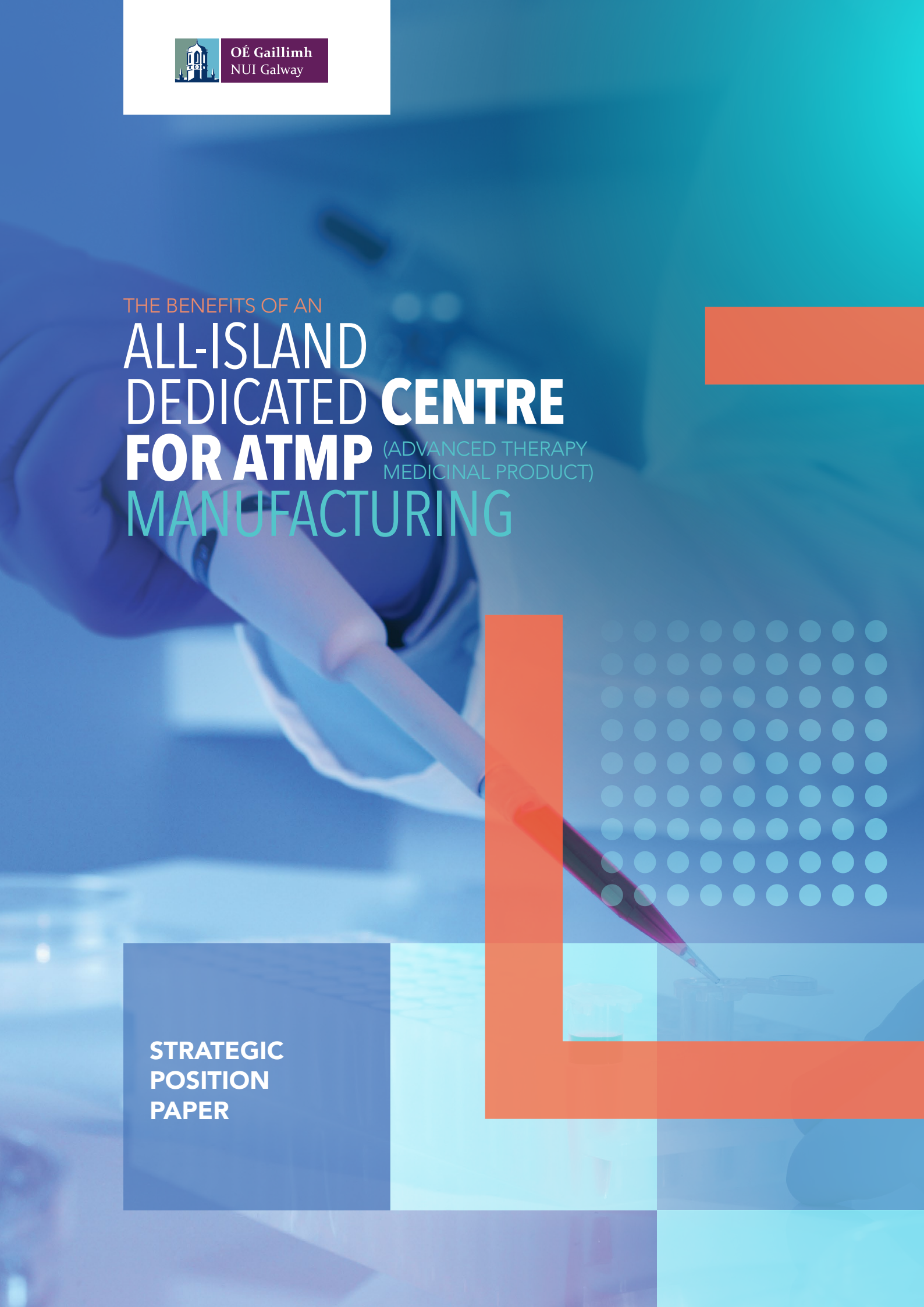
OÉ Gaillimh
NUI Galway

THE BENEFITS OF AN

ALL-ISLAND DEDICATED CENTRE FOR ATMP (ADVANCED THERAPY MEDICINAL PRODUCT) MANUFACTURING



STRATEGIC POSITION PAPER

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SUMMARY

The post-war blooming of the fields of genetics and molecular biology has led to a deeper understanding of many fundamental biological processes as well as enabled the development of novel therapies largely based on recombinant DNA (rDNA) technologies. Since the licensing of the first such rDNA medicine in 1982 this field has rapidly developed to provide effective therapies for many previously untreated medical conditions. The majority of the major pharma companies have set up facilities for their production in Ireland to the extent that biopharma exports are now a key component of the islands economy with a significant fraction of our all-island GDP resulting from the economic impact of this sector. In light of this importance to the all-island economy, this project considers what actions need to be taken to consolidate and further develop this importance as a whole new category of biopharmaceuticals – the Advanced Therapy Medicinal Products (ATMPs), emerges with new challenges and opportunities. An ATMP may be broadly defined as a medicine "*that is based on genes, cells or tissue engineering*", albeit USA and European regulatory bodies use slightly different sub-classifications. In the EU there are four major types: gene therapy, somatic cell therapy, tissue-engineered therapies, and combined advanced therapies. Dr. Peter Marks, Director of the USA FDA's Center for Biologics Evaluation and Research and one of the leading regulators in this area – stated at a 2019 meeting of the Alliance

for Regenerative Medicine: "*We're going to see more and more products reach market… we are on this essentially very steep portion of a growth curve.*". Many other jurisdictions, recognising the importance of the ATMP area for future medicines industrial sector, have already undertaken significant investments in the area to enhance their attractiveness as a location for the anticipated new wave of industries in this area and the lessons that can be gleaned from a number of these will be described.

The impetus for this paper emerged from NUI Galway and its specific interest in the cell therapy class of ATMPs and consequently the high-level goal of this work is to identify approaches and strategies that will enhance the attractiveness the island of Ireland as a location for the development and commercialization of ATMP Cell Therapies.

This paper proposes that there is a need to ensure that Ireland invests adequately in ATMP related areas to be competitive both in creating indigenous companies in this space and in attracting mobile foreign companies to locate their ATMP related activities here. This will require a) leveraging the existing investments in Ireland in this field; b) creating a vehicle (all-island preferably) to drive a comprehensive co-ordinated program of activities in this area and c) developing an infrastructure (again all-island ideally) that will facilitate the development, manufacturing and commercialisation of ATMPs and related technologies.

Creating such an infrastructure will require significant investment in

a) related education and training;

b) further development of the single existing GMP (Good Manufacturing Practice) grade ATMP Production Facility – CCMI at NUI Galway;

c) discovery science in the ATMP field;

d) translational science in ATMPs and;

e) ATMP clinical trial facilities.

The desired outcome of such investment would be the creation of an all island **ATMP ecosystem** that could facilitate and accelerate the development of indigenous ATMP focused enterprises while simultaneously increasing the attractiveness of Ireland as a location for ATMP related foreign investments.

In helping to define the most effective mechanism or, structure(s) to enable this objective we solicited the views of experts in this area and studied some of the existing overseas initiatives in this space with particular reference to their scope, their ambition, their governance and the scale of funding involved. As our primary focus is on the Cell Therapies area we emphasise this aspect while recognizing that the key points identified may have a broader applicability to the overall ATMP field in Ireland.

Prepared on Behalf of the College of Medicine, Nursing and Health Sciences, NUI Galway. By Frank Hallinan PhD and Elaine Harris PhD, Innovation 21 Ltd.

1. PROJECT SCOPE AND PROCESS

The scope of this project was the development of a strategic position paper on the potential benefits that would arise from the establishment of an all-island dedicated Centre for ATMP Manufacturing and how NUI Galway could position its existing expertise to lead a dedicated All-Island Centre in this area. It is the intention that this strategic position paper will be used to inform and influence internal and external stakeholders, while describing the benefits accruing from all-island investment in such a centre.

The process selected involved engagement with NUI Galway staff members and targeted external stakeholders in Ireland and overseas to capture the information necessary to assess current capabilities and capacity against those required to establish a dedicated all-Ireland Centre for ATMP Manufacturing and to establish such a proposal is appropriate in the context of the wider vision for Ireland to be a globally recognised centre of excellence for innovation and development in biopharmaceutical manufacture and supply, and the location of choice for the launch of new products.

Additionally a review of relevant activities and initiatives in countries with an established ATMP ecosystem (UK, USA, Canada, the Netherlands and Sweden) was undertaken with a view to ascertaining best practice and learnings that could be applied in an Irish context.

The power of our collective knowledge in the biomedical domain has been dramatically brought home to everyone by the speed and

effectiveness of our response to the ongoing COVID 19 pandemic: within weeks of the identification of a novel coronavirus as the causative agent of the emerging respiratory disease in Wuhan, China, its gene sequence had been determined and within a year novel, potent nucleic acid based vaccines to protect against this virus have been developed, proven clinically and made available for mass vaccination programs at a global level. This power is the result of the post-war blooming of the fields of genetics and molecular biology that has enabled technologies to help us develop a deeper understanding of many fundamental biological processes as well as enabled the development of novel therapies largely based on recombinant DNA (rDNA) technologies. The first such rDNA medicine – genetically engineered human insulin was first licensed in 1982. Since that time this field has rapidly developed so that today over 200 rDNA therapeutic proteins have been given marketing authorization, with more than 100 being approved since 2014[1]. These therapeutics range from small proteins like insulin to large complex glycosylated proteins such as humanized monoclonal antibodies and fusion proteins and provide effective therapies for many previously untreated medical conditions. In addition, biosimilars – the biological counterpart of 'generic' medicines in the small molecule domain are also now available for many of the first generation rDNA proteins. This burgeoning field of biopharmaceuticals continues to thrive and expand, with the majority of the major pharma companies now having set up facilities for their production in Ireland to the extent that biopharma exports are now a key component of the island economy[2]. In light of this importance of the Pharmaceutical, and specifically the Biopharmaceutical, manufacturing sector to the Irish economy, this project considers what actions need to be taken to sustain this importance in light of the increasing importance to the sector of a new class of biopharmaceuticals – the Advanced Therapy Medicinal Products (ATMPs).

Fortunately, Ireland is today very well positioned in the medical device and pharmaceutical manufacturing and late stage development sectors, with the majority of the multinational companies having significant investments in this space in Ireland and a significant fraction of GDP resulting from the economic impact of these industries. A key question for this paper is how Ireland can maintain this leading position for the ATMP generation of products – are new initiatives required or, will leadership be a natural consequence of our current position? It is clear that other jurisdictions – big and small – recognise the importance of this new field and are proactively mounting efforts to make their areas attractive for both local and multi-national investment in this area. A number of these examples will be described in the first instance.

Thus, a high level goal of this work is to identify approaches and strategies that will enhance the attractiveness of the island of Ireland as a location for the development and commercialization of ATMP Cell Therapies.

Many countries that have recognized the importance of the ATMP area for future medicines have commenced significant national investments in this area e.g. the Cell and Gene Therapy Catapult (CGTC) in the UK, the Centre for Commercialisation of Regenerative Medicine (CCRM) in Canada,

1 https://www.frontiersin.org/articles/10.3389/fbioe.2019.00420/full

2 https://www.irishtimes.com/business/economy/irish-exports-surge-to-record-160bn-in-2020-despite-pandemic-1.4485219

the California Institute for Regenerative Medicine (CIRM) in the US State of California and ATMP Sweden to name but a few. Dr. Peter Marks, Director of the US FDA's Center for Biologics Evaluation and Research and one of the leading regulators in this area – stated at a 2019 meeting of the Alliance for Regenerative Medicine: "*We're going to see more and more products reach market…we are on this essentially very steep portion of a growth curve.*"[3]

> "Ireland has an opportunity to become a hub for the global supply, management and manufacture of a new generation of personalised medicines and Cell & Gene Therapy treatments, but only if we can build on the foothold of the industry to catch these innovations as they scale to production level."
>
> **EY Report Oct 2020 "Staking Ireland's claim to the next pharmaceutical frontier"**
>
> https://www.ey.com/en_ie/life-sciences/staking-irelands-claim-to-the-next-pharmaceutical-frontier

There is a need to ensure that Ireland invests adequately in ATMP related areas to be internationally competitive in creating indigenous companies in this space and in attracting mobile foreign companies to locate their ATMP related activities here. This will require a) leveraging the existing investments in Ireland in this field; b) creating an all-island vehicle to drive a comprehensive program of activities in this area and c) developing an all-island infrastructure that will facilitate the development, manufacturing and commercialization of ATMPs and related technologies.

Creating this infrastructure will require significant investment in

a) related education and training;

b) development of GMP grade ATMP Production Facilities;

c) discovery science in the ATMP field;

d) translational science in ATMPs and

e) ATMP clinical trial facilities.

The outcome of such investment would be the creation of an **ATMP ecosystem** on the island of Ireland that could facilitate and accelerate the development of indigenous ATMP focused enterprises while simultaneously increasing the attractiveness of Ireland as a location for ATMP related foreign investments.

A key question for this paper is to help define the most effective mechanism(s) or, structure(s) to enable this objective. In addressing this question we solicited the views of experts in this area and studied some of the existing overseas initiatives in this space with particular reference to their scope, their ambition, their governance and the scale of funding involved. As our primary focus is on the Cell Therapies area we will emphasise this aspect while recognizing that the key points identified may have a broader applicability to the overall ATMP field.

3 http://alliancerm.org/wp-content/uploads/2019/11/ARM_Q3_2019_FINAL-1.pdf

2. INTRODUCTION

2.1 ATMPs AND THEIR RELEVANCE TO THE IRISH BIOPHARMACEUTICAL SECTOR

With the continued growth in the basic scientific knowledge in the field of molecular biology in the period since the early 1980s, opportunities for the creation of new ever more complex therapeutics have become more common and arguably we are now at the start of a new chapter for health care and its associated industries with the introduction of Advanced Therapy Medicinal Products (ATMPs). These next generation medicines are based on the use of therapeutic genetic agents, therapeutic cells or tissues. While the first ATMPs were authorized in Europe in 2009 (ChondroCelect®) and in 2010 in the USA (PROVENGE®) the ATMP era only fully commenced in 2017 with the licensure of the first two genetically modified cell therapies – so-called chimeric antigen receptor T cell products (CAR T) Kymriah® and Yescarta®, as well as the first FDA licensed gene therapy Luxturna®. This was the tipping point for the recognition that a whole new category of medicinal products was going to become available (See Appendix 3 for details of EMA/FDA approved ATMPs).

ATMPs are emerging as a new group of highly complex medicines with the potential to provide unprecedented benefits to patients. Within this category, cell therapies are particularly noteworthy as we increasingly have the technical capability to take not only the very common prevalent categories of cells but also relatively rare sub types of cells with potentially highly potent biological effects e.g. a USA company founded in 2020 on basic research at UCLA, Appia Bio[4], received initial Series A funding of $52 million to develop CAR-engineered invariant natural killer T (CAR-iNKT) cells using their technology platform for allogeneic cell therapy.

> "A scientific revolution is changing how we think about medicines. Next generation CAR T therapies will combine with other technologies to enhance potency and targeting. Genetic modification will allow scientists to turn therapies on or off, while gene editing platforms could help to create more potent cells. We will equip the human body to fight cancer — and the full potential of cells as medicines will bring extraordinary benefits to patients."
>
> **Bruce Levine, Barbara and Edward Netter Professor in Cancer Gene Therapy at the University of Pennsylvania, ARM Board Director**
>
> http://alliancerm.org/wp-content/uploads/2021/08/ARM-H1-2021-Report.pdf

Such invariant natural killer T cells are a small population of αβ T lymphocytes with several unique features that made them exceedingly attractive agents for developing cancer immunotherapies. However, the extremely

4 https://www.appiabio.com/

low frequency of such cells in cancer patients (approx. 0.001%–0.1% in blood), as well as their rapid depletion post-stimulation were major factors limiting the success of their clinical use for cancer immunotherapy. The UCLA discoveries on which Appia Bio was founded provides a means to provide unlimited supplies of long lasting iNKT cells that may overcome these limitations. Another US company GentiBio[5], launched in 2020 is using gene editing technology developed in the academic research of some of the company's founders to enable production of high levels of another low prevalence type of cell, Treg cells. These cells have important immune system regulatory properties and are being developed as cell therapies to treat autoimmune, alloimmune, autoinflammatory, and allergic diseases. Thus, cell therapy is entering a new more powerful period where we will largely cease to be limited by the natural prevalence of available cells and, thereby, new therapeutic opportunities will open up.

