Pilot Study of a Swedish Institute for Cell Therapy

Vinnova project, Dnr. 2016-04749

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Executive summary

In December 2016 the Swedish Innovation Agency Vinnova granted funding to RISE Research Institutes of Sweden for the project “Pilot Study of a Swedish Institute for Cell Therapy”. The overall project objective was to investigate the prospects for a Swedish Centre for Cell Therapy, by performing a mapping of the Swedish ATMP landscape, identifying actors and projects, and their needs and challenges, with a special focus on industrial perspectives.

The project gathered and analysed information from various public sources and by dialogue and interviews with different Swedish and international stakeholders in the field. The project also made links with important national infrastructures and supporting competencies such as regulatory aspects and health economy, which were tested in cases where selected projects received support on specific challenges. During the project, three seminars were organized to highlight the variety of Swedish ATMP projects, and to provide opportunities for national networking and interaction with leading international experts. The project also arranged two workshops, where challenges related to regulatory aspects and process development and production aspects were discussed.

The work consisted of the following work packages: WP1 Mapping of the Swedish ATMP landscape; WP2 Needs, barriers and support functions; WP3 Case studies testing support functions; WP4 A Swedish action plan for Gene Therapy; and WP5 Management and dissemination activities.

The mapping of the area shows that Sweden has a growing activity in the area, with at least 12 companies pursuing commercial development of ATMPs targeting diseases such as cancer, diabetes or immunological deficiencies. Most of these are SMEs but also include a few international big pharma companies. The majority of the projects are in or close to entering a clinical development stage. A larger number projects are pursued in an academic/hospital setting, several of which are in a clinical development stage. In an international perspective, and taking into consideration its size, the ATMP activity in Sweden holds a good position, although there is potential for improvement.

The needs and challenges expressed by the ATMP-developing companies cover a broad range, and are very dependent on the specific product being developed. The most important needs fall within the following categories: (i) scientific/technical challenges related to process development, product characterization and production, (ii) fulfilling regulatory requirements, and (iii) financial aspects, such as health economy, reimbursement and business models. Although gaps exist, much of the necessary infrastructures and competencies to meet these needs and challenges do exist in Sweden, but for different reasons they are not optimally used. One reason may be that most of the infrastructures and supporting competencies are operating in an academic/hospital setting and not readily available or adapted to meet industrial needs. National coordination and initiatives are necessary to coordinate and make the existing infrastructures and competencies more accessible and to build those that are lacking.

The RISE pilot study has interacted and contributed with input to the two national ATMP initiatives that were initiated 2017, the Centre for Advanced Medical Products and the Swelife-ATMP project, respectively. These two initiatives constitute an important step towards building the more cohesive innovation system that is necessary if Sweden is to become more competitive in the rapidly evolving ATMP field.

Background and introduction

This report deals with the Swedish landscape in pharmaceutical products based on gene, cell or tissue engineered products intended for human use in treating or curing disease conditions, or to repair, regenerate of replace tissues. The Committee of Advanced Therapies (CAT) of the European Medicines Agency (EMA) describes such products as Advanced Therapy Medicinal Products (ATMP)[1]. In the US, such products are designated by the Food and Drug Administration (FDA) as drugs for regenerative medicine advanced therapy (RMAT) [2]. In this report we will use the terms "ATMP", and when relevant use the ATMP subcategories "gene therapy", "cell therapy" or "tissue engineered products".

The ATMP field holds great potential for providing new improved treatments, or even cure, to severe diseases such as cancer, neurodegenerative disease or musculoskeletal disorders. However, as pharmaceutical products they introduce a whole new level of complexity compared to traditional medicines, due to the fact that they are based on genetic or living material and often a high level of patient individualization. This complexity in turn puts exceptionally high demands on the level of control in their production, to comply with regulations and ensure patient safety and clinical efficacy. The complexity of the products, often combined with relatively small patient populations, also means high production and treatment costs, which introduces new economic and commercial challenges for ATMP developers.

Despite the challenges involved, the ATMP field is rapidly growing globally, and it is expected to continue to do so. Major public investments in the 100-1000 million USD range have been made in countries such as the US, Canada, UK and Japan to boost the translation and commercialization of ATMP projects. In Sweden, a significant investment was made in the period 2007-2017 by the Swedish Association of Local Authorities and Regions (SALAR) which granted 120 MSEK for investments in tissue establishments at major Swedish hospitals. Commercially, the field has not yet made a breakthrough. During the last decade ca 15 ATMPs received market approval in Europe or the US, and more approvals are expected at an increased pace within the coming years. Notably, several of the products that have received market approval have been withdrawn from the market, some for commercial reasons.

In view of the high international activity within the ATMP field and contacts taken with some key Swedish actors, during 2016 RISE carried out a prestudy of the ATMP field in Sweden, which in November 2016 was summarized in a preliminary report "Swedish Centre for Cell Therapy". The report briefly outlined the Swedish ATMP landscape and a possible organization in the form of a center for supporting the development within the field in Sweden. Based on the report, a proposal for a broader and deeper study was submitted to Vinnova. The proposal was funded by Vinnova with the motivation that the report drafted by RISE showed that "the prospects were good for a competitive center for cell therapy in Sweden and that it therefore was considered important to continue investigating the prospects further". The current, approved project was the next step in the prestudy, involving additional competences and a more detailed study of needs and prospects for a Swedish Centre for Cell Therapy.

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[1] REGULATION (EC) No 1394/2007 https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf ; EMA/CAT/600280/2010 rev.1, May 2015: Reflection paper on classification of advanced therapy medicinal products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187744.pdf

[2] https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm

Since the approval of the present project, the Swedish conditions have changed significantly. In spring 2017 a proposal for a national Centre for Advanced Medical Products (CAMP) was submitted to Vinnova's call "Centres for Development and Production of Biologicals". The proposal was coordinated by Umeå University and involved 22 additional partners from health care, industry and academia including RISE. Late spring 2017, a proposal for a strategic project on ATMP was submitted to Vinnova by Swelife, a national strategic innovation programme in Life Science. Both of these proposals were granted funding from Vinnova, with a recommendation to interact with the RISE pilot study. The approval of the Swelife-ATMP project with start date June 2017, and the CAMP centre with start date Jan 2018, meant the focus of the RISE pilot study shifted from exploring the prospects for a new centre, to activities that would provide useful input for and facilitate the set-up and operation of the two other initiatives.

Project objectives and structure

As explained in the Introduction, the establishment of the two initiatives CAMP and Swelife-ATMP lead to a shift of the overall objective of the project. Instead of putting the main focus on studying the needs and prospects for a National Swedish Center for Cell Therapy, the activities were directed towards achieving the following specific objectives, also stated in the original application:

- to make ATMP project in Sweden visible and map their needs and challenges, with particular focus on industrial projects
- to coordinate, complement, and make expert knowledge available to these projects
- to build a strong national network with a multitude of different stakeholders
- offer access to international expertise in the field

Working towards these objectives served to provide input for planning relevant activities in the CAMP and Swelife-ATMP initiatives, especially regarding industry needs.

Project structure and methods

The project has been carried out in five work packages, each with a designated WP-leader.

- WP1: Mapping of the Swedish ATMP landscape (WP leader: Marcel Frankowiack)
- WP2: Needs, barriers and support functions (WP leader: Jim Lund)
- WP3: Case studies; testing of support functions (WP leader: Jim Lund)
- WP4: A Swedish action plan for Gene Therapy (WP leader: Marcel Frankowiack)
- WP5: Management and dissemination activities (WP leader: Jukka Lausmaa)

The detailed contents of the different work packages and their results are described under separate headings in this report.

The main methods used for conducting the work have been:

- Collection and analysis of information from:

  - publicly available media (scientific literature, databases, internet home pages, …)
  - structured interviews with different stakeholders
  - dialog and consultation with different stakeholders
  - study visits to national and international ATMP milieus

- Seminars and workshops with invited speakers and interactive content
- Support from a national expert group (WP4) and an international advisory group
- Support to selected project cases, in collaboration with external actors.

Throughout most of the project period, the project team has interacted and provided input to the project activities with the Swelife-ATMP and CAMP projects.

Activities and results

WP1: Mapping of ATMP projects in Sweden

Objective

The objective of this WP was to obtain an overview of Swedish ATMP projects, including their stage of development and main needs and challenges, with a focus on industrial projects.

Swedish projects and companies

A survey was conducted to identify ATMPs currently being developed in Sweden and define the main challenges faced by companies and academic groups conducting the development. Projects were identified through literature research (https://www.ncbi.nlm.nih.gov/pubmed and https://webofknowledge.com), a clinical trial database (https://clinicaltrials.gov/) and discussions with a wide range of stakeholders from the field. Information was also obtained from the Swedish Medical Products Agency. We identified ca 40 projects, of which 14 were within a commercial (driven by companies) setting, and the remainder were operated by academic or healthcare investigators. We cannot exclude that additional projects exist, partly because the classification as ATMP is not certain for many projects and the classification for projects in early phases is uncertain. Since the focus of the project had an industrial perspective, a complete survey of Swedish academic ATMP projects was not conducted.

