Regenerative Medicine

Stem cells and biomaterial for implantation

2012-08-20
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Project summary
Regenerative medicine focuses on replacing or regenerating organs or tissues to restore normal function. Stem cell based therapy and biomaterials open up new possibilities to treat severe diseases that have no or lacking treatment today. A lot of research in the field of stem cells and new biomaterials is performed and one important driving force is to bring new knowledge to clinical practice. Region Västra Götaland has the necessary competences, infrastructure and networks to become one of the leading regions for development of new stem cell based therapies and biomaterials for treatment of patients with severe diseases.

Introduction
A stem cell is a cell that can divide and differentiate into various cell types and renew itself to produce more stem cells. Stem cells can be differentiated into various cell types and can be used in regenerative medicine to replace the injured tissue or stimulate the body's own repair mechanisms to heal previously irreparable tissues or organs. Today regenerative medicine is used within bone marrow transplantation, skin transplantation, and cartilage regeneration.

There are different types of stem cells; embryonic stem cells are pluripotent and can be differentiated into all cell types in the body, whereas the adult stem cells only can differentiate into some specific cell types. Stem cells hold the promise for a limitless source of cells for therapeutic applications in various conditions, including metabolic, degenerative and inflammatory diseases, cancer and for repair/regeneration of damaged or lost tissue. Various stem cell types can be isolated from different tissues of the human body, expanded or differentiated in \textit{in vitro} culture conditions, and subsequently administered to patients. Donated fertilized human eggs can be used to establish human embryonic stem (hES) cells lines. These stem cell lines can be cultured \textit{in vitro} and treated in different ways to differentiate into all possible specialized cell types in the body. The aim is to produce specialized cells that can be used to treat serious diseases and injuries.

There is a long tradition and a genuine knowledge how to perform clinical trials in Sweden. Region Västra Götaland has a excellent track record and is a leading actor for clinical trials in Sweden. To further facilitate the possibilities for clinical trials in Region Västra Götaland, Gothia Forum was established as a collaboration platform between industry, healthcare and academia. Gothia Forum offers support to secure high patient safety and competence in the area of clinical research.
The Regenerative Medicine Project
The aim of the Regenerative Medicine Project is to take bench science in the fields of stem cell and biomaterial research to clinical practice; and thereby benefit the patients. This will be done by creating an innovative environment in regenerative medicine for industry, healthcare, and researchers in Region Västra Götaland and to increase knowledge within the regenerative medicine field and form strategies on how to transfer stem cell research into the clinic as an advanced therapy medicinal product (ATMP).

Organization interfaces
Region Västra Götaland is in the forefront of clinical trials and the collaboration between industry, academia and healthcare is substantial. There are several companies (Cellectis Stem Cells, Novo Nordisk, Vitrolife, and AstraZeneca as well as biomaterials and medical implants companies) and academic research laboratories in the area of stem cell research and biomaterials in the region. In combination with a leading transplant unit as well as Gothia Forum and the Clinical Trial Center (CTC), with substantial knowledge in clinical trials, the Gothenburg area is an attractive region for clinical trials with new ATMPs. Most companies and academic research laboratories are localized in close proximity to the Sahlgrenska University Hospital [Fig 1].

Figure 1. The partners in the Regenerative Medicine Project.

Gothia Forum
Gothia Forum serves as a point-of-contact for clinical trials in the collaboration between the research industry, the healthcare sector (Sahlgrenska University Hospital) and the academy (University of Gothenburg, Sahlgrenska Academy and Chalmers University of Technology) and is a part of Region Västra Götaland [Fig 2]. Gothia Forum offers services related to communication, strategic development, project support and quality support. All resources that are needed in clinical trial projects can be accessed through Gothia Forum including electronic medical record databases and quality registries. The project support organization works in close collaboration with most large clinical research companies, including major contract research organizations (CROs). Several trial opportunities are presented for the trial units in the region on a daily basis. Gothia Forum also serves as the management organization for various multicenter trials in Sweden, Scandinavia and Europe.
Figure 2. An illustration of a potential cell therapeutic collaboration in the diabetes area, where Gothia Forum will work as the point-of-contact in the collaboration between industry, healthcare and academy.

