

## INNOVATIVE MEDICINES INITIATIVE CONSULTATION ON FACILITATING THE TRANSLATION OF ADVANCED THERAPIES TO PATIENTS IN EUROPE

### 1. INTRODUCTION

- 1.1. The Association of the British Pharmaceutical Industry (ABPI) welcomes the opportunity to submit comments to the open consultation that will inform the future selection of an IMI ATMP portfolio of projects to be launched from 2017 onwards.
- 1.2. The ABPI represents innovative research-based biopharmaceutical companies, large, medium and small, working to bring life-saving and life-enhancing medicines to patients. Our members supply 90 per cent of all medicines used by the UK National Health System (NHS), and are researching and developing over two-thirds of the current medicines pipeline, making sure that the pharmaceutical industry remains a core government focus and keeping the UK at the forefront of disease prevention and cure.
- 1.3. The comments submitted focus on the identification of key challenges across the journey from science to the market and patients. These are based on the consolidated inputs from its member companies as well as ABPI's contributing role in a number of key UK initiatives on ATMPs. The latter include the recently launched ministerial **Advanced Therapies Manufacturing Taskforce**<sup>1</sup> and the UK **Medicines Manufacturing Industry Partnership (MMIP)**<sup>2</sup> established jointly by the UK Government and the biopharmaceutical industry in 2014.
- 1.4. The responses contained herein are tabulated, so that the IMI's consultation project recommendations can be vetted against key incentives for industry investments, short versus long-term solutions and the key advantages that work with IMI presents, alongside any independent company and/or country activities.
- 1.5. **ABPI recognises the strong momentum to roll out an IMI program on ATMPs, as a priority area for 2017 onwards and we endorse the four areas identified as key enablers for the field's progression, namely preclinical development, clinical development, manufacturing and market access (including pricing and reimbursement).** We also feel that the UK can play a pivotal role in future IMI led collaborative efforts and we have laid out a number of strong leverage points, as well as suggestions on ongoing initiatives that the UK can contribute in this respect.
- 1.6. We recommend that the four key areas are addressed through separate initiatives and we have used this submission to further explore the particular issues to be discussed in relevant scoping actions for future calls. However, since ATMP discovery, development, manufacturing and licensing/coverage assessment steps are less linear and predictive than traditional drug discovery we also recommend the development of an overarching framework for the coordination of the different ATMP initiatives, to ensure that outputs can progress the entire pathway from discovery to delivery of these transformative products
- 1.7. Given the complex and cross-disciplinary nature of the ATMP space, we also recommend that any future IMI initiatives on ATMPs should consider mapping out, as well as including all the stakeholders necessary to strengthen the joint efforts of industry with academia, at the outset. Finally, an important step towards the success of any future projects will entail leveraging the

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<sup>1</sup> Industry taskforce launched to secure the future of manufacturing advanced therapy medicines in the UK <http://www.abpi.org.uk/media-centre/newsreleases/2016/Pages/230316.aspx>

<sup>2</sup> <http://www.abpi.org.uk/our-work/mmip/Pages/default.aspx>

experience and successes of previous and ongoing IMI consortia, which could be expanded, linked or adapted, to inform the nascent space of ATMP's.

## **2. TIMELINESS AND URGENCY FOR ACTION**

- 2.1.** The field of Advanced Therapy Medicinal Products (ATMP's), classified per the European regulation EC1394/2007, comprises a diverse group of novel treatment approaches, covering cell therapies, gene therapies, and tissue engineered products. To match the focus of the IMI's consultation document, we are mainly concentrating on cell and gene therapy products, as these are of most relevance to our members.
- 2.2.** One of the distinctive characteristics of this diverse field, is the unprecedented promise for long-term management and even cure of disease, especially in areas of high unmet medical need like cancer, genetic disorders and rare diseases. Based on recent publications from the Alliance for Regenerative Medicine, over 550 clinical trials were on ATMPs in 2015<sup>3</sup>. Under that purview, the socioeconomic and patient benefits of building an ATMP enterprise could be immense, as the recent volume of investment, especially in gene therapies for rare diseases and immuno-oncology further demonstrate.
- 2.3.** Although the field was historically kept largely within the confines of academia and small, often spin-out companies, the recent uptick in promising clinical results, predominantly in immuno-oncology trials<sup>4,5</sup>, and the success of treatments like the ADA-SCID therapy, has prompted biopharmaceutical companies to focus more on developing experience in the field, often via collaborations. Signs of a maturing global ATMP ecosystem are certainly on the horizon, with a current estimate of more than 700 companies in the space generating a combined market cap of \$10bn globally.<sup>6,7</sup>
- 2.4.** The biopharmaceutical industry recognises this potential, demonstrated by the recent increase in ATMP products in the industry's pipeline, as well as in the number of acquisitions, joint ventures and collaborations<sup>8</sup>. Strimvelis, developed by GSK, one of ABPI member companies, is one recent success example. The product received a Positive Opinion for the treatment of ADA-SCID on April 2016, making it the first gene therapy authorized for any form of SCID (severe combined immunodeficiency), a rare and life-threatening genetic disorder that leaves children without a functioning immune system.
- 2.5.** However, clinical successes currently emerging are the outcome of decades of trial and error that oftentimes fuelled genuine concern among the research and commercial communities that these treatments would never become a reality. And still, to date only 6 ATMPs have been granted a marketing authorization in the EU, with two withdrawn from commercial activities due to lack of clinical uptake<sup>9</sup>.

