A national infrastructure for development, manufacturing and commercialization of advanced therapy medicinal products (ATMP)

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ATMP Sweden
A world leader by 2030

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CCRM is excited about Sweden's initiative to launch an accelerator and build process development and clinical-stage facilities in support of the ATMP sector for the Nordic region. We believe the Nordic region, with its history of scientific excellence in this field, is well suited for investment in the sector and is poised to grow its domestic industry. We see significant alignment with CCRM's efforts to develop a global network in the ATMP sector and look forward to seeing the Nordic region join with like-minded hubs from across the globe.

Michael May, CEO, Centre for Commercialization of Regenerative Medicine (CCRM)

Advancing cell and gene therapies requires collaborations that make technologies and solutions accessible to early-stage researchers. Creating an infrastructure that provides access to scalable and flexible solutions will enable research to progress at greater speed. Cytiva is proud to work with CCRM to help accelerate the development of next generation therapeutics.

Catarina Flyborg, Vice President Cell & Gene Therapy, Cytiva

Early access to manufacturing capabilities is a main translational driver to bring advanced therapies to the clinic for the benefit of patients. Given Swedish strengths in this area, as well as the potential of cell and gene therapies to address today's unmet medical needs, we are truly supportive of the report's findings regarding the need for increased manufacturing capacity for such therapies.

Johan Hyllner, Head of Cell Therapy, BioPharmaceuticals R&D, AstraZeneca

We have spent a lot of time, money and effort looking for services and expertise in process development and GMP production of virus vectors here in Sweden where we are based. The providers of these services are of the utmost importance to a gene therapy company because of both the complexity of these services and because it is a commitment to the rest of the product life cycle. It was very disappointing for us when we realised that we had to go abroad to find our partners. We would, of course, have preferred an actor who could support us with these services in a physical location here in Sweden. The proposed model in the report is a very exciting concept that would have significantly accelerated our development process. Based on our experience, this is what Sweden would need to be part of this rapidly growing area.

Jan Nilsson, CEO, CombiGene AB

VERIGRAFT started to prepare for a clinical proof-of-concept using its unique technology for personalization of vascular grafts in 2017. Since then, ATMP manufacturing, logistics and clinical trial infrastructure have been built up and authorized in two EU-countries since these services couldn´t been sourced in Sweden at that time. My estimation is that three times as many persons could have been engaged in Sweden compared to the current situation, should Sweden been able to efficiently provide such ATMP-services when our project took off.

Petter Björquist, CEO, VERIGRAFT AB

Executive Summary

Advanced therapy medicinal products (ATMP) are pharmaceutical products based on genes, modified cells or engineered tissues, intended for treating or curing disease in humans. They have potential to provide unprecedented benefits to patient and to become a major industrial segment of Life Science. Globally, the field is on the verge of a breakthrough. The first ATMPs with proven efficacy and commercial viability have entered the market during the last three years and in the coming 5 five years, tens of new ATMP products are expected to receive market approval. The current status of the industry can be summarized by the following numbers from year 2020:

- Worldwide, close to 1100 companies are developing ATMP for a wide range of diseases.
- 1200 ATMP clinical trials are ongoing of which more than 150 are in Phase III.
- Private investment in the ATMP company sector reached an all-time high of almost 20 billion USD.

In order to fulfil the potential, a number of challenges unique to ATMPs must be solved - not only technological and medical but also system challenges associated with regulatory aspects, health economy and reimbursement. The potential and challenges are globally recognized and several countries are making substantial public investments to support ATMP development in order become internationally competitive and to secure access to relevant infrastructure in this rapidly developing field.

Sweden has many of the attributes required to become an internationally competitive and attractive country for ATMP development. We have strong research activities and a growing number of innovative companies in the field. But we also have challenges that need to be solved if we are to become internationally competitive. One major gap in the Swedish ATMP innovation system is the lack of accessible and efficient infrastructure for supporting the ATMP-developing SMEs in the critical step of translating their projects to clinical phase. This is manifested by and has the following consequences:

- Swedish investors in the Life Science sector have so far not entered the ATMP field, most likely due to high perceived risks or uncertainty.
- There are very few CDMOs and CMOs with capacity and competence in ATMPs active in Sweden.
- The existing infrastructures for development and GMP manufacturing of ATMPs exist mainly in academic and hospital settings and are not primarily organized for, and do not have the capacity or incentive to meet the needs of industry regarding process development and production.
- The lack of capital and critical supporting infrastructure has led to:
    - A limited number of SMEs have built the capacity in-house at great cost and effort.
    - The majority of the SMEs are outsourcing development and manufacturing abroad.
    - Companies are highly dependent of foreign capital investments, often in return for equity.

The majority of the Swedish ATMP SMEs and their development projects have their origin in publicly funded academic research, which has been transferred to a start-up company to enable further development and future commercialization. The current situation, where the “post-academic” development is depending on foreign capital and service providers, means that much of the revenues as well as job- and value creation around the SME-driven ATMP projects occurs abroad. Sweden does not get full return from its investments in research unless we the gap is bridged so that ideas generated in Sweden also get the necessary ATMP-development, manufacturing and commercialization support. and make Sweden a country that is more attractive for ATMP-development. Such an investment would not only benefit Swedish SMEs but could also attract foreign companies to establish their business in Sweden.

Based on the discussion above, a substantial public-private investment is proposed to establish a nationally accessible infrastructure to support development, manufacturing and commercialization of ATMPs and related technologies. The new infrastructure shall fill critical gaps and complement and collaborate with the currently existing national ATMP ecosystem.

A survey of examples from abroad show that the most successful initiatives for supporting ATMP development, translation and commercialization are centralized and organized as independent entities. The new infrastructure is proposed to be based on the model which has been successfully developed since 2011 by the Centre for Commercialization of Regenerative Medicine (CCRM) in Toronto, Canada, and is characterized by:

- An independent not-for-profit entity founded and owned by a partnership of organisations and governed by a Board of Directors where the majority represents industry and business.
- Highly specialized in ATMPs, providing facilitated access to venture capital, supporting company creation and offering cost-efficient support by competence and technological services around bioanalytics, process development, and GMP manufacturing for Phase I and II clinical trials.
- Strategic partnerships with investors, industry and academia.
- Financially sustainable business model, meaning that the entity within a few years after an initial public-private start financing achieves a positive operative financial result and becomes independent on direct public funding.
- Reinvests profits into the ecosystem by supporting academic projects, providing in kind and cofounding in publicly funded projects, and building in-house competence and capacity.
- Is part of a global network of independent CCRM hubs that collaborate and share knowledge and expertise.

The proposed initiative, CCRM Nordic, should be a national endeavour and will initially focus on the Nordics as its client base. Based on a market analysis, projected number of companies and projects in the Nordic countries up to 2030, a conservative assumptions of market share, the required scale to fulfil the expected demand six years after start-up would be:

- Modular bioanalysis and process development laboratory, approximately 1000 m^2
- GMP compliant cell therapy production (10 cleanroom suites) and gene therapy production (4 production suites), in total approximately 2000 m^2

Based on expected number of projects in different categories and development phases, combined with data on expected start-up costs for construction and equipment and operating costs, prices of the services provided, and assuming a stepwise scaling up of the facility, a financial forecast over the period 2022-2030 shows that CCRM Nordic will generate a positive operative result from year 2027 and onward. In order to cover operating losses and start-up costs and to fulfil the mission to support academic projects during the first 5 years, a start-up financing (public-private investment) of ca. 500 MSEK will be required. At full-scale sustainable operation 20% of the operative profit will be used for competence development and capability building and 80 % will be invested back to the ecosystem by providing financial support to academic projects and support to new and existing SMEs.

Expected impact and effects

The impacts and effects of the proposed infrastructure are expected to include:

- Engagement with early stage academic projects and providing them with support at favourable financial terms and with an industrial “frame-of-mind” will increase the number of research project that successfully transition to commercial stage development.
- Facilitating and accelerating the development programs of Nordic ATMP companies, thereby increasing their international competitiveness.
- An effective “ATMP ecosystem”, of which the proposed infrastructure is a key component, will in the longer term attract foreign investments and companies to the Nordic region.
- Strengthening of the Nordic Life Science ecosystem by accelerating the development of a new, promising segment.

1. Introduction and background

This report presents the insights and results from work done in the Vinnova-funded innovation system development project "Sweden a leader in advanced therapies 2030 (Vinnova Dnr. 2019-04510). The work has been conducted as an activity towards one of the overall goals of the project, which is to create improved conditions for ATMP development and commercialization in Sweden. Specifically, the task has been to investigate and create the possibilities to establish an infrastructure for development and manufacturing of ATMPs in Sweden, based on the model developed at Centre for Commercialization of Regenerative Medicine (CCRM) in Toronto, Canada. In this report the proposed infrastructure initiative is referred to by the working name "CCRM Nordic".

1.1. Advanced therapies - Medicines of the future

Advanced Therapy Medicinal Products (ATMPs) include cell therapy, gene therapy, and tissue engineered products and are now emerging as a new category of medicines with the potential to offer unprecedented benefits for patients and healthcare. They have the potential to provide highly effective treatments for, and in many cases also curing, several diseases and conditions that currently lack effective treatment options. ATMPs are widely expected to lead to a paradigm shift in medicine, where traditional one-size-fits-all pharmaceutical treatments treating symptoms will be replaced by highly personalized medicines that directly target or remove the root cause of the disease.

ATMPs differ from traditional molecule-based drugs in many respects, such as technological complexity, mode of action, ways of administering and not the least potential clinical efficacy and patient benefits. Whereas the innovation processes, infrastructures and ecosystems around traditional medicines are well established, the novel features of ATMPs lead to new challenges when it comes to their development, manufacturing and implementation in health care. Some of these differences, exemplified for cell therapy products are summarized in Table 1 below.

Table 1: Differences between cell therapy development and "traditional" biopharmaceutical development.

	Cell therapies	Traditional biomanufacturing
Time to market	Extensive competition + accelerated programs for product candidates	High competition + conservative programs for product approvals
Development	Changes and development at fast speed incl. GMP regulations	Moderate changes and development at lower speed incl. less GMP changes
Complexity	HIGH – many process steps and variables	MEDIUM – fewer process steps and variables
Scale	SMALL (LAB) scale + Therapy targeted for smaller patient populations	LARGE scale + products targeted for larger patient populations
Tech availability	Non-GMP, rapid evolvement, advanced	GMP availability + tailormade for industry + finetuning of available platforms
Automation	Limited possibilities at early stages of manufacturing	Range of possibilities + proven technologies

Source: H. Schubert and C. Dragsbaek Ravn, *The cell and gene therapy transition: From research to early clinical manufacturing. (available at: https://www.nne.com/techtalk/cell-and-gene-therapy-from-research-to-early-clinical-manufacturing/).*

The great medical and industrial potential of ATMPs is globally recognized. As described in Section 2 below, this is reflected by major public investments and national initiatives to accelerate the development of the field in several countries. In terms of the number of ATMP-developing companies, clinical trials, and private financings, the field has seen a strong growth over several years. Up to date, over 50 gene- cell- or tissue therapy products have received marketing approvals by authorities in North America, Europe or other regions. (It should be noted that not all of these are ATMPs, since ATMP is a European regulatory classification and regulations differ somewhat between different global regions.) Regulations and reimbursement models are developing, with the aim of accelerating patient access without compromising patient safety. Based on the global trends combined with the current pipeline of ATMP projects, it can be expected that the number of market approved ATMPs will increase at a growing rate in the coming years.