**Cellectis Stem Cells**
Cellectis Stem Cells, created in November 2011 from Cellartis AB and Ectycell S.A., possesses broad expertise in pluripotent stem cells, including hES cells, induced pluripotent stem (iPS) cell technology, genetic engineering and specialized cells. The Swedish company Cellartis AB has more than a decade of experience in pluripotent stem cell handling and has been one if the pioneers in the field. This experience and Cellartis technology base is today incorporated into Cellectis Stem Cells, a business unit of the French company Cellectis SA.

Today, Cellectis Stem Cells is a world leading stem cell businesses and has one of largest stem cell banks in the world, including a stem cell line free of animal-components. With a quality controlled good laboratory practice (GLP) facility and ethically derived hES cells and clean, non-genetically modified iPS cell lines suitable for clinical therapies, Cellectis Stem Cells is preparing for good manufacturing practice (GMP) grade laboratories. To enable the use of the iPS technology in clinical therapies, Cellectis Stem Cells has, as the first company in the world, acquired the necessary commercial license from Professor Shinya Yamanaka (Kyoto, Japan). As a first step towards cell based therapy, Cellectis Stem Cells is developing insulin-producing cells with the aim to propagate cells as a potential therapy for diabetes.

**Clinical Trial Center**
The Clinical Trial Center (CTC) is a core facility for clinical research at the Sahlgrenska University Hospital. CTC constitute a platform for both internal and external clinical trials in different treatment areas as well as different phases of clinical trials. CTC is approved to execute anything from first-in-human studies to phase IV studies and can run 20-25 studies simultaneously. During the past 5 years CTC has performed more than 100 clinical trials and has in total more than 30 beds available for in- or out-patient evaluations. In 2011 CTC was selected as the clinical trial site to initiate the pilot study of SCAPIS (Swedish CArdioPulmonary bioImage Study) initiated by the Swedish Heart-Lung Foundation. The full scale study will evaluate in total 30,000 individuals. CTC also serves as the training center for clinical trial staff in Region Västra Götaland.

**Unit of Reproductive Medicine**
The unit of Reproductive Medicine was established in the late 70-ties and performs different kinds of diagnostic procedures and treatments within the field of infertility/subfertility. The unit has since the beginning been leading in the field of implementing new techniques resulting in the first Nordic
babies born after in vitro fertilization, intracytoplasmic sperm injection and preimplantation genetic diagnosis respectively. Since 2001 the unit has been collaborating with Cellartis/Cellectis Stem Cells in establishing hES cells lines. The unit performs 1800-1900 in vitro fertilization (IVF) treatments annually and actively runs several research projects and clinical trials. The unit is ISO 9001:2008 certified.

**The Stem Cell and Tissue Laboratory**

The stem cell and tissue laboratory at Sahlgrenska University Hospital performs stem cell culture for transplantations at Sahlgrenska University Hospital and Queen Silvia Children’s Hospital. By having a clean room laboratory, which fulfills the GMP criteria for human cell therapy, the stem cell and tissue laboratory is also available for culturing cartilage cells that are used in a clinical transplantation trial for cartilage injuries as well as mesenchymal stem cells for clinical trials in disc degeneration. The laboratory prepares and bank heart valves for transplantation purposes. The National Blood Bank for Umbilical Cord Blood is also a part of the stem cell and tissue laboratory that collects stem cells from donated umbilical and placental blood. The stem cell and tissue laboratory is approved by The National Board of Health and Welfare (SOSFS 2009:30,31,32) and accredited by JACIE (Joint accreditation committee ISCT/EBMT).

**The Sahlgrenska Transplant Institute**

Sahlgrenska University Hospital is one of the largest University Hospitals in Europe. The Sahlgrenska Transplant Institute (Transplantationscentrum) was founded in 2007, and focuses primarily on performing highly specialized care in parity with the best centers in Europe. Research within the areas of transplantation immunology, new surgical methods for efficient use of donated organs and regenerative medicine is performed at the Sahlgrenska Transplant Institute. The care of patients is localized in a new, modern building, customed for organ and cell transplantation with a capacity of 30 patients.

