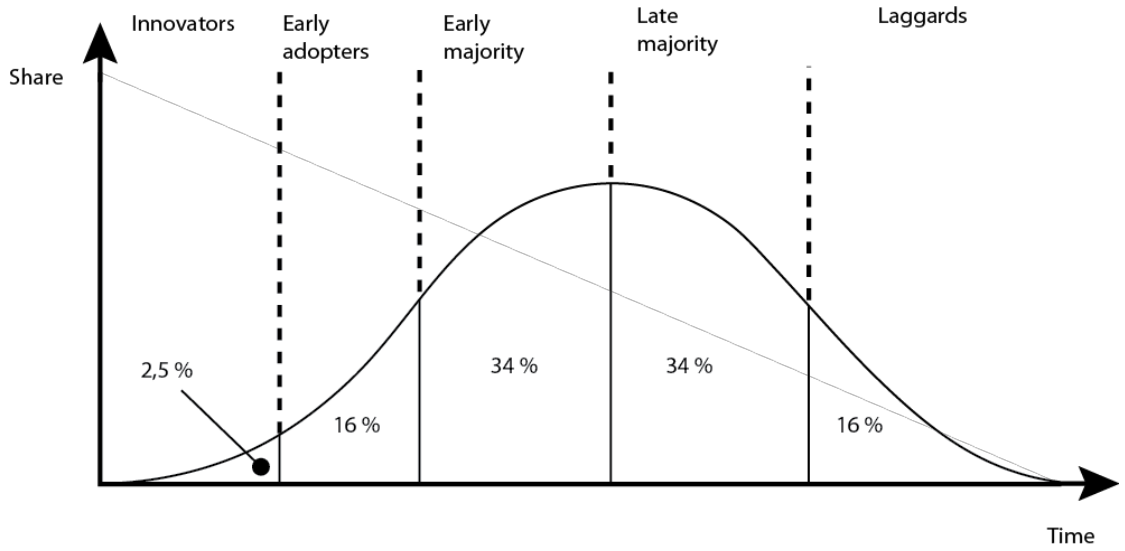

Figure 7. Diffusion of products explained by Rogers (1983). The figure is inspired by Rogers (1983).

3.7 Chromatography – the Basics

To understand the technology that Bio-Works produce and sell, one needs to understand the basics of chromatography. Chromatography is a technique that separates proteins and other molecules depending on their different properties. Thus, there exist several different chromatographic approaches which make it usually possible to find a technique suitable the molecule of interest. See Appendix II for more information about the different chromatography techniques.

Chromatography is carried out in a column filled with a chromatography matrix, called stationary phase, which will facilitate the separation. The column is equilibrated to create ideal conditions using a buffer, called liquid phase, before the separation of a mixed sample is carried out and is chosen depending on the matrix and sample. After equilibration the sample is loaded onto and eluted through the column at a certain flow depending on the properties of the columns and molecules.

3.7.1 Chromatographic Workflow

Before carrying out chromatography samples are collected from different sources, including cow's milk or extracted leaves from example plants or within bacteria. After disruption of cells and removal of cell debris, the *crude sample* is then collected and clarified to be put onto the column for purification.

Today, much of the protein purified for commercial pharmaceutical use is produced in large fermentation tanks using engineered bacteria or eukaryotic cells to produce large quantities of therapeutic proteins. Since the bacteria or eukaryote secretes the protein, it allows faster and cheaper production of purified protein.

3.7.2 Chromatographic Matrix

The most important component for chromatography is the matrix. Which work as a base for the separation. Different ligands are attached to the matrix, making different types of chromatography possible. Materials used to manufacture the matrix differ from agarose, silica to glass. Some have magnetic beads inserted. Choice of material depends on the sample molecules of interest.

The matrix is made from beads in a size range of a few micrometers to six hundred micrometers, and contains millions of nanopores. All pores in the beads lead to a vast total surface area and increases the effectiveness of the separation. One can compare a bead with the kind of ball used in floorball, but with more pores inside. The molecules of the sample will flow through the bead differently depending on the properties of the sample molecules. If the principle property is size, the smallest molecules will enter the pores and the larger ones pass outside the bead.

3.8 Competitor Analysis - Investigating Enemies

The market for chromatography has several large actors with GE as the markets flagship company, but also smaller actors competing such as Cube Biotech. Chromatography can be used in many possible markets which makes the competition strong, but with many possible customers to attend. The distinct difference between a challenger and an established player are stronger finances in larger companies, where the smaller companies are under financed. On the other hand, smaller companies are more flexible due to their size and can satisfy customers with customized solutions.

3.9 Marketing Action and Launch Tactics for High-Technology Products

A problem facing small entrepreneurial firms that is of economical character, is finding a foothold and conveying the benefits of their products. Usually, not a lot of resources can be put on proper marketing, and the producer itself needs to find a way to communicate the specifics of the products. It is important to plan ahead to get the most value for the money spent. Problems of technological character is not heavily emphasised in the business to business market, even though the product is of advanced technical origin. This is because a certain degree of technological expertise is expected from the people active in the biotechnology field.

As for all high technology firms, technological development must strive forward with a clear strategic intent to reach the customer market. If this intent is not formulated clearly, the technology is at risk to be lost in a vast and ever changing market. Launching products to grab the markets attention can be done in many ways, but Beard and Easingwood (1996) have presented a model with four critical stages suitable for high technology products, where the launching actions can be tweaked to accommodate the needs for each specific market.
The authors of the 1996 study explain that the launch of high-technology products tends to be based upon the process in figure 8. Marketers divide the strategic tasks into four tactics, *Market Preparation*, *Targeting*, *Positioning* and *Attack*. The first action taken in a launch process is to prepare the market for the upcoming launch, something that tends to be done while the product is still in the development phase.

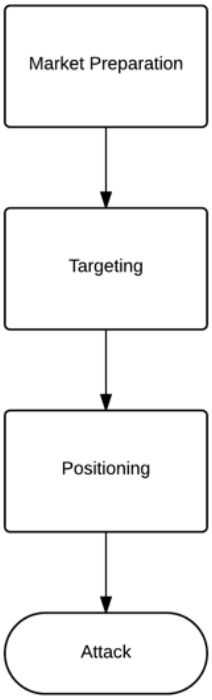

Figure 8. Workflow launch of high technology products. Figure inspired by Beard and Easingwood (1996).

3.9.1 Market Preparation and Attention

Beard and Easingwood (1996) explain that one key tactic for companies with restricted monetary asset are to release product-related information before the actual launch of the product. This includes releasing information to the media, give pre-hand demonstrations or hold conferences. If the technology is to be launched into a new market or market position, it might be necessary to make special distribution arrangements. These can include looking for new dealers in new and/or existing markets, form a joint venture with another producer or give distributions rights to competitors if the market is new and unknown.

The products that Bio-Works are currently selling did not have a proper launch, and therefore not much was done to prepare the market or to grab the markets attention. They knew they had a good product but launching and marketing is expensive and at the time they did not have the resources to afford it. They made the product available for the market and planning to launch it this autumn. For future launches, the plan is to properly prepare the market to ensure more attention. Providing pre-launch information and create special distribution

arrangements could come to be important strategic tasks for Bio-Works, which they have already started with through the survey used in this study.

3.9.2 Targeting Tactics

Targeting tactics will play an important role in marketing strategies. Target markets are often defined in terms of the groups that adopt at different stages of the product life cycle. These are commonly divided into five different groups (not to be confused with the five groups defined by Rogers), *Innovators, Early Adopters, Late Adopters, Existing Customers* and *Competitors Customers* (Beard and Easingwood, 1996). For each of these divisions, there are actions that need to be taken when marketing. If the producers of a certain technology are launching on a market where the products have already been accepted or diffused to a large degree, that's when you want to appeal to the late adopters. This category of customers is large and often very profitable once they have been found. Targeting the late adopters is what Bio-Works is planning on. The products they manufacturing are already well-known and cannot be described as a disruptive technique. This adoption group is widely scattered around the world, meaning that the market potential is big.

3.9.3 Positioning Tactics

To understand your positioning tactics is vital for producers with wide-ranging technology, and it can be based on tangible or intangible characteristics. For new technology the tangible characteristics are the technological advantages of a certain product, and the intangible are which image the product is portraying. For a small challenger company, the image of the technique might be more important than the technological advantages. To build a positioning tactic on intangible characteristics is commonly done when the benefits of a product is not easily differentiated from the competitors, as it is in the case of Bio-Works. For small firms with limited marketing resources, it is wise to appeal to *heavy users* (customers who account for nearly two-thirds of the market revenue). If the scarce resources can be scattered on only a few potentially heavy users, it could mean an increased sales volume with only little money spent (Beard and Easingwood, 1996).

Another tactic would be to emphasise a *low price*, something that would seem successful, but is hard to execute on the technological market. A low price can easily signal inferior quality, and it is advised by Beard and Easingwood (1996) that the maximum price should always reflect market expectations rather than technical excellence.

For well-established producers, positioning their technology as a *safe bet* is a powerful form of positioning. Here, a heavily emphasis is made on reliability and service to make the product a choice you can never go wrong with. This is difficult for small, new-to-market producers to execute, but a similar approach is to sell the image of *exclusivity*. Small, high-tech firms often need to justify their low levels of production with a higher price. The product is then carefully designed to be visually appealing or the quality of the engineering is stressed to fulfil the image of exclusivity. This positioning is popular among new, small producers, but cannot readily be established. For firms such as Bio-Works, to fight oligarchs positioned as the safe bet is one of the biggest hurdles to overcome. As mentioned before, GE is one of these oligarchs that have remained the strongest player in the market for a long time.

3.9.4 Market Attack

Market attack tactics is concerned with establishing the most powerful force there is in the world of diffusing innovations; *word-of-mouth*. To get the market to talk about your product means more people will be interested in trying it and it can in some cases be regarded as "free

marketing". Beard and Easingwood (1996) refer to seven different ways to developing this force. They also stress that market attack tactics depend on the objective of the launch and that the objective is connected to the state of the technology and the knowledge the market have about said technology.

Using opinion leaders is a great way of initiating word-of-mouth. Industry celebrities that are experienced users of the technology will give their views and the market follows. Another way is to use reference sites where the customer agrees to take on the new technology in return for trying it out, debug and provide feedback. This is done on favourable terms for both parties, and this approach is great for system-type products (Beard and Easingwood, 1996).

The most generic approach to performing a market attack is to use market education. It is more suitable when the technology is unknown to the market. This tactic is often used to image a vision that the producers wish to connect to the technology, and seminars, lectures and roadshows is used to portray this vision. In the life science market, this is an extensively used tactic. Finding new technology is often done during seminars and roadshows and is seen as a credible source. For small firms with limited resources, this can pose another problem because it is often connected with costs for flight tickets and similar costs. To educate the market is a mean to get the word-of-mouth going, and producers using this strategy learn how important it is to communicate with the service and media infrastructure of the industry to build credibility and acceptance, according to Beard and Easingwood (1996).

3.10 Ethical Dilemmas Related to the Case Company and Research

The project group needs to consider ethical dilemmas toward the case model and project principal, Bio-Works. Sensitive material such as information about how they work, what they plan to do and develop in the future are considerations that the project group came in contact with during the project process. Sensitive information and data needs to be treated with caution and is not to be spread among others than agreed on. It is also important that it does not violate the privacy of the parties involved. Secondary data collection was carried out through literature studies and other research. Focus has been on credible sources and interpretation of the correct information.

Since the thesis has a shared interest between the academic task and work with the company, the project group has strived to establish both parties to be satisfied. Although, since the study has been limited, all the aspects that may be interesting from a business point of view could not be studied. It was important to follow the guidelines of the academic purpose.

After analysing Bio-Works, the project group has made an interpretation that the company works well from a corporate social responsibility (CSR) perspective, both environmentally, economically, and socially. They work long-term and have sustainable solutions, they also have plans on making their product process line more environmentally friendly by replacing a hazard and toxic substances with less toxic choices. Information about if and how their subcontractors are working with CSR questions are unknown, meaning that Bio-Works might influence the society in a bad way indirectly and unintentionally.

Discussions about whether it is ethically right to run a company that exposes employees and the environment to the hazard components that are being used in product development process can be made. In this kind of market, there will always be a balance between using hazardous components and the positive outcome of the work. The project group believes that Bio-Works

is working to contribute to the welfare of the world, meaning that they serve a greater purpose, contributing with products that will help the world. One cannot forget that they follow restrictions and laws to minimise the impact on both environment and the health of the employees.

4. Empirical Data

This chapter contains the empirical data collected from interviews with employees at the project company, conjoint analysis and the online survey. The empirical data from interviews with employees at Bio-Works gave important qualitative data for analysing a small challenger company. The conjoint analysis collected qualitative data that was reinforced by the open monologue that the respondent had after the card ranking. These two methods for data collection were backed up with a survey to get input from all over the world. Only parts of the survey are used in this analysis since several questions were meant for the case company.