## **3. IMPORTANCE OF PRECOMPETITIVE COLLABORATION**

- 3.1.** Of key importance in scoping this emerging sector is the realization that ATMP discovery, development, manufacturing and licensing/coverage assessment steps are less linear and

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<sup>3</sup> The Alliance for Regenerative Medicine; <http://alliancerm.org/page/clinical-trials-products>, accessed 16/05/16.

<sup>4</sup> Keys to the CAR, Bass 2014, SciBx 7(25)  
<http://www.nature.com/scibx/journal/v7/n25/full/scibx.2014.725.html>

<sup>5</sup> Paving the Road Ahead for CD19 CAR T-cell Therapy, Nellan and Lee 2015, Current Opinion in Haematology 22:516-520 [http://journals.lww.com/co-hematology/Abstract/2015/11000/Paving\\_the\\_road\\_ahead\\_for\\_CD19\\_CAR\\_T\\_cell\\_therapy.10.aspx](http://journals.lww.com/co-hematology/Abstract/2015/11000/Paving_the_road_ahead_for_CD19_CAR_T_cell_therapy.10.aspx)

<sup>6</sup> Proteus Regenerative Medicine; <http://proteus.18birds.com/about-us12>, accessed 19/07/16

<sup>7</sup> Alliance for Regenerative Medicine; <http://alliancerm.org/page/industry-snapshot>, accessed 19/07/16

<sup>8</sup> Proteus Regenerative Medicine; <http://www.proteusvp.com/about-us12>, accessed 16/07/16

<sup>9</sup> Summary Review on ATMPs Approved in the EU <https://ct.catapult.org.uk/news-events-gallery/news/summary-review-atmps-approved-eu/>

predictive than traditional drug discovery for small chemical assets or large biomolecules. Manufacturing and quality aspects have to be considered much earlier in discovery, while clinical assessment and adoption are seamlessly linked, posing a number of unique and unprecedented challenges in securing patient and market access.

- 3.2.** Examples like Provenge and Chondroselect highlight the unique intricacies of the field, whereby scientific understanding, policies, skills, and services are largely co-evolving with the technology, in real-time. Alongside the many persisting scientific and technical gaps, the lack of prior clinical experience calls for a shift from traditional predictive approaches to real-time monitoring of development and treatment outcomes to increase confidence in benefit/risk criteria. This often leaves current ATMP innovators having to simultaneously tackle regulatory complexity and manufacturing variability, negotiate complex reimbursement models and HTA criteria, while maintaining access to R&D support mechanisms.
- 3.3.** As a result, securing patients' access to these therapies requires a more coordinated approach to product development across the entire value chain; from discovery, to clinical development, manufacturing, as well as delivery to the market and the cycle of care. Another practical aspect is that many of these activities are more co-located than in established supply and operational chains in medicines manufacture. This calls for an unparalleled level of coordination among players not traditionally connected; from academic innovators and manufacturers, to regulators, HTA assessors and patients, among others.

#### **4. MAKING A DIFFERENCE THROUGH THE IMI**

- 4.1.** As a result, not only should the key challenges and opportunities for ATMPs be considered holistically, but actioned through ever stronger partnership and coordination between stakeholders in research, clinical delivery, and manufacturing. With a number of other prominent global players like USA and Japan investing heavily in pioneering flagship research programmes, like the US Cancer Moon-shot 2020 in Immuno-oncology<sup>10</sup>, it is paramount that Europe continues its investment and collaboration to address the complexity of underpinning scientific, translational and adoption challenges. This is key to maintaining a globally competitive position on the discovery and commercialization of ATMPs, attract investment, and reap the offerings from a rapidly growing industry for the benefit of its patients and the economy.
- 4.2.** Moreover, science and research intelligence in this field reside within both universities and company R&D divisions. However, this know-how is largely unconnected and spread across European countries. A key step in gaining momentum depends on building a strong community that can enable knowledge and skill transfer, both between academic and commercial entities, but also across member states. It could also enable easier sharing of materials, as has been the case with IMI's EBISC and StemBANCC pioneering stem cell projects.
- 4.3.** The IMI, as the world's largest public private partnership in the life-sciences currently, is in a unique position to provide a safe-haven environment and join up all key stakeholders in addressing the magnitude and complexity of ATMP challenges. With a strong legacy of more than 70 IMI1&2 projects, it also holds a wealth of knowledge on the multidisciplinary inputs needed across a variety of disease and scientific areas, from rare diseases and antimicrobial resistance, to novel data systems and real-world outcome monitoring, that can be repurposed to inform the ATMP space.
- 4.4.** The fact that UK organisations are currently leading the initial two IMI projects in stem cell science (EBISC and StemBANCC) validate both the UK's prominence in this field and its support to EU-wide initiatives that can propel the field's clinical and commercial potential. Besides

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<sup>10</sup> <http://www.cancermoonshot2020.org/>

enabling collaboration between industry and academia, important synergies can also be leveraged through linkage with existing IMI and other national initiatives and partnerships, such as the many included in the UK's growing ATMP ecosystem.

## 5. UK'S STRONG ATMP FOUNDATIONS AND INVESTMENT

5.1. The UK historically holds a world-leading research legacy in this field, exemplified by a number of Nobel Prize winners, with most recent addition the 2012 Nobel Prize in Physiology or Medicine awarded jointly to Sir John Gurdon. Building off of these foundations, the UK has been investing significantly in cell and gene therapy research, translation, manufacturing, and associated infrastructure, through a number of public and private initiatives and investments that continue to enhance its global position in the space.