Organ transplantations have been performed at the Sahlgrenska University Hospital for more than 40 years. Last year, 310 transplantations were performed at the hospital. Furthermore, Sahlgrenska University Hospital is the leading hospital, and selected for “rikssjukvård” (national center for specialized care), for liver, heart and lung transplantations and is also the only hospital in Scandinavia with a complete transplantation program for all organ transplantations, including small bowel and multi-organ transplants, for both adults and children. Several pioneering transplantations have been performed here. The first heart transplantation in Sweden was performed at Sahlgrenska University Hospital in 1984 by Professor Göran William-Olsson. The first intestine and multi-organ transplantation in Scandinavia was performed on a 4 year old child in 1998 by Professor Michael Olausson. In 2011, for the first time in the world, researchers at the Sahlgrenska Academy managed to create a new connection between the liver and the intestines in a young girl by using a donated blood vessel (treated so that only the supporting tissue was left) covered with blood vessel cells developed from stem cells collected from the girls bone marrow.

Uterus transplantation is approaching implementation at the Sahlgrenska University Hospital. The Regional Research Ethics Committee in Gothenburg has given its approval and the first transplantations are planned to be performed in the autumn of 2012. Professor Mats Brännström at Sahlgrenska University Hospital, is leading a research project concerning uterus transplantation [1].
Biomaterial Research
Encapsulation is a promising approach for stem cell treatment whereby potential immunological problems can be minimized. In such an approach, the area of stem cell based therapy meets the area of biomaterials research, which is focused on the interaction between cells and material and on the development of new materials for implant applications. Region Västra Götaland has a very strong track-record in the development, clinical application and commercialization of biomaterials. The research environment includes the two national Excellence Centers BIOMATCELL and SUMO Biomaterials, of which the former is strongly involved in stem cell research. The research environment also includes SP Technical Research Institute, which is carrying out applied biomaterials R&D and verification work in quality assured laboratories.

Region Västra Götaland thus has the necessary competences and infrastructure for studies related to development, characterization, selection and testing of material candidates for encapsulation of stem cells.

The Regenerative Medicine Project group
Kaj Stenlöf (MD, PhD) – Exec dir, Gothia Forum
Anne Börjesson-Hanson (MD, PhD) – Senior consultant, CTC
Johan Hyllner (PhD) – CSO, Cellectis Stem Cells
Petter Björquist (PhD) – Senior principal scientist, Cellectis Stem Cells
Bo Norrman (PhD) – Dept. for regional development
Anders Lindahl (MD, PhD, Prof) – Dept. of Clinical Chemistry and Transfusion Medicine
Michael Olausson (MD, PhD, Prof) – Transplantation Surgery
Åsa Särlvik – Communication officer, Gothia Forum
Jenny Palming (PhD) – Project manager, Gothia Forum
Christina Bergh (MD, Prof) – Unit of Reproductive medicine
Peter Thomsen (MD, PhD, Prof) – Department of Biomaterials
Legal framework
Somatic cell therapy is a classified biological medicinal and an Advanced Therapy Medicinal Product (ATMP) in the European Union (EU) when the biological characteristics of the somatic living cells have been substantially manipulated or when the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor in order to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. The medicinal products can be used in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) origin. If biomaterials are used in combination with the stem cell therapy it is classified as a combined advanced therapy medicinal product.

Similarly, “tissue engineered product” means a product that contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerate, repair or replace a human tissue. Cells or tissues shall be considered “engineered” if they have been subject to substantial manipulation, or if they are not intended to be used for the same essential function or functions in the recipient as in the donor. Tissue engineered products are also classified as ATMP in the EU.

Swedish laws
The legal framework for performing clinical trials with stem cells and biomaterial in Sweden has been reviewed in a separate report. The laws that have been included in the review are the following:

- Act (2006:351) on Genetic Integrity
- Act (2003:460) on Ethics Review of Research Involving Humans
- Biobanks in Medical Care Act (2002:297)
- Transplant Act (1995:831)
- Act (2008:286) on standards of quality and safety in use of human tissues and cells
- Medicinal Products Act (1992:859)

Legal Framework
In the evaluation of the legal framework for development of new treatments based on regenerative medicine, where the stem cells originate from donated fertilized egg, the laws have been interpreted on the fact that there is no physical donor. Note, if the donor needs to be traced it will be possible to have the medical history, but not the identity, of the donating couple and the genetic information of the fertilized egg.