4.1 Conjoint Analysis

Table 2 is a summary of how the respondents valued the levels of the attributes evaluated in the conjoint analysis. *Utility Estimate* show values representing how valuable the levels were to the respondents, where the highest value of each attribute level is highlighted. The table was produced using the statistical software SPSS, which uses mathematical models to calculate the values for each attribute.

A higher value of utility estimate means that the attribute is valued more compared to a lower value. For an easier comparison the highest utility estimate is highlighted for each attribute. By choosing the attributes with highest utility estimate the respondents find the most attractive column coming from GE Healthcare at a price of 1000 SEK with express delivery and 24/7 email support.

Table 2. A summary of the respondents' answers of each level of the conjoint analysis.

		Utility Estimate
Brand	GE Healthcare	0,719
	Bio-Rad	-0,250
	Bio-Works	-0,250
	VWR	-0,219
Ordering	Confirmation e-mail	-0,208
	Delivery Confirmation	-0,240
	Express delivery (1 day)	0,448
Customer Service	Tech Support on Site	0,094
	24/7 e-mail Support	0,188
	Office Hours Phone Support	0,031
	More Than One Way to Contact Company	-0,313
Price	1000 SEK	-2,312
	1200 SEK	-4,625
	1400 SEK	-6,937
	1600 SEK	-9,250

SPSS also produce a summary for all attributes to produce an importance value table to easier compare the attributes with each other. For this analysis, price was almost twice as important as the second most important attribute ordering. Brand and customer service are valued least on almost identical values. The highest value is highlighted in grey.

Table 3. Summary of which factors are most important for respondents.

	Importance Values
Price	46,105
Ordering	24,353
Brand	16,344
Customer Service	13,198

4.2 Survey

The survey was sent to 17,775 people and came back with 526 answers of which 360 were complete and could be used for the analysis using SPSS. The answer rate was thus 2.0 %. Most answers came from Europe and North America with an almost equal distribution at 34 % and 38 %, respectively. North America and Europe are thus confirmed being the largest markets in this business. Japan is separated from Asia & Pacific because it is often seen as a separate market. In this study Japan only had one respondent and thus the percentage is rounded to zero and Asia and Pacific holding 20 % of the respondents. 4 % of the respondents came from South America and respondents from rest of the world were also 4 % of the total.

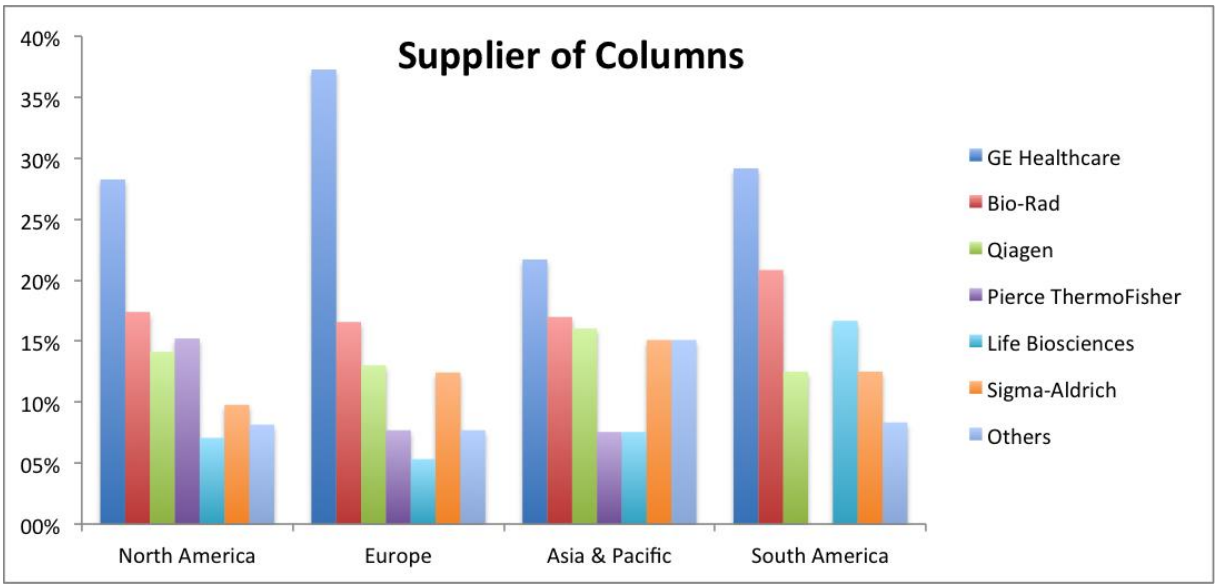

Figure 9. A selection of the major suppliers of columns used by scientists, divided by regions in the world. Suppliers with few users have been excluded from this graph due to insignificant influence on larger suppliers.

What suppliers are most commonly used in each region was asked in the survey. From the answers collected it was evident that GE's columns are most common in all regions with Bio-Rad and Qiagen competing about second place, see figure 9. This confirms the strengths of GE being well-known globally. On average GE seems to hold just under 30 % of the market share. Japan is excluded from the graph since it only had one user using Bio-Rad.

The respondents were asked how they place their orders and, using *central purchasing* within the company or faculty is by far used most, around 50 % in each region as seen in figure 10. Email and website is also common and is the channel that a company can influence by having a modern and easy navigated website with email address visible. For South America ordering by email is most common, but one must keep in mind that the number of answers from South America is just 15 which the project group considered to be too few respondents to draw justified conclusions.

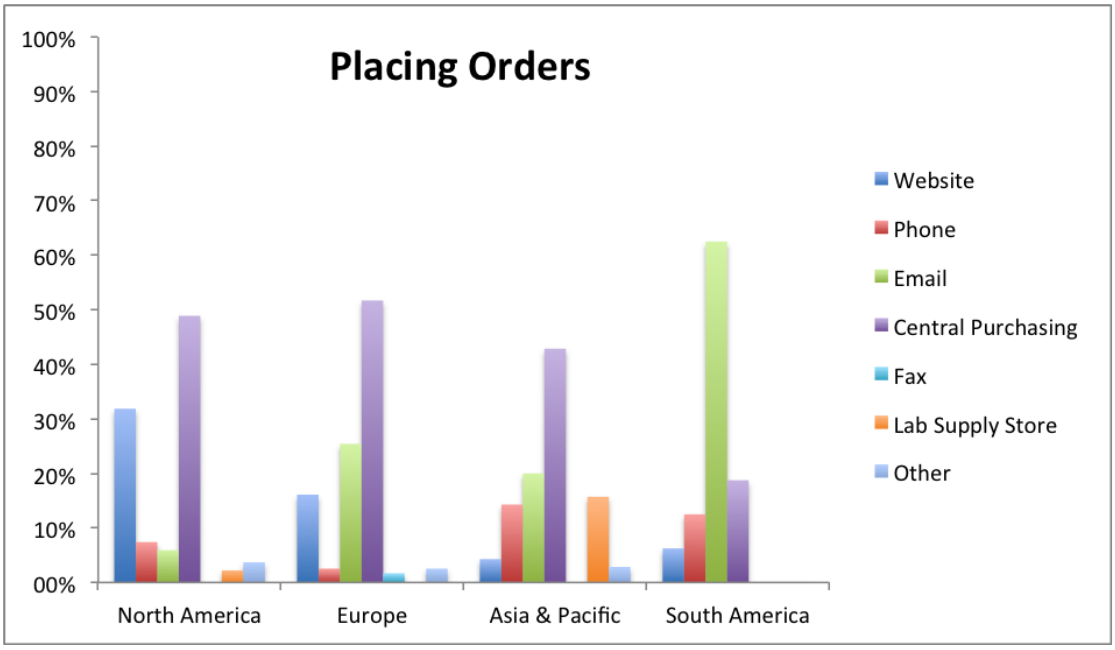

Figure 10. Distribution of how scientists place their orders, divided by region in the world.

What users value when choosing columns are, with recommendations from the project principal, divided into the two most abundant markets, Europe and North America. The overall results are the same for Europe and North America with some smaller differences. As seen in figure 11 and 12, performance is what users value most compared to other specifications. Close second is reliability of the products with price coming further down the ranking. Tech support and customer service is clearly least valued which also have been notified in the conjoint analysis.

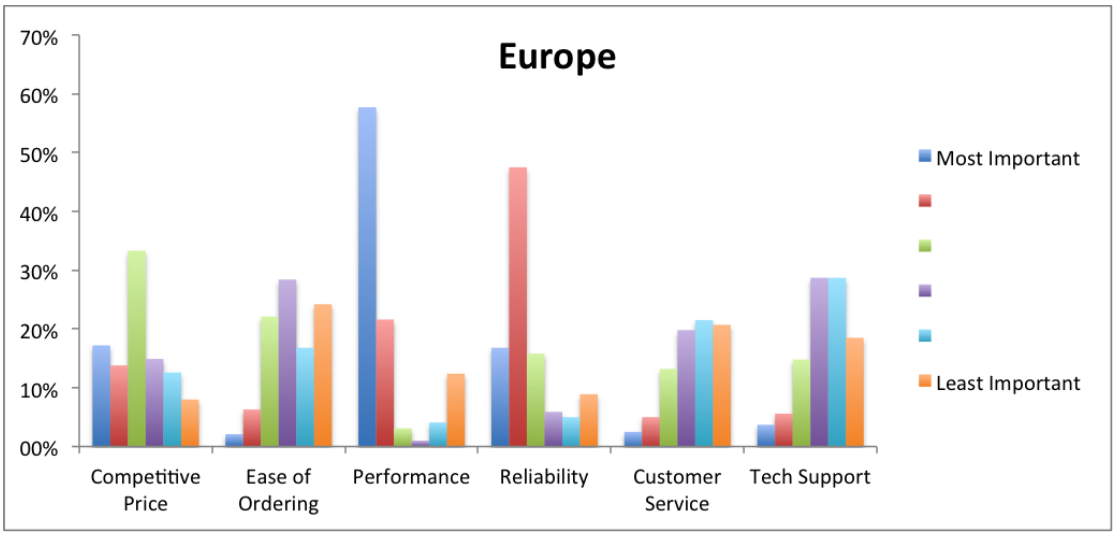

Figure 11. Distribution of what users value when choosing columns in Europe.

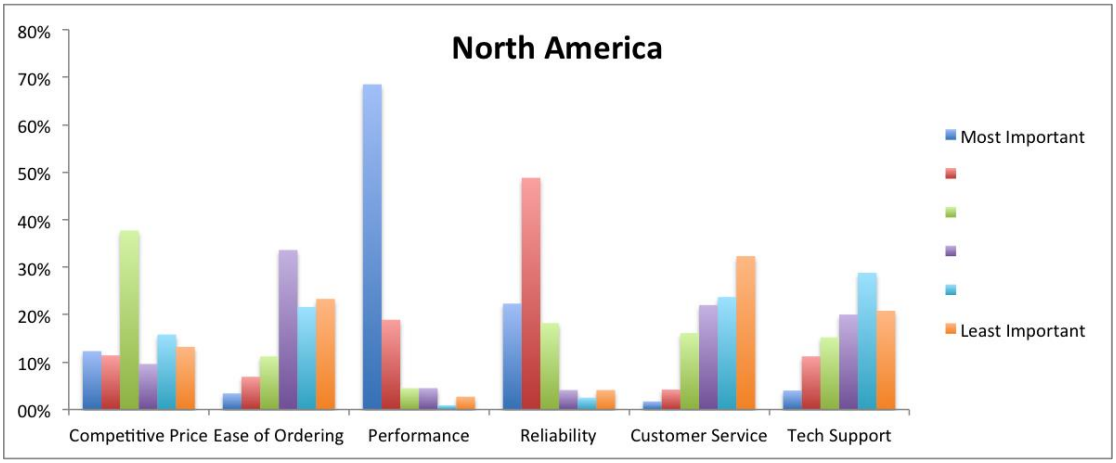

Figure 12. Distribution of what users value when choosing columns in North America.

To analyse the data for how users of chromatographic columns search for information the choices *often* and *second most often* are summed together to *most often*, and the choices *never* and *rarely* are summed to *never* to get a clearer view of the results. This can be seen in figure 13 and 14 for Europe and North America respectively. Journals of different sorts are clearly a well-used source together with recommendations from colleagues/associates coming second. Social events such as conferences and seminars are also common channels for gaining information about new technology. Rarely used channels are YouTube and LinkedIn.