Table 1 lists the companies that were identified as having an active ATMP development in Sweden. Also listed is the targeted indication of the companies' lead candidate, the type of ATMP being developed, and the development phase (again for lead candidate). Big Pharma companies with their main activity abroad but with presence in Sweden, such as Pfizer and Novartis, are not included in the list but are important actors as they are active in clinical trials in Sweden. Neither does the list include the ecosystem of companies, CRO's and CMO's that provides equipment, materials or other supplies and services to the ATMP developing companies. These include international companies such as GE Healthcare, Cobra Bio and Miltenyi Biotec and Takara Bio, and specialized service or technology providers and consultants such as, for example, Anocca, Evox, Tataa Biocenter, Institute for Health Economics, Your Special delivery Service, TSS, and Vera Franzén Consulting.

Table 2 summarizes the number of clinical ATMP trials approved in Sweden, according to data provided by the Swedish Medical Products Agency. The number does not include trials conducted under the hospital exemption. Another indicator of the activity is the number of Scientific Advices the Swedish MPA has provided to investigators, (Table 3). Note that the numbers for 2017 are up to 1 Sept in both Table 2 and 3.

Table 1: ATMP developing companies

Company	Indication*	Category	Development
Astra Zeneca	Cardiovascular	GT	preclinical
Cell Protect	Multiple myeloma	CT	clinical
CellSeed Sweden	Esophagus cancer	CT/TEP	clinical
Combigene	Epilepsy	GT	preclinical
Idogen	Haemophilia A	CT	preclinical
Immunicum	Cancer	CT	clinical
Islet one	Acute respiratory distress syndrome	CT	clinical
LongBoat Explorers	N.D.	CT	preclinical
Nextcell Pharma	Diabetes type 1	CT	preclinical
ParkCell	Parkinson disease	CT	preclinical
Verigraft	Venous insufficiency	TEP	preclinical
Xintela	Cartilage regeneration	CT	preclinical

* Indication of lead candidate, CT=cell therapy, GT=gene therapy, TEP=tissue engineered product, ND=Not disclosed or not yet determined

Table 2: Clinical ATMP trials in Sweden approved by Swedish MPA

	GT		CT	
Year	Acad	Ind	Acad	Ind
2014	2	1	1	0
2015	1	2	0	3
2016	0	0	1	1
2017*	0	1	2	0

* Up to 1 Sept 2017

Table 3: National scientific advice provided by Swedish MPA

	GT		CT	
Year	Acad	Ind	Acad	Ind
2014	1	1	1	1
2015	0	4	4	3
2016	0	0	8	3
2017*	0	4	2	3

*Up to 1 Sept 2017

Interviews

Out of the ca 40 different ATMP projects, 27 agreed to be interviewed. The 27 projects consisted of projects both in a commercial (14) and academic (13)setting. The interviewed projects included a few companies not developing their own ATMP, for example one company supplying stem cells to external ATMP developers. Most of the 27 projects were interviewed in structured quantitative interviews, in a few cases information was obtained from qualitative interviews. The interviewed projects are listed below.

Commercial projects:

Anocca (Södertälje), AstraZeneca (Mölndal), CellProtect Nordic Pharmaceuticals (Stockholm), CellSeed (Stockholm), CombiGene (Lund), Evox Therapeutics (Stockholm), NextCell Pharma (Stockholm), Idogen (Lund), Immunicum (Gothenburg), IsletOne (Stockholm), VeriGraft (Gothenburg), Takara Biotech (Gothenburg), Xintela (Lund).

Academic /collaborative projects:

Akademiska University Hospital (Uppsala), Karolinska Institute (Stockholm), Karolinska University Hospital (Stockholm), Sahlgrenska University Hospital (Gothenburg), AlzeCure (Stockholm), AstraZeneca/Gothenburg University, Longboard Explorers (Lund), Procella (Stockholm), Angelica Loskog & Magnus Essand (Uppsala)

The questionnaire comprised:

- General information (Project name, project owner)
- Project type
- Number of fulltime employees
- External collaborators (number and location)
- Product category (cell therapy, gene therapy, regenerative medicine)
- Developmental phase (current TRL and self-reported projection)
- Business model (indication, production process and equipment used)
- Financing (type and scope)
- Knowledge gaps in preclinical research, clinical research, regulatory affairs, process development, health economics, productification, logistics, traceability, financing
- Acute needs.

The data is self-reported and should be considered as subjective views of the interviewed individuals, and not necessarily the official position of the respective company.

In addition to the structured interviews, qualitative interviews and dialog were conducted with additional Swedish stakeholders involved in the ATMP field comprising, big pharma, SME and academic research groups.

Results and analysis of interview responses

The results of these interviews show that academic and commercial projects differ in their development phase, their funding situation as well as in needs for expertise.

Number of full time employees

All of the projects employ less than 10 people with the exception of 3 academic projects and 1 commercial project that employ less than 20 people.

External collaborators

The interviewed projects collaborate mainly with commercial enterprises (such as CDMOs and consultants). There were nine academic partnerships reported (universities, university hospitals, research organizations) and two Horizon 2020 projects. The vast majority of collaborations are done within Sweden. Other important countries that the interviewed projects have collaborations with are Germany and the USA. For example the CAR-T trial performed by Loskog et al employed protocols developed in the USA

The interviews suggest that the ATMP community in Sweden is to a degree secluded from international expertise and knowhow. This holds true for academic and commercial projects alike.

Type of therapy

Although there are different classifications for ATMPs, we have chosen to use the following categories: (autologous/allogenic) cell therapy, gene therapy, (autologous/allogenic) regenerative medicine.

By far the most frequent therapies that are currently developed and tested in Sweden are autologous cell therapies. Gene therapy and allogenic cell therapy rank second and third, and one or two of the projects can be classified as tissue engineered products.

Development phase

Of the interviewed academic projects, more than 70 % are currently preparing for or conducting a phase 1 or phase 2 clinical trial (Table 2). The remaining 30 % are in the preclinical research phase.

Commercial projects, are mostly (70 %) in a late preclinical research phase. 30 % of the projects are currently preparing for or conducting a phase 1 clinical trial.

Production process

The interview partners have been asked whether they have established a GMP-conforming production process. Around 80 % of all academic and commercial projects report that they have an established production process. Only around 20 % said that they don’t have an established process yet.

Financing

The projects interviewed rely mostly on a single source of funding. is only one source of funding for most academic (ca. 70 %) and commercial (ca. 70 %) projects alike.

Concerning the type and the scope of funding, we identified five different categories:

Type of funding	Scope of funding	Examples for source of funding
Public	Short-term	National grants
Public	Medium-term	EU grants
Private	Short-term	Donations
Private	Medium-term	Investments
Private	Long-term	Stokes, financier

Interestingly, private funding is exclusively available to private projects, while some private projects use public funding. For, example, two Swedish SMEs (Verigraft AB and Idogen AB) have recently received funding from the prestigious H2020 SME-instrument. Moreover, there is no public equivalent to private long-term funding (Figure 3).

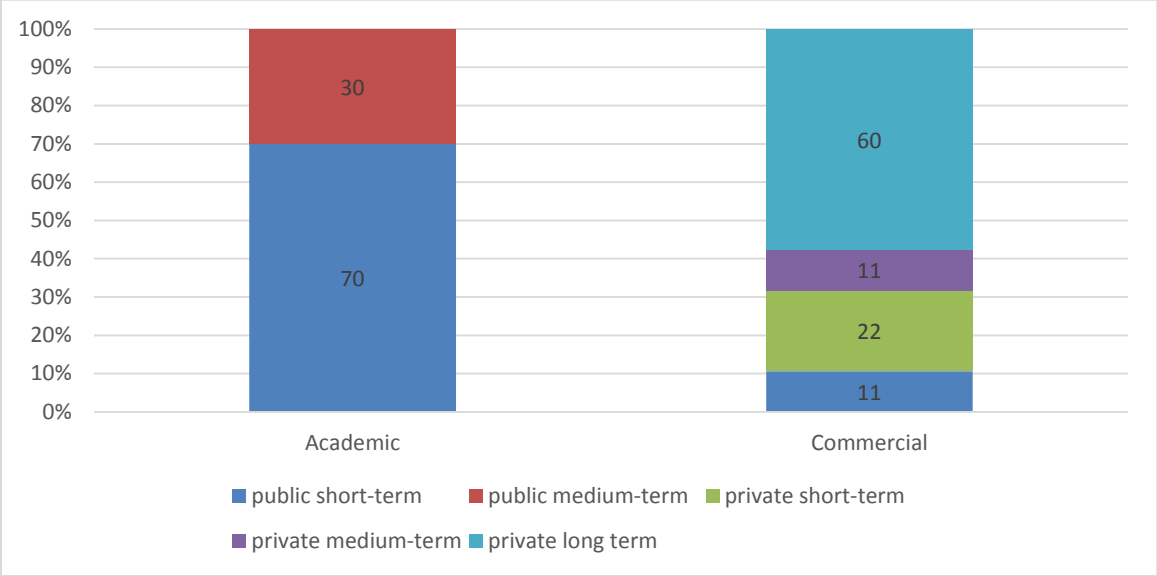

Figure 3: Scope and source of funding. Numbers correspond to the percentage of responders, not amount of funding.