This prediction is also supported by the US Food and Drug Administration, which in January 2019 stated that: *"… by 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year based on assessment of the current pipeline and the clinical success rates of these products."*. Thus, it can be stated that the ATMP field is on the verge of a clinical and commercial breakthrough.

The strong potential of ATMPs for patients, healthcare and Life Science industry has also been recognized by the Swedish Government; in its Life Science Strategy, advanced therapies in combination with precision medicine is identified as an important future area for the Swedish Life Science sector. In recent years, several initiatives in the form of research centres, strategic projects, and other national activities have been initiated to support the development of the ATMP field in Sweden, and are now gathered under the umbrella ATMP Sweden (see www.atmpsweden.se). With the exception for a 1.2 BSEK investment made between 2007-2017 by the SKR (the Swedish Association of Local Authorities and Regions - SALAR) to enable academy- and hospital-sponsored clinical trials to comply with new ATMP EU regulations introduced 2007, Swedish public investments in the ATMP field are relatively small and fragmented in an international perspective (see examples in Section 2).

The background to the infrastructure initiative described here stems from a Vinnova-financed project during 2016-2017, in which RISE Research Institutes of Sweden conducted a mapping of the Swedish ATMP landscape, with focus on the industry and their needs for support regarding development of ATMP based therapies. The initiative has since then "matured", being an activity within the Vision Driven Health project "Sweden a leader in advanced therapies 2030". That project aims at building a sustainable ATMP Innovation system in Sweden. This is done by identifying barriers and gaps that hinder the development of the ATMP field in Sweden, as well as engaging relevant stakeholders to develop solutions to the gaps and challenges. One of the challenges and goals of the project is to improve the conditions for development and commercialization of ATMPs in Sweden. From dialogue with stakeholders and a recent mapping and analysis of the Swedish position (see below), it can be concluded that Sweden has most of the prerequisites for becoming a leader, but that there exists a gap in the national ATMP ecosystem when comes to infrastructure for development, commercialization and manufacturing. Investing in such an infrastructure is thus both a necessity and opportunity for Sweden to become attractive and competitive in the rapidly developing ATMP field.

1.2. Global outlook

Steady global growth

Figure 1 below summarizes the status of the ATMP industry 2020, with respect to number of ATMP-developing companies and on-going clinical trials. Currently there are close to 1100 companies worldwide that are developing ATMPs. The majority of these are small or medium sized biotech and pharma companies. Most big pharma companies are now also heavily invested in the space, via in-house development, and/or partnerships or via M&A. Around 50% of the companies are located in North America, with Europe and Asia as other strongholds.

In 2020 there were over 1200 clinical trials ongoing worldwide. Out of these the majority were in Phase I or Phase II. A significant number of clinical trials had reached Phase III, i.e., were approaching the process for seeking marketing approval from authorities. The ongoing clinical trials are addressing a wide range of indications, of which over half are in oncology. Also included are other prevalent indications such as cardiovascular and neurological diseases, musculoskeletal conditions, and diabetes. Several clinical trials are also addressing rare, but severe, diseases, for which there are currently no existing treatment options.

Whereas the 2020 figures provide a snapshot in time, the data in Table 2 shows that the field has undergone a steady growth during the last years. Especially notable is the steady growth in number of companies globally (albeit with some regional exceptions), and the significant increase in both clinical phase III trials and capital raised between 2019 and 2020.

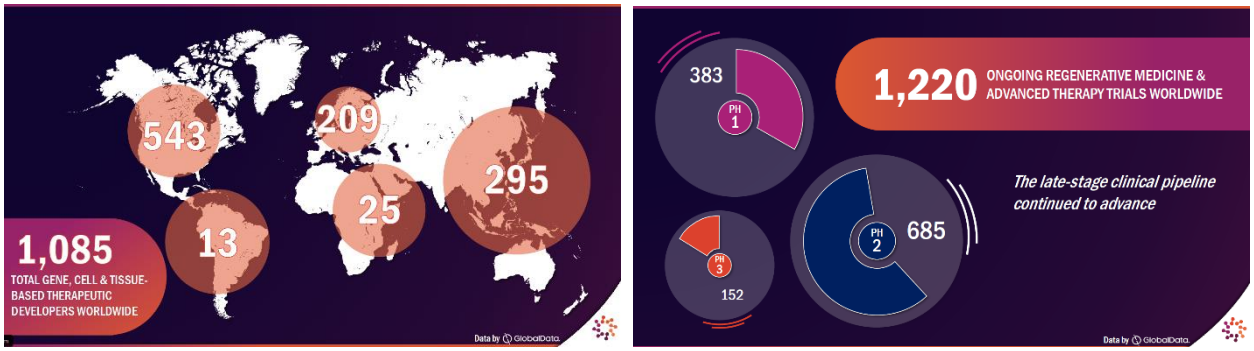


Fig. 1: Number of companies developing cell, gene, and tissue-based therapies (left) and ongoing advanced therapy trials (right). Source: Alliance for Regenerative Medicine (available for download at: *http://alliancerm.org/wp-content/uploads/2021/01/SOTI-2021-pdf.pdf*)

Table 2: Development of global ATMP industry with respect to some indicators. (Data compiled from Alliance for Regenerative Medicine Annual Reports 2016-2020).

Indicator	2017	2018	2019	2020
Companies	854	906	987	1085
North America	*460*	*484*	*534*	*543*
Europe & Israel	*234*	*241*	*237*	*209*
Asia & Oceania	*144*	*165*	*202*	*295*
South America	*15*	*15*	*13*	*13*
Africa	*1*	*1*	*1*	*25*
Clinical trials	946	1028	1066	1220
Phase I	*314*	*341*	*381*	*383*
Phase II	*550*	*595*	*591*	*685*
Phase III	*82*	*92*	*94*	*152*
Billion USD raised	7,8	13,4	9,8	19,9

Global lack of process development and manufacturing capacity

As the ATMP field develops and a growing number of projects are entering the clinical phase, the demand for quality assured and industry grade process development infrastructure and GMP manufacturing facilities is increasing. There is currently a global lack of manufacturing capacity, especially when it comes to viral vector production for gene therapies and gene-modified cell therapies such as CAR-T. The major CMOs active in the space are predicting a continuing great future demand for commercial manufacturing services and have recently significantly invested in ATMP manufacturing capabilities. Billion USD investments have also been made by major pharmaceutical companies active in the ATMP space during the last three years (for examples, see P. Van Arnum, *Cell and Gene Therapies: A Manufacturing View*, April 2019, https://www.dcatvci.org/5933-cell-and-gene-therapies-a-manufacturing-view?tmpl=component&print=1).

1.3. Sweden's position

As previously mentioned, RISE conducted a mapping of the Swedish ATMP landscape in 2016-2017, with focus on the industry and its needs. This mapping was followed by a study done by Monocl Strategy and Communications (MSC Nordics) in 2020 as part of the Innovation Milieu project. The study provides a snapshot from October 2020 of Sweden's research and industry position in the ATMP field that will serve as a baseline for monitoring the evolution of the field in Sweden. The mapping study is available at:

https://atmpsweden.se/wp-content/uploads/2020/10/RISE_baseline_ATMP_16Oct2020opt.pdf. The infographics in Figure 3 and 4 summarizes some key findings from the report by MSC.

Bibliometric analyses and other data bases available to MSC shows that Sweden has a strong position when it comes to scientific productivity in the ATMP space. In absolute numbers, (not shown) the UK and Germany take the top positions among the compared countries when it comes to publications in the last 10 years, whereas Denmark and Sweden come out on top after adjusting for population size. Most of the major Swedish universities have activities in the field, with Karolinska as a clear number one followed by Uppsala University, Lund University and Gothenburg University. Since the development of ATMPs in most cases start with academic research, the strong position of Swedish research in the field provides a solid foundation for the future pipeline of ATMP projects.

Around 20 Swedish companies are developing ATMP products, all of them SMEs. This is a significant increase since the previous mapping by RISE which identified ca 15 companies. Sweden holds the third place among the compared countries when it comes to ATMP developing companies, only surpassed by Germany and the UK. The study also shows that Swedish SMEs in the field come out on top when it comes to attracting funding from European R&D programs.

It should be noted that AstraZeneca is not included in the number of Swedish companies, as its headquarters is located in the UK. AstraZeneca has significant R&D activities in the ATMP field in Sweden and these are expected to grow significantly as a result of their recent decision to locate their global cell therapy R&D at their Gothenburg site. The Swedish industry ATMP landscape also includes a broad range of technology and service providers, , for example: supporting or enabling technologies, instrumentation or other equipment, cell lines, culture media or other consumables, regulatory services, or logistics services. Several international big pharma companies have subsidiaries in Sweden, mainly focusing on market access.

Notably, Sweden has very few commercial CDMOs or CMOs active in the ATMP field. On the other hand, as a result of the aforementioned investment made by SALAR between 2007-2017, GMP-compliant facilities and tissue establishments have been built up within several Swedish university hospitals. Serving as core facilities for the hospitals and associated universities, these infrastructures are focused on supporting academic and hospital-sponsored projects. Facilities for ATMP process development also exist within the labs of research groups or in joint structures that have been established at the universities. No dedicated infrastructure or CRO for providing commercial developers with ATMP process development services is available in Sweden.