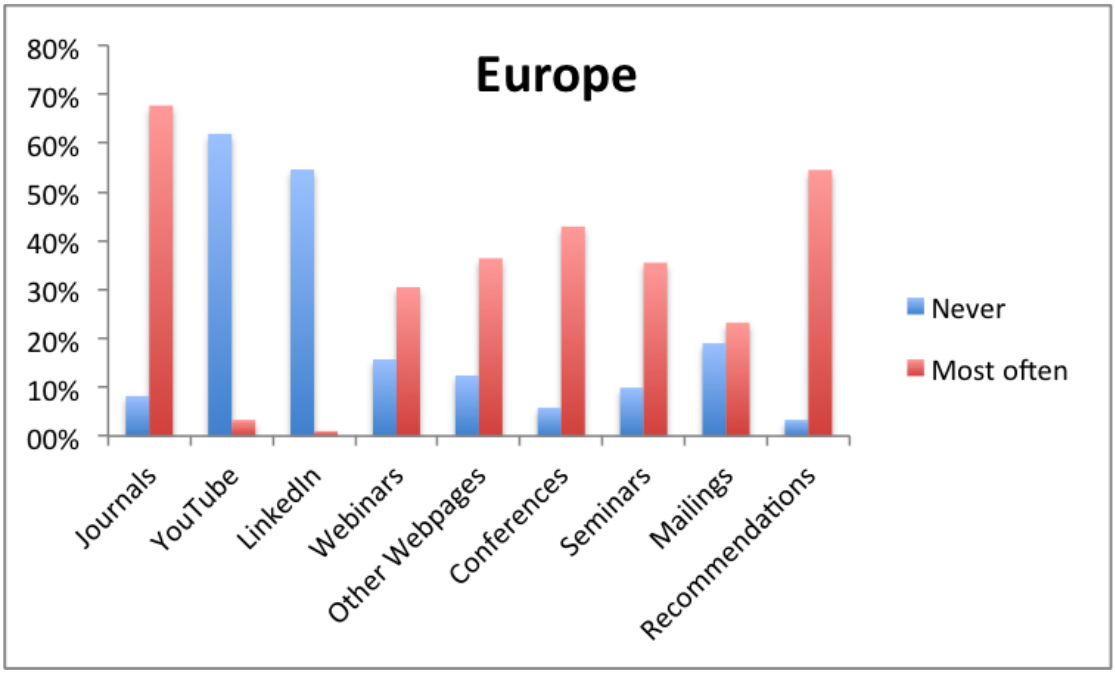

Figure 13. Visualizes the relevance of different channels for search of information on new technology used by scientists in Europe. Data shown in percentages for easier comparison.

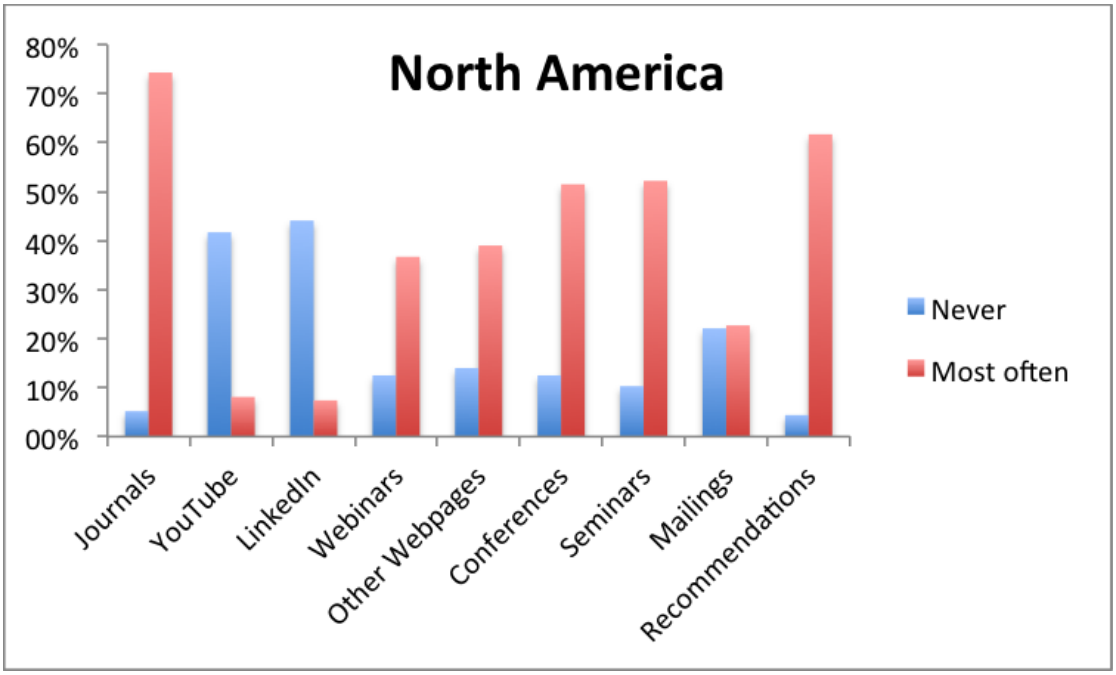

Figure 14. Visualising the relevance of different channels for search of information on new technology used by scientists in North America. Data shown in percentages for easier comparison.

One path in the survey was aimed toward people working in manufacturing, which got 39 respondents. These 39 respondents were asked how many chromatography steps they use in a purification process to see if a chromatographic kit would be desirable. Three steps are clearly most commonly used by almost 70 % of the respondents, see figure 15. Using only one step is used by about 10 percent of the respondents. The branch standard is to often use three chromatography steps for best purification results which is confirmed by these results.

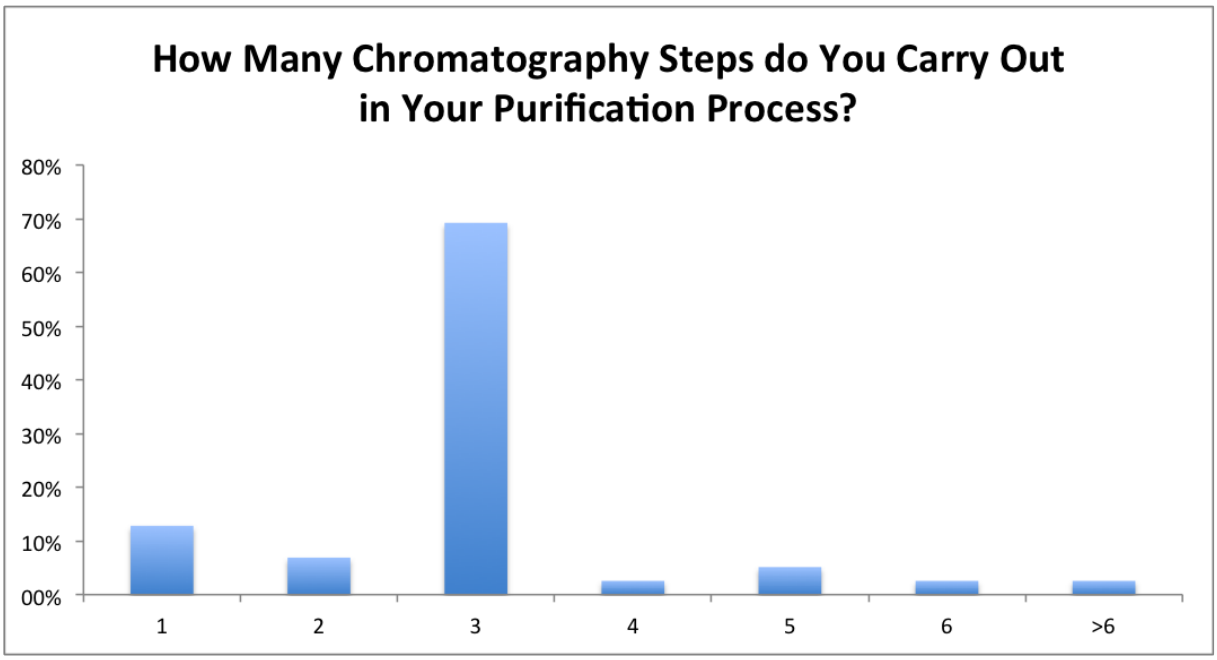

Figure 15. Amount of chromatography steps used in a purification process by users from manufacturing.

4.3 Interviews

Interviews with employees at Bio-Works gave a good picture of the company, the culture and relations that function within their walls and also where Bio-Works might be heading next. Since Bio-Works are very few people and work fairly close with each other, several employees compare the company to a family, where one often can speak open and freely about things. However, there are some disagreements among a few employees about how the company should work and what direction the company should take in the future. The differences in opinion seem to sometimes take its toll on the group dynamic and cooperation.

The family feeling brings flexibility into the company and the lack of competition between employees makes everyone help each other out to reach the set goals. Coffee breaks are vital in Bio-Works company culture where they get to know each other better, exchange ideas and nurture this family feeling within the company. The group feeling is said to be informal which reflect some parts of the company with loose structure, except work protocols that needs clear structure.

Several employees have been in the company for several years, some from the start, and stay because the feeling of belonging to the company. Almost like it being a vital part of their lives. This feeling of belonging to the company has emerged from dedication to their work with early mornings and late nights. The recent new hirings, which lowered the average age, has further fueled the family feeling with incentives to do activities such as after-works.

The new CEO, Kristopher, is meant to bring new energy by creating a more clear direction for the company with a distinct goal on increasing sales. Only five months have passed since he joined the company so his intentions have not yet gotten effect but his energy seems to fuel new hope into the employees. His vision and excitement about the company and how it can expand is communicated through the interview and seems to have spread among some of the employees. Kristophers' lack of experience from the chromatography industry has its doubts among some employees but is compensated from his personality and his experience from previous positions in large corporations.

Kristopher described Bio-Works as being on a journey going from a phase where all means where metaphorically in gas form as ideas. Later transitioned into liquid after a few years when some products began to sell and just recently the means went to crystallised form. With crystallised form meaning that Bio-Works now have good products that can satisfy customers and are now in the process of setting up realistic goals for the company.

To increase sales and make the business grow Kristopher needs to create a more clear structure within the company, which also is a demand from the new board that has more distinct intentions for Bio-Works. This change of creating more structure is welcomed by some but also seen as an unnecessary change since they like their structure now. The expansion of Bio-Works is seen as a call for more structure to make investors and customers to believe in the company and their business.

Bio-Works have gotten several investments, first smaller ones and just recently a large one about 30 MSEK, which implies that there are people believing in the business model. However, to keep alive and create a sustainable business they need to increase sales which are reappearing in the interviews, described more in the in chapter 5 under section *Surviving the Monetary Gap*. Today they survive thanks to the investments, but Kristopher's clear intentions to increase sales and expand Bio-Works turnover about 12 times brings hope to get black number in the near future. Several employees emphasise the quality of the products and that they have large stocks ready to ship, but the lack of sales is the company's Achilles heel at the moment.

When asked about Bio-Works future there is a positive consensus and that the future looks bright, but still with an emphasis on the importance of selling their products to survive. As mentioned the CEO has great hopes on their products and finding new customers. They see a potential in the laboratory market and have some projects going on, without going into specifics. The ongoing restructuring of the company is also thought to have an effect in the near future.

5. Analysis

This section will analyse effectuation, human capital and knowledge and company culture that has been identified as important and influential factors for a small entrepreneurial company. Analysis of the results is made in relation to relevant field of research

5.1 Risk Taking and Effectuation

As can be concluded from the interviews, the vision and the atmosphere that permeates Bio-Works bears much resemblance to that which defines an entrepreneurial company according to Read *et al*. (2011). The management, with Allan Simpson in the forefront, have clear visions of what they want to achieve, and are using all the means possible to achieve it. Just as Read *et al*. (2011) describes, they calculate risk on a daily basis, and now stands before the decision to "change or die" (Jacobsen, 2013). The entrepreneurial team behind Bio-Works, which started out strong in the early phase of starting up, seems to be bursting at the seams. The founders and the management are at odds about what is the appropriate path to take, where most founders are happy with the effectuation based workflow that has taken Bio-Works where it is today. It is evident from the interviews that this is where the opinions gets divergent. The management is set on building a more causation based structure, which make the founders unhappy.

It was concluded that Bio-Works are at the last phase, the sustainable returns phase, in the model described by Vohora *et al*. (2004). The company is relatively stable and is trying to become more structured. This rhymes well with the reasoning of Vohora *et al*. (2004). The entrepreneurial commitment needs to be honoured for Bio-Works to be able to achieve long term sustainability.

5.2 A Changing Company - the Negative and Positive Aspects

Helfat and Lieberman (2002) conclude that people with experience from industry especially from the same industry as the startup, have accumulated important human capital vital for the business. This industry-specific human capital, which includes work experience and industry-specific experience described by Brüder *et al*. (1992), brings knowledge about the market, technology and often comes with a valuable network of people that can be important for the business.