Needs

The interview partners (including academic and industrial projects n=27) were asked to assess the urgency for accessing:

- Infrastructure, such as a GMP facility,
- knowhow in regulatory affairs, health economics and process development
- funding for research and development, production and clinical trials
- national networks such as NAT (Nätverket för Avancerade Terapier) and regional networks (e.g. Gothia Forum in Gothenburg)
- a business incubator (for helping with the design of a business model)

- a business association for commercial ATMP makers

A scale from 1 to 7 with 7 being an acute need and 1 being a fairly low need was used.

The results showed that there is a generally high need for assistance with regulatory affairs and process development.

The needs expressed in order of urgency were

1. Funding for research and development was expressed by all categories
2. Access to GMP facility
3. Process development competence
4. Networks
5. Regulatory affairs competence
6. Health economics competence

Funding was a general need expressed by all projects although some were well funded in the short to medium term.

There is an expressed need for funding of research and development, production and clinical trials.

Access to GMP facility was a pronounced need for all projects moving into the clinical phases, especially for the commercial projects.

Process development competence was an expressed need especially methods for quality assurance etc.

Networks to access competence was listed as a significant need from the partners. The projects are scattered geographically and could benefit from greater interaction.

Regulatory affairs was considered a greater need from the academic projects whereas the commercial parties had invested the time and effort to train staff and gain the necessary experience.

Expertise in health economics is a less pronounced need which might be due to that most projects still are in a relatively early development phase. Hence, their focus is on establishing a regulatory compliant production process.

Regional initiatives and national networks are appreciated and needed. A business association and business incubator are considered moderately interesting.

We note that the expressed needs of Swedish ATMP developers are those in a comparable country, the Netherlands. In a Dutch study the hurdles in clinical implementation of ATMP were investigated. Quality interviews were conducted with different stakeholders involved in ATMP development. Stakeholders included parties from academic groups, national authorities and patient organizations. Qualitative interviews were conducted with 29 academic PIs and project leaders from 10 institutions. In total 45 ATMPs were included.

The main in hurdles identified in the Dutch study were inadequate financial support, rapidly evolving field, study-related problems, lacking regulatory knowledge, lack of collaborations and responsibility issues for commercialisation. These results are similar to the observations in the current survey, however the Dutch study had an academic perspective and which may explain why industrialisation and GMP production was not brought up as the most urgent needs. (Ref: de Wilde et al, *Cytotherapy*, vol. 18, 797-805 (2016))

The Swedish ATMP scene in an international perspective

Brief global outlook

In order to assess the Swedish ATMP landscape in an international perspective, some basic information about the global scene was collected. During the last decades or so, the ATMP field has evolved strongly, from being primarily a research field into an area that is now being translated into clinical practice and becoming a new industry. Table 5 provides some key indicators that illustrate the state of the industry, based on annual reports from the Alliance for Regenerative Medicine (ARM)[3]. Globally, there are now over 850 companies active in developing gene-, cell- or tissue therapies for a wide range of both common and rare severe diseases such as, for example, cancers, musculoskeletal or central nervous system disorders and diabetes. Half of the companies are located in the North Americas, about one quarter in Europe. The number of on-going trials is approaching one thousand. The by far largest indication categories is Cancer (ca 50%), followed by Cardiovascular, CNS, Musculoskeletal and Endocrinic, Metabolic & Genetic Disorders.

Whereas relatively few ATMPs have reached market approval during the last decade, 2017 saw four new market approvals, two of which are CAR T-cell therapies, one a gene therapy, and one an allogeneic cell therapy. In 2017, 12 candidates in the US also received the Regenerative Medicine Advanced Therapy (RMAT) designation, which makes them eligible for FDA's expedited programs, including accelerated approval, and priority review.

Table 5: Some key indicators of global industrial activity

	2015	2016	2017
No. companies	672	772	854
Capital raised (billion USD)	10.8	5.22	7.5
Clinical trials	631	804	946
Phase I	*192*	*261*	*314*
Phase II	*376*	*475*	*550*
Phase III	*63*	*68*	*82*
Sources: ARM Annual Data Reports 2014-2016 and ARM State of the Industry 2018			

Swedish position in a global perspective

Comparing quantitative indicators for the Swedish ATMP scene, such as number of active ATMP-developing companies (12), clinical trials (15), and approved products (0), it may appear that the activity in Sweden is very modest. However, ATMP-development in Sweden has to a large extent been, and continues to be, conducted in an academic/health care setting, with clinical trials done under the hospital exemption. Although we did not make a survey of academy-driven clinical trials, the real number of ongoing trials can safely be assumed to be significantly higher than reported here.

In terms of Swedish public funding ear-marked for the ATMP-field, Figure 4 provides an indication of the situation during the last decade. Up to 2017, the annual level of funding has been around 100 MSEK, strongly dominated by the investment made by the Swedish

[3] Alliance for Regenerative Medicine https://alliancerm.org/page/arm-2017-annual-data-report#overlay-context=

Association for Local Authorities and Regions for building production infrastructures at the major Swedish hospitals. As of 2018, the level is expected to be around 15 MSEK per year counting with the currently approved initiatives. It should, however, be noted that significant additional funding is provided to the area via the regular funding programs operated by the Swedish Research Council (VR), Vinnova, Swelife, and the Strategic Research Foundation (SSF). That funding is, however, subjected to competition from other fields of Life Science. Significant support to the ATMP field is also obtained via major programs such as the Wallenberg Centres for Molecular Medicine and SciLife Labs. The fact still remains, that Swedish public investments ear-marked for Regenerative Medicine and ATMP, are relatively small, especially when comparing to the major investments done in e.g. the UK (Cell and Gene Therapy Catapult), Canada (Centre for Commercialization of Regenerative Medicine), or Spain (Andalusian Initiative for Regenerative Medicine).

Based on numbers only, Sweden cannot be argued to hold a strong position in the global ATMP-scene. However, in view of the small population size and the relatively small public investments made, Sweden has managed to maintain a respectable position, with several examples of excellent or pioneering research groups in the field and a well-structured health care system. The fact that two ATMP-developing Swedish SMEs received funding in 2017 from the extremely competitive SME-instrument of the H2020 program, is further testament to Sweden's position.

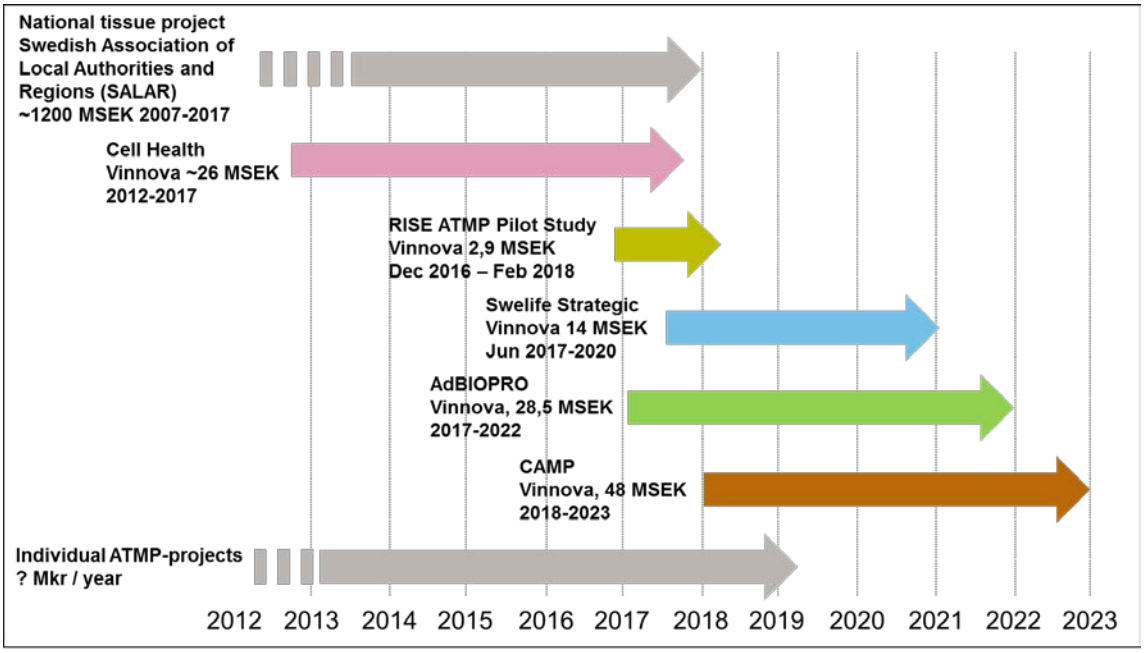

Fig. 4: Swedish public investments, earmarked for ATMP research and development.

