



# UPPSALA UNIVERSITET

*DYNAMICS OF UNIVERSITY- COMPANY RELATIONSHIPS IN THE LIFE SCIENCE  
INDUSTRY*

*--- CASE STUDIES FROM GE HEALTHCARE, DOXA & ASTRA ZENECA, SWEDEN*

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## ***TABLE OF CONTENTS***

1. Introduction	4
1.1 University-Company & Company-company relationships	5
1.2 Scenario in the Life Science Industry	6
1.3 Industry Science Links	6
1.4 Early years of Biotech & Pharmaceutical Industry	7
1.5 Social Benefits	8
1.6 Benefits for the University	8
1.7 Benefits for the Company	9
1.8 Disadvantages of University-Company relationships	10
1.9 Long Tradition of working together	11
2. Aim of the Study	12
3. Research Methodology	14
3.1 Procedure	15
4. Case Study	19
4.1 BIACORE Technology from GE Healthcare	20
4.1.1 Impact of Biosensors on Life Science research	20
4.1.2 Background and Rationale behind Biacore	21
4.1.3 The Technology behind Biacore Systems	22
University's role in the following:	
4.1.4 The timing	23
4.1.5 Physics Basics of the Technology	23
4.1.6 Surface Chemistry	24
4.1.7 Detection	27
4.1.8 Sample Handling	27
4.1.9 Assays and Methodology	27
4.1.10 Applications and testing	28
4.1.11 Business Aspects	29
4.1.12 Recent developments and future outlook	31
4.2 Case Study 2- Ceramir® Crown & Bridge ( DOXA AB)	32
4.2.1 Evolution of Bioceramics as a successful Dental Solution	32
4.2.2 Background behind CERAMIR®- DOXA's Core competence	33

4.2.3 Technology behind CERAMIR	34
4.2.4 Materials for Dental Problems	35
4.2.5 Nanostructures integrating CERAMIR®C&B	36
4.2.6 Physical and Sealing Properties	37
4.2.7 Optimal sealing	37
4.2.8 Surface chemistry	38
4.2.9 Assessing the Clinical Performance and Applications	38
4.2.10 Market opportunities & future outlook	39
4.3 Case study 3- Amyloid detection in Alzheimer’s disease in cooperation with KI	41
4.3.1 AD- The major cause of Dementia	41
4.3.2 Purpose of the experiment	41
4.3.3 University’s role in clinical performance analysis	41
4.3.4 Method development- KI & ASTRA ZENECA collaboration	42
5. Results & Discussion	44
5.1 Cross case comparison of the 3 cases	47
6. Conclusion	51
7. Acknowledgements	52
8. References	53
9. Appendix- Interview guide	60

## *1. INTRODUCTION*

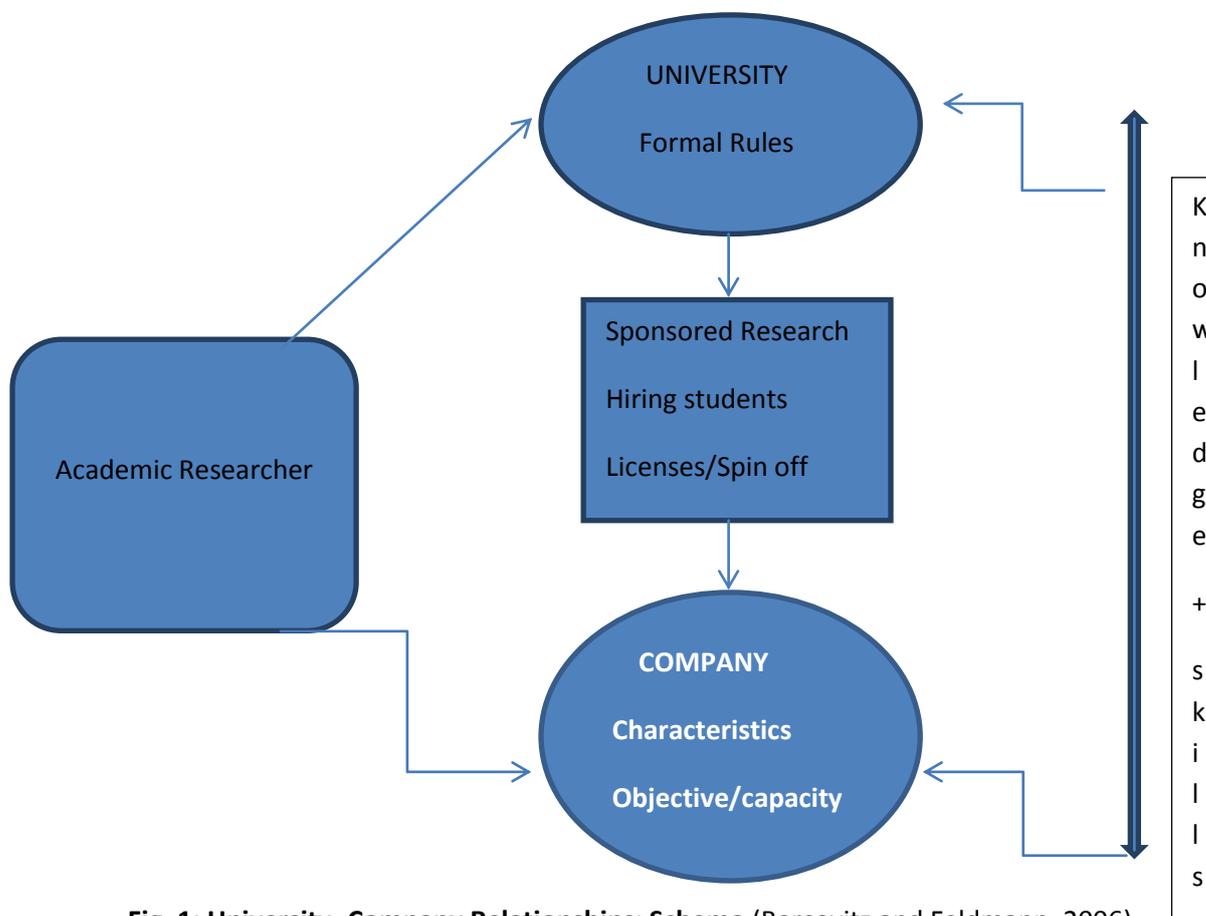
This section is an introduction to the main focus of my thesis- the three case studies: BIACORE, BIOCERAMIR and Drug development for Dementia detection in Alzheimer's disease. The entire thesis revolves around the university- company relationships in the evolution of these three technologies. This section in particular provides a brief description of the current scenario of university- company relationships in the present life science industry, the various ways in which they collaborate over projects in the section Industry- Science links. In this section, I also discuss the social benefits of university-company relationships to specific benefits for the university and the company in this working relationship. Finally, it briefly sheds light on the drawbacks of university-company relationships.

The basic technology underlying the entire Life science industry has its roots in the University laboratories and research institutions. The intellectual origin of the Life Science industry dates back to the time from when DNA was first mapped by Watson and Crick. From then on, universities have played a crucial role in the emergence of Life Science industry not only as a place for educating scientists but also as the main inventors of breakthrough techniques which have fostered scientific and technological innovation. The science and technology behind the development of Life Science Industry are inextricably intertwined with the diffusion of knowledge from the University (Geuna, 1998, pp. 5–6). In any discussion on the production and diffusion of knowledge into the society, universities figure prominently since they have served long as a source of technology advances for the life-science industry (Baldwin, and Green, 1984–1985). Innovations in the life science industry, especially in the three main sectors representing Life science industry- Pharmaceuticals, Medical technology and Biotechnology are getting increasingly dependent on the Triple Helix of university- industry- government interactions. In a knowledge- based economy, the universities are seen as the generator of knowledge and are extremely important to innovation, as their role becomes significantly important in the creation of new products. The next key actor is industry where the knowledge created in the university is implemented in the form of innovative products, and the government being the third actor, is the source of contractual relations maintaining the stable exchange of knowledge between the university and industry ( Etzkowitz, 2008).

## 1.1 UNIVERSITY-COMPANY & COMPANY-COMPANY RELATIONSHIPS

University-Firm relationships are considered to be different from the traditional relationships between companies like- strategic partnerships for the development of a technology, mergers, acquisitions, competitor and complementor and consulting agreements with other companies. The key reasons of the difference in University-Company relationship as compared to company-company relationships are –

- Technology and knowledge generated from the academic sector is often novel compared to the knowledge generated from other sources like customers and external consultants. (Rosenberg and Nelson, 1994) Differences in fundamental approach towards knowledge diffusion (Bierly III and Daly, 2007; Jensen and Thursby, 2001)
- The difference in time-orientation. While universities take long term projects being more oriented towards perfection in research, firms require faster results. Commercial viability being the focus of a project
- Differences in research culture and organizational structure. The research objectives are more profit oriented in companies in comparison to the University.



**Fig. 1: University- Company Relationships: Schema** (Bercovitz and Feldmann, 2006)

## ***1.2 SCENARIO IN THE LIFE SCIENCE INDUSTRY***

The life science industry could be the best example of a sector where foundational scientific and technical knowledge have originated from universities. From there, the breakthroughs with significant commercial potential attract industry investment in university research. In many interviews, life science firms have reported that firm sponsorship of University projects and collaboration research is usually done with two main objectives:

- Firstly, to tap the technical expertise from academicians, this in turn effectively enhances the technological vitality of the company.
- Secondly, promote experimentation to investigate new research possibilities and directions with a profit objective (March, 1991; Levinthal and March, 1993)

In addition to these objectives, University-firm relationships are also characterized by different levels of on-going involvement from each side. When a firm considers a university as its R&D partner, it may involve a single collaboration project, producing ‘ready to use’ results or a long-term and deep relationship as a part of its R&D strategy. Depending upon the research target of the company, the type and content of interaction differs. A few companies invest a significant amount of their R&D budget in university projects but since their resources are spread over many research groups, the nature of their relationship with the particular University becomes more than just the single business relationship for the project (Von Hippel, 1998; March, 1991; Cockburn and Henderson, 1994; Rosenkopf and Nerkar, 2001). During the course of working together with the University, the firm may engage in several activities like hiring Master students for short term projects, hiring graduate students, creating multiple sponsored research projects in the University for their Benefit, establishing strong ties to faculty member in the department of their interest, sponsoring open ended projects, licensing inventions. ( Allen, 1977 or Matkin, 1990)

## ***1.3 INDUSTRY-SCIENCE LINKS***

Industry-Science Links for the exchange of knowledge and technology between University and Companies fall in one of the following formal forms. (Allen, 1977 or Matkin, 1990)

- ***Collaborative research***

In this case, the University and the company define together, the research goals. Further, R&D projects are jointly conducted on bi-later basis or involving a research consortium.

- ***Start- up enterprise***

Technology oriented enterprises are created by the researchers from the science base at the university

- ***Contract research***

University and company conduct research based on a formal contract. This may also include consulting on technical-know how by the company

- ***Co-operation*** in educational activities like training for staff, exchange of research staff between the University and Company, joint employment of researchers, industrial graduate programs

- ***IPR as an indication of technology competence***

Universities consider the development of Intellectual Property Rights as an indication of their technology competence and for serving as the main base for licensing their technology to companies. The IPRs are to protect their technology, design topologies, databases and rights on research materials ( eg. Tissue bank, gene banks) ( Allen, 1977 or Matkin, 1990) . When a company cooperates with a university for the research and development of its technology, both have some percentage of ownership on the technology's IPR and the ownership of the research is protected by both of the cooperating partners. In case the university owns the design or the method behind the experiment or the product, the cooperating company will have the first right to refuse if the university decides to license its technology to any other company for the development of a different product based on the same technology thus providing the company an edge over its competitors in the market.