Several employees, among them some of the founders, have experience from larger corporations where most of them have been working at Pharmacia/GE for several years. Allan and Kristopher, two key persons in the firm, thus have the mindset of managers in large corporations and can be valuable to bring to Bio-Works smaller business. The benefits with this corporate baggage is that they know how to run a business effectively, have years of experience and have many contacts in this field of operation that they can make use of, all which corresponds with the thoughts of Helfat and Lieberman's (2002) conclusions. Even though they have much experience from larger companies they need to be aware of how smaller companies work. According to the CEO, Kristopher Fain, the company is applying a model fit for larger companies to make Bio-Works more efficient, but also that the model is adapted to fit the size of the company.

Bio-Works has, since January 2016, a new CEO, Kristopher Fain. The board gave him clear directions that he needed to focus all his efforts on sales, meaning that Bio-Works changed their focus from research and development to sales. The project group concluded that this is a clear indication that the new CEO, with directions from the board, has introduced and implemented theory E with a focus on structure and system over theory O, that focus on organisational culture (Nohria and Beer, 2000). Changing from theory O to theory E is not recommended by the authors of the article, because of the risk of creating feelings of betrayal among employees. Nohria and Beer (2000) suggest that it is possible to use both strategies in parallel but in that case, goals need to be clear and the focus needs to be evenly divided between the strategies. In Bio-Works case, the interviews revealed that the development of new products is paused and the goals have changed direction, now toward increasing sales. This means that what the shareholders' value is the legitimate measure of success for now.

Through the interviews, it was noticed that some employees know that they do not deliver what is expected of them. If the focus needs to be on sales, they should evaluate every employee's work tasks, set clear goals and expectations. It is very hard for a small entrepreneurial company to evolve and succeed if the motivation is low among employees. If Bio-Works consider Rubenowitz (2004) theories about keeping a good psychosocial environment, by considering especially two of the factors; letting the employees controlling their own work together with having a positive work management climate, the project group believe that the motivation will stay.

According to employees, Bio-Works is still a small company that gives the personnel room for flexibility, which creates a feeling of "*what I do makes a difference*". Even though the employees like the flexibility, they point out that they have expanded fast and that it is time for more structure and requirements. If there are no demands, the employees will do what is expected but not more than that. This is thought to be something employees have brought from earlier experiences, a consequence of many employees coming from large companies.

Some of the employees do not like the changes that are implemented or going to be implemented. Comments regarding minimal industrial wisdom or that the board does not consist of the right people, that they are not entrepreneurs and do not think about what is best for the company have been communicated to the project group. We can see positive consequences of more structure in the company, the requirements on the employees will give them a clearer view of their work tasks. The focus on their actual tasks will increase and other "time consuming" tasks will decrease.

The reason to resistance toward change can be based on several things (Oreg, 2006; Armenakis *et al*., 1993; Jacobsen ,2013), *i.e*. disagreement about if the change is necessary or not. The change of focus in Bio-Works might not be supported by everyone. Rubenowitz (2004) state that change in organisations can lead to psychological stress and a feeling of loss of identity *i.e*. if a new employee is hired with almost same work tasks that another has. New requirements can lead to fear of new or more things to do, which one might not be interesting to invest their time in. The project group has identified another issue that can occur, the symbolic, a new CEO can mean that the relation of power need to change. This can be small things as changing offices or where one sits. This can also be done as a symbol for that the company is going through changes, actually they plan to change offices as a symbol for changes at Bio-Works right now.

5.3 A New CEO without Industrial Wisdom

To include a co-worker without any previous experience in the specific area can be both good and bad according to the employees at Bio-Works. Kristopher has a lot of experience working in large companies with sales but has no industrial wisdom in the protein purification branch, which can lead to "stupid" questions or statements. Even though questions can be categorised as "stupid", the project group believe that they can raise other questions that an expert would not think about. This means that they can get new angles from which they can confront their business. Not to be forgotten is that breaking patterns or change routines can raise new opportunities.

The project group thinks that Kristopher is a very charismatic leader that brings a lot of energy to the company. So far changes within the company has not been noticed to any greater extent except for the sales force where a change has been noticed, according to the employees. The demands on sales are higher, which puts Kristopher up to the task to motivate all employees at the company.

Kristopher says that he concentrates on numbers and sales and is trying to decrease the diffusion of Bio-Works, *i.e*. he is very strict about the focus. To be the person organising and structuring is not an easy task, and the project group has noticed that it is not always popular. With Kristophers' great experience from big companies he brings knowledge about both sales and structuring, and one thing that he has already implemented is, according to other employees, better interdisciplinary discussions through workshops. He has, as mentioned, brought a lot of energy and new approaches to discussions and workshops but the fact that he has no industrial wisdom cannot be neglected, and it can in some cases be negative. In the life science industry, all persons interviewed mentioned that knowledge is important, *e.g*. if Bio-Works participate in a conference and Kristopher is the one representing the company, it is important that he knows what he is talking about. Saying something wrong can, according to employees, cause problem where possible customers might think that the company does not know what they are talking about.

5.4 The Company Culture

Many of the employees see the company culture at Bio-Works as familiar, happy, informal and enjoyable where you can argue intensely, but solve any problem among the people discussing. They stress that they work flexibly. Most employees enjoy working at Bio-Works and see it more as a hobby rather than a workplace.

A theory about number of employees was raised during the interviews, as if there are less than six to eight people in the company, there exist only one group, where everyone can be well informed about what is going on each site. When a company grows and the number of employees increases, the group will be divided. This can, according to the interviewee, be hard to handle because one does not longer know what everyone is doing, or that one do not know which group they want to be a part of.

When the company expands and hire more people, the familiar feeling decreases and some interviewees perceive that it is more political now than before. Another thing mentioned about the company culture is that structure will bring more formality. This does not necessarily mean that the familiar feeling will fade, but that it will be clearer when a decision is made or not.

Some employees at Bio-Works mentioned the need of working 10 000 hours to get great knowledge and experience in a field. The authors to this paper believe that experience is important but in the end it will come down to how passionate one is about their work. The project group believes that maintaining the passion in Bio-Works will be a key driving force for them to achieve great things. A person with a genuine interest in a field will bring both happiness, and will infect others with their burning interest. Employees mentioned that it does not matter if some see their work as a competition, and others are satisfied to have a job to go to everyday, as long as passion exists. To expand we believe that the mix of people is needed to vision how big and good a small challenger company such as Bio-Works can get.

Today Bio-Works is very careful when it comes to money, if they succeed in expanding and with sales, they can make room in the budget to send employees to *e.g.* inspiring seminars, which the project group believe will raise the motivation level.

5.5 Assessing the Market

Since Bio-Works already have made their entry on the column chromatography market some years ago, they have already gone through the entry phase. However, there are still some barriers that a small entrepreneurial challenger company continuously battle with, the capital requirements for instance. According to employees, Bio-Works does not yet show any black numbers, and is still reliant on investment money. Although the latest investment round gave them 30M SEK, they still need to increase their sales for the company to be sustainable in the long run. As previously mentioned, this is something that new CEO Kristopher Fain is tackling by hiring a whole new sales team that will be lead under his guidance.

Switching costs are also something that Bio-Works continuously need to battle. The legacy of big companies in the branch *i.e.* Pharmacia/Amersham/GE Healthcare is not easily forgotten, and through both interviews with employees and the discussions with respondents to the conjoint analysis, many of the customers in the market still rely heavily on these companies and their system with columns. They also mentioned that as long as the customer's current system (in most cases the GE-ÄKTA system according to the survey results) works with no notable problems, the chance that the customers will switch to another system or columns is low. One of the participants in the conjoint analysis stated that *"as long as my system does not break down completely, there is no chance at all that I will change it. It requires too much effort on my part searching for alternative columns (or other parts) even though there might be a reduction in cost associated with switching"*.

The threat of buyer is somewhat less prominent for firms that produce chromatography media and columns than for other markets. Since this market is oligopolistic, the customers are used to paying whatever price is asked for the products. According to employees at Bio-Works, playing competitors against each other and forcing down prices is not something that usually takes place. Since the media and columns are high quality products, the customers have been accustomed to the "reign" of the oligarchs.

Even though this might seem as a tough environment to start a business in, it is also where Bio-Works (as an example of a small challenger company) see their opportunities. They mean that customers might be inclined to switch to another producer if their service needs are not satisfied and that producer can offer a more competitive price. The main players of the market can be both a challenge and an opportunity for a small challenger.

Substitutes on the market can be regarded as a threat because of the possibility that they place a ceiling on the prices and thus lower the profitability on the market. A small challenger company can be regarded as such a substitute, offering lower prices than the industrial leaders. The columns that Bio-Works offer will have a competitive price, but will still reflect the market expectation to avoid being regarded as low-budget (meaning inferior quality). Substitutes that can compete with Bio-Works prices are, according to employees, unlikely to appear in the nearest future.

Bio-Works, being a biotechnology company, needs to be supplied with various chemicals for the daily production to proceed. The chemical industry is highly regulated, all chemicals produced need to uphold a certain standard. Therefore, several employees mean that it is not likely that suppliers could exert bargaining power over Bio-Works by lowering the quality of the goods. Prices can of course be raised, meaning that it could be hard for Bio-Works to keep selling their media and columns at the current prices.

Rivalry among existing firms is one of the reasons that Bio-Works was founded. They compete, first and foremost, with GE for customers. Bio-Works has assumed the position of the underdog, where they do not have a lot of means to start price wars or advertisement battles. This role is, as previously stated, connected both with opportunities and challenges. GE might not regard Bio-Works as a credible competitor until they already started gaining some of GE's market shares. On the other hand, Bio-Works need to be really careful with what approaches to take due to the limited financial resources.

5.6 Surviving the Monetary Gap

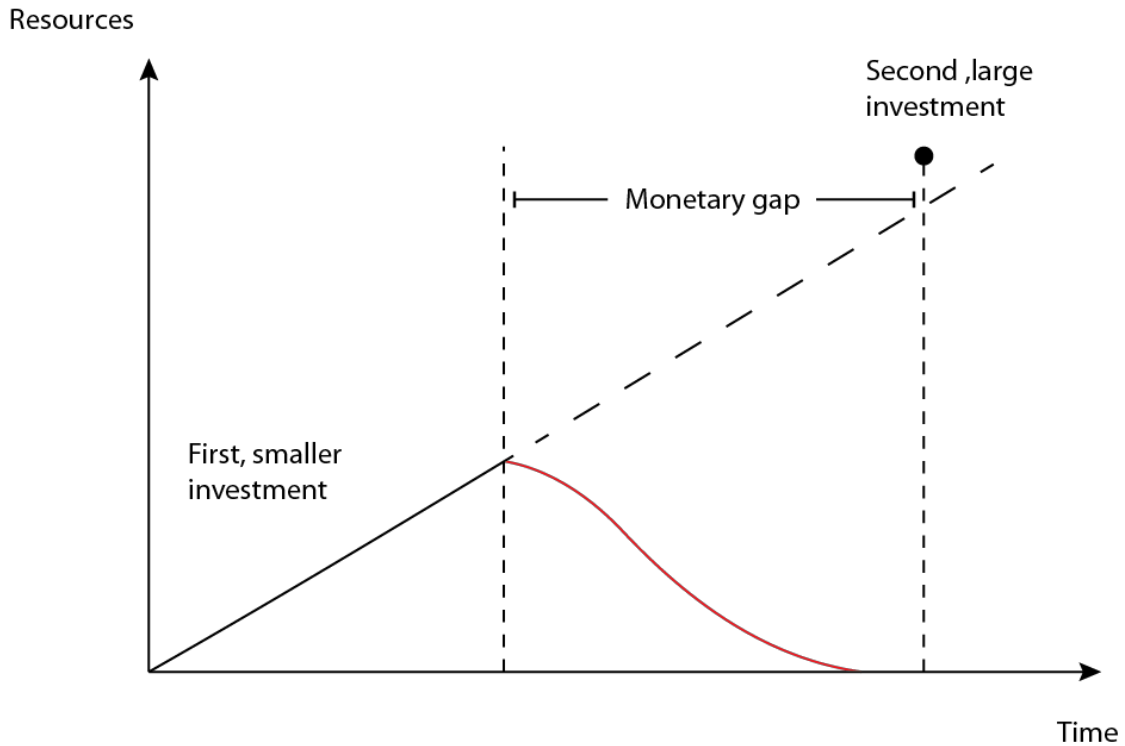

Figure 16. A schematic picture of the importance of investments among start-ups.

For a small challenger company reliant on investments for survival, there will exist a monetary gap between the first, smaller investment and the second larger investment in which the company need to sustain itself. As stated by Lindström and Olofsson (2001), it is more difficult for technology based start-ups to receive funding. Therefore, it can be concluded that surviving in between potential investments is vital for a small challenger company. Unfortunately, most start-ups fail due to different reasons, were running out of money is the second largest (CB Insights, 2016-05-09). Together with the COO of Bio-Works, the following models regarding the survival with scarce resources were outlined. Both of the models are based on hypothesis of the project group and the COO, and are aiming to explain how a small company in this market can survive in between investments.