WP2: Challenges and needs, support functions

Identified challenges and needs

Based on dialogue with stakeholders and the workshops arranged within the project (see WP5), the major challenges faced by ATMP-developers during the pre-clinical development or when entering clinical trials mainly fall within the following categories:

- Financing
- Process development and production
- Regulatory aspects
- Health economy

As financing is a challenge for virtually every development efforts this category will not be further discussed. The other three categories are further discussed below.

Process development and production

Compared to other pharmaceutical products, ATMPs (with the exception for gene therapy products) are comprised of living materials. The complexity and variability associated with these poses major challenges when it comes to their production. ATMPs must be manufactured in compliance with Good Manufacturing Processes (GMP) and it is the responsibility of the manufacturer to make certain that the manufacturing process is adequate to ensure both the quality and consistency of the product. Early development efforts on ATMPs generally originate from within the academic community where the understanding of both drug development and regulatory compliant production processes and the demands related to these activities are variable. In order to be able to allow relevant specifications to be established you will need comprehensive knowledge about production, characterization, quality management and relevant assays, tools and methods for these events. Some specific needs and insights from this project are listed below.

Quality and assay related:

- Pre-clinical models
- Risk and safety
- Method validation
- Potency assays

Production for clinical trials:

- Existing infrastructure not used to full potential
- Lack of of key competences, i.e. Quality Assurance (QA) and Qualified Person (QP)
- Existing infrastructure not readily available or have not sufficient capacity for commercial actors
- A number of companies produce outside of Sweden and builds their own GMP labs

Regulatory issues

In Europe, ATMPs are regulated as pharmaceuticals, and are defined and categorised in the legislation (Part IV – Annex 1 to Directive 2001/83/EC) as gene therapy, somatic cell therapy

and tissue engineered products. The ATMP Regulation (EC) No. 1394/2007 introduced by the European Medicines Agency (EMA) provides a harmonised regulation of ATMPs which are intended to be marketed in the EU. This regulation is a *lex specialis* which introduces additional provisions to Directive 2001/83/EC and contains specific rules concerning the authorisation, supervision and pharmacovigilance of ATMPs within EU. [4] The cornerstone of the Regulation is that a marketing authorization must be obtained prior to the marketing of ATMPs. Whereas market approval is required on a European level, approval for clinical trials is issued on a national basis by respective national competent authorities.

Specific challenges and issues regarding regulatory aspects were:

- Stringent regulatory demands that are challenging to meet
- Regulatory landscape is perceived as difficult to navigate
- Each product is unique and can be very diverse in nature
- Few regulatory experts in Sweden
- MPA is very competent and gives good advice but the waiting time is perceived as long

Health economics

Pricing and reimbursement are potentially major challenges for ATMPs due to their high cost/high effectiveness profile. In the end it is the health economic calculation based on extensive clinical data that will decide the specific value and therefore price roof of the released product. If drugs that are released are not considered to be cost-effective by the national authorities such as The Dental and Pharmaceutical Benefits Agency (TLV) they will not reach reimbursement and therefore not be viable on the market. Therefore the early use of health economical models to assess the potential cost-effectiveness of ATMPs already during the development phase could provide valuable information for the developers.

- Competence available for HTA modelling in general, but competence specialized on ATMPs is scarce
- Complete health economic assessment requires considerable clinical data, but valuable results can be obtained by modelling based on assumed clinical efficacy
- Uncertainties regarding reimbursement

Existing infrastructures and supporting competencies

Manufacturing infrastructure

A detailed survey of Swedish infrastructures and functions required for ATPM development has previously been published.[5] The main current manufacturing infrastructure resides within the Swedish healthcare system. Vecura in Huddinge have been active since 1996 and have produced ATMPs for over 400 patients in their total of 9 clean room suites. Vecuras main purpose is to provide researchers at the Karolinska University Hospital with clinical grade GMP processed cell and gene therapies and to date 40 GMP products have been manufactured for clinical trials. The facility is also open as a contracting resource to academic labs and the biotech industry and is approved under EU license by the Swedish Medical Product Agency and Health and Social Care Inspectorate.

[4] J.W McBlane, Regulatory landscape for cell therapy, *Biologicals*, Vol. 43, pp 433-436 (2015)
[5] The Advanced Therapy Portal in Gothenburg as a Node in a Swedish National Translational Research Network, VGR/Gothia Forum, Author: R. Strehl, Aug 2015

The cell and tissue laboratory at the Sahlgrenska University Hospital in Gothenburg is a tissue establishment with a manufacturing permit for ATMPs. The laboratory supports clinical practice and research at SU and is audited by the Swedish medicinal products agency and IVO. The laboratory performs stem cell culture for transplantations at Sahlgrenska University Hospital and Queen Silvia Children´s Hospital. Via its 3 cleanroom suites it have produced cells for over 2100 autologous chondrocyte implantations.

Takara Bio has built a commercial GMP lab in their lab in Gothenburg which is currently awaiting approval from the MPA. The lab will contain one Grade B room and will also be approved as a tissue establishment.

WP3: Project cases

Objective

To provide hands-on support to selected projects on specific challenges in their development.

Selection process

In order to test and demonstrate the capability of the support functions and partners organizations, five projects case were selected. Companies taking part in the interviews conducted in WP1-2 were invited to suggest project cases, addressing specific challenges in their development process. The selection of project cases was made by the project team in a process approved by Vinnova, so as to include a portfolio of cases that together fulfilled the following criteria:

- Provided generic knowledge and experience which could benefit other companies than those directly involved.
- Included challenges around regulatory aspects, health economy, and/or technological aspects on production, quality assurance or logistics.
- Included gene, cell and tissue products.
- Feasibility in terms of resources needed and the time available.
- In-kind co-funding by the company involved.

Invitation for project cases was communicated in June and August 2017 and the selection was made in September. For several of the project cases, mutual NDAs were signed.

Selected project cases

A total of eight case proposals were received. Three additional ones were discussed but did not develop into written proposals. The following five cases were selected:

- ***Quality assurance and transport of tissue engineered product for cancer treatment (in cooperation with Vecura, Stockholm):*** The logistics involved between the time of manufacturing and administration to patient introduces possible changes that could negatively affect the safety and efficacy of ATMPs. This case involved making a first plan for the regulatory aspects and what type of data that need to be considered when setting up a logistics chain.

- ***Certification of quality and preclinical data for an NK-cell therapy of multiple myeloma:*** Certification is a process offered by the EMA, which if successfully conducted and approved can be seen as a quality stamp and can also be expected to facilitate future development.
- ***Health economy assessment of tissue engineered product for CVI-treatment (in cooperation with Institute for Health Economy, Lund):*** Health economic assessment of an ATMP uses models to assess the economic value of the treatment, and provides important data for the commercial headroom of an ATMP.
- ***Health economy assessment of allogeneic cell therapy for cartilage regeneration (in cooperation with Gothia Forum):*** See above.
- ***Prestudy of toxicology and biodistribution testing of gene therapy product:*** Toxicology studies and biodistribution assays are required to ensure the safety and fulfil regulatory requirements before clinical trials can initiated.

The outcome of the five project cases is presented in Appendix 2

WP4: Gene therapy in Sweden

A panel of experts (Appendix 1) were invited to three sessions to discuss gene therapy development in Sweden. The objective was to describe and discuss the status of the field in Sweden and to provide recommendations that can be included in future strategies to foster the development of the field in Sweden.

This section of the report is based on the input from the experts at the meetings conducted in 2017. The panel consisted of people from the life science industry, the pharmaceutical industry, clinical research, academic research. The views expressed should be regarded as the personal opinions of the experts and not necessarily the official position of their respective organization.

The panel discussions were divided into three topics.

1. Current status in Sweden
2. Goals and guidelines for development of the field
3. Activities needed to promote the field

Before presenting the findings of the work, a brief overview of the general global situation of the gene therapy field, including on-going clinical trials and some specific examples, are given in the next section.

Overview: definitions of gene therapy?

The area of gene therapy is complex. Different therapies can be classified by their mode of action, target cell, the genetic material used, the mode of administration of genetic material, and the therapeutic area.

The US Food and Drug Administration (FDA) defines *gene therapy* as “a technique that modifies a person’s genes to treat or cure disease. Gene therapies can work by several mechanisms:

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease." [6]

The European Medicines Agency (EMA) uses the term *gene therapy medicines*. These gene therapy medicines contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources."[7]

Interestingly, both definitions have certain things in common, such as they both stress the curative nature of the therapy. EMA in comparison to FDA also include prophylactic or diagnostic effects. Neither the FDA nor EMA specifically mention the modification of gene expression (esp. an increase of expression). Both definitions exclusively focus on one type of nucleic acid polymers, DNA.

In this document, we follow the suggestion by N. Mount and colleagues for cell-based therapy technology classifications using the following categories: genome editing, *ex vivo* gene modifications with viral vectors and *in vivo* gene modifications with viral vectors.[8]

This classification allows for a standardization of the developmental process and the translational challenges for each new gene therapy and thereby reducing the level of complexity significantly.