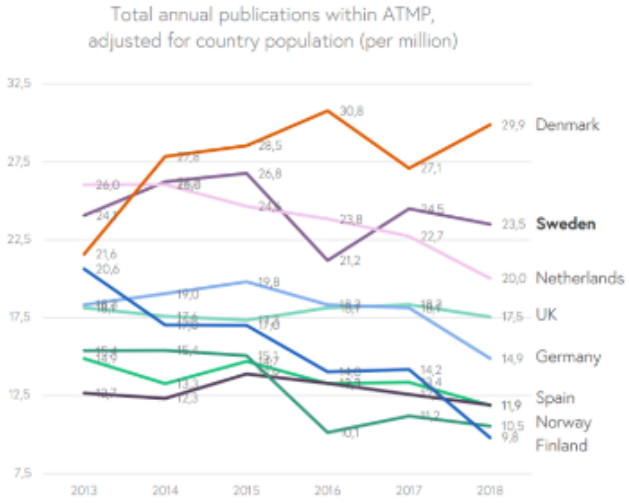
Figure 4 provides a summary of the pipeline under development by the Swedish ATMP-developing SMEs. Circa 50 ATMP development projects were identified. Out of these, 30 were in the preclinical phase, and the remaining ones in phase I or phase II clinical trials. The type of therapy is fairly evenly distributed between gene and cell therapies. It is reasonable to assume that some of the projects identified as gene therapies include CAR-T therapies, which from a regulatory point of view are classified as gene therapies but in many respects similar to cell therapies technologically. The development projects are targeting a wide range of indications, and over half of them are immunotherapies.

The mapping of projects did not include projects run by academic or clinical investigators, as this was beyond the scope of the mapping study. Based on the Swedish research activity within the field, it is reasonable to assume that the number of ATMP academic projects is a least equal to that industry-driven projects and that the majority of them are in a preclinical phase. However, several of the academy- and hospital driven projects have successfully reached clinical phase and can be considered as pioneering.

Sweden is a highly productive country within several ATMP areas, related to scientific excellence

Executive summary

- As a complement to the industry landscape, an analysis was performed related to published research, ATMP related researchers and research financing focused on ATMP in Europe.
- Germany is the leader across the different ATMP therapies based on total number of ATMP related published research per year. In absolute numbers, Sweden is in fourth place among the countries in the comparison set. However, when this data is adjusted for each country's population size, Sweden emerges as the second most productive country based on the number of ATMP related publications in 2018.
- Measured based on the number of ATMP researchers in Europe, Sweden qualifies in the top 6 rank within cell therapies without any adjustment made for country populations. Stockholm, Uppsala, Lund, Göteborg, Umeå and Linköping are all contributing to these statistics.
- Sweden is the leading European country in attracting R&D funding by the EU to finance ATMP projects.



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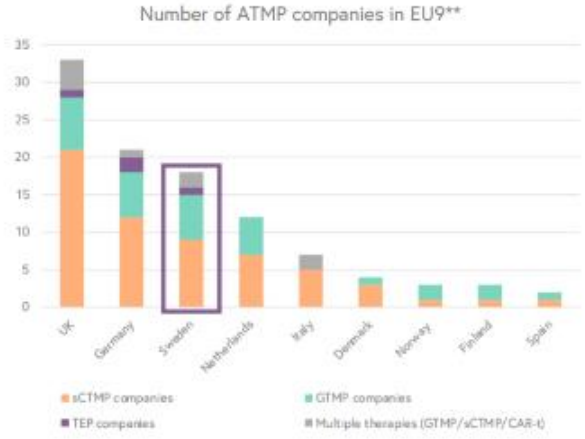
MSC STRATEGY & COMMUNICATION

Sweden is amongst the top 3 countries based on the number of identified therapeutic ATMP companies

Executive summary

- 19 companies in Sweden are developing ATMP of which most of the projects are in pre-clinical stage and a few have reached an early clinical phase.
- To compare Sweden's position with other European countries, a comparative analysis was done. Amongst these focus countries, UK stands out as the country with the highest number of identified therapy-developing ATMP companies (33), followed by Germany (21), Sweden (19) and the Netherlands (12).
- In Sweden, the number of companies developing cell or tissue therapy (13*) is twice the number of companies focusing on gene therapy (6*). In parallel to this, a higher proportion of active projects are found within cell therapy.
- Overall, a high focus was identified with projects related to immunotherapies (26), followed by focus on neurodegenerative diseases (5) and metabolic & endocrine disorders (5).



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* Includes companies offering multiple therapies within ATMP.
** EU9 (European countries selected by RISE for comparable analysis): UK, Germany, Sweden, Italy, Denmark, Spain, Norway, Finland, Netherlands.

MSC STRATEGY & COMMUNICATION

Figure 3: Infographics showing Swedish position, as compared to 8 other European countries. (sCTMP = cell therapy, GTMP = gene therapy, TEP = tissue engineered products).

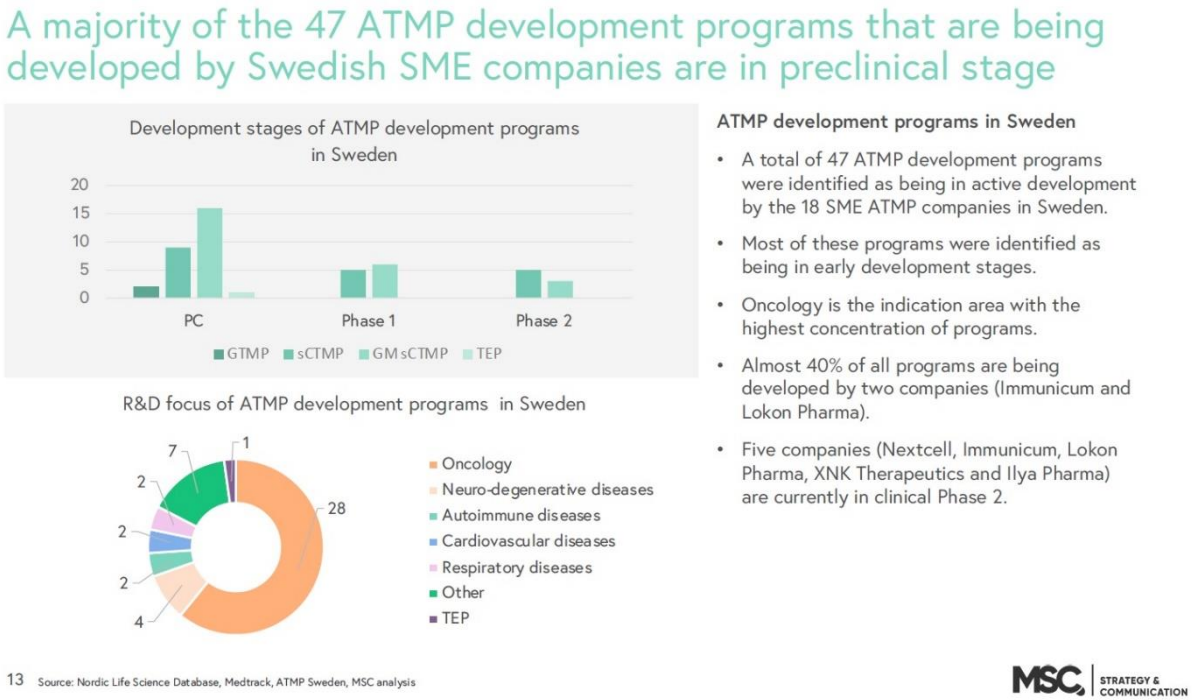

Figure 4: Infographics providing an overview of ATMP pipeline pursued by SMEs (sCTMP = cell therapy, GTMP = gene therapy, TEP = tissue engineered products).

1.4. Lack of support and infrastructure for commercialization of ATMP is a major gap in Sweden

As described above, Sweden has many of the attributes required for becoming a leader in developing ATMPs:

- Advanced therapies is recognized by the Government as one important future area for Swedish Life Science.
- We have excellent academic research activity in ATMP and related fields, providing a foundation for future projects.
- The growing number of innovative SMEs and ATMP product pipeline shows that there is a strong ambition to translate the research into clinic and products on the market.
- ATMP centres have been established, or are under planning, at several University hospitals to facilitate access to clinical studies.

The last three years has also seen a significant change in the Swedish ATMP ecosystem. The national Vinnova-funded initiatives CAMP, Swelife-ATMP and ATMP Sweden Innovation Milieu are engaging most of the stakeholders of the Swedish ATMP community in collaborations addressing the challenges and barriers that exist in the Swedish ATMP innovation system. The tables in Appendix I is an attempt to give an overview of the type and focus of some selected national ATMP initiatives and the challenges currently addressed by these and other structures.

The overview of the current ecosystem and the dialogue with the Swedish ATMP-developing SMEs indicates that there is a gap in the Swedish ATMP ecosystem when it comes to infrastructure for efficiently supporting commercial development of ATMPs. The Swedish ATMP-developing companies, which except for AstraZeneca are all SMEs, have very limited resources to build up all the necessary competences and laboratory facilities needed for their development projects. Entering clinical phase is a particularly challenging development step, as it introduces regulatory challenges and stringent requirements on

compound manufacturing control (CMC), safety data, and manufacturing according to GMP. Successful clinical Phase I/II trials are important milestones in the development process, and key to attracting the major investments necessary for taking the next steps towards commercialisation and market.

In addition to "soft" support functions on e.g. regulatory aspects and financing, there is a need for easy access to infrastructure that can provide cost- and time-efficient services related to process development and GMP manufacturing. According to several representatives of the Swedish ATMP industry, the infrastructures that have been established at the university hospitals are either not readily accessible or lack the capacity to provide support to a standard that meets industry requirements. In combination with the lack of CROs, CDMOs and CMOs active in Sweden within the ATMP field in Sweden this has led to a situation where the majority Swedish ATMP-developing companies outsource their GMP manufacturing to CMOs abroad, whereas a few of them have built these capacities in-house at great cost and effort. Another major challenge for Swedish ATMP developers is the lack of private risk capital to support the costly development. Several of the Swedish ATMP developing companies are not publicly listed and therefore strongly dependent on financing against equity by foreign investors.

The shortage of private capital and lack of easily accessible, cost- and time-efficient services for supporting ATMP development and commercialization in Sweden is a competitive disadvantage for Swedish ATMP-developers, since several other countries have made major investments and offer better conditions for ATMP development (see Section 2 below). As a consequence, ***the strong reliance on foreign service providers and foreign venture capital mean that much of the value creation of Swedish ATMP development takes place abroad, and that Sweden as a country does not get full return on its public research investments.*** Ultimately, these shortcomings can lead to a situation where Sweden falls behind in the rapidly evolving and competitive ATMP field. To counteract such a scenario, it is important that Sweden now makes the necessary investments in the field.

2. Examples of international commercialization initiatives and centres

In this section some prominent international commercialization initiatives are described. The initiatives are not heterogenous and vary in scope, funding and operational capacity and are described to illustrate different examples on how to accelerate innovation at the national or regional level.