Couples visiting the unit for Reproductive Medicine at Sahlgrenska University Hospital for in vitro fertilization may donate fertilized eggs that are not used for embryo transfer or cryopreservation for research and commercialization. The donated fertilized oocytes are anonymized before they are formally transferred to the University of Gothenburg for further culturing. The central cells of the blastocyst (approximately 30 cells) are isolated with the aim to create a stem cell line, whereas the other cells of the blastocyst are destroyed. Since the stem cell line is anonymized the cell line cannot be traced back to the donating couple any longer. After the establishment of stem cell lines in
collaboration with Cellectis Stem Cells, the stem cell lines may be transferred to stem cell companies, which can develop biological medicinal products for somatic cell based therapy by differentiating the stem cell line to different kinds of cells. The differentiated cells are transferred back to the Sahlgrenska University Hospital and used for administration to patients.

In order to ensure an exact location, and future removal of the differentiated stem cells, a biodelivery device (e.g. capsules) may be used for surgical implantation. Such medical devices could be approved with CE-marking (The Medical Devices Directive 93/42/EEC; LVFS 2003:11). CE-marking is an assurance by the manufacturer that the device will perform as stated and that the clinical benefit of the device outweighs any side effects when it is used for the intended purpose and in the intended way. The documentation underlying this assurance shall include a clinical evaluation. The evaluation shall be based on clinical data obtained from relevant scientific literature and/or clinical investigations. Clinical investigations shall be undertaken only when necessary information concerning the performance, safety and clinical benefit of the device cannot be obtained by other means than testing it on human beings. Alternatively the combined medical device can be developed and registered parallel to the development of cells. Under the latest scenario the clinical trial will investigate the two elements, the cells, the device under development and the combined product. Later on, the combined product may be assessed by the European Medicines Agency (EMA) only or by both the EMA and a Notified Body for the device piece.

When the stem cell line is anonymized, the cells can be commercialized and used as e.g. medical products. For safety reasons, a sample of each cell line is deposited at the Sahlgrenska University Hospital’s cell bank. It will thereby be possible to trace a specific stem cell line back to the primary cells of that specific cell line. Medical information about the donating couple will be saved together with a deposition of the stem cell line. According to Directive 2004/23/EC (of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells) this information will be saved for at least 30 years after they have been used in the clinic – however no tracing to the donating couple will be possible.

**Risk evaluation**

The use of stem cells and biomaterials in humans may be associated with specific risks to the patient and to the third parties. These risks are determined by various risk factors, which are related to the quality, safety, biological activity and application of the product. The risk evaluation will start during product development. Example of risks that may be associated with cell-based medical products could be: the origin of cells; the ability of cells to proliferate and differentiate; the ability to initiate immune response; the level of cell manipulation; aspects of the manufacturing process; non-cellular components; the mode of administration; and the duration of exposure.

For each stem cell administration project in Region Västra Götaland classified as an ATMP the “Draft guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC for Advanced Therapy Medicinal Products” [2] will be used to identify the specific risks within each project (Table 1). It will also be used to justify the extend of the quality, non-clinical and clinical data generated for the future product and for the Marketing Authorization Application (MAA). By using this guideline, the following information will be gathered about each project 1) the scientific relationship between the risk factors and the risks; 2) the studies performed to address this...
relationships; 3) the locations of these studies in the Common Technical Document (CTD) or Investigational Medicinal Product Dossier (IMPD) documentation of the application.