#### ***1.4 EARLY YEARS OF DEVELOPMENT- BIOTECHNOLOGY AND PHARMACEUTICAL INDUSTRY***

During the early 1970s, even the globally established pharmaceutical companies remained in sidelines. The pharmaceutical industry was already in a highly profitable situation and this is when, the biotech industry was emerging, as a competence-destroying innovation since it was built on a different science base ( more on molecular biology and immunology) and was significantly different from the knowledge base ( clinical applications of organic chemistry) of the more stable pharmaceutical industry. This is when, the Life Science Industry as a whole assumed an organizational model with an open architecture with the key elements provided by

‘external sources’ and major projects were done jointly with external collaborators. During the beginning stages, most of the Life Science firms were started by scientists from the university partly due to the industry’s closeness to fundamental science. This was the time when the universities were also facing tight financial situation, difficulties in patenting and when the existing sources of research funding were becoming stagnant so universities started providing incentives to firms to develop their technology. (Howell et al. (1998), Meyer-Krahmer and Schmock, 1998 and D’Este et al, 2005) These conditions led to a re shaping of the traditional working relationships between professors and private companies altering the R&D opportunities for budding scientists and the new identity, scientist-entrepreneur emerged.

### ***1.5 SOCIAL BENEFITS OF UNIVERSITY- COMPANY PARTNERSHIPS***

The result of Industry sponsored university research is the development of innovative products with practical applications which benefit the society. The new improved medical devices, therapies and techniques, efficient biosensor equipment and affinity study equipment not only benefit many sectors of life science like immunology, protein biotechnology and molecular medicine studies. Apart from this, University-Company partnerships in a country also place it at a competitive advantage over other countries. Along with the increase in employment rates, the local, federal and state tax bases also expand with the growth of Industries. These are just a few advantages and social promises of University-company relationships.

### ***1.6 BENEFITS FOR THE UNIVERSITY***

From the university’s side, the benefits of interactions with life science companies are usually planned out before a partnership (Howell et al., 1998; Meyer-Krahmer and Schmock 1998 and D’Este et al. 2005). There are several reasons why a university seeks industrial partnerships. Firstly, some universities develop a working relationship with Life Science Companies for potential financial returns on patents and licenses from commercialization of academic research. The revenues from patents are used by the universities to support activities like teaching mission of the institutions and also as means by which universities decrease the gap in governmental funding.

Secondly, academic researchers also get an access to cutting edge equipment, which is not available in university labs. This access enables the academic researchers to pursue additional research contributing to faculty productivity ultimately leading to attracting additional external funds and increased publications. (Branstetter , 2003 and Verbeek et al. 2002)These advantages enhance the institutional prestige, attract top students, and attract public funding. A third very important factor is a pressure on the Swedish universities from the national government policy right from the 1990s. A government bill passed in 2002 has plays a major role in making the universities a mandatory participant in the national innovation system as a ‘Third Mission’ along with teaching and research ( Baraldi, Lindahl & Severinsson, 2011)

All these factors combine to increase the legitimacy of the institution. Interactions between universities and Firms further enhance future employment opportunities for undergraduate and graduate students through connections.

### ***1.7 BENEFITS FOR THE COMPANY***

Apart from stimulating a company’s internal research and development, researchers from the University help the industrial scientists in identifying current research. This is very useful for the development of useful design of innovative processes ultimately leading to potential products.

University-Company association also enhances the company’s reputation. When researchers from the University and Company coauthor journal articles describing joint research results, companies use it as a public relations tool that add to their prestige. The following are the concrete benefits to the company from University-company relationship (Bercovitz, and Feldman, 2004):

- Access to new ideas
- Building trade secrets leading to new, potentially profitable patents
- Further, when a company sponsors a project in the University and ultimately develops a patent, the company gains the first right of refusal to license the product and technology thus gaining the possibility of becoming first to market certain product in their industry.
- Universities provide lab space to conduct company research

- Medical companies use University-company partnerships to test their devices and emergent techniques
- Pharmaceutical Companies on the other hand gain access to both laboratories for drug testing and University hospitals, which in turn have an access to large number of patients.
- University-company interaction strengthens companies' research and development. University researchers help the company scientists solve concrete technical problems. Often company employees learn new research techniques from their working partners at the university.

### ***1.8 DISADVANTAGES OF UNIVERSITY-COMPANY RELATIONSHIPS***

There are a few significant normative issues related to University-Company relationship. There are situations when the academic researchers get caught between the compelling interests of both the sides because of their relationship with companies which sponsor the research. (Howell et al. 1998, Meyer-Krahmer and Schmock, 1998 and D'Este et al. 2005). Sometimes, they are compelled to approach research and put in their maximum efforts in a project without any regard for its commercial benefits, share their results with peers to be examined and validated.

There may be problems for academic researches to set their own research agenda since they have to work and design research projects in accordance with the need of the University and available funds from the Company. High profile agreements and legal disputes have raised concerns on the issue.

Secondly, ownership issues can also arise between Companies and Universities in research relationships, causing Universities to develop more formal relationships through formal contracts which stipulate data ownership. For example, company contracts stipulating that University researchers will not be able to share research material and results with other academic scientists automatically assume that research results generated from University researchers may contain proprietary information. (Hall, 2001)

Overshadowing certain issues, in general, University-Company relationship in the Life Science Industry have resulted in advantageous and positive effects on the quantity and quality of basic and applied research and this additional research done together by the

Company and university is needed for an accurate assessment and for commercialization of any technology. (Yong Lee, S.)

### ***1.9 LONG TRADITION OF WORKING TOGETHER***

Sweden is a country with a very long tradition in the development of biotech instruments and medical devices. The beginning of this tradition was marked with the development of the Nobel Prize winning Ultracentrifuge technique. Uppsala University Professor Svedberg was the inventor of this technique. The electrophoresis technique is yet another example where Uppsala University Professor Arne Tiselius was instrumental in the development. The noteworthy point here is that Swedish companies Pharmacia Fine Chemicals AB and LKB Produkter AB ( both a part of GE Healthcare now) were responsible for achieving commercialization of these technologies and entertained close relationships with both professors and their research groups at Uppsala University ( S. Löfas, 2008)

In Sweden, close working relationship between academic researchers and scientists in Life Science has been observed from a very long time. This may partly be the reason as to why; most innovations here are novel especially in medical technology and biotech field. (Mansfield, 1998; Cassiman & Veugelers, 2006).

## ***2. AIM OF THE STUDY AND SPECIFIC RESEARCH QUESTIONS***

The three technical areas of biosensors, bioceramics and drug development could be considered as a representation of the entire Life Science Industry as most companies are based on a cutting edge technology from either of these fields. My study is based on three main technologies taken as a representation from each of the three fields of Life Science industry, that is, biotechnology, medical technologies and drugs. These three technologies are:- BIACORE from the area of biosensors ( biotech) in collaboration with Linköping University and Uppsala University, BIOCERAMIR for bioceramics (med tech) in collaboration with Malmö University and Uppsala University and a current experiment of Amyloid detection in Alzheimer's disease developed by Astra Zeneca in collaboration with Karolinska Institutet. These three cases were chosen in specific because each one represents one area from the Life science industry. All three companies are based in Sweden and each technology is a success story in biosensor, bioceramics and drug development areas of Life science research and so taken as are representation to the larger picture of Life science industry in Sweden.

The aim of this thesis is comprised of three specific purposes, to make a detailed technology-centered study of:

- The biological/ surface chemistry, technology aspect of the BIACORE, CERAMIR and Amyloid detection in Alzheimer's disease.
- Determine for each of the three technologies under investigation, the patterns of interaction between the company and university in each phase of technology development- from basic research to testing and commercialization activities, from production to marketing
- Identify the contribution of academic researchers in technology transfer from university to firms during the early phase of development of these technologies.
- Make a cross case comparison from the three cases to determine the levels of interaction between the universities and companies and more importantly to understand how important the universities are placed as cooperating partners from the interview responses of the company representatives in each case study.

The specific research questions addressed during the interview sessions are:

- What are the specific roles of the collaborating university mentioned by the companies in scientific method development for each of the technology discussed in the case studies?
- Considering each technology discussed as a representation to the company's research cooperation with the mentioned university, how important does each of the company place the university in terms of their R& D Cooperation partners?
- How does the geographic proximity of a university to the company make it a preferred research cooperation partner?
- company's weightage to formal and informal contacts for exchanging general and specific knowledge for the development of the technology
- What are the values and effects of this working relationship with the cooperating University to the company?
- What are the barriers perceived by the company in collaborating with the mentioned university?

### ***3. RESEARCH METHODOLOGY***

The purpose of my thesis work is to analyze the dynamics of University- Company relationship in the evolution of technology behind three breakthrough innovations in Life Science Research. Case study methodology was employed to investigate the role of University right through basic research- development- applications testing- trouble shooting- Marketing- Diffusion. The case study methodology was adopted in order to gain a better insight on the role of university/ academic researchers in both, the scientific aspect and industrial aspect of each chosen technology. I chose to adopt this method since it is particularly useful for unraveling a complex issue by adding strength as an empirical inquiry to investigate research questions which already have been researched previously. The case study method provides an advantage over other methods since here the material is collected and analyzed from multiple sources. ( Yin, 1984)

The empirical material was obtained from the following major sources:

- Written documentation on the scientific aspect- the physics, surface chemistry and Biology behind each core technology
- Workshops attended in GE Healthcare, Uppsala and Doxa AB, Uppsala
- Semi structured interviews with the Life- Science relations managers- R&D, and scientists in the company

### ***3.1 PROCEDURE***

People from two categories were chosen in each of the case study:

***Category 1:*** People who could give details on the dynamics of University-Company relationship for the technology in question

***Category 2:*** A researcher suggested from the core management of the company who is actively involved with the applications of the product and can provide an insight to the technical details

In GE Healthcare AB, BIACORE was taken as the core technology representing one research collaboration between GE Healthcare and its University partners in the development of this technology- Linköping University and Uppsala University were considered. In the research group developing this particular product, among the two people interviewed, one was the Vice president- Life Science relations and one researcher suggested by the VP who could provide an insight on the technology aspect of the product. As the technology aspect right through biomolecular interaction, detection, sample handling, surface chemistry, the assay methodology and applications of the product has been discussed in the previous sections based on the empirical material collected through information provided by the company and work sessions and interviews from researchers in the category 2, the semi structured interviews with the VP- Life Science Relations, were more based on open ended questions discussing the dynamics of the company's relationship with their research collaborating partners in the Biacore project.

Likewise, in the case study 2: The Ceramir® Crown & Bridge technology was the core technology exemplifying one research collaboration between DOXA- The mother company of this technology and its University cooperation partners Uppsala University and Malmo University, Sweden. From the group involved in the research and development of this product, the VP- Life Science Relations was interviewed and with his suggestion, the entire research group was interviewed on the technology aspect of the product. The physical sealing properties of the product, its composition, the surface chemistry, clinical performance and applications discussed through the previous sections of technological aspects are covered based on the interviews with the research group and work sessions in DOXA AB, while the more complex issue of the University's role in the development of this technology right

through its origin and the role it is playing now was based on the interview with the VP- Life Science relations.