2.1. Cell and Gene Therapy Catapult (United Kingdom)

The Cell and Gene Therapy Catapult (CGTC) is part of a network of world-leading centres designed to transform the UK's capability for innovation in specific areas and help drive future economic growth. UK Catapults are funded as "not for profit" companies. The Cell and Gene Therapy Catapult is a centre of excellence in innovation, with the core purpose of building a world-leading cell and gene therapy sector in the UK as a key part of a global industry. Supported by Innovate UK, our mission is to drive the growth of the industry by helping cell and gene therapy organizations across the world translate early stage research into commercially viable and investable therapies. The CGTC was founded in 2012 and have to date received funding of over 300 M£ (~3000 MSEK) of which £70m was used to build a large-scale GMP manufacturing centre and 30 M£ to establish Advanced Therapy Treatment Centres that will develop robust systems for the routine delivery of ATMPs as a standard of care. So far, the CGTC have been continuously funded by the government. In 2019 approximately 60% of its revenue came from public sources.

2.2. Centre for Commercialization of Regenerative Medicine (Canada)

Centre for Commercialization of Regenerative Medicine, or CCRM as they are commonly known, is a Canadian, public-private partnership supporting the commercialization of cell and gene therapies with strategic funding, dedicated infrastructure, and specialized business and scientific expertise. By partnering with leading research institutions to launch new ventures, enabling industry providing innovative contract

development manufacturing (CMDO) services, and scaling emerging companies by catalysing investments, CCRM is accelerating the translation of promising technologies, processes and therapies into life-changing health outcomes for patients. The CCRM was established as an excellence centre in 2011 awarded 15 MCAD (~120 MSEK) from the Canadian government. As of 2019 they had raised approximately 100 MCAD (~800 MSEK), in both public and private financing, in addition to the excellence centre grant. In 2020 CCRM received 10% of their revenue from public sources.

The CCRM model is based on a holistic approach and their operational structure have integrated support competences, functions and infrastructure in 6 separate business units.

Figure 5: The infrastructure would have business units that follows the CCRM model. ATTRACT focuses on support for investors including technology discovery and assessment of interesting technologies. LAUNCH, launches new companies and perform Ideation and IP development for established companies. ADVANCE is examining preclinical data, regulatory strategy and development. BRIDGE is the modular process development facility closely linked with the clinical grade GMP-manufacturing facility DELIVER. SCALE is focused on company growth and consider issues such as manufacturing change requirements and facilitating further investments. Courtesy of CCRM.

2.3. Fraunhofer IZT (Germany)

The Fraunhofer Institute for Cell Therapy and Immunology IZI investigates and develops solutions to specific problems at the interfaces of medicine, life sciences and engineering. One of the institute‘s main tasks is to conduct contract research for companies, hospitals, diagnostic laboratories and research institutes operating in the field of biotechnology, pharma-ceuticals and medical engineering.

The Fraunhofer IZI develops, optimizes and validates methods, materials and products for the business units Cell and Gene Therapy, Drugs and Diagnostics. Its areas of competence lie in cell biology, immunology, drug biochemistry, bioanalytics and bioproduction as well as process development and automation. The institute works in close cooperation with hospital institutions and performs quality tests besides carrying out the GMP-compliant manufacture of clinical test samples. Furthermore, it helps partners obtain manufacturing licenses and permits.

The Institute is located at four sites, the biggest one in Potsdam. According to the annual report for 2019, total project revenues were 34.4 MEURO, of which 26,6% were received as German national and regional grants.

2.4 ElevateBio

ElevateBio is a creator and operator of a portfolio of innovative cell and gene therapy companies. Working with leading academic researchers, medical centres, and corporate partners, ElevateBio’s team gathers scientists, drug developers, and company builders with the aim of creating a portfolio of therapeutics companies within cell and gene therapy and regenerative medicine. ElevateBio have a centralized 15 000 m^2 state-of-the-art innovation and manufacturing centre, providing fully integrated capabilities, including basic and transitional research, process development, clinical development, cGMP manufacturing, and regulatory affairs across multiple cell and gene therapy and regenerative medicine technology platforms.

2.5. BioInnovation Institute (Denmark)

BioInnovation Institute (BII) is an international hub for research-based innovation and entrepreneurship and embraces every development phase of early-stage life science start-ups within biotech, pharma and medtech. In BII, projects have access to a vibrant life science community and 2,300 square meters of state-of-the-art lab and office facilities, business acceleration programs, start-up business incubation, commercial support, unique funding opportunities and access to high-level mentoring and international networks.

Table 3: Key characteristics of foreign initiatives to support ATMP development.

Name/Country	**Scope / Focus**	**Organisational model**	**Funding model**	**International scope**
Cell and Gene Therapy Catapult (United Kingdom)	One-stop shop; process development and GMP manufacturing, training and education, coordination of advanced therapy treatment centres at hospitals	Independent not-for-profit legal entity	~3000 MSEK from government, 60% direct public funding (2019)	National focus but also attracting non-UK companies, no expressed plans for additional locations
Centre for Commercialisation of Regenerative Medicine (CCRM), Canada	Company creation, commercialization support, process development and manufacturing for early stage ATMP clinical trials, talent development	Independent not-for-profit company owned by public founding partners. For-profit subsidiaries.	~340 MSEK from federal government, supplemented by industry co-funding.	Global collaboration via independent regional hubs (Australia, Netherlands, Israel, …)
Elevate Bio (Boston, USA)	Creates and operating a portfolio of cell and gene therapy companies that benefits from their fully integrated capabilities including process development and production	Private company	3700 MSEK private investors	Focus on the United states, but not excluding
BioInnovation Institute (BII), Denmark	Innovation and commercialization support and incubator for life science projects and start-ups, including but not specializing in ATMPs	Independent foundation	~4700 MSEK from Novo Nordisk foundation over 10 years	Focusing on Denmark, but not excluding other countries

3. A national infrastructure for ATMP development and commercialization

3.1 The proposed infrastructure fills an important gap in the Swedish ATMP ecosystem

For a new emerging area such as advanced therapy development it is crucial to adopt an ecosystem-based approach in order to cover the most essential aspects of the development and commercialisation process. To support the ecosystem there are 5 strategic pillars that are all crucial to effectively develop these products. Each individual pillar will require their expertise, infrastructure and funding and should support and complement each other. *A key aspect of the proposed infrastructure is therefore that it should complement and fill gaps and in the existing ecosystem, and to collaborate with relevant parts of it.*

Table 4: The strategic pillars of ATMP development. The proposed infrastructure will have its main activity in the shaded fields and complement and collaborate with other infrastructures available in Sweden.

	Strategic Pillars for ATMP Innovation				
	Pre-Clinical Development	**Clinical Translation**	**Company Creation**	**Manufacturing**	**Talent Development**
Expertise/team	• Product/technol. development • Project management • Researcher network	• Regulatory • Trial design • Clinical network of university hospitals • Patient organizations	• Business and investment experienced team • Investor and industry network	• Process development • GMP manufacturing • Industry network	• Training programs • Collaboration with institutions (uni's and colleges) • Recruitment • Industry network
Infrastructure	• Laboratories • Hospital ATMP centre networks	• Laboratories • Hospital ATMP centres	• Incubators, TTOs	• Process development lab • GMP clinical stage facility	• Training suite • Curriculum
Funding	• Public funding • Private investors • Foundations	• Academic and private developers • Vinnova • VR • Regional	• Public and private investors	• Vinnova • Private companies • Foundations • Philanthropists	• Institutions • VR • Apotekarsocieteten, Läkemedels-akademin

Some of the necessary pillars are already developed, or under development, in Sweden through focused ATMP initiatives such as the Centre for Advanced Medicinal Products (CAMP), the SweLife-ATMP project, the Vision-driven Health project "Sweden a world Leader in ATMP 2030", and the NextGenNK centre (see brief descriptions in Appendix 1). Other national or local initiatives, activities or structures focusing on ATMPs and contributing to the ATMP ecosystem with different roles include:

- Hospital ATMP centres; Providing single point of entry to hospital clinics and supporting access to clinical trials and readiness for implementation of market approved ATMPs.
- Hospital GMP cleanrooms and tissue establishments; core facilities providing sourcing of starting materials (e.g., for autologous cell therapies) and small-scale production of investigational ATMP products, primarily in academy and hospital-driven projects.
- Vävnadsrådet, VOG Cell: Group of hospital representatives coordinating and sharing competence within cell therapy.
- NT-rådet (New Therapies Council); Group assembled by SKR, consisting of representatives from the hospital regions. NT-rådet assesses market approved new therapy products based on health

economic analyses performed by TLV (The Dental and Pharmaceutical Benefits Agency) and gives recommendations to the regions on their use or not. It also carries out horizon scanning by identifying and keeping track of ATMP candidates that have reached an advanced clinical trial stage and near a possible market approval.

In a wider sense, the ecosystem also contains several major national Life Science initiatives or structures that are not focused on ATMP, but nevertheless relevant due to their unique capacities and competencies and potential to contribute. Examples include:

- Research Centres in Vinnova's program "Biologicals"; Although the majority of these competence centres are focusing bioprocessing technologies for protein and antibody-based drugs, some of them have activities in cell processing. Some of the technologies and competencies built in these centres are generic with a potential to be adopted in the ATMP field.
- Testa Center; A public-private partnership focusing on and providing state-of-the-art facilities for bioprocess development. No activities in ATMP, but an example of a new entity created by a joint private-public partnership to fill a gap in the Swedish ecosystem around biopharmaceuticals, and thereby a potential source of valuable experiences of the process.
- SciLifeLabs; A national infrastructure for supporting the Swedish Life Science sector with competence and state-of-the-art experimental facilities and technologies. The main mission of SciLifeLabs is to support academic projects in the earlier development stages, but also has activities aimed at supporting and providing services to industry. Activities and specialize competence in ATMPs are, however, very limited.
- Genomics Medicine Sweden (GMS) and Biobank Sweden (BiS): National initiatives, connecting hospitals and universities around development and implementation of new diagnostics based on molecular biology, and coordinating biobanking facilities in Sweden, respectively. These are highly relevant to the ATMP-field, in the sense that GMS is dealing with platforms for gene sequencing and precision medicine and biobanks are important infrastructures for clinical research and ATMP development. .