The expert panel (see Appendix 1) has for the discussion here decided to use a more inclusive definition and therefore also include methods that modify gene expression as a complementing fourth category.

Clinical development/curative potential

In April 2017, 2,463 gene therapy clinical trials had been conducted worldwide according to the journal of Gene Medicine and its Gene Therapy Clinical Trials Worldwide database, which covers the years 1989-2017. Major indications are cancer diseases (ca. 65 %), monogenic diseases (ca. 11 %) cardiovascular diseases (ca. 7 %), and infectious diseases (ca. 7 %) (see Figure 5).

[6] Research C for BE and. Cellular & Gene Therapy Products - What is Gene Therapy? [Internet]. [cited 2017 Sep 29]. Available from: https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm573960.htm

[7] European Medicines Agency - Overview - Advanced therapy medicinal products [Internet]. [cited 2017 Sep 29]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0

[8] Mount NM, Ward SJ, Kefalas P, Hyllner J. Cell-based therapy technology classifications and translational challenges. Philos Trans R Soc Lond B Biol Sci. 2015 Oct 19;370(1680):20150017

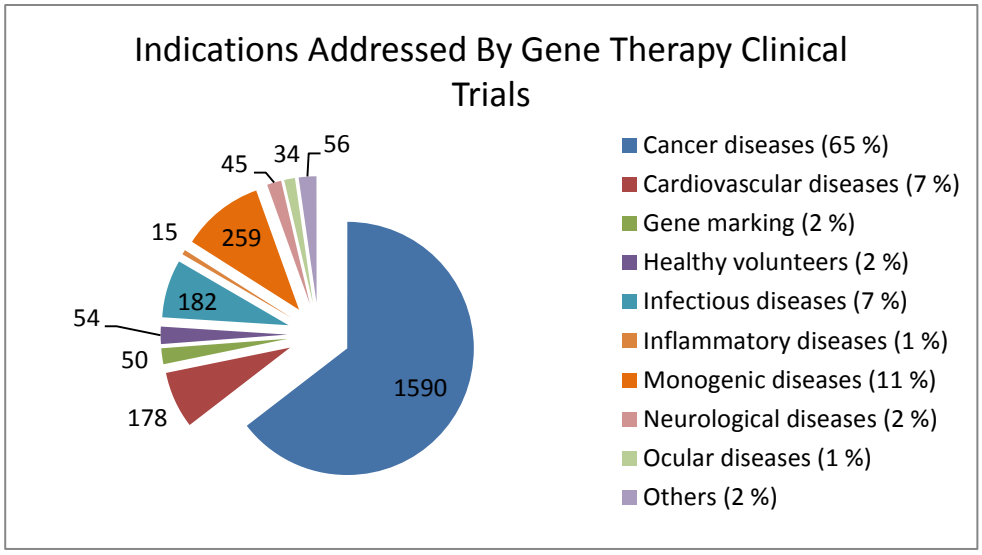

Figure 5: Indications addressed by gene therapy clinical trials worldwide according to Gene Therapy Clinical Trials Worldwide database.

The vast majority (ca. 57 %) of these trials are in phase 1 (see Fig. 6). Around 37 % of the trials are in phase 1/2 or phase 2.

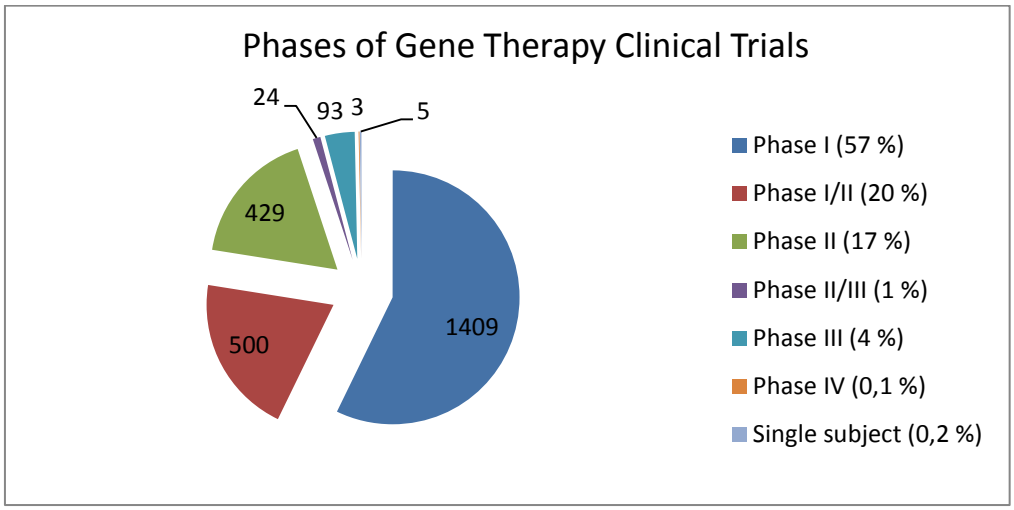

Figure 6: Phases of Gene Therapy Clinical Trials worldwide according to Gene Therapy Clinical Trials Worldwide database.

The majority of clinical trials worldwide have been conducted in the USA (1550), followed by the UK (219) and Germany (92) China (68) and France (57) Sweden is on rank 15 with 12 trials.

Commercial potential

Most of these therapies were designed to provide a long lasting therapeutic benefit or even a ”cure” for incurable, terminal or severely disabling conditions after a single treatment. However, only a few therapies have reached the market, despite the great potential.

One reason is that most of the results are rather new and it is too early to be expecting commercial products. Furthermore, developers are facing big challenges trying to satisfy quality, safety and efficacy standards set by the authorities.

The first product was approved in China in 2004. Since then, four gene therapies have been approved by European regulatory authorities: Glybera, Imlygic and Strimvelis and Zalmoxis. The manufacturer of Glybera, UniQure, has announced to withdraw the product from the European market when its approval ends on 25 October 2017 due to the “extremely limited” use of the drug.[9]

Great hopes lie on the CAR-T cell technology, because theoretically, it is possible to modify patients own T-cells to attack different types of cancer. This opens great clinical and commercial potential. Therefore, the interest of the research community, the media and commercial entities is high. In August 2017, the first-ever CAR-T cell therapy has been approved by the FDA. CAR-T cell therapy is a personalised treatment using patients own T cells. The drug KYMRIAH (tisagenlecleucel) is offered by Novartis for treatment of Acute lymphoblastic leukemia (ALL).[10,11] In October 2017 the second CAR-T cell therapy, Yescarta (axicabtagene ciloleucel) was approved by the FDA. Yescarta was developed by Kite pharma and is approved for use in adult patients with large B-cell lymphoma after at least two other kinds of treatment have failed, including DLBCL, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. [12]

The limited number of approved therapies makes a proper and trustworthy estimate of the market value of gene therapies more difficult. There are, however, reliable number on the investments made into gene and gene-modified cell therapy. According to reports from the Alliance for Regenerative Medicine,[13,14] the investment increased from 2.73 billion $ in all of 2016 to 2.04 billion $ during the first six months of 2016. These numbers include IPOs, follow-ons, corporate partnerships with upfront payments, venture capital, pipes and mergers and acquisitions.

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[9] GL_PR_Glybera withdrawal_FINAL_PDF.pdf [Internet]. [cited 2017 Sep 29]. Available from: http://uniqure.com/GL_PR_Glybera%20withdrawal_FINAL_PDF.pdf

[10] Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah™ (tisagenlecleucel, CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice [Internet]. Novartis. [cited 2017 Sep 29]. Available from: https://www.novartis.com/news/media-releases/novartis-receives-first-ever-fda-approval-car-t-cell-therapy-kymriahtm-ctl019

[11] First cancer gene therapy to treat leukaemia approved by US regulators [Internet]. [cited 2017 Sep 8]. Available from: http://www.telegraph.co.uk/news/2017/08/31/first-cancer-gene-therapy-treatleukaemia-approved-us-regulators/

[12] FDA News Release 18 Oct 2017: FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma, available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm

[13] ARM_2016_Annual_Data_Report_Web_FINAL.pdf [Internet]. [cited 2017 Sep 29]. Available from: https://alliancerm.org/sites/default/files/ARM_2016_Annual_Data_Report_Web_FINAL.pdf

[14] ARM_Q2_2017_Web.pdf [Internet]. [cited 2017 Sep 29]. Available from: https://alliancerm.org/sites/default/files/ARM_Q2_2017_Web.pdf

Global challenges

Great advances have been made in manufacturing and characterising gene therapy vectors. Vectors with higher potency and increased transduction efficiency were designed and produced with greater purity during the last years.

There has also been a major increase in the understanding of biological processes, such as methods in *ex vivo* handling, effective monitoring and management of patients. Other important trends are the aggressive licensing of promising gene and cell therapies developed by academic centres in Europe and the USA, and a de-risking of the development of new therapies through the active cooperation of academic centres and industry.[15,16,17]

Although treatments are being approved the development of gene therapy products is still in an early phase. The commercialization of gene therapy community faces several challenges.

