Document title
National Strategy for the Development of Clinical Cell Therapy in Sweden

Contact:
National Cell Therapy Group **Att:** katarina.leblanc@ki.se

National Strategy for the Development of Clinical Cell Therapy in Sweden

Abstract

This document describes a strategy for development of cell therapy in Sweden. It also includes a proposal for sharing of existing resources and a plan for future investments in the area. This task was assigned to the National Swedish Cell Therapy Group established by the Swedish Association of Local Authorities and Regions (SALAR) National tissue project.

1 Introduction 4
1.1 Scope, purpose and authors 4
1.2 Background 4
1.3 Funding 4
1.4 Purpose of the strategy 5
2 Brief survey of strategies for cell therapy in other European countries 5
2.1 National level 5
2.2 Pan European level 5
3 Current ongoing cell therapy activities in Sweden 5
3.1 Established cell therapies 6
3.2 Cell therapies, early clinical applications 6
3.3 Cell therapies, close-to clinical application and developing projects 7
3.4 Facilities, equipment and methods used for cell processing 7
3.5 National and international collaboration 8
4 Present facilities and capabilities 8
4.1 Premises used 8
4.2 Quality system 9
4.3 Documentation and IT system 9
4.4 Number of employees 10
5 Future cell therapy activities in Sweden 10
6 Changes or resources needed to fulfill tissue regulation requirements 10
7 Analysis of as-is situation, and desired situation in 5 and 10 year's perspective 11
7.1 Current situation 11
7.2 5 year perspective 11
7.3 10 year perspective 12
8 Analysis of different possibilities for collaboration including sharing qualified services 12
8.1 Facilities 12
8.2 Sharing of qualified services 13
8.3 National testing 13
8.4 Educational programme 14
8.5 National document repository 14
9 Strategy for national coordination 14

9.1 Objectives 14
9.2 Organization 15
9.3 Forms for collaboration 16
9.4 Next step to reach objectives 16
9.5 Financing (Present – 5 years) 16
10 Summary 16

1 Introduction

1.1 Scope, purpose and authors

The scope of this document is to present a strategy for development of cell therapy in Sweden. The aim of the strategy is to foster, strengthen and optimize the collaboration between the cell therapy establishments when implementing the conditions of the EU tissues and cell directives and regulations. The strategy originates from the decision from the Swedish Association of Local Authorities and Regions (SALAR) National tissue project about grant distribution for investments in tissue establishments. The strategy ultimately aims to make cell therapy development successful. The strategy is authored by the National Cell Therapy Group consisting of Katarina LeBlanc (chair), Claes-Göran Axelsson, Pontus Blomberg, Olle Korsgren, Gunnar Kratz, Anders Lindahl, Stefan Scheding and Mikael Wiberg

1.2 Background

1.2.1 Legislation

At the European level there are several directives (2004/23/EC, 2006/17/EC and 2006/86/EC) and a regulation (1394/2007) that describe how cells and tissues intended for human use should be handled. This has been transposed into a Swedish law (SFS 2008:286) that regulates tissues and cells used for human applications. Additional information is found in regulation SFS 2008:414. The Swedish Medical Product Agency (MPA) has issued provisions (LVFS 2008:12) for cells and tissues classified as pharmaceuticals or intended for pharmaceutical production. For cells and tissues not classified a pharmaceuticals, the Swedish National Board for Health and Welfare (NBHW) has published provisions on donation and procurement of organs, tissues and cells (SOSFS 2009:30), tissue establishments (SOSFS 2009:31) and use of cells and tissues in health care and clinical research (SOSFS 2009:32). The provisions are currently under implementation in the Swedish health care system.

1.2.2 Cell therapy in Europe and Sweden

Cell therapy is a novel treatment modality that has potential to provide cure for diseases and injuries that are not possible to treat today or diseases and injuries for which treatments are inefficient. Most cell therapy projects are still conducted as experimental procedures and it was not until last year (2009) that Europe got its first market approval for a cell therapy product. The situation in Sweden and Europe is similar. A number of Phase I and pilot studies are carried out or are underway to enter the clinic development phase. Some examples of projects are listed in Section 3. The complexity of the area is demonstrated by the plethora of different cell types and disease indications represented.