In the case of Bio-Works, the investments were 5 MSEK and 30 MSEK, respectively. In between the investments, the company needed to sell products to keep afloat on its own. To get a first investment, a company can sell the visions for their business model. But, to get an additional, larger investment, the company has to provide a viable product (or service) that will bring in revenue and make the investors believe in the company. The red line in figure 16 represents the decline in resources that forces many startups into the grave after the first, initial investment. The dotted line represents the revenue that has to come from sales when the money from the initial investment has run out. This is where many small companies fail, *i.e.* they cannot overcome the monetary gap. Bio-Works successfully overcame this gap, but not with more than a narrow margin.

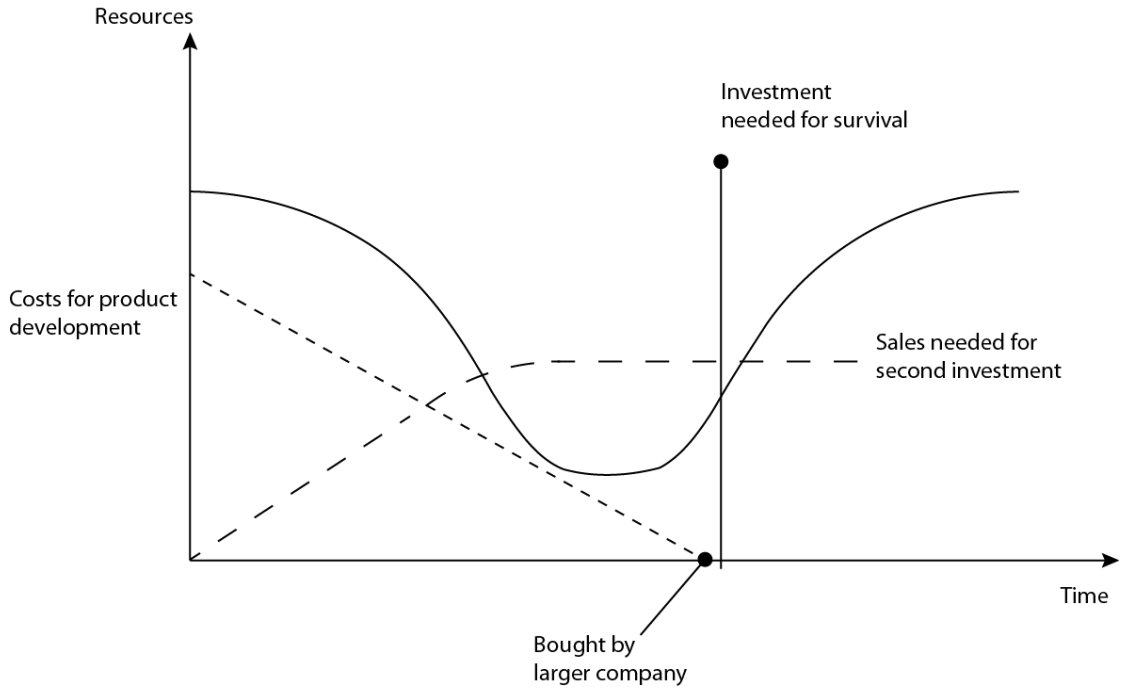

Figure 17. A schematic picture of how investment and costs for product development progress together with needed sales rates.

This reasoning can be extended to explain the development of new products in a business. The curved solid line in figure 17 represents the fluctuation in resources over time when developing new products. Initially, there is an investment from external sources making the development phase possible. The new development drains the monetary resources and if the sales are not sufficient enough to follow the survival curve (dashed line), the company will be completely drained of financial means and is likely to be bought by a larger corporation or be liquidated (end of dotted line). Eventually a second investment is needed to be acquired (for process scale up *etc*.).

5.7 Bio-Works Strategy to Remain Competitive

Weaknesses that they need to assess are their fragile financial position and not being recognized by potential customers. Competitive threats from companies such as GE and social concerns about using hazardous chemicals to produce potential lifesaving products align with Porter's external limits of the model. These external limits are closely related to the industrial environment described by Lekvall and Wahlbin (2001), where they mention that competitors, suppliers and customers on a business influence a company's business to a high degree.

The strengths in Porter's model are what build Bio-Works business environment, as explained by Lekvall and Wahlbin (2001). They further discuss the importance of working closely with customers to create a long lasting relationship, which is what Bio-Works are trying to do by visiting potential customers and following up their satisfaction of the products.

Roger's (1983) five attributes to innovation, explained in section 3.4, concludes that Bio-Works products do not hold any technological advancements or innovative changes but instead add a product into a well-known and explored technique for chromatography. Bio-Works products can thus be said to be attractive to late adopters, explained by Schilling (2013) who now know that the products work well and choose products much based on price. The importance of price has been verified in in the conjoint analysis.

5.8 The Importance of Market Analysis

The survey that was sent through GEN magazines mail list was customised for Bio-Works and the data that they wanted to collect. Although customised, it is a general example of how a market analysis can be carried out for a small challenger company in the life science market and a great way to do market preparation and get brand attention, described by Beard and Easingwood (1996). The survey concerned six different aspects that are vital in the process of gaining market shares; location of customers, competitors, where to reach out with their products, what techniques that are sought after in the market, channels for marketing, and future product development.

The respondents in the survey were asked to specify their location according to continent as a mean to try to segment the global protein purification market. Understanding where the biggest market potential is located in the world can significantly increase the chances of survival for a small company. This information goes hand in hand with knowing which players on the market are your most important competitors. In the Bio-Works survey, the respondents were asked to name the brand of columns that they currently use. This made it possible to confirm that GE indeed is their biggest competitor and they can tailor their strategic plan to be viable in the market. The importance of knowing your competitors are emphasized in Beard and Easingwood's (1996) product launch model's third step, positioning tactics, explained in section 3.9.

For a challenger company to be able to reach out with their products, sometimes they need to find a different approach than established players. This could be hard in a market such as the biotechnology market, where conservative forces apply. Nevertheless, it is crucial that you know where customers purchase products so that they are visible to as many as possible. For Bio-Works, a question was raised as to how the protein purification community places their purchasing orders to be able to understand where to offer their products. Which channels the

respondents used for seeking new information about high technology products was also asked in the survey. Knowing these channels means they know where to advertise.

One of the needs of Bio-Works was to understand what techniques are used by purchasers of columns. This is also something a small challenger company needs to address, where is there a gap in the current product line that could be used as a starting point for a new product or service? This information can also be utilised in improving the present products they produce.

5.8.1 How Scientists Place Orders

For a small challenger company, it is important to know how their customers place their orders, so that they can have a fair chance to reach as many customers as possible. According to the results from the survey, central purchasing is the most common way of placing orders for scientists followed by website and email, respectively, see figure 12. The result from this question is interesting because of the differences among region in the world. One can see that North America use websites in a greater extent than Europe, that rather use email than websites. In Asia and Pacific it is more common to use email, lab supply stores and phoning before websites. South America differ the most, the respondents mean that it is more common to place order by email then central purchasing.

To enter and increase market shares in the different regions one need to have different approaches. In Europe three parameters are regarded as more important; Central purchasing, Email and Website; while in North America there are two factors that are more important than others: Central purchasing and Website. When trying to enter the market in North America and Europe one can conclude that it is important to reach the responsible purchaser for central purchasing thus this is the most important and common way for scientist to place orders.

If a small challenger company want to enter the chromatography column market in Europe it is important to have a visible email that is easy to find, the third most important factor is website meaning that they need a good system for ordering products and overall a modern website. If one wants to enter the market in North America, email is not that common but it is important to have a functional, modern and easy-to-order website. Central purchasing is most common when placing orders in Asia and Pacific followed by Email, phone and lab supply store. For South America, email is the one most common way of placing orders meaning that companies that want to enter the market there need to expose their email in a good way.

5.8.2 Important Factors when Choosing Columns

Figure 13 and 14 depicts what users' value when they are choosing chromatography columns. We chose to analyse Europe and North America because those regions had the highest number of survey respondents. One can see that the trend is very similar between Europe and North America where performance is the most important factor followed by reliability and a competitive price. Tech support and customer service is least desired. Ease of ordering can be seen as a bonus but is a subordinate to performance, reliability and price. This means that a challenger company must offer a column with high quality and that it would be very hard to enter as a low-price company with good customer service.

5.8.3 Channels for Information about New Technology

In both Europe and North America, it is evident from the survey that journals and recommendations from associates are the most important channels when searching for new information. In figure 17 the two most important channels has been summarised for Europe, where it can be seen that journals still represent the most important channel followed by

recommendations from associates and conferences. In a shared third place there are other webpages and seminars.

North America differs a little from Europe in this aspect. From the survey, it could be concluded that the summary of the most and second most important factors (see figure 20), journals and recommendations from associates are most important. Conferences and seminars share the third place. Least important channels in searching for informations about new technology are the same as in Europe, YouTube and LinkedIn. Even though the survey showed that YouTube and LinkedIn was rarely used as channels for information, the project group foresee an upswing in the importance of social media channels, such as previously described YouTube and LinkedIn. A parallel can be drawn to the upswing in job advertisements on social media sites like LinkedIn and Facebook.

5.8.5 Speculation about the Future

When the respondents of the survey were asked to predict what they would want to change or improve upon existing columns without any kind of restriction, the most prominent answer was to lower price on columns. In second place, increased yield and increased flow rates were requested. Price is always an important factor when selling and buying products, and naturally one wants to get the best product for the cheapest price, so it came as no surprise for the project group that lowering price was highly requested. This could also be a sign of customers being tired of buying overpriced columns, and a chance for challenger companies to create their niche in the market.

Requested increase in yield and flow rate is also connected to money in a way, since time is money. If yield and/or and flow rate are increased, with kept purity one must add, would make the user purify more proteins in less time and thus save money. The thing that often stops one from using higher flow rates is that resolution and purity often gets lower when increasing flow rates too much, according to employees, since the purification process does not get enough time to work properly.

Wishes for automation and easier connections for columns onto chromatography system, such as no screw attachment, were also prominent. Today there are many different producers of chromatography systems, most of them with similar connections, but one easy way to connect and uniform type of connection seems to be desirable.

After going through the answers of what the respondent think will be next in column chromatography the majority answered faster separation, where some of them were the same respondents that answered faster separation when asked to improve columns. There might be a wish among the answers to tell that the future might bring faster columns as well, but the idea is probably not far off. Many improvements today are about automation, speed and simplicity, all which can increase revenue and save cost.

Disposable columns were number two among the respondents, which probably relates to the simplicity of doing quick and general purifications for analytical purposes. Thirdly, which also is more of a technological origin than the other two, is purification in nanoscale or beads in sub-micron size. This technological advancement could make it possible to purify even smaller molecules and viruses, possibly for vaccines among other areas. The project group believe that a small challenger company would increase market shares if manage to produce these beads for separation of smaller molecules, *i.e.* getting a better product than competitors.

In figure 15, one can see that there is very common with three purification steps. There is common for companies to sell purification kits today and this survey support a three step kit. The project group believes that offering a kit to the market, possible reduced in price, might help a small challenger company to gain market shares.

5.9 What do Customers Value?

Do not produce a product that no one wants to buy, this is according to the project group, one of the cornerstones in business development and entrepreneurship. To be able to know if what you are doing is right, the best way is to ask the potential customers what they want. For the present project, this was done with the send out of the survey, but also through a conjoint analysis. With this approach, the project group could get a more personal discussion about what customers value in a product. To really get down and personal with potential customers is a loophole for small companies to enter a market that they previously have not been active on. It is a way to uncover potential voids that are not satisfied by already established players, and can serve as map towards establishing a position in the market.

From the conjoint analysis we can conclude that the respondents valued the attributes differently depending on their experience. We compared results from less experienced users with more experienced users and could see differences in the attributes *brand* and *customer service*. Less experienced users did not value a specific brand as much as experienced users, their attitude towards brand were less biased and did not influence the ranking much. More experienced users valued brand more than other attributes, and the project group believe that it is due to habit and relations to products or companies of different brands. The other attribute where differences could be seen was customer service. This was not important to experienced users but, less experienced users valued customer service more especially when it came to technical support.

Results from the conjoint analysis can be questioned both due to the low amount of respondents and also because some of the participants had been working at some of the eligible companies. If two cards showed the same levels except one, and the level that differed was the attribute brand, the participant preferred to choose the card with the brand that they previously had worked for over the other, *i.e*. they were biased. Bryman and Bell (2013) calls this a non-random or non-probabilistic sampling method which is negative because it affects the respondent's answer, and the result can be misleading. If the respondent has connections to parameters in the study the order of the ranking won't be subjective. The interviews in connection with the ranking were very informative and critical for the understanding of the respondents thought process. The interviews correspond well with the results from the ranking.

