



# Effects of regional multilateral R&D collaboration

## A case study of a stem cell project in Western Sweden

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## **Executive summary**

In efforts to spur cluster formation and regional growth it is not uncommon with research and development (R&D) projects involving several parties, including for example academic research groups, companies or bridging organizations. The overall question addressed in this study is if such multilateral projects constitute an effective means to spur innovation and create economic growth in a region. Differently put, what kind of effects does multilateral projects generate, and which prerequisites are needed to achieve these effects?

In order to explore these questions a case study has been carried out on a regional multilateral project in the field of regenerative medicine, aiming to develop a stem cell-based screening platform to be used in drug development. The project involved three R&D performing actors, all located in the Gothenburg region: AstraZeneca's R&D site in Mölndal, Cellartis and a research group at the Sahlgrenska Academy headed by Professor Anders Lindahl. In addition, there was a fourth participant in the form of a bridging organization (GöteborgBIO).

The purpose of the present report is to describe this case and analyze the effects.

The effects of the investigated R&D project have been analyzed using a so-called effect chain approach. It is based on the assumption that public support of research leads to three types of primary effects – namely on knowledge development, on network formation, and on education and training – which are followed by a series of other chain-linked effects.

The empirical data has been collected mainly through personal interviews with ten key individuals from the four participating organizations. Other complementary sources include written documents about the project and informal discussions with representatives of GöteborgBIO.

In terms of knowledge effects, the analysis shows that the project, despite unexpectedly difficult scientific and technological challenges, has generated new valuable knowledge for all participating actors and that this knowledge will be an important input to continued work. The original project, supported by GöteborgBIO among others, has been finished but all three R&D-performing partners are now discussing a possible continuation of the R&D activities in a somewhat different form.

In terms of network development, the project has had important effects primarily on the relationships between the participating actors. The joint research activities that have taken place have resulted in the establishment of new relationships as well as strengthening of existing ones.

This project did not have any explicit goal to use the research results for educational purposes. However, some effects can be observed, such as training of two post-docs who could be employed thanks to the project.

A general conclusion that can be drawn on the basis of this case study is that given the right circumstances multilateral projects can be used as an effective means to build regional R&D networks and stimulate regional innovation, at least in research-intensive industries like biomedicine. Investing in such projects therefore seems to be a useful strategy for regional development initiatives which aim to stimulate growth by increasing intra-regional collaboration.

Another general conclusion, related to the prerequisites for a successful outcome of multilateral projects, is that there is a need for a bridging organization which can play a neutral role – for example by providing seed funding, helping to form the project and coordinate the collaborative work. In order to be able to perform this role the neutral party needs to have certain financial resources to invest and be staffed with people who have appropriate competencies and experiences within the field (i.e. biomedicine in our case). The staff of the bridging organization also needs to have detailed knowledge of the regional innovation system as well as good contacts within the actor network and legitimacy within the academic as well as industrial and policy communities.

Other important issues that have to be dealt with in an appropriate way are the legal matters (e.g. regarding intellectual property rights), the setting of clear and realistic goals and the timing.

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# 1 Introduction

In efforts to spur cluster formation and regional growth it is not uncommon with joint projects involving several partners. Such a regional multilateral project is here defined as one involving a minimum of three partners, at least one of which is located in the focal region. The partners may be, for example, academic research groups, companies or bridging organizations. While regional multilateral projects may be of varying types, the focus in this study is on research and development (R&D) projects.

The overall question addressed in this study is if regional multilateral projects constitute an effective means to spur innovation and create opportunities for business development and economic growth in a region. Differently put, we ask what kind of short-term and long-term effects multilateral projects generate, and which prerequisites are needed to achieve these effects.

In order to explore these questions a case study has been carried out. It focuses on a regional multilateral project in Western Sweden, involving the bridging organization GöteborgBIO. This is the brand name of a long-term regional development initiative aiming to develop the biomedical industry in Western Sweden and stimulate regional growth. The initiative is financed over a ten-year period by Vinnova (the Swedish government agency for innovation systems) and a range of regional actors from the public and private sectors. One of the cornerstones of the initiative's strategy is to stimulate innovation by increasing collaboration among actors in the regional innovation system, that is, primarily companies, academic researchers and healthcare providers. In fact, support of multilateral R&D projects is one of the means used to accomplish this goal. During its first year of operation, 2005, the initiative launched several such projects – in parallel to other efforts to support the development of the biomedical industry in the region.<sup>1</sup>

Our case study thus focuses on one of these regional multilateral projects: an R&D project in the field of regenerative medicine, aiming to develop a stem cell-based screening platform to be used in drug development. This project involved three R&D-performing parties – a large pharmaceutical company, a small biotech firm, and an academic research group. In addition, there was a fourth participant in the form of a bridging organization. The purpose of this paper is to describe this case and analyze the effects that the focal project has had on the participating actors and on other parts of the regional research and innovation environment.

The report is structured in the following way. First, in section 2 we describe our theoretical and methodological approach. Second, we describe the general background to the case by presenting the three R&D-performing partners and their stem cell activities (section 3), before the specific background to the focal project and how it was started is depicted (section 4). In the subsequent section the project activities and the results are portrayed (section 5). After that follows an analysis of the effects of the project as related to the different actors involved and the regional innovation system as a whole (section 6). In the final section, our observations are discussed and we draw conclusions regarding the focal project specifically, and regarding regional multilateral innovation projects in general.

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<sup>1</sup> This includes an incubator dedicated to biomedicine, a school of entrepreneurship in bioscience, and brand-building communication activities.

## 2 Theoretical and methodological approach

### 2.1 The question in focus

Despite the increasing globalization of the economy, it is argued that the regional level is still often the locus of innovation (see, e.g., Lundvall and Borrás, 1997; Asheim and Isaksen, 2002; Gertler, 2004). In other words, localized learning processes can be seen as a means to develop effective regional innovation systems, where, for example, firms and universities build competitive advantages through interaction with localized capabilities (Maskell and Malmberg, 1999).<sup>2</sup> Indeed, while many early industrial districts were based on the local availability of traditional inputs and resources, recent clustering of firms and other actors often relies on localized knowledge bases. For example, life science firms tend to be situated in regions characterized by agglomeration of technology-intensive firms, universities and research institutes (Cooke, 2001; 2002). Importantly, the resources available comprise both the region's own resources and the ones available through import from other parts of the world (Maskell and Malmberg, 1999, p. 173). Thus, the region needs to build relationships with actors and entire regions located outside its own borders.

Today, governments and policy-makers in various ways want to induce both 'regional interaction' – i.e. interaction among regional actors – and regional actors' collaborative patterns with actors outside the region.<sup>3</sup> In such endeavors to prompt cluster creation and regional innovation, a frequent tool is to encourage joint development projects of varying kinds. Such projects may involve several types of partners such as firms in various parts of the value chain, research institutes, academic research groups, industry associations, and bridging organizations. Indeed, a regional multilateral project may be delineated by that it engages a minimum of three partners, at least one of which is located in the focal region.

Such projects may have a wide variety of focuses, ranging from joint scientific advance, to product or service development, market-related network building, etc. While such regional multilateral projects may be of varying types, the focus in this study is on R&D projects. Each specific project naturally has its preset goals, as related to the individual goals of the participating organizations. What is of particular interest to issues of regional innovation and growth, however, is the way in which such regional multilateral projects may be a means to not only reach these specific goals, but also to give effects beyond the project per se. Such effects may be to create new links between actors – links that go beyond the project activities – thereby building a base for the regional sharing and learning process the literature tells us being essential for innovation. Indeed, knowledge diffusion and learning patterns are potential effects to hope for. Also, effects may include spin-off activities as follow up on the specific multilateral project.

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<sup>2</sup> In accordance with how the term innovation system is customarily used by academics and policy-makers (e.g. at Vinnova), the innovation system as we see it encompasses all the actors that in various ways contribute to the generation, use and diffusion of new knowledge and innovation. The innovation system also includes the knowledge and the artefacts related to the specific innovation, the networks between actors, and the institutions guiding any actions. In this study, using the innovation systems approach means that we focus on the key actors involved in the project and how they interact with each other and with other regional actors.

<sup>3</sup> In fact, as Asheim et al. (2003) point out there are a range of ways in which policy strives to address network-building to enhance innovativeness, including schemes directed at individual actors and those aimed at larger groups – as well as schemes aimed to provide the needed resource base, and those wanting to accomplish institutional change.