An ATMP can be broadly defined as a medicine "for human use that is based on genes, cells or tissue engineering"[6]. US and European regulatory bodies use slightly different sub-classifications of these advanced therapies, in the EU there are four major groups, i.e., gene therapy, somatic cell therapy, tissue-engineered therapies, and combined advanced therapies; in the US, the sub-classification covers two major groups of products, i.e., gene therapy and cellular therapy[7].

ATMPs are centrally regulated at the European level through Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13th November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004.

An alternative route for patient access in Europe is through the Hospital Exemption (HE), which allows the use of ATMPs under the supervision of a medical practitioner, on a non-routine basis, and in restricted circumstances, in a single member state[8]. This is a route that has been exploited by many academic/institutional ATMP researchers.

In the US ATMPs are more commonly referred to as Cell and Gene Therapies (CGTs) and there are some differences to how the FDA approaches legislation and regulation of them. Both the EMA and FDA have expedited development programs in order to enable new medicines reach the market as early as possible and in many cases ATMPs fit the criteria to be eligible for these pathways. The FDA has developed the Breakthrough Therapy[9] and Fast Track designation[10] programs while the EU launched the adaptive licensing and afterwards the PRIority Medicines (PRIME) designation scheme[11].

One of the main regulatory differences between EU and US is that the FDA oversees clinical trials, whereas in the EU clinical trials are controlled at a national level, thereby making their operation at an overall

5 https://www.gentibio.com/

6 https://www.ema.europa.eu/en/glossary/advanced-therapy-medicinal-product

7 https://www.frontiersin.org/articles/10.3389/fphar.2019.00921/full

8 https://www.leru.org/files/LR-BP-ATMP.pdf

9 https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy

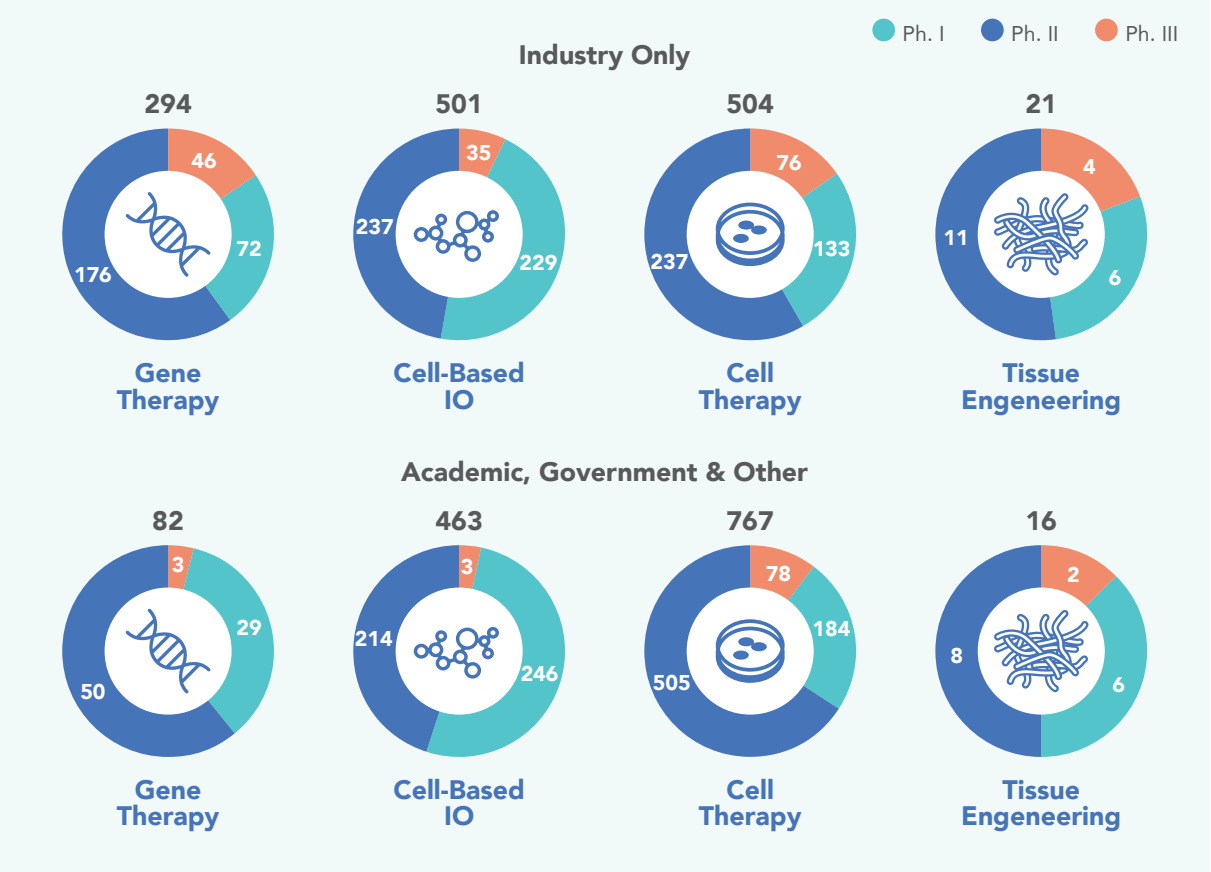
10 https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review

11 https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines

EU level more complicated. In terms of marketing authorisation, each region has specific legislation depending on the legal categorization/type of product. In the EU, they are licensed under article 8.3 of Directive 2001/83/EC, while in the US, ATMPs are licensed under section 351 of the PHS Act. Both Agencies have their own specialized committees to evaluate advanced therapies. Appendix 1 contains details of all ATMPs with Marketing Authorisation from either the FDA or the EMA.

Academic institutions play a major role in the R&D of ATMPs. Many ATMPs are initially developed by universities and/or associated teaching hospitals and more than half of the current clinical studies with ATMPs are sponsored by universities[12] In part, this is because university medical centres have the necessary disease-specific expertise, the capacity for innovative research and direct access to donor and patient material. As can be seen from Figure 1 academic, government and other non-industry sponsors dominate early stage (Phase I/II) clinical research, while industry is more involved in late stage clinical development.

Figure 1: Current clinical trials of ATMPs H1 2021 (source Reference 12)



12 https://alliancerm.org/sector-report/h1-2021-report/ (pg 12)

It is widely anticipated that ATMPs are likely to become a major growth sector in the biopharmaceutical world, the global ATMPs market size was valued at US$7.9 billion in 2020 and is expected to expand at a compound annual growth rate (CAGR) of 13.2% from 2021 to 2028[13]. Thus, to maintain its leading global position in Pharmaceutical and Biopharmaceutical manufacturing it is clearly imperative that Ireland is aware of, and prepared for, these new challenges from discovery to delivery, regulatory assessment, and manufacture for clinical use and ultimately manufacture of commercial products authorised worldwide.

2.2 RECENT IRISH INITIATIVES ON ATMPs

The growing importance of ATMPs to the biopharmaceutical sector has been recognised in Ireland. This has led to a number of initiatives and reports proposing strategies and actions to help Ireland leverage its excellent reputation in pharmaceutical/ biopharmaceutical manufacturing into achieving a similar leadership position in the ATMP field. These include developing activities within the clinical and research spheres as well as the development of an Irish ATMP ecosystem. Examples include:

2.2.1 IDA Report:

In 2019-2020 the IDA commissioned a report entitled "Policy and strategy development in the field of Advanced Therapy Medicinal Products (ATMPs)"[14]. Recommendations from this report included one to establish an "ATMP Coordination Forum" to ensure stronger collaboration across funding agencies and other necessary relevant areas of the ecosystem. This is essential to realise the full strategic and economic potential associated with the ATMP opportunity. Development of a successful ATMP sector requires a high level of coordination between and input from public agencies, clinical and educational institutions, and industry to ensure maximum impact and synergy.

The IDA have recently produced an infographic outlining the benefits to locating ATMP development and manufacturing facilities in Ireland.

13 https://www.grandviewresearch.com/industry-analysis/advanced-therapy-medicinal-products-market#:~:text=products%20market%20growth%3F-,b.,USD%2021.2%20billion%20by%202028.

14 Funding for this report was from the European Union via the Structural Reform Support Programme and in cooperation with the European Commission's DG REFORM

Figure 2: IDA Ireland "Why Ireland for Cell and Gene Therapy Development and Management"[15]

2.2.2 EY Report:

The consultancy company EY has facilitated a series of industry roundtables with key stakeholders and has recommended that consideration should also be given to the establishment of a new national research centre for Cell & Gene Therapy under the aegis of Science Foundation Ireland (SFI)[16].

2.2.3 PwC SWOT Analysis:

The consultancy company, PwC, set the scene for the BioPharma Policy Forum with a SWOT analysis of Ireland's biopharmaceutical industry by key stakeholders including the IDA and BPCI and presented their findings in March 2020[17]. Conclusions from this forum included the following:

- Innovation districts or hubs should be developed near universities or health research centres. These are possible in Dublin and in other locations. Policies to support the development of districts or hubs could borrowed or adapted from other countries like Belgium.
- Ireland needs to establish a team, led by the State but with participation from industry and others, to set out and implement a roadmap for developing CGT capability.
- Ireland will compete to manufacture ATMPs. It could compete to treat patients, too. Initially, ATMPs will focus on rarer, hard-to-treat disorders that will require skilled delivery. Patients may have to travel to centres of excellence outside Ireland for treatment if the skills and infrastructure are not available here.

15 https://www.idaireland.com/newsroom/publications/why-ireland-for-cell-and-gene-therapy-development

16 https://www.ey.com/en_ie/life-sciences/staking-irelands-claim-to-the-next-pharmaceutical-frontier

17 https://2hmcriw3psofj2qo3f8w6f17-wpengine.netdna-ssl.com/wp-content/uploads/2021/01/Globally-Networked-Innovation_Perspectives-on-Irelands-Future-in-Medicines.pdf

2.2.4 BPCI Strategic Theme:

BioPharmaChem Ireland (BPCI) as part of their strategic themes 2019-2023 has a goal to make "Ireland a global leader in ATMP (cell and gene) characterisation, manufacturing and supply" and envisage that the formation of a cluster which it defines as "*when the business model is characterised by a dynamic ecosystem involving multinationals in different sectors generating local small/ medium enterprises (SMEs) and partnering with the indigenous sector along with higher education, health and research institutions*"[18]. The strategy calls for:

- a design of a national framework; aligning academia and cluster needs to develop support services.
- investment in advance therapeutic research infrastructure, funding for Regulatory Science Ireland and developing Clinical Research Ireland.
- making Ireland a global leader in ATMPs by enhancing data analytics of manufacturing, supply chain and patient and supporting BioPharma 4.0.

The IDA is supporting the maturing of the biopharmaceutical sector and facilitating the development of a robust ATMP eco-system in a number of ways including supporting strategic investment into the expansion of National Institute for Bioprocessing Research and Training (NIBRT) which it states will "*serve as a major catalyst for developing the future skills need of the industry, while simultaneously developing the significant research capabilities underpinning CGT manufacturing*"[19].

2.2.5 Cell and Gene Therapy Forum:

In 2018 NIBRT and other interested partners established the Cell and Gene Therapy (CGT) Forum focused on the need for a coordinated approach to maximize opportunities for Ireland in the ATMP area. A white paper entitled "The Case for Cell & Gene Therapy Manufacturing in Ireland" was produced in 2019[20]. This forum now has over 100 members representing a variety of different stakeholders including: government agencies, national funding agencies, multinational and indigenous companies, academics, equipment vendors, design/engineering houses and specialist recruiters etc.

In Q1 2021 seven (7) working groups were established to focus on specific areas it believed should be prioritised in order to ensure success:

Working Group 1:

Development of a CGT & Vaccine manufacturing technical/capability 'strengths-map' for Ireland

Working Group 2:

Understanding the big challenges facing CGT & V manufacturing

18 http://agenda.ibec.ie/t8sexa9di4x
19 https://issuu.com/retailnews/docs/summer_pharma_2021_web pp10-11
20 https://www.nibrt.ie/research/

Working Group 3:

Influencing Ireland investment/ funding decision-making in CGT & V manufacturing

Working Group 4:

Influencing European decision-making in CGT&V manufacturing

Working Group 5:

CGT Education & Training

Working Group 6:

CGT and Vaccine indigenous start-ups and SMEs

Working Group 7:

CGT Clinical Trials

In 2021 following a significant investment by the IDA it was stated that NIBRT was to develop significant training and non-GMP research capabilities in ATMP manufacturing.

2.2.6 HRB Review of Clinical Research Infrastructure Report:

A key enabler of a robust ATMP ecosystem is a fit for purpose and agile clinical trial environment. As will be described later in this paper, many other countries have actively developed /encouraged co-located ATMP research and clinical trial facilities; (ATTC (UK) and NecstGen (The Netherlands) for example). To date Ireland's clinical trial/ research capabilities have not been seen as a significant strength for the development of an Irish ATMP ecosystem.

A recent (2019) Health Research Board (HRB) report[21] concluded "International benchmarking shows that despite significant improvements in the clinical research infrastructure in Ireland in recent years, there is still a significant difference in our level of clinical trial activity (interventional studies) compared with our European counterparts. In 2018, there were approximately 370 clinical trials either open or recruiting in Ireland, compared with 1,200 in Denmark, 700 in Norway and 530 in Finland". Figure 3 summarizes all HPRA facilitated ATMP trials to date and demonstrates the low level of such trials to date.

21 https://www.hrb.ie/fileadmin/2._Plugin_related_files/Publications/2019_Publication_files/Review_of_clinical_research_infrastructure_in_Ireland.pdf

Figure 3: Summary of HPRA authorised Clinical Trials (Source: HPRA presentation Sept 2021)

HPRA authorised ATMP clinical trials
9 ATMP trials authorised 6 Phase I/II 3 Phase III
5 Gene Therapy Medicinal Products 4 Cell-based Medicinal Products
Therapeutic Areas: Cardiovascular, haemophilia, osteoarthritis, SMA

The Irish Pharmaceutical Healthcare Association (IPHA) recently called for major reforms in clinical research to help accelerate new medicines development[22]. The process reforms the IPHA has called for included:

- Introduce an Ireland-wide standard site contract (the Clinical Trial Agreement) so that trial start-up delays in hospitals are reduced;
- Implement protected research time for clinicians and hospital staff;
- Improve Recognised Ethics Committee (REC) review and approval timelines;
- Standardise processes for all RECs, with no specific requirements at individual RECs;
- Require that hospital sites adhere to patient recruitment commitments;
- Demand consistency in the approach to clinical research across all institutions;
- Establish the National Research Ethics Committee to drive performance and ensure accountability for all clinical trials;
- Implement electronic patient records across all hospitals; and,
- Facilitate sharing best practice across hospital sites.

2.2.7 Other capacity and capability building initiatives:

There are some positive initiatives that aim to increase capacity, capabilities and opportunities in this area.

In The HRB's "Strategy 2021-2025: Health research – making an impact"[23] there is a recognition for a strategic approach and one of the key actions is to improve both capacity and capabilities in the clinical research by "working with partners" to "invest in a coordinated clinical trials infrastructure to deliver benefits for patients and the innovation agenda, and with enhanced integration into the health system."