### 5.2. Government strategy:

5.2.1. The commitment of the UK government in this field was recently accented through the launch of the **Ministerial Taskforce on ATMP Manufacturing**, a short-term group exploring how to leverage existing strengths to build up the manufacturing and associated supply chains for these therapies in the UK. The taskforce was established through the stewardship of the **Medicines Manufacturing Industry Partnership (MMIP)**, a public-private partnership including the ABPI, BIA and UK's top industry manufacturers.

5.2.2. The **Regenerative Medicines Expert Group (RMEG)** was also established in 2014 to develop a roadmap for ATMP delivery to the UK National Health Service (NHS), assessing its preparedness for adoption and delivery, as well as the current status of policy and regulation. Its initial 2014 report produced a number of key recommendations, several of which are already being tested, notably the **NICE mock technology appraisals**. An update from RMEG on progress in the UK was published in March 2016.<sup>11</sup>

5.2.3. The **Accelerated Access Review (AAR)**, is a new government scheme that aims to speed up uptake and access to innovative drugs, therapeutics and diagnostics for NHS patients. ATMPs are amongst the key examples considered in this work. An interim report on AAR work to date was also published in March 2016<sup>12</sup>.

### 5.3. Science and research

5.3.1. The **UK Regenerative Medicine Platform programme (UKRMP)**<sup>13</sup>, is a £25M joint initiative by the UK's Medical Research Council (MRC), Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC). The UKRMP has established 5 interdisciplinary research hubs that have the critical mass and expertise to address key knowledge-gaps in the translation of basic discovery towards novel ATMPs applications.

5.3.2. Moreover, the Research Councils alongside **Innovate UK's program in Regenerative Medicine and Cell therapies**, have made a number of additional significant investments in the space, including the **Edinburgh Centre for Regenerative Medicine** and the **Cambridge Stem Cell Institute**, the establishment of the £13M **Welcome Trust/MRC Human Induced Pluripotent Stem Cell Initiative (HipSci)**, as well as the launch of 3 **Centres for Doctoral Training in Regenerative Medicine** (funded jointly by EPSRC/MRC).

### 5.4. Translation and clinical development

5.4.1. On a similar ground, the UK is well positioned to lead in the translation of ATMP science into the clinic, with a number of world-leading centres and initiatives. The **Cell and Gene**

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<sup>11</sup> <https://www.gov.uk/government/publications/regenerative-medicine-a-uk-pathway>

<sup>12</sup> <https://www.gov.uk/government/publications/aar-interim-report-feedback>

<sup>13</sup> <http://www.ukrmp.org.uk/>

**Therapy Catapult (CGTC)**<sup>14</sup> comprises a long-term investment of the UK government in building national capacity and infrastructure to propel this field through to clinical and commercial application. Through a number of in-house science, translation, manufacturing and market experts, the Catapult has been working across academia and the commercial base to support and accelerate the translation of these therapies into the clinic.

5.4.2. A number of European and global translational partnerships are also being pursued by UK based companies. Examples include the strategic collaboration of GSK with Milan based Ospedale San Raffaele (OSR) and Fondazione Telethon on the joint development of Strimvelis, as well as several partnerships and joint ventures of the CGTC with European companies (ie. Tx-Cell, France)<sup>15</sup> or the Centre for Commercialization of Regenerative Medicine (CCRM) in Canada<sup>16</sup>.

5.4.3. Besides its research and translational foundations, the UK has also been focusing on driving the necessary regulatory adaptations, actioned through the global leadership role of the **Medicines and Healthcare products Regulatory Agency (MHRA)**. Following the recommendations of the RMEG report, the MHRA proceeded to simplify its regulatory offering, through a '**one stop shop**' that converges all major UK regulators in the field. These include the Health Research Authority (HRA), the Human Tissue Authority (HTA), the Human Fertilisation and Embryology Authority (HFEA) and the MHRA, to provide a consolidated and coherent advice to ATMP developers.

5.4.4. In addition, the MHRA's **National Institute for Biological Standards and Control (NIBSC)**, whose new Chief Executive, Dr Christian Schneider, is one of Europe's leading experts on regenerative medicines, has been playing an early and proactive role in supporting this fledgling industry, focusing on a number of stem cell banking projects, as well as on the development of new standards, guidelines and reference materials.

5.4.5. The **MHRA's Innovation Office** is also a valuable novel platform for navigating existing flexibilities for innovative product development, through earlier and comprehensive regulatory discussions.

5.4.6. Moreover, with its **National Institute for Health Research (NIHR)** the UK has been also preparing to facilitate clinical research in this field.

## 5.5. Manufacturing:

5.5.1. The scale up, quality assurance and consistency of ATMP manufacturing are extremely complex challenges, requiring the convergence of multiple scientific fields outside biomedicine. UK has been traditionally strong in these areas, with a number of universities combining innovations and know-how in biology with engineering; the University of Sheffield Advanced Manufacturing Research Centre, the Bioprocess Engineering centre at UCL, and the Loughborough EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, providing just a few examples.

5.5.2. More recently, Innovate UK has committed additional funding to establish a **National Cell Therapy Manufacturing facility in Stevenage**, through the CGTC.

## 5.6. Market Access

5.6.1. Any progress, as well as investment in this breakthrough sector ultimately has to give rise to meaningful socioeconomic and healthcare outcomes, calling for greater readiness of the HTA, reimbursement, and health delivery systems in Europe to adopt and apply these

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<sup>14</sup> <https://ct.catapult.org.uk/>

<sup>15</sup> <https://ct.catapult.org.uk/wp-content/uploads/2016/03/The-Cell-Therapy-Catapult-Annual-Review-2015.pdf>, accessed 19 July 2016

<sup>16</sup> <https://ct.catapult.org.uk/working-with-us/our-partnerships/>, accessed 19 July 2016

treatments. The UK's **National Institute for Health and Care Excellence (NICE)** has been proactive in exploring the evaluation ATMPs using existing and proposed frameworks, through their recent **mock technology appraisals**. Notwithstanding these proactive approaches, the above issues will still need to be progressed to resolution if the HTA environment is to be fully ready to appraise ATMPs in a timely manner and with a reasonable chance of success.