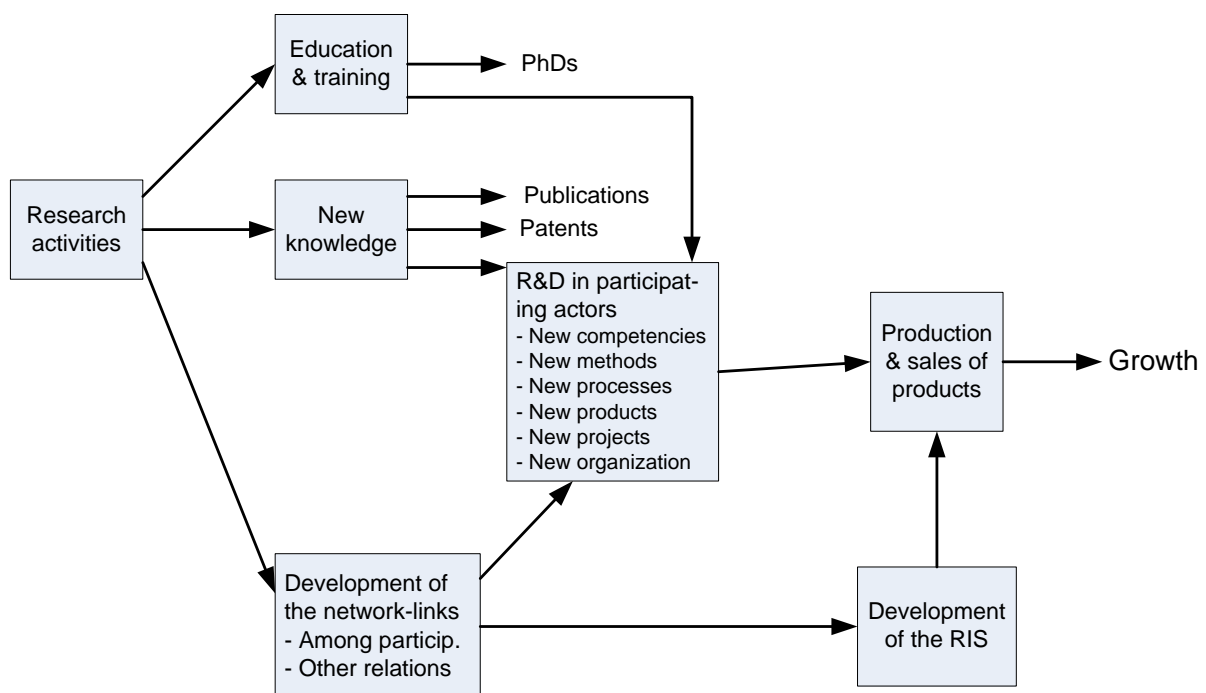
This study sets out to discuss to what extent policy actors or regional actors are wise in betting their resources on initiating and supporting regional multilateral projects. Therefore we are both interested in the various types of effects – in the short or long term - multilateral projects may generate, and which prerequisites are needed to achieve these effects.

## 2.2 The effect chain approach

To analyze the effects of the project we use what can be called an *effect chain approach*. Here we have been inspired by an analytical method often used, for example by Vinnova, to analyze long-term effects of public research investments made over a longer period of time and within a broadly defined area. The approach implies that public support of research leads to chain-linked effects stretching from funding via academic research projects and development of research environments to academic results and industrial applications and finally to end-results, for example, in terms of better health and economic growth. Different but related effects are thus assumed to take place according to a chain logic, where one type of effect may lead to other follow-on effects.<sup>4</sup>

Based on this kind of thinking and applying it specifically on a publicly supported R&D project, the research activities are assumed to create a number of chain-linked effects as illustrated in Figure 1, which depicts our analytical model. It has been used as a frame of reference for the present case study. Simply put, this means that the case description and the subsequent analysis center on the boxes and arrows in the model.

*Figure 1. Effect chain model*



<sup>4</sup> See Laage-Hellman et al (2009) for a more detailed description of the method and an example of how it is used to analyze effects of life science research on academia and industry.

The model in Figure 1 thus describes the types of effects we may expect from a multi-lateral R&D project. The research activities are those activities carried out in the project, and funded at least partly by public money. We distinguish three types of primary effects (i.e., effects that are direct outcomes of the research activities). First, the activities carried out in the project generate new knowledge. Second, the project may lead to development of network-links, among the participating actors and possibly also with other actors in the environment. Third, the research project can be used as a means to educate and train researchers.

Creation of *new knowledge* is of course the main purpose of research. Typically, some knowledge is explicit and stored in the form of, for example, written documents, computer software, drawings and prototypes. Other knowledge is of a tacit nature and tied to individuals. As illustrated in the figure, the new knowledge that comes out of the project can have various types of effects further downstream the chain. Certain research results may be published in scientific journals, which is of course of interest primarily to academic participants. The project may also lead to new intellectual property (IP) in the form of patent applications. Patenting may of course be an important prerequisite for commercialization. Importantly, the R&D activities carried out by the participating actors can be affected by the new knowledge in different ways. The research results may be further developed into new (or improved) products (goods or services) or new (or improved) manufacturing processes. The knowledge can also take the form of new competencies or new scientific methods which are useful in other projects. Moreover, the knowledge can give rise to new R&D projects – e.g. in order to take advantage of unforeseen results – or lead to organizational changes that for instance facilitate exploitation of the results.

If the continued R&D activities carried out by firms become successful this may as indicated in the model lead to production and sales of new products and, further on, contribute to growth in terms of increasing revenues and employment (directly in the innovating firm or indirectly in supplier companies). Needless to say, the commercialization of new products also brings benefits to the buyers/users of these products. In the case of biomedical products better healthcare is an important effect of innovation.

Another possible primary effect is the development of *network-linkages*. Here, collaboration within a joint project may lead to the development of new or strengthened inter-organizational relationships. It can be among those actors formally participating in the project, but it can also be with other actors who need to be contacted in the course of the work. As one of the arrows in the figure indicates this development of the network can in itself have importance for the continued R&D activities that follow on the original research project (e.g. the establishment of a close relationship between two parties can facilitate the successful completion of a new product development project).

The creation of new or strengthened links among actors in the region also means that the regional innovation system (RIS) as such is developed in terms of its innovation capability. Thus, the established links improve the conditions for innovation-related interaction and may lead to new collaborative projects that are not directly related to the results of the original research. In this way, the project may thus have certain indirect effects on the long-term growth opportunities in the region.

As to *education and training* the research project may provide an opportunity to fund PhD students and this may in turn result in the graduation of new PhDs. Another type

of possible educational effect is that new knowledge from the project can be used in courses given at different levels. Finally, the training of researchers that takes place in the project can have effects on the actors' R&D activities by offering opportunities to recruit skilled personnel.

### 2.3 Empirical data collection and analysis

The empirical data describing the case has been collected by four channels. First, the authors' long-term engagement with GöteborgBIO provided a general knowledge of the biomedical field, the regional actors, policies and activities, and the history and role of GöteborgBIO. Second, written documentation in the form of an official project presentation and an application to Vinnova provided the basic understanding of the project. Third, the main part of the information was obtained through personal interviews. The list of interviewees (see Appendix 1) includes all the key individuals involved in the project from the four participating organizations and also senior managers in the two companies. Fourth, informal discussions within the GöteborgBIO management group added to the interviews and helped to verify the case description.

The interviews can be characterized as semi-structured. They typically lasted 1½-2 hours and centered on how the project had evolved from the perspective of the individual respondent. Questions based on the analytical model were asked in order to catch the different types of effects that might appear. The open interview guide used on each occasion enabled the respondents to discuss aspects not included in the model.

In terms of analysis the various data sources have been used to build the picture presented in this report. Triangulation of different sources helped us to sort out differences among interviewees regarding for instance their view on the course of events and the effects. To verify our description of the case and the identified effects a draft version of the report was sent to the interviewees in order to give them a chance to check the correctness of facts and comment on our descriptions and conclusions.<sup>5</sup>

## 3 The empirical background

### 3.1 Regional stem cell research

A number of scientific breakthroughs in the 1990s have created around the world an increasing interest in using human embryonic stem cells (hESCs) as means for treating various diseases. This includes cell therapeutic methods where tissue/organs are built outside the body or made to regenerate in the body. It has been shown, for example, that so-called pluripotent stem cells could be extracted from fertilized cells and later on, through various techniques, be differentiated into various functional cell types.<sup>6</sup> While the sources of hESCs may vary and be debated, the most common supply is In-Vitro Fertilization (IVF) practices, where there is usually a surplus of embryos which are not needed for reproduction, and therefore otherwise discarded. By obtaining consent from the donor it has become possible, at least in certain countries (including

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<sup>5</sup> Another purpose of this review round was to make sure that the case did not contain any confidential information.

<sup>6</sup> Pluripotent cells may differentiate into any fetal or adult cell type, but cannot contribute to extraembryonic tissue.

Sweden) depending on the ethical regulations, to use such embryos for producing stem cells. These can then be used for research and therapy.

Gothenburg has a long tradition in stem cell research. It dates back to the 1980s when pioneering work on IVF was carried out at the Sahlgrenska University Hospital and the Medical Faculty of the University of Gothenburg. Out of these activities several research groups working on stem cell technology emerged. One of them was headed by Professor Anders Lindahl, one of the partners in the present research project. He is now a professor at the Institute of Biomedicine at the Sahlgrenska Academy (SA)<sup>7</sup> and also medical director of the cell transplantation unit at the Sahlgrenska University Hospital. The research group focuses on regenerative medicine with emphasis on two areas, namely cartilage repair and cardiac regeneration respectively. In the latter field the group is collaborating with the Sahlgrenska Center for Cardiovascular and Metabolic Research (CMR), which has a long clinical experience of cardiac insufficiency (heart failure). Besides Anders Lindahl himself the group consists of one post-doc, five PhD students and eight technicians. It has access to a good infrastructure at the department including advanced research equipment and a GMP laboratory approved for human cell therapy.

In 2001 six senior university researchers, one of them being Anders Lindahl, took the initiative to start a biotech company called Cell Therapeutics Scandinavia AB (later renamed Cellartis AB).<sup>8</sup> None of the founders became employed by the company but some of them have maintained close collaboration with the company ever since its start. There are several finished as well as ongoing research collaborations, the focal heart stem cell project being one of them.