Regarding support to development, manufacturing and commercialization of ATMPs, it may seem that most of the necessary infrastructure for this already exists in Sweden. All universities and many of the hospitals have established organisations to support innovation and company creation, in the form of, e.g., incubators and tech transfer offices. Some hospitals have or are in the process of establishing, ATMP centres tasked to provide support and facilitate the translation of investigational and market approved ATMPs to the clinic and patients. Facilities for GMP manufacturing already exist at several of the University hospitals. The largest one is Vecura at Karolinska University Hospital, that has long experience from GMP manufacturing of different ATMPs for early clinical trials. Therefore, a strategy could be to further invest in developing the existing infrastructure which exists in the academic and hospital settings. There following arguments show why this is not the best strategy:

- ATMP development, manufacturing and commercialization is a highly complex endeavor, requiring special competencies that are hard to find. The innovation support structures that now exist at the universities and some hospitals have the task to support a wide range of fields. They lack many of the specialized competences required for ATMP development and commercialization. Building up those competencies and capabilities at several universities or hospitals would be very challenging.
- With a few exceptions, the existing physical facilities for supporting ATMP development and manufacturing exist in an academic or hospital setting. The main mission of these infrastructures is to support the respective university's or hospital's ATMP projects. Their organisation, staffing, and working procedures are set up for fulfilling that mission. Although there are examples where industry has successfully received manufacturing services from hospital GMP facilities, they are not organized and lack strong incentives for supporting commercial industry projects. Instead, performing industry development projects within the hospital setting introduces several

challenges such as legal/contractual matters, as well as prioritization and possible conflicts of interest with respect to their "own" projects. The experience from most of the SMEs active in the field In Sweden is that the current hospital-based facilities are not easily accessible and/or lack the capacity to provide efficient support to industrial projects.

Based on the above, it is argued that ***for a small country such as Sweden, a more efficient approach would be to centralize the necessary competencies and functions into an independent and highly specialized organization that is nationally accessible and focused on infrastructure for manufacturing and company creation/investing***. Such an entity should not compete with or replace existing components of the existing Swedish ecosystem, but instead complement and collaborate with it. As seen from the examples of initiatives briefly described in Sect. 2, this is also the route taken by several other countries in their initiatives to support the ATMP field.

3.1. The CCRM model is the best fit for Sweden

Sweden is a relatively small country which has limited resources that need be used wisely. Rather than "trying to re-invent the wheel" the strategy should be to learn and draw on previous experiences, both successes, mistakes and failures, made by others. This is especially important when considering major national efforts and investments in a new, complex field such as advanced therapies. Fortunately for Sweden, several initiatives and models to support the development and commercialization of advanced therapies exist in different countries. The most prominent ones (to our knowledge) were briefly described and compared above.

Based on the analysis of the Swedish position and the comparison of international initiatives, and the ambition that a Swedish initiative should be sustainable without significant base funding from the state, *we conclude that to bridge the gap of GMP manufacturing for developers the CCRM model is the most suitable model that could be successfully adopted to Swedish/Nordic conditions*. The following unique combination of attributes of the CCRM model are particularly attractive:

- 10 years of experience, demonstrating a strong growth and international recognition as a leader in supporting the commercialization of advanced therapies.
- Strongly collaboration-driven, based on partnering and alliances on different levels with academy, healthcare, industry and investors.
- Facilitating access to capital, via de-risking of projects and engaging with investor network.
- Significantly smaller start financing required, compared to other initiatives, such as CTG Catapult and CIRM.
- Business model demonstrating financial sustainability, i.e., not dependent on public funding within a few years after initial investment.
- Reinvests profits into the ecosystem by supporting academic projects, start-up companies and SMEs.
- International perspective and globally scalable concept, that aim to catalyze the establishment of regional independent CCRM-like hubs that will form a global collaborative network.
- Already engaging with Swedish companies and in the national Swedish ATMP centre CAMP.

In February 2020, a small Swedish delegation with representatives from CAMP and Vinnova visited CCRM in Toronto. Since that visit, the authors of this report have been in dialogue with CCRM and Swedish stakeholders about establishing a CCRM hub in Sweden (CCRM Nordic), acting on a Nordic market. The discussions have resulted in a strong mutual interest in realizing this. In addition, the legal, economic and funding conditions essential to establish a hub in Sweden have been evaluated, mostly in dialogue with key stakeholders within the funding bodies, authorities, academic societies, SMEs, industry and investors.

In the following sections, the position of a CCRM Nordic in the Swedish ATMP ecosystem and its scope, contents and organization are outlined.

3.2. Scope of operations

The proposed infrastructure will be focused on commercialization of cell and gene therapies with a scope of operations stretching from late pre-clinical work up to and including pivotal clinical trials (Phase II). It includes the relevant competences and facilities in order to progress the development through that particular part of the commercialization process. This will allow Swedish actors to perform efficient pivotal clinical trials according to industry standards and thereby increase the value that is generated as a result of Swedish research. The operational model of the infrastructure is partly based on the Centre for Commercialization of Regenerative medicine (CCRM) concept developed in Toronto, Canada, and is intended to be part of a global collaboration network of independent CCRM hubs. To ensure that the operations are truly focused on commercialization and industrialization the majority of board of directors will represent either industry or investor perspective but should be independent i.e. not represent the interest of a specific company but rather the field as a whole.

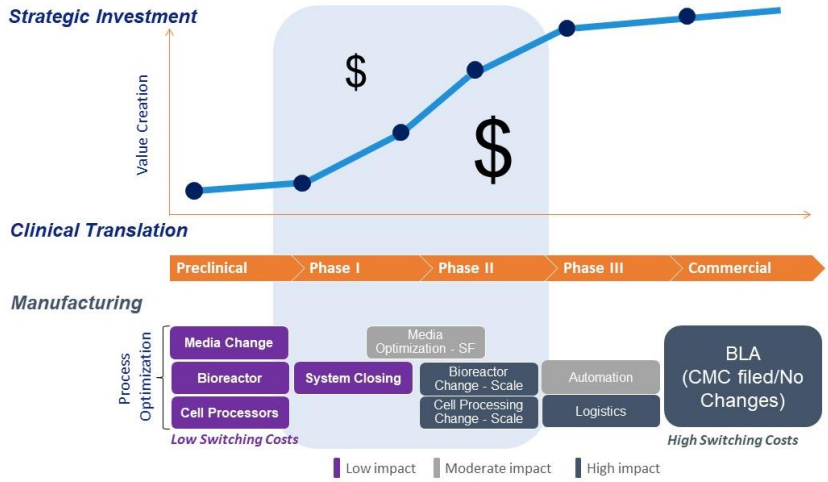

Figure 6: The scope of the proposed commercialization infrastructure marked in blue. Courtesy of CCRM.

As Sweden currently has low commercial manufacturing capabilities the proposed infrastructure will bridge important gaps in the current ecosystem and significantly strengthen the strategic pillars. Therefore, the core functions of the CCRM hub are:

1. Create new viable companies through scouting and facilitation of funding to projects with promising commercial potential.
2. Offer analytical and process development capabilities and evaluation and development of associated technologies such as cell culture, gene transduction or cell processing.
3. Offer GMP production of ATMPs for phase I and II clinical trials.
4. Leverage strategic industry collaborations to enhance technology development and commercial manufacturing capabilities
5. Assist in company growth and ecosystem development through strengthening alliance partners.
6. Complement and collaborate with the Hospital GMP-centres and labs.
7. Provide soft support i.e. business development, IP management or regulatory support to both created and existing companies with a focus on SMEs.

3.3. Physical infrastructure and competencies

The physical infrastructure is tightly connected with its highly specialized functionality. The majority of the space is therefore allocated for the process development and GMP production areas. In addition to the physical infrastructure relevant competences should be available based on ecosystem gaps. CCRM will have staff that is skilled within market analysis, business development, technology transfer and

assessment, IP management, sales, regulations, process development, production and several secondary consulting service offers. Where strategic alliances with key competencies are favorable that option should be preferred. During the startup phase CCRM Nordic could leverage existing competences for "soft services" in the CCRM Network so that those services can be established locally when they can be sustained within the CCRM Nordic organization. In terms of office, meeting room and storage space it is estimated that approximately 1000 m2 will be sufficient. The laboratory facilities, summarized in Table 5, should be customized in accordance to their specific function and the expected demand from customers and collaborators. The scale of the infrastructure proposed here is based on an analysis of the Nordic market and projected number of projects assuming that the infrastructure captures a certain market share of the demand of services (see Section 4 below and Appendix 3).

Table 5: Key characteristics of the process development facility and GMP manufacturing facility. The scale of the proposed facilities is based on a modeling of the expected demand in the Nordics up to 2030.

Process development facility key characteristics/figures	**Cell and vector production facility key characteristics/figures**
▪ ~40 Employees ▪ Bioanalytics ▪ Manufacturing technology development ▪ Process development ▪ 1000 m^2 modular laboratory ▪ Strategic partnership with manufacturing technology companies	▪ ~40 Employees ▪ 10 Class B cell processing cleanrooms ▪ 4 viral vector production suites ▪ QC/QA laboratory ▪ Phase I/II clinical scale ▪ 2000 m^2 ▪ Strategic partnership with CDMOs

The process development facility will enter strategic partnerships with manufacturing technology companies but also function as an open test bed for companies developing enabling technology. As an example, the CCRM Toronto process development facility was started as a strategic partnership with GE Healthcare (now Cytiva) but also contain equipment from other companies. Likewise, the GMP facility should leverage, not compete with, our local ecosystem and form strategic collaboration wherever possible. The long-term effect goal would be to facilitate large scale manufacturing capabilities with synchronized SOPs and equipment to make tech transfer faster and cost efficient.

3.3. Partnerships and alliances

The Swedish CCRM hub would leverage the engagement framework that is based on entering strategic partnerships and alliances with industry, investors and academic institutions at different engagement levels. The goal is to support industry and in the long term contribute to an ecosystem with increased public and private risk funding to the field for developers in industry as well as in academy. The initiative should strengthen the different stakeholders in the following manner:

- Industry: strategic partnership, enable industrialization of both technologies and therapies
- Academy: development and technological support, increase investments and grants
- Investor: increase value and decrease risks

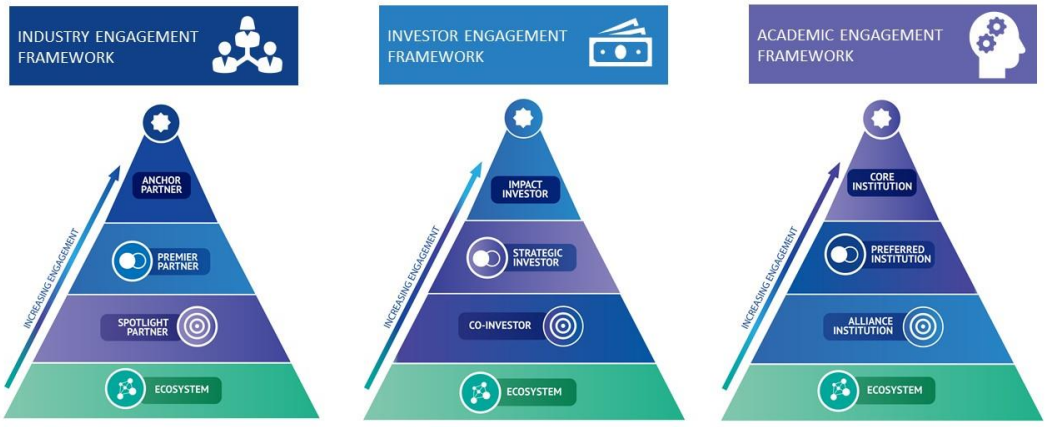

Figure 7: The CCRM engagement frameworks for industry, investors and academic institutions. Courtesy of CCRM.