5.10 Future Outlook

What all employees agree on is that they need to increase sales. In the future they hope to expand even more, to increase both sales and market shares. This means that they need to be more visible on the market with high quality products. The project group means that it is important for Bio-Works to participate in seminars and conferences.

According to employees, the company needs to define their market, focus on what they already are producing, that is, play on their strengths. Craving for, and focus on future products can be counterproductive in this stage, mentioned by some employees. The

employees have trust in the products and are confident in that they can offer better products, service and prices than their competitors. To increase sales, the project group believes that they need to focus on existing products and highlight the characteristics that are better than competing products.

When discussing which areas the employees predict to be Bio-Works future, they emphasise; research and laboratory market, process development for scale up and manufacturing, food and beverage and pharma. Although the lab market is large, there are split opinions regarding entering it. Some mean that it could be stupid because big actors as GE would outrank them. Kristopher wants Bio-Works to work on the packaging, to offer something complete, slowly expand and enhance market shares invisibly. He means that "Bio-Works can live on fruits, we do not need the whole forest". The opportunity to expand business further, from today's 10 million SEK to a maximum of 150 million SEK while maintaining their current production facilities is something he think that they should take advantage of.

A small entrepreneurial company will more often than not be subject for change in the organisation sooner or later if they are to remain in the market (Jacobsen, 2013). Through the interviews we have learned that while this is welcomed by most of the people connected to the company, it is not an opinion shared by all employees. Freedom for employees is very important, since the employees are one of the most valuable resources for such a company. But, learned from the theory, freedom is not the only driving force that will drive a company forward, especially not when it comes to changes. The project group believes that stability, structure, and clearly specified tasks must become a part of the organisation, otherwise the chances for survival will diminish significantly, and this due to that Nohria and Beer (2000) could conclude that 70% of changes within a company fail due to loss of focus. In this process, stability and structure will be more implemented at the expense of freedom and flexibility, *i.e*. implementation of theory E (Nohria and Beer, 2000).

The effectuation work process that usually defines small entrepreneurial firms (Lemos and Andreassi, 2015) is a really helpful tool in the beginning of establishing a company and carry out changes (Charles and Oystein, 1998; Read and Sarasvathy, 2005), when you use the means you have to create something. But just as freedom and flexibility, its dominant position will decrease when more stability is needed, *i.e*. during the company's growth phase, and causation will play an important role in the work process (Lemos and Andreassi, 2015).
The project group thinks that small companies that mature should keep on working with effectuation to understand the competitors and the environment (Charles and Oystein, 1998; Read and Sarasvathy, 2005), also to work with the resources you have got.

6. Conclusions

This section presents the conclusions based on the analysis, which aims to answer the questions and the purpose of this study.

The purpose of the study was to; "*Map out challenges and opportunities of a small entrepreneurial challenger company associated with establishing a foothold, build a position and create a viable company in a rigid and conservative high technology life science market*."

The first research question was "*What approaches could a small company in the life science market take to increase their chances of gaining market shares?*"

According to results from the survey, a small challenger company in the life science market should increase their market shares by using right channels when marketing themselves and their product. The channels identified as important were to use journals and recommendations from associates. To be able to reach out to many key opinion leaders, the company should participate in conferences and seminars. At these public events they are surrounded with skilled and knowledgeable people in the area where can spread the word about the company and their products, to get a "word-of-mouth" effect between other users and companies.

Small challenger companies that sell products that are updated versions of an already existing and well known technical solution, makes the late adopters, as described by Schilling (2013), the main target group. To target late adopters is not uniformly done throughout the life science market, but differs of course depending on the technology being sold. Through the interviews and conjoint analysis the project group recommends targeting less experienced users and young people that yet not have been biased to the large, oligopolistic firms. More experienced users seem to be framed which lead to conservatism and resistance to adapt new technology even though it concerns the same technique.

Because the branch is conservative, users often stick to the same systems, techniques and brands they have always worked with because it works and is "*good enough*". The attitude toward innovations is curious but there is resistance among users to adopt them. Through interviews with employees and discussions with the respondents in the conjoint analysis the words "good enough" were repeated several times, and they agreed upon that implementing new systems etc. without the urgent need, does rarely happen.

To carry out market research, one approach could be to send out an online survey and ask potential customer about their opinions. Another way, although more time consuming, is to interview customers and have them participate in *e.g.* a conjoint analysis. A lot of information can be extracted from the data collected with these both approaches. It is important for a challenger company to market their products through right channels and having a good website that allow orders and email contact.

When trying to establishing a foothold on the market of a start-up life science company, it is beneficial to build the company around an entrepreneurial team for a greater chance to survive (Harper, 2008). Since the life science market is mostly a business-to-business market, the understanding of the technology is not a big hurdle to overcome, thus homophilic communication, as described by Rogers (1983) as persons with common background and knowledge, is not a problem in the diffusion process. People active on this market are anticipated to have a certain degree of technical expertise. In this case the project group

believes that this supports Harpers (2008) theory about the benefits of a founding entrepreneurial team due to a wider network within the industry.

The second research question was "*What do users value most in high-technology products such as chromatographic purification columns?*"

According to the survey and the conjoint analysis users value performance, reliability and price most. This means that a challenger company in this high technology life science market needs to have a good product and that it would be very hard to gain market shares with price as a unique selling point. It might be interpreted as being not as good as the more expensive products.

A small entrepreneurial challenger company in a high technology life science market has the challenge to develop products that can be confirmed to be better than existing products from competitors. Because the price plays an important role when choosing products, a strategy could be to set a price just under competitors', but still resemble the market expectation as described by Easingwood and Beard (1996).

The third research question was "*What can a small challenger company do to use the restricted monetary resources in the best way possible?*"

Most small challenger companies have restricted monetary resources. To be able to use these resources in the best way possible they should focus on developing high quality products, and making sure these products are marketed properly so they can be reached by customers. Surviving the entry phase in a market with limited financial resources is made possible by thorough planning. In this, market research plays an important role to know what products to develop, where to market, and how to reach the customers. Entrepreneurial companies need to focus their restricted means to the proper channels.

The last research question was "*What value does corporate culture and structure have for small companies as they are maturing?*"

The human resources is one of the most valuable resources a company have, especially when there are people with industrial and specific technological wisdom (Helfat and Lieberman, 2002; Brüder et al., 1992) and therefore important to treat the employees well. When a company undergoes changes and matures it is important to prepare for changes, communicate and making every employee a part of the process. The feeling of participation brings motivation and a feeling of responsibility among employees. Corporate culture and structure have a high value for small challenger companies in a high technology market. It is not only an indication of an evolving company, having a well-defined company structure send out a positive signal to customers. A structured company is a credible company, where people with valuable knowledge work. It is a company that potential investors can find interesting.

7. Recommendations to Bio-Works

Users and buyers of chromatography columns value high quality on the product and their performance, thus Bio-Works should always focus on producing high quality items. Their specialty is the media for the columns so for their pre-packed columns they have to find high quality producers of the columns they are going to use when packing columns.

To increase sales they need to find a good sales team that can exude good confidence and sell Bio-Works as a company that can be trusted. The sales team also needs to have a high level of knowledge of the products Bio-Works are selling. Customers not doing their orders through central purchasing within their company and institution seem to favour electronic ways to order their products such as email and website. Bio-Works thus need to have a modern web page that is easy to navigate with a clear form to purchase their products.

Marketing is expensive but when Bio-Works choose to do aimed marketing they should choose scientific journals, seminars and conferences which is channels many of their customers pay attention to. Recommendations from associates are also a popular channel of finding out about products and techniques which implies that they would benefit from word-of-mouth from well-known scientists. Distributing products that key opinion leaders could use are therefore a way of getting the word-of-mouth effect going.

Users often do more than one purification step to purify their target molecule and three steps seem to be most common, often with different type of columns. Putting together a purification kit for a specific type of purification is therefore a good idea to increase their product portfolio. Several competitors such as GE Healthcare and Pierce ThermoFisher have these kinds of kits, so it is nothing new but it is a good way to make customers try more of their products or for the first time.

According to results from the survey, price play an important role when users determine which products to buy, Bio-Works should consider a lower price, yet not too low so they can be seen as a company with inferior products. The project group recommends Bio-Works to introduce a first-time/try-out offer to catch possible customers attention for trying their products.

As discussed above, Bio-Works is going through changes. Their new CEO has restrictions from the board to increase sales, and his task is now to motivate all co-workers. The project group recommends that Bio-Works should keep a certain plan for spontaneity within the organisation, that is, according to Nohria and Beer (2000), to combine both strategy E and strategy O. When it comes to changes resistance is, as mentioned above, very common among employees. To prevent and reduce these feelings of resistance toward changes, Bio-Works should keep the employees aware about the coming changes and prepare them well before they are implemented. It is also important for the management to communicate why changes are needed and what positive effects the outcome will have. To focus on the positives has showed to be important for reducing resistance.

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Appendix I - Conjoint Analysis Cards

Figures I to V depict the cards with different attributes of a chromatographic column that were used in the conjoint analysis.

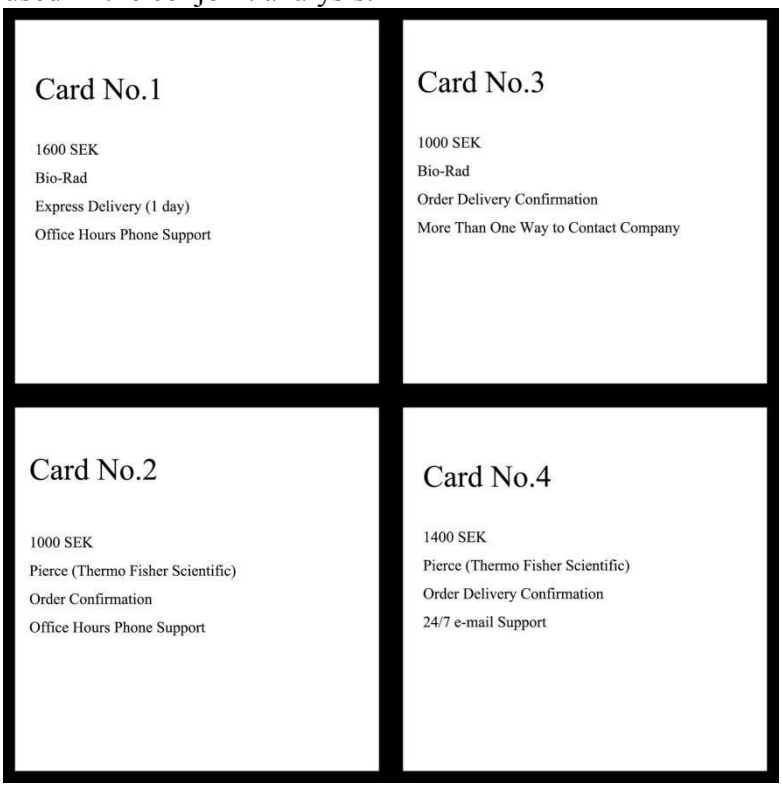

Figure I. Conjoint card no 1-4.

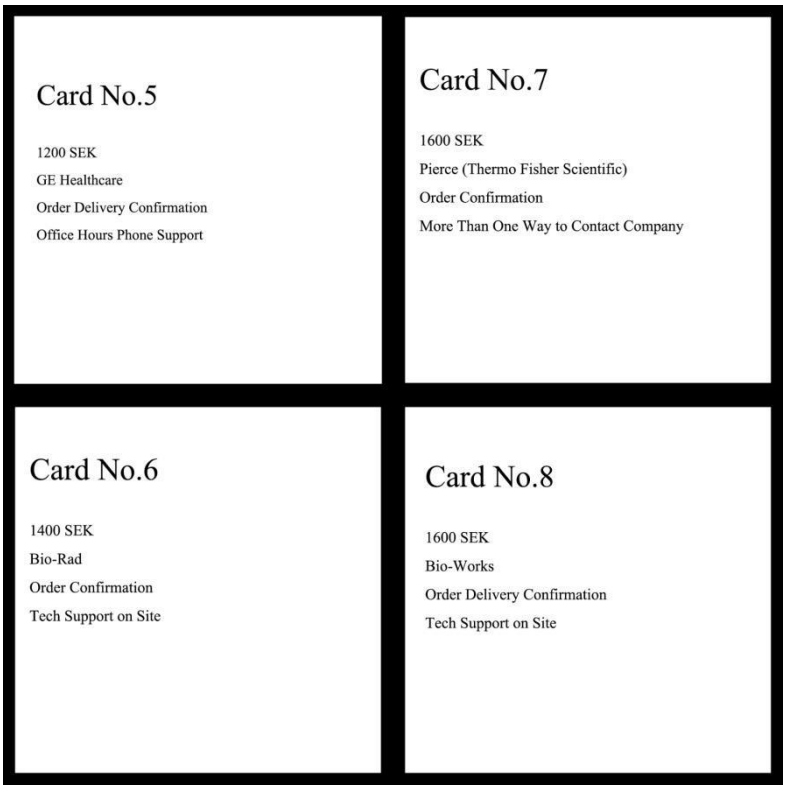

Figure II. Conjoint card no 5-8.