1.3 Funding

Current clinical applications are under development and are not yet established as routine standard of care. This means that the costs of these projects mainly have to be covered by external grants. However, running clinical studies is very expensive and such costs are normally not something that would fit within a research budget for an academic clinical

researcher. Furthermore, the processing of cells and tissues for human use requires new methodology and advanced laboratory facilities. Thus, to secure that the processing of cells and tissues for human use is compliant with the new EU legislation, tissues and cell establishments must invest in advanced facilities. Although the construction costs are high as such, it must be emphasized that in a running perspective such infrastructures are strongly characterized by high maintenance costs.

1.4 Purpose of the strategy

At present there is no Swedish governmental strategy for the development of the cell therapy area. Instead, each medical specialty is responsible for the strategy of further development of needed or proposed therapies. The existing establishments are operating fairly independent of each other. However, cell therapy is a complex area and collaboration between tissue establishments is important for success in the cell therapy field. Thus, the purpose of the strategy is to foster, strengthen and optimize the collaboration between the cell therapy establishments to fulfill the tissue regulations in a resourceful and efficient way.

2 Brief survey of strategies for cell therapy in other European countries

2.1 National level

In Great Britain, Germany, Holland and Belgium there are no national strategies for cell therapy development. However, there are several interest groups and working parties in these countries, with focus on specific cell types and treatments, but a coordinated strategy is not in place.

2.2 Pan European level

Given the large resources required to take a cell therapy product from the laboratory bench to the clinic, several EU programmes have been initiated to promote collaboration and sharing of resources between different countries. Examples of such networks are the European Clinical Infrastructure Network (ECRIN), European Advanced Translational Infra Structure (EATRIS) and Clinigene. There is Swedish representation in all these networks

3 Current ongoing cell therapy activities in Sweden

There are a large number of various cell therapy programmes at Swedish hospitals and research institutes. The projects in these programmes are in various phases ranging from early development to clinical applications. Below are some examples.

3.1 Established cell therapies

3.1.1 Autologous chondrocytes for treatment of localized cartilage injuries in the knee.

Application of chondrocytes for cartilage repair was pioneered by Professor Anders Lindahl at Sahlgrenska more than 20 years ago. Today more than 1500 patients have been treated. The methodology has been developed from open knee surgery to artroscopic procedure.

3.1.2 Donor leukocyte infusion (DLI)

This is an established treatment for relapse after allogeneic stem cell transplantation that is performed at the university hospitals.

3.1.3 Islet cells for diabetes

In a Scandinavian programme, headed by Professor Olle Korsgren at the Uppsala university hospital, insulin producing islet cells are isolated from donated pancreas and used for the treatment of severe diabetes. These cells are distributed to hospitals in the Nordic countries. More than 100 patients have been treated within this programme since 2000, establishing the program as one of the largest worldwide.

3.2 Cell therapies, early clinical applications

3.2.1 Mesenchymal stem cells

Professor Katarina LeBlanc at Karolinska University Hospital, Huddinge has for a number of years been conducting research on application of mesenchymal stem cells in treatment of cancer. More than 100 patients have been treated for various indications, mainly complications of hematopoietic stem cell transplantation.

3.2.2 T cells for cancer

A program of adoptive T cell therapy for high-grade malignant melanoma is running since 2005 at Uppsala university/Academic hospital and is headed by Professor Thomas Tötterman. Thirty patients have been treated with approximately 50% (CR+PR+SD) anti-tumor responses. This is the first series in Europe and the second largest globally.

A clinical study, where treatment of patients with advanced malignant melanomas are treated with a combination of autologous Tumor Infiltrating Lymphocytes (TIL) and a melanoma Dendritic Cell vaccine, has been approved by the Swedish Medical Product Agency, is headed by Rolf Kiessling and Giuseppe Masucci, Cancer Center Karolinska (CCK). This is the first TIL therapy approved by the Swedish MPA, and so far 3 patients have been accrued to the study.

3.2.3 Sentinel node based immune therapy for cancer using autologous cells

Currently, a randomized Phase II study on metastasized malignant melanoma, Mel-Swe-01, is under way. The trial is conducted in cooperation with several clinics around the country. The next clinical trials that SentoClone AB will undertake are studies on pleural cancer (malignant mesothelioma), renal cancer and urinary bladder cancer.

3.2.4 NGF producing cells for Alzheimer's disease

Encapsulated cells expressing NGF have been used in a Phase I trial to treat patients with Alzheimer's disease. This trial is a collaboration between Professor Maria Jönhagen at Karolinska University Hospital, Huddinge and NsGene, Denmark.