The case study 3, though has not yet resulted in a commercial drug, the ongoing research is the first, novel technique for the diagnosis of amyloid plaques during the early onset of Alzheimer's disease and a technique that might hopefully result in a drug to cure dementia. The ongoing research collaboration is between Karolinska Institutet and Astra Zeneca, Sweden, was the best example of University- Company relationship, the Life Science Relations Manager and Chief Scientist at Astra Zeneca had mentioned during the interview. For the category 2 interview, a joint employee/ project manager of this experiment was interviewed who had provided an insight to the technical aspects of the experiment and a researcher from the same experiment who could elaborate on the effects and values of their collaboration with Karolinska Institute and KI- University hospital was interviewed.

Each of these interviews lasted for minimum 45 minutes. While most of them were done directly, the follow-up of a few interviews were carried out on telephonic conversations.

The interview sample and details of sessions with technology experts are summarized as follows in table 1 and table 2 below

Interview	Organization	Name	Designation	No. of Interviews
1	DOXA AB	Jesper Lööf	VP- Life Science Relations	2
2	GE Healthcare	Stefan Löfas	VP- Life Science Relations	1
3	GE Healthcare	Lars- Erik Nyström	Project Manager	2
4	Astra Zeneca	Håkan Larsson	VP- Project Manager	1
5	Astra Zeneca	Lars Johansson	Joint employee of Astra Zeneca and KI- Project Manager, Molndal	2
6	Astra Zeneca	Lars Farde	Chief Scientist and Life Science relations	2

			Manager	
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Total: 10

**Table 1: Summary of the Interviews**

Organization	Session	No.
GE Healthcare, Uppsala	BIACORE Demo	4
DOXA, Uppsala	BIOCERAMIR Demo	3

Total: 7

**Table 2: Summary of Technology Demo Session**

The choice of doing a qualitative analysis on 3 case studies each, from each different branch of life science research was inspired from my participation to larger quantitative research on about 600 Life Science companies in Uppsala- Stockholm region of Sweden. This quantitative study is ongoing and directed towards the aim of addressing two important questions:

1. The importance of Swedish Universities as key collaborating partners among life science research companies in Uppsala- Stockholm. Since two leading Swedish Universities- Uppsala University and Karolinska Institutet are located in Uppsala- Stockholm region, the analysis is more oriented more towards the relationship of the companies with these two universities.
2. To analyze from various types of Life science companies, their perception and opinion about the innovation strategies adopted by Swedish Universities in collaboration and commercializing their research

For the quantitative study, a questionnaire with closed ended questions and a few open ended question was formulated to be sent out online to all the companies. The first step being the creation of a database with about 600 companies with their main business areas being one among the following- Pharmaceuticals, Medical devices and diagnostics, equipment for research and production in Life Science research, and IT tool providers for research. The database creation and validation was based on the information given by personnel from each company in the entire list through telephonic and e- mail confirmation.

The questionnaire consists of a total of 44 questions out of which, 28 were related to the company profile and the rest 16 specific to the company's relationship with the UU and KI. Keeping the questionnaire more open and unbiased, the option of mentioning any other

significant collaborating University partner was also provided. For companies choosing both UU and KI as significant collaboration partners, they answer the set of 16 questions twice. Similarly, companies with no relationship at all with Universities answer only 20 questions in the entire questionnaire. The heterogeneity among the respondents in terms of size, phase of the company and core research area were important determinants to get an idea on the specific benefits obtained due to interaction with universities.

Starting from questions about the profile of the company in the first 12 questions, it proceeds on to the importance of geographical location of the company, and then to more complex issues like features, contents, values and effects from both- present and future perspectives. Finally the questionnaire broaches up on the most important area of analysis- the perceived innovation strategy of UU and KI.

The questions were formulated in a way that the respondents were asked to assess an effect or value using a 5 point scale in most questions. The rationale behind each question in the questionnaire was to be able to obtain statistically relevant value to quantitatively measure the Company's perceptions of the University innovation strategy. To make case specific study on the three chosen technologies, the interview guides for the three case studies were to some extent based on the questionnaire.

#### ***4. CASE STUDIES***

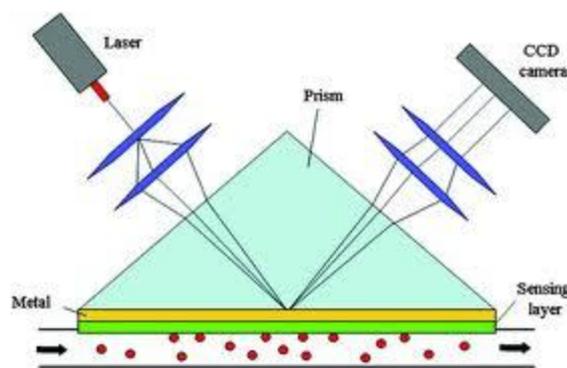
This section is a detailed analysis of three case studies. Three products: BIACORE from GE Healthcare, Ceramir® Crown & Bridge from DOXA, Amyloid detection experiment by Astra Zeneca in collaboration with Karolinska Institutet.

## 4.1 CASE STUDY 1:

### BIACORE TECHNOLOGY FROM GE HEALTHCARE

#### 4.1.1 IMPACT OF BIOSENSOR TECHNOLOGY

**Surface Plasmon Resonance**- The principle by which, the impingement of light beam onto a metal film, at a specific resonance angle causes the surface plasmons to resonate with the light is called Surface Plasmon resonance(Heinz Raether, 1988) This principle is by far, mostly used in the Kretschmann configuration as shown in the figure below.



**Fig.2: Principle of SPR- Kretschmann Configuration** (Heinz Raether (1988))

Liedberg et al. in 1983, suggested the first use of this principle in the field of Biotechnology. Since then, it has been used in various studies asserting its break-through application that developed into the BIACORE product

Since the early 1980s, there has been a tremendous impact of the Biosensor technology on life science research as a whole. There have been significant achievements with

- The formulation of working principles for various applications
- Better commercialization of the biosensor equipment
- A greater understanding of the advantages and limitations of biosensors.

The development of commercial optical biosensor instrument based on the principle of Surface Plasmon resonance by the Swedish Company- Biacore AB, has however stood out as a successful business case among many other failed examples of commercially successful innovations among Biosensors.(Ivarsson et al., 2002)

The label-free technique making real-time interaction analysis possible in the study of protein-protein and biomolecule interaction within drug discovery, academic research in life

science and food analysis has its origin in the mid-1980s when Biacore AB ( formerly, Pharmacia) started its research and technology development. Further breakthroughs in surface chemistry, sample handling with microfluidics system launched the first bioanalytical instrumentation (Myszka et al., 2000) based on the principle of SPR. This technology, later stood to be the inspiration of a series of analytical systems based on the same principle. And a series of improvised versions have been introduced until the recent Biacore 3000, which is a very advanced version of the Biacore 2000 with smaller flow cells, more sensitive with online sample recovery and data subtraction options ( Rich et al., 2000)

Throughout the technology-refinement phase, an innovation to be noted in the existing Biacore system is the additional software support of BIAevaluation 4.1 useful for the transformation of primary data providing a simulation for interaction making computer aided simulations possible.(Myszka, 1998)

About 90% of publications on biosensor commercialization strategies focused on the Biacore instrument in 1998-1999 ( Myszka et al. 2001) In all, the use of SPR technology in Biacore instruments has been a break-through invention in exploring the intricacies of biomolecule interactions, protein-protein, lipids, drug-cofactor interactions.

#### ***4.1.2 BACKGROUND AND RATIONALE BEHIND BIACORE***

Sweden is a country with a long history of academic researchers working with Industrial partners. This tradition of working together to develop instruments, tools and methodology for the life science industry has led to the invention of many Nobel prize winning techniques like the electrophoresis technique invented by Professor Arne Tiselius from Uppsala University. Another academic researcher who was instrumental in the development of the ultracentrifuge was Professor Theodore Svedberg in 1930s.(Rich et al., 2005) these successful technologies were later commercialized by Swedish companies- Pharmacia Fine Chemicals AB and LKB Produkter AB ( Now, a part of GE Healthcare) and are currently designing tools for molecular analysis.

The potential of the Biosensor technology was so apparent from the early 1980s, which led to the founding of a new company called- Pharmacia Biosensor AB by Pharmacia AB only to carry out basic and applied research on Bioanalytical systems. This new identity- Pharmacia Biosensor AB consolidated by Pharmacia AB comprised of a team in which staff were

recruited from the already existing Pharmacia group and students from various research groups from the University. ( Löfas, 2008) This is where, the first collaboration between academic researchers their industrial partners on this case started. Close contacts and good working relations among the academic and industrial community in Sweden sparked the foundation of this company. Professor Ingemar Lundström, in 1970s formed an expert team in Linköping University to initiate a research around detection and clinical analysis. This team also collaborated with the National Defense Research Institute in Sweden who were then researching on technologies for detecting Biological/ Chemical warfare agents.( Liedberg et al., 1983)

The cross-disciplinary team comprising of people from mechanics, electronics, software development, chemistry and Biochemistry, carried out the technology development and design for the instrument based on SPR in the three year time period 1985-1988 with the novel technology breakthrough in surface chemistry and invention of microfluidics based sample handling. Following the application development in which, Linköping University was instrumental, the first product launch happened in 1990. During the phase of product launch, the various business aspects of technology were evaluated resulting in the main focus on development of products for protein and biomolecular interaction analysis studies for the life science research community in industry and academia. The commercial and technical competition in areas of clinical diagnostics were also analyzed.( Liedberg et al., 1983 )

The growing needs to analyze biomolecular interactions were met by the well-timed entry of real-time, label free interaction analysis provided by SPR based instruments. Further, with a revolution in molecular biology in 1980s, efficient tools were designed for antibody formulations, protein mutant variants and for oligonucleotide collections. This revolution triggered the need for quantitative determination of specific functions of these biomolecules in relation to their structural variants. This was effectively met by Biacore's first system- a high quality, versatile tool which could provide reliable, quantifiable information on the parameters like: binding kinetics, affinity and specificity of biomolecules.

#### ***4.1.3 BIACORE SYSTEMS- TECHNOLOGY***

In the early 1980s, Professor Lundström's group was among the pioneers in Sweden, who published their studies on the potential of optical detection systems based on SPR in their publications. The changes in the refractive index near the sensor surface depending upon

changes in mass concentration due to biomolecular interaction is the technology behind the working of Biacore systems.

Professor Lundström's group in Linköping University designed the entire experimental set up- the optimum configuration of SPR detector used in Biacore system aiding reflexivity measurement at an angle halfway below the reflectance minimum. There are many possible configurations used in SPR detectors but the best configuration for accurate measurement used in Biacore system was the brain child of academic researchers in Linköping University. The knowledge contribution by academic research group from the University in creating solutions for limitations in other existing technologies, data acquisition and errors in sensitivity checking was the key to the creation of such a successful system. In particular, the Lundström research group worked on 3 major issues in this technology

- Optical detector design
- Biospecific coating of sensor surface
- Controlled microfluidic cartridge based sample delivery

These were the major innovations in the Biacore system and made this technology stand out as the most successful biosensor case among so many other existing systems.( Myszka., 1998)

#### ***4.1.4 THE TIMING***

The timing of introduction of its first commercial product- BIAcore® was perfect because this was the time when significant investments were made by Pharmacia and Swedish risk capital. Following this, the situation was difficult during the early 1990s with a gradual research focus shift towards genomics. This was the time when research in therapeutics and protein analysis became less and less favored. A situation which existed until a revolution in proteomics study that came about in the late 1990s.