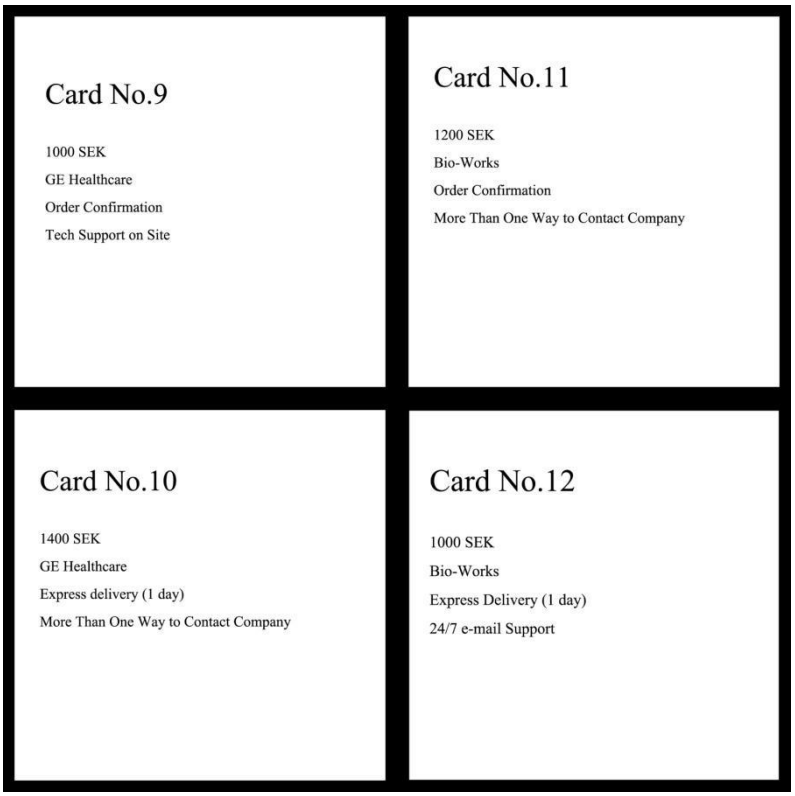

Figure III. Conjoint card no 9-12.

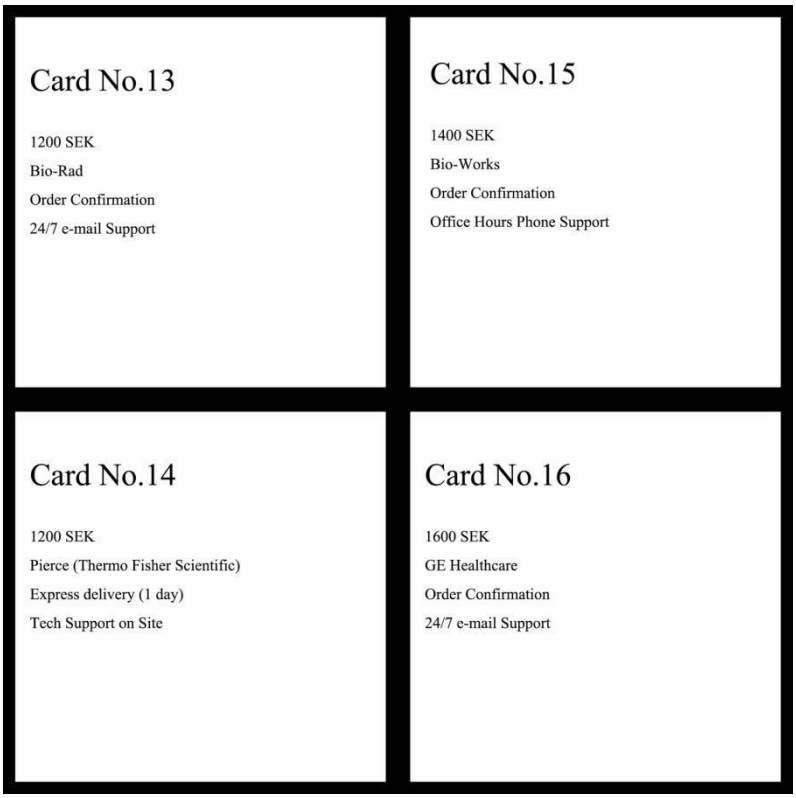

Figure IV. Conjoint card no 13-16.

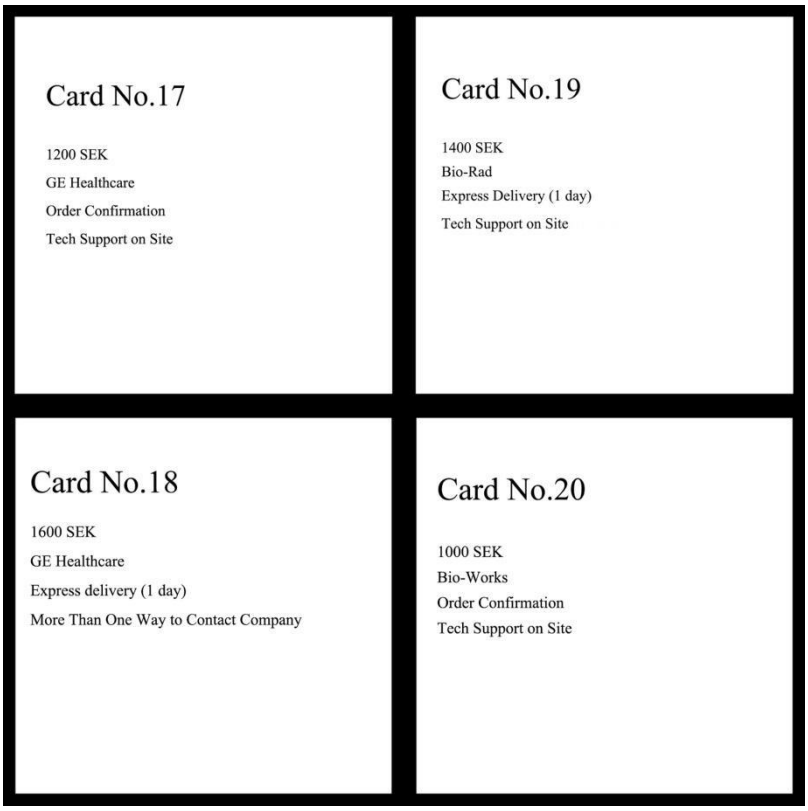

Figure V. Conjoint card no 17-20.

Appendix II - Chromatography Techniques

1. Size Exclusion Chromatography

Size exclusion chromatography (SEC), sometimes called gel filtration chromatography, separates molecules according to size and shape (Sepsey *et al*. 2014). Small molecules will penetrate and enter the sieves of the beads to a greater extent than large molecules (see figure I), meaning that large molecules will travel faster through the column than small ones (Duong-Ly *et al*. 2014).

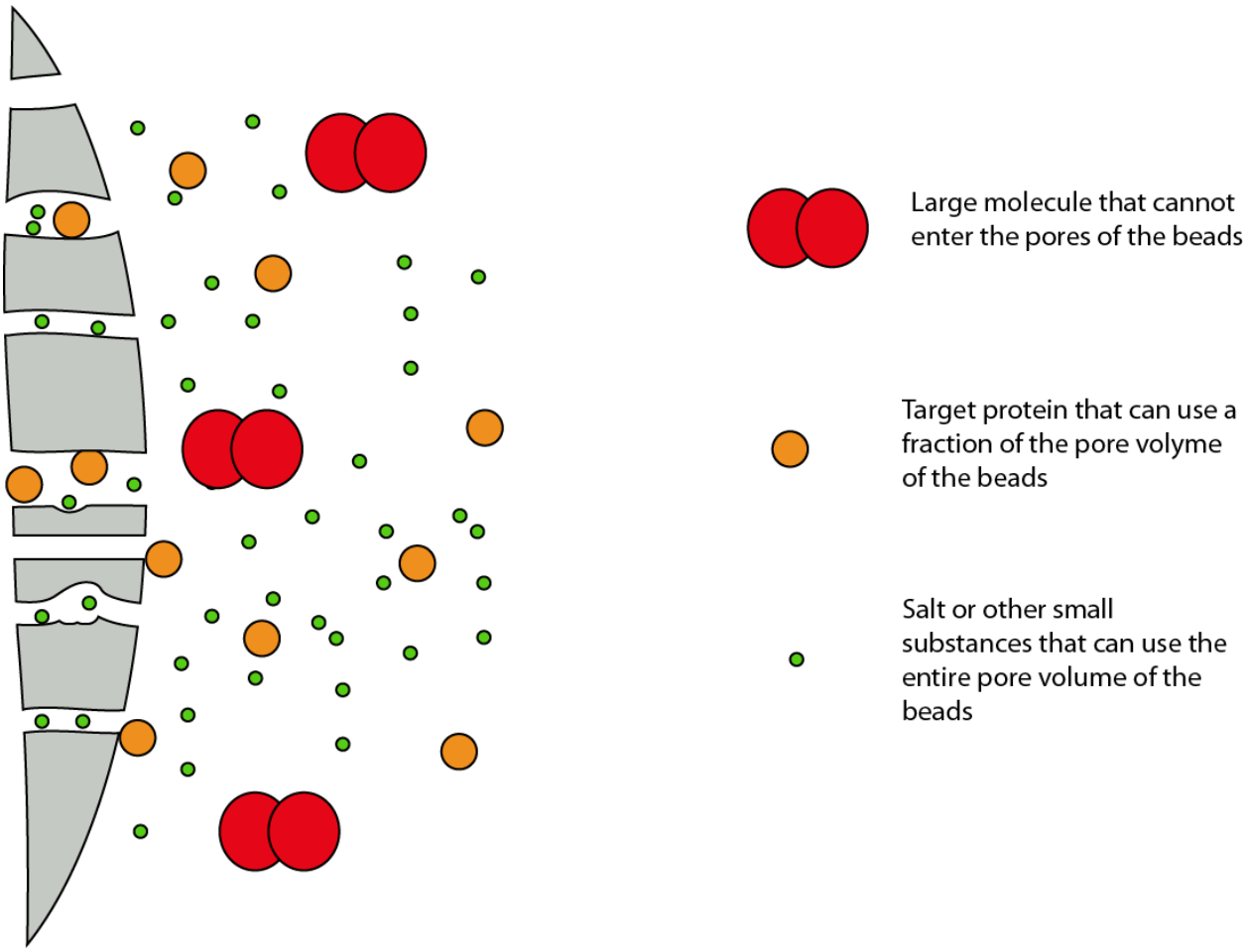

Figure I. Larger molecules (red) cannot enter the pores and thus travels faster down the column compared to the smallest molecules (yellow). They will enter the pores and travels a longer distance, making them elute last. Mid-sized molecules (orange), use some of the pores and will therefore elute in the time range between the largest and the smallest molecules. Figure inspired by Strategies for Protein Purification – Handbook, GE Healthcare 2010.

SEC is often used as a so called *polishing step*, which means that the last step in a purification series is done using SEC to obtain the highest purity possible. Sometimes several polishing steps can be conducted if the product needs to be really pure, such as in pharmaceuticals.

Separation using SEC is dependent on the amount of time the molecules spend in the column, thus making the length of the columns vital for the resolution gained during the separation. This is not the case using other chromatography techniques that have ligands on their surface to perform the separation.

2. Ion Exchange Chromatography

Ion exchange chromatography (IEC) separates molecules based on surface charge, see figure II. Most molecules have a positive or negative surface charge and get attracted to a ligand on the matrix with opposite charge.

Depending on the net charge of the target molecule there are two different ligands to choose from, either a positively charged anion exchanger or a negatively charged cation exchanger (Duong-Ly *et al*. 2014, GE Healthcare (2010)). Molecules with opposite charge compared to the ligand will interact with the matrix and thus bind to the matrix while the molecules with the same or no charge will flow through.

IEC have a high loading capacity, for example compared to SEC, because the interaction between ligand and molecule is strong and fast and when all ligands are occupied by molecules the other molecules will just be eluted. An analogy is a full bus, when all seats are taken no more can have a seat. When the column is loaded the liquid phase is changed having a different pH and thus changing the interaction between molecule-ligand resulting in the elution of the target molecules.