3.3 Cell therapies, close-to clinical application and developing projects

3.3.1 NK cells for cancer

At Karolinska University Hospital, Huddinge, two different NK cell based projects for treatment of cancer are approaching clinical treatment. In one project Dr. Karl Malmberg is using activated NK cells to treat cancer. In the second trial conducted by Dr. Hareth Nahi in collaboration with Avaris AB, expanded autologous cells will be used to treat myeloma.

3.3.2 Hepatocytes

Hepatocytes are isolated in Uppsala and Stockholm with the intention to treat severe liver failure.

3.4 Facilities, equipment and methods used for cell processing

A process for the processing of cells for cell therapy applications typically involves: 1) isolation of cells, 2) separation of cells and/or culturing of cells, 4) activation of cells, 5) infusion of cells into the patient. The cell processing steps normally take place in a clean room environment which requires a dedicated facility. There is a large variety in the equipment used in cell processing for cell therapy. For clinical production it is important that the processes and equipment are validated, properly maintained and that all critical steps are described in SOPs. The processes have to be carried out by specially trained staff that has the required skill and know-how.

3.4.1 Clean room facilities

Open handling of cells and tissues will require A-class environment in order to prevent contamination. Class A environment with a Class D background environment is required when tissues and cells are intended for transfusion. This type of environment is achievable by using a LAF-device for Class A and a ventilation system designed to achieve Class D background. Production of sterile pharmaceuticals generally requires Class A environment with Class B background. To operate a Class A with Class B or Class C background facility, substantial investments and careful planning is needed in creating optimal ventilation systems and lay-out of the clean rooms.

3.4.2 Cell isolation

Procedures for the collection, separation and concentration of cells from blood or bone marrow are often carried out at blood establishments using well established centrifugation technologies.

Hepatocytes and islet cells are enzymatically separated from donated organs. The concentration and isolation is performed by centrifugation technology. The procedures take place in a LAF unit in a clean room facility. This is also the case for the isolation of chondrocytes.

The CliniMACS technology based on magnetic beads coupled to antibodies is a fairly novel technology for cell separation. This is a closed system consisting of bags and tubings that may be operated in a less strict environment, i.e. in a Class D environment.

3.4.3 Cell separation

Separation may be carried out by centrifugation by blood establishments. The CliniMACS technology based on magnetic beads coupled to antibodies is a fairly recent technology for cell separation. This is a closed system consisting of bags and tubings that may be operated in a less strict environment. Separation of cells can also be done by FACS.

3.4.4 Cell culturing

Depending on scale and cell type/tissue a number of systems are used for cell culturing. These ranges from tissue culture dishes and flasks to closed systems like cell factories, cell cubes and Wave bioreactors for large scale production. The volume scale ranges from mL to 10L.

3.5 National and international collaboration

Collaboration is ongoing both at the national and international level. One such example of a successful collaboration is development of mesenchymal stem cells for treatment of graft-versus-host disease as part of European multicenter studies. A second example is the insulin producing islets cells that are processed in Uppsala and distributed throughout the Nordic countries. A third example of collaborated utilization of an infrastructure is the Good Manufacturing Practice (GMP) facility at Karolinska. This facility is used for cell therapy purposes by Swedish and international academic researchers, as well as Swedish and foreign biotech companies and pharmaceutical industry.

4 Present facilities and capabilities

4.1 Premises used

Processing of cells for patient treatment in Sweden is carried out at several different tissue establishments that are presented below. In addition to the listed facilities, cell processing within public health care providers, is taking place at blood bank establishments.

4.1.1 Stockholm

In the Stockholm area there are several facilities for manufacturing and processing of cells for cell therapy. Vecura at the Karolinska University Hospital, Huddinge is a state-of-the-art multi-purpose GMP facility for production of gene therapy vectors and cells for cell therapy. The facility, which has been in operation since 1996 was rebuilt in 2006-2008 to accommodate manufacturing of cell therapy products, has capacity to carry out simultaneous production of up to ten different products. The facility is licensed by MPA and NBHW. At the Cancer Center Karolinska (CCK) in Solna there is a second facility which is mainly focused on cells for immune therapy. A third facility consisting of two clean rooms is to be constructed at the blood establishment at Karolinska Huddinge for donor lymphocyte infusions (DLI) among other things. Sentoclone AB has recently built a GMP approved clean room facility in Sundbyberg for commercial processing of sentinel node cells.