### 3.2 Cellartis

By gaining access to fertilized eggs from IVF activities at hospitals in Gothenburg Cell Therapeutics immediately after its foundation began to build up a set of human embryonic cell lines, where each line originated from one egg (the company now has more than 30 such cell lines). The original business idea was to use this unique resource for development of stem cell-based therapies for different diseases. However, as will be described in more detail below, the company after some years of operation chose to shift its business focus.

Cell Therapeutics got what we may call a flying start. When the previous US president George W. Bush in 2001 decided that federal research grants were not allowed to finance the creation of IVF-based stem cell lines, the interest from the US in using Cell Therapeutics' existing cell lines increased dramatically. In 2002, representatives of the National Institutes of Health (NIH) visited Sweden to encourage Swedish researchers to apply for American grants to make stem cell lines available to American researchers (in order to be approved by NIH the stem cell lines had to undergo extensive testing and documentation). As a result of this initiative Cell Therapeutics in 2003 received a

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<sup>7</sup> Sahlgrenska Academy was founded in 2001, when the three faculties of medicine, odontology and healthcare science were merged into a health science faculty.

<sup>8</sup> The other founders were Christer Betsholtz (now professor at the Karolinska Institutet), Sven Enerbäck, Peter Eriksson, Lars Hamberger, and Henrik Semb (now professor at Lund University). Other initial investors were A<sup>+</sup> Science (a venture capital firm related to the University of Gothenburg) and Vitrolife (a previous spin-off company from the university's IVF research).

SEK 3 million research grant from NIH. Later on it received grants also from other US government agencies, such as the Juvenile Diabetes Research Foundation (JDFR).

In those days the main activity of Cell Therapeutics was research, but it had a long-term vision to develop and commercialize cell therapies. In addition to the external research grants from NIH and other national and foreign sources the company financed its activities by raising venture capital (VC). The first major investment was done by the Gothenburg-based InnovationsKapital in 2002.

After a few years it became evident to the company's management and its owners that building an economically sustainable business in cell therapy would take longer time than expected. Without totally abandoning the therapeutic ambitions the company in 2003-04 refocused its main business from cell therapy to drug discovery tools. There was an increasing interest in the pharmaceutical industry in using cells derived from hESC lines as models for efficacy and safety testing during preclinical drug discovery (as an alternative to, e.g., animal models and engineered tissue – models that are not sufficiently reliable). Thus, the core business became to develop stem cell-based tools to be used for screening and toxicity testing in drug research. The market potential was lower than for cell therapy. But instead it was expected that the new approach would shorten the time to market, increase the probability for commercial success, and reduce the amount of new capital needed. To signal the new orientation the company was re-named Cellartis AB.

The new orientation helped Cellartis to raise more capital required to run the company and develop the products. Since then several Nordic VC firms have invested in Cellartis.<sup>9</sup> To finance the R&D Cellartis has also successfully managed to land new research grants from various sources, including the EU, and to secure research contracts with potential customers in the pharmaceutical and biotech industry.

Today's Cellartis can thus be characterized as a "biotech tool company". The first products for efficacy and safety testing during preclinical drug discovery were introduced in the market in 2008 (seven years after the founding of the company) and have since then been followed by several others. Much of this product development has been carried out in close cooperation with potential customers. In early 2006, for example, Cellartis entered collaboration with AstraZeneca to develop improved safety screening systems based on hESC-derived cardiac and liver cells. In February 2009, the two companies announced that the collaboration had been extended, and that there were good hopes that the method would help AstraZeneca to more accurately detect side effects for new drugs and achieve a lower attrition rate. Pfizer is another important R&D partner, together with whom Cellartis since 2008 is developing improved screening systems for detection of toxicity.

In 2007, Cellartis established a second site in Dundee, Scotland. With financial support from ITI Life Science (a Scottish government agency) Cellartis is building up large-scale and automated production of specialized cells derived from its hESC lines. The plant is the world's first for mass production of human embryonic stem cells and based on technologies developed by Cellartis in Gothenburg. Another reason for choosing Scotland as location of its plant, besides the financial support, is the strong research and innovation environment which provides interesting opportunities to

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<sup>9</sup> Major VC investors besides InnovationsKapital (currently with 36% ownership) are Catella Healthcare Investments (22%) and BioFund Venture (19%).

establish collaboration. The deal comprises, for example, joint research with the University of Glasgow and the University of Dundee, which are strong in the stem cell area. Furthermore, the region is home to a large number of companies working on stem cells or regenerative medicine.<sup>10</sup>

In parallel to its current core business focused on research tools, Cellartis has continued to work on therapeutic applications related to regenerative medicine. Here, Cellartis is pursuing two different approaches. First, while it has no ambition to develop its own cell therapy products, it takes a role in the value chain of developing traditional cell replacement therapy. Cellartis does that by partnering with pharmaceutical or biotech companies, where it supports these companies' development by making its own stem cell lines and technologies available. An early collaboration, established already in 2004 and still ongoing, was established with Tanabe Seiyaku in Japan (now Mitsubishi Tanabe). This collaboration is focusing on developing a therapy for Parkinson's Disease. More recently, in October 2008, Cellartis announced a new research agreement with Novo Nordisk of Denmark, a world leader in diabetes care, and Lund University.<sup>11</sup> This project aims at developing insulin-producing cells from hESC, which can be used to treat Type 1 diabetes.

The second approach to regenerative medicine is based on in-vivo activation of endogenous stem cells by using traditional small molecule drugs. This is the concept which the investigated heart stem cell project is based upon, and it will therefore be described in more detail below. Here, it suffices to say that for Cellartis this means development of hESC-based model systems that can be used by the pharmaceutical industry for screening of chemical compounds (i.e. potential drugs).

### **3.3 AstraZeneca**

AstraZeneca is one of the world's largest pharmaceutical companies with headquarters in London, UK. It was formed in 1999 after a merger between Astra of Sweden and the British-based Zeneca Group. Research and development is carried out in a global organization with major R&D facilities located primarily in North America, Great Britain, and Sweden. The R&D site in Mölndal is one of the largest with some 2 500 employees. Much of the work carried out there is focused on the cardiovascular and gastrointestinal fields, where the site has historically contributed a range of successful products. Today, after having implemented some major strategic changes a couple of years ago, the main focus of the cardiovascular research is on the so-called metabolic syndrome, that is, diseases such as diabetes, obesity and arteriosclerosis.

Like many of its competitors, AstraZeneca's interest and engagement in stem cell research and related products has shifted over time. In the late 1990s the research community and the pharmaceutical and biotech industry had strong hopes in cell therapy as an effective cure for many diseases. After the ending of this stem cell hype, the expectations for rapid progress began to weaken in the 2000s – when it was realized that there were too many difficult challenges to be overcome before the concept could be translated into clinical practice. During the last 2-3 years, however, thanks to new scientific advances the interest among pharmaceutical companies in stem cell research and regenerative medicine has resurged. The new US president Barack Obama's recent

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<sup>10</sup> See Bergqvist (2008, p. 104-109) for a case study on Cellartis' establishment in Scotland.

<sup>11</sup> The partner at Lund University is the Stem Cell Center headed by Professor Henrik Semb, a co-founder of Cellartis.

lifting of the restrictions on federally funded stem cell research has also contributed to spur interest, especially in the USA. Several of the large pharmaceutical companies are now making large investments in stem cell research, including cell therapy as well as cell-based tools for development of traditional drugs. Pfizer, for example, has established two new research centers, located in Cambridge, UK and Boston, USA respectively. GlaxoSmithKline has invested large sums in Harvard Stem Cell Institute and is now setting up a major regenerative medicine research center in Shanghai, China.

AstraZeneca has so far chosen a different, more distributed approach, where each Research Area (such as the cardiovascular and gastrointestinal one, managed from the R&D site in Mölndal) develops its own strategy for stem cell research. Thus, the resources and activities are spread throughout the group, but are linked and coordinated when needed through global networks involving internal R&D units as well as external collaboration partners, such as Cellartis and the Sahlgrenska Academy.

Against the background of the ethics debate regarding the use of human embryonic stem cells, and especially the previous US administration's policy in the field, AstraZeneca for many years chose to keep a low profile, and did not publicly announce any involvement in such activities. This has now changed. The company is now signaling to the outside world that it believes in the potential of using stem cell technology and is making R&D investments in the field.<sup>12</sup> However, presently this does not include traditional cell therapeutic methods, based for example on hESC lines. The development of this approach is left to other companies. Instead, AstraZeneca follows three other tracks. The first one is cell-based disease models used for screening and safety-testing purposes. As already mentioned, AstraZeneca in one project collaborates with Cellartis.

The second track is regenerative medicine in a true sense, that is, trying to improve the repair capability of endogenous stem cells by using small molecule drugs. The project on cardiac progenitor cells falls into that category.

Thirdly, AstraZeneca is interested in exploiting the new scientific advances offered by so-called IPS cells (induced pluripotent stem cells). Recent research has shown that such cells, which are derived from adult cells (e.g. skin) through forced expression of certain genes, have similar properties as natural stem cells. This opens up the possibility to develop stem cell-based therapies without the controversial use of embryos. For AstraZeneca, using IPS cells offers interesting opportunities within the area of personalized medicine and it is for this purpose looking for external partnerships.