In July 2021 the HRB announced that it was to continue funding the HRB-Trial Methodology Research Network (HRB-TMRN) with its

22 https://www.ipha.ie/ipha-urges-major-reforms-in-clinical-research-to-help-accelerate-new-medicines-development/
23 https://www.hrb.ie/fileadmin/2._Plugin_related_files/Publications/2021_publications/2021_Corp/Strategy_2021_2025_Health_research_making_an_impact.pdf

role of "strengthening the methodology and reporting of trials in health and social care in Ireland" with a further €3 million investment. Led by NUI Galway, the HRB-TMRN is a collaborative initiative between a number of Irish and international higher education institutes and methodology centres across Ireland in NUI Galway, University College Cork, University College Dublin, Trinity College Dublin and University of Limerick. The Network also works closely with UK partners in the University of Aberdeen and is a member of the MRC/NIHR-Trials Methodology Research Partnership in the UK.[24]

The launch of new Research Governance Framework by the Health Service Executive (HSE) is a positive initial step on the path to developing a clinical trial system that could potentially be beneficial for the Irish ATMP ecosystem, but it should be noted that there is no explicit mention of any explicit support for ATMP-specific trials[25]. Launched in September 2021 this initiative seeks to establish a Governance, Management and Support of Research (GMRS) framework. Its implementation will nurture a research culture in the HSE and recognise that research is a crucial activity, which contributes to the improvement of services and benefits patients, their families and the public. In order to facilitate this implementation will require "*reform of the HSE Research Ethics Committee system as well as the development of capability for research management and support within the service.*"

In May 2021 the IPHA published the 'Pathfinder Study on the Adoption of Cell and Gene Therapies in Ireland' which was carried out by the global professional services firm, PwC[26]. Its main recommendations focus on assessment, access and reimbursement of novel therapies and include:

- The development of a CGT adoption policy, guided by a structured dialogue led by the Department of Health, which draws together proposals for tackling the related strands of assessment, access and reimbursement;
- Introduce novel reimbursement models for CGTs that ensure broad access and value for money for patients;
- Improve the information infrastructure and implement new policy initiatives to enable real-world evidence collection for key disease areas likely to benefit from CGTs in the short term and the start of planning for a broader rollout of CGTs in other areas in the medium term; and,
- Continue to invest in facilities and staff to ensure a smooth national rollout of CGTs, exploring the creation of centres of excellence at certain hospital sites and allied investment in training and engagement for clinicians and patients.

24 https://www.hrb.ie/news/news-story/article/hrb-invests-e3-million-to-make-clinical-trials-more-relevant-accessible-and-influential-for-all/

25 https://hseresearch.ie/wp-content/uploads/2021/09/HSE-Framework-for-the-Governance-Web-Optimised.pdf

26 https://2hmcriw3psofj2qo3f8w6f17-wpengine.netdna-ssl.com/wp-content/uploads/2021/05/CGT-Pathfinder-Study-May-2021.pdf

Figure 4: High level recommendations from IPHA's Pathfinder report
(source: https://2hmcriw3psofj2qo3f8w6f17-wpengine.netdna-ssl.com/wp content/uploads/2021/05/CGT-Pathfinder-Study-May-2021.pdf)

2.3 CURRENT AND FUTURE CHALLENGES

It is widely anticipated that ATMPs are likely to become a major growth sector in the biopharmaceutical world. Thus, to maintain its leading global position in Pharmaceutical and Biopharmaceutical manufacturing it is clearly imperative that Ireland is aware of, and prepared for, these new challenges from discovery to delivery, regulatory assessment, and manufacture for clinical use and ultimately manufacture of commercial products authorised worldwide.

As with any new high potential technological area there are many challenges associated with the realization of their full potential by any particular jurisdiction.

In this regard ATMPs pose multiple varied challenges for those wishing to excel in this area.

Firstly, it is clear from the examples of jurisdictions already heavily engaged in this space that significant monetary investment is needed to make any location seriously competitive. The examples studied here demonstrate that this requires multiple millions of €/$ to build the expertise and the facilities required as well as sustained governmental support over a number of years for the operational costs associated with this effort.

Nonetheless, as the CIRM (See Section 4.5) study of its economic impact demonstrates, the particularly large investment by the State of California of $2.67 billion over 14 years has resulted in a quantified economic impact on

the entire U.S. economy of $15.4 billion of additional gross output and a large number of jobs concentrated in medical and health related research, manufacturing, and service sectors. Likewise in the UK (See Section 4.1) which has been a leader in Europe in recognizing the potential of this area its investment in the cognate basic science and translational science via the CGT Catapult has led to the establishment of over 90 ATMP development companies and a growth of 45% in related clinical trials in this area in the UK.

A recent study by a group at the Dutch Medicines Evaluation Board points out that the manufacture of cell therapies is very expensive and estimated that in 2018 across multiple facilities they ranged between €23,033 and €190,799 per batch, with batch yield varying between 1 and 88 doses[27]. In addition, very high upfront capital investments are required to develop the required facilities and there are ongoing operational costs even when the facility is not in use. This requires guaranteed long term funding that does not fit easily into the conventional third level institution funding and/or the Research Project type funding provided by governmental institutions. The authors consider that initiatives of shared public–private expert center facility as in the UK CGT Catapult that provides infrastructure and expertise for translation and early-phase manufacture to help overcome development challenges (e.g., safety, effectiveness, scalability) can overcome these problems and could help small scale developers advance their products without having to make speculative and substantial high upfront investment.

Similar observations regarding the financial challenges have been made by ATMP Sweden who compare the Canadian CCRM system that provides for its ATMP developers "*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.*" While in Sweden "*…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.*"

Secondly, there are a range of governance models that have been and are being used in different jurisdictions, but typically these involve varying levels of public as well as private funding and are not typically in the sole ownership of any single academic institution. The model that is appropriate for Ireland needs to be agreed, but learnings from the international examples presented in this report would indicate that a cluster model as demonstrated by NecstGen (Holland) or a wider collaborative model as employed by CCRM or, proposed for Sweden ("CCRM Nordic") may offer the best guidance. A review of international best practice indicates the need for a collaborative model with access to appropriate clinical facilities and expertise aligned with a well-funded research base, active engagement with companies involved in early stage product development and a cGMP (current Good Manufacturing

27 MT Renske et al (2020) What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings. Cytotherapy 22, 388-397

Practice) manufacturing facility with a multi-annual funding stream that is not heavily reliant on funding from a single academic institution. In order to function appropriately such a model would require coordination with the stakeholders and input from stakeholders in an "ATMP Coordination Forum" (2.2.1).

Thirdly, there are a variety of technical challenges different from those of the traditional rDNA biopharmaceuticals in that ATMPs are more complex to manufacture for two key reasons:

- The technologies on which ATMP products are based are diverse but are primarily based on gene therapy: somatic-cell therapy and tissue-engineering. Consequently, all ATMPs are inherently significantly more complex than rDNA proteinaceous entities, presenting novel challenges at all stages of the ATMP life cycle.
- ATMPs are a heterogeneous class that may be manufactured at a personalised level (i.e. for a single patient) or, an industrial scale for multiple patients. An excellent example of this is in the area of the CAR T cell therapies: the currently authorised products such as Kymriah® and Yescarta® are autologous, each individual treatment is essentially a unique batch produced from and destined for a single patient, but there are other companies working on the development of a next generation of so-called allogeneic CART therapies where cells donated from healthy individuals are processed to produce a cellular product that can be used to treat multiple patients.

Thus, while autologous CART products will by their nature always be personalised small scale products, their allogeneic counterparts will be industrial scale products used to treat multiple patients.

2.4 ALL-ISLAND ASPECT

The feasibility of utilizing highly specialized expensive technological facilities in the Irish Republic in an all Island context was included in the remit of this project. The planned approach was to seek the views of experts in both jurisdictions i.e. Irish Republic and Northern Ireland (NI) on such an approach. While the response from the interviewees from the Irish Republic was generally positive to such an approach and its benefits appreciated, unfortunately the NI experts largely declined the opportunity to be interviewed on the overall project and consequently the views of this key population is unknown. Nonetheless, as

a/ there seems to be little objection to other all-island initiatives in technological areas;

b/ as it seems to be a more efficient use of resources for a small jurisdiction and

c/ as other jurisdictions see the benefits of transnational collaborations in this area (eg Netherlands and Belgium in NecstGen) we would encourage further evaluation of this option going forward.

3. FOCUSED INTERVIEWS AND FEEDBACK

As part of the preparation of this report the Project Team interviewed over 30 stakeholders in Irish industry, public agencies, research organisations and government departments, as well as industry experts in the US, the UK and the Netherlands. The interviews were semi-structured to allow for collection of qualitative data from the interviewee.

Many of those interviewed were very aware of initiatives in other jurisdictions which means that Ireland is lagging in its approach to developing an all-island strategy for the development of a thriving ATMP ecosystem. Many stressed the urgency of developing a **national coordinated** ATMP offering, if Ireland is to compete. The risk of not doing so, according to those interviewed would be to also miss out on the second wave of ATMP development, where the many therapies in development are manufactured and sold at scale.

Although there was some variation in feedback from the interviews there were some key trends that emerged:

1. Need for national policy, strategy and initiatives:

Many interviewees noted that ensuring that Ireland continues to be a preferred location for the biopharma industry manufacturing and late stage development in the ATMP era will require a well-planned and coordinated national approach. Many highlighted the need for high-level policy and strategy development and coordination. Most interviewees cited international strategic decisions which led to best practice examples like Catapult CGT (UK), NecstGen (the Netherlands) and ATMP Sweden. A common sentiment expressed was that unless **a cohesive strategy at government level**, with an **effective champion** at the cabinet table, is developed in the near term, a key opportunity to establish a viable ATMP eco-system will be difficult to establish and the benefits accrued through our reputation for biopharmaceutical manufacturing will be squandered.

Comments included:

- We lack a sponsor of a program at governmental level to help drive this forward holistically.
- The focus should be on leveraging the existing infrastructure as Ireland will never have the technology or, innovation edge relative to locations like Boston and California with large powerful basic science centers at the leading edge.
- [Interviewee] liked the idea of an all island centre as [Interviewee] thought that there were good skill sets in NI and such an approach would enable us to leverage the UK expertise in this area also. In addition, [Interviewee] thought such an approach would enable patients from NI to be treated on the island.
- Ireland was 15 years behind the UK and we need to collaborate with the UK as well as investing in indigenous Irish companies as well as large multinationals. We need Government to put money into these enterprises.
- [Interviewee] said that establishment of a robust ATMP ecosystem needed a conscious decision and directed effort to which [Interviewee] referenced the UK CGT Catapult the Netherlands NecstGen as the type of initiatives that seemed likely to be effective.

- [Interviewee] commented that we did need a national approach and that this required a specific governmental policy with an associated strategy. [Interviewee] thought that an All Island approach would be always relevant politically and that there would be benefit to that approach.
- [Interviewee] thought that the biggest gap in this area was complacency/ ignorance in the political system and the challenge was how to develop a policy and to then get political support and understanding of the relevance of that to our future so that it gets funded.

2. Need for National Centres of Activity:

Many interviewees stressed the benefits of having a central resource of expertise and support for ATMP researchers and developers. The UK CGT Catapult Centre and the approaches in Sweden and the Netherlands were cited as possible models in this respect. Although some suggested the development of a new national centre, many discussed this as the coordination and funding of existing facilities, actions, and initiatives to facilitate interaction between ATMP stakeholders i.e. a virtual centre.

Comments included:

- Build on the success of the CGT working group and establish 'ATMP Ireland', a network of ATMP 'interested' stakeholders – HEI researchers, clinical researchers, clinical trials organisations, Irish regulator, SME expert staff, Irish domiciled MNC expert staff, enterprise agency staff, HSE related staff, NIBRT staff, CCMI staff, Clinical Research Facilities (CRFs) etc.
- Set up a 'virtual' ATMP centre involving NIBRT, REMEDI/CCMI, HEIs, regulator, CRF etc.
- Use a model of international collaboration to fast track Ireland's entry into the ATMP sector, increased collaboration with Catapult/ATTCs was highlighted as a key opportunity
- Build on existing ATMP-relevant international collaborations that Irish academics are engaged in: LERU, for example.
- Important that a cGMP cell manufacturing facility be an independent entity owned by the Government with representation for the major constituents.
- Developing a self-coordinating ecosystem is vital to include players including CCMI/Trinity Translational Medicine Institute (TTMI)/APC (VLE) / NIBRT
- [Interviewee] thought that the UK CGT Catapult might be a very successful model but speculated if, as a much smaller island, we should prioritise certain areas rather than aiming to cover everything. [Interviewee] thought this was a difficult area and maybe we should look at the companies already here, but that we would need to invest €20million + to begin to make an impact. [Interviewee] wondered if the failure to publish the recent IDA ATMP report was due to the reluctance to make visible the high scale of investment needed to be a player in this area.

- A national centre with a range of skill sets across all the various disciplines and technologies necessary to create cell therapies would be a big step forward.
- [Interviewee] thought that Ireland needed an equivalent of the UK Catapult system but was nervous about State funded centres as often not the right people to connect with industry are involved. On balance a Public/Private partnership was considered the ideal approach.
- [Interviewee] emphasised the importance of ensuring that there were good linkages to hospitals and clinical materials to support this work and that Ireland could not become an ATMP world leader without such a Centre.
- [Interviewee] stated that governance should ensure that all stakeholders were engaged. This would require a wider body involved than currently in a University situation as he thought lots of University people would be focused on simply funding this own short term research rather than having a whole life cycle approach. [Interviewee] thought that the important thing about locations would be that it be close to a strong R&D location.
- [Interviewee] suggested that governance (of such a facility) should not belong to any single college but should clearly be national in its focus.
- [Interviewee] We needed a strategic investment to bring together key players and that could facilitate the growth of indigenous companies as well as attract external companies to locate here.

3. Leveraging Ireland's manufacturing reputation:

Ireland's reputation for pharmaceutical manufacturing expertise was referenced by many of those interviewed. However, the need for a specific effort to ensure appropriate expertise, processes and support systems was emphasised to ensure continued success as a centre for manufacturing as the ATMP sector of the industry gains traction. Several interviewees cautioned that the success Ireland has had in transitioning from small molecule to biopharmaceutical manufacturing does not mean that it will automatically be replicated as the ATMP manufacturing sector develops.

Comments included:

- The cultural alignment between Ireland and the US was very important – we are recognised as being focused, problem solvers who are highly collaborative and in addition, the Irish GMP compliance record is outstanding.
- Ireland was a world leader and commented that it is the envy of the UK with the financial targets for Scotland being way behind the financial output from Biopharma being achieved by Ireland currently. Attributed this to the tax incentives in the first case. Also thought that NIBRT was fundamental in attracting investment and enabled the development of a talent base. Also that our location as an English speaking part of the EU was very important
- [Interviewee] said HPRA were widely respected globally which was another important factor. [Interviewee] felt

that Irish staff were flexible and willing to travel which gave them great experience and thought that the tax benefits must have had a big impact also. [Interviewee] felt that our culture was also important and that compared with Puerto Rico (as another low tax location) Ireland is seen as a safe environment without extremes in weather or political environment. Finally [Interviewee] thought that going forward Brexit would be a big advantage as Ireland would be the only English speaking location in the EU.

- [Interviewee] agreed with the current leading role and mentioned various examples of this reality including 19 of the top 20 companies having operations in Ireland and the fact that Ireland was one of the largest pharma exporters worldwide. [Interviewee] also noted that we had particular expertise in Supply Chain management and were also very strong in the regulatory compliance and quality areas. [Interviewee] attributed this leading position to the tax policy and pro-business stance of all the recent governments so companies saw a stable environment within the EU. [Interviewee] thought that the development of NIBRT and upskilling of staff was important as was the increased level of Process development research.
- [Interviewee] did not think that leadership (in the area of ATMP manufacture) was a given that would occur naturally as the environment in Ireland has really been very much associated with commercial large scale manufacture while ATMPs will be smaller scale, closer to R&D and more associated with SMEs.

4. Training and Expertise Development:

Although many interviewees cited the excellent service NIBRT is providing in this area, they also pointed out that there are other areas where a facility like CCMI might be used to complement/supplement this to ensure all the different skills sets necessary in the cell therapy development and manufacturing space are addressed.