Table 1. Overview of risk factors and risks that may appear in a project within the field of regenerative medicine and implantation of stem cell and biomaterials into patients.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Tumor formation</th>
<th>Unwanted immunogenicity</th>
<th>Treatment failure</th>
<th>Disease transmission</th>
<th>Unwanted tissue formation</th>
<th>Toxicity</th>
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<tbody>
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<td>Cell starting material</td>
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<td>Culture/feeder cells and growth factors</td>
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<td>Cell population, heterogeneity and differentiation potential</td>
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<td>Ancillary substances devices</td>
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<td>Genetic stability</td>
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<td>Biodistribution</td>
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<td>Relevance of the animal model</td>
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<tr>
<td>Patient-related</td>
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<td>Disease-related</td>
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<td>Medical procedure related – dose</td>
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<td>Medical procedure related – concomitant treatment</td>
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<td>Medical procedure related – mode of administration</td>
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Advisory board for risk evaluation

For evaluating the risks associated with stem cell implantation an external advisory board including experts from the clinical therapeutic area, stem cell therapy, transplantation surgery, laboratory medicine, and regulatory affairs will be formed. The advisory board will be counseled for the study designs, protocol developments, safety and ethical issues before, and during, the conduct of a clinical trial, as well as for review of application strategies.
Stem cell projects within Region Västra Götaland
There are several ongoing stem cells projects in Region Västra Götaland, examples of which are listed below:

Cornea transplantations
A new cornea may be the only way to prevent a patient going blind, but there is a shortage of donated corneas and the queue for transplantation is long. Only a few clinics are currently able to transplant corneas, and approximately 500 of the about 100,000 cornea transplantations in the world every year are performed at the Ophthalmology clinic at the Sahlgrenska University Hospital. Scientist Charles Hanson and Professor Ulf Stenevi at the Sahlgrenska Academy, have for the first time successfully cultivated stem cells on defective human corneas, which may, in the long term, reduce the need for corneas from donors [3].

Chondrocyte transplantations
There is an ongoing clinical trial where chondrocytes are cultured at the stem cell and tissue laboratory at the Sahlgrenska University Hospital, for treatment of cartilage injuries. The technology was pioneered in Gothenburg over 20 years ago and today the technology is spread worldwide with more than 35,000 treated patents in 2011.

Clinical trials
Several randomized controlled trials are performed in kidney and liver transplanted patients every year. These may range from phase I to Phase IV studies and investigator driven trials (IDT).

Autologous stem cell therapy for repairing disc degeneration
About 7000 back surgeries are performed in Sweden every year. Chronic back pain could be caused by e.g. disc degeneration. Associate professor Helena Brisby has identified stem cells niches in close connection to the intervertebral discs, and these stem cells could contribute to recovery of the discs. Studies in animals have shown that injected human stem cells survive and produce proteins that contribute to heal the discs [4]. Autologous stem cell therapy of degenerated discs could be a more lenient way to treat some groups of patients with lower back pain. A clinical trial using stem cell based therapy will start late 2012.

Human Pluripotent Stem Cells
Embryonic stem cells
Stem cells can be isolated from a variety of sources and they are typically classified based on their tissue of origin. hES cells are, as the name indicates, derived from the inner cell mass of pre-implantation stage blastocysts. These cells possess the quality of pluripotency, i.e. the ability to differentiate into all kinds of cells and tissue found in a human body. The development in the field of hES cells during the last decade are remarkable, and the scientific achievements have substantially furthered our understanding of the opportunities these cells provide for basic and applied research as well as for regenerative medicine applications. There is a plethora of research papers published describing methods to drive undifferentiated (i.e.naïve) hES cells to the desired differentiated, or specialized, cell types such as cardiomyocytes, hepatocytes and insulin producing beta cells.
For any clinical application of either hES cells or derivatives such as insulin producing beta cells, a scaled up and quality controlled manufacturing process is paramount. Today, Cellectis Stem Cells is a global leader in the field of industrial scale and quality controlled manufacture of both hES cells and also induced pluripotent stem (iPS) cells (see the iPS cell section). The promise of stem cell based therapy is the main driving force to generate high quality clinically compliant hES cell lines, which can be used for future cell based therapy in humans. As such, the cell lines need to be manufactured according to Good Manufacturing Practice (GMP) in order to comply with Good Clinical Practice (GCP), which is a set of internationally recognized ethical and scientific quality requirements that must be observed for conducting clinical trials in human subjects. Currently there are clinical trials ongoing using hES cell derivatives; Advanced Cell Technologies in collaboration with a number of hospitals in the USA are conducting phase I/II trials for both Stargardt’s macular dystrophy and age related macular degeneration, the latter is also conducted in parallel in the UK [5].