#### ***4.1.5 PHYSICS BASIS OF THE TECHNOLOGY***

There is an occurrence of electron oscillations in a coherent fashion in a certain point at the interface of two materials where a change in the dielectric charges occurs. An interchange of charges (electron delocalization) occurs in some points in a condition where two dielectric surfaces are in contact with each other. It is in these points where the light falling over the

biosensor loses its capacity to reflect and a decrease in the reflection capacity is observed, which can also be observed by changes in image patterns due to refraction (Kittel, 1996)

To understand the physical basis of the technology, it is first important to know what a surface plasmon positron is. When electrons oscillating in a low-energy state couple with a photon, they get to an excited state. And in this excited state, the hybridized form is referred to as surface plasmon positron. For the practical application of the SPR technique, the surface plasmons are triggered to emit positrons in two important configurations- The Otto configuration and Kretschmann configuration. The application of kretschmann configuration was the one first used by Professor Lundström group in Linköping University to suggest the basic design for the Biacore instrument. (Karlsson., 2004 )

#### ***4.1.6 SURFACE CHEMISTRY BEHIND THE TECHNOLOGY***

An exploration of the principles of Surface Chemistry behind the Biacore instruments was done in the department of Analytical Chemistry- Uppsala University. During their initial research for biochemical detection, some potential interaction partner was first tagged on to the metal surface. This experiment initially was not a big success due to the fragile nature of the proteins to denature during adsorption to solid surfaces. The observed alteration to the binding properties was not a favorable outcome of the experiment. To set these drawbacks right, the application testing was carried out as an elaborate process in Uppsala University to come up with a working sensor surface on which any technique of immobilization would work for various types of biomolecules.(Franklin et al., 2004 ) The research on novel methods of surface attachments in the label free technique was a corner stone in the development of Biacore instrument. The research in Uppsala University resulted in

- Decrease in denaturation
- Avoiding non-specific binding
- Covalent coupling of biomolecules made easier in biomolecules due to functional group tagging.

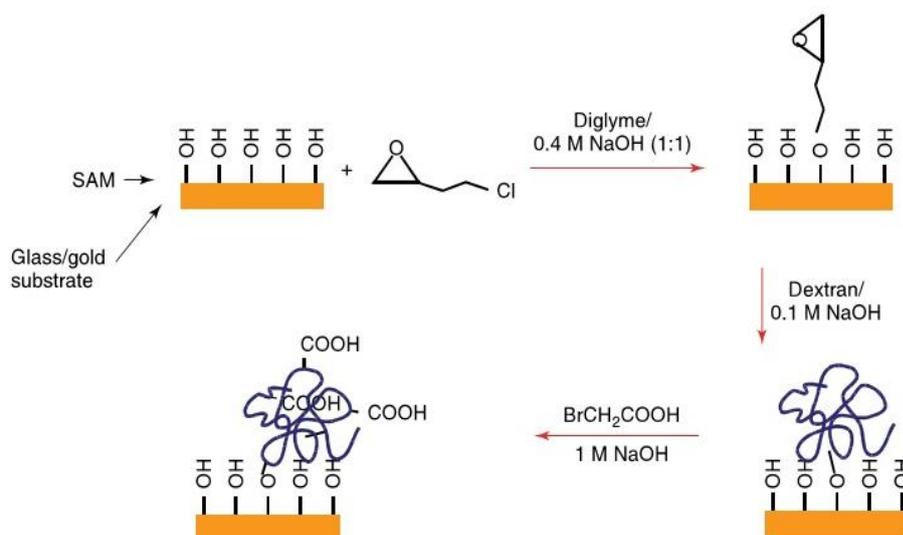
Hydroxyl-terminate thiol alkanes were designed primarily for the formation of Self Assembled Molecular monolayers of disulfide or thiol molecules. The SAM model was initially developed by Allara and Nuzzo for Interface studies. And this layer is responsible for the low absorbing interface, which is further treated with Carboxymethyl dextran for further step wise derivatization. The polymer layer, which is hydrogel- gel like, is mainly made of

unbranched glucose units for better water solubility. The introduction of carboxymethyl group, further activates the step wise immobilization of biomolecules.

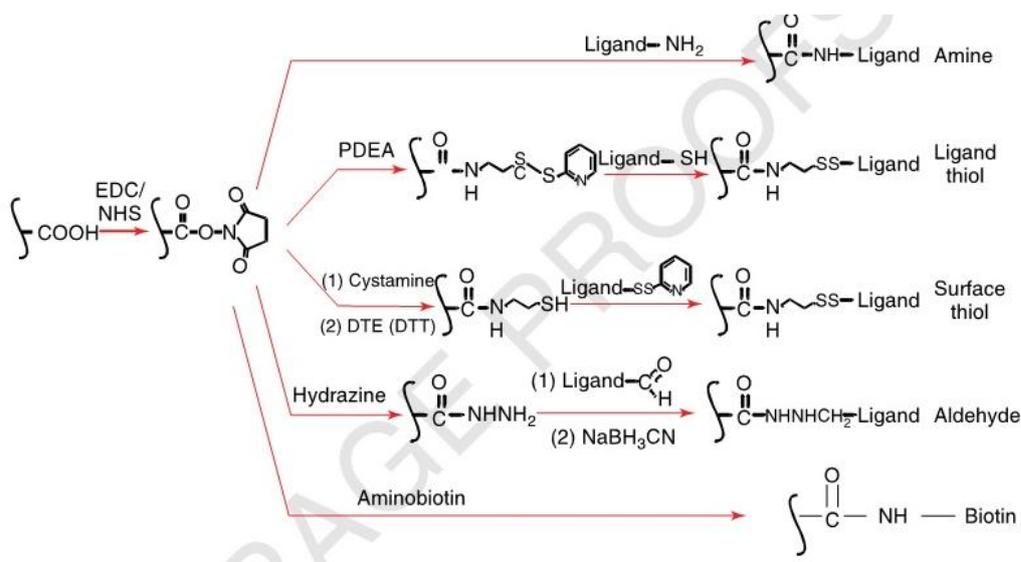
This modification in the initial procedure plays a major role in increasing the efficiency of SPR based technology by the following properties:

- Non- specific protein adsorption made possible due to the hydrophilic environment provided by the hydrogel-gel like environment
- Increase in binding capacity due to the presence of extended polymer structure
- Better covalent immobilization of proteins with dextran

The following figure shows how the carboxylic acid residue in dextran-CM coating can be either directly made to react with amine groups or converted based on thiol reactions, carboxylic acid condensations or in biotin capture reactions. The amine coupling method was first tested in Uppsala University and until now is the most effective and widely used strategy for immobilization in the Biacore instruments (Löfas, 2008)



**Fig.3a: Thiol Reactions** (Löfas,S., 2008)



**Fig.3b: Amine Coupling in BIAcore** (Löfås,S., 2008)

Achieving increased levels of immobilization depends on the electrostatic attraction of proteins to an N-hydroxysuccinimide ester-activated surface on which carboxylic groups remain unreactive. The protein concentrations used here can even be of lesser concentrations than the one used usually and also, the reaction times are shorter than usual. When Small fractions of nucleophilic groups like the unprotonated lysine residues or amino groups are reactive, coupling effects are observed resulting in effective immobilization points, avoiding cross linking activities and preserving the highest activity.(Stenberg et al., 1991)

#### 4.1.7 DETECTION

After effective testing in Linköping University and Uppsala University, it was decided that, the kretschmann configuration would work best with the Biacore system.(Liedberg et al., 1983) The sensor chip was back illuminated through a prism and a diode emitting light was used as the light source. This reflection through a prism results in the formation of a wedge-shaped light beam and a photodetector array was used as the imaging system. The changes in the reflection angle are monitored over time with an increased dynamic range and linearity due to this configuration. In the first commercialized Biacore system, the flow cells were embedded using integrated microfluidics system which required a lot of technical knowledge to handle the instrument. (Löfås., 2004)

But after two years of research by Helena Danielsson group in Uppsala University, an innovative solution was developed to make the handling more user- friendly. Sensor surface embedding a thin gold coating on a separate sensor surface for better resonance interaction

was designed. This research was a great contribution to Biacore technology as a better optical contact between the surface of the prism and the surface of the sensor was achieved creating an efficient optointerface comprised of a coating of an elastomer layer ( with matching refractive index) on a glass substrate. This was a novel and highly innovative improvement in Biacore system (Nuzzo et al., 2009) A collaboration team formed by industrial scientists from Pharmacia Biotechnology and Uppsala University also designed a built-in docking mechanism to facilitate repeatable units of detectors, optointerface, embedded microfluidics and sensor chip in the instrument.

#### ***4.1.8 SAMPLE HANDLING***

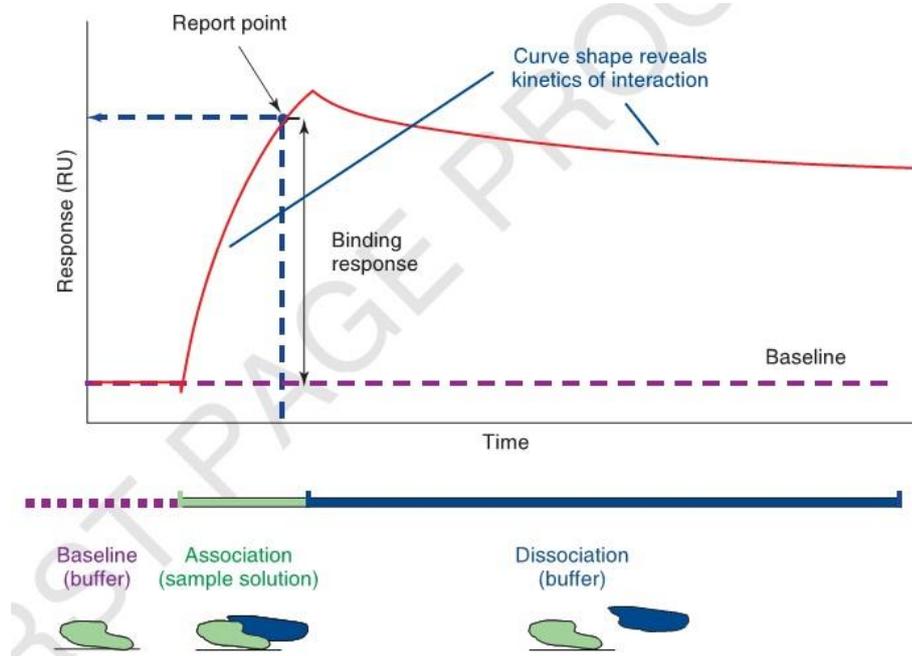
The intended application of Biacore- real time measurement of Kinetic and specificity of Biomolecular interactions triggered the demands of precision, quality, regulated sample delivery amount to the SPR detector's biosensor areas. To fulfill these requirements, a new type of integrated fluidic handling cartridge (IFC) for regulated liquid delivery over sensor surface had to be developed. Flow cells with a dimension of 1.6-mm long, 500-micrometres were built to allow effective mass transfer conditions in a linear flow (Sjölander et al., 2008)

#### ***4.1.9 ASSAYS AND METHODOLOGY***

A new set of terminology was designed to analyse the data output from Biacore systems. The association and dissociation of biomolecules observed during biomolecular interaction was observed and the signals were sent to a sensor chip. These signals are called sensograms. Changes in signals are observed when molecular interactions take place and this generates a response. The responses are measured using an arbitrary unit- RU ( resonance unit). After the observation of responses at specific times (report points), the analyte dissociates from the biosensor surface. And by the injection of a potential binding solution, the already bound analyte is removed. The absolute response is measured and with the removal analyte, the sensor surface is ready to be used for a new cycle of analysis.