Comments included:

- [Interviewee] thought that different skill sets would be needed even within the Cell Therapy domain for products that were derived from minimally manipulated donor cells Vs those that came from genetically manipulated continuous cell lines.
- [Interviewee] commented that the technology and infrastructure required for ATMPs were very different from the Biopharma requirements eg ATMPs required a far higher skill level for Operatives and the Lab analysts might in some cases require individuals with PhD level expertise. Talent retention was an ongoing problem and the whole field was moving very quickly.
- [Interviewee] said the key point was that ATMPs will be a key area for the Pharma industry going forward and that the actual manufacturing was not that difficult as it was generally at a smaller scale. The real challenge was in the R&D phase but support was needed for the area to grow.
- [Interviewee, CEO, US] asked how

do you leverage the expertise that is required to get all this (R&D) done. [Interviewee] considered that in this regard Ireland has a fantastic foundation as there is a large number of very well trained people available. [Interviewee] mentioned the work that NIBRT are doing in this regard

5. Need for cGMP Facilities

There was unanimous support for the development of appropriately funded and managed cGMP cell manufacturing facility with a focus on supporting the translational research of academic and commercial centres. The need for an appropriate governance model was highlighted with support for such a facility having an "all-Ireland/all-island" mandate and a multi-year funding model that was not included in any individual HEI's budget.

Comments included:

- Room in the ecosystem for GMP service activities in the academic space.
- Quality of many commercial CDMOs [in the interviewee's] experience had been that their level of maturity and competence was poor.
- The ability to produce CT Batches under GMP conditions and scale up under GMP were big gaps in an Irish context.
- From the location view point one issue with Galway was accessibility, in that in the Boston/Cambridge model a big positive was the synergies created by proximity in that it was easy for informal meetings with other experts as all were in a relatively small area with excellent transport links whereas Galway is relatively difficult to get to.
- Catapult might be a good model for Ireland and that potentially we could get satellite sites of Catapult in Ireland as an entry for them into the EU.
- CCMI is a valuable resource but highly expensive and [Interviewee] questioned whether it is commercially viable.
- Centre would be good as not least because cell therapies in many cases do not travel well and Irish cancer patients need these to be available to them.
- [Interviewee] thought that REMEDI/CCMI needed to look to becoming an international Centre of Excellence in ATMP Cell Therapy that like the UK Catapult proactively developed talent in this area while facilitating the start-up and growth of indigenous companies. It needs to be a commercially driven entity with Government funding that supports clinical and commercial cell therapies as a business.
- [Interviewee] thought it was difficult transitioning from a research type situation to routine pharma manufacturing as the latter required a low attrition rate whereas in the research environment a high level of attrition was normal. [Interviewee] also thought that there were great difficulties identifying a competent CDMO to do their manufacturing as the current companies they worked with were not satisfactory and because all the CDMOs in this space are full and it is very difficult to get manufacturing time with them.

- [Interviewee] thought that such a licensed centre was important in at least demonstrating to external entities that Ireland has capability in this area.

6. Clinical Trial/Clinical Expertise/ Facilities

For many current cell therapies the starting point is donated human cells and this means that there is a need for ongoing strong interactions between the teaching or academic hospital system, blood banks and researchers and start-up cell therapy companies. Many of those interviewed had direct experience of clinical trials in the ATMP space and spoke of the advantages of co-located cGMP facilitates with research institutes/hospitals such as the ATTCs in the UK, the Karolinska Institute in Sweden and facilities in Boston, Philadelphia etc. in the USA.

Comments included

- Getting sufficient patients for CTs was a big issue
- [The interviewee] was aware of a situation where a large Pharma with a facility in Ireland decided to base their cell therapy facility on continental Europe despite detailed lobbying from the Irish location. This was primarily due to the ease of proximity to the patients.
- The recent start up by Takeda of the Alofisel CT activity in GC is a great example of success.
- [Interviewee] spoke about visiting the Karolinska Institute in Sweden and observing all the GMP facilities in the University setting which would mean that much more patient related industrialisation type work could be done there than with the facilities available to [Interviewee] in Ireland.
- [Interviewee] aware that of an Irish company in this space who had go to the UK for execution of their clinical trials so there seemed to be a gap in the CT area in Ireland.
- [Interviewee] thought that the proximity to hospitals and strong relations with clinicians to facilitate access to clinical materials was critical and that this did not seem to be highly developed in Ireland like it is in the Netherlands. [Interviewee] also thought that a GMP facility was essential for the development of the field and this need not necessarily be within a University situation but could be associated with other types of situation like Blood Banks.

> "We are very good at manufacturing, we are getting good at development, but we have some way to go in clinical research."
>
> **Matt Moran, BPCI**
>
> https://www.irishtimes.com/business/innovation/partner-profile-ibec/a-litmus-test-for-ireland-s-biopharma-and-chemical-sector-1.4019814

7. Research & Development

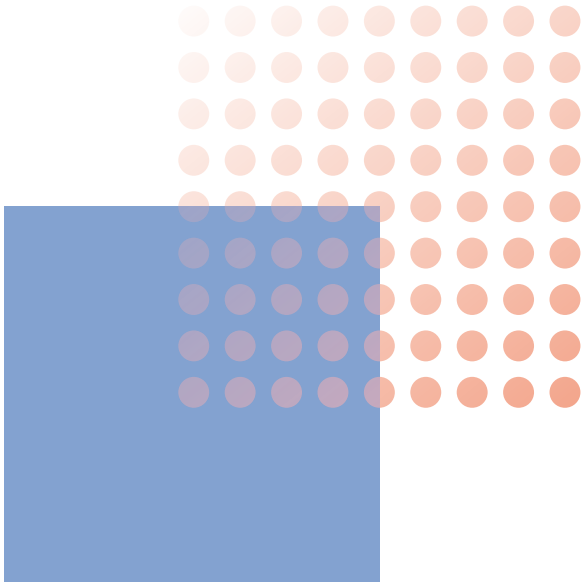
Many of the interviewees familiar with the Irish research funding environment stressed the need for new specific targeted funding in the area, through perhaps a targeted SFI call. Many were aware of and positively disposed towards DTIF funding – an instrument that has been used by a number of HEIs and SMEs in the area of ATMP development. There was an awareness amongst those interviewed that there are a finite number of research areas that can and should be funded within this space, but there was agreement that there is an urgent need for collaborative early stage research.

- There needs to be strong connections with leading academic institutions. While today MABs had highly standardised process technology this is not the case for ATMPs and [this interviewee] mentioned specifically the need for unique controls for certain raw materials. Ireland had a good regulatory partnership, that strong expertise in cell biology was needed and [interviewee] felt that there was weak collaboration between different academic institutions in Ireland.
- Novel ideas for ATMPs have come out of basic research, so strength in this field is very important as well as supporting the development of SMEs in this area from this research. However, [Interviewee] thinks that shortage of venture/early stage capital is deterring the start-up of such SMEs in Ireland.
- [Interviewee, US-based CEO] recognised that there were significant needs in the development and commercialisation of the new ATMPs and many critical "choke points" particularly in the translational space ie the movement of products from the Lab into a GMP level commercial situation so that assets were developed through the clinical research phase. Because of those needs the focus of [redacted company name] on the early translational stage as many of the scientists engaged in the early research do not appreciate how to do drug development.
- [Interviewee] thought that in Ireland we were clearly not spending enough on research and could easily double our expenditure and still be relatively low on global R&D spending scales.
- [Interviewee, researcher, Ireland] "after a period the SFI funding stopped and all activities have stopped and we were left on our own with no co-ordinated effort." [Interviewee] felt that this was a lost opportunity and that it led to a loss of momentum in the research effort.

4.

REVIEW OF ACADEMIC/EARLY DEVELOPMENT STAGE ATMP MANUFACTURING CENTRES AND INITIATIVES IN OTHER JURISDICTIONS

As the importance of ATMPs for medicine and its potential economic impact becomes clearer many countries, regions or, transnational/cross border areas are now undertaking specific initiatives in various areas related to the development and use of ATMPs, in addition to the investigator driven research projects that have been occurring in individual academic institutions for many years. In this section, our focus is on a number of examples from different countries that offer ideas for how an Ireland or, all-island specific program related to ATMPs could be organized. Our emphasis is therefore on the manner in which these initiatives are organized and in particular their financing and structure. This is not an all-inclusive analysis as there are other instances in other jurisdictions, but these were considered to be useful exemplars.



4.1 UK

The UK has invested very significantly in a series of new technology areas through the Innovate UK Group within the UK Research & Innovation (UKRI) Agency whose mission is to "*drive productivity and economic growth by supporting businesses to develop and realise the potential of new ideas, including those from the UK's world-class research base.*" One important mechanism used by this Agency has been the creation of a series of "Catapults" to turbo charge innovation and these are conceived as "*physical centres with cutting-edge R&D infrastructures including hubs, laboratories, testbeds, factories and offices, as well as technical experts that prove and adopt breakthrough products, processes, services and technologies.*"

The Cell and Gene Therapy Catapult (CGT Catapult) was established in 2012 to advance the growth of the UK cell and gene therapy industry, by bridging the gap between scientific research and full-scale commercialisation[28]. CGT Catapult has developed expertise in industrialisation, manufacturing, and the specific supply chain for ATMPs. Companies are able to access and leverage this expertise, accelerating their development. The Catapult consists of a development center in central London, which has 70+ scientists working on industrialisation technologies and a manufacturing center in Stevenage, which is designed specifically to help companies develop their manufacturing at a scale sufficient to satisfy the requirements, both in terms of purity and quantity, for clinical trial materials. Following on from an initial investment of £55 million a further £12 million was awarded in 2017 from the UK Government's Industrial Strategy Challenge Fund to double the existing size

28 https://www.stevenagecatalyst.com/community/organisations/cell-gene-therapy-catapult/

and capability of the CGT Catapult large-scale GMP manufacturing centre. So far, the CGT Catapult has been continuously funded by the government. In 2019 approximately 60% of its revenue came from public sources.

In addition, a network of Advanced Therapy Treatment Centres (ATTC) was established in 2018, operating within the NHS framework and coordinated by the CGT Catapult to address the unique and complex challenges of bringing pioneering ATMPs to patients. The aim is to smooth the path to adoption and develop ways of working within and across these centres and supply chain that will support the increased clinical use of ATMPs. The centres include:

- Innovate Manchester Advanced Therapy Centre Hub (iMATCH),
- Midlands-Wales Advanced Therapy Treatment Centre (MW-ATTC, comprising Birmingham, Bristol, Cambridge, Cardiff, Leicester, Nottingham and Swansea)
- Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC, comprising Edinburgh Glasgow, Leeds and Newcastle)

The network was initially supported by the Industrial Challenge Strategy Fund delivered by UKRI and has recently received a further £9.5 million to fund an additional 12 months of the programme[29].The centres leverage existing clinical and research facilities and capabilities within the network and the collaboration across the industrial and NHS partners has begun to produce guidance documents and approaches to standardisation approaches to treating patients with ATMPs.

Recently the University of Sheffield, in collaboration with Pfizer, announced that it had received funding of £25.5 million in an initiative forming a new consortium that aims to standardize and accelerate the development of ATMPs, allowing potentially transformative treatments to reach patients sooner. The new, five-year consortium with industrial and clinical partners including Pfizer, Accelerating Research and Innovation for Advanced Therapies (ARDAT) is supported by the European Innovative Medicines Initiative (IMI) and brings together the leading expertise of 34 academic, nonprofit and private organisations from across Europe and the US.[30 31]

The UK now has a very strong leading position in the early-stage development of ATMP products being the chosen location of over 12% of all global clinical trials in this space (154 on-going in 2020[32]). As of 2020 there are over 90 ATMP developers based in the UK, which constitutes the largest cell and gene therapy cluster outside of the USA[33]

29 https://ct.catapult.org.uk/news-media/general-news/advanced-therapy-treatment-centre-network-awarded-%C2%A395m-further-investment
30 https://www.eurekalert.org/news-releases/548219
31 http://ardat.org/new-consortium-aims-to-standardize-and-accelerate-development-of-advanced-therapy-medicinal-products-in-e25-5-million-project-2/
32 https://ct.catapult.org.uk/clinical-trials-database
33 https://www.futuremedicine.com/doi/10.2217/rme-2020-0140

4.2 SWEDEN

ATMP related activities in Sweden have been driven by its national innovation agency - Vinnova - which helps "*to build Sweden's innovation capacity, contributing to sustainable growth.*" Vinnova has funded a series of Projects in this area including **ATMP Sweden**. This is a national network for activities within medicines based on genes, cells or tissue engineering, classified as ATMPs in Europe. The Swedish government committed to a 320 Million SEK (approximately €32 million) spend with the aim of making '*Sweden a world leader in development and implementation of advanced therapies by 2030.*"[34]

The ATMP Sweden network was founded through the Vinnova funded projects CAMP (Centre for Advanced Medical Products) and Swelife-ATMP. The activity is now supported by the Vinnova funded ATMP Innovation Milieu. Other Swedish ATMP-specific National networks within the ATMP Sweden umbrella include NextGenNK focused on cost effective development of Natural Killer (NK) cell based therapies and SWECARNET, Sweden's network for clinical use of CAR T cells.

The role of ATMP Sweden is quite broad:

- As a national network for activities within medicines based on genes, cells or tissue engineering.
- With a goal of promoting "the collaboration and communication that is needed for accelerated and effective ATMP based patient solutions."
- To provide centralizing, coordination and communication functions to Swedish ATMP stakeholders.
- To act as a central contact point both nationally and internationally for the Swedish ATMP field.

A document that outlines the roadmap to achieving the aim of becoming a global leader in the area of ATMP development and implementation was published in 2020[35]. Although it concludes that Sweden has many of the attributes required to become an internationally competitive and attractive country for ATMP development, there are a number of key challenges that need to be addressed to enable this objective. One major gap identified 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. According to the report this lack 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.

34 https://atmpsweden.se/about-atmp-sweden/current-initiatives/about-innovation-milleu/
35 https://atmpsweden.se/wp-content/uploads/2021/04/20210406-ATMPInfrastructure-final.pdf

- 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.

Following on from a survey of the approaches other countries have taken this paper proposes a new infrastructure based on the model which has been successfully developed by the Centre for Commercialization of Regenerative Medicine (CCRM) in Canada. This would include:

- 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 cofunding 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 plan proposes that the model, termed 'CCRM Nordic', should have an overarching national framework and should be trans-national with its initial focus on the Nordic countries as its client base. Based on a market analysis, projected number of companies and projects in the Nordic countries up to 2030, 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.

Following the proposed business model and 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 predicts that CCRM Nordic will generate a positive income 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 (approximately €50 million) is required. At full-scale sustainable operation the report suggests that 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.

A separate report carried out in October 2020 by Monocl Strategy & Communication AB on behalf of RISE (Research Institutes of Sweden AB) identified the top ATMP research centres in Europe[36]. The metrics chosen for this study are very useful in contextualizing the research capabilities and capacities in countries developing a strong ATMP-research base. The scope of the report was to map the following with a view to comparing Swedish outputs with other selected European countries:

- ATMP developing and supporting companies in Sweden
- Ongoing therapeutic ATMP R&D projects in Sweden
- EU financed R&D projects in Sweden
- Trends in ATMP related publications from Sweden
- Demographics of ATMP related researchers

The results of the exercise clearly demonstrate the synergistic effect that the cluster model, combined with a centralized and strategic funding approach can have and it is intended that these metrics will be tracked across the 2020-2030 timeframe to evaluate the level of success in achieving the aim of making Sweden a world leader in the development and implementation of advanced therapies.

4.3 THE NETHERLANDS

The Netherlands Center for the Clinical Advancement of Stem Cell & Gene Therapies (NecstGen) is the most recent initiative in the Netherlands to support the continued development of their ATMP ecosystem. It is a non-profit spin out of Leiden University Medical Center (LUMC) and will be located in a purpose-built facility on the largest bio-cluster in the Netherlands, Leiden Bio Science Park (LBSP). NecstGen aims to increase the development and GMP production capacity available for cell and gene therapies and facility is open to partners based worldwide, focusing on academic clients, hospital-based clinicians or start-up companies. The

36 https://atmpsweden.se/wp-content/uploads/2020/10/RISE_baseline_ATMP_16Oct2020opt.pdf

facility will act as a hub to foster public-private interaction within the cell and gene therapy community, creating a network to link relevant stakeholders, therapy developers, service providers, government, regulators and investors. The first development lab opened in August 2021 and the GMP suite is expected to be commissioned in 2022[37].