**Induced pluripotent stem cells**

In 2006, Yamanaka and co-workers generated and published the very first report on how somatic rodent cells could be reprogrammed to become induced pluripotent stem cells [6]. Already the year after, two independent groups, including professor Yamanaka’s, reported the successful reprogramming of human somatic cells into iPS cells by introducing different transcription factors into the cells. These proofs of principle definitely opened up a new avenue. Within short, words such as patient-specific and personalized medicine were found making headlines as the news spread around the world. The pharmaceutical industry quickly realized that iPS cells could possibly provide them with a pluripotent stem cell source derived from individual patients with specific clinical conditions. Further, iPS cells derived from many different donors could provide a broad range of genetic variety for in vitro experiments. Today, several technologies are available that allow reprograming of iPS cells without introducing any foreign DNA into the cells, the clean iPS.

Most severe diseases that plague mankind are associated with breakdown of cellular functions, sometimes due to genetic disorders. The high morbidity and mortality of such diseases have implications on the rapidly increasing health care costs worldwide, underscoring the importance of novel treatments. The technology of establishing iPS cells from somatic cells provides a tool for disease modeling and has given new hope for cellular treatments especially in conjunction with correction of the genetic defect. The technique has an enormous medical potential and although rather simple from the very beginning when using viral vectors, the technique has now evolved to circumvent the use of the potentially hazardous viral vectors generating iPS cells devoid of genetic mutations and insertions.

The iPS cell technology has been implemented at the Sahlgrenska Academy in order to establish a core competence center with the aim to establish disease specific iPS cells to be used as disease models and for drug discovery.
Implantation of insulin producing hES cells to patients with Diabetes mellitus type-1

Background
Diabetes mellitus type 1 is an autoimmune disease where the insulin producing beta cells in pancreas are destroyed. This results in decreased insulin levels and thereby increased glucose levels. The incidence of diabetes mellitus type 1 varies among different populations, with the highest incidence in Scandinavia (35/100,000). All patients with diabetes mellitus type 1 need to monitor the blood glucose levels and be treated with insulin. Diabetes mellitus type 1 is associated with several complications e.g. vascular and microvascular complications. Beta cell preservation is an important target in the management of diabetes mellitus type 1 and in the prevention of its related complications.

Islets transplantation would be an ideal therapy for treating patients with severe diabetes to prevent hypoglycemic shock and irreversible diabetic complications. However, there is a shortage of tissue donors and the immune system of the transplanted patients will also attack properly functioning transplanted cells and thereby weakening the therapeutic benefit. The transplanted patients also need to take immunosuppressive therapy, to not reject the transplanted islets. These immunosuppressive drugs are toxic to the islets and associated with new onset of diabetes after transplantation (NODAT). Therefore the encapsulation technique has been used to prevent an autoimmune attack and make the use of immune suppressive agents unnecessary when islets have been transplanted. The capsule is developed and designed as a soft, semi-permeable membrane that protect the cells from the immune system, but allows the islet cells to sense the glucose level and secrete insulin in response to the blood glucose levels (Figure 3). There is diligent and energetic research in the field of biomaterials to improve the capsulation technique.

Diabetes care and research in Gothenburg
Diabetes care and research is central in Gothenburg. The National Diabetes Register (NDR) is located in Gothenburg and is one of four registers in Sweden operating within the highest certification level. NDR was started 1996 to increase the quality of care for adult patients with diabetes and in year 2000 SWEDIABKIDS was founded for children with diabetes; since 2008 all diabetes patients in Sweden, both adult and juvenile, are registered in NDR.

The Diabetes Center at the Sahlgrenska University Hospital is a center for many different specialties within diabetes care. The Lundberg Laboratory for Diabetes Research (LLDR) at the department of
Molecular and Clinical Medicine, focuses on the adipose tissue and its importance for insulin resistance, type 2 diabetes and diabetes associated complications. The clinical research at the LLDR uses both experimental and clinical methods for phenotyping and characterizing molecular mechanisms and clinical trials. The LLDR is a well-known research laboratory within its field and has published an excess of 400 articles in national and international journals.