## **4 The heart stem cell project: background and start-up**

### **4.1 Scientific background**

The basic idea behind this project – that is, to use traditional small molecule (low molecular weight, LMW) drugs to trigger regenerative processes in-vivo – has been

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<sup>12</sup> For example, in its latest annual report (for 2008) AstraZeneca writes “We believe that human embryonic stem cell research may present such an opportunity” (i.e. to deliver better medicines for patients) (p. 21). It also writes that since the company does not yet have all the necessary skills and technologies in-house, it is working with external partners who have the capabilities and expertise. It is also mentioned that AstraZeneca is a founding member of the public-private partnership, Stem Cells for Safer Medicines, in the UK, which brings together academia, government and pharmaceutical industry.

around for some years. Research in the late 1990s had shown that in certain parts of the body, for example the brain, there are so-called progenitor cells, that is, resident, endogenous stem cell-like cells which are immature and have not yet acquired the functional features of tissue/organs. Under certain conditions such progenitors can mature and differentiate into functional cells, thereby helping to repair damaged tissue. In the early 2000s there was emerging evidence, confirmed later on, that in contrast to earlier belief progenitor cells existed also in the heart, and that there was a potential for medical treatment – either through stem cell therapy or by interfering in the regulatory system. The problem is namely that in humans, unlike certain other species such as zebra fish, the natural capability of cardiac progenitor cells to divide is insufficient. One of the emerging ideas was thus to use these cardiac progenitor cells (“CPCs”) as targets for drug therapy. Simply put, the effect of the drug would be to speed up the differentiation of the progenitors into (functional) heart muscle cells (also called cardiomyocytes) and help to cure chronic heart failure/insufficiency, which is a common disease following upon myocardial infarction.

These paradigm-shifting findings regarding the presence of progenitor cells in the heart were noted by Anders Lindahl, and his group very soon after the findings had been published started up its own research in the field. The focus was on identifying and characterizing CPCs in the human heart.

This use of CPCs as targets for drug therapy constitutes a totally novel approach to the treatment of ischemic heart disease, which has attracted interest among pharmaceutical companies.<sup>13</sup> In order to identify new chemical compounds that induce or increase differentiation of these endogenous CPCs into specialized heart muscle cells, the pharmaceutical industry needs access to isolated CPCs to be used for screening of such compounds. Research results published 7-8 years ago had shown that human embryonic stem cells (unlike bone marrow stem cells, for example) could form new heart muscle cells. hESC lines, such as those owned by Cellartis, were thus seen as a potential and promising source for CPCs.<sup>14</sup>

## 4.2 Formation of a multilateral project

### *The genesis*

In early 2005, a 10-year regional development initiative was started up to support biomedical activities and actors in the Gothenburg region. The initiative is called ‘Biomedical Development in Western Sweden: a New Innovation System’ (BMV), but it is better known under its brand name GöteborgBIO.<sup>15</sup> BMV is financed by the government agency Vinnova (through its Vinnväxt program) and a set of regional actors from the public and private sectors.

In the formation of the BMV initiative two profile areas were selected, namely, Cardiovascular and metabolic diseases (CVM) and Biomaterials and cell therapy.

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<sup>13</sup> Myocardial infarction is the major cause of chronic heart failure. It leads to loss of heart muscle cells typically followed by fibrosis and cardiac insufficiency. Ischemic heart disease has high prevalence (about 2% of the population in the Western world) and is associated with high mortality (50% within five years).

<sup>14</sup> An alternative would be CPCs isolated from human tissue – a method that requires access to human biopsies and surgical techniques for their retrieval.

<sup>15</sup> This is the communication platform of BMV, but also the collective name used for the region’s entire biomedical activities in promotional contexts. That is why we in this paper have chosen to use BMV as name of the initiative. For further information about GöteborgBIO and BMV see [www.goteborgbio.se](http://www.goteborgbio.se).

A main reason for selecting CVM as a prioritized area was that AstraZeneca was one of the principals of BMV and therefore also one of its financiers. For BMV it was important to establish at an early stage collaborative R&D projects involving AstraZeneca and other actors – academic and/or industrial – as part of its strategy to strengthen the regional innovation system for biomedicine. Astra's research site in Mölndal had a long tradition of successful collaboration with the medical faculty of the University of Gothenburg and commercialization of academic research findings. However, for some years, and especially after the merger between Astra and Zeneca in 1999, the extent of collaboration had decreased. For the management of BMV it therefore became an important goal to tie AstraZeneca Mölndal closer to the regional environment and by so doing increase the innovation capability of the whole region. Thus, starting up new collaborative R&D projects was seen as an opportunity to help restore a fruitful collaborative relationship between AstraZeneca and the university.

In the search for suitable projects where BMV could play a facilitating role, those individuals responsible within BMV, who had long worked in the biomedical field, talked to many people in the region, both within academia and industry. The new therapeutic concept described above came up as a natural project idea. Both Cellartis and the research group of Anders Lindahl had an obvious interest in the field. As being one of the founders of Cellartis, Anders Lindahl already had collaboration with Cellartis, and cardiac stem cells were one of the common interests. He comments that the new scientific discoveries had opened up his eyes and proved that this was an important research field and that the new knowledge had importance to drug discovery. It was true that heart stem cells were not the main research interest of Anders Lindahl himself, but rather cartilage repair. However, as professor he felt the responsibility to help younger researchers to establish themselves in new fields.

AstraZeneca R&D site in Mölndal was a natural partner to Cellartis and the Sahlgrenska Academy since cardiovascular drugs were one of its core businesses where large R&D resources were invested. Furthermore, to realize a project on the new therapeutic concept there was a need for someone who could do the screening of chemical compounds and was interested in using the new cell-based platform for drug discovery. AstraZeneca had in Mölndal an existing large-scale facility for High Throughput Screening (HTS). Both Cellartis and Anders Lindahl had some contacts with AstraZeneca.<sup>16</sup> However, in order to establish the right connections for starting up this particular project several individuals within the BMV organization played an instrumental role. This includes Johan Anstrén who was responsible for the CVM area. Like several others in BMV he had worked for Astra and had good knowledge of the organization and people at the Mölndal site. He therefore knew which people to approach. The key person, who later on got the task to coordinate the project within AstraZeneca, became Per-Ove Sjöquist, head of arrhythmia within the Bioscience Department of the Cardiovascular and gastrointestinal (CVGI) Research Area.

AstraZeneca was well aware of the new scientific discoveries and therapeutic ideas that the proposed project was based upon. There was a general need for new therapies to treat patients suffering from chronic heart failure (e.g. following on myocardial infarction). The long-term goal of the project therefore offered interesting business opportunities for a company like AstraZeneca.

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<sup>16</sup> For example, the chairman of Cellartis' board of directors was a previous head of the R&D site in Mölndal.

It can be noted that in parallel to these discussions, AstraZeneca and Cellartis had discussions regarding another collaborative project. This one concerned safety testing, where Cellartis' hESC lines would be used to develop a new method for drug testing in pre-clinical research.<sup>17</sup> These discussions, which resulted in the signing of a 2-year agreement in July 2006 (later extended), contributed to make people in the two companies acquainted with each other and therefore had some impact on the discussions regarding the proposed BMV project.

It can also be noted that in the same time period, AstraZeneca had taken some initiatives to improve the environment for collaboration with the University of Gothenburg. This included, for example, financing of several post-docs. The proposed heart stem cell project fitted in very well in that context.

Within BMV a separate steering group had been formed for the CVM area. It consisted of representatives of academia, industry and a venture capital firm (Innovations-Kapital, one of Cellartis' investors). One of the members was a senior manager from AstraZeneca. In the late spring of 2005, the project idea was presented to the steering group, which gave its approval to start up a project.<sup>18</sup>

### *Objectives*

The overall and long-term objective of the collaboration was to develop a screening platform for heart regenerating drugs (representing a radically new method for treatment of heart failure). However, the more immediate and specific goal of the project was formulated in the following way: "to characterize the signalling pathways in order to find chemical substances with ability to stimulate propagation and differentiation, and migration of cells".<sup>19</sup> It was thus expected that such knowledge about CPCs would enable the development of a screening platform to find chemical substances which have an ability to interfere in the regulatory mechanisms, stimulate regenerative processes, and therefore have a potential to be developed into pharmaceuticals.

The project was regarded by all parties as a high risk project. There was at the time little knowledge about the phenotype of CPCs, and the therapeutic concept as such was new. Therefore, for Cellartis – given the high uncertainty and the exploratory and academic character of the project – it would have been impossible at that point in time to raise money internally without having complementary seed funding from BMV.

## **4.3 Financing and organizing**

As a first step to start up a collaborative 3-party project, the CVM steering group decided to give a grant for employment of a full-time project leader. The choice fell on Caroline Améen, who had recently finished a PhD at the Sahlgrenska Academy, and she commenced her work in September 2005. The grant, originally for 1½ years but extended once for approximately half a year, was for practical reasons given to Cellartis where Caroline Améen became formally employed. However, her tasks were to coordinate the project as a neutral person financed by BMV and also to carry out experimental work both at Cellartis and the Sahlgrenska Academy. However, after some time it became evident that performing this type of research work in two differ-

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<sup>17</sup> For example, target and lead validation, compound screening and drug metabolism studies.

<sup>18</sup> At the same time one more research project was awarded an early grant within the CVM area. Although of potential relevance to AstraZeneca this project did not have any commercial partner.