NecstGen is one of a series of facilities that will benefit from strategic investments by the Dutch government to accelerate the development of a robust ATMP ecosystem. In April of this year, it announced the investment of €56 million by the Netherlands Government Growth Fund into the establishment of a "pilot factory" for regenerative therapies. NecstGen and three other facilities will form a chain covering the development and manufacturing of cell therapies, biomaterials, microtissues and macrotissues. The funding has been awarded to RegMed XB, a collaboration of research institutes (including LUMC), governments, provinces, health funds and industry in the Netherlands and Flanders aimed at the development of regenerative therapies and technologies[38]. RegMedXB is particularly interesting in that it involves a cross border collaboration between the Netherlands and Belgium.

4.4 CANADA

CCRM (The Centre for Commercialization of Regenerative Medicine) was established in 2011 as a not-for-profit organisation funded by the Government of Canada, the Province of Ontario, and leading academic and industry partners with the aim of supporting the commercialization of "regenerative medicine-based technologies, and cell and gene therapies, with strategic funding, dedicated infrastructure and specialized business and scientific expertise"[39]. CCRM is hosted by the University of Toronto and is the commercialisation partner of the University of Toronto's "Medicine by Design". CCRM's mission extends beyond Canada and it currently has involvement in both NecstGen (Netherlands) and Sweden ATMP.

CCRM's model is a broad one, encompassing many of the facets of early stage ATMP development; partnering with leading research institutions to launch new ventures, enabling industry by providing innovative contract development and manufacturing organization (CDMO) services, and scaling emerging companies by catalyzing investment[40].

In late 2020 CCRM signed a letter of intent with McMaster Innovation Park to partner in the development of a biomanufacturing campus focused on regenerative medicine-based technologies and cell and gene therapies. Through this partnership it intends to develop a CDMO facility to produce cells and viral vectors for Phase III clinical trials and commercial-scale manufacturing[41].

37 https://necstgen.com/necstgen-launches-its-first-development-lab/
38 https://regmedxb.com/news-events/news/56-million-euros-from-national-growth-fund
39 https://www.ccrm.ca/about-us-regenerative-medicine-cell-gene-therapy/
40 https://www.ccrm.ca/wp-content/uploads/2021/02/CCRM-5165-AR-2020-Final-sml.pdf
41 https://www.ccrm.ca/wp-content/uploads/2021/02/CCRM-5165-AR-2020-Final-sml.pdf

4.5 USA

The USA is the unassailable leader in the area of ATMP research, development and manufacturing. Significant hubs of ATMP research and industry are located in Boston, CA, Columbus, OH and Philadelphia supported by active local research universities and Venture Capital companies. There is also significant activity across the US and specialist centres and initiatives have been established at both federal and state levels to support this sector. They include the California Institute for Regenerative Medicine (CIRM), National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and the recently established LandmarkBio. The thriving research and funding ecosystem has led to the US being home to over 55% of existing ATMP companies. Many of the major pharma companies are also headquartered in the US and these have been developing their ATMP pipelines predominantly through acquisition of promising start-ups worldwide. A report entitled "Cell manufacturing Roadmap to 2030" was recently prepared for the National Science Foundation Engineering Research, Center for Cell Manufacturing Technologies (CMaT), the Georgia Tech, the Marcus Center for Therapeutic Cell Characterization and Manufacturing (MC3M), and the National Cell Manufacturing Consortium (NCMC)[42].

The high priority included in this strategy which aims to identify "current challenges the cell manufacturing community must overcome, and outlines activities needed to achieve large-scale, cost-effective reproducible manufacturing of high-quality cells" are described in Figure 4 .

The NCMC had previously issued a detailed document entitled "*Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells - A Technology Roadmap*" in 2016. This report recognised that there are various categories of novel cell based health care products being marketed or, in development that will likely have significant public health and economic benefits including stem cell therapies, regenerative medicines, immunotherapies as well as cell-based devices and diagnostics and that one common unifying feature for all such products is the need to have available cost-effective, large-scale, reproducible processes for the production of cells of appropriate quality. The report concluded that enabling necessary, suitable large-scale cell manufacturing will require investment in advanced technologies and techniques to increase cell production scale and speed with improved quality, lower cost, greater reproducibility and consistency in production and strengthened IT security.

The strategy to achieve this was built around five key cell manufacturing activity areas:

- **Cell Processing and Automation**
- **Process Monitoring and Quality Control**
- **Supply Chain and Transport Logistics**
- **Standardization, Regulatory Support, and Cost Reimbursement**
- **Workforce Development**

The NCMC concluded that while progress can and will be made to address the activities outlined in this roadmap through individual research efforts, a more extensive and

42 https://cellmanufacturingusa.org/sites/default/files/Cell-Manufacturing-Roadmap-to-2030_ForWeb_110819.pdf

Figure 4: Summary of high priority activities from the Cell manufacturing Roadmap to 2030 (Reference 42).

coordinated cell manufacturing community, supported by public private-philanthropic partnerships, is critical for maximizing U.S. cell manufacturing industry progress and ensuring success of the emerging bioeconomy. It provides some examples of such public-private partnerships that demonstrate increased U.S. emphasis and investment in the advancement of cell manufacturing, regenerative medicine, and biopharmaceuticals.

A number of such ongoing public private partnership initiatives in this space included:

(NSF) Engineering Research Center for Cell Manufacturing Technologies (CMaT) was established in September 2017 as an NSF-funded engineering research center supported by a consortium of universities led by Georgia Tech. The mission of CMaT is to enable cell therapy product manufacturing scale-up by developing innovative tools, systems, and technologies that better ensure product quality, potency, safety, and cost effectiveness. The center also focuses its efforts on workforce development in collaboration with industry partners such as GE, ThermoFisher Scientific, and Lonza, among others.

Marcus Center for Therapeutic Cell Characterization and Manufacturing (MC3M) was established in 2016 at Georgia Tech, to focus on establishing world-class collaborative infrastructure to facilitate the characterization and manufacturing of therapeutic cells. The Center, which used the *Achieving Large-Scale, Cost Effective, Reproducible Manufacturing of High-Quality Cells* roadmap to inform its direction and focus. It is funded by an initial investment of $23 million, including a $15.75 million philanthropic donation from the Marcus Foundation. MC3M aims to accelerate cell therapy research and technology, process and assay standards, and workforce development, particularly in the areas of critical quality attributes, process analytics, potency assays, sensors for non-destructive evaluation, process automation, and supply chain logistics.

National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) was established in March 2017 with the mission of accelerating biopharmaceutical manufacturing innovation, supporting the development of standards that enable more efficient and rapid manufacturing capabilities, and educating and training a world-leading biopharmaceutical manufacturing workforce, fundamentally advancing U.S. competitiveness in this industry. NIIMBL is funded by a $70 million cooperative agreement from the National Institute of Standards and Technology and leverages additional commitments from partners from industry, academia, and non-profits. To date, NIIMBL has funded over 86 technical, workforce development, and Global Health projects with a total investment of approximately $72M. The NIIMBL community is comprised of more than 180 members from academia, industry, government and non-profit organizations all sharing a common goal to advance biopharmaceutical manufacturing.

Boston, Mass has for many years been one of the most important locations for the discovery and development of biopharmaceutical medicines. Its significance has been powered by the quality of the clinical and basic biological science research undertaken in the various world class Universities and Hospitals located in the city and the State of Massachusetts. In 2017 as the importance of the emerging field of ATMPs began to be widely recognized along with the challenges of getting such products industrialised, a

dialogue commenced in the Boston area among industry and academic leaders within the Massachusetts Life Sciences Strategies Group who recognised two key challenges – firstly, that there were significant bottlenecks inhibiting progress towards the potential implementation of the novel cell and gene therapies and gene editing technologies in treatment of life threatening diseases and secondly, how Massachusetts could ensure it was a global leader in this new field which was articulated by the Harvard Provost, Professor Alan Garber, as "How can we best position our region to be preeminent in the life sciences in the decades to come? We have a vibrant life-sciences community, with some *of the world's greatest hospitals, universities, and life-sciences companies of all kinds. We also have a strong financial sector that helps to spawn and support new companies. So the elements for rapid progress in the life sciences — particularly in the application of the life sciences to human health — are all here. But with such a rapid pace of innovation, it's easy to fall behind.*"

These discussions led to the creation in 2019 of a private non-profit organisation called the Center for Advanced Biological Innovation and Manufacturing (CABIM) that was supported by more than $50 million pledged by its partners - Harvard, MIT, and industry partners Fujifilm, Alexandria Real Estate Equities, and GE Healthcare Life Sciences. Other members included certain Harvard-affiliated teaching hospitals: Massachusetts General Hospital, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Boston Children's Hospital, and the Dana-Farber Cancer Institute; as well as the Commonwealth of Massachusetts and the life-sciences company Millipore Sigma.

The initial plan envisaged a phased opening of a retrofitted 40,000 square feet space spread over two floors of an existing building near a number of biotech startups in the Watertown Life Science Cluster to commence in January 2022. The facility is planned to have dedicated manufacturing and innovation spaces. In July 2021, a founding CEO was announced for the organisation, Dr Ran Zheng, and it was renamed as **LandmarkBio**. The facility will open in stages, as its reconstruction is completed. The first stage will be offices, with laboratory, innovation, and manufacturing space to come later. Together, it is envisaged that *"the facility's different facets are intended to overcome a hurdle in the production of cell and biological therapeutics that has slowed progress of the development of the most advanced generation of tools to treat genetic diseases, cancer, diabetes, and other ailments. A major focus will be ensuring that supplies of biological materials, such as genetically altered cells, are available so clinical trials of promising discoveries can go forward."* It includes eight planned clean rooms designed to provide the tight process control necessary to manufacture materials that can be used in human trials. Nearby laboratory space will be reserved for promising late-stage research coming out of academic labs or early start-ups. Leading experts, capable of refining new concepts for GMP standard patient application, will provide professional guidance and enable the emerging therapies to seamlessly migrate from the research lab to the patient in the clinic. When completed, the facility is expected to have more than 120 staff members in process development, advanced biological manufacturing, quality control and quality assurance, regulatory sciences, and business operations. Zheng said the facility will be flexible and reconfigurable in order to allow changes as it adapts to the rapidly developing field. In addition to

space for manufacturing, Landmark Bio will also have dedicated innovation space where ideas that have left the lab but are not ready for corporate investment can be further developed. The facility also aims to be a site for training in the operation of advanced equipment used in cell manufacturing as a way to achieve another of Landmark Bio's goals: increasing the region's pool of workers skilled in biological manufacturing.

"*Cell and gene biological manufacturing is so important for innovation today. Without manufacturing you cannot move toward the next step to provide patients life-saving treatments,*" Zheng said. "*It's a still-nascent field, but there is lots of promise.*"

Ireland should look to Cambridge, Massachusetts as an example of skills nurturing and industry-academic collaboration. The proximity of world-class universities and industry leaders means the talent ad ideas pipeline is strong. This promotes excellence in academic research, cross-functional collaboration and better innovation. It draws venture capital and government funding, as well as new industry investments.

https://2hmcriw3psofj2qo3f8w6f17-wpengine.netdna-ssl.com/wp-content/uploads/2021/01/Globally-Networked-Innovation_Perspectives-on-Irelands-Future-in-Medicines.pdf

The overall plan for LandmarkBio's operations is summarized schematically in the following diagram:

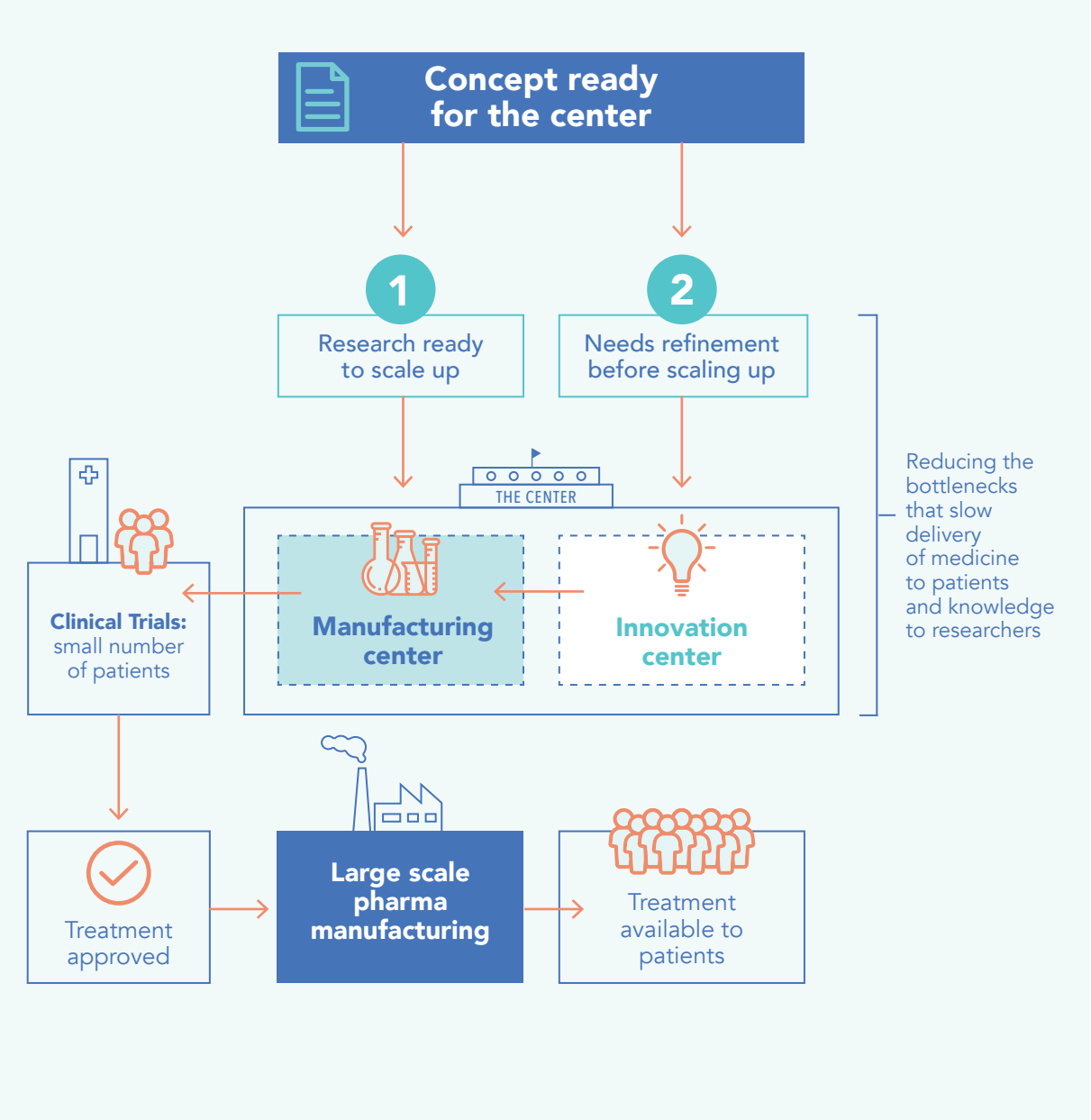


Figure 5: LandmarkBio's plan for operation

It has been organized as a private nonprofit organisation and the center will be supported by more than $50 million pledged by its partners. It will be staffed by a team of at least 40, experienced in the latest cell-manufacturing techniques and trained in the use of the latest equipment. Among its goals is disseminating badly needed skills into the Boston life-sciences workforce. The facility intends to provide researchers and emerging companies outside the consortium with access to excess material, though organizers said they expect it to be in high demand by center partners.