Industry engagement

CRRM forms an industry consortium that they engage with according to the Engagement framework. In Canada the industry is not part of the CCRM founders but instead have a strong representation in the board to ensure that CCRM keeps focused on its mission to commercialize ATMPs and relevant technologies. CCRM also operates within both industry initiatives as well as publicly funded research consortia. CCRM focuses on small and mediums size enterprises who do not have the capacity to invest in their own process development or manufacturing facilities but also collaborates closely with large multinational companies.

Investor partnership

CCRM Nordic will provide investors with access to local emerging companies or opportunities coming from CCRM's international hubs as well as access to its in-house specialized scientific team to inform decisions and de-risk investments. CCRM could work with investors in partnerships that may take the form of co-investment in current opportunities, creation of co-branded biotech funds, or direct investments in CCRM's company creation engine. During the last year several Swedish investors have been surveyed as to whether a potential collaboration with an entity such as the CCRM Nordic would be of interest. The majority have replied positively.

Academic engagement

CCRM actively provides support to academic researchers and groups from their academic network. The most interaction is with the core institutions who are well involved and informed on CCRM's operations and strategy. But CCRM also works with product and business development together with all academic stakeholders who want to accelerate commercialization. The model is built to be able to provide resources to the academic community, including financing.

CCRM Global hub collaboration

One long term objective of CCRM is to catalyse several CCRM-like hubs worldwide that will make the backbone of a global collaboration called CCRM Global. Each hub will establish a universal platform that generates local impact and connects to the global network. The hubs will have similar management and operating structures and will share IP, infrastructure and expertise. They are meant to collaborate on topics such as company creation and funding, training, legal/regulatory, manufacturing and global market access but also aim to build a significant shared venture fund.

In addition, CCRM would also engage in strategic alliances with relevant national initiatives such as Sci-Life Labs, Testa center, MAX IV, the hospital ATMP centres and AstraZeneca BioVenture Hub, etc.

4. Financial aspects

As the objective of the infrastructure is to bridge gaps and be a vital part of the Swedish ATMP development landscape, parts of which are to be financed by both public and private stakeholders it is crucial that the financial aspects are carefully considered. In order to ensure that this critical infrastructure is available and functional over time we propose that, based on the CCRM model, a new legal entity is formed and that the entity should aim to be sustainable within a foreseeable future. In order to achieve this, the entity will form ventures, on its own or preferably as joint strategic collaborations with industry, that will be operating under a well thought-through business model to generate revenue for the primary entity. As a not-for-profit, the entity will not distribute its profit to its shareholders, but can instead invest in building new capacity, acquire competence and re-invest in the ecosystem.

4.1. Business model

An overview of the CCRM Nordic's value propositions is shown in the business model canvas in Appendix 2. The CCRM Nordic organization would be established as a public private not-for-profit partnership-company. At its core the economic framework should enable the facility to be successful in its mission to provide support, process development and GMP-production services to developers and tech companies in a cost efficient manner and at the same be sustainable and thereby not require additional direct public funding for public sources. In order to achieve this, the CCRM model builds on a highly specialized organization that can generate revenue by:

- acting as a parent company and establishing for-profit daughter companies that offer services for fees on the open market
- having the ability to co-generate future customers by facilitating access to strategic funding from its international investor network
- investment by in-kind contribution and helping to develop projects, start-ups and SMEs and enable them to grow in the phase from late preclinical development until Phase I and II clinical trials. After a pivotal trial is performed the shares will be sold and returns will cover costs or investments of the parent not-for-profit organization.

In order to nourish the innovation ecosystem CCRM will also provide support for academic projects that will provide a pipeline for future clients and company creation.

The CCRM model, as implemented in Toronto, has been proven to be financially sustainable. Starting as an Excellence Centre in 2011 with 15 MCAD public start funding (ca. 120 MSEK), followed up by additional public-private investments, CCRM has grown into an internationally renowned initiative which now employs 120 skilled persons, houses 3000 m2 lab and clean-room space for process development and GMP production for early stage clinical trials, and is independent of direct public financing.

4.2. Costs

The costs can be divided into, mainly one-time costs, that are incurred during the start-up phase, and operative costs when the infrastructure is up and running.

Start-up costs include the following major items:

- Design, construction and commissioning of laboratory and clean-room space, with special requirements on the ventilation system including both negative and positive air pressure spaces. This is expected to involve extensive use of external consultants.

- Equipment for process development and bioanalytical laboratory, clean rooms for GMP-production and a QC-laboratory. The types of necessary equipment include, for example, controlled air flow cabinets, different types of bioreactors for cell culture, bioanalytical instrumentation, freezers, microscopes, sterilization equipment, and equipment for fill and finish.
- Setting up and obtaining a certified Quality System, qualification of personnel, validation of instrumentation and methods, and acquiring necessary permits and accreditations.

Operative costs consist of the following major categories:

- Personnel costs
- Maintenance costs; service contracts for maintenance of instrumentation and ventilation systems, maintaining permits and accreditations
- Consumables in process development, GMP-production, and collaborative research projects
- Rent for laboratory, cleanroom, office and storage space
- Other costs (IT-infrastructure, travel, indirect costs…), estimated at 25% salary costs)

Ultimately, the cost of using the services will be borne by the users which means that in order to be capital efficient it is of paramount importance to keep overhead costs and other unnecessary costs to a minimum. This will also decrease the time needed to reach "the point of sustainability" described below.

The estimated cost for running the facility (see 4.5 Financial forecast below) are based on similar infrastructures concerning the equipment, staffing, and space required. Some costs such as consumables, which are high in this kind of projects, will always be directly transferred as a cost in the specific projects and are therefore not a risk from a financial point of view. The same can be seen from the salary point of view, where any increases in number of staff and personnel costs will be governed by demand in terms of projects. A minimum number of staff is however required to run a GMP facility, since there are several fixed positions required. The major uncertainty in the cost estimations are the rent per m^2 of the facility, as always there are several options in negotiating rents for a facility and the prices are highly depending on location.

4.3. Revenues

The majority of revenues are expected to come from service for a fee kind of work offered at market prices. To support the eco-system, non-commercial projects (academic projects) will be offered at subsidized rates. The services provided include:

- Company creation and "soft" commercialization support, including facilitating access to venture funding, IP management, business development, regulatory strategy, due diligence and partnering with relevant supporting technologies
- Technological and analytical services around process development and product characterization
- GMP-production for early stage clinical trials

Participation in publicly financed R&D projects in collaboration with academia and industry will also contribute to revenues. Licensing of IP generated by publicly financed projects is expected to generate revenues but are for simplicity's sake not included in the revenue calculations in this prospect.

Of the services offered it is estimated, based on data from CCRM in Toronto, that the majority of revenues will come from the GMP related services and that the process development will provide a revenue that is around a quarter of that. "Soft services", like business development, are expected to provide ca 25% the process development revenues. In Toronto CCRM generate revenues from ventures it has invested in and exited from and whether this could be possible or even wanted within CCRM Nordic has to be investigated further.

4.4 Financial forecast and path to sustainability

A relatively small country such as Sweden needs to use utilize its money wisely and responsibly and therefore propose that a Swedish infrastructure for commercialization of advanced therapies should be sustainable. We therefore here present scenario of how and when we expect or reach our "point of financial sustainability" i.e., at which point the revenues are equal to the costs. Obviously, an endeavor of this type will not be able to bear its costs from start but will require a substantial start funding. The idea is that the initiative manages to secure sufficient funding from public and private actors to be confident that it is a relatively low financial risk for all involved parties before a go/no go decision is made.

Method and assumptions

To assess the financial feasibility of the initiative, make a financial forecast, and estimate the required start financing, the following actions and assumptions were made:

1. In order to prognose the expected demand for the type of services that will be offered by the infrastructure an analysis of the current and projected market in the Nordic region (Sweden, Denmark, Finland and Norway) was conducted.[1] Selected data are shown in Appendix 3. The number of existing (as per Dec 2020) ATMP-developing companies as well as the number of industry-driven ATMP development projects in the Nordics was mapped. Using different sets of CAGR calculations, the number of companies and projects in different categories (gene therapies, cell therapies, and tissue engineered products) and development phases (preclinical, clinical phase I, and clinical phase II) were then projected for the period up to year 2030. The analysis resulted in an expected growth of companies from 30 to 80 companies in the coming 10-year period. Similarly, the total number of SME-driven ATMP projects in the Nordics was projected to increase from 75 in year 2020 to 180 in year 2030. Given that some infrastructure already exists or is under development in other settings in the Nordics, it was then assumed that the infrastructure proposed here would capture a 20% share of the Nordic market for the type of services provided. We consider this to be a realistic and conservative scenario.
2. The number of expected projects year 2030, was then used for setting the scale at full operation of the infrastructure, in terms of number of staff and size of office space, process development laboratories, and the number of operative GMP cleanrooms required to need the expected demand. The start-up and scale-up of the infrastructure was then assumed to be stepwise, based on demand:
    - The first two years (2022-2023): A start-up phase with recruitment of personnel at C-level and other key personnel. Detailed planning of the operation and process development facilities and GMP rooms. Procurement and installation of equipment, obtaining all the necessary approvals, and business development.
    - 2024: Process development facility operational and first GMP clean-rooms operational. First process development and GMP manufacturing projects executed.
    - 2025-2030: Ramping up of the capacity by recruitments and increasing the number of operational GMP-rooms based on demand. Increased number of process development and GMP-manufacturing projects executed, according to forecasted number of projects in the market and market share.
3. Costs for equipment purchases and the yearly operative costs and revenues were projected based on the infrastructure and personnel required to carry out the expected projects. Prices and costs of projects in different categories were taken as average numbers obtained from different sources (CDMO's, CMOs, ATMP-developing SMEs, and CCRM in Toronto). It should, however, be pointed out that the numbers for price and cost of projects vary over a large range.

[1] Analysis performed by MSC Nordics, as part of their partnership in the project "Sweden a Leader in Advanced Therapies 2030". Report is available at https://atmpsweden.se/wp-content/uploads/2021/03/Report-infrastructure-RISE_v4.pdf

Financial forecast of costs and revenues 2022-2030

Based on the method and assumptions described above and in more detail in Table 6, a financial forecast of costs and revenues was made for the period 2022-2030. The detailed numbers of the resulting forecast are presented in Table 7. From Table 7, it follows that the infrastructure will accumulate an estimated negative operative financial result of ca 188 MSEK between 2022-2026, after which it is expected to start generating a positive annual result. In addition, substantial start-up costs for design, construction and commissioning and equipment purchases, estimated at 290 MSEK, will be incurred during the initial 5-year period.