## 6. INPUT IN THE PRELIMINARY RECOMMENDATIONS FROM THE IMI CONSULTATION

### 6.1. Science and preclinical development

<p><b>Challenges identified by the IMI workshop:</b></p> <p>The bulk of suggestions focused mainly on gene therapy and the need to develop a novel toolkit to increase predictive capacity during early preclinical, PoC and PoP studies. Suggestions to bring Europe ahead of the curve in breakthrough innovations, like genome editing and cell/tissue organoids were also made.</p>	
<p><b>Additional considerations for IMI projects:</b></p> <p>A number of persisting scientific questions continue to hinder progress in the space, from stem cell niche characterization, to the elucidation of meaningful pharmacokinetic/dynamic parameters, to robust and rapid safety assessment of such therapies.</p> <p>However, realising the field's potential spans beyond continued advances in basic scientific and disease knowledge, necessitating further innovation in cell line and vector design, manufacturing and analytics.</p> <p>A recent cross-stakeholder symposium led by the <b>UK Knowledge Transfer Network<sup>17</sup></b>, identified a number of these challenges, further highlighting key opportunities to navigate the collaborative space.</p>	
<p><b>IMI proposed topics:</b></p>	<p><b>UK identified priorities:</b></p>
<p><b>New model systems, including organoids and hiPSCs</b></p>	<ul style="list-style-type: none"> <li>- <b>New <i>in vitro</i> / <i>in vivo</i> models</b> for toxicology, metabolism and biodistribution studies for ATMPs are a known gap. UK is currently focusing particularly on the application of the "3 R's concept" (replacement, refinement and reduction) to overcome animal use. The UK's NC3Rs organization<sup>18</sup> has already started working on this field, and in 2015 launched a CRACK-IT funding call, also supported by industry, to improve gene therapy preclinical risk assessment with the use of combined <i>in vitro</i> / <i>in silico</i> assays<sup>19</sup>.</li> <li>- <b>Human organoids:</b> commercial activities in this space are still limited, largely because of the gap in regulatory standards and clear qualification criteria. In light of progress already achieved by the EBISC and stemBANCC projects, there is opportunity to expand the precompetitive work between industry and academia. In the UK,</li> </ul>

<sup>17</sup> Knowledge transfer Network report: Gene Therapy, Viral Vectors and Therapeutic Vaccines Workshop, June 2015, accessed 19/7/2016

<https://connect.innovateuk.org/documents/3112383/28624028/Gene+Therapy+Viral+Vector+Workshop+Outputs/dd71e901-531d-442f-9715-9940cea9bced>

<sup>18</sup> <http://www.nc3rs.org.uk>

<sup>19</sup> <http://www.crackit.org.uk/challenge-21-inmutagene>

	<p>industry-academia consortia are already starting to form (ie. The Milner Therapeutics Institute in Cambridge, including companies like GSK, AZ and Astex Pharmaceuticals)<sup>20</sup>. <b>However, despite the rapid progress and promise of this field, it is not strictly limited to the ATMP sector and as such could provide the scope for a broader enabling project for IMI.</b></p>
<p><b>New vector systems</b></p>	<p>The design of new vector and expression systems has been proposed as a key priority for collaborative work in the UK, with 3 main focus areas:</p> <ol style="list-style-type: none"> <li>1. Improving cell targeting,</li> <li>2. Optimizing tracking and insertion studies</li> <li>3. Developing new <i>in vitro</i> models for characterization</li> </ol> <p>Successful cell targeting, for example in moving from B-cell to T-cell leukaemias or from blood to solid tumours in immuno-oncology, remains an important hurdle, calling for better exploration of vector biology and genetic engineering. This will also have to be complemented by improved transgene integration and tissue transformation studies.</p> <ul style="list-style-type: none"> <li>- Vector design elements discussed include: <ul style="list-style-type: none"> <li>o Improved understanding of basic biology to target vector longevity or single integration events.</li> <li>o Genetic engineering innovation in plasmid technology, ie. Kill switches</li> <li>o Improved dosage definition studies to predict production needs.</li> </ul> </li> </ul> <p>The latter is particularly important, as application of <b>Quality by Design</b> approaches at the early vector design stage can help overcome downstream considerations in the scalability, manufacturability and GMP bioprocessing of gene therapy products.</p> <ul style="list-style-type: none"> <li>- However, <b>IP in this space</b> is extremely crowded, traditionally deploying exclusive licensing approaches that have restricted collaboration, as well as data and knowledge sharing. Under that purview, although collaboration in the proprietary and insular space of new vector designs may be tricky, strong precompetitive opportunities still exist for the creation of a knowledge space on basic vector biology and characterization, to bridge the academic with the SME and industry communities.</li> </ul>
<p><b>Targeted gene editing</b></p>	<p><b>CRISPR/ Cas9 and nuclease systems:</b></p> <ul style="list-style-type: none"> <li>- The optimization of targeted genome editing technologies and their application in the gene therapy space holds unprecedented potential for increasing the accuracy and precision of treatments in this field.</li> <li>- Besides issues of insertional mutagenesis or transgene expression / efficiency levels that are common to all gene therapy approaches,</li> </ul>