California Institute of Regenerative Medicine (CIRM) was established in 2004 by the voters of the State of California via their approval of California Proposition 71 with a budget of $3 billion to last until 2017. Its implementation was delayed until May 2007 when the Supreme Court of California upheld Proposition 71 as constitutional, thereby permitting CIRM to fund stem cell research in California. By late 2019, CIRM had provided more than $2.67 billion in grant funding across the six broad categories of 1/ physical and institutional infrastructure, 2/ basic research, 3/education and training, 4/ translational research, 5/research application and 6/clinical trials.

Some examples of CIRM funding have included:

- In 2018, UC San Francisco (UCSF) received a $12 million grant to study severe combined immunodeficiency (SCID). The subsequent UCSF research program contributed in part to a potential Lentiviral Gene Therapy based cure in 2019.
- In 2017, CIRM awarded $2 million to a UC San Diego scientist searching for a cure for the Zika infection. Research led to successfully finding a pre-approved drug to block Zika virus replication and infection, as well as its transmission from mother to child.
- In 2011, CIRM made its first award ($25 million) to support a human clinical trial. The award was for a spinal cord injury trial to Geron Corporation which was later taken up by Asterias Biotherapeutics and led to significant benefits to a paralyzed high school student who was able to regain function in his upper body.

The economic impact of CIRM was evaluated in a study in 2019 i.e. after 14 years of its operation in a study by two economists at the Schaeffer Center for Health Policy and Economics at the University of Southern California. Their report found that through the end of year 2018, CIRM had committed more than $2.67 billion across six broad categories of grants to fund physical and institutional infrastructure, basic research, education and training, research translation, research application, and clinical trials. The report focused on the various economic impacts of CIRM over and above its main functions of improving health and well-being, in particular estimating the increases in economic output, employment and tax revenues. These additional benefits emanate not only from CIRM direct funding commitments but also from various other leveraged funding. The report quantified not only the direct impacts but also various indirect impacts as CIRM and related expenditures ripple throughout the economies of both the State of California and the USA as a whole. The total quantified economic impacts of CIRM on the entire U.S. economy were estimated to be:

- $15.4 billion of additional gross output
- $840 million of additional state/local

tax revenue and $935.2 million of additional federal tax revenues

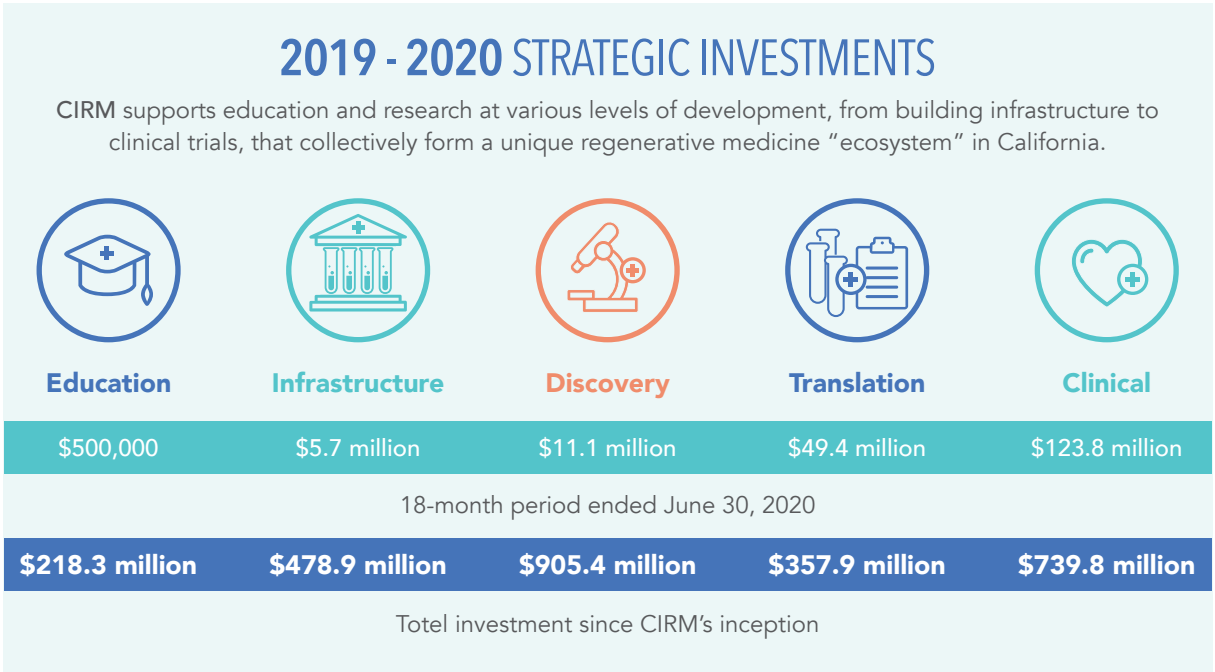
- 82,365 additional jobs
- About 38.4% of the gross output increase and 36.0% of jobs created are concentrated in medical and health related research, manufacturing, and service sectors.

Approximately 66% of these economic impacts were estimated to have occurred specifically within the State of California. The major sectors of the Californian economy impacted by CIRM direct and related funding were: Scientific Research and Development Services, Health Care Services, Construction of New Nonresidential Commercial and Health Care Structures, Professional Services, and Real Estate.

In its most recent 18 month Report covering the period 2019-mid 2020 CIRM states that it has now supported 64 programs in California to find new cell based therapies that have advanced to clinical trials as well as funding another 30 earlier-stage projects that subsequently advanced to the clinical stage of development, including two that have been approved by the FDA. These therapies emerged from the completely new field of medical science built on stem cell and gene-based therapies enabled by CIRM.

Of the CIRM-supported clinical trials, four are in the final stage before FDA approval (Phase III), as of June 2020.

Figure 6: CIRM's investment to date and 2019-20 Strategic Investment



It is evident from this data from the CIRM Report that CIRM funding is increasingly being used to support clinical trials of the new therapies translated from a long period of support for the applicable basic science within a well-established infrastructure.

4.6 OTHER RELEVANT INITIATIVES

4.6.1. Other European Initiatives

Several other European countries have invested substantially in the development of a robust early-stage ATMP eco-system. Relevant examples include:

Iniciativa Andaluza en Terapias Avanzadas (IATA) / Andalusian Initiative for Advanced Therapies (AIAT), a public foundation belonging to the health ministry and is part of the Spanish healthcare system. It is associated with the main public hospitals and the blood and tissue banks in the region. The healthcare authorities make the decision as to what trials get public funding. AIAT coordinates all the research topics in the ATMP field in the public healthcare system. It builds and runs GMP facilities (10 currently) located as close to the patients as possible in the main hospitals and the blood and tissue banks with manufacturing capacity in the four main capitals of Granada, Seville, Malaga and Córdoba. To date it has treated more than 700 patients with ATMPs and is engaged with 18 hospitals. AIAT is a networking hub. It works with hospitals, biobanks and cell manufacturing units. It is a clinical trials sponsor (24 to date) and assists companies to develop and license their own ATMPs. It is a policy influencer continuously working with the Spanish healthcare authorities and collaborating with other European healthcare agencies.

Trans-European collaborations that have specific goals in the development of the ATMP eco-system include:

EATRIS is a non-profit European Research Infrastructure Consortium (ERIC). This specific legal form is designed to facilitate the joint establishment and operation of research infrastructures of European interest. EATRIS's organisational model is based on country membership and its focus is the curating of European Infrastructure for Translational Medicine. From an ATMP perspective funded and supported research is in the pre-clinical/ clinical development stages.

The Innovative Medicine Initiative (IMI) is a partnership between the European Union and the European pharmaceutical industry. IMI is the world's biggest public-private partnership (PPP) in the life sciences. IMI's mission is "to improve health by speeding up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need." In November 2020 the IMI[43] announced that it was supporting the University of Sheffield and Pfizer in the launch of a €25.5 million consortium that aims to standardize and accelerate the development of ATMPs. The consortium aims to develop standardized models for predicting ATMP immunogenicity in humans; build understanding of ATMP drug metabolism within a host; identify adaptive immune responses that could affect ATMP safety, efficacy and persistence; and engage regulators to help support filings that address standardized regulatory, safety and efficacy concerns[44].

LERU is the League of European Research Universities and its aim is to be a "prominent advocate for the promotion of basic research at European research universities"[45]. It has 23 member universities across Europe including

43 https://www.sheffield.ac.uk/news/university-sheffield-and-pfizer-lead-new-eu255-million-project-accelerate-development-advanced https://www.eurekalert.org/news-releases/548219
44 https://www.eurekalert.org/news-releases/548219
45 https://www.leru.org/

TCD. In 2019, it issued a report entitled "Advanced Therapy Medicinal Products" that highlights the important role universities play in ATMP development and further argues that this role could be improved, and expanded, if specific hurdles were addressed[46]. It makes several recommendations as to how this could be achieved including:

- Improving interactions with, and help provided by, support organisations, such as EMA, industry and other universities, to cover better the whole product development pathway and to ensure support (including financial) at all stages of development.
- Universities should focus on new innovative products that address an unmet medical need and have a high chance of success and on products, which are unlikely to be attractive to industry.
- Retaining the Hospital Exemption, but harmonising its application, improving its assessment and using it only in product development or for products not suitable for Marketing Authorisation. A registry should be developed to record information on ATMP use under the Hospital Exemption.
- Improving transparency, both in ATMP trials and in the use of the Hospital Exemption, which will help organisations active in this field to learn from others' successes and failures.

4.6.2 Survey of US academic institutions with cell and gene therapy manufacturing facilities.

Stanford University held a symposium in 2018 on "developing, qualifying and operating a cell and gene therapy manufacturing facility" in academic environments. Prior to the symposium the university surveyed the estimated 40 such facilities it identified in the US and they collated and discussed the responses from 25 of these institutions. The results provide some useful insights into challenges, opportunities and the funding models employed in this environment.

The majority (83%, n = 15) of academic centres reported manufacturing 10 products[47] or less per month. Two centers reported 11-25 products per month and one reported 26-50 per month.

The majority (70%, n=15) of academic centres surveyed offered Contract Manufacturing Organisation (CMO) services to investigators or entities outside of their academic centers. However, these CMO-like activities represented less than 10% of overall manufacturing activities and were not considered a critical source for financial sustainability. There was a general consensus that projects that generated new intellectual property had the potential to provide revenue from out-licensing and royalty payments but required 8-10 years to mature to a revenue-generating state.

Major barriers to operations captured by this survey included identifying, hiring and retaining qualified staff. Offering competitive salaries to trained staff was difficult.

46 https://www.leru.org/files/LR-BP-ATMP.pdf

47 A review of the paper indicates that it is likely that this refers to individual autologous batches rather than products in the more usual definition in the pharmaceutical industry.

One model employed by some groups was to develop close collaborative ties with the research laboratories and employ staff from the project sponsors laboratory as subject matter experts to help with the nuance of the biology of materials in individual projects. In this model, the GMP facility staff members are mostly ensuring compliance with GMP practices and overseeing process specific procedures requiring equipment unfamiliar to the research staff. A downside of this model, is that the scientific expertise for manufacturing products is not consistent over time, and the cumulative experience of the cGMP staff is limited.

Many institutions employ a lean staffing model (including Stanford), resulting in cross-cover on projects and staff scheduling conflicts within and across manufacturing disciplines. To resolve this, one approach implemented is the use of project-specific teams that have the appropriate training and skill sets to handle project specific manufacturing tasks. According to the feedback at the symposium this worked well for high-accruing studies but is not efficient for low-accruing studies in which months may pass between patients enrolled on trials. Where projects are in related disciplines (for example CAR T and regulatory T cells) staff may be shared as the projects are similar enough in nature for the staff to understand and comply with the regulatory requirements.

The study concluded that no single staffing model emerged as a best practice, key overarching messages about recruiting and retaining cGMP-focused staff emerged from the symposium including the following:

Prioritize staff engagement; ensure compensation (including incentive bonus plans) that is industry-market competitive combined with cGMP-specific job descriptions

Cross-train staff for multiple projects to build redundancy; however, keep the number of projects (and project complexity) per person in check (three/four per person maximum)

For manufacturing-focused positions, create opportunities, as possible, for small-scale process development to ensure task diversity within jobs and avoid "clean-room burnout".

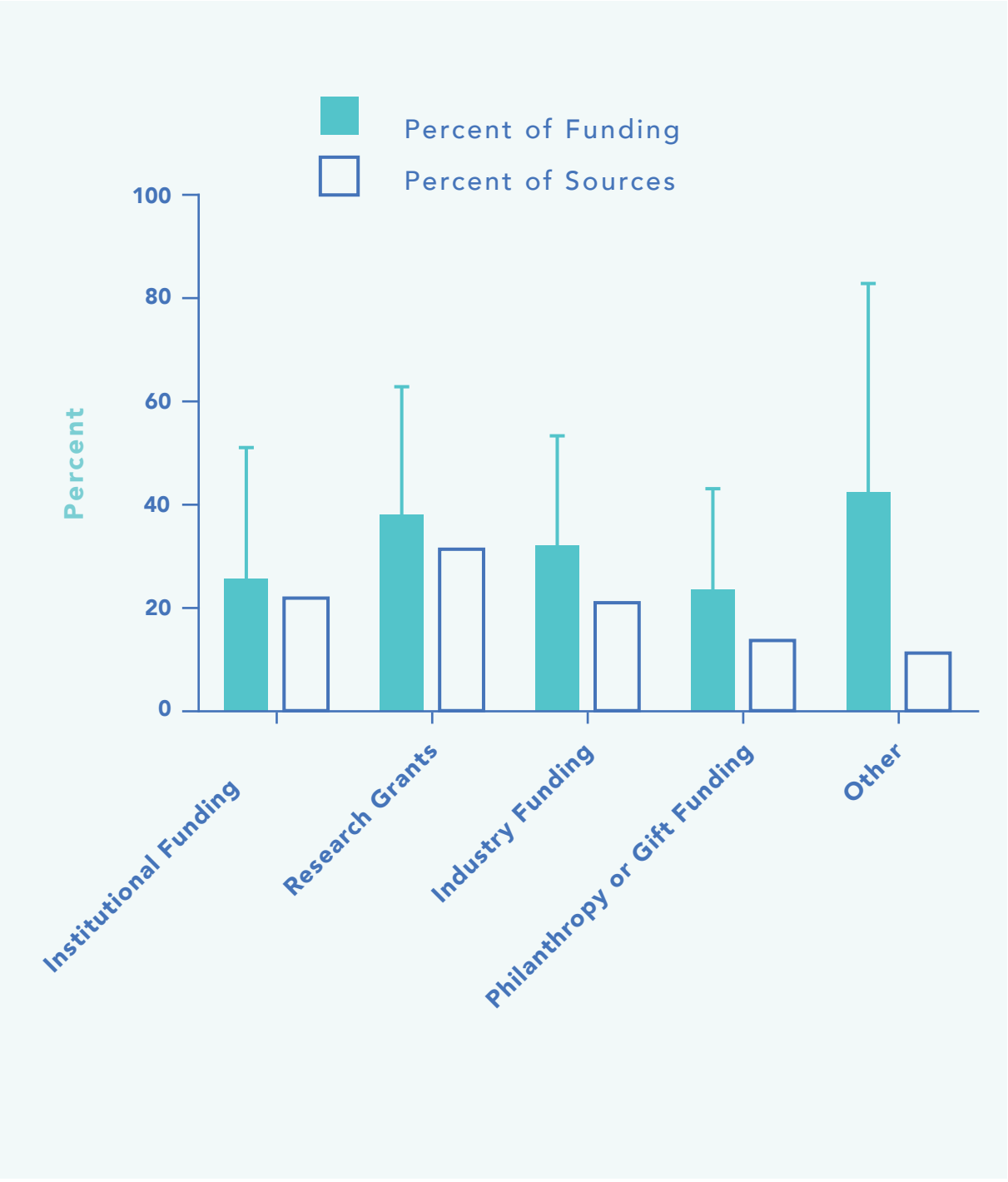
Consider dedicated, fixed-term staffing for larger-scale production projects and rely on industry- or philanthropy-sponsored projects to fund dedicated staff

One additional point to note was that identifying a champion "who informs and influences hospital and institutional leadership" was considered critical to ensuring that academic cGMPs are forward-focused toward a well-defined.