**Actors in the process of bringing stem cells and biomaterials to implantation**

1. **Unit of Reproductive Medicine**  
   Contact person: Christina Bergh

   Couples that are unable to naturally conceive children receive assisted conception treatment at the Sahlgrenska University Hospital. Surplus fertilized eggs that will not be transferred or cryopreserved can be donated by the couple for research and development, with a possible commercial endpoint through the development of a product based on research performed on the donated fertilized egg.

   The donated fertilized eggs are deposited in the Sahlgrenska University Hospital’s biobank and are subsequently anonymized, i.e. the original identity of the donating couple is made impossible to trace. After this process, the donated fertilized eggs are formally transferred to the University of Gothenburg.

   The collaboration between the unit of Reproductive Medicine, Sahlgrenska University Hospital and Cellectis Stem Cells (former Cellartis AB) was initiated 2001. The collaboration resulted in several hES cell lines and these were later characterized and proven to possess pluripotency; the ability to differentiate from stem cells into various somatic cell types.

2. **University of Gothenburg**  
   Contact person: Anders Lindahl

   The University of Gothenburg will in collaboration with Cellectis Stem Cells isolate the central cells (approximately 30 cells) of the blastocyst to establish a hES cell line. The other cells of the blastocyst are disposed. The traceability will be guaranteed by a deposition of the anonymized hES cell line at the Sahlgrenska University Hospital’s cell bank. The stem cell line can thereafter be transferred from University of Gothenburg to Cellectis Stem Cells.

3. **Cellectis Stem Cells**  
   Contact person: Johan Hyllner

   Cellectis Stem Cells will derive clinical grade hES cell lines in newly built state of the art GMP laboratories. The hES cell lines will be banked, fully characterized and safety tested before the required number of clinical grade hES cell lines will be provided to the customer. Depending on the scenario and the customer’s decision it is also possible for Cellectis Stem Cells to build further GMP production facilities to handle the pilot production and manufacturing of hES cell and differentiation to insulin producing cells for clinical trials at the Sahlgrenska University Hospital.
4. Biomatcell and partners
Contact person: Peter Thomsen

Biomatcell and partners (department of Biomaterial, department of Transfusion Medicine and SP Technical Research Institute) will help with the choice of encapsulation materials. Primarily the commercially and approved materials will be considered, but if new encapsulation materials would be preferable, such materials will be developed in a parallel project. Biomatcell will encapsulate the cells and thereafter characterize and verify the encapsulated cells in vitro, e.g. the viability and function, immunology and the permeability of the capsule. Depending on the available documentation and risk analysis, Biomatcell can also perform in vivo animal studies to ensure safety and efficacy.

5. Gothia Forum
Contact person: Kaj Stenlöf

In the development of new treatment using regenerative medicine, Gothia Forum will act as the coordinating organization, and be responsible for project management and facilitate the contacts between the University, the healthcare provider organizations, and the engaged research companies. Gothia Forum will provide support for applications, budgeting, contracting, and execution of clinical trials. During the planning process Gothia Forum can provide access to various databases that can be used to perform health economic evaluations and feasibility studies. Any communication activity related to a clinical trial project from dialogue meetings with regulatory bodies, recruitment of study participants to media interactions can be managed by Gothia Forum. A number of specific resources such as biobanks/cell banks, legal counselors, statistician, monitors, project managers, clinical trial managers, etc. are easily identified through Gothia Forum.

6. Clinical Trial Center
Contact person: Anne Börjesson-Hanson

The Clinical Trial Center (CTC) is a core facility of the Sahlgrenska University Hospital. CTC will provide state of the art resources for clinical trials evaluating new treatments using regenerative medicine. Head physicians at CTC, with several years of experience from evaluation and testing of new medical treatments, will provide guidance and support during the study planning period and submission process. A separate advisory board for risk evaluation will be set up by CTC upon request. At CTC both small series of patients and larger groups can be studied. All beds at the department are equipped with technique for continuous monitoring of vital signs and ECG recordings. CTC has resources to manage patients twenty-four hours a day, all days, prior to and during the post-surgery period. CTC is audited on a routinely basis by regulatory bodies and commercial organizations, and has a separate department for quality assurance. In studies evaluating new treatments using ATMP CTC can assure excellent and efficient collaboration with any entity within the Sahlgrenska University Hospital.