<sup>19</sup> Quoted from Project presentation: Cardiac Progenitor Cells for Treatment of Heart Disease, GöteborgBIO.

ent places was not a practical solution. In spring 2006 it was therefore agreed that Caroline Améen, besides coordinating the project, would carry out experimental work only at Cellartis (on hESC lines) and that another person would be recruited to do the corresponding work at the Sahlgrenska Academy (on stem cells from human tissue).

For a variety of reasons, AstraZeneca was unable to formalize a collaboration with Cellartis in this project. It was instead agreed that as a complement to the BMV grant, AstraZeneca would support Anders Lindahl and his group to work on the interesting area of adult stem cells. The grant was for two years (August 2006 to July 2008) and enabled Anders Lindahl to finance a newly recruited post-doc (Julia Asp), who took over after Caroline Améen, and a technician.

The BMV money was thus given to Cellartis, where it was used to finance project coordination as well as practical research work. The grant did not cover all costs for the research. Cellartis estimates that the company has contributed roughly an equal amount of money, that is, around SEK 750,000 for almost two years (September 2005 to summer 2007).

In line with the project idea, there was a clear division of labor among the three partners – based on their respective competencies and resources. The role of Cellartis was to use its expertise and its existing stem cell lines to make CPCs with ability to propagate, differentiate and migrate to the damaged part of the heart. Such cells, provided that they resemble those resident in the human heart, would be useful as model for measuring in-vitro the regenerative capability of various chemical compounds (potential drugs).<sup>20</sup>

Cellartis had two motives for engaging in this project. The first one was to develop a screening platform for AstraZeneca and other pharmaceutical companies working in the cardiovascular field. The second motive, related to the up-scaling efforts, was to develop the production technology for making CPCs. That would enable the production of functional (fully matured) heart muscle cells by starting halfway from an intermediary cell population (CPCs), instead of the stem cell lines. That would save time and cost in the future. In other words, the interest of Cellartis in the project was broader than just helping AstraZeneca to develop a screening platform.

The main task of Anders Lindahl's group was to find, characterize and isolate CPCs from human tissue. They had competence to do this work and, thanks to collaboration with surgeons at the hospital, access to heart biopsies from which resident CPCs could be isolated.

In a following step, the hESC-derived CPCs had to be compared with the human CPCs in order to find out whether they had the right properties (phenotype) to be useful for drug screening.

The next step would be to do the screening of compound libraries by using CPCs both from Cellartis and from the Sahlgrenska Academy. This was the role of AstraZeneca which had the necessary resources and expertise to carry out this work. The goal was to identify substances that are able to induce the maturation of endogenous CPCs into specialized heart muscle cells (cardiomyocytes).

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<sup>20</sup> By contrast to the immature CPCs, the cells used for safety testing of drugs consist of fully matured functional cells, also derived from hESC lines.

As we have seen, the roles of the three partners were clearly defined from the beginning and complementary to each other. This was considered very important and contributed to create favorable conditions for an efficient collaboration. As a means to coordinate the activities, the key people in the participating organizations had regular meetings organized by the coordinator (more about this below).

## 5 Project activities and results

The work carried out by the research group at the Sahlgrenska Academy was thus directed at isolating, culturing, characterizing and propagating CPCs from the human heart (adult as well as neonatal) and also testing their in-vitro functionality. The cells originating from the human tissue were used as a reference for Cellartis in its work with hESC-derived CPCs. In other words, in order to verify the usefulness of the latter cells their features had to be compared with those of cells derived from human tissue. This comparative evaluation of the phenotypes of CPCs from different sources was carried out at the Sahlgrenska Academy in close cooperation with Cellartis.<sup>21</sup>

This effort was thus financed initially by BMV and later on by AstraZeneca. In parallel, another related research project was started up by Anders Lindahl and his co-workers with funding from the EU. The project is called InvitroHeart and is coordinated from Linköping University. Cellartis is one of the other partners. It is a 3-year project running from 2007 to 2009 and aiming at developing in-vitro models for hESC-based cardiomyocyte toxicity testing that can be used by the pharmaceutical industry. Thus, the project has an objective related to that of the BMV project and requires similar research activities. At the Sahlgrenska Academy the same person who worked for the BMV project also worked on InvitroHeart. At Cellartis, however, a new person was recruited for the latter. Here the work on the two projects was not interlinked to the same extent as it was at the university.

While Cellartis was one of those who had initiated InvitroHeart, the academic group's participation in the project was a direct consequence of the activities started up with financial support from BMV and AstraZeneca.

For the academic group, a fourth source of funding used to finance its research on heart stem cells was the Heart and Lung Foundation. Furthermore, in December 2009 the group received additional funding from the Swedish Research Council (SRC) and from Region Västra Götaland. It means that the project is funded for at least three more years (until 2012).

In parallel to the academic group, and in collaboration with them, Cellartis worked on the characterization of CPCs derived from its different stem cell lines and tried to develop culture conditions for propagation of CPCs. This work was mainly carried out by Caroline Améen, but periodically other people from the same research group were involved.

According to the project plan, AstraZeneca's main deliverables were to come at a later stage, that is, to use CPCs from Cellartis for high throughput screening. However, to start up some research activities, in parallel to Cellartis' work on hESC and the university group's work on adult and neonatal stem cells, the AstraZeneca team began some small-scale testing of embryonic stem cells from mouse. The purpose was to see if it

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<sup>21</sup> Part of this work was carried out by a bioinformatics researcher from the University of Skövde.

worked and then apply the same methodology to screening of human cells. Later on AstraZeneca received some human cells from the Sahlgrenska Academy for testing. However, the team could not use, as intended, the automated HTS facility in Mölndal. The screening capacity was in short supply and other projects within the company had higher priority. This means that the screening had to be done manually and allowed testing only of a few compounds. In other words, no “real screening” took place before the team had to stop working on the project in mid-2008 (see discussion on AstraZeneca’s research strategy below).

From the project start in September 2005 the three partners had regular meetings, around once a month, with rotating hosting. Those who attended these meetings were usually Caroline Améen and Peter Sartipy from Cellartis, Anders Lindahl and Julia Asp from the Sahlgrenska Academy, and Per-Ove Sjöquist with two co-workers from AstraZeneca. Johan Anstrén from BMV also attended many meetings. His role was not to contribute scientifically, but instead he was a driving force and helped to move the project forward, especially in the early phase. Over time, more and more of the coordinating duties were taken over by Caroline Améen. The other participants appreciated very much Johan Anstrén’s efforts and ability to manage the project. As already mentioned, his contacts within AstraZeneca were also useful to the other partners.<sup>22</sup>

The scientific discussions that took place at these regular meetings were very productive. Besides helping the participants to coordinate the activities to be carried out they learnt a great deal from each other (as will be further commented in our effect discussion below; see Section 6).

As already mentioned the entire collaboration involving all three partners was not formalized. Instead, there were separate agreements regarding the grants between BMV and Cellartis on the one hand and between AstraZeneca and Anders Lindahl’s group on the other. Cellartis would have preferred to have a formal agreement with AstraZeneca and made efforts to get one. In their view, if there had been an internal project within AstraZeneca, the company could have invested more resources in experimental work. That would have increased the speed of the research and facilitated for the project to reach more rapidly its original goals. Johan Anstrén of BMV also pushed for an agreement. However, at the time AstraZeneca did not feel comfortable with such an arrangement, although this position has now been changed as we will discuss further below.

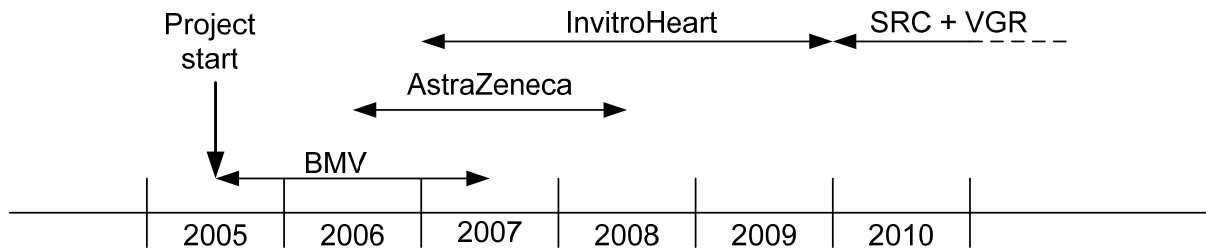
In commenting the lack of an overall agreement, one of the interviewees says that this was a consequence of missing top management support within AstraZeneca as well as within the broader environment in Gothenburg. And this in turn had to do with the fact that BMV was a new initiative which in his view was not sufficiently well anchored within the key actors in the region (i.e. the two universities, the large companies and the healthcare organization). He believes that if BMV had had as a promoter and “ambassador” a strong, high-profile individual it would have been possible to get an

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<sup>22</sup> Johan Anstrén, as representative of a regional development program (BMV), also took other initiatives with the purpose of broadening the collaboration. For example, he mediated contacts with a Chinese university in Shanghai that performed similar research as Cellartis. Meetings have taken place both in China and Sweden, but so far no concrete collaboration has been started. But the contact has been established and the parties are trying to identify common interests that can lay foundation for joint activities. Johan Anstrén also made an attempt to start up a similar, multilateral project in a different disease area. However, this effort came to nothing due to AstraZeneca’s unwillingness to invest resources in this field.

agreement, which for example would have regulated the ownership of intellectual properties (IP).