When looking at the funding sources from these academic manufacturing facilities it was interesting to note that it did not conform to the Fraunhofer model that is often cited as best practice in these type of facilities with a significant portion of the funding coming from "other" sources including venture capital and fee for service[48].

48 https://www.isct-cytotherapy.org/article/S1465-3249(18)30576-0/fulltext

Figure 7: Funding sources for academic CGT manufacturing facilities according to survey from Stanford symposium (Reference 48).



5. CONCLUSIONS

With the increasing recognition of the growth potential in the ATMP sector arising from the associated basic science advances of recent years, many countries have adopted a strategy of investment in this field with the objective of ensuring they become a desired location for future commercial operations related to ATMPs. Typically there are two primary driving forces for these developments: scientific experts or, governmental technocrats who recognize the importance of ATMPs for both public health and economic health. That is, either coming from high profile scientific/ medical experts in the field who proactively bring attention to its importance or, those individuals in government with a particular focus on technological innovation as a critical component for future healthcare and/ or economic well-being. In the examples we reviewed the focus is typically on the development of national or regional clusters with capabilities and capacities across the ATMP development spectrum from early stage academic research through to clinical trials as well as support for training and commercial manufacturing. The IDA vision outlined in their recent ATMP infographic recognizes the manner in which the need is for interconnectedness across multiple aspects to be a desired location. Our conclusion is that the future of the REMEDI/CCMI facility in NUI Galway needs to be considered in the context of the development of an all-Ireland or, potentially all island 'ATMP ecosystem' in which the various constituent elements interact synergistically such that the whole is greater than the individual parts. In such a vision, a facility like CCMI is a critical constituent and arguably without it the ATMP ecosystem could not be effective. This criticality is due to the need to be able to provide GMP quality cell therapy products as part of the translational science effort whereby the basic science investment ultimately yields usable clinical and

commercial ATMP products. An ecosystem yielding such outputs will both make available people with the appropriate expertise to staff new ATMP facilities and provide a level of confidence to external investors that Ireland is a safe location for investment in this area.

We also conclude that the most important success to date of the NUI Galway CCMI initiative is having achieved a manufacturing authorisation (MIA) from the HPRA and its ability to maintain this over many years of operation. Such authorizations are difficult to achieve as it requires a high level of proficiency in the field of Good Manufacturing Practice (GMP). This is essential for the manufacture of human medicines but is a demanding and costly set of operational practices that are quite bureaucratic and alien to the normal operational practices of academic institutions. In addition, it does not readily fit into an environment that is relatively lean budgetarily and that operates on the basis of short term project-based funding when the need is for an established operation with assured multi-annual and long term funding. Being licensed CCMI has a strong foundation for ongoing operation but its operational budgetary needs must be recognized and appropriately accommodated if it is to meet its full potential. This will require further consideration and possibly the development of a new, more ambitious and bold vision of CCMI as a key part of this new all-island ATMP ecosystem. If this is achieved there is no reason CCMI cannot succeed to a greater extent going forward and be internationally competitive in its mission, while facilitating the further strengthening of the biomedical product development and manufacturing industry in Ireland for the next generation of products in the ATMP area.

"In all of the years I have been tracking and helping to drive biotech innovation, I can say with conviction that the industry is at an important inflection point now. This will see bold new biopharmaceutical breakthroughs become marketable products at a rate we barely could have imagined a decade ago. As product developers increasingly see ambitious cell and gene therapies do well in clinical trials, and achieve marketing authorization, momentum will continue to build as innovators are able to picture their own routes to market opening up."

Christian K. Schneider, MD Head of Biopharma Excellence / Chief Medical Officer

https://www.biopharma-excellence.com/biopharmas-big-inflection-point-theres-never-been-a-better-time-to-innovate-with-next-generation-medicine/

6. PROPOSED ACTIONS

Following a review of activities, actions and initiatives undertaken in other jurisdictions and the feedback from the experts interviewed as discussed earlier, the actions here are recommended in relation to the creation of an Irish ATMP active ecosystem.

6.1 AN ACTIVE BASIC SCIENCE RESEARCH EFFORT IN THE UNDERPINNING BIOLOGICAL SCIENCES ENABLING RELEVANT DISCOVERY;

6.1.1 RATIONALE:

While Ireland now has a medium level of support for scientific research since the setting up of SFI in 2003 much of this activity is in areas related to various research centres which are often criticized by the basic science community as being too applied in their focus with decreasing amounts of funding being available for the basic sciences. It is clear that the development of the ATMP sector is completely reliant on a strong basic science effort in the underpinning biological sciences. This connection goes back to the discovery of the first key molecular biological tools – restriction endonucleases by Arber, Smith and others in the late 1960s to that of the gene editing CRISPR-Cas9 system by Doudna, Charpentier and others in 2012[49]. This type of fundamental research enables the identification of new opportunities for medically useful products and provides a cohort of highly trained scientists with the expertise to enable the exploitation of these findings.

6.1.2 ACTIONS:

Within the activities of the biomedical sciences, agencies (SFI, HRB and potentially others) funding a series of research areas related to the scientific disciplines underpinning ATMP development should be identified **and multi annual funds in the national science budget** earmarked for work in this area. This funding should be visible and attractive to attract new principal investigators into the salient areas. As many of the key ATMP applications (e.g. CAR T products and gene therapies) have originated from research in Hospital Research Laboratories these should be specifically encouraged to be included in this funding stream.

6.2 AN INFRASTRUCTURE OF LABORATORIES AND TRANSLATIONAL FACILITIES INCLUDING GMP MANUFACTURING FACILITIES THAT FACILITATE THE GENERATION OF ATMP MATERIALS SUITABLE FOR CLINICAL USE;

6.2.1 RATIONALE:

It is evident that much of the funding globally in initiatives supportive of ATMP development includes support for GMP grade ATMP facilities as the initial steps in translating promising basic scientific research into potential products is to manufacture

49 https://www.science.org/doi/full/10.1126/science.1225829

materials that can be administered in a clinical environment to human subjects. Such activities will not be permitted unless the potential product has been produced under GMP conditions which includes it having been produced in a GMP grade facility. Such facilities are expensive to construct and to maintain in a fully operational condition. They must be licensed by, and are subject to ongoing rigorous inspections by the national Medicines Regulatory Agency (HPRA in the instance of the Republic of Ireland and MHRA in Northern Ireland).

6.2.2 ACTIONS:

There is currently one such licensed GMP facility in the non-commercial ATMP sector in the island of Ireland, CCMI within REMEDI in NUI Galway. CCMI is currently licensed for the production of cell therapy ATMPs for clinical use and is funded via the NUI Galway budget. In view of the critical importance of this facility to the islands ATMP "ecosystem" and the risk of a (3-5) year delay in getting any new facility designed, constructed, commissioned and licensed should CCMI be unavailable and/or cease to be licensed, a strategy needs to be developed to designate this as a "Designated Centre" with a funding model potentially along the lines whereby the UCC based Microelectronics Research Centre became the Tyndall National Institute. The CCMI Facility is arguably the most critical single component of an effective ecosystem and in the absence of such a GMP facility, any argument that Ireland is active in the ATMP area will not be credible externally.

6.3 AN ACTIVE TRANSLATIONAL SCIENCE EFFORT WITH THE CAPACITY AND EXPERTISE TO CONVERT THE BASIC SCIENCE DISCOVERIES INTO POTENTIAL THERAPEUTIC PRODUCTS;

6.3.1 RATIONALE:

As can be seen from this report, it is clear that in all jurisdictions developing a robust ATMP eco-system, that activity in the Translational Science area is recognized as an essential component. The most recent and notable instance of this is in the LandmarkBio Centre in the Massachusetts area in the USA and NecstGen in Leiden in the Netherlands. The academic primacy of this area on the USA in the basic biosciences is unchallenged globally, but the local leaders (in the UK, Sweden and the Netherlands amongst others) recognize that a key component is to employ a cluster model approach, where the basic research is translated into proven products that will continue to be manufactured locally. A similar scenario has existed since the foundation of CIRM in 2004 and over 13% of the total spend of 2 b$ has been devoted to the translational science effort. This is essential, as once the basic science observations indicates that a potentially important ATMP appears feasible the inherent complexity of such products means that there are usually always additional scientific challenges to be overcome before the ATMP is eventually realized and ready for clinical trials.

6.3.2 ACTIONS:

Translational Research is more focused work akin to Process Development in an industrial centre rather than the 'green field' publication focused approach of basic science. In this context, it is best done in a dedicated mission-focused research centre where the emphasis is on delivery of the therapeutic product. The most effective mechanism to achieve this outcome and the best location for such a centre requires more evaluation but it could potentially be within an SFI type Research Centre that might incorporate CCMI.

6.4 CLINICAL TRIALS (CT) EXPERTISE FOCUSED ON ATMP DELIVERY AVAILABLE I.E. HOSPITALS WITH ADEQUATE NUMBER OF PATIENTS, CLINICIANS AND REGULATORY EXPERTS WITH THE TIME, AND INTEREST TO UNDERTAKE OR, CONTRIBUTE TO TRIALS THAT ENABLE THE CLINICAL USE OF ATMPS AS WELL AS A NATIONAL CT REGULATORY SYSTEM FACILITATING SUCH TRIALS;

6.4.1 RATIONALE:

Clinical Trials (CTs) are by necessity very complex and highly regulated in the best interest of protecting the participant while facilitating the development of new medicines. As pointed out by the LERU paper discussed in section 4.6.1 most ATMPs are initially developed by universities and more than half of the EU clinical studies with ATMPs were sponsored by universities. This is the reality because typically university medical centres have the necessary disease-specific expertise, the capacity for innovative research and direct access to donor and patient material. Consequently universities dominate early stage (phase I/II) clinical research, while industry is more involved in late stage clinical development. As evidenced by the recent (Sept 2021) HSE publication "HSE National Framework for Governance, Management and Support of Health Research" the CT framework in Ireland is undergoing significant change. Under these circumstances and in light of the inherent technical complexity of all ATMPs, organizing all the necessary elements to make CTs happen can become a very difficult, time consuming and expensive exercise without proactive support from the various involved parties.

6.4.2 ACTIONS:

This is the most challenging issue for an effective ecosystem and there is no simple immediate solution. Nevertheless a start can be made by a/ training a cohort of ATMP Technical experts in the organization and execution of Clinical Trials along with b/ the full implementation of the HSE Report with an additional focus on ATMP small scale trials and c/ more use of the Hospital Exemption (HE) system for patient access

to use of ATMPs under the supervision of a medical practitioner, on a non-routine basis, and in restricted circumstances, in Ireland in line with the LERU recommendation. Finally, d/ the implementation within the HPRA of a process whereby notwithstanding the independence of that Agency's role, HPRA personnel with technical expertise in ATMPs would proactively work collaboratively with interested parties to help them navigate the complexities of the CT Authorisation system for ATMPs.

6.5 AN ADEQUATE SUPPLY OF WELL-TRAINED TECHNICAL EXPERTS FROM THE PRIMARY DEGREE TO DOCTORATE LEVEL;

6.5.1 RATIONALE:

The development and licensing of ATMPs will challenge in multiple aspects the current systems of control of medicines and the assurance that all lots of all products being used by patients and/or healthy participants throughout the life cycle of such products are fit for purpose. Providing these assurances will require ongoing training of all who work in the area and the availability of experts in many different fields at primary degree and doctoral levels. Consequently, there needs to be new training and education programs implemented to ensure there is an adequate supply of such individuals available.

6.5.2 ACTIONS:

A start has been made in this area whereby CCMI and REMEDI at NUI Galway offer an MSc in Cellular Manufacturing and Therapy and via NIBRT who intend expanding into the ATMP area from their initial remit to support rDNA protein manufacturers and this is very welcome. The CGT working groups have also identified key skill gaps in the educational and training areas, which should form part of any strategic planning by NUI Galway/CCMI in this area. In addition, there needs to be a broader effort to identify the key skills that will be required and to ensure that existing Biotechnology/Pharmaceutical Science or, other cognate disciplines are adjusted to also contribute to this effort. A program organized through SFI or, other agencies would also be useful.

6.6 AN INDUSTRIAL SUPPORT SYSTEM THAT ENCOURAGES "START-UP" COMPANIES IN THIS FIELD.

6.6.1 RATIONALE:

It is clear from the analysis of the ATMP development programs in various other jurisdictions that there is a general recognition that systems needs to be put in place that support the development of new spin off companies from academic research. Ireland will need to adapt its systems to support new companies in this area through their early foundation and development within the ATMP ecosystem

6.6.2 ACTIONS:

There are already various supports available through IDA and EI to support high potential start ups and disruptive technologies. Indeed, the Dept of Enterprise Trade and Employment's €500 million Disruptive Technologies Innovation Fund (DTIF) is already supporting some projects in this space. This and similar initiatives need to be further expanded with a specific bias towards the ATMP area going forward with the remit to enable an ATMP ecosystem.

6.7 CCMI SPECIFIC RECOMMENDATIONS

6.7.1 RATIONALE:

In light of CCMI being currently licensed by HPRA for clinical ATMP production and the criticality of such licensed GMP grade ATMP cell therapy manufacturing facility to an effective ATMP ecosystem CCMI must be retained and indeed strengthened in the future so that it can undertake a full role and ideally expand its capabilities to include other categories of ATMPs in addition to cell therapies.

6.7.2 ACTIONS:

6.7.2.1 CCMI needs to develop a clear vision of its mission and develop an ambitious 3-5 year strategy to roadmap its trajectory and funding/income stream. This mission should build on its successes to date as a cGMP facility and existing expertise in clinical trial batch manufacture is a valuable asset that needs to be nurtured

6.7.2.2 CCMI needs to ensure that this mission and its implications are clearly understood by all potential partners and interested parties.

6.7.2.3 CCMI needs to engage a Business Development Director as part of its senior management team with the specific responsibility to develop and implement a Business Plan which captures the new mission/ vision that will enable CCMI to achieve its full potential as a core component of a strong ATMP ecosystem.

6.7.2.4 CCMI Leadership should develop a Governance system for the organisation that will enable and drive its activities as a true designated centre with wider collaborations in Ireland (or further afield) and supportive of the existing activities of other participants in the ATMP ecosystem (e.g. NIBRT's CGT working groups).

6.7.2.5 CCMI Leadership should actively promote learning from other ATMP-research active countries and seek to be part of a cluster / hub model (ATTC, NecstGen, CCRM Nordic models)

6.7.2.6 CCMI leadership should explore further options outside core GMP offerings, in particular options to provide training needs of industry/academia that are not/will not be met by NIBRT.

6.7.2.7. CCMI leadership should seek to build on previous funding successes and explore further funding options with a focus on the DTIF scheme (or similar). These opportunities will help further cement CCMIs position as the cGMP cell manufacturing facility of choice for academic /early stage clinical development.