1. Small patient populations.
2. High risk of failure.
3. High pricetag of treatment.
4. High developmental costs.
5. The need for long term investment.
6. A demanding regulatory environment.

Most potential diseases that these therapies are developed for are rare diseases with a limited number of patients. Moreover, most gene therapy products are designed to provide a long lasting therapeutic effect or even a cure with a single dose.

Challenging quality, safety and efficacy standards set by the authorities increase the development costs and are major contributors to the overall costs of the new product.

Reimbursement bodies worldwide are therefore requesting more advanced health economic data and long-term clinical data for the treatment effect.[18]

Challenges on the technical and biological side are, amongst others, the specificity of treatment (cell tropism), reduction of side effects of some treatments (such as cytokine release syndrome), toxicity of the viral vectors, and a global lack of production capacity of viral vectors (see meeting minutes from first meeting of gene therapy group).

Results

The results of this work package are summarised in the mindmap in Appendix 3. The project group agreed upon the goal to strengthen the activeness of the R&D environment for gene therapy in Sweden. A number of sub-goals have been formulated (see goals section). In order to reach these goals, guiding policies were chosen that should help align all activities to meet

[15] Collins M, Thrasher A. Gene therapy: progress and predictions. Proc Biol Sci. 2015 Dec 22;282(1821):20143003
[16] Mavilio F. Developing gene and cell therapies for rare diseases: an opportunity for synergy between academia and industry. Gene Ther. 2017 May 25
[17] Naldini L. Gene therapy returns to centre stage. Nature. 2015 Oct 15;526(7573):351–60
[18] Why are there only 8 cell and gene therapies on the EU Market? [Internet]. Labiotech.eu. 2016 [cited 2017 Sep 29]. Available from: https://labiotech.eu/atmps-cell-gene-therapies-availability/

the common goals. The guiding policies are mentioned in the green boxes above and under the main activity-frame in the middle of the figure.

The recommended goals for development of the area in Sweden should include:

- Increased industry investment in Sweden.
- Increased industry-academy collaboration in Sweden.
- Increased visibility of the area and its active organizations in Sweden.
- An increased willingness to apply new therapies in Sweden.

Current situation in Sweden

Competitive advantages

The professor's privilege (lärarundantag) is by some considered an advantage. Sweden also has a low overhead cost for industry research projects at the university. Sweden also has an reputation for a well-developed and competent health care system. Additional advantages and assets that were identified are:

- Academic research. There is academic research in Sweden addressing the major application areas and enabling technologies, for example;
  - genome editing (CRISPR-Cas9)
  - *ex vivo* gene modification with viral vectors
  - gene delivery technology platforms based on nanoparticles
- Industrial project pipeline, Astra Zeneca conducts development in Mölndal on gene therapy for cardiovascular indications.
- Vecura, the core facility at Karolinska University Hospital, which has a long-standing experience and track-record in the field.
- Industrial research center, foundation for strategic research, SSF; a 75 million grant was awarded to an academic-industrial consortium to form a centre working (2017-2024) on functional delivery of nucleotide based therapies.
- Investment in industrial production facility by Cobra Biologics.

Strategic weaknesses

Sweden has a number of strategic weaknesses. The relatively small number of clinical trials within gene therapy conducted in Sweden might be interpreted as a lack for strategic interest by decision makers. Consequently, Sweden becomes less interesting for foreign investments.

The absence of a centre of gravity for gene therapy activities in Sweden makes it difficult to obtain information about the research projects that are conducted, especially for private enterprises and foreign researchers.

Funding and especially risk capital for research, but also for commercialisation of research is relatively small.

Since immunity studies in animals are very restricted in Sweden, there is a need for new toxicity models that do not require animals. These models are important because they allow a proper understanding of disease background and the mode of action of new gene therapies is

crucial. They also help avoiding an immunological reaction by the patient's immune system against the treatment.

There is a lack of knowhow for scale up of production, a lack of GMP facilities that can produce materials in large quantities as well as production capacities for viruses and oligonucleotides.

The industry is also lacking an overview of the landscape and active groups and organizations working with gene therapy in Sweden. The perception is that the area has low visibility and that it is difficult to identify partners in academia for collaboration.

A number of systemic hurdles have been identified for clinical trials. There is a lack of personal within the health care systems. Any additional activities compete with the supply of healthcare for resources.

Hurdles and needs

There is an expressed need for improved collaboration between academia and industry in Sweden. The panel also expressed a clear need for innovation in the manufacturing process to meet demand for material quantities required in clinical trials, for example a greater degree of automation and process control. Process development know-how is a key component for development of improved cell culture processes for the production of highly concentrated viruses or exosomes. AAV production capacity is considered crucial, and lentivirus production is technologically even more challenging.

Several biological hurdles or knowledge gaps remain regarding e.g., immune reactions towards employed viruses, the need for improved domain specific delivery vehicles, and the reduction of side effects such as cytokine release syndrome.

Additional specific research needs that were brought forward were:

- Research on gene editing technologies (based on CRISPR)
- Research on biomarkers that allow prediction of success
- Genome editing
- Improved delivery systems
- Research on novel vectors (e.g. AAV) and transduction methods to increase tissue specificity and expression levels
- Immunotoxicology to understand immune reactions triggered by vectors. Immunotoxicology studies with animals is very restricted in Sweden and there is consequently a great need for new toxicity models that do not require animals

The panel also identified and discussed challenges and issues related to system aspect, as decribed below:

Health economics

How to calculate the effect size and determine the value of the treatment. Gene therapy requires a different paradigm for payment assessment compared to traditional pharma. Definition of success criteria for treatment is difficult, e.g. when to pay for a life-long treatment?

Business models

Current payment and reimbursement models are not optimal. New models are needed to deliver value and profit. Intellectual property is another hurdle i.e. what part of the therapy can be patented? Today, usually the vector is protected by a patent.

Quality assurance

Improved methods for characterization and validation of biological material is needed.

Implementation in health care

Education of health care professionals and society stakeholders on the payer side about recent developments in the field of gene therapy.

General suggestions for guidelines in development of the area in Sweden

Recommended guidelines for future strategic work is to:

- Adopt an inclusive and holistic approach with focus on value creation for patients and society.
- Address the field in a national or preferably Nordic perspective.
- Prioritize funding of academic industry collaboration.
- Promote education of health care professionals in gene therapy

Suggested approach

An area of gene therapy that deserves special attention is the field of gene therapy delivery. Not only are there promising projects and collaborations between companies and academic research groups, the field has matured during the last years and it offers a platform technology based on delivery systems using extracellular vesicles, viral vector or peptides that can be applied in multiple contexts.

Patient stratification and biomarker discovery are especially important for gene therapy. Having clinically validated disease markers that allow for the identification of the right target population and to measure treatment success is crucial, because most therapies target rare diseases.

The Wallenberg Centres for molecular medicine may play an important role as project partner in the search and validation of new biomarkers.

Proposed activities - Short term (1 year)

In the short term the goal is to identify and enable collaborations that effectively utilize the available resources in Sweden. Activities are needed to facilitate the dialog between the various stakeholders in the field. This includes the gathering of information, facilitation of interaction and bringing in international expertise for advice.

Create an overview of activities

Continue the work initiated in this pilot to monitor current projects and expertise to enable new collaborations. A comprehensive, continuously updated and reviewed listing of projects and research groups would facilitate the collaboration between academia and industry.

Establish a forum for dialog

Organize meetings to facilitate the creation of new collaborations and projects a forum for dialog. Suggestions include recurring workshops or events centered on specific topics in the area. This activity complements the overview and could be arranged within CAMP or Swelife.

Start a national conference

A national conference to gather all stakeholders in Sweden should be established. Such a conference was recently arranged within the framework of the CAMP and Swelife initiatives, under the project leadership of RISE.

Establish an international advisory board

Involve international experts to review the area and advice for example funding agencies on policies and prioritizations in the field.

Search for collaboration opportunities

Proactively search for collaboration opportunities. The interviewed parties and expert panel agree that establishment of collaborations is difficult and time consuming. Resources are needed to facilitate.

Appoint a resource to proactively help exchanging ideas, finding new project partners and helping companies (from Sweden and abroad) identifying research groups that work on topics they need help with.

Proposed activities - Medium term (2-3 years)

Prepare a research agenda

Prepare a research agenda for the field based on input from stakeholders including industry academia healthcare and policymakers. The starting point for the agenda should be based on insights gained through the short-term activities.

Initiate new projects

Facilitate the formation of industry academic collaborations and use existing funding schemes to initiate new collaborative projects. For example EU funding and domestic public funding programs.

Strengthen financing

Promote the area towards funding agencies to strengthen the public financing of activities in the field.

Create a center

A center for development of gene therapy that concentrates the knowledge and resources to facilitate development. During the project period the CAMP center was awarded funding by Vinnova in 2017. However, the initial partnership and work packages have a lesser focus on gene therapies.