In a direct binding assay, it is important to measure how an immobilized interactant binds with an injected analyte. It is easier to measure the parameters like binding kinetics, specificity and affinity. The subsequent verification using sandwich assay and competition based assay were performed as a testing parameter by the group of scientists in the department of Analytical Chemistry in Uppsala University. The competition based assay was developed

to measure the components during food analysis. ([http://www.biacore.com/food/technology/assay\\_principles/following\\_an\\_interaction](http://www.biacore.com/food/technology/assay_principles/following_an_interaction) )



**Fig.4: Binding Kinetics curve of BIACORE** (Löfås,S., 2008)

#### ***4.1.10 APPLICATIONS AND TESTING***

The main reason for the wide acceptance and use of Biacore's technology has been, beyond doubts attributed to its competitive edge over all other existing technologies in the measurement of biomolecular interaction with quantitative kinetics and affinity analysis. The papers published on this technology has been peer reviewed steadily from 1990 and more than 4500 papers until 2005 are based entirely on Biacore instruments. This is seen as a proof of reliability in analysis using the technology. Myszka and collaborators have published the contents of almost all articles on a regular basis underlining the versatility of the technology and projecting it to be a stable and established biophysical tool like certain technologies like mass spectrometry and analytical chromatography- which have been the standard tools since the beginning of analytical measurements in biotechnology.

Among the overabundance of various applications, interaction studies among antibodies were among the earliest and most common target during the launch of the first Biacore systems since monoclonal antibody technology was the a breakthrough technology during the early 1980s (Rich et al., 2005). Antibodies and certain binding biomolecules are seen as potential materials in biomarker research which is a recent demand. The research on humanized

antibodies and its variants has contributed to a great extent in the development of therapeutics research. Research in this area has now reached to an extent that, about 20 antibodies have been given the approval for their use as therapeutic drugs and more than 100 are in the stage of clinical trial. And, Biacore system is the standard instruments for these clinical trials. They are used for the selection of potential antibodies, their optimization by measuring binding kinetics (Johansson et al., 1991)

The unwanted immune responses and adverse effects like immunogenicity is monitored using Biacore technology. Real time monitoring is performed using Biacore systems (Frankin et al., 2004) The efficiency of receiving data is very hard and almost impossible to achieve using certain commonly used techniques like ELISA (enzyme-linked immunosorbent assay).

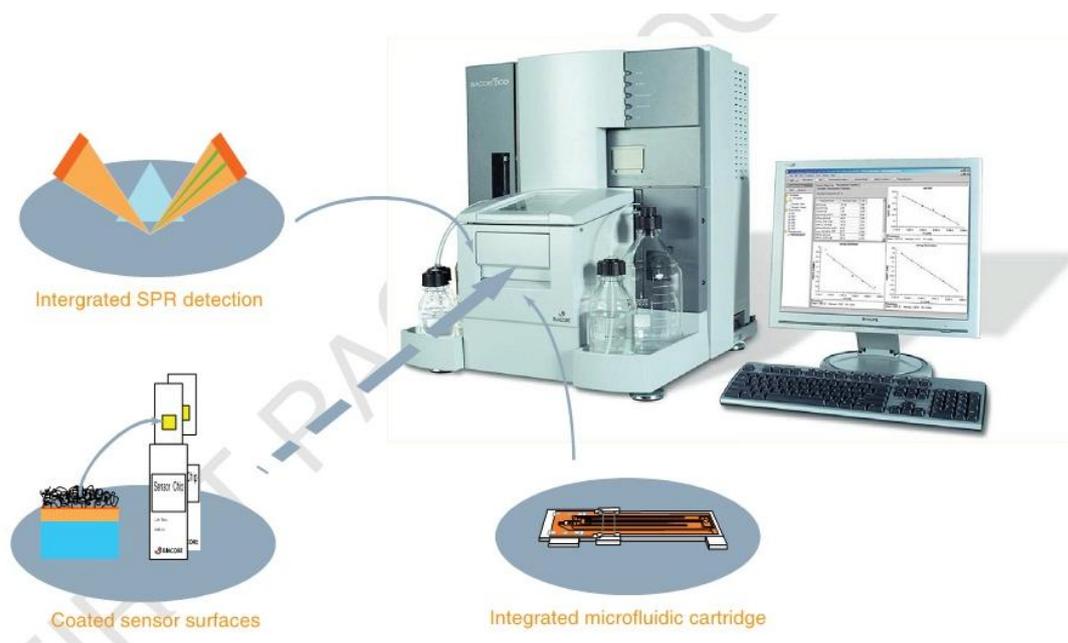
Uppsala University was instrumental in testing the application of Biacore system in various disease areas like- Cancer, neuroscience and infection with an aim to understand cell signaling processes which are important to determine potential therapeutics for Cancer research (Stefan Maier., 2007) This application was developed with the help of analytical chemistry department in UU, where binding properties potential cancer causing agents and substances affecting the interaction of growth factors were measured.

Constant testing the performance of Biacore instruments by industrial scientists and academic researchers has improved the technology over the period of time. Kinetics studies and affinity analysis have opened up new perspectives in the drug discovery area. It has now become a reliable tool for the selection and optimization of potential drug candidate. The potency of a drug candidate is usually measures by measuring its binding affinity and this is directly related to the therapeutic efficacy of the drug candidate. Usually, these components have a very weak affinity to bind to target proteins despite being potential candidates for therapeutic drugs. With the advent of new approaches to drug screening like fragment-screening library, Biacore system is the only analytical technique to detect transient bindings even in traces of millimolar ranges. This technique was developed and tested by Prof. Helena Danielson's Biochemistry research group in Uppsala University (Löfas., 2004)

#### ***4.4.11 BUSINESS ASPECTS***

The first commercial Biacore system was launched in 1990. soon after its launch, Biacore AB had established its own marketing organization in the US and European Market. This was made possible through contacts and recruitment of people from its sister company- Pharmacia

who already had a well- established customer base and a good insight on the present and future needs of a company with an emerging technology. Using Pharmacia's collaborators and distributors in Japan and certain other parts of Asia, an introduction to the basics of this technology were established. During the early phase of sales and marketing, this technology was suggested to research in limited areas like antibody research but the early users took the risk in testing the application in wider areas of research. The first symposium- Biasymposium was conducted in London in 1991 followed by similar events in the US, Japan and European counterparts. As a preliminary step towards promoting the technology, users were encouraged to present their research findings using Biacore technology and a platform for interaction between potential buyers, other users and experts involved in the development of this technology from academia and the industry was created (Rich et al., 2000)



**Fig.5: Latest BIACORE system** (Löfås,S., 2008)

Academic researchers from Linköping University and Uppsala University were invited to attend the interaction sessions to give the markets a better picture of Biacore's application. And with these initial efforts, the sales has increased to an annual revenue of around 600-700 million SEK. Besides the sale of the entire instrument, consumables like the reagents, biosensor chips also generate a significant percentage of sales (Rich et al., 2002)

Publishing papers with academic researchers from Linköping University and Uppsala University had become a very successful marketing tool during 2006, when more than 4500 peer-reviewed publications were observed with a list that covered a plethora of applications of the Biacore technology in diverse fields. From the initial use of this technology in studying protein and small biomolecular interaction in the academia, the technology was exploited in the downstream processing and applications in drug discovery research. The diffusion was further observed in food research for determining the concentration of various vitamins in food. Developments of kits for a range of vitamins notably, the B- Vitamin like the folic acid, biotin; drug residues like beta lactams and clenabuterol were a breakthrough in Life Science research

([http://www.biacore.com/food/technology/assay\\_principles/following\\_an\\_interaction](http://www.biacore.com/food/technology/assay_principles/following_an_interaction))

#### ***4.1.12 RECENT DEVELOPMENT AND FUTURE OUTLOOK***

Since the introduction of the first Biacore system in 1990, the technology underlying has seen a constant, ever- increasing improvement. While the first instrument was used to measure the interactions of proteins and peptides more than 5000 Da, the recent ones, Biacore T100 ( introduced in 2005) can readily detect the interaction of biomolecules weighing only 100 Da. Millimolar and Picomolar measurements are now very common. The T100 instrument is simply a thermodynamics wizard that runs large scale experiments with automated energy parameter- control and detects temperature changes in no time. (<http://www.biacore.com/lifesciences/research> )

It has come a long way from data analysis on the first Biacore system to the advanced instrument used today. Today the technology is centrally accepted as a significant biophysical tool in the characterization of biomolecular interaction. With the research for high – through put, configuration of assay and data analysis from Uppsala University, it is likely to maintain its position in the market as a global leader in measuring biomolecular interaction. Proteomics is likely to be the next exciting research area for drug discovery in the coming decade and Biacore is expected to contribute well to the key biomedical research in this phase.

## **4.2 CASE STUDY 2**

### ***CERAMIR® CROWN & BRIDGE TECHNOLOGY FROM DOXA***

#### **4.2.1 EVOLUTION OF BIOCERAMICS AS AN EFFECTIVE DENTAL SOLUTION**

As a part of increasing importance of biomaterials in the world of medical devices, bioceramics has found its niche in dentistry, orthopedics- the main areas of medical, dental applications. The manmade, non-metallic, inorganic, bio compatible material refined with the heat treatment, sintering process is called 'bio ceramics' (Livage et al., 1988). The crystalline materials like hydroxyapatite, zirconia and non- crystalline materials like bioactive glasses are also essential components of bioceramics used in dental replacements. The term bioceramics is constantly applied in the bone, joints or teeth replacements or in the repair of any component of the human skeletal system (Doeuff et al., 1986)

Early applications of bioceramics can be seen in the field of orthopedics for joint replacements in the 1920s using tricalcium phosphates as the biomaterial to aid bone repair gaps. This was later developed with alumina substitutions and partially stabilized zirconia (Faris et al., 2006). The use of higher strength bioceramics in medicine began in 1975. This was the era from when the focus was on the production of extremely small, grain sized raw materials with perfection using heat treatment and sintering procedures (Löf et al., 2004). The remarkably improved versions with better mechanical properties were made with heat treatment processes. The achievement of higher purity, porosity and minimal defect sizes gradually led to the use of the new-perfected biomaterials in dentistry. Their special property of being resorbable lattices- a property due to which, they are dissolved as a part of the body during the tissue- rebuilding process of body instead of being antigenic (Gregg et al., 1982).

In the recent past, there has been a greater rush to dental implant treatments in most cases of premature, permanent tooth damage. And good endodontic treatment is the key to restorative dentistry. The use of bioceramics in dentistry is one major cause leading specialists to produce excellent results in replacement endodontic (Dubok et al., 2000). This advancement in endodontic material science has been rapid especially in the past decade. This improvement in material science has created simpler and effective solution for dental problems (Best et al., 2008).

One question to be asked time and again is- *What are the major advantages of biomaterials in dentistry?*

The key to this question is using the natural tooth as the base and building block on which the bioceramic can be embedded. Apart from being bioinert, bioactive, biodegradable and resorbable, they do not shrink and are chemically stable in most ranges of biological environment. Even during an excessive use during filling or replacement process, bioceramics do not cause an inflammatory response. These properties make bioceramics an excellent complement in dentistry. And from a clinical perspective, the ability to infuse anti bacterial property, enhance biocompatibility, PH stability and ease of use make them an excellent choice (Engqvist et al., 2005 )

#### **4.2.2 BACKGROUND BEHIND CERAMIR®- DOXA's CORE COMPETENCE**



**Fig. 6: latest CERAMIR® Crown & Bridge kit (www.doxa.se)**

The above figure depicts the latest CERAMIR® kit.