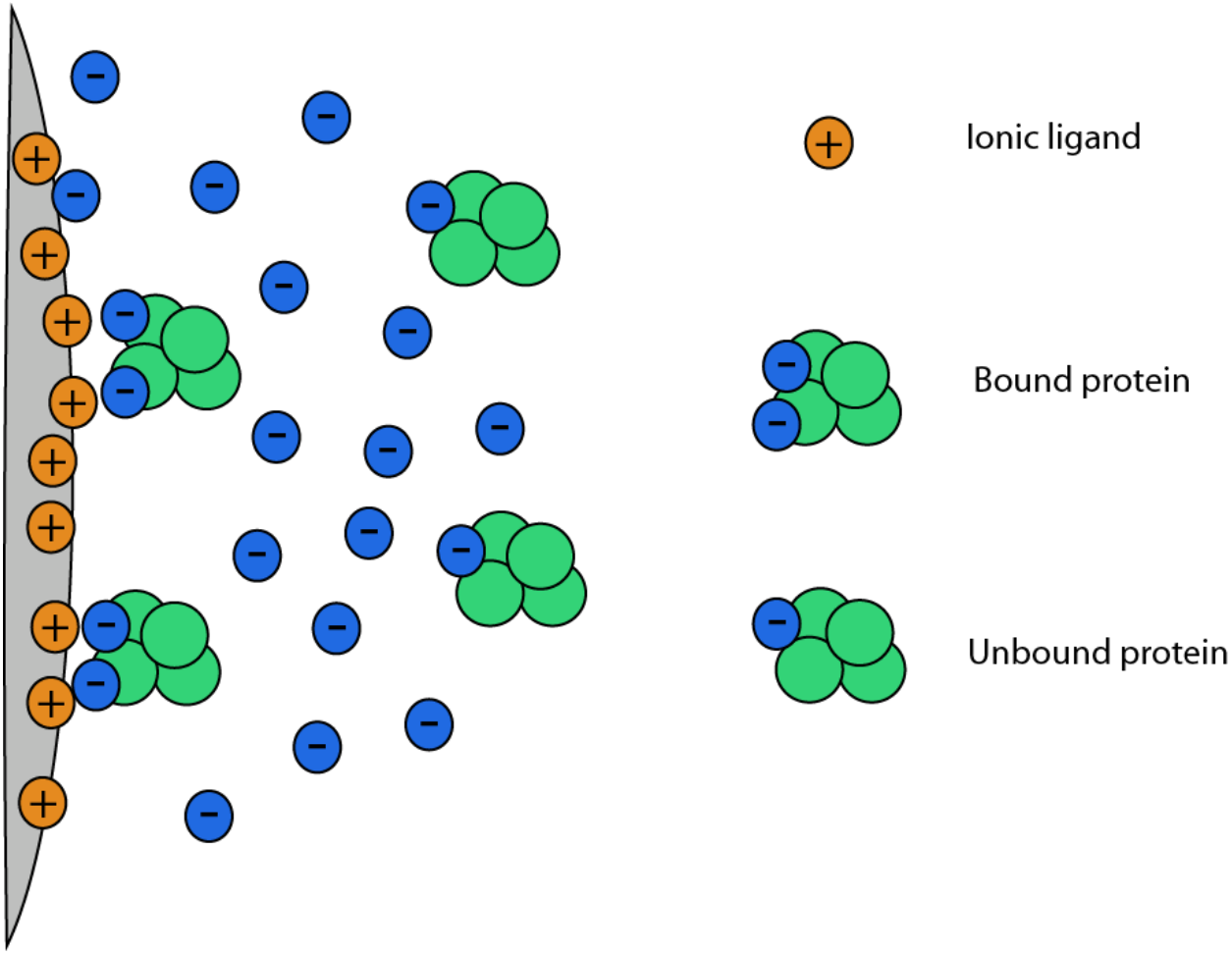

Figure II. An anion exchanger where target protein (green) interact with the ligand to let unwanted proteins and molecules flow down the column. Figure inspired by Strategies for Protein Purification – Handbook, GE Healthcare 2010.27

3. Affinity Chromatography

Affinity chromatography is a technique based on reversible and specific bindings, where the binding often is found in biological interactions, see figure III. The interaction occurs between a ligand attached to the matrix and the target molecule (Hage *et al*. 2015). As with IEC the target molecules are immobilised to the matrix and eluted by changing the liquid phase to change the binding conditions. Affinity chromatography is often used as a first step in a separation and often needs a polishing step afterwards if no impurities are tolerated (GE Healthcare, (2010)).

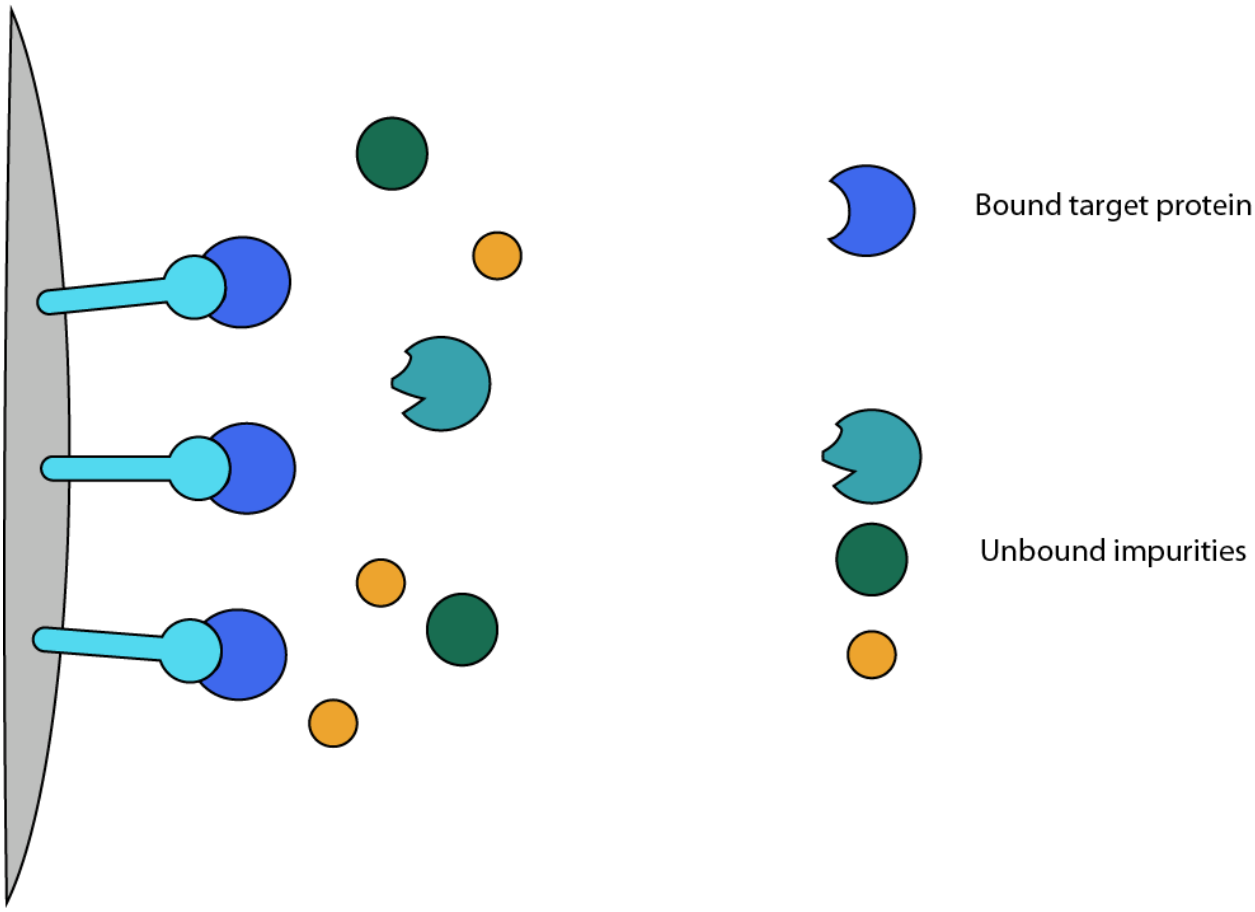

Figure III. Very specific binding of target protein by using affinity chromatography where impurities are eluted out of the column. Figure inspired by Strategies for Protein Purification, GE Healthcare 2010.

4. Immobilised Metal Ion Affinity

Immobilised metal ion affinity chromatography (IMAC), separates molecules based on affinity. The interaction between electron donor groups on surface proteins such as cysteine, histidine and tryptophan, and the immobilised metal ion in the matrix (often Zn(II), Cu(II), Ni (II), and Co(II)) will facilitate the separation (Porath *et al*. 1975). The interaction can form specific complexes which makes IMAC very specific (Chi Fai Cheung *et al*. 2012).

5. Hydrophobic interaction chromatography

Proteins have polar and non-polar regions as well as hydrophobic and hydrophilic regions. Hydrophobic interaction chromatography (HIC) uses the interaction between the non-polar hydrophobic characteristics in some proteins and the immobilized ligands in the chromatography matrix for separation, see figure IV. The separation is controlled by the salt concentration in the liquid phase and determines the adsorption strength (Queiroz *et al*. 2001), meaning that proteins gets eluted by decreasing salt concentration that lower the adsorption for the ligands.

HIC is often used for purification of biological macromolecules according Lienqueo (2007) and is gentle on biological molecules compared to other chromatographic techniques (Queiroz *et al*. 2001).

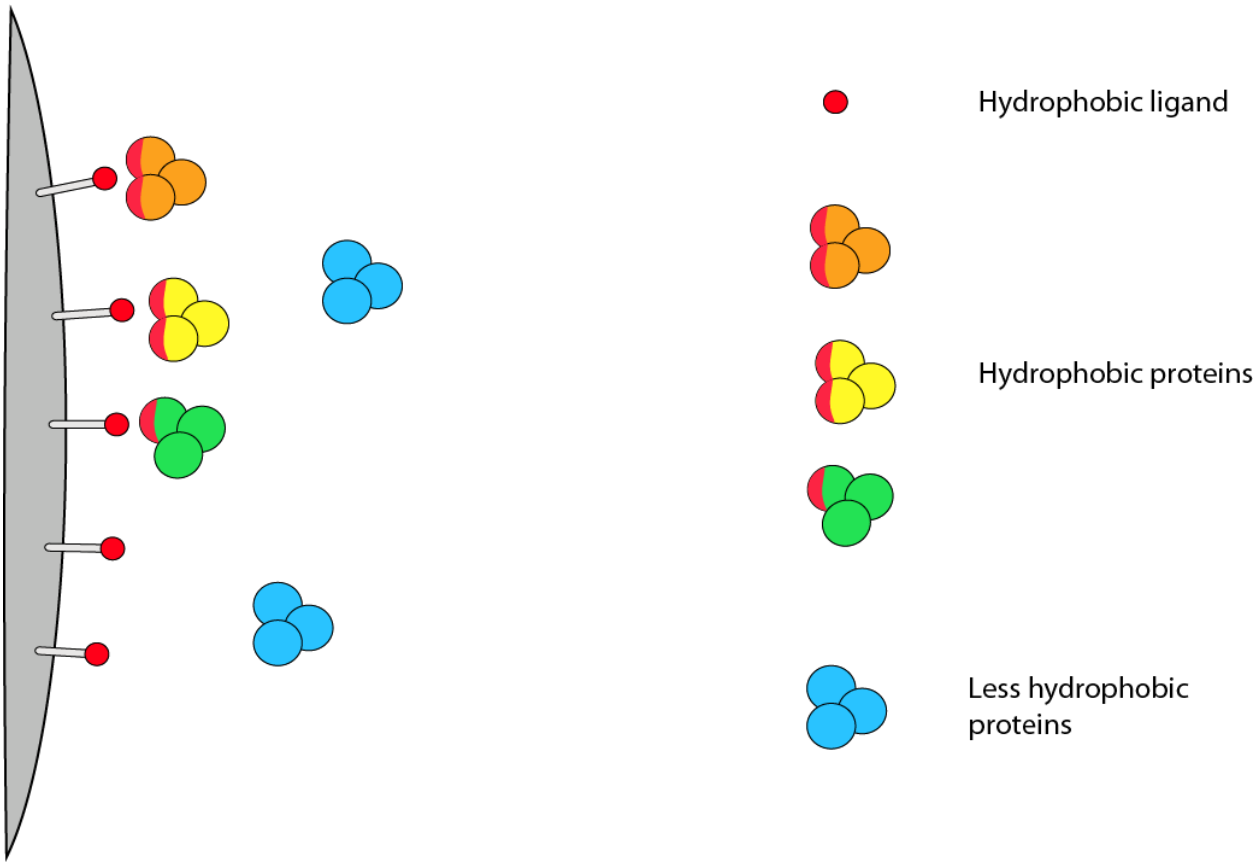

Figure IV. Specific binding of target protein by using hydrophobic interaction chromatography where impurities are eluted out of the column. Figure inspired by Strategies for Protein Purification, GE Healthcare 2010.