4.1.2 Uppsala

In Uppsala there is a clean room facility at the Rudbeck university laboratory. The facility consists of 14 clean room suites. Ten of these may be classified as Class B and 4 Class C. However, at present these rooms will be operated as Class C and D. The facility will be in full use by the end of 2010. At present, stem cells, islet cells, and T-cells are handled at the facility, whereas fibroblasts are handled in another laboratory. Both laboratories are approved by the NBHW. In the future, corneas, hepatocytes and T-regs may be handled at the facility. Approximately 30 people will be working at the facility when running at full capacity.

4.1.3 Skåne (Lund)

At the blood establishment in Lund a clean room suite that meets GMP requirement are planned to be built (rebuilt). There is considerable activity in basic research (stemTherapy, HematoLinné) in the cell therapy field in Lund and it foreseeable that some of this research may reach the clinic in a near future.

4.1.4 Östergötland (Linköping)

In Linköping there are 3 laboratories for cell processing that have GMP classification. The laboratories are new and were inaugurated in 2010. In these clean rooms keratinocytes, melanocytes, urothelial cells (from autologous urethreas), human skin, and corneas are processed. Clinical trials are planned for trans-differentiated fibroblasts that will be processed at the facility.

4.1.5 Norrland (Umeå)

Umeå University is currently constructing a second clean room (Class B) that is intended for cultivation of mesenchymal stem cells and Schwann cells. The first clean room (Class B) was built under instructions and advise from the NBHW and is currently used for isolation and culturing of mesenchymal stem cells; the isolation is at present in clinical practice. Two more rooms (Class D) for hematopoietic stem cells and corneas and one additional Class B room will be constructed.

4.1.6 Västra Götaland (Göteborg)

In Göteborg there is one GMP-classified clean room for processing of cartilage cells for transplantation. One additional room for heart valves will be constructed during 2011. Permits for tissue establishment for cartilage cells and heart valves have been obtained from MPA and NBHW, respectively.

4.2 Quality system

European and Swedish legislation present quality system for the handling of tissues and cells intended for the treatment of humans (Commission directive 2006/68/EC, SOSFS 2009:31, LVFS 2008:12). Compliance to these regulations is required to obtain approval as tissue establishment by NBHW and MPA.

4.3 Documentation and IT system

The existing laboratories operate independently of each other. The different facilities have their own documentation system and there is presently limited exchange of experience and

documents between the sites. Since most cell therapy treatments are experimental and involve small patient groups, the limited amount of data generated can be handled manually and the need for IT systems is not imminent.

In the Regulation (EC) No 1394/2007 it is stated that the Commission shall draw up detailed guidelines relating to traceability, including documentation of starting and raw materials, substances which may have been into contact with the tissues or cells during handling (including transportation), etcetera and that information must be kept for at least 30 years after their expiry date. These guidelines have not yet been published.

4.4 Number of employees

The interdisciplinary nature of most cell therapy projects makes it difficult to estimate the number of employees involved in cell therapy research or individual projects in Sweden. Some of the facilities are multi-purpose which means that it will depend on the number of projects and which type of project is running at a given time point. As an example; at the Vecura facility at Karolinska there is eleven permanently employed core staff members, but the total number of people working in the different projects are around thirty full time workers.

5 Future cell therapy activities in Sweden

Cell therapy is currently a very active research field in Sweden and there is no indication that this will change. There will be an increasing number of projects that will reach a state where their feasibility has to be tested on patients. The majority of these treatments will be applied on small patient groups. The treatments are often autologous or otherwise specific for a certain patient. A bottle-neck in the translation from the bench to the clinic has been certified facilities for the processing and handling of cells. However, the governmental funds distributed by SALAR will have a major and pivotal impact on this problem, since facilities have received grants to adapt and maintain the infrastructure including document handling so that they will be able to comply with the recent legislation.

Future practice of cell therapy in Sweden will continue to require funded expensive laboratory facilities, as well as, special equipment and will for these reasons be limited to the university hospitals. It is conceivable that an increasing number of cell therapy based treatments will be introduced in routine clinical practice in a not too distant future. Some of them will need approval from the NBHW alone, others will need a license from the MPA and most of them will probably need marketing authorization from the European Medicines Agency (EMA) as advanced cell therapy products.

6 Changes or resources needed to fulfill tissue regulation requirements

Fulfillment of the tissue regulation or medical products requirements and current legislation requires substantial resources.