<sup>20</sup> <http://www.cam.ac.uk/research/news/cambridge-researchers-and-pharma-in-innovative-new-consortium-to-develop-and-study-early-stage-drugs>

	<p>genome editing systems are particularly prone to off-target effects, the long-term impact of which is still poorly understood.</p> <ul style="list-style-type: none"> <li>- Value certainly exists in investigating persisting gaps in our understanding of basic biology and delivery of genome editing systems.</li> </ul>
<p><b>Regulatory considerations:</b></p>	<ul style="list-style-type: none"> <li>- The regulatory system for ATMPs presents a number of intricacies, covering a variety of different products, but also largely evolving in parallel with emerging scientific and technological progress, leaving the regulators on a steep learning curve. Still, regulators in both the UK and EU have been extremely proactive, with NIBSC / MHRA and EMA, respectively, engaging early with the ATMP communities to provide advice, clarity and support for therapy development.</li> <li>- Other leading countries in the space, like the US, Japan and Canada, have proactively set out to design regulatory pathways that accelerate approval and patient access, to maximize their global competitiveness. Therefore, it will be useful for Europe to provide the environment and funding necessary to foster the level of dialogue needed to design and test novel 'fast track' pathways, tailored to the connected nature of the ATMP space.</li> <li>- The EMA has already launched novel development schemes, such as PRIME or the Adaptive Pathways scheme, providing creative opportunities that can be further investigated and derisked through <b>new or ongoing IMI consortia</b>. Projects like <b>ADAPT-SMART</b>, currently elucidating the Adaptive Pathway paradigm, could be deployed to investigate and model ATMP use cases, to allow the prospective planning of actual regulatory approaches for the future.</li> <li>- This level of precompetitive interaction can also enhance current trends for harmonization in medicines regulation, occurring across Europe and globally. This is of particular value for manufacturing and clinical standards, as well as material sharing or the mutual recognition of testing requirements.</li> <li>- In addition, there is growing value from early dialogue and interaction, particularly in emerging and poorly understood areas like genome editing, to limit country variations around research and clinical ethics and set well rationed and proportionate boundaries and guidelines.</li> </ul>
<p><b>Additional project suggestions</b></p> <ul style="list-style-type: none"> <li>- <b>Other enabling technologies:</b> Besides organoids, a number of other technologies of key significance for the space were also identified in the UK, including new genome sequencing (NGS) platforms, microfluidics and multiple-flow cytometry assays, as well as the development of new bio/materials to enable gene and cell therapy specific processes and platform development.</li> <li>- <b>Immunology focused projects for predictive safety.</b> The natural complexity of the cellular and vector systems under development, as well as their long-term interaction with the body is an outstanding barrier. The use of basic immunological knowledge in both vector design and product discovery is significantly lagging behind. A repository of applied immunological knowledge, as well as a battery of novel assays will be necessary to</li> </ul>	



increase confidence in product development, for example to measure precision of integration or monitor transduced cells (ie. T-cells in immunotherapies).

## 6.2. Clinical:

### **Challenges identified by the IMI workshop:**

- A number of key clinical considerations have been outlined and discussed, focusing on the design of proof of concept and exploratory clinical trials, primary endpoint investigation (including dose finding), as well as secondary endpoint (biodistribution and efficacy) and new surrogate biomarker discovery.
- Trial design particulars involved building the necessary confidence for single-arm trials, as well as use of historical or disease-specific control population cohorts. Further complexities were identified, as overall benefit-risk criteria and monitoring requirements continue to be updated in light of emerging disease knowledge.
- Still, the biggest challenge remains the difference between ATMP classes, necessitating greater capacity for flexibility on a case-by-case assessment. This naturally hinders opportunities for the development of standardised and predictive regulatory pathways and frameworks. Early engagement and continuous regulatory involvement thus becomes paramount for the smooth clinical evaluation of new products.
- Still, the report was less prescriptive on theme suggestions for this stage of ATMP development. A key area for collaboration naturally comprises the use of historical and real-world evidence to compensate for the uncertainties of non-conventional clinical plans. The mapping of existing sources (ie. from registries, hospital exception and compassionate use records) and investigation of the clinical utility of resulting data packs spans beyond the capacity of single organizations, or even stakeholder groups, providing a fruitful basis for collaboration and sharing.

### **Additional considerations for IMI projects**

- Clinical assessment of ATMPs is particularly challenging, for a number of reasons.
  - First and foremost, trial designs are highly case and disease dependent, tailored for much smaller patient populations with highly irregular enrolment plans.
  - In addition, ATMPs hold the promise for life-long disease management or curative effects, calling for novel systems to monitor long-term patient and socioeconomic outcomes.
  - The range of treatment areas for these approaches is also likely to expand, as our scientific understanding of disease continues to evolve.
- ATMP's therefore call for a different approach to product R&D that requires greater and continuous evidence generation and adaptation of ongoing development and commercialization plans. For example:
  - Long-term patient follow up becomes paramount in establishing safety and efficacy evidence requirements, with a focus on real-world patient outcomes.
  - Batch specificity of ATMP products, also calls for new monitoring and tracking systems and infrastructure.
  - Regulators and industry are also asked to devise workable and forward looking models on the assessment of both anticipated and unanticipated risks (adaptive risk management frameworks).