7. ABBREVIATIONS

7. ABBREVIATIONS

AIAT	Andalusian Initiative for Advanced Therapies
ARDAT	Accelerating Research and Innovation for Advanced Therapies
ARM	Alliance for Regenerative Medicine
ATMP	Advanced Therapy Medicinal Product
ATTC	Advanced Therapeutic Treatment Centre
BCPI	BioPharmaChem Ireland
CABIM	Center for Advanced Biological Innovation and Manufacturing
CAR T	Chimeric Antigen Receptor T cell
CAR-iNKT	(CAR)-engineered invariant natural killer T cells
CCMI	Centre for Cell Manufacturing Ireland
CCRM	Centre for Commercialization of Regenerative Medicine
CDMO	Contract Development and Manufacturing Organisation
cGMP	Current Good Manufacturing Practice
CGT	Cell and Gene Therapy
CMaT	Center for Cell Manufacturing Technologies
CMO	Contract Manufacturing Organisation
CPD	Continuing Professional Development
CRF	Clinical Research Facility
CTs	Clinical Trials
DBEI	Department of Business, Enterprise and Innovation
DTIF	Disruptive Technologies Innovation Fund
EI	Enterprise Ireland
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDI	Foreign Direct Investment
GMRS	Governance, Management and Support of Research
GMP	Good Manufacturing Practice
HE	Hospital Exemption
HEI	Higher Education Institution
IATA	Iniciativa Andaluza en Terapias Avanzadas
IDA	Industrial Development Agency
IPHA	Irish Pharmaceutical Healthcare Association
IPPOSI	Irish Platform for Patient Organisations, Science & Industry
hMSC	human Mesenchymal Stem Cells

HPRA	Health Products Regulatory Authority
HRB	Health Research Board
IMI	Innovative Medicine Initiative
LBSP	Leiden Bio Science Park
LERO	Irish Software Research Centre - an SFI centre
LERU	League of European Research Universities
LUMC	Leiden University Medical Centre
MHRA	Medicines and Healthcare Products Regulatory Agency
MIA	Manufacturer's Importer's Authorisation
MNC	Multi-national Corporation
NCMC	National Cell Manufacturing Consortium
NecstGen	Netherlands Center for the Clinical Advancement of Stem Cell & Gene Therapies
NIBRT	National Institute for Bioprocessing Research and Training
PI	Principal Investigator
rDNA	Recombinant DNA
REMEDI	Regenerative Medicine Institute
RISE	Research Institutes of Sweden AB
SE	Subject matter Expert
SFI	Science Foundation Ireland
SMA	Spinal Muscular Atrophy
SME	Small to Medium Enterprise
SRSP	Structural Reform Support Programme
SSPC	Synthesis and Solid State Pharmaceutical Centre – an SFI centre
TTMI	Trinity Translational Medicine Institute

8. APPENDICES

Appendix 1: Adapted from a PWC briefing paper produced for BioPharma Ambition March 2020

	Ireland	Netherlands	USA	Canada	Sweden	UK	Ireland's Position
Supportive Clinical Trial Environment	9 CT instigated in past 5 years Review time up to 180 days Launch of new Governance framework for research HSE	Approx 50 on-going ATMP trials	550 of the estimated 1200 current ATMP clinical trials[50]	More than 200 ongoing ATMP trials	MPA (Swedish Regulator) have recruited an ATMP coordinator to allow increased collaboration with national actors in relation to sharing information and knowledge.	154 ongoing trials (2020) 12% of all global ATMP trials[51] ATTC networks [52] ARDAT	Lagging
Favourable Tax Environment and R&D Incentives	12.5% corporate tax rate* 25% R&D tax credit Knowledge development box	Innovation box R&D tax credits up to 25% (sliding scale)		Scientific Research and Experimental Development (SR&ED) tax credit (volume)- 35% up to a maximum of $3M (Can)	Sweden is placed below the OECD average in terms of total government support to business R&D as a percentage of GDP[53]	17% Corporate tax rate R&D tax credits Patent box	Leading
Excellence in Academic and Clinical Research	NIBRT CCMI TTMI CURAM/SSPC Newly launched Research Governance Framework (HSE)	NecstGen RegMed XB	World leading academic /hospital groups	CCRM	CCRM Nordic	ATTC network of iMatch Midlands Wales Northern Alliance	Lagging

50 https://oximio.com/the-logistics-of-extending-the-footprint-of-advanced-therapy-trials/
51 https://ct.catapult.org.uk/clinical-trials-database
52 https://www.theattcnetwork.co.uk/
53 https://www.oecd.org/sti/rd-tax-stats-sweden.pdf

	Ireland	Netherlands	USA	Canada	Sweden	UK	Ireland's Position
Strong funding for entrepreneur and Startups	N/A		$11.8 Billion raised in 2020 by US headquartered companies BioElevate		Coordinated targeted approach in ATMPs (under ATMP Sweden umbrella). Proposed spend of €50M on CCRM Nordic	£0.85 Billion raised by UK ATMP companies in 2018	Lagging
High Quality Manufacturing Facilities		NecstGen GMP facility will contain 8 class B spaces, 2 class C spaces, and a QC laboratory. 4,000 square metres in total.	Numerous initiatives	Numerous initiatives including Alberta Cell Therapy Manufacturing The Ottawa Hospital's Biotherapeutics Manufacturing Centre	GMP compliant cell therapy production (10 cleanroom suites) and gene therapy production (4 production suites), in total approximately 2000 m2. **	20,000m2 footprint 25 manufacturing facilities including Catapult	Lagging
Dynamic Innovation Ecosystem	Small number of companies in this space	12 companies developing ATMPs	Over 500 companies developing ATMPs Landmark Bio	Approximately 20 companies developing ATMPs CCRM	19 companies developing ATMPs	33 companies developing ATMPs	Lagging

*Due to change to 15%

Appendix 2: Cell Manufacturing Facilities Academic-based

Name	Location	GMP	Business Model	Funding	Facilities	Other Information	Collaborators
CCMI	Galway	Yes	Grant funding and 150k per annum from College of Medicine, Nursing and Health Sciences (CNMHS)	Reddstar (FP7) Visicort (FP7) (€1 million approx.) Nephstrom (H2020) (€1 million approx.) ADIPOA2 (H2020) (€1 million approx.) DTIF (€1.3 million) Factor Bioscience Inc. (€125K)	250m2 cleanroom facility Two independent production suites (Suites 1 & 2) Each suite has 3 production cleanrooms meeting Grade A/B Suite 1 operates under positive pressure, while Suite 2 operates under negative pressure Self-generating LN2 plant In house QC lab- Rapid sterility, rapid mycoplasma, rapid endotoxin, Flow Cytometry, Karyology. In house microbiology laboratory		Charité Research Organisation GmbH, Galway Blood and Tissue Establishment Interdivisional GMP Facility Leiden University Medical Centre Istituto di Ricerche Farmacologiche Mario Negri CHRU Montpellier Factor Bioscience Inc. Onk Biotherapeutics
NecstGen[54]	U Leiden, Netherlands	Yes	PPP	€17million from Dutch govt[55] €2million from Zuid Holland govt [56]	8 Class B rooms, 2 Class C rooms and a QC laboratory, and will cover a total of 4,000 m2		CCRM (Toronto) RegMedXB

54 "new facility will allow the Netherlands to remain independent of foreign initiatives and will strengthen the national biotechnology ecosystem"

55 Dutch cabinet announced the investment of €56 million into the establishment of a "pilot factory" for regenerative therapies. NecstGen and three other facilities will form a chain covering the development and manufacturing of cell therapies, biomaterials, microtissues and macrotissues. The funding is awarded to RegMed XB, a collaboration of research institutes, governments, provinces, health funds, and industry in the Netherlands and Flanders aimed at the development of regenerative therapies and technologies. This funding is from the "Growthfund for Regenerative Medicine"

56 https://www.zuid-holland.nl/actueel/nieuws/mei-2021/e2-miljoen-innovatieve-geneeskunde-leiden-bio/

Name	Location	GMP	Business Model	Funding	Facilities	Other Information	Collaborators
Fraunhofer	Various	Yes	PPP		3 GMP facilities 10 separate clean room suites (21 clean room grade B manufacturing rooms) 120 staff	Further details of equipment/facilities[57]	
Centro di Medicina Rigenerativa 'Stefano Ferrari'	U Modena	Yes	PPP	€13 million	2000 sq meters GMP facility containing 17 independent Class B rooms	Run by a University spin-off; Holostem Terapie Avanzate	
UCSF	UCSF's Mission Bay campus	Yes	PPP		44,000-square-foot, state-of-the-art cell therapy development, manufacturing and collaboration centre[58]	Expected to open in 2022 The site will offer clinical and commercial cGMP cell therapy manufacturing services, along with associated technology development support, to UCSF and other partners.	Thermofisher
Andalusian Network for the Design and Translation of Advanced Therapies	Across a number of locations in Andalusia	Yes	Government funded		12 GMP laboratories belonging to the Andalusian Public Health System across a number of locations [59]		

57 https://www.izi.fraunhofer.de/en/departments/leipzig-location/gmp-cell-and-gene-therapy/equipment.html
58 https://thermofisher.mediaroom.com/2021-05-19-Thermo-Fisher-Scientific-and-University-of-California,-San-Francisco-to-Open-Cell-Therapy-cGMP-Manufacturing-and-Collaboration-Center
59 https://www.sspa.juntadeandalucia.es/terapiasavanzadas/index.php/es/

Name	Location	GMP	Business Model	Funding	Facilities	Other Information	Collaborators
Landmark Bio	Watertown MA	Yes	PPP	$76 million	40,000 sq ft facility GMP manufacturing capacity in approximately eight cleanrooms for the production of cell and viral vector products and other related raw materials that may be used for phase 1 or phase 2 clinical trials.	FUJIFILM Corporation, will provide GMP contract process development and manufacturing services as part of its role in the new manufacturing and innovation center. Formerly the Center for Advanced Biological Innovation and Manufacturing	Harvard, MIT, Fujifilm Diosynth Biotechnologies, Cytiva and a number of hospitals
TTMI (TCD)/ CRF	St James, Dublin	Yes – for compounding for gene therapy clinical trials.	Funding sources include Wellcome HRB		725m2 research facilities Genome sequencing lab High content analysis and LBCAM Bioresource unit Biobanking facilities Category 3 lab Flow cytometry[60]		

60 https://www.tcd.ie/strategy/documents/trinity-st-james-cancer-institute-booklet.pdf

Name	Location	GMP	Business Model	Funding	Facilities	Other Information	Collaborators
CCMI	Galway	Yes			250m2 cleanroom facility Two independent production suites (Suites 1 & 2) Each suite has 3 production cleanrooms meeting Grade A/B Suite 1 operates under positive pressure, while Suite 2 operates under negative pressure Self generating LN2 plant In house QC lab- Rapid sterility, rapid mycoplasma, rapid endotoxin, Flow Cytometry, Karyology. In house microbiology laboratory		
CCRM Nordic*	Sweden	Yes	PPP		Modular bioanalysis and process development laboratory, approximately 1000 m2 GMP compliant cell therapy production (10 cleanroom suites) and gene therapy production (4 production suites), in total approximately 2000 m2.		CCRM

* Proposed spend/design

**Proposed under CCRM Nordic plan.

Appendix 3: ATMPs with Marketing Authorisation by the FDA or EMA

Therapeutic	Company	Indication	Allogeneic or Autologous	FDA /EMA approval	MA date
ABECMA (idecabtagene vicleucel)	Celgene Corporation, a Bristol-Myers Squibb Company	Adult patients with relapsed or refractory multiple myeloma	B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell	FDA	March 2021
Alofisel	Takeda	Complex perianal fistulas in adult patients with Crohn's Disease	Allogeneic stem cells	EMA	March 2018
ALLOCORD (HPC, Cord Blood)	SSM Cardinal Glennon Children's Medical Center	Used in unrelated donor hematopoietic progenitor cell transplantation procedures	Allogeneic cord blood hematopoietic progenitor cell therapy	FDA	2013
BREYANZI (Liso CEl in EMA)	Juno Therapeutics, Inc., a Bristol-Myers Squibb Company	Adult patients with relapsed or refractory large B-cell lymphoma	CD19-directed genetically modified autologous T cell immunotherapy	FDA	Feb 2021
CLEVECORD (HPC Cord Blood)	Cleveland Cord Blood Center	Used in unrelated donor hematopoietic progenitor cell transplantation procedures	Allogeneic cord blood hematopoietic progenitor cell therapy	FDA	Sept 2016
Ducord, HPC Cord Blood	Duke University School of Medicine	Used in unrelated donor hematopoietic progenitor cell transplantation procedures	Allogeneic cord blood hematopoietic progenitor cell therapy	FDA	2012
GINTUIT	Organogenesis Incorporated	Topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	FDA	2011

Therapeutic	Company	Indication	Allogeneic or Autologous	FDA /EMA approval	MA date
HEMACORD (HPC, cord blood)	New York Blood Center	Used in unrelated donor hematopoietic progenitor cell transplantation procedures	Allogeneic cord blood hematopoietic progenitor cell therapy	FDA	2011
HOLOCAR	Chiesi	Limbal stem-cell deficiency	Ex-vivo autologous stem cell / tissue engineered product	EMA	Feb 2015
HPC, Cord Blood	Clinimmune Labs, University of Colorado Cord Blood Bank	Used in unrelated donor hematopoietic progenitor cell transplantation procedures	Allogeneic cord blood hematopoietic progenitor cell therapy	FDA	2011
HPC, Cord Blood - MD Anderson Cord Blood Bank	MD Anderson Cord Blood Bank	Used in unrelated donor hematopoietic progenitor cell transplantation procedures	Allogeneic cord blood hematopoietic progenitor cell therapy	FDA	July 2018
HPC, Cord Blood - LifeSouth	LifeSouth Community Blood Centers, Inc.	Used in unrelated donor hematopoietic progenitor cell transplantation procedures	Allogeneic cord blood hematopoietic progenitor cell therapy	FDA	2013
HPC, Cord Blood – Bloodworks	Bloodworks	Used in unrelated donor hematopoietic progenitor cell transplantation procedures	Allogeneic cord blood hematopoietic progenitor cell therapy	FDA	2016
IMLYGIC (talimogene laherparepvec)	BioVex, Inc., a subsidiary of Amgen Inc.	Melanoma	Gene therapy	FDA EMA	Oct 2015 Oct 2015

Therapeutic	Company	Indication	Allogeneic or Autologous	FDA /EMA approval	MA date
KYMRIAH (tisagenlecleucel)	Novartis Pharmaceuticals Corporation	Chronic lymphoid leukemia and diffuse large B-cell lymphoma in patients Adult patients with relapse/ refractory (r/r) large B-cell lymphoma,	Autologous CAR T	FDA EMA	2017/18 2018
LAVIV (Azficel-T)	Fibrocall Technologies	Nasolabial fold wrinkles in adults	Autologous cell therapy	FDA	2011
LUXTURNA	Spark Therapeutics, Inc.	Treatment of patients with vision loss due to a genetic mutation in both copies of the RPE65 gene	Gene therapy (AAV)	FDA EMA	2017 Nov 2018
MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane)	Vericel Corp.	Repair of symptomatic, full-thickness cartilage defects of the knee in adult patients	Autologous Cultured Chondrocytes on a Porcine Collagen Membrane	FDA	Dec 2016
PROVENGE (sipuleucel-T)	Dendreon Corp.	Patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC)	Autologous cellular immunotherapy	FDA EMA	2010 Withdrawn 2015
RYPLAZIM (plasminogen, human-tvmh)	Prometic Biotherapeutics Inc.	Patients with plasminogen deficiency type 1	Plasma-derived human plasminogen	FDA	June 2021
SPHEROX	CO.DON	Knee cartilage defects	Autologous cell therapy	EMA	July 2017
SKYSONA	bluebird bio	Adrenoleukodystrophy	Autologous gene therapy	EMA	July 2021

Therapeutic	Company	Indication	Allogeneic or Autologous	FDA /EMA approval	MA date
STRATAGRAFT	Stratatech Corporation	Adult patients with thermal burns containing intact dermal elements	Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen – dsat	FDA	June 2021
TECARTUS (brexucabtagene autoleucel)	Kite Pharma, Inc.	Treatment of adults with mantle-cell lymphoma (MCL)	Autologous CAR T	FDA EMA	July 2020 Jan 2021
STRIMVELIS	Orchard (originally developed by GSK)	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)	Autologous gene therapy	EMA	May 2016
YESCARTA (axicabtagene ciloleucel)	Kite Pharma, Incorporated	Diffuse large B-cell lymphoma (DLBCL); Primary mediastinal large B-cell lymphoma (PMBCL)	Autologous CAR T	FDA EMA	Oct 2018 Aug 2018
ZOLGENSMA (onasemnogene abeparvovec-xioi)	AveXis, Inc.	Spinal muscular atrophy	Gene therapy	FDA EMA	Mar 2019 May 2020

Reference sources[61]

61 https://alliancerm.org/available-products/, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

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