Facilities need to be constructed or re-constructed in order meet the specifications stipulated in SOSFS 2009:31. For example, at present there are only a limited number of laboratories that maintain Class A environment in a Class B or C or D environment, which in many cases are mandatory for processing of cells. This work, which is already ongoing in Uppsala,

Stockholm, Linköping, Umeå, Lund and Göteborg, has been partly financed by government funding through SALAR. Following construction, the facilities need to be validated which is a costly and time consuming exercise. Once this is completed there does not seem to be an immediate need for additional facilities.

The resources required to operate the lab over time should not be underestimated and may well exceed the construction cost. Environmental monitoring must be done on a frequent basis, ventilation filters needs to be checked and replaced when needed, and cleaning programmes have to be in place. The production processes that will be used for manufacturing need to be developed and validated.

An essential part of the infrastructure is the documentation system. The documentation system describes all the processes and activities at the facility including organization, cleaning procedures, gowning procedures, validation, environmental monitoring, production processes, educational programmes, maintenance, self-inspections, procedures for release, record keeping, recalls etc etc. The documentation system needs constant updating and revision and requires substantial resources in order to be compliant, as well as accessible for a considerable time, at least 30 years.

Last but not least, the facilities need to be operated by staff members with proper training and experience to operate a clean room facility, as well as, the knowledge to carry out state of the art cell processing procedures.

7 Analysis of as-is situation, and desired situation in 5 and 10 year's perspective

7.1 Current situation

At present cell therapy treatment in Sweden is carried out at the university hospitals in Umeå, Uppsala, Linköping, Stockholm, Lund and Göteborg. Governmental funds have been made available through SALAR to make necessary constructions and adjustment in order to meet the new Swedish legislation. Since lack of infrastructure has limited innovation, this is also a very significant contribution towards full development of these new therapies in Sweden.

The facilities operate fairly independent from each other. This is partly due to the fact that they specializes in different cell types and have different expertise. Nevertheless, cells processed at a certain facility at a specific hospital are frequently shipped to other Swedish hospitals for use.

7.2 5 year perspective

In a 5 year perspective, the number of clinical cell therapy treatments is expected to increase. Given the nature of the treatment (small pilot studies, expensive infrastructures, transplantation), future development is still mainly driven by academia and public health care.

The current construction phase is gradually replaced by an operational phase where the constructed or reconstructed facilities are operating at full capacity. To reach this phase it is crucial that sufficient resources are made available so that the facilities may continue to operate in compliance with the new legislation.

The industry will continue to play a role in developing and providing reagents and equipment. Small and middle-sized enterprises may also participate in processing tissues on a contract basis. Some of them may even develop new therapies and put them on the market. However, most cellular therapies will not have sufficient commercial value to be subject for marketing by private enterprises. Small scale cell therapy projects will therefore most likely be handled by tissue establishments within the university hospitals.

7.3 10 year perspective

In 10 years, cell therapy will be part of clinical routine practice and it is foreseeable that some programmes have been made available to large patient groups. This will require additional facilities with high capacity that are purpose built for specific applications. However, the need for increased advanced clean room capacity is difficult to foresee at this time. For example, there is currently an ongoing development towards closed production systems that might be operated outside a clean room, i.e. in a Class D environment.

8 Analysis of different possibilities for collaboration including sharing qualified services

Cell therapy is a very diverse field, including projects where small patient groups are being treated for various disorders in a number of different studies. This type of project is generally very costly and requires expensive infrastructures. For this reason it is important to coordinate such efforts in a resourceful way.

At the European level there is considerable work on the integration and maintenance of existing facilities into a European-wide infrastructure. This includes sharing of knowledge in cell processing, training of staff, sharing of SOPs, and sharing of laboratory facilities.

For a small country like Sweden with limited resources it is even more important to coordinate such efforts in a resourceful way. There are several areas listed below where such a national, or even Nordic coordinated effort would be pertinent.

8.1 Facilities

Since there are high costs associated with running cell processing facilities the proposed solution is to concentrate cell processing to a limited number of sites. In Sweden such solutions are to some extent already the case and at present there are several well established cell processing facilities that specialize in certain cell types. This includes a facility for preparation of islet cells in Uppsala, a facility in Gothenburg for preparation of chondrocytes and a facility in Linköping for fibroblasts. In Stockholm, Vecura at Karolinska University Hospital is processing several different cell types including mesenchymal stem cells.