CERAMIR® Crown & Bridge is a revolutionary bio ceramic dental luting cement developed by DOXA Dental AB, Sweden- the parent company of DOXA Dental Inc., setting the golden standard for cementation processes like crowns and partial dentures, inlays, prefabricated cast dowels, onlays and high strength ceramics in full-zirconia and alumina crown replacements.

Year	Breaking news
1987	DOXA was founded.
1999	Prototype dental restorative was developed
2000	CE approval of first generation dental restorative.
2001	ISO certification.
2002	FDA approval of dental restorative.
2003	CE approval of second generation dental restorative.
2005	Successfully completed clinical studies of Xeraspine®
2006	Introduction of CERAMIR®
2007	Successful clinical studies with CERAMIR®
2009	Introduction of the dental cement Ceramir® Crown & Bridge in Germany And US. Doxa re-structured from R&D company to a dental marketing and sales company.
2010	New Product Innovation 2010" awarded to Doxa for CERAMIR® by Frost & Sullivan. Exclusive distribution agreement with AB Nordenta .

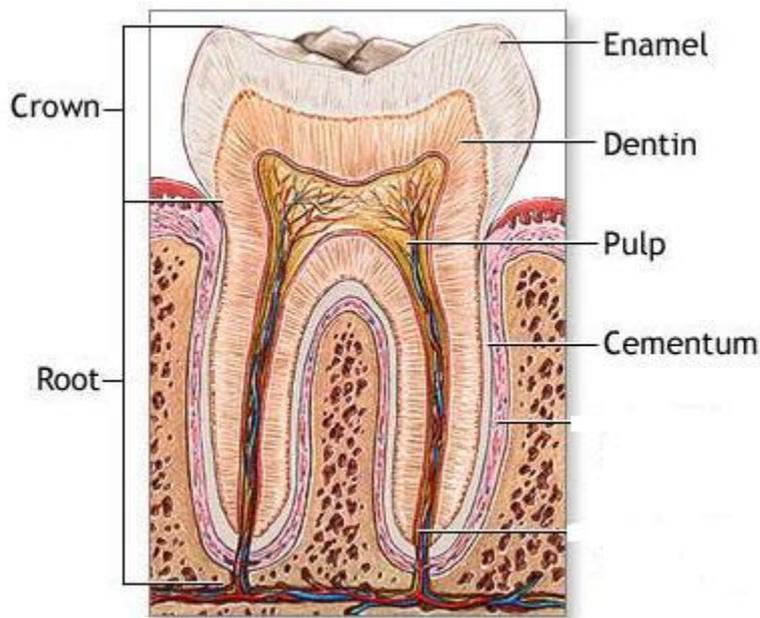
#### ***4.2.3 TECHNOLOGY BEHIND CERAMIR***

The technology used, is well backed by extensive research and clinical trials conducted in the University hospitals of prestigious Universities in Sweden like Uppsala University and Gothenburg Universities. They also have their collaboration partners in Germany and parts of the US (interview by Jesper Lööf )

The company was founded by a professor at Uppsala University- Dr. Leif Hermansson, a professor of Material Science in 1987. During the initial years of founding, the focus was on selling and marketing dental products.(interview by Jesper Lööf) with the current number of 22 employees(interview by Jesper Lööf) and longer investments in research, the company has now started developing bioceramic products. through the years from 2009, after 21 years of founding, the first series of dental ceramic products were out in the market. During initial years of bioceramics use in dentistry, improper sealing was a big disadvantage overcome by the first dental product in Swedish market, CERAMIR® designed by the DOXA AB, faculty of Odontology, Malmö University and the department of Material Science, Uppsala University. During the fall of 2009, DOXA AB signed their 3 year research cooperation in Bioceramics research for clinical and preclinical evaluation of CERAMIR®. Apart from research, the application testing and clinical studies were made at Uppsala University hospital and bioceramics research through projects and doctoral research (interview by Fredrik Alpsten).

#### 4.2.4 MATERIALS FOR DENTAL PROBLEMS

A very common problem in the present world is the dental problem (Coppa, A. 2006). These problems have been ever persistent right through the ages even in the ages of Romans and Egyptians that traces of these cavities are even found in the skulls of people in Neolithic ages.



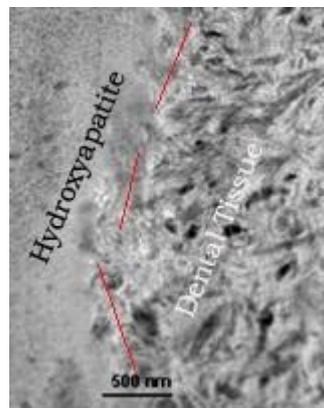
**Fig.7: Tooth in Natural Environment** (Faris, A. 2006)

The constantly changing biological environment of the teeth with respect to the temperature and PH and the constant calcification of dentin around the tissues of teeth pulp make them vulnerable to Streptococcus infection and the Lactobacillus from sugars, glucose and sucrose in food to lactic acid ultimately resulting in demineralization of tooth due to increased acid presence and its decay ( Torabinejad et al.,1992)

Many solutions to dental issues have been used over a period of time like resin based composites, glass ionomer cement, metal alloys and porcelain-metal fused substances.( Hermansson., 2006)

Research headed by Prof. Håkan Engqvist (group head of Materials in Medicine), Angstrom Materials Academy in bioceramic synthesis, nanobioceramic materials in tissue repair and drug delivery methods in Uppsala University has been an important contribution in the development of CERAMIR®. With over 90 research papers, 35 patents and role in Industry-

Academia for Bioceramics research, Prof. Engqvist and his group have been a part of several deals in University- Industry partnerships, acquiring IPR and licensing over the years and he has been instrumental in the founding of 2 companies (<http://www.berzelii.uu.se/index.php?page=personellpresentation>). The suggestions for the use of hydroxyapatite- natural calcium mineral in the bioceramic composition in bone replacement and tooth filling in CERAMIR® was researched on by Leif Hermansson (department of Materials in medicine) and group in Uppsala University before its use in the product by DOXA AB. (Quanzu Yang et al., 2003)



**Fig.8: Hydroxyapatite as a bioceramic in natural Dental Tissue** (Faris, A. 2006)

#### ***4.2.5 NANOSTRUCTURES INTEGRATING CERAMIR® C&B***

CERAMIR® C&B is composed of a proportionate mixture of glass ionomer and apatite. The mixture of apatite and distilled water resulting in a paste of hydroxyapatite and this mixture is applied on the tooth during the crown or bridge replacement process, the crystals already present in this mixture recrystallizes into nano crystal hydrates. Altering the composition of the apatite by mixing it with water resulting in a new mixture slightly alters the physical properties of this new material making it extremely similar to natural teeth (Gregg et al., 1982)

The hydroxyapatite so formed has the new property of integrating and complementing the natural biological tissue. This material also protects the acid attacks from the lactic acid deposition in the mouth during bacterial infections. In CERAMIR®, when the ceramic powder is dissolved in distilled water, hydroxide ions are released increasing the PH and this

high PH makes it resistant to any kind of acid corrosion caused by a bacterial infection (Faris et al., 2006).

#### ***4.2.6 PHYSICAL AND SEALING PROPERTIES***

The main properties in any dental products are:

- Thermal properties like conductivity and expansion
- Tensile strength
- Bio compatibility and bio degradability

The thermal properties of the bio materials are to be considered the most important among all other factors judging the functionality of the bioceramic product. And this thermal property holds the bioceramic material together during sudden changes in the biological environment. But this happens only in an optimal condition. In the absence or change in these optimal conditions, gaps are formed between the material and the tooth in which it is used leading to the failure of the product on market.(Cornelis et al., 2011)

The construction of the material influences the thermal properties of dental bioceramics to a large extent. ( O'Brien 2008). CERAMIR® was designed by the Surface Chemistry department in Uppsala University to mimic natural thermal properties of teeth. The concept of designing a perfect dental restorative product is to have the system very similar to the physical properties of teeth and gums. The thermal stress, and tensile elastic modulus very similar to the natural teeth reduces the pressure of thermal shocks of bioceramics with regular use also reducing the risk of gap formation between the artificial filling and tooth making it an ideal bioceramic material (Cornelis et al., 2011)

#### ***4.2.7 OPTIMAL SEALING***

Dental materials are handled differently by clinicians and the preparative methods adopted by different clinicians involve different procedures to first suspend the biomaterial on the dental tissue. So, the sealing property of biomaterial is very important to prevent any kind of damage to the dental tissues. The hardening property of CERAMIR® was tested in Uppsala University ( Moharamzadeh et al. 2009).

#### ***4.2.8 SURFACE CHEMISTRY***

The attachment of bioceramics on dental tissue happens with certain mechanism. The major types of interactions may be hydrophobic or hydrophilic interactions helping the ceramic to bind with the dental tissue. The dental tissue has a natural tendency to bind in case of hydrophilic interactions but the process of hydrophobic interaction with dental tissue is complex. This is where an intermediate binding material is required which would bind with both the tooth and the bioceramic material in a hydrophilic and hydrophobic interaction respectively. The difference in the type of interaction makes a strong binding possible. General adhesion is the safest and most effective way. Antibacterial properties of CERAMIR® were incorporated by the research carried on by Hakan Engqvist's group in the division of Applied Material Science, Department of Engineering Sciences, Uppsala University (Engqvist et al., 2006).

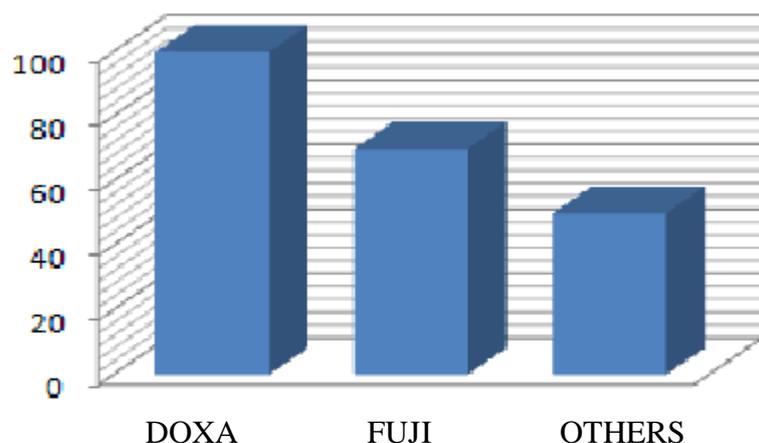
#### ***4.2.9 ASSESSING THE CLINICAL PERFORMANCE***

CERAMIR® C&B was certified and tested as per the ANSI standards (ANSI/ADA#41) for biological and dental material (Pameijer 2009). A major part of the clinical studies were conducted in Uppsala University. Four major clinical studies were performed in UU. Two studies on human primates and the other two for humans. Two types of dental capping were done- a direct capping on the pulp where it comes in contact with the pulp and the other indirect capping where the ceramic does not come in contact with the dental tissue. The hypersensitivity of the pulp was the parameter measured here.