Table 6: Assumptions and input parameters for financial forecast

Assumptions and input parameter	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**
Management (average salary 100 kSEK/month)	3	4	5	6	6	7	7	8	9
Personnel (average salary 50 kSEK/month)	3	15	40	60	80	100	110	110	120
Rent Office and storage space (m2), 2500 SEK/m2 year	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000
Rent, Lab and GMP space (m2), 4000 SEK/m2 year		2 000	2 000	2 000	2 000	2 000	2 000	2 000	2 000
Design and construction of PD lab and GMP cleanrooms	152 000								
Purchased equipment PD lab and GMP cleanrooms	90 000	16 000	12 000	12 000	8 000				
# Operative GMP clean rooms	0	0	2	4	6	9	12	13	14
# "soft support" projects (average price 380 kSEK)	2	4	6	8	10	12	13	14	15
# research projects (average grant 760 kSEK)		1	2	4	6	8	9	10	10
# process development projects (average price 3 800 kSEK)			10	12	14	16	18	19	20
# GMP manufacturing projects (average price 15 200 kSEK)			2	4	6	10	12	12	14

Table 7: Financial forecast of costs, revenues and operating result 2022-2030

Costs (kSEK)	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**
Personnel costs	8 640	22 080	48 000	69 120	88 320	109 440	119 040	120 960	132 480
Rent	2 500	10 500	10 500	10 500	10 500	10 500	10 500	10 500	10 500
Design and building of lab and GMP facilities	152 000								
Equipment purchases	90 000	16 000	12 000	12 000	8 000	0	0	0	0
Start-up costs GMP labs	38 000	38 000							
Service and maintenance	4 500	5 300	5 900	6 500	6 900	6 900	6 900	6 900	6 900
Consumables in projects	0	0	20 520	31 920	43 320	63 840	75 240	76 380	86 640
Other costs (XX% of salary costs)	1 728	4 416	9 600	13 824	17 664	21 888	23 808	24 192	26 496
Total costs	**297 368**	**96 296**	**106 520**	**143 864**	**174 704**	**212 568**	**235 488**	**238 932**	**263 016**
Operating costs	*55 368*	*80 296*	*94 520*	*131 864*	*166 704*	*212 568*	*235 488*	*238 932*	*263 016*

Revenues (kSEK)	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**
Soft support projects	760	1520	2280	3040	3800	4560	4940	5320	5700
Research projects (Vinnova, EU, …)	0	760	1520	3040	4560	6080	6840	7600	7600
ProcDev project	0	0	38000	45600	53200	60800	68400	72200	76000
GMP projects	0	0	30400	60800	91200	152000	182400	182400	212800
Total revenues	**760**	**2280**	**72200**	**112480**	**152760**	**223440**	**262580**	**267520**	**302100**

	2022	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**
Operating result	**-54 608**	**-78 016**	**-22 320**	**-19 384**	**-13 944**	**10 872**	**27 092**	**28 588**	**39 084**
Accumulated operating result	*-54 608*	*-132 624*	*-154 944*	*-174 328*	*-188 272*	*-177 400*	*-150 308*	*-121 720*	*-82 636*

Start financing and reinvestment of generated profit

Due to the high initial start-up costs and an expected period of several years of negative operative financial result, a substantial start-up financing investment will be required. In order to form a public-private partnership, it is required that all partners are willing to invest funds into the partnership.

To effectively launch this initiative, we propose that in the initial start-up or establishment phase the funding would come from the public sector. However, as the initiative progresses, as a PPP, the up-front financing in the building and implementation phase will be borne by both private and public sector. Thanks to the sustainability approach of the CCRM model the start financing should come as a one-time public-private investment, possibly divided into annual tranches. After the "point of sustainability" is reached it is estimated that only 10-20% of the revenue will come from the public in the form of national, European and international grants acquired in competitive calls.

According to the forecast, the infrastructure is expected to generate a positive financial result after the first five years. To cover the start-up costs and operative losses and to maintain liquidity during the first 5-year period, a starting financing of ca 480 MSEK will be needed. In order to fulfill CCRM Nordics mission to invest in the ecosystem and future pipeline of projects, specifically supporting academic projects by subsidized services, an additional 36 MSEK is proposed for the period until 2027. The total proposed start financing is thus 514 MSEK, distributed according to Table 8 below. This amount is what is required to reach full operations, as described in the forecast. It could also be possible to start with a lower start-up financing but that would force the initiative to have to raise additional funding to reach full operations which is associated with significant uncertainty and potential risks.

Table 8: Distribution of proposed start-up financing

Start financing (kSEK)	2022	2023	2024	2025	2026	2027	2028	2029	2030	Total
Covering operative losses	54 608	78 016	22 320	19 384	13 944					188 272
Start-up costs; construction and equipment	242 000	16 000	12 000	12 000	8 000					290 000
Support to academic projects		5 000	7 000	9 000	9 000	6 000				36 000
	296 608	99 016	41 320	40 384	30 944	6 000				514 272

After reaching its point of sustainability, as a not-for profit entity (in Swedish: "icke vinst-utdelande bolag") CCRM will reinvest any positive financial result (operative profit) into the ATMP ecosystem in different ways:

- Supporting academic projects by providing subsidized services.
- In kind support and co-financing of publicly funded projects
- In-house competence development and capacity building
- co-investing in future expansion of capacity for early stage projects

5. Location

This section will cover a number of criteria and characteristics and their respective importance in relation to the physical location of a Nordic or national infrastructure.

- Ability to attract private and public funding (Impact 5/5)

In order to launch the building phase and cover operative deficits during the first years we have estimated approximately 514 MSEK will be required to reach full operations. The initiative could be started with less but additional funding will be able to improve capacity, equipment and offered services. The ability to attract private and public funding is therefore one of the most critical and important criteria for the placement of the infrastructure.

- Time projection for building physical infrastructure (Impact 5/5)

Another important criterium is the time projection for when the physical infrastructure can be operational. There are currently several European countries that are investing in the advanced therapy area and in order to effectively seize the opportunity currently presented and at the same time meet our growing national needs a hasty timeline is warranted.

-The possibility for expansion and for strategic partners to find suitable space in the vicinity (Impact 4/5)

To prepare for the future and for a rapid expansion of strategic partners and associated businesses the location should offer these possibilities. Preferably the location should be suited to be able to host future facilities capable of larger scale manufacturing of market approved ATMPs.

- Current and future surrounding ecosystem (Impact 4/5)

Collaboration and access to major hospital(s) and patients is important not only to facilitate clinical trials but also for capturing medical needs. As the ATMP field evolves, the ability of the surrounding ecosystem to also contribute with supporting and evolving technologies or competencies will be an important aspect. Such supporting competencies could be, for example, bioprocess, diagnostic and analytical technologies, AI, digitalization, automation and logistics.

- Prerequisites to attract competence (Impact 4/5)

One challenge will be to attract personnel with the required competences, and with the current competence base in the Nordics this means that an international recruitment policy must be used. In order to be successful, this will require a location with high international attractivity and critical mass of other life science actors. Attractive living conditions with all that entails, such as communications and other infrastructure, employment prospects for spouses, housing, schools, children's daycare etc. will be important.

- Logistical conditions (Impact 3/5)

Vicinity to airport, position in relation to ATMP centres of gravity in Denmark, Finland and Norway.

6. RISK analysis

The table below presents a risk analysis for the initiative.

Table 10: Risk analysis for establishing a sustainable operation.

Risk	**Probability (1-5)**	**Consequence (1-5)**	**Preventive/mitigating actions**
Failure to raise required start funding	3	5	Initiative will not be started without critical funding level has been secured. Smaller scale and/or slower build-up will be planned for in case of lower secured financing.
Difficulty in attracting competent personnel	4	4	International recruitment policy will be adopted. National education and training initiatives to secure competence for future needs are under planning. CCRM global consortium has identified training and talent development as a prioritized area of collaboration.
Delays in construction of facilities	3	3	Construction timeline an important criterium for selection of location. Use experience and knowledge from CCRM Toronto and its global consortium.
Construction and costs are higher than anticipated	2	4	Use experience from CCRM Toronto and other regional CCRM hubs. Investigate costs and the factors that causes them to increase.
Growth of Nordic projects less than expected or competing actors appear.	2	3	Financial forecast is based on very conservative market share of the Nordic market. Global market will be addressed.
Unable to generate enough revenue to ensure liquidity and sustainability	2	4	Organic growth; expansion of personnel and facilities will be adapted to the demand.

7. Time plan

Assuming that a decision of public funding for continued planning of the initiative is taken during Q2 2021, the following time plan is envisaged:

2021: Planning project initiated, including an in-depth analysis of financial, legal, geographical and organizational aspects. Letter of Intent from founding organizations, hub establishment agreement signed with CCRM Toronto.

2022: Final prospect drafted, including description of the facility and its operation, organization and ownership, geographical location, commitments from founding and associated partners. Registration of CCRM Nordic legal entity, decision on location, Recruitments, design, construction, detailed planning, procurement and installation of equipment.

2023: Recruitments, installation and validation of equipment and processes, obtaining required approvals, business development;
Milestone: Process development facility and first GMP clean room operational

2024: Organic expansion, based on demand;
Milestone: First process development and GMP manufacturing projects completed.

2027-
2029: Continued organic expansion based on demand;
Milestone: Positive financial result (operating costs < revenues from projects)

2030-: Full scale operation.

8. Conclusion

The prospects of establishing a CCRM hub in the Nordics have been investigated. Following a visit in Toronto in February 2020 a productive dialogue with CCRM has been established. The concept has been discussed with key stakeholders such as ATMP developing SMEs, CDMOs, investors, academic researchers, key opinion leaders and financiers. Most stakeholders that have been interacted with have been predominantly positive to the idea of establishing a specialized infrastructure to bridge the gaps for ATMP developers that currently exists in the Nordic ecosystem and that there are strong private actors interested to discuss a Public Private Partnership. The financial forecast based on a market analysis of the Nordics indicates that a entity based on the CCRM model could be sustainable within a foreseeable future and generate enough revenues to be independent of additional public funding, reinvest in the ecosystem and be a contributing partner to the CCRM Global collaboration.