With a few exceptions, cell therapy is still mainly an experimental procedure. The feasibility for its role in public health care is investigated in a number of different clinical trials where various cell types are being applied for a wide variety of diseases. This means that the processing, manufacturing and clinical protocols are very diverse. A trial may take several years to complete and the need for the manufacturing facility may be sporadic. For these reasons, it is not resourceful at this point to establish facilities for each and every treatment. Instead, existing centers for cell processing may well serve the need for cells for novel treatments already tested in pilot and Phase I trials. Such centers will have both the required expertise and infrastructure to set up and validate new production processes for various cell

types. Once the treatment protocol is established or in clinical practice, a limited number of product specific cell processing units might be considered, but should as far as possible be carried out in collaboration with established blood establishments.

8.2 Sharing of qualified services

8.2.1 Cell culturing

Cell culturing of cells is a key step in many cell based therapies. Establishing conditions for optimized cell growth is a daunting task that may include optimization of growth media, growth factor cocktails, development of serum free conditions, harvest times etc for fulfillment of quality requirements. Furthermore, it is important to keep in mind that some cell types are not suitable for distribution and need point-of-care processing.

8.2.2 Cell processing

Processing of cells usually takes place in close context to cell culturing. However, some protocols do not require cell culturing, i.e. preparation of hepatocytes for transplantation, preparation of islet cells, selection and activation of NK-cells, selection of lymphocytes. In analogy with cell culturing, some of these procedures may be centralized to one or a few centers. For example the islet processing facility in Uppsala is providing cells to all the Nordic countries. This requires that the cells are able to be transported and that there is a well-functioning infrastructure for shipping and receiving of cells and tissues. As mentioned above, this in not always the case, or the cells are simply just not robust enough the survive shipping. In such cases a local cell processing facility may well be motivated. An alternative that may be considered is that the patient (if in good enough health) may travel to a processing site for treatment.

8.2.3 Distribution

Centralized facilities will require a system for distribution of cells between the tissue establishments and hospitals. This system should as far as possible be based on already existing services.

8.2.4 Storage

There are a number of different cells that potentially could be stored for subsequent use or as reference cultures. However, at present there is no need for collaborative storage.

8.3 National testing

The produced products have to be tested so that they meet the preset quality criteria prior to delivery and patient use. The testing should not be carried out by the same staff that is carrying out the cell processing.

Testing of the produced products can be very expensive and is in many cases done by external contract laboratories specializing in such testing. Efficacy testing of cell therapy products is somewhat complicated since novel tests need to be developed for each specific cell type and indication. Sweden has considerable knowledge and expertise in the cell therapy area and it is suggested that a national testing programme is put in place in order to facilitate testing and to lower the costs. Furthermore, such a programme would facilitate the development of tests for novel cell therapy treatments, as well as, the cost of standardized testing.

8.4 Educational programme

The cell therapy area is rapidly evolving and a number of different novel treatments are being investigated and applied in the clinic. The processing of the cells is often carried out by research personnel with expertise in handling a specific cell type but with limited experience in quality assured manufacturing. For this reason it is proposed that an educational programme is established which allows staff that will work at tissue establishments and GMP facilities to get training in quality assured manufacturing of cell therapy products. The programme should contain sessions on legislation, documentation, aseptic techniques, validation of instruments and new processes etc. The programme should contain theory, as well as, hands-on work shops.

8.5 National document repository

Documentation is an essential part in the operation of a tissue establishment. The documentation system should handle everything from organization to SOPs for specific steps in cell processing, as well as, specific donor and patient information for safety and tracing purposes. However, establishment of a documentation system is a taxing task that requires substantial resources. Currently, documentation systems are not in place in all Swedish tissue establishments. A national document repository for sharing of documents and SOPs would be a valuable asset in creating and maintaining documentation systems. An example of such a system already in use is the E-archive at the Stockholm County Council Archive and Biobank center. This system can be adjusted to accommodate the repository.