- **ATMP registries** are of particular interest, covering not just long-term pharmacovigilance requirements, but also individual treatment batches. This point underscores the strong connectivity needed across the value chain for this field, with integrated evidence and data systems spanning from clinical to manufacturing and the real-world space.
- **Data integration** will also be important at a European level, where greater connectivity across jurisdictions may be needed to support long-term patient follow up, as well as product monitoring tracking and traceability.
- The clinical space is also linked with the ultimate adoption of ATMP products into the healthcare system, largely defining Europe’s attractiveness as a destination for investment in ATMP development. National and international reviews have been pointing out the need for the establishment of **Specialized Centres** for the clinical development and delivery of ATMP products, gathering the necessary, resources and skillsets to propel adoption<sup>21</sup>.
- Such specialized centres will require that the necessary data collection frameworks are in place to ensure that decision makers, including regulators, payers and health systems, can have adequate decision making evidence for unobstructed patient access to ATMP products.
- However, there are already learnings to be mined, as a significant proportion of ATMPs under development target rare or orphan diseases. Ongoing IMI initiatives which are investigating orphan and precision medicine applications, those looking into the use of real-world data (ie. GetREAL), the development of patient and disease registries (ie. The CSA for Big data for Better Outcomes), or the Adaptive Pathways roll-out (ADAPT-SMART) can be tailored further to include and feed back into the ATMP work.

### 6.3. Manufacturing:

- **Ecosystem-level approach:** Based on the above, ATMP manufacturing calls for seamless and coordinated innovation across the pathway from the bench to the patients; from starting material sourcing and control, to process development and assurance, to regulatory standards and GMP guidelines, as well the development of a battery of novel, fast, accurate and robust analytics.
- **IMI** is therefore presented with an opportunity, and challenge, to identify manageable chunks of manufacturing activities (or themes) and provide the safe-haven platforms for actors from different organizations, stakeholder groups and disciplines to come together and drive the necessary technological innovations and integrated systems.
- **Convergence points should also be leveraged by future consortia;** a good example is the development of novel characterization assays, which can impact both initiatives for product development, but also those on process maturation.

#### **Challenges identified by the IMI workshop:**

A number of areas were proposed:

<sup>21</sup> Building on our own potential: a UK pathway for regenerative medicine. A report from the Regenerative Medicine Expert Group, 2014 (pg 19)

- A **'Bioforum'** to investigate persisting issues around the scalability, industrialization, consistency and variability characteristic of ATMP manufacturing was proposed. Indicative issues included raw material and reagents supply and quality control, as well as GMP guidelines and new engineering and production skill sets.
- Initiatives to tackle issues around bioprocess development and scalability were also suggested. This would involve the integration of robotic, automation and closed engineering systems, as well as analytics technology for process measurement and QC control, especially at the micro-level.
- The paper also addressed product variability in ATMPs, looking at specific gaps in cell and gene therapy manufacturing:
  - Viral vector production and characterization: a collaborative platform developing innovative tools for vector production, purification and characterization, including expansion into regulatory standards on safety, stability, robustness and validation.
  - Cell Therapy manufacturing (including adult stem cells, iPSCs, T-cells, etc), looking at cell variability and quality control aspects.
  - A consortium on the investigation of immunogenic properties of cell effectors was suggested, probably also feeding into work around the development of 'universal cell platforms' for allogeneic cell therapy.

#### **Additional comments – the opportunity for precompetition**

- **Innovation:** Innovation at the ATMP manufacturing space has been lagging behind that achieved at the target identification and product discovery phases, where the bulk of investments and decision making takes place. However, progress in manufacturing processes, technologies and tools will be critical, if advanced therapies are to move from niche indications towards wider conditions; particularly as our understanding of disease progresses. The level of funding, resources and know-how necessary to achieve these outstrips the capacity of single organizations, and especially the SME and academic pioneers currently leading the space.
- **Variability:** ATMP manufacturing is also confounded by process variations, for example between cell and gene therapies, as well as variability of starting cell, tissue and genetic materials. Although cell and gene therapies share a number of common technology and manufacturing challenges, they also have a number of key differences, with vector gene therapies generally being less time-limited than patient-derived cell therapies. For ATMPs derived from standardised or donor tissue and where cryopreservation is feasible, more traditional supply chain routes can be deployed. However, for autologous products or where product shelf -life is a limiting factor, such as GSK's Strimvelis, there is need for specialized access and treatment centres, as well as for much tighter supply chains.
- **Regulation and Quality assurance:** A number of subsequent challenges involve the design of innovative manufacturing and quality control strategies, as well as the adaptation of relevant Good Manufacturing Practice guidelines. With individual batches essentially corresponding to a different product, ATMPs also face unique challenges in product inspection and release testing requirements.
- **From supply chains to stakeholder connectivity:** As a result, ATMP manufacturing lends itself to a greater degree of connectivity between basic science, preclinical and clinical stages. Manufacturability can become a consideration as early as vector design (Quality by Design, QbD), whereas at the healthcare space, the role of **Clinical Centres** in the