Proposed activities - Long term (4 years)

Invest in infrastructure

There is a lack in production infrastructure to meet increasing demand of biological material. With this in mind the case for investing in infrastructure in Sweden should be reviewed continuously to ensure that industry needs are met.

WP5: Coordination and dissemination

Objectives

To ensure an efficient implementation of the project, communication with stakeholders, dissemination via seminars and workshops, and reporting to Vinnova.

Activities

Interaction with stakeholders

The project has kept regular contacts and interacted with a wide range of stakeholders, including representatives of:

- industry, including SME, large companies, CRO's and CMO's, service providers and consultants
- academic research groups and healthcare professionals throughout Sweden
- coordinators of the CAMP and Swelife-ATMP initiatives
- the Swedish MPA
- networks such as the national Network for Advanced Therapies and the Forum for Regenerative Medicine coordinated by Gothia Forum
- support organizations such as Business Region Göteborg and Invest Skåne
- Vävnadsrådet, Vinnova and others.

The modes of communication have been via mail, telephone contacts and physical face-to-face meetings. During the project period, two information mails providing information about the objective of the project, its status, and forthcoming events and activities were sent to a list of recipients comprising ca 200 persons representing a wide range of stakeholders.

The ambition has been to have a transparent and inclusive approach in both the collection of information and opinions and in the dissemination from the project and judging from numerous feedback this has been mostly successful and appreciated.

Dissemination and networking events

During the project three one-day seminars were arranged, with the aim to expose ATMP activities in Sweden. All three workshop included invited presentation from international experts, to provide inspiration and opportunities for Swedish stakeholders to build international contacts and networks. The three seminars were.

- *"From bench to bedside - What are the translational challenges in ATMP development?"* RISE Biosciences and Materials, Stockholm, 10 May 2017.
- *"Advanced Therapy Medicinal Products – A game changer in medicine?"*, Malmömässan, Malmö, 13 September 2017. (In conjunction with Nordic Life Science Days, arranged by Invest Skåne, Business Region Göteborg and RISE Research Institutes of Sweden, in collaboration with Medicon Valley Alliance, Copenhagen Capacity and Japan Bioindustry Association.
- *"Advanced Therapy Medicinal Products"*, AstraZeneca, Mölndal, 14 December 2017.

Two one-day workshops containing invited lectures and interactive activities (group discussions or moderated discussions) were arranged on specific topics and towards more specialized participants:

- *"Regelverket kring ATMP"*, Gothenburg, 5 October 2017
  (in collaboration with Gothia Forum and Swelife-ATMP-project)
- *"Workshop on ATMP Process Development and Production"*, Karolinska Institute Science Park, Flemingsberg, Stockholm, 26 October 2017
  (in collaboration with Vecura, Karolinska Cell Therapy Center)

All seminars and workshops have been fully booked, with attendance between 60 and 120 and 30-40 participants, respectively. The program of the seminars and workshops can be found in Appendix 4.

International advisors

The project has been in contact with and benefited from the support of two international experts and key opinion leaders that represent two of the leading international ATMP initiatives:

- Johan Hyllner, Chief Scientific Officer, Cell and Gene Therapy Catapult, London, UK
- Michael May, Chief Executive Officer, Centre for Commercialization of Regenerative Medicine, Toronto, Canada

Meetings with the advisors were held in conjunction with the seminars.

Summary and Conclusions

A survey of the Swedish ATMP landscape was carried out with focus on commercialization and industrial aspects. The mapping of the field showed that there are currently 12 Swedish companies, mostly SMEs, that are developing ATMPs for indications such as, e.g., cancer, neurodegenerative diseases, musculoskeletal conditions or immune diseases. The majority of the Swedish companies are developing cell therapies, whereas gene therapies or tissue engineered products are pursued by 1-2 companies each. Most of the projects are in a late preclinical stage or already in clinical trials. In addition to the commercial ones, several projects are also carried out in an academic/health care setting, several of these are in clinical trials stage, usually conducted under hospital exemption.

Based on interviews, dialog and insights from seminars and workshops, it can be concluded that the different projects have varying needs and challenges, depending on their particular product and stage of development. In agreement with other international studies, most challenges fall within the categories: (i) infrastructure and technology related to process development and production, product characteristics and safety and efficacy assays, (ii) regulatory aspects, and (iii) economic aspects such as financing, health economy, reimbursement and business models. Infrastructure and competence to meet these needs are partly lacking in Sweden. Those infrastructures and competencies that do exist, need to be coordinated and adapted in order to make them more accessible for industry.

In an international perspective, the level of ATMP activity in Sweden cannot be argued to be high. Despite the relatively modest public investment made to the area the Swedish ATMP scene is vibrant, with examples of excellent research groups and highly competitive companies. However, if Sweden is to achieve a more competitive position is this rapidly advancing field of Life Science it is necessary to create better conditions for national collaboration that will maximize the output of available resources and future investments. This project has contributed to the first steps in this direction, by being part in the creation of the two new national initiatives Centre for Advanced Medical Products (CAMP) and the Swelife-ATMP project.

Appendix 1: Contributors

International advisors:

Johan Hyllner, Chief Scientific Officer, Cell and Gene Therapy Catapult, London, UK

Michael May, Chief Executive Officer, Centre for Commercialization of Regenerative Medicine, Toronto, Canada

Expert Group on Gene Therapy:

Johan Brun, Pfizer

Qing-Dong Wang, Astra Zeneca

Roger Strömberg, Karolinska Institutet

Samir El-Andaloussi, Karolinska Institutet

Jöns Hilborn / Oommen Varghese, Uppsala Universitet

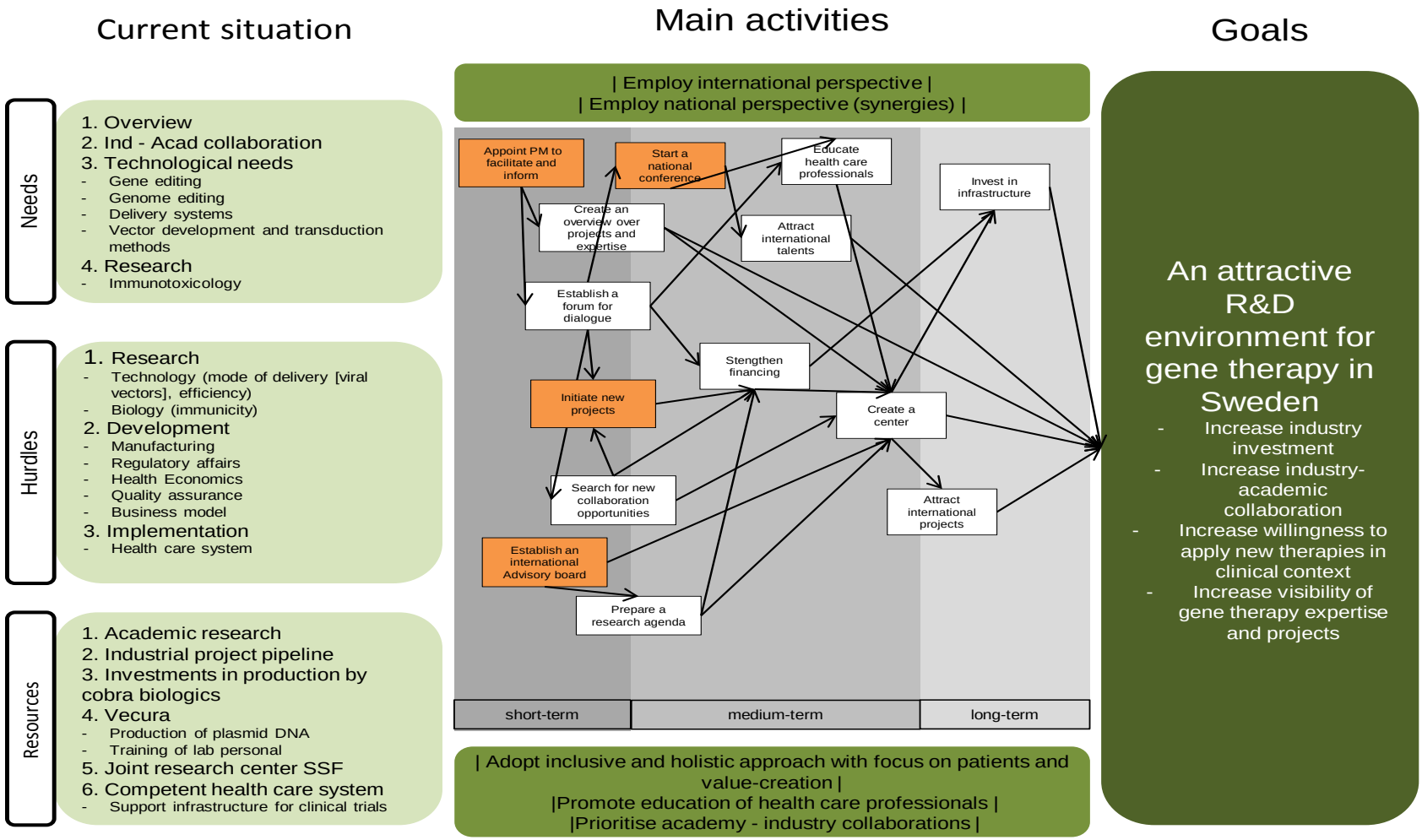
Angelica Loskog, Nxt2b

Daniel Smith, Cobra Biologics

Hadi Valadi, Gothenburg University

Erik Heegaard, Novartis

Appendix 3: Gene Therapy Mindmap



Appendix 4: Seminars and workshops

Seminar and discussion:
From bench to bedside - What are the translational challenges in ATMP development?