**Figure 2. Different funding sources over time**



## 5.1 Results

The collaboration between the three parties can be said to have ended in mid-2008, when AstraZeneca's funding of the academic group ceased (see Figure 2 for a graphical illustration of the use of different funding sources during different time periods). BMV's funding of Cellartis had finished one year earlier, but the company had continued to do some work financed in-house. For example, Caroline Améén had been offered a permanent employment and devoted some of her time to the project. The main scientific results achieved at that point in time can be shortly summarized as follows:

- Identification of stem cell populations in the human heart.
- Creation of hESC-derived populations of CPCs (i.e. potential screening cells).
- Characterization of CPCs derived from human tissue and from hESC lines.

Another important outcome, in addition to these research findings, is that the researchers learned many other things by working on the project. For example, they developed new applications for different methods (e.g. PCR and FACSscan). This is knowledge that has become useful also in other contexts.

However, despite these valuable results it must be concluded that the overall objectives as stated when the project was started were not achieved. This can mainly be attributed to the difficult scientific challenges that became apparent during the research process. For example, the culturing of adult stem cells turned out to be more complicated than envisaged. And Cellartis did not succeed to isolate the CPCs in large quantities (i.e. the number of cells was too low). With hindsight it was realized that the initial goals had been too optimistic. Thus, it became impossible to develop a functioning screening platform within the frame of the project. But still, all partners agree that the project as a whole had moved in the right direction and they are content with the outcome. Valuable knowledge about CPCs and how to transform them into functional heart muscle cells had been gained, although with slower pace than planned.

An important result is that Cellartis based on these findings could file a patent application regarding how to isolate CPCs made from hESC lines. This was done in July 2006 and the application is currently in the PCT phase. This was an important accomplishment since this type of intellectual property is part of Cellartis' core competence

and therefore vital to protect. It can be noted that due to the lack of a written agreement for the entire project Cellartis had full ownership of all results based on its own research.

Neither the research group at the university nor AstraZeneca have filed any patent applications.

There are a number of scientific publications in the pipeline. Anders Lindahl and his group have already one accepted article and two finished manuscripts. It is expected that in total there will be 6-7 articles related to all research on cardiac stem cells (as funded by BMV, AstraZeneca, InvitroHeart and others). Some of these papers will be co-authored with researchers from Cellartis and possibly also from AstraZeneca, depending on their intellectual contributions. For Cellartis, publishing is not a key issue but it is rather seen as a bonus thing that would have a positive effect on the brand building.

## **5.2 Continuation after the project ended**

Given all these promising outcomes of the project Cellartis had strong interest in continuing the work on CPCs after ending of the BMV funding – not least for the purpose of developing the production technology (motive 2 as mentioned above). However, since AstraZeneca did not have at the time an internal project in the area it had to minimize its spending of resources. AstraZeneca had made a strategic decision at the group level to cut its cardiovascular research in certain disease areas such as hypertension and heart failure. Instead, the resources should be concentrated on projects related to the metabolic syndrome. Thus, the collaborative research with Cellartis and Anders Lindahl did not fit the new R&D strategy and therefore it became difficult for the involved researchers at AstraZeneca to spend time on the project. The regular meetings ended, but informal discussions continued to take place. For example, meetings within the other collaborative project between AstraZeneca and Cellartis (on safety testing) partly involved the same people and provided opportunities to discuss broader issues and keep the idea alive.

Both Cellartis and Anders Lindahl knew from the beginning that BMV's and AstraZeneca's funding would have an end, and they realized at an early stage that these grants would not be enough to finalize the project and achieve the ambitious goals that had been set up. Already in 2006, they started to search for alternative funding from various external sources – including industry as well as public agencies. As part of these efforts an application was sent to Vinnova (the SAMBIO 2006 program). The project was titled "Myocardial stem cells in drug discovery" and had basically the same objectives as the BMV project. AstraZeneca did not want to be officially involved but supported the application by writing a letter of interest. However, Vinnova did not grant any money. It found the project to be in a too early phase and too far from commercialization. Later on other joint applications were submitted, for example, to other Vinnova programs. None of these were successful, though (with the exception of InvitroHeart which concerned a different but related project).

Given the lack of funding of the joint project, the activity level at Cellartis has been relatively low during the last two years. When AstraZeneca's funding of the research at the Sahlgrenska Academy ended, the group could continue its work on heart stem cells thanks to the InvitroHeart project, which will go on until the end of 2009. Future survival of the emerging research group for heart stem cells is dependent on new fun-

ding. Therefore, it was good news when the group in late 2009 received additional grants from the Swedish Research Council (for three years) and from Region Västra Götaland (for 2010) with aim to develop assays for toxicity testing and drug discovery. The money will be used to finance one senior researcher, one PhD student and one technician.

During the second half of 2009, the possibilities to get a restart of the collaboration among the three partners in the BMV project have improved substantially. As mentioned in Section 3.3 AstraZeneca has now decided, like several of its competitors, to invest in research on stem cells and regenerative medicine. And these intentions have also been publicly announced. Moreover, AstraZeneca has also started to reconsider its research strategy in the cardiovascular field. It is true that heart failure is still a non-prioritized disease area. But if stem cell-based therapy can prove itself to be an efficient treatment, then AstraZeneca would be prepared to invest in the development of a product also in this field.

Cellartis, which has kept on working toward the project goals, welcomes the increasing interest from AstraZeneca, and discussions between the two companies regarding mutual interests have intensified. Cellartis has good hopes that it will be possible to start up the collaboration on heart stem cells again and that it can be formalized this time. Anders Lindahl is also taking part in these discussions.

In the current situation, AstraZeneca is primarily interested in establishing what they call “a network for stem cell research in Gothenburg”. That would not be a straight continuation of the previous project, but a broader form of collaboration and knowledge exchange. It might not be necessary to have it formalized through a written agreement, they think. It is believed that such an interaction among the three partners could possibly lead to the start of more specific projects. For instance, the development of a screening platform according to the ideas developed in the BMV-supported project might pop up as one type of joint research activity within the network.

There is no doubt that it is the previous BMV project that has paved the way for establishing such a collaborative network. Thanks to the interaction that has taken place in that project the three partners have learned to know each other and gained a good understanding of each others’ competencies and resources. The parties expect that this will facilitate future collaboration and lead to higher efficiency and more rapid results.

## **6 Effects of the project**

In this section, the actual as well as potential effects of this project will be discussed. In accordance with our analytical model in Figure 1, we distinguish three types of primary effects, that is, those related to knowledge creation, network-building, and education & training respectively. Under these three headings we will discuss the effects appearing at this first “link” in the chain as well as other downstream effects.

### **6.1 Knowledge effects**

The ambitions of this project were high, namely, to develop a CPC-based screening platform for heart drugs. This goal, due to scientific and technological difficulties, turned out to be unrealistic and impossible to achieve during the time frame of the project. Nonetheless, the results in the form of new scientific knowledge about how to produce CPCs and their characteristics are considered by the parties to be important

and promising. The new knowledge represents a vital step forward and constitutes a valuable basis for continued work toward the development of a screening platform as well as other possible applications of cardiac stem cells. Today, all three partners express interest in restarting the research collaboration, but it remains to be seen whether these intentions will be materialized and what the goals will be.

In the case of Cellartis, parts of the new knowledge have been used in a patent application. If the collaboration, as wished, can be restarted and ultimately succeeds this will undoubtedly strengthen the position of Cellartis as one of the world's leading stem cell companies. It is impossible to forecast what the exact results will be. But for example, the development of technology for large-scale production of CPCs would be useful for different purposes, including the development of a drug screening platform. In case of the latter, Cellartis would have at its disposal a new, unique product in regenerative medicine.

For AstraZeneca, the project has led to increased knowledge about the possibility to use stem cells to repair the heart of patients who suffer from heart failure. The knowledge, which goes beyond what can be learnt from the literature, does not only come from the research results of the project itself, but also from the broader knowledge exchange that took place among the partners in connection to the regular project meetings. One of the AstraZeneca researchers says that:

For us the project was a fast way to get into the business. It was easier to get the knowledge compared to reading articles. It also provided more detailed information than you can get through the literature, for example, what is easy and what is difficult. We also got a lot of spill-over knowledge.

Likewise, both Cellartis and the research group learned from AstraZeneca. For example, they got valuable information about specific drugs to test, and this type of knowledge helped them to make the research more efficient.

AstraZeneca thus sees the knowledge base created through the BMV project and other related research activities (e.g. the EU project) as a valuable foundation for continued collaboration with Cellartis and the Sahlgrenska Academy. To look further ahead, if this future work will help AstraZeneca to develop new drugs, for example for treatment of heart failure, this would most probably have substantial effects on AstraZeneca's future revenues and long-term growth. But needless to say, given the long lead times in drug development such a product would be available in the market only in the far future (maybe around 2020).<sup>23</sup>

For the research group at the Sahlgrenska Academy the research carried out so far will lead to a number of publications. This proves that a substantial amount of new scientific knowledge has come out of the project. It is expected that these publications will strengthen Gothenburg's position as an eminent research environment in the stem cell area.

Also as regards BMV, the present project has generated valuable knowledge and insights. First of all, the outcome confirms that BMV as a "cluster-creating" organization can play a key role in multilateral R&D projects – as initiator as well as facilitator and coordinator. Thus, the original objective to help building networks and

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<sup>23</sup> It can be noted that the production of such products would not take place in the Gothenburg region, since AstraZeneca's production plants are located elsewhere.

strengthen the regional environment for research on stem cells and regenerative medicine was fulfilled. The same type of experiences has been gained from parallel multilateral projects in the biomaterials field.