The results from the first clinical studies by Pameijer and in 2004 were used for this study. Initial studies using calcium aluminate as the filling material were used. In these studies, calcium aluminate was used as a filling for bone repair in baboons. There were no signs of inflammation and from then on, calcium aluminate was used as a bio-compatible material. (Jefferies et al., 2009)

Human trials using CERAMIR® C&B were carried out at a much later stage and 2 years results in endodontic studies of 18 patients in which calcium aluminate was found suitable as a retrograde filling material (Kraft et al. 2008). 3 intervals of pre cementation for the effect of x-rays were measured and it was found that in 2 years of study 21 out of 22 healed with no inflammation or hypersensitivity were observed. Similar studies were also performed in glass

ionomers. These studies were successful with almost nil failures and or any hypersensitivity, inflammation or infections.



**Fig.9: Results from first Clinical Trials of CERAMIR®. The graph signifies the satisfaction levels of customers using the Bioceramic products from DOXA, FUJI Dental labs and a few firms from Germany. (www.doxa.se)**

#### ***4.2.10 MARKET OPPORTUNITY AND FUTURE OUTLOOK***

Market opportunity in the field of dentistry is expanding in direct proportion to the competition. Globally, there are about 1 million dentists with individual practices. And small companies like DOXA has adopted the strategy of forming alliance with global distributors like LIFCO ( known as Nordenta in Sweden) for the distribution of sealant and manufactured products like CERAMIR®. about 60 percent of 15- 17 year olds in Sweden have some kind of filling or sealant products in their teeth (Whelton et al. 1998) creating an increasing demand of selant products in the market. The current research in DOXA in collaboration with the Malmo University, is working on the manufacture of sealants with better properties and improvising CERAMIR® as a better sealant. Currently occupying 2.5 percent share in the global market, DOXA is currently is in its research phase for the launch of better sealants by the end of the year- 2012 or early 2013. In addition to the research activities in collaboration with universities in US and Germany, and Uppsala University and Malmo University in Sweden, DOXA is also working on expanding the customer base with a current list of about 100 clinics and 200 dentists with individual practice in Sweden. The expansion of CERAMIR® product in the US and European Continent was implemented right through

March- April 2011 and in a period of next 5 years, it is estimated to grow from the 2.5 percent to 20 percent share in the global market.

CERAMIR® is the only product in the global market which holds a promise for DOXA's global potential in market after being awarded the 'New Product Innovation 2010' by Frost and Sullivan being one of the most innovative and best dental bioceramics.

### **4.3 CASE STUDY 3:**

#### **4.3.1 ALZHEIMER'S DISEASE- THE MAJOR CAUSE OF DEMENTIA**

Over 30 million people in this world are affected with dementia and Alzheimer's disease is one of the major causes of dementia (Wimo et al., 2006). So the first step of detecting dementia is to detect the symptoms of Alzheimer's disease. And this diagnosis is usually done by the identification of beta- amyloid plaques in the intraneuronal neurofibrillary tangles. Therapeutic agents by far are the most effective way of removing the accumulating beta-amyloid deposits (Kunk et al., 2004)

Alzheimer's disease is difficult to diagnose at the early onset but recent developments in radioligands with positron emission tomography (PET) for the detection of amyloid deposition in patients holds promise for better diagnosis even before the onset of symptoms (Jhonson et al., 2009). The first experiment to confirm the suitability of using radioligands for this detection was performed by Astra Zeneca, Södertlje, one of the leading Pharmaceutical companies in collaboration with the PET centre, Department of Clinical Neuroscience, Karolinska University hospital, Sweden.( interview with Håkan Larsson)

This research collaboration has resulted in the development of a very novel technique- the new putative ligand ( AZD 2184- 5-(6{[tert-butyl(dimethyl)silyl]oxy}-1,3-benzothiazol-2-yl)pyridine-2-amine which has a greater affinity towards amyloid fibrils. The reference ligand used for this experiment is [c11] PIB but [c11]AZD2184 has a better affinity to amyloid fibrils than even the reference ligand (Cai et al., 2007)

#### **4.3.2 PURPOSE OF THE EXPERIMENT**

The current radioligands of positron emission tomography (PET) for the detection of beta-amyloid aggregation does not provide enough data for quantification. And the first clinical evaluation to improve the noise ratio levels to signal for quantification was the breakthrough development of radioligand [c11] AZD2184 with clinical evaluation in the PET centre Karolinska University Hospital. (interview with Håkan Larsson)

#### **4.3.3 UNIVERSITY'S ROLE IN CLINICAL PERFORMANCE ANALYSIS**

This study was conducted at the PET Centre, KI- University Hospital with patients of Alzheimer's disease from the Hospital Memory Clinic, Huddinge, Sweden. The study was designed by Dr. Lars Farde, Dr. M.E. Jönhagen in the department of Clinical Neuroscience,

KI. This study was conducted in accordance with the Good Clinical Practice guidelines in the Helsinki International Conference. Two groups of study patients- four females (age range: 55-76) and males (range: 23-36) being the control group with a diagnosis of Alzheimer's Disease symptoms with Mini-Mental State Examination procedure being one. The age of the control group was determined with minimum amyloid pathology (Odano et al., 2009)

#### ***4.3.4 METHOD DEVELOPMENT- KI and ASTRA ZENECA'S COLLABORATION***

The research methodology was developed by Prof. Andersson at the department of Clinical Neuroscience, Karolinska Institutet (Andersson et al., 2009). The production of [C11]AZD2184 was done according to the method proposed by Prof. Andersson and group following the steps:

- Hitting 16.4 MeV protons from the PET trace cyclotron on  $^{14}\text{N}(p,\alpha)^{11}\text{C}$  with Nitrogen and 10% hydrogen, methane was produced  
The methane thus produced, was passed through a column containing Iodine to produce- Methyl Iodide.
- 5-(6-(tert-butyldimethyl-silyloxy)benzo[d]thiazol-2-yl)pyridine-2-amine), potassium hydroxide (10mg)DMSO (300 microlitre), 2.5 mg- precursor with [C11]methane, it was heated with water at again transferred to room temperature for 2 minutes for the formation of [c11]2184. It is further purified with HPLC to purify it from pyrogens.

The methodology of [C11] AZD 2184 production was done through the research collaboration between Astra Zeneca and KI followed by the imaging analysis performed in the University Hospital. (Andersson et al., 2009)

Imaging procedures and signal analysis with the four AD subjects were made in KI. Specific radioactivity and injected radioactivity were studied with the aim of evaluating [11C]AZD2184 for the beta-amyloid deposition in the patients. The contrast between the deposition of amyloid plaques in different regions of the brain were detected from the PET scan. The radioactivity levels were measured across all the regions of the brain. The differences between maximum and minimum contrasts were measured.

Research on complete kinetic analysis is still ongoing but from the current results, high contrast images and their relationship to low, non-specific binding and specific bindings were

observed concluding that AZD2184 is a very promising radioligand for the detection of amyloid depositions in living brain.(Lopresti et al., 2005)

Since this experiment is still in the research stage, Astra Zeneca is currently waiting before starting the product development stage. And the drug to be designed using this detection experiment is one of the on-going collaboration project between Karolinska Institutet and Astra Zeneca's R&D department.( interview by Lars Johansson)

## 5. RESULTS AND DISCUSSION

		BIACORE	BIOCERAMIR	Amyloid detection- PET
1	R&D Cooperation of the company	Customers Suppliers University Private research Institutes Competitors	Customers Competitors Suppliers Private research Institutes/ University and University hospitals	University/University hospitals Private research Institutes Supplier Customers/ competitors
2	Collaborating University Partners	Linköping University Uppsala University	Uppsala University Malmo University Universities in US and Germany	Karolinska Institutet
3	Geographic Proximity to the collaborating University	Not a very important reason for collaboration but there are a few benefits	Very important reason to collaborate	Not at all important for the collaboration
4	Importance of the following as an important factor for the collaboration	Formal Contracts, but research goals are discussed over a period of time	Informal Connections, previous contacts with academic researchers	Formal Contracts with pre-defined research goals
5	Values and Effects of the Selected University relationship	Opening up a new perspective Acquisition of general knowledge Acquisition of specific knowledge Access to unique valuable equipment Solving Concrete technical problem Recruiting qualified	Opening up a new perspective Acquisition of general knowledge Acquisition of specific knowledge Solving Concrete technical problem	Opening up a new perspective Acquisition of general knowledge Acquisition of specific knowledge Access to unique valuable equipment Solving Concrete <b>technical</b> problem Speeding up the company's R&D processes

		<p>personnel</p> <p>Improving the Company's recognition</p> <p>Opening up other relationships with other actors</p> <p>Gaining new customers and sales by using this University as a reference customer</p>		<p>Speeding up market launch of its products</p> <p>Improving other internal processes</p> <p>Recruiting qualified personnel</p> <p>Improving the Company's recognition</p> <p>Opening up other relationships with other actors</p> <p>Gaining new customers and sales by using this University as a reference customer</p>
6	Barriers in developing the relationship	<p>Bureaucracy in the University</p> <p>Time orientation in projects. Short term goals of companies VS. long term projects carried out in University</p>	<p>Bureaucracy in the University</p> <p>Time orientation in projects. Short term goals of companies VS. long term projects carried out in University</p>	<p>Bureaucracy in the University</p> <p>Time orientation in projects. Short term goals of companies VS. long term projects carried out in University</p>

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The interview guide comprised of standard questions for all the three companies. The interview responses from the 3 companies, considering each person interviewed as the representative of the company is summarized in the following tables:

## *5.1 CROSS CASE COMPARISON FROM THE THREE CASES*

The table summarizes the response of Mr. Lars Farde from Astra Zeneca, Mr. Stefan Löfas from GE Healthcare and Mr. Jesper Lööf from DOXA- holding the designation of Vice President- Life Science relations in the respective companies. The main parameters measured through the open ended questions during the interview were:

1. R&D Cooperation of the company
2. Collaborating University partners
3. Geographic proximity of the company to the collaborating University
4. Importance of formal contracts / informal contacts for the exchange of general and specific technical knowledge
5. Values and effects perceived from a working relationship
6. The barriers perceived by the Company in their relationship to the University research partners.

The main symmetry to be observed in all three cases chosen as the case study is that, they are technology-centric. The cases were chosen carefully in order to be able to determine where and what exact role is played by the University in the development of each technology right from the beginning. It is observed that, while the scientific method development has been the main strength of University in each of these cases, the role of Universities was restricted to the early stages of technology research. And, interviews from big companies like GE Healthcare and Astra Zeneca, have not really attributed the technology's success in the market to their University research partners from point of view that it may open up a new perspective in the market or create additional opportunities in expanding their business. In this section, I discuss how important the research groups in each of technologies consider the above parameters to play a role in their relationship with their University research partners. Each of the parameters listed above (1), (2), (3), (4), (5), (6) were questions asked in the interviews with the Vice Presidents of the 3 mother companies of the technologies.

The First parameter- R&D Cooperation of the companies was discussed to gain an insight as to how important each of these three companies would refer to Universities as their main research partners considering the single technology taken as a representation. Here, R& D Cooperation refers to the collaboration between the companies with a partner for the scientific

method design in technology development. If each case study here is considered as a representation to the company's working relationship with the specified University. In this question, the three companies were asked to prioritize the following as their main cooperating partners: customers, suppliers, competitors, university/ university hospital, private research institutes in the order of their priority. From the table, it is evident that while GE Healthcare placed Uppsala University in the third place after customers and suppliers for the development of Biacore, Astra Zeneca ranked Karolinska Institutet to be most important actor in their experiment. Evidently, DOXA ranked their research partner Universities at Germany, USA, Uppsala University and Malmo University in a least significant place among the other actors. From the interview, the VP- DOXA responded to the question quoting that " our relationship with universities is more in the form of buying materials from the University if necessary. Initially, there used to be many collaboration projects, but over a period of time, we do not have much research with University as a key partner. Products have become more customer, market specific. At the moment, not much effort is being made to explore the possibilities of a research partnership with Universities ". With the fierce competition in dental market, a small company like DOXA is fighting to survive this competition and selling their successful products in the first place. And they mainly have partnership with companies like Nordenta AB to market/ sell their products and do not require universities for this purpose. But, the empirical material that I collected from other sources like combined research publications with university scientists at Uppsala University and the many experiments with BIOCERAMIR suggests that the development of the BIOCERAMIR product and its application testing was done by a group of scientists at Uppsala University and Malmo University.