As coordinators of the VINNOVA funded pilot project "National Centre for Advanced Therapy Medicinal Products", we cordially invite you to attend a seminar and interactive discussion on challenges that the Swedish ATMP community is facing. Together, we can find and leverage the hidden potential at the interface of healthcare academia and industry.

Date: **10 May, 2017**
Venue: **RISE Bioscience and Materials, Drottning Kristinas väg 45 (KTH Campus), Stockholm**

Program:

0930-1000 Registration and coffee

1000-1010 Welcome & Intro

1010-1035 Michael May
CEO, Centre for Commercialization of Regenerative Medicine, Toronto, Canada
Presentation title to be announced

1035-1045 Aaron Dulgar Tulloch
Director, BridGE@CCRM, Toronto, Canada
Presentation title to be announced

1045-1100 Johan Hyllner (via video link)
CSO, Cell and Gene Therapy Catapult, London, UK
Barriers and opportunities in ATMP based therapies.

1100-1130 Anders Lindahl
Professor, University of Gothenburg/Sahlgrenska University Hospital, Gothenburg
Cartilage regeneration with cultured chondrocytes – a 30 year perspective.

1130-1150 Kristina Runeberg
Site Head/Senior Director, Takara Bio Europe AB, Gothenburg
Takara Bio, a Japanese company, establishes a GMP facility in Sweden to meet client needs within the cell therapy industry.

1150-1210 Evy Lundgren-Åkerlund
CEO, Xintela AB, Lund
Developing ATMP for cartilage repair.

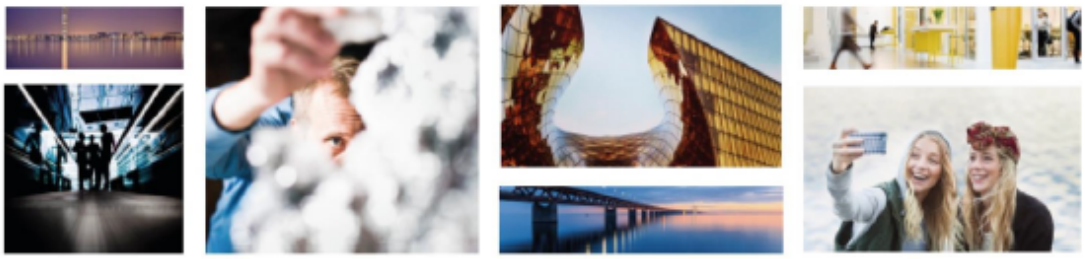
Lunch

1300-1350 Facilitated group discussions

What are the barriers and challenges in translating ATMPs from lab bench to clinic and commercial products, and how can Sweden become competitive in this field?

1355-1400 Concluding remarks and end of seminar

Registration: https://simplesignup.se/event/93280
Registration is open until Friday 5 May (only a few places are left)



Advanced Therapy Medicinal Products – A game changer in medicine?

Venue: Malmömässan, Room Hamlet, Malmö, September 12, 13-17
Moderator: Petter Björquist, CEO, VeriGraft AB

Time	PROGRAM	
12.45	Registration	
13.00	Welcome by Medicon Valley Alliance - Petter Hartman, CEO	
Block 1:	**FOCUS Global Pharma**	
13.10	Modified mRNA for treatment of ischemic vascular diseases; From preclinical to clinical studies. Regina Fritsche-Danielson, Senior Director, Head of Bioscience Heart Failure, AstraZeneca	
13.25	Challenges in developing ATMPs – What makes us different? Sven Kili, Vice President, Head of Cell & Gene Therapy Development, Glaxo Smith Kline	
13.40	Barriers and opportunities in ATMP based therapies. Johan Hyllner, Chief Scientific Officer, Cell and Gene Therapy Catapult	
13.55	Coffee and networking	
Block 2:	**FOCUS Japan**	
14.20	Forum for Innovative Regenerative Medicine (FIRM) - Setsuko Hashimoto	
14.35	CellSeed - Camilla Huse-Bondesson	
14.50	Takara - Kristina Runeberg	
Block 3:	**FOCUS Start-up - Pitch presentations**	
15.00	Bioneer - Christian Clausen	NextCell Pharma - Anders Essen-Möller
	CellProtect - Karin Mellström	RISE Research Inst of Sweden – Jim Lund
	Combigene - Jan Nilsson	TAK Biopharma - Dang Quang Svend Le
	Idogen - Lars Hedbys	Tataa Biocenter - Mikael Kubista
	Immunicum - Sijme Zeilemaker	VeriGraft - Raimund Strehl
	Miltenyi Biotech - Nicolas Danzenbächer	Xintela - Evy Lundgren Åkerlund
16.00	Discussion led by moderator	
16.20	Concluding remarks by Hironori Tanaka, Director, Japan Bioindustry Association	
16.30	Refreshments and networking	

The seminar is arranged by Invest Skåne, Business Region Göteborg and RISE Research Institutes of Sweden, in collaboration with Medicon Valley Alliance, Copenhagen Capacity and Japan Bioindustry Association.

invest in skåne

BUSINESS REGION GÖTEBORG

RI. SE

Seminar on Advanced Therapy Medicinal Products

14 December, 2017

AstraZeneca Conference Center, Meeting room Lambda
Pepparedsleden 5, Mölndal (for directions, see next page)

Program

10.45 - 11.00 Registration

11.00 - 11.10 Welcome and introduction - Regina Fritsche-Danielsson, AZ and Jukka Lausmaa, RISE

11.10 - 11.25 The European ATMP scene - Johan Hyllner, CGT Catapult, UK

11.25 - 11.40 The North American ATMP scene - Michael May, CCRM, Canada

11.40 - 11.50 Gene Therapy Manufacturing - Daniel Smith, Cobra Bio, UK

11.50 - 12.15 Swedish national initiatives;

Center for advanced medical products - Mikael Wiberg, Umeå University
SweLife strategic ATMP project - Kristina Kannisto, Karolinska Cell Therapy Center

12.15 - 13.00 Lunch

13.00 - 14.00 Results and insights from RISE pilot ATMP project – RISE project team

14.00 - 14.30 Questions and Discussion

14.30 - 15.00 Coffee and networking

Practical information:

Note that the meeting venue is at Astra Zeneca Conference Center in Mölndal. You should use the PGN Conference Center Entrance (see map on next page) and not the main entrance.

The entrance will be open from 10.30. If you arrive earlier or after 11.30, please call either Jukka Lausmaa (+46 70 392 4172), or Jim Lund (+46 70 610 5251).

The Conference Center has a designated parking space (see map), but there may a shortage of spaces at the actual time.

Transportation from central Gothenburg to AstraZeneca is approximately 30 min from Gothenburg Central Station or Landvetter Airport. For public transport options, see www.vasttrafik.se and search for travel options to AstraZeneca.

Program

• 10:00-10:15	Registrering & Kaffe
• 10:20-10:40	Inledning (Jukka Lausmaa, Ann Novotny och Kristina Kannisto)
• 10:45-11:30	Vera Franzén, Vera Franzén Consulting AB
• 11:30-12:15	Björn Carlsson, Läkemedelsverket
• 12:15-13:00	LUNCH
• 13:00-13:05	Inledning till workshop (Peter Löwenhielm)
• 13:10-14:40	Workshop: Diskussion i grupper
• 14:40-15:00	Kaffe
• 15:00-16:00	Diskussion, frågor & sammanfattning

Workshop on ATMP Process Development and Production

Karolinska Institute Science Park, Flemingsberg, Campus Huddinge
October 26, 2017, 10-16

Programme:

10:00	Registration and coffee
10:15	Introduction - Pontus Blomberg and Jukka Lausmaa
10:25	Swedish Medical Product Agency - Lennart Åkerblom
11:00	Process and production facilities within hospitals/academy (4 x 15 min) Karolinska/Vecura – Pontus Blomberg Medicon Village – Marjana Andersson Sahlgrenska – Cecilia Boreström Uppsala University/Akademiska Hospital/Karolinska – Kristina Wikström
12:00	Lunch
13:00	ATMP production in industry (4 x 15 min) Cobra Biologics – Lars Fahlander AstraZeneca – Lennart Lindfors Takara Bio – Kristina Runeberg VeriGraft – Sandra Holmgren
14:00	Coffe and fruit break
14:30	Round table discussion
15:30	Lab visit at Vecura