<p>sourcing of patient material, as well as final product administration, is paramount. The latter can turn health systems from procurement customers (as is the case with traditional drugs) into manufacturing partners.</p> <ul style="list-style-type: none"> <li>- <b>Getting the right actors together:</b> so far, ATMP manufacturing has been largely residing within academia and the investigational space, conceivably bearing little GMP congruence. In addition, feedback loops between improvements in scalability and industrialization from the commercial space, and the technology innovation from academia, have been largely absent. This leaves a significant space for connectivity and collaboration. Besides academic scientists, opportunity for process and platform innovations also derive from smaller companies, especially developers from other sectors, as a good part of equipment currently missing will be either bespoke or repurposed. Access to funding and knowledge sharing can also provide a key incentive for more SMEs, as well as CMOs to engage in this novel space and fill some of the current capacity gaps.</li> </ul>	
<p><b>UK identified priorities:</b> Three relevant thematic opportunities have been identified, with primary focus on:</p>	
<p><b>1. Manufacturing Industrialization and Scale-up</b></p>	<p>Although small scale ATMP studies are currently doable, rapid and cost-controlled scale-up for commercial viability remains outstanding. Important considerations include:</p> <ul style="list-style-type: none"> <li>- Poorly understood effects of process development on potency and stability.</li> <li>- Majority of existing technologies are at the academic prototype level, as well as tailored to specific products or applications.</li> <li>- Platform technologies for multiple applications or vector types needed.</li> <li>- Incorporation of advances from small and large molecule manufacturing, including continuous processing, flexible manufacturing and automation should be considered.</li> <li>- Adaptive manufacturing and regulatory discussions to develop the accompanying regulatory flexibility is of particular value, as small clinical trial sizes and unpredictable enrolment rates pose additional risks.</li> <li>- For the gene therapy space, scalability also involves maintaining viral titre and infectivity; also key for moving the field into less niche indications.</li> <li>- Some of these concerns can also be embedded earlier in product development, ie. vector designs for higher titres (QbD) (also relevant to proposal below)</li> </ul>
<p><b>2. Viral vector manufacturing: Characterization and analytics</b></p>	<p>A variety of different vector types have shown clinical promise, resulting in fragmentation of the space and restricting standardization of assays. Persisting challenges include:</p> <ul style="list-style-type: none"> <li>- Gaps in viral vector specific technology development, especially in downstream process.</li> </ul>

	<ul style="list-style-type: none"> <li>- Rapid and robust analytics are still missing for the characterization vector infectivity, uptake and integration. Examples include particle sizing, identification of empty and full capsids, and accurate quantification of transduction efficiency, specificity and potency assays.</li> <li>- Development and expansion of platforms for vector characterization: NGS, flow cytometry and microfluidics, imaging and other physical characterization tools (nanoparticle tracker/imaging).</li> <li>- Gaps also in standards and reference materials for vector integrity, longevity and stability, identity, maturation and integration patterns.</li> <li>- Standardisation would also be greatly assisted by the creation of stable producer cell lines.</li> </ul>
<p><b>3. Cell Therapy Manufacturing</b></p>	<p>One of the key factors hindering industrialization in this space is the significant variation across the sources and types of cells that can be effectively and cost-efficiently scaled-up, as these differ for adult, embryonic, iPSC, as well as donor vs patient derived cells. Cost and production efficiencies and risks also differ between suspension and adherent cultures.</p> <p>A number of changes and innovations have to be investigated further:</p> <ul style="list-style-type: none"> <li>- Incorporation of engineering technologies in cell bioprocessing lines, including, automation, robotic and monitoring systems.</li> <li>- Closed culture systems and control methodologies</li> <li>- GMP and scalable banking of cell lines and cell therapy products, including novel banking standards.</li> <li>- Standardization and quality aspects, in particular, are significantly lagging behind in this space, compared to chemical and large molecules. Existing QbD approaches provide an abundance of learnings that can be mined for consideration in this space.</li> </ul>

**6.4. Pricing, reimbursement and market access:**

<p><b>Challenges identified by the IMI workshop:</b></p> <p>The consultation also included a number of initial deliberations around the unique pricing and commercialization consideration of ATMPs. Although additional discussions will be needed to nail down the project details, prioritization has been given to:</p> <ul style="list-style-type: none"> <li>- HTA key considerations: including comparator selection and study designs, long-term monitoring requirements, and ongoing alignment efforts between fast track regulatory and downstream pricing assessment.</li> <li>- Hospital exception, related registries and implications for business and market incentives.</li> <li>- Novel reimbursement and payment schemes, including managed entry agreements (MAEs), Annuity mechanisms and special designation for one-off treatments with long-term effects.</li> </ul>
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Although it is unclear whether these critical issues can be better addressed at the level of the European Commission, collaborative platforms for early cross-stakeholder dialogue and data sharing for the piloting of new schemes and mock appraisals can be beneficial.

**Additional UK considerations:**

- Under that purview, discussions in the UK between government, industry, regulators and NHS have shed light on a number of key topics that will have to be further addressed to derisk investment in the space.
- ATMP products face unique challenges in health technology assessment (HTA) and adoption into health systems. A large proportion of ATMPs are potentially curative, meaning that lifelong benefits must offset the development costs, whereas evidence and confidence on the long-term effects at the point of approval and pricing are limited.
- In addition, the number of manufacturing and supply issues yet to be resolved significantly inflate industry's development and production costs.
- A key concern that demonstrates further the unique to ATMP interdependencies across the pathway from the bench to the market, entails the 'hospital exception'. This has ended up being used as an exception clause from the established safety, efficacy, and quality assessments for products 'prepared on a non-routine basis', thus providing a non-regulated, informal route to market. Although not a concern for the UK, There are several examples in Europe, whereby the broad interpretation of this clause has been not only diluting the regulatory oversight, but undermining investment incentives.
- Policies affecting health system commissioning, funding availability, data collection and clinical pathways can thus significantly affect appetite and confidence to invest, for the industry and VCs alike.
- To capture these challenges, new commercialization models that can accommodate the progressive accumulation of product use evidence, as well as novel assessment frameworks should be considered for both anticipated and unanticipated risks.
- UK can contribute its early experiences gained through a number of pioneering initiatives, such as the Accelerated Access Review (AAR)<sup>22</sup> and the NICE T-cell therapy mock appraisal<sup>23</sup> that followed from the RMEG report. The latter was an important attempt to determine the fitness of the existing HTA frameworks in assessing cell and gene therapies.
- A number of other European countries have also resorted to creative funding schemes, and give their health systems greater budgetary control that will allow the uptake of high risk/high promise products. Examples include the rare disease fund in Finland, Switzerland's scheme for genetic disorders, as well as the innovation fund in Italy.
- **Case for collaboration:** All these interdependencies call for a platform that will allow stakeholders to have the discussions and trade-offs needed allow timely patient access to ATMP products. Most importantly, collaborations will be principal in drawing together the range of expertise needed to both assess product value and proportionately manage health system budgets, while ensuring the return on investment necessary to sustain and grow this emerging enterprise.