7. The Sahlgrensa Transplant Institute
Contact person: Michael Olausson

The ATMP will be transferred to the Sahlgrenska Transplant Institute where the differentiated stem cells will be implanted into patients with type 1 diabetes.
Specialists at the Transplant Institute, with experience from ongoing islet cell transplantation, will be responsible for recruiting patients. The transplantation will be monitored by world-leading researchers such as Prof Rorsman at the Transplantation Laboratory.

**Study design**
A first-in-human clinical trial of the safety, tolerability, immunogenicity and efficacy of the encapsulated insulin producing stem cell derived beta cells (ATMP) in patients with type 1 diabetes will be performed at the department of Surgery and at CTC, Sahlgrenska University Hospital. A suggested process for the first-in-human clinical trial is shown in Figure 4 and details for the different parts are listed below.

![Figure 4](image)

**Recruitment and screening**
Suitable patients with diabetes mellitus type 1 will be recruited from the Diabetes Center at the Sahlgrenska University Hospital. A first screening visit will take place at CTC to identify patients fulfilling the criteria for participation in the clinical trials.

**Treatment and evaluation**
After meeting the inclusion and exclusion criteria the patients will have a capsule implanted at the Transplantation Institute at the Sahlgrenska University Hospital and will thereafter be transferred to the phase I unit at CTC for 14 days in-house evaluations. During this period the patient must stay at the hospital and not leave the phase I unit without being accompanied by staff. All meals will be specified according to the content of carbohydrates, fat and protein. The plasma glucose will be monitored with a subcutaneous glucose sensor and in case of plasma glucose levels increase above 15 mmol/L insulin will be administered subcutaneously according to an established algorithm.

Suggested daily evaluations:
- Fasting C-peptide, in the morning
- Plasma glucose × 4 (Capillary blood, Hemocue®)
- Electrolytes: sodium, potassium and creatinine once daily, but more frequently when needed (e.g. if pH decrease)
- Venous pH, bicarbonate and Base Excess, twice daily
- Urine ketones, twice daily
Body temperature and vital parameters, twice daily

Immune reaction to the implant may be evaluated with:
- Endothelial cell antibodies (XM-One)
- HLA antibodies

During the in-house stay at the phase I unit we suggest the following tests to further evaluate the function of the implanted insulin producing beta cells:
- Standardized meal test day 2 and day 12 (C-peptide and glucose measured at 0, 30, 60, 90 and 120 min after the meal)
- Glucagon test day 3 and day 13 (C-peptide measured at baseline and 6 min after intra venous glucagon administration)
- Arginine test day 6 (at hyperglycemia, monitoring of insulin, C-peptide and glucagon 45 min after intra venous arginine administration)

**Capsule removal**
After 13 days the capsule will be removed at the surgical department, and pre-trial insulin regime will be reinstated. The patient will be monitored for an additional 24 hours period.

**Follow-up**
Follow-up visits will take place at CTC after one (day 30) and three months (day 90). At these visits metabolic control measured as HbA1c, HLA and endothelial antibodies will be evaluated.

**Costs**
The costs below are estimations for a first-in-human patient and are covering the costs facilities at CTC and Transplant Institute.

**Screening**
6,000 SEK
Screening and identifying suitable patients for the clinical trial at CTC

**Implantation**
30,000 SEK
Implantation of encapsulated insulin producing stem cell derived beta cells in patients with type 1 diabetes at the Transplant Institute

**In-house evaluation**
280,000 SEK
In-patient care for 14 days at the phase I unit at CTC including 2 days post-treatment care after capsule removal Blood samples and analysis Tests – standardized meal test, glucagon test and arginine test

**Capsule removal**
30,000 SEK
Removal of the capsule at the Transplant Institute

**Follow-up**
4,000 SEK
Patient follow-up at CTC

**Total cost per patient**
350,000 SEK
References