9 Strategy for national coordination

9.1 Objectives

9.1.1 Facilities (Present - 3 year perspective)

- An integrated coordination of existing processing facilities is needed such that overlap is minimized. To this end it is suggested that cell processing are centralized when possible and motivated. At present this is exemplified by successful processing of islet cells in Uppsala, skin cells in Linköping, chondrocytes in Göteborg and mesenchymal stem cells in Stockholm. Furthermore, in the event of an increased need, the most resourceful way to meet this demand is to increase the capacity of the existing units rather than establishing new ones.
- Clean room facilities should be available at the university hospitals in Göteborg, Stockholm, Linköping, Lund, Umeå and Uppsala. The reason for this is that it should be possible to carry out pilot studies at these hospitals. Another reason is that cells sometimes can be very sensitive to transportation and needs to be processed in close proximity to the patient. These already established facilities, that also should serve as national centers for processing of cells, may be operated under GMP.
- Since most clinical trials currently are rather small, it is not justified to construct new clean room facilities complying with GMP standards for individual projects. Instead, it is suggested that the already established GMP facilities at the university hospitals should serve as national resource centers for cells that requires processing in a Class A/Class B environment.

- In a long-term perspective it is likely that there will be an increased need for facilities for cell processing. It is foreseeable that in a near future cell therapy treatments will be available to larger patient groups. This will require larger purpose built facilities. However, it is very difficult to assess future need for clean room facilities at this time. Novel closed systems for cell processing are currently being developed and this could decrease the need for clean rooms. With such equipment available cell processing that today requires advanced clean room environment could be carried out at tissue establishments in a Class D environment.

9.1.2 National resources for coding of cells (1 year perspective)

- The new legislation requires that cells and tissues for use on humans are coded. Since the cell therapy area consists of many different cell types that are processed in a variety of ways there is a great need for support in the designation of codes to these cells.

9.1.3 Educational programme and work-shops (1 year perspective)

- Since working at a tissue establishment requires special skills an educational programme should be created. This programme should cover documentation, record keeping, aseptic procedures, validation of equipment and processes as well as legal aspects of manufacturing of cells and tissues for use on patients. This programme should contain theoretical classes and hands-on training relating to manufacturing of cell therapy products.

9.1.4 National repository (3 year perspective)

- A national repository for SOPs (cleaning, gowning, environmental monitoring, production processes, product testing), applications to authorities, should be created.

9.1.5 System for distribution of cells (3 year perspective)

- Cell therapy programmes centralized to one or a few tissue establishments will require efficient systems for shipping of cells between tissue establishments and hospitals in different parts of the country. System for national distribution including traceability and cross reference capabilities needs to be developed.

9.1.6 National testing programme (5 year perspective)

- Since testing is very costly and difficult to establish a national programme for testing of produced products should be coordinated.

9.2 Organization

- During the course of the SALAR-Tissue Project the National Cell Therapy Group has been very successful in creating a strong platform formed of leading representatives for different cell therapy areas and hospitals in Sweden. This group will continue to meet and may very well serve as an operational committee, under the National Council for Cells and Tissues, for the realization of the national strategic plan presented in this document.

9.3 Forms for collaboration

- Collaboration between scientist and clinicians in the cell therapy field is already well established. The educational programme including work-shops and seminars will strengthen collaborations between the facilities. Meetings arranged by the national cell therapy group will also serve as an important occasion to meet with colleagues.

9.4 Next step to reach objectives

- The proposed objectives will be initiated by the National Cell Therapy Group that will make a 2-year implementation plan. The group will also identify individuals that will be responsible for the implementation of the different programmes as well as participating as national experts in the process of new European and Swedish legislation on cell therapy.

9.5 Financing (Present – 5 years)

- During the next 5 years the construction phase is changing to an implementation phase. In order for the establishments to maintain compliance funds have to be allocated to cover operation of the facilities. Funding is also needed for the educational programme, the national repository and the resource for coding of cells.

10 Summary

- Clean room facilities should be restricted to the university hospitals in Sweden.
- Future need of additional clean room capacity should be met by increasing the capacity of existing facilities before deciding on establishing new ones.
- Processing of chondrocytes, islets and mesenchymal stem cells should be carried out at established facilities in Göteborg, Uppsala and Stockholm respectively.
- The advanced clean room laboratories at the university hospitals, that may handle several projects in parallel requiring Class B or Class C background environment, should offer service to research projects which are lacking such resources for processing of cell therapy products.
- The already established GMP facilities at the university hospitals should serve as national resources that may be used for projects requiring GMP-production in Class A and B environment for Phase I and later phase studies.
- An education programme should be implemented.
- A national resource for support in coding of cells should be established.
- A national repository for documents should be established.
- The national cell therapy group will establish a detailed two-year action plan for the implementation of the national strategy.
- Future funding is instrumental for carrying out the described strategy.