<sup>22</sup> <https://www.gov.uk/government/organisations/accelerated-access-review>

<sup>23</sup> NICE publishes report on approaches to assessing innovative regenerative medicines  
<https://www.nice.org.uk/news/press-and-media/nice-publishes-report-on-approaches-to-assessing-innovative-regenerative-medicines>

- As in the case of hospital exception and the country-specific reimbursement funds, the lack of harmonization in the market conditions across Europe may compromise its offering against other global leaders. Discussions on the feasibility and necessary conditions for the successful setup of Centres of Excellence for the assessment and adoption of ATMPs would be important.

## 6.5. ADDITIONAL PROPOSALS:

### 6.5.1. SKILLS:

- 6.5.1.1. As in the case of ATMP policies and regulation, a key challenge moving forward remains the lag in the evolution of skills and know-how compared to that of ATMP technology and scientific innovations. Europe's capacity to compete at the global level will depend heavily on its capability to train and provide a sustained supply of skilled workforce with specialization on ATMPs, from scientists and technicians, to the clinical and medical personnel<sup>24</sup>.
- 6.5.1.2. Industry - academia collaborations can prove extremely powerful, allowing companies to frame the key sector requirements, and work together with the higher education and public organizations to design relevant training schemes. IMI has been traditionally strong in the scoping of knowledge generation and management consortia. As such, it comprises an ideal platform for the level of coordination required to secure that short and long-term needs for specialized workforce are met across Europe.
- 6.5.1.3. A number of UK organizations, including the ABPI and MMIP have dedicated teams looking into Skills and Education<sup>25</sup>, canvassing the particular needs and gaps for a skilled workforce in ATMPs.

### 6.5.2. PUBLIC OPINION & PATIENT ENGAGEMENT:

- 6.5.2.1. The complexity of the ATMP development pathways also requires a compelling patient-centric approach throughout research, development, and delivery pathways. However, given the field's early days, public understanding of their nature, mode of action and impact in disease management is still limited.
  - 6.5.2.2. Therefore, general public communication plans to raise awareness of these unique and potential transformative treatments, in addition to patient engagement packages in disease areas where ATMPs are starting to be applied, will be paramount to propel this dynamic further.
- 6.5.3. **ETHICS:** A key consideration will be to maintain a clear distinction between the different types of ATMP products and technologies, for example allogeneic vs. autologous cell therapies. The necessity of such distinctions became apparent recently, with the wave of ethical concerns and discussions on somatic vs. germline gene editing potentially impacting the applicability of this emerging technology<sup>26</sup>.

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<sup>24</sup> Building on our own potential: a UK pathway for regenerative medicine. A report from the Regenerative Medicine Expert Group, 2014 (pg 22)

<sup>25</sup> <http://www.abpi.org.uk/media-centre/newsreleases/2015/Pages/111115.aspx>

<sup>26</sup> Statement on Genome Editing Technologies and Human Germline Genetic Modification [http://www.hinxtongroup.org/hinxton2015\\_statement.pdf](http://www.hinxtongroup.org/hinxton2015_statement.pdf)

## **Conclusion:**

Europe holds a leading position in the fledgling ATMP sector, with a strong science base spread across its Universities and research institutes, as well as a growing clinical translation base. The UK, in particular, has established early on an internationally recognised scientific and translational foundation, through proactive and sustained government commitment in Regenerative Medicines, as well as Cell and Gene Therapies.

However, in the face of strong and growing international competition, including the US, Japan and Canada, it will be imperative that its research excellence, regulatory and clinical pathways and adoption strategies are consolidated, if Europe is to offer a comprehensive and competitive value proposition, and become the global destination for the development, manufacture and commercialisation of ATMP products. The UK can play a pivotal role in these IMI led collaborative efforts and we have laid out a number of unique strengths, as well as pioneering initiatives it can contribute in this respect.

Given the complex and cross-disciplinary nature of the ATMP space, not only should persisting challenges and opportunities be considered holistically, but actioned through ever stronger partnership and coordination between stakeholders in research, clinical delivery, as well as manufacturing and the commercial space. As the world's largest public-private partnership, the IMI provides a strong platform to tackle the unique ATMP sector challenges, drive progress in the science, educate highly skilled individuals and secure that these transformative therapies and their supply chains are in place, for the benefit of patients and the economy.

ABPI endorses the proposal to launch an IMI program on ATMPs, as a key focus area for 2017 onwards. We also ratify the four areas identified as key enablers for the field's progression, namely preclinical development, clinical development, manufacturing and market access (including pricing and reimbursement). Although these challenges can be addressed through separate initiatives, we are suggesting the design of an overarching framework of coordination, to advance the overall pathway of these products to the market and the clinic.

We also recommend that any future IMI initiatives on ATMPs should consider mapping out, as well as including all the stakeholders necessary to strengthen the joint efforts of industry with academia, at the outset. Finally, an important step towards the success of any future projects will entail leveraging the experience and successes of previous and ongoing IMI consortia, which could be expanded, linked or adapted, to inform the nascent space of ATMP's.

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