The management of BMV also made some more specific lessons. For example, it was learned how sensitive this kind of project is to the macro-political development – that is, the policy of the US administrations toward stem cell research. The vulnerability of the project due to large companies' strategic decisions is another lesson. Furthermore, as one member of the project management points out the project illustrated how important it is, in order to secure commitment of resources, that the project is well anchored at a high organizational level and that there is a formal contract among all the parties.

To summarize, we can conclude that the project, despite unexpectedly difficult scientific and technological challenges, has generated new valuable knowledge to all participating parties and that this knowledge will be an important input to continued work.

### *Organizational effects*

Above, we have seen how the results in the form of new knowledge have impacted on the R&D activities carried out by the participating actors. For example, the acquired competencies have (or will) become useful in other projects. Another interesting type of observed effect on the R&D activities is what we may call organizational changes. They seem to be of particular importance from a regional point of view.

First, AstraZeneca's site in Mölndal has strengthened its position within the group as an attractive place for conducting stem cell research. In other words, the knowledge built up in Mölndal has increased the probability that future investments in stem cell research and regenerative medicine more generally will take place in Mölndal. Referring to our effect chain model (Figure 1) this illustrates how new knowledge and competencies generated by a particular project can have effects on how future R&D activities are organized.

Second, also for the Sahlgrenska Academy organizational changes, partly related to the multilateral project, lie ahead. For example, it is expected that a new independent research group, specifically focusing on the cardiovascular field, will be formed around Julia Asp, the post-doc who was recruited thanks to the AstraZeneca grant. It is unlikely that such a development (i.e. the creation of a new group) would have taken place without the initiative of BMV, which came at an early and critical stage. Anders Lindahl emphasizes the importance of timing. He means that due to the extremely rapid development within this scientific field during the last couple of years, it would be too late today to enter the field and become a leading player. "We would have been helplessly behind", he says.

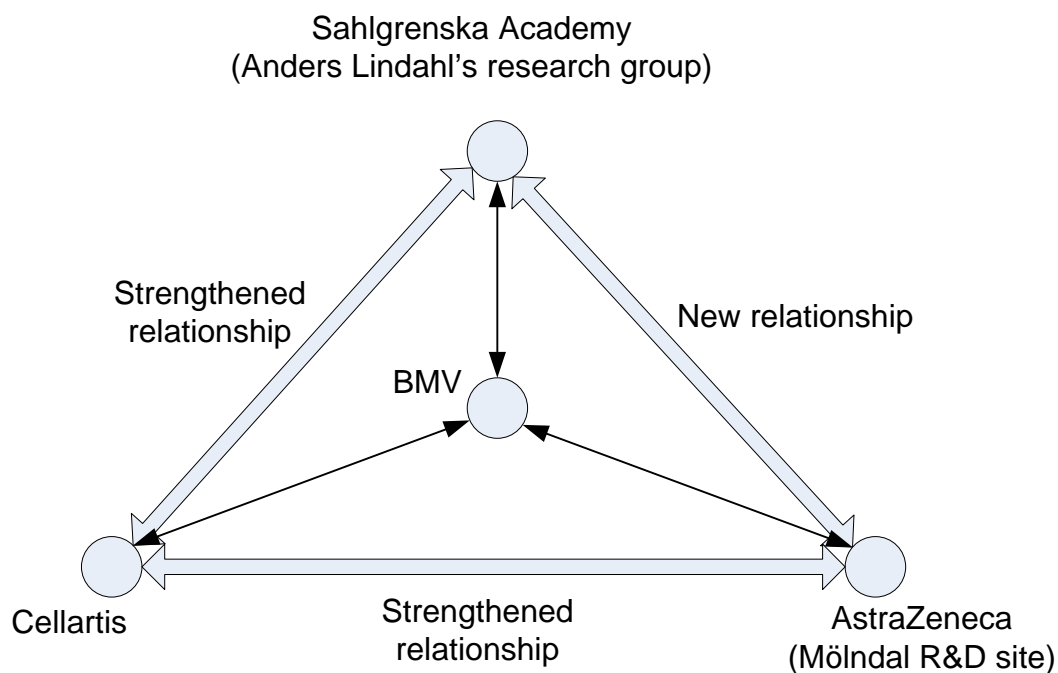
## **6.2 Network effects**

### *The collaborating partners*

Besides the generation of new knowledge the project has had important effects on the relationships between the participating actors. This is illustrated in Figure 3. Thus, the joint research activities that have taken place in the project have resulted in the establishment of new relationships and strengthening of existing ones. AstraZeneca had not

had any previous collaboration with Anders Lindahl and his research group at the Sahlgrenska Academy. This was thus a new link established in the innovation system. The relationship between AstraZeneca and Cellartis was at the time in an embryonic stage and could be further developed thanks to the BMV project (and the other parallel project on safety testing). The relationship between Cellartis and Anders Lindahl was an old one, but still the project contributed to extend the collaboration and further strengthen the ties between the two.

**Figure 3. Effects on relationships between collaborating partners**



Through the project the three parties have got to know each other. They have also learnt more about each other, for example in terms of their respective capabilities, and acquired a shared knowledge base. This may enable each party to better evaluate what the others can offer and what can be achieved by joining forces. In other words, future collaboration among the three parties will be facilitated and the probability of a successful outcome will potentially increase. As it seems today, the tight links that have now been formed among the three partners have a good chance of leading to a broader collaboration that goes beyond the goals of the original project.

Thus, this multilateral project has contributed to strengthen the relationships between Cellartis, AstraZeneca and the research group of Anders Lindahl at the Sahlgrenska Academy. All of them are key actors in the small, and as yet rather embryonic, stem cell 'cluster' existing in the Gothenburg region.<sup>24</sup> In this way, it can be argued that the regional innovation system (RIS) in biomedicine has been positively affected by the project. The tightening of three critical network linkages will enhance the development

<sup>24</sup> There are so far few other actors in this emerging cluster. There are a couple of other research groups at the University of Gothenburg, one of which is now collaborating with Cellartis. On the industry side there is Vitro-life, an older university spin-off and a small start-up, CellMatrix, founded by Anders Lindahl.

capability of the innovation system and possibly lead to new collaborative projects, new products, new business and economic growth. Obviously, BMV's goals to strengthen the relationship between AstraZeneca and the university and to make AstraZeneca a more integrated part of the local research environment have been achieved.

As regards BMV itself, the fourth party in the project, its close contacts with all the others enabled it to play a central role in this network-building process. It is reasonable to assume that BMV's active and successful involvement in the project has strengthened its position and credibility in the network – and this will probably facilitate for BMV to have an impact in other situations where the other parties are involved.

One may ask the question what had happened if BMV had not taken the initiative to start this project. It cannot be excluded that sooner or later some kind of collaboration among the three partners would have emerged. But as pointed out by Anders Lindahl among others the whole process would have been delayed. And given the big investments currently taking place in other parts of the world, the Gothenburg cluster would have been too much behind in order to be internationally competitive.

Interestingly, representatives of AstraZeneca point out that this project from their point of view is unique, in the sense that it is multilateral and comprises partners both from the biotech industry and from academia.<sup>25</sup> AstraZeneca as a group has many R&D partnerships with academic as well as industrial partners around the world. But normally each collaboration is bilateral. The experience of working together with Cellartis and the Sahlgrenska Academy in a joint project (in this case coordinated by BMV) is very positive. It illustrates the advantage of bringing together world-class experts from several organizations in an unconventional way.

### *Other actors in the region*

From a network-building point of view it is good enough that the relationships among the three R&D-performing partners have been strengthened. As we have pointed out all of them are key actors in the innovation system and it is therefore positive that they have been brought closer to one another. While no new relations have been created to or between other actors in the region as a direct effect of the project, some indirect or future effects should be highlighted.

First, the newly established biomaterials center within the Sahlgrenska Academy – BIOMATCELL – integrates needs-driven research on biomaterials and stem cells. The fact is that the research carried out within the InvitroHeart project funded by the EU paved the way for starting the stem cell-related research that is now being carried out at this center. And, as we have already seen, the researchers' involvement in InvitroHeart was in turn a consequence of the BMV-supported project.

Second, looking ahead, there is a potential for Cellartis to use the results from the project in other collaborative activities, within the region or outside. But this has not happened yet, partly because the company has chosen to prioritize other research areas. Recently, as part of its plans to continue developing a cardiovascular screening platform a new development project involving a small Gothenburg-based biotech tool company is planned.

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<sup>25</sup> In the biomaterials field BMV has supported several other multilateral projects involving industrial and academic partners. These projects have been coordinated by the Institute for Biomaterials and Cell Therapy.

Third, if a new research group dedicated to heart stem cells can be established at the Sahlgrenska Academy, a likely effect is that the collaboration with the Center for Cardiovascular and Metabolic Research will increase in the future. The two research environments would have a common interest in using stem cells for cardiac applications and have complementary resources.

### **6.3 Effects on education and training**

Commonly, one of the important effects of publicly funded research projects is that the knowledge developed is used in education and training.<sup>26</sup> While in this case there were no such explicit goals, the grants provided by BMV and AstraZeneca made it possible to employ two post-docs (one at Cellartis and one at the Sahlgrenska Academy). This provided an opportunity for two young PhDs to get advanced training in a scientific field where large resources are now invested around the world and which belongs to a prioritized profile area for the region. One of these PhDs has now got a permanent employment at Cellartis. Furthermore, Anders Lindahl has more recently recruited a couple of new PhD students working on heart stem cells. This means that in the coming years there will be 1-2 doctoral theses in the field.