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Appendix 1: Overview of publicly funded ATM initiatives in Sweden

Table 1: On-going initiatives focused on ATMP (Nov 2020)

Name	What is it?	Objective and focus	Who are part of it?	Duration
CAMP	• National centre in Vinnova program "Biologics"	• Create national public-private partnership • R&D activities around ATMP process development, manufacturing and logistics • Coordination of ATMP infrastructure	• Currently 32 partners from healthcare, industry and academia • Partnership regulated by Centre agreement	Jan-18 - Dec-23
Swelife ATMP	• Strategic project within Swelife	• System challenges around ATMP development and implementation	• Open to partners that committ to contribute to the projects • Partnership regulated by Centre agreement	July-17 - June-21
VDH Innovation Milieu	• Project in Vinnova Vision Driven Health program	• Build sustainable innovation system for the ATMP field by vision-driven collaboration across sectors. • System challenges and gaps in the Swedish innovation system for ATMP	• Currently 20 formal partners from healthcare, industry, academia, authorities and associations. • Flexible partnership and budget • Partnership regulated by agreement	Nov-20 - Nov-24
NextGen NK	• Centre within Vinnova Competence Centre program	• R&D around NK cells for therapies	• Partnership regulated by agreement • X partners from academy, healthcare and industry	2020-2025
ATMP Sweden	• Brand name • Not a formalized organization	• "Shop window"/umbrella organization that gathers Swedish ATMP activities and community • Communication activities	• Open to all in Sweden who are somehow involved in ATMP • No formal partnership	2018 -

Table 2: National ATMP challenges or topics (not in order of priority) and where these are currently addressed (x = addressed, X = strong focus, (x) = partly addressed)

Topic/challenge	CAMP	Swelife ATMP	VDH	Other
"Basic research"/Technology development	(x)			Universities, VR, SSF, (Vinnova)
Process development for ATMP manufacturing	X			AdBioPro, CellNova, FormulaEx, Vinnova
Translational research projects	X	x	x	VR, Swelife, Cancerfonden, LUA-ALF , …
Regulatory support to developers in academy		x	x	(LV), hospital ATMP centres
Regulatory support to developers in hospitals	x	X	x	(LV), private actors
Regulatory support to developers in industry		x	X	(LV), private actors
Harmonisation of small scale and industrial scale GMP production	x		X	
GMP production in hospital setting	X			VOGCell, hospital GMP labs
GMP production in industrial setting			X	
Commercialization support		x	X	
Implementation in health care – processes and organization		X	X	SWECARNET, Hospital ATMP centres, Vårdanalys
Implementation in health care - health economy and payment models		X	(x)	TLV, NT-rådet
Patient perspective		(x)	x	TLV, NT-rådet
Communication		X	X	ATMP Sweden
Internationalization	x	X	X	ATMP Sweden
Education and learning - securing future competence needs	x	X	X	VOGCell
Access to financing			X	

Appendix 2: Business model canvas

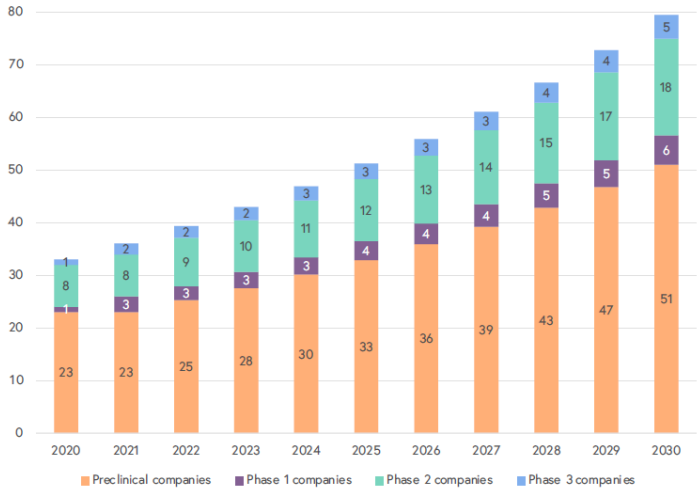
CCRM Nordic Business Model Canvas

Appendix 3: Projection of companies and projects on Nordic market

Projected number of ATMP companies in the Nordics

The number of ATMP companies in the Nordics, are expected to increase to about 80 companies by 2030 from 33 in 2020

Projection of companies in each phase, based on current company distribution in Nordic ATMP companies



Key assumptions

- 2020 number of companies and distribution between phases was used.
- Assumed amount of time in trials was 13 years, based on marketed products:
  - Preclinical: 4 years
  - Phase 1: 3 years
  - Phase 2: 3 years
  - Phase 3: 3 years
- The phase success was based on Hay et al. (2014) for biologics and Takebe et al. (2018).
- The growth rate of 109% from 2020 to 2030 was compiled by four sets of growth calculations;
  - A Compound Annual Growth Rate (CAGR) based on the number of ATMP trials in Europe was added to account for growth in the market.
  - A CAGR based on a similar organization's growth data.
  - A CAGR based on the growth in Nordic companies 2018-2020.
  - A CAGR based on the historical average number of companies founded in the Nordics 2015-2020, based on companies identified in earlier parts of this report.

39 Source: MSC analysis; ARM Annual reports; Hay, M., et al., 2014. Clinical development success rates for investigational drugs. Nature Biotechnology, 32(1), pp.40-51.; Takebe, T., et al., 2018, The Current Status of Drug Discovery and Development as Originated in United States Academia: The Influence of Industrial and Academic Collaboration on Drug Discovery and Development

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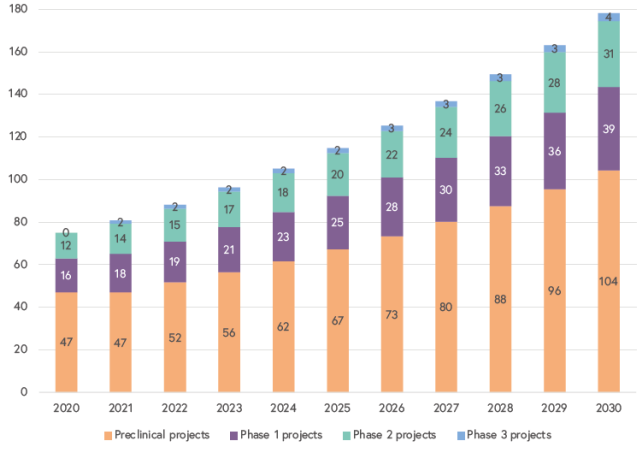
Projected number of SME-driven projects in different development phases in the Nordics

The total number of ATMP projects in the Nordics are expected to increase from 75 to 174 between 2020 and 2030

Projection of companies in each phase, based on current project distribution in Nordic ATMP projects



Key assumptions

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- Assumed amount of time in trials was 13 years, based on marketed products:
  - Preclinical: 4 years
  - Phase 1: 3 years
  - Phase 2: 3 years
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- The phase success was based on Hay et al. (2014) for biologics and Takebe et al. (2018).
- The growth rate of 109% from 2020 to 2030 was compiled by four sets of growth calculations;
  - A CAGR based on the number of ATMP trials in Europe was added to account for growth in the market.
  - A CAGR based on a similar organization's growth data.
  - A CAGR based on the growth in Nordic companies 2018-2020.
  - A CAGR based on the historical average number of companies founded in the Nordics 2015-2020, based on companies identified in earlier parts of this report.

40 Source: MSC analysis; ARM Annual reports; Hay, M., et al., 2014. Clinical development success rates for investigational drugs. Nature Biotechnology, 32(1), pp.40-51.; Takebe, T., et al., 2018, The Current Status of Drug Discovery and Development as Originated in United States Academia: The Influence of Industrial and Academic Collaboration on Drug Discovery and Development

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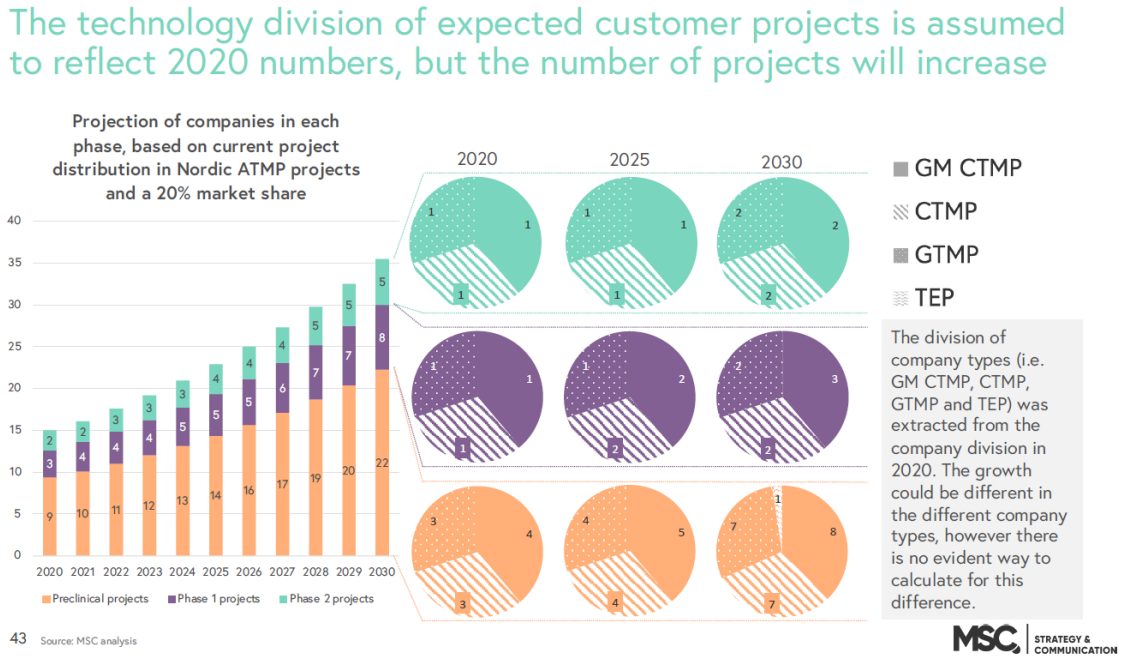
Expected number of projects in different development phases and categories, assuming 20% share of Nordic market



Appendix 4: Stakeholder discussions and contributors

During the course of this work, a large number of stakeholders and organizations have been contacted, consulted and informed about the progress of the initiative. We are deeply thankful for the organizations, companies, project partners and other stakeholders that have contributed to this prospect by providing feedback, support, and different perspectives. The engagement and positivity we have encountered throughout this process is much appreciated. Financial support from Vinnova is also acknowledged.

Stakeholders that the project has been in contact includes, but is not limited to, the following:

AstraZeneca

AstraZeneca Bioventure Hub

CCRM Toronto

Cobra Biologics

Cognate Bioservices

Combigene

Cytiva

Getinge

Immunicum

MSC Nordics

Nextcell Pharma

Karolinska Cell Therapy Center / Vecura

TestaCenter

Verigraft

XNK Therapeutics

The complete contents, findings and statements in this report do not necessarily reflect the opinions of all these organizations.