To the same question, response from GE Healthcare shed light in a different way, the VP- Science relations responded that their relationship with the University on Biacore technology was during the initial research phase where Linköping University was involved in the design and working methods of Biacore system and the Analytical Chemistry department in Uppsala University was involved in its Application testing. After the initial research phase, the company takes the credit for the launch and success of the product from the sales, market perspective, improving the product over the years. They felt that University could probably play a major role during the research phase but speeding up the market launch or opening up new perspectives was not the way they would say that the University worked with Biacore. GE Healthcare, presently has over 20 research cooperation with Universities in Sweden,

especially with Uppsala University. And in most cases, their working agreements and contracts with University are in the research phase of a concept. Astra Zeneca responded in a similar way for this parameter in most of their research projects with Universities as cooperation partners but in this specific case study of Amyloid detection in AD, the VP of the company responded that, Karolinska Institutet is mainly involved in the research phase of the experiment. And, since the experiment is still in this phase, it is quite difficult to predict the role of the University for the moment. But in most of their research projects, Universities have played a major role, both as their reference customers as well as in method developments as they use University Hospitals to for beta-testing medicinal drugs.

The parameters (2) - mentioning the collaborating university partner and (3) - geographic proximity as a reason to collaborate, have a connection. The companies were first asked to list their University partners in research in the order of important relationship for the three technologies and a connection was drawn between the reasons behind collaboration to the geographic proximity of the company to their University partners. While GE Healthcare felt that even though, their major reasons to collaborate with the University for Biacore project was mainly for the technical expertise of Linköping University and problem testing with Uppsala University, the research team felt that collaborating with a University which is close by always had some advantages in terms of speeding up their research, being able to have a better clarity of the progress of the project, periodic meetings was advantageous in building new relations and contacts to explore new research areas. Astra Zeneca, however responded saying they do not consider collaboration with a University for the reason of geographic proximity.

The parameter (5)-‘values and effects to the company by having a working relationship with the university mentioned in (2)’ was responded to by a similar response from all the three companies considering the activities in the order how important the specified elements of the relationship are tabulated above. All three companies felt that, for the case studies discussed, acquisition of specific technical knowledge, consulting University’s researchers and Beta-User testing/ clinical trials for medicinal drugs was the most important reasons to collaborate with their University research partners. While employing students for their degree projects and recruiting permanent employees from University were moderately beneficial, University had no role to play in opening up new perspectives in terms of sales or speeding up the company’s R&D or gaining customers using University as a reference (Interview with Mr. Stefan Löfas, GE Healthacare)

An understanding of barriers/ difficulties in research cooperation with Universities comes from the parameter (6). GE Healthcare had an opinion that, the barriers of collaborating with UU were not much. They have an easy reach to the academic researchers, fast contact. Uppsala University's approach towards creating a platform to collaborate with the industry researchers is a great way to work together on research projects that would benefit the University as well as the company. While, Astra Zeneca's experience with Universities in general was a different experience- they found the bureaucracy within the University and their difference in time orientation ( Universities have a larger time span for projects compared to short term, result oriented projects taken up by Companies) to be the main barrier in collaboration. The VP of DOXA however felt that Collaborating with Uppsala University on the Bioceramir project had no significant barriers in their research phase. They felt that in future, they would certainly consider collaboration with University research partners in projects where basic and applied research had more roles to play. And from this statement, it is evident that experience from past interactions with Universities may be a reason why small, developing companies like DOXA may want to collaborate with academic researchers.

The final question asked to each of the company was how they perceived the innovation strategy of their main University research cooperation partners. Two strategies were explained, while the first strategy related to the strategy adopted by a University by collaborating with a University that focuses on commercializing their discoveries via spin offs and licensing, the second strategy is the one adopted by Universities to build long term relationships with companies in order to define together current and future cooperation possibilities. The companies were asked how they perceived the strategy of their partner University to be and which among the two were beneficial and preferred by the companies. While GE Healthcare perceived Uppsala University's strategy to be the second one, Astra Zeneca responded saying that they preferred the first strategy to the second. They perceived it more result-oriented with drug development being already a very long process. On the other hand, VP-DOXA did not respond to the question since they have never perceived a difference in innovation strategy among the Universities.

## *6. CONCLUSION*

Summarizing the results, the empirical evidence from the previous sections on the technology development behind each product in the case studies strongly supports the central idea that joint research between University research partners and a company have resulted in most breakthrough discoveries resulting in commercially successful life-science business stories. Previous studies also suggest that companies try to strengthen their research capabilities over a period of time by establishing working relationships with Universities. The impact of an article written jointly by a professor at the University and company's researchers on the on-going research or scientific papers about product evaluation play a significant role in product promotion.(Interview by Dr. Lars Farde)

In all three cases discussed over the various sections across the entire thesis, it is evident that the University had a major role to play from the technology and method development process. And all three companies, through interviews responded in similar ways to each factor measured.

The three technologies discussed as case studies, each represent a major share of the Life Science industry as a whole. While Biacore is one successful technology in the field of Biosensors, BIOCERAMIR and Amyloid detection in AD are a mini representation of the medical technology and Pharmaceutical industry respectively. Each case has created a revolution in Life Science industry. From the three cases discussed through each section of the thesis, one significant point to be observed in that for the development of the three breakthrough technologies, the companies have referred to universities as preferred research cooperation partners in comparison to a variety of options available to partner their research with. This may be due to a company's preference in carrying out exploratory research to develop cutting edge technology and to gain an overall competitive edge over other companies. Another observation from the interview results is that, though universities are advantageous research cooperation partners, while companies think that universities come to play in solving concrete technical issues or for application testing and methodology and design development, they do not have a greater role to play in speeding up the internal R&D activities of the company, market launch of a product or promoting sales to a larger extent. The driving factors behind a company's choice to form research partnership with universities would be an interesting future scope to this study. But the three case studies essentially shed

a light on the important parameters, values, effect, advantages and barriers in a company's relationship to their research partner University from the company's perspective.

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## 9. APPENDIX

### **INTERVIEW GUIDE**

Dynamics of University- Company relationships

Questions were asked to the Company representatives to get an insight on the following parameters of University- Company relationships with respect to the 3 specific projects (BIACORE, BIOCERAMIR and Alzheimer's detection project)

- 1. R&D Cooperation of the Company**
- 2. Collaborating University partners**
- 3. Geographic proximity of the company to the collaborating University**
- 4. Importance of formal Contracts/ informal contacts for the exchange of general and specific technical knowledge**
- 5. Values and effects perceived from a working relationship**
- 6. The barriers perceived by the Company in their relationship to the University research partners**

The following questions were asked during the interview

*(A). Personal Information/ Introductory questions*

- (i) Name
- (ii) What is your educational background?
- (iii) What position do you currently occupy in the Company and for how long have you been in the current position?
- (iv) Have you been previously working within academia ( In a University)?
- (v) If yes, which University, in which position and for how long have you worked in the academia?

*(B). Company Profile*

- (i) Which is the main business area of the company?
- (ii) In which phase would you place your company with respect to this the particular technology – ( BIACORE, BIOCERAMIR and Drug development for the detection of Alzheimer's disease). Would you say that the company is in the Research phase/Development/Pre market launch or sales?
- (iii) How many years ago did the Company launch its first product in this these fields of research- Biosensors, Bioceramics and in Drug development?

*(C) Academic researchers and Industry researchers*

(i) Could you please indicate the percentage of academic researchers employed in the particular project- BIACORE, BIOCERAMIR or Drug development for detection of Alzheimer's disease? (Indicate the number of Academic researchers on Scientific advisory boards/ technology specialists/ people who are jointly employed on the project/ Industrial PhDs within the project)

#### **PARAMETER 1: R&D COOPERATION OF THE COMPANY**

1.1 How many sub- projects under the major BIACORE, BIOCERAMIR or the Alzheimer's detection project would you say involved external collaboration partners for the company recently ( past 3-5 years)?

1.2 If you had to compare Importance of the following actors as cooperation partners in R&D- How would you comparatively rate them in order of their importance for the specific project- BIACORE, BIOCERAMIR and Alzheimer's detection? The actors being- Customers, Suppliers, Competitors, Universities ( including University Hospitals) and Private research Institutes

#### **PARAMETER 2: COLLABORATING UNIVERSITY PARTNERS**

2.1 Could you please Indicate which are your important Collaborating University partners for the 3 specific projects?

#### **PARAMETER 3: GEOGRAPHIC PROXIMITY TO THE COLLABORATING UNIVERSITY**

3.1 Is the headquarters of the Company located in Sweden?

3.2 Which unit of the company is presently working on the specific projects? (BIACORE, BIOCERAMIR and Alzheimer's detection)?

3.3 In your opinion, how important is it for the company to locate it's project unit geographically close to the collaborating University for these specific projects?

#### **PARAMETER 4: FORMAL CONTRACTS Vs. INFORMAL CONTACTS**

4.1 For how long, has the company been engaging academic researchers for these specific projects? (no. of years)

4.2 In the good functioning of the relationship ( for these 3 specific projects), how important do you think the following elements are: Formal Contracts, Informal contacts ( social meetings, friendships)

#### **PARAMETER 5: VALUES AND EFFECTS OF THE SELECTED UNIVERSITY RELATIONSHIP**

To what extent do you think that the following activities add value to the company in it's

relationship with the University? If you had to list them in the order of importance to the company- how would you list the following elements? ( with respect to the specific project only)

Opening up a new perspective, Acquisition of general Knowledge, Acquisition of specific knowledge, Access to Unique valuable equipment, Solving concrete technical problems, speeding up the company's R&D processes, Speeding up market launch of the product, Improving other internal processes, Recruiting qualified personnel, Improving the Company's recognition, Opening up other relationships with other actors, Gaining new customers and sales by using University as a reference customer

#### **PARAMETER 6: BARRIERS IN DEVELOPING THE RELATIONSHIP**

6.1 With respect to relationship with the University ( for the 3 specific projects), would you say that you have experienced barriers in developing your relationship with the Universities?

6.2 Could you mention a few barriers that you have perceived?

6.3 If you had to rank the following as barriers to developing the company's relationship with the Universities (with respect to these 3 specific projects), how would you arrange them? (From most impact to least impact)

Bureaucracy in the University, Bureaucracy in the Company, Lack of resources and time at the University, Lack of resources and time at the Company, Lack of Interest by the researchers at the University, Cultural differences between the University and the Company, The company's needs a quick response, but the University follows a long term logic, Intellectual property problems, example, risk of confidentiality breach despite non- disclosure agreements, the teacher's exemption ( University researchers owning the rights to their discoveries), the Commercial orientation of the University towards pushing spin offs and licenses

Please, Indicate any other barrier you may perceive in developing your relationship with the University with respect to the specific project ( BIACORE, BIOCERAMIR and Alzheimer's disease detection project)