Lastly, it is worth mentioning that knowledge emanating from the collaborative research on heart stem cells has been included in PhD courses in medicine and in the new post-graduate school for biomaterials and cell therapy called BIOSUM.

## **7 Discussion and conclusions**

The questions posed for this study were what types of effects regional multilateral projects may generate, and which the prerequisites are to achieve such effects. The underlying question as related to policy is if regional multilateral projects may be a good tool to spur regional innovation and growth.

The case analyzed in this report is one of several multilateral research projects supported by BMV. It is exploratory from a scientific point of view, but has a long-term goal to enable the development of an industrially useful screening platform. This platform would in turn make it possible for the pharmaceutical industry to develop new heart drugs based on a novel and pioneering approach within regenerative medicine. In that sense, despite the exploratory nature of the research activities, the project is strongly application-oriented and aims at generating innovation and long-term growth. The project builds upon R&D collaboration among three actors who contribute complementary resources and competencies and play different roles. Clearly, it would have been impossible for any of the partners to carry out this project alone. Effects of the project have been highlighted above, both in terms of what has already taken place and what might be future effects. We do not know what will come out of this process at the end, but the current discussions among the partners indicate that more resources might be invested in heart-related stem cell research in the region. If this happens this will have positive effects on the stem cell cluster in Gothenburg and possibly lead to future growth in the companies.

Generalizing our findings to regional development broadly, it is suggested that multilateral projects can be used as an effective means to build regional R&D networks, at

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<sup>26</sup> See, e.g., Laage-Hellman et al (2009).

least in research-intensive industries like biomedicine. Investing in such projects therefore seems to be a useful strategy for regional development projects which, like BMV, aim to stimulate growth by increasing intra-regional collaboration.

In the discussion that follows we will comment on and draw conclusions from our case as related to a) effects and b) prerequisites and the role of bridging organizations.

## 7.1 Effects of regional multilateral projects

The description and analysis of this case illustrates what type of effects that regional multilateral projects can generate. All three primary effects specified in our model in Figure 1 could be distinguished. The project thus led to valuable new knowledge appropriated by all participating actors. The network effects, especially on the relationships among the R&D-performing partners, were significant and have undoubtedly improved the prerequisites for fruitful cooperation in the future. The project did not have education and training as an explicit purpose, but still there are some effects that should not be disregarded.

As assumed in the model there are chain-linked effects. In other words, the case demonstrates how the direct project outcomes have affected the R&D activities carried out by the parties. The effects take the form of new competencies and methods, the start of new research activities, and organizational changes. These effects can be observed. However, further effects on production and sales of new products and economic growth have not been realized yet. Here, we can only speculate about the possibilities – both regarding the continuation of the focal project and the effects of the strengthened regional innovation system.

In line with these observations we conclude, as the project management of BMV also did, that regional multilateral R&D projects can be used as an effective tool to develop a regional innovation system – provided that the right circumstances are at hand. Thus, it does not go without saying that a successful outcome is guaranteed. Naturally, there are many factors that affect the innovation process and the effects of the project. In the next section, we will highlight some prerequisites that we find to be essential based on our analysis of the stem cell project.

## 7.2 Prerequisites and the role of bridging organizations

### *The role of BMV*

The probability for a successful outcome of a regional multilateral project is dependent on the role played by the bridging organization, and how effectively this role is performed. In our case, it seems fair to claim that without the initiative and efforts of BMV this collaborative undertaking would not have taken place – at least not during the period in question. In other words, BMV helped to kick-start an innovation process within one of the region's focus areas in biomedicine (i.e. regenerative medicine). The contribution of BMV was crucial in several respects. First, by having good contacts within the region the representatives of BMV helped to identify the project idea and form a constellation of actors (both at the organizational and individual level) who could carry out the work. Second, BMV provided seed funding for coordination and execution of experimental work. Third, it contributed professional project management capability. This took place at two levels – through the employed coordinator within the project and through BMV's Johan Anstrén, who was responsible for the CVM focus

area. He took a broader view and tried to link the project to the wider environment, for example, by mediating contacts with actors outside the region.

Thus, by taking an active part in the project BMV not only enabled the partners to start up certain joint research activities but also contributed to push the project forward through various coordinating and managing activities. The case illustrates how BMV, as being a regional development initiative, made it possible to start a multilateral collaboration where existing resources controlled by several regional actors were brought together and used in a high-risk project with potential long-term growth effects on the region. Now, as we have seen this collaboration leads its own life independently of BMV. This is thanks to the new knowledge and competencies that were created through the project and the tight relationships that emerged.

We conclude based on the experiences from the investigated case that BMV, having the task to support the development of the regional innovation system (for biomedicine), if it wishes can have a role to play as initiator of multilateral innovation projects. Such undertakings have a potential to create new and unique knowledge by bringing together competencies and resources residing in different parts of the innovation system. As the case illustrates it is possible to produce research results that are both scientifically high standing and industrially relevant. Furthermore, as also exemplified, such projects may start a chain of related activities, where for instance the outcome of the initial project triggers the starting of new projects. Thus, under favorable conditions BMV can contribute to create a development process which extends beyond the purpose and scope of the originally supported activity.

### *Bridging organizations as initiators and coordinators*

A general conclusion is thus that in order to successfully start up and run multilateral projects, there is a need for a neutral party who can:

1. Form the project – both idea wise and from an organizational point of view
2. Provide seed funding
3. Coordinate the work

In order to be able to perform this role the neutral party needs to have certain *financial resources* to invest. However, as the present case shows good results can be achieved even with a relatively small amount of money.

Furthermore, in order to be able to fruitfully interact with potential and selected project participants the neutral party must be staffed with *people who have appropriate competencies and experiences* within the field (in the case of BMV the persons who managed the multilateral projects, in both focus areas, had had senior management positions in biomedical companies in the region). The staff of the bridging organization also needs to have detailed *knowledge of the regional innovation system and its actors*, for example, know where to find different types of resources. Needless to say, it must also have *good contacts* within the actor network. Finally, it is important to have *legitimacy* within the academic as well as industrial and policy communities. Strong support from leading actors in the region is very useful in this context.

### *General prerequisites*

Besides those aspects discussed above, related to the role of the bridging organization, there are of course many other factors determining whether a certain multilateral pro-

ject will become successful or not. To conclude the paper, let us comment on some more general prerequisites that we have already touched upon.

First, one important aspect of organizing the collaboration is *the handling of legal matters*. This includes, *inter alia*, the management of IP rights. In our case, there was never any formal agreement covering the entire collaboration, which at least some persons regretted. It is hard to say what difference it would have made if there had been such an agreement. It seems that at the operative level the cooperation worked well as long as the project lasted. This was probably due to the trustful relations that emerged among the individuals involved and the limited resources invested in that phase. What hampered the development more than the lack of an agreement *per se* was the fact that AstraZeneca did not have an internal project, which in turn made it impossible to allocate larger resources to the collaboration. But if and when AstraZeneca becomes prepared to invest larger resources in a joint project in this field it will certainly be necessary to have a formal agreement.

Thus, we assume that in general successful execution of multilateral R&D projects requires the existence of an agreement that regulates the ownership and use of IPs, among other things. However, it is difficult to draw any conclusions regarding the IP issue on the basis of this case study. Therefore, this is a research question that we should bring with us to our further studies of multilateral projects.<sup>27</sup>

Second, in general the successful outcome of a R&D project is much dependent on *clearly and realistically set goals*. In the case of projects carried out for the purpose of regional development, such a goal should perhaps not only relate to the direct aim (e.g. solving a specific scientific or technological problem), but be expressed also in terms of the different types of effects analyzed in this paper. For example, one could formulate explicit goals regarding the effects on the network and the development of the innovation system. This may affect, for example, which actors that are invited to participate. Furthermore, having a predefined goal for how the new knowledge should be used in education may increase the likelihood that the appropriate actors are engaged in the process.

Third, *the right timing* is an essential condition. In our case, early entry into the research field seems to be crucial for the ability to establish a strength position, as pointed out for example by Anders Lindahl (see Section 6.1).

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<sup>27</sup> As pointed out by Edgar (2008), there is an increasing importance of public-private partnerships (PPPs) as tools for commercializing university research and creating innovations – not least in the biomedical field. He concludes that a key step in preparing for PPPs is to consider how to claim the IP rights and how their ownership should be managed.

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## Interviews

### Cellartis

Caroline Améen, Scientist	15 September, 2009
Johan Hyllner, Chief Scientific Officer	28 May, 2009
Peter Sartipy, Group Leader	23 June and 7 October, 2009

### AstraZeneca

Sotirios Karathanasis, Vice President Bioscience	29 May, 2009
Per-Ove Sjöquist, Bioscience Department	13 August, 2009
Qing-Dong Wang, Bioscience Department	13 August, 2009

### Sahlgrenska Academy

Anders Lindahl, Professor, Institute of Biomedicine	24 August, 2009
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### BMV

Johan Anstrén, Project Leader Cardiovascular and Metabolic focus area	25 September, 2009
Bengt Belfrage, Project Director BMV	30 November, 2009
Christer Hedman, Business Region Göteborg	24